EFFECT OF NORMAL COMPRESSION ON THE SHEAR MODULUS OF SOFT TISSUE IN RHEOLOGICAL MEASUREMENTS

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Effect of Normal Compression on the Shear Modulus of Soft Tissue in Rheological Measurements

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This is to certify that I have examined this copy of a master's thesis by

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and have found that it is complete and satisfactory in all respects,
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ABSTRACT

In experiments performed to characterize rheological properties of viscoelastic solids, some amount of compression is necessary to prevent the slippage between the sample and the parallel plates of a rheometer. While the effect of normal compression on the shear rheological properties of viscoelastic materials has been already acknowledged and reported in few studies in the literature, to our knowledge, no systematic study has been conducted to investigate this effect in detail to date. In this study, we perform two sets of experiments to investigate the effect of normal strain and strain rate on the dynamic shear moduli of bovine liver. First, we apply normal compressive strain to the cylindrical bovine samples up to 20% at loading rates of v = 0.000625, 0.00625, 0.0625, 0.315, 0.625 mm/s. Second, we perform torsional shear loading experiments in the frequency range of ω = 0.1 to 10 Hz under varying amounts of compressive pre-strain (ε = 1%, 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5% and 20%) applied at the quasi-static loading rate of v = 0.000625 mm/s. The results of the experiments show that the shear moduli of bovine liver increase with compressive pre-strain. A hyper-viscoelastic constitutive model is developed and fit to the experimental data to estimate the true shear moduli of bovine liver for zero pre-compression. With respect to this reference value, the mean relative error in measurement of shear moduli of bovine liver varies between 0.2% and 243.1% for the compressive pre-strain varying from ε = 1% to 20%. The dynamic shear modulus of bovine liver for compressive pre-strain values higher than ε = 2.5% are found to be statistically different than the true shear moduli estimated for zero compressive strain ($p < 0.05$).

ÖZET

Viskoelastik malzemelerin reolojik özelliklerini karakterize etmek için gerçekleştirilen deneylerde, test numunesi ile reometrenin paralel plakaları arasındaki kaymayı önlemek amacıyla bir miktar sıkıştırma uygulanması gereklidir. Bu sıkıştırmanın viskoelastik malzemenin reolojik burulma özellikleri üzerine etkisi literatürdeki birkaç çalışmada farkedilmiş ve raporlanmış olmasına rağmen, günümüze kadar bu etkinin detaylarını araştıran sistematik bir çalışma gerçekleştirilmemistir. Bu çalışmada, normal yöndeki gerinim ve gerinim hızının dana karaciğer dokusuna ait burulma modülleri üzerine etkisini incelemek amacıyla iki farklı deney gerçekleştirilmiştir. Öncelikle silindirik karaciğer doku örneklerine v = 0.000625, 0.00625, 0.0625, 0.315, 0.625 mm/s hızlarında, %20 miktarında normal gerinim uygulanmıştır. Daha sonra sanki-statik (quasi-static) yükleme hızı olan v = 0.000625 mm/s hızında, değişen sıkıştırma normal ön gerinim miktarları altında (ε = 1%, 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5% and 20%) ve ω = 0.1 to 10 Hz frekans aralığında dinamik burulma yüklemesi deneyleri gerçekleştirilmiştir. Deney sonuçları, dana karaciğer dokusu burulma modüllerinin artan sıkıştırma normal ön gerinimleri ile arttığını göstermiştir. Bir hiper-viskoelastik malzeme modeli oluşturulup deney sonuçlarına uydurulmuştur, bu sayede dana karaciğer dokusunun normal yönde ön gerinim olmadan göstereceği doğru burulma kesme modülleri belirlenmiştir. Bu referans değer ile karşılaştırıldığında, %1-%20 aralığında uygulanan normal ön gerinim altında ölçülen burulma kesme modülü değerlerinde %0.2-%243.1 aralığında ortalama bağıl hata yapıldığı görülmüştür. ε = 2.5% ve üzeri miktarlardaki normal ön gerinim altında ölçülen dana karaciğeri burulma modülleri değerlerinin, normal yönde ön gerinim olmadan ölçülen referans değerden istatistiksel olarak farklı olduğu görülmüştür ($p < 0.05$).

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NOMENCLATURE

v	loading rate in normal direction
ω	frequency
ε	normal strain
γ	shear strain
γ_{LVR}	linear viscoelastic range for shear strain
$\boldsymbol{\sigma^e}$	hyperelastic stress tensor
$\boldsymbol{\sigma^v}$	viscoelastic stress tensor
$\boldsymbol{\sigma^t}$	total stress tensor
R, Θ, Z	radius, angle and height of the sample in initial configuration
r, θ, z	radius, angle and height of the sample in deformed configuration
$\boldsymbol{X}$	location of a point on tissue sample in initial configuration
$\boldsymbol{x}$	location of a point on tissue sample in deformed configuration
λ	stretch
$\boldsymbol{F}$	deformation gradient
$\boldsymbol{F_c}$	deformation gradient in the case of pure uniaxial compression
$\boldsymbol{F_s}$	deformation gradient in the case of torsional shear
K	angle of twist per unit length
$\boldsymbol{B}$	left Cauchy-Green deformation tensor
$\boldsymbol{C}$	right Cauchy-Green deformation tensor
I_1, I_2, I_3	invariants of the left Cauchy-Green deformation tensor
W	strain energy function
μ	linear shear modulus
p_e, p_v	undetermined hyperelastic and viscoelastic pressure
μ	linear shear modulus

E	linear elastic modulus
$\boldsymbol{E}$	Green strain tensor
$m(t)$	sum of series of relaxation function
ρ	relaxation time
$\dot{\boldsymbol{E}}_{\boldsymbol{c}}, \dot{\boldsymbol{E}}_{\boldsymbol{s}}$	strain rate functions for compression and torsion
G^*, G_S, G_L	complex, storage and loss dynamic shear moduli

Chapter 1

INTRODUCTION

One of the most frequently used experimental methods for characterizing the viscoelastic material properties of soft tissue is the dynamic oscillation experiment. In this test, small periodic strains at varying frequencies are applied to the sample and the stress response is recorded. These small-amplitude oscillatory tests are commonly performed in shear using a rheometer. In rheological shear measurements, a cylindrical viscoelastic sample is placed between the plates of a rheometer, and some amount of compression is applied before the measurements to ensure full contact between the sample and the plates and hence to reduce the slippage. Subsequently, small oscillatory shear is applied to the sample in the linear viscoelastic range (LVR) to measure its torque response. The shear stress is then calculated from the measured torque response based on the sample geometry. Finally, the shear stress is divided by the shear strain in frequency domain to obtain two shear moduli at each frequency: one in-phase with the applied strain, called shear storage modulus, and the other 90 degrees out-of-phase with the applied strain, called shear loss modulus.

Using a shear rheometer, the frequency-dependent shear material properties of liver (Ayyildiz et al. [1], Kiss et al. [2], Klatt et al. [3], Liu and Bilston [4], Tan et al. [5], Wex et al. [6]), brain (Garo et al. [7], Hrapko et al. [8]), and kidney (Nasseri et al. [9], Nicolle and Palierne [10]) have been measured. However, the effect of normal compression on the shear material properties of soft tissues has been reported in few studies only. Hrapko et al. [8] showed that increasing the normal force applied on the brain tissue samples results in

overestimation of shear modulus. Tan et al. [5] showed that the magnitude of pre-compression alters the storage shear modulus and LVR of bovine liver and recommend not applying more than 10% pre-strain in the normal direction. Despite these observations, to our knowledge, no systematic study has been conducted to investigate this effect in detail to date. In this study, we perform two sets of characterization experiments (compression and dynamic shear loading) to examine the effect of compression on the dynamic shear moduli of bovine liver. A hyper-viscoelastic constitutive model is developed and fit to the experimental data to estimate the dynamic shear moduli of bovine liver for different values of compressive pre-strain. The existing constitutive models developed so far for material characterization of liver tissue have aimed to describe either its linear (Ayyildiz et al. [1], Klatt et al. [3], Liu and Bilston [4]; Yarpuzlu et al. [11]) or nonlinear (Nasseri et al. [9], Nicolle et al. [12]) dynamic viscoelastic response in shear loading only, but not under the combined loading of compression and shear. Hence, the earlier studies have failed to model the effect of normal compression on the shear material properties of liver tissue.

Chapter 2

MATERIALS AND METHODS

2.1 Preparation of Tissue Samples

In order to obtain cylindrical liver samples, fresh bovine livers are harvested from 3 animals in a local slaughterhouse and immediately put into the Lactated Ringer's solution for preservation. The livers are transferred from the slaughterhouse to our laboratory while cold preserved in the Lactated Ringer's solution at +4°C. Cylindrical tissue samples with a diameter of 25 mm and a thickness of 2.5±0.5 mm are obtained from each liver using the tissue slicing and sampling apparatus developed in our earlier study (Ayyildiz et al. [1]). A total of 28 tissue samples are obtained from each liver. The samples are kept in sterile specimen cups containing Lactated Ringer's solution until the time of testing. Each sample is tested within 30 minutes to ensure that its material properties are not affected significantly from dehydration. All experiments for each liver are completed within 12 hours after harvesting. Hence, the rim of our samples was covered with the preservation solution during the experiments and they were not exposed to air until the evaporation of the preservation solution (Nicolle and Palierne [10]).

2.2 Experimentation

The tissue samples are tested by a shear strain-controlled, parallel plate rheometer (Anton Paar MCR 102, see Fig. 2.1). In addition to a torque sensor for shear measurements, our rheometer is also equipped with a force sensor, having a range of 0.01 N to 50 N with a resolution of 0.01 N, for measuring forces in the normal direction. In order to prevent slippage between the sample and the plates, sand paper is applied to the upper and lower plates of the rheometer. The initial height of each sample is determined by moving the upper plate with a very low velocity of 0.000625 mm/s towards to the sample until a contact force of 0.1 N is reached. Then, the movement of the upper plate is stopped and the gap between the upper and lower plates is measured and taken as the initial height of the sample. In addition to the usage of sandpapers, an initial normal force is applied on the soft tissue samples to avoid the partial contact between the plates and sample due to the inevitable surface roughness of the soft tissue samples. Hence, perfect adhesion is ensured even at very low compression strains. During the tests, temperature is kept at 24°C by the Peltier module (P-PTD200/56/AIR) of the rheometer.

In order to investigate the effect of pre-compression on the dynamic shear response of bovine liver, normal compression and dynamic shear loading experiments are performed on the samples.

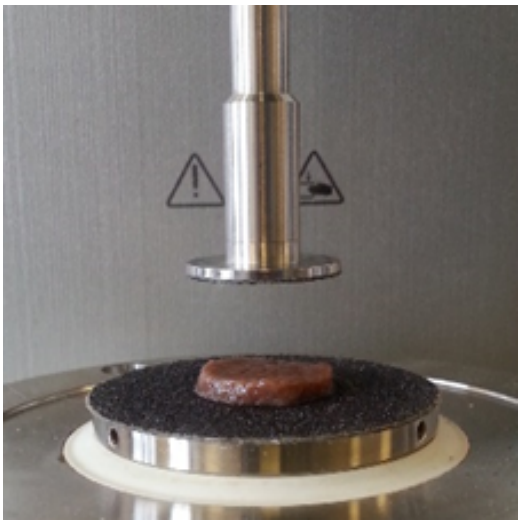

Figure 2.1: A liver tissue sample on the lower plate of the rheometer.

2.2.1 Compression Experiments

The samples are compressed in normal direction up to 20% strain. Each sample is compressed only once at a loading rate of v = 0.000625, 0.00625, 0.0625, 0.315, 0.625 mm/s and the force response is recorded as a function of displacement. The compression experiments are repeated 4 times at each loading rate with a different sample. Hence, a total of 60 tissue samples are examined in compression (4 samples per loading rate × 5 loading rates per liver × 3 livers).

2.2.2 Dynamic Shear Loading (DSL) Experiments

In order to determine the LVR of the samples, first amplitude sweep experiments are performed under normal compressive strains of ε = 5%, 10%, 15% and 20%, with four samples taken from each liver (4 samples per liver × 3 livers = 12 samples). The samples are oscillated in torsion at a constant frequency of ω = 10 Hz while the shear strain amplitude is

varied from γ = 0.1% to 5%. It is observed that LVR of the bovine liver is decreased with increasing pre-strain, as reported in Tan et al. [5]. The shear strain corresponding to lowest LVR, γ_{LVR} = 0.5%, is used in all frequency sweep experiments, which are performed in the frequency range of ω = 0.1 Hz to 10 Hz under varying amounts of compressive pre-strain (ε = 1%, 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5% and 20%), applied at the quasi-static loading rate of v = 0.000625 mm/s. The frequency sweep experiments are repeated with four samples from each liver (4 samples per liver × 3 livers = 12 samples). In all experiments, the torque response is recorded as a function of frequency.

2.3 Constitutive Model

A hyper-viscoelastic constitutive model is developed to investigate the material properties of uniaxially compressed cylindrical liver tissue under torsional shear loading. It utilizes a single parameter Neo-Hookean material model to characterize the quasi-static hyperelastic behavior of liver tissue under large deformations and a twelve-parameter viscoelastic model to characterize it's the rate and strain-history-dependent behavior. Hence, the total stress response of the liver tissue under combined loading of compression and torsion is assumed to be $\boldsymbol{\sigma^t = \sigma^e + \sigma^v}$, where $\boldsymbol{\sigma^e}$ and $\boldsymbol{\sigma^v}$ are the hyperelastic and viscoelastic Cauchy stress tensors (see Figure 2.2). In the following sections, formulatıon of each stress component is further explained.

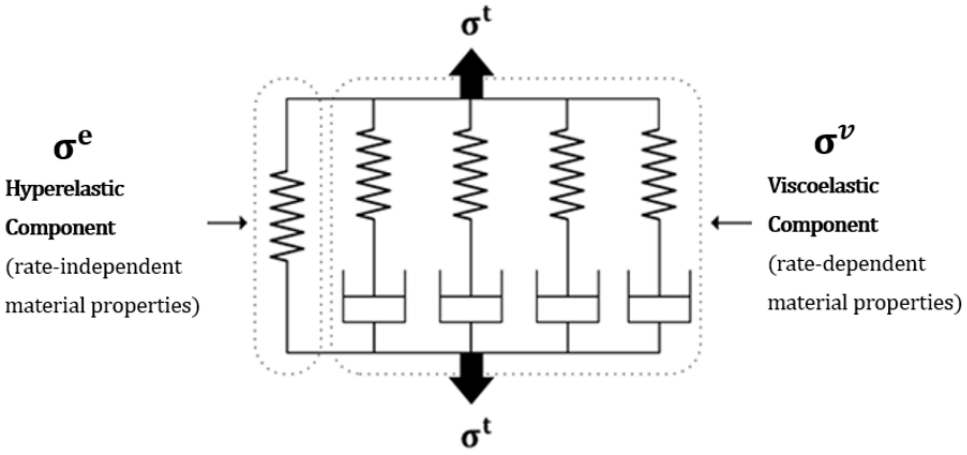

Figure 2.2: The proposed hyper-viscoelastic soft tissue model.

2.3.1 Hyperelasticity

We assume that the soft tissue is isotropic, homogenous, and incompressible. Using the cylindrical coordinates, a point in the tissue sample is initially located at $\boldsymbol{X}=\boldsymbol{X}(R,\Theta,Z)$ with respect to the reference configuration and at $\boldsymbol{x}=\boldsymbol{x}(r,\theta,z)$ with respect to the deformed configuration.

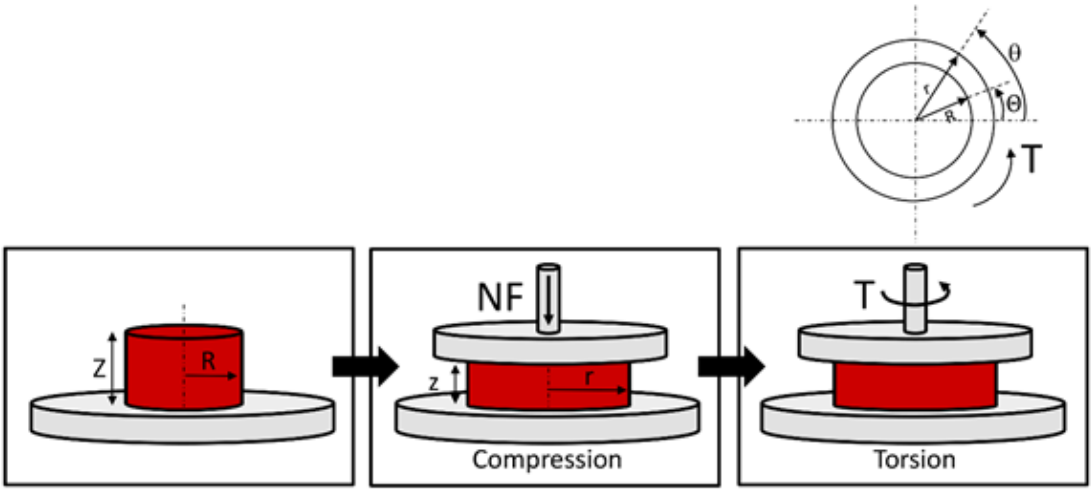

Figure 2.3: The tissue sample in reference configuration is compressed first and then torsion is applied. In the figure, NF and T represent the normal force and torque, respectively.

Then, the deformation gradient for the tissue sample is defined as $\boldsymbol{F} = \partial \boldsymbol{x}/\partial \boldsymbol{X}$. In the case of uniaxial compression of the sample, $r = R/\sqrt{\lambda}, \theta = \Theta, z = \lambda Z$, where, λ is the stretch (see Figure 2.3). Hence, the deformation gradient of a cylindrical tissue sample under pure uniaxial compression is given as

$$\boldsymbol{F_c} = \begin{bmatrix} 1/\sqrt{\lambda} & 0 & 0 \\ 0 & 1/\sqrt{\lambda} & 0 \\ 0 & 0 & \lambda \end{bmatrix} \tag{2.1}$$

In the case of simple torsion of the sample, $r = R, \theta = \Theta + KZ, z = Z$, where K is the angle of twist per unit length (see Figure 2.3). Then, the deformation gradient of the cylindrical tissue sample under sımple torsional shear loading is defined by $\boldsymbol{F_s}$ as

$$\boldsymbol{F_s} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & \gamma \\ 0 & 0 & 1 \end{bmatrix} \tag{2.2}$$

where, $\gamma = rK$ is the torsional shear strain. Hence, the deformation gradient of an initially compressed cylindrical tissue sample under torsional shear loading is defined by $\boldsymbol{F} = \boldsymbol{F_s} . \boldsymbol{F_c}$ as

$$\boldsymbol{F} = \begin{bmatrix} \frac{1}{\sqrt{\lambda}} & 0 & 0 \\ 0 & \frac{1}{\sqrt{\lambda}} & \gamma\,\lambda \\ 0 & 0 & \lambda \end{bmatrix} \tag{2.3}$$

Accordingly, the resulting left Cauchy-Green deformation tensor, $\boldsymbol{B} = \boldsymbol{F}.\boldsymbol{F}^T$, is calculated as

$$\boldsymbol{B} = \begin{bmatrix} \frac{1}{\lambda} & 0 & 0 \\ 0 & \gamma^2\,\lambda^2 + \frac{1}{\lambda} & \gamma\lambda^2 \\ 0 & \gamma\,\lambda^2 & \lambda^2 \end{bmatrix} \tag{2.4}$$

The principle invariants of the left Cauchy-Green tensor are calculated as $I_1 = tr(\boldsymbol{B}) = \gamma^2\lambda^2 + \lambda^2 + 2/\lambda$, $I_2 = 1/2\left(tr(\boldsymbol{B})^2 - tr(\boldsymbol{B}^2)\right) = \gamma^2\lambda^4 + \gamma^2\lambda + 2\,\lambda + 1/\lambda^2$, $I_3 = |\boldsymbol{B}| = 1$. Using the left Cauchy-Green tensor, the constitutive relation for isotropic, homogenous, and incompressible hyperelastic soft tissue can be written as

$$\boldsymbol{\sigma}^e = \alpha_1\boldsymbol{B} + \alpha_2\boldsymbol{B}^2 - p_e\,\boldsymbol{I} \tag{2.5}$$

where, $\alpha_1 = 2\left(\frac{\partial W}{\partial I_1} + I_1\frac{\partial W}{\partial I_2}\right)$, $\alpha_2 = -2\frac{\partial W}{\partial I_2}$, and p_e is the undetermined pressure due to incompressibility condition, and **I** is the identity tensor. For a Neo-Hookean material, the strain energy function is defined as $W = \mu/2\ (I_1 - 3)$, where μ is the linear shear modulus.

2.3.2 Viscoelasticity

The constitutive relationship for an isotropic, homogenous, and incompressible viscoelastic soft tissue can be defined as (Pouriayevali et al. [13], Shim et al. [14], Yang et al. [15])

$$\boldsymbol{\sigma}^v = \boldsymbol{F}(t)\,.\,\boldsymbol{\Omega}\{\boldsymbol{C}(\tau)\}\,.\,\boldsymbol{F}^T(t) - p_v\boldsymbol{I} \tag{2.6}$$

where, $\boldsymbol{\Omega}$ is a matrix functional describing the effect of strain history on stress, $\boldsymbol{C}$ is the right Cauchy-Green deformation tensor defined as $\boldsymbol{F}^T.\boldsymbol{F}$, p_v is the undetermined pressure due to incompressibility condition, and t is the time. Based on the constitutive model shown in Figure 2.2, the function $\boldsymbol{\Omega}$ takes the following form (Yang et al. [15])

$$\boldsymbol{\Omega}\{\boldsymbol{C}(\tau)\} = \int_0^t \beta\ (I_1, I_2)\ m(t-\tau)\ \dot{\boldsymbol{E}}(\tau)d\tau \tag{2.7}$$

where, the Green strain tensor is defined by $\boldsymbol{E} = (\boldsymbol{C} - \boldsymbol{I})/2$, β is a function defined as $\beta = A + B\ (I_2^c - 3)$. The material parameters A and B are analogous to the linear and nonlinear tangent moduli of the spring in each Maxwell arm shown in Figure 2.2, respectively. The term $B\ (I_2^c - 3)$ accounts for the nonlinear viscous energy dissipation. For infinitesimal deformation, $I_2^c - 3$ is approximately zero and hence, the proposed viscoelastic model reduces to the generalized Maxwell model (Yang et al. [15]). Here, it is important to

note that the second invariant $I_2^c = \frac{1}{2}\left(tr(\boldsymbol{C})^2 - tr(\boldsymbol{C}^2)\right)$ is related to the deviatoric aspects of the stress and strain. The function $m(t)$ represents the sum of series of relaxation functions defined for each Maxwell arm as

$$m(t-\tau) = \sum_{i=1}^{N} e^{-(t-\tau)/\rho_i} \tag{2.8}$$

where, ρ is the relaxation time and N is the number of Maxwell arms connected in parallel. In our earlier studies, we observed that N=2 is sufficient for characterizing the viscoelastic response of liver tissue under compression (Samur et al. [16]). With the same notion, we utilize two additional Maxwell arms for modeling the viscoelastic response of the liver tissue under torsional shear loading. Hence, the rate-dependent viscoelastic behavior of the liver tissue in combined loading of compression and torsional shear is characterized by using a total of four Maxwell arms as

$$\begin{aligned}\boldsymbol{\Omega}\{\boldsymbol{C}(\tau)\} = &\int_0^{t_c} \sum_{i=1}^{2} \left[A_{c,i} + B_{c,i}(I_2^c - 3)\right] e^{-(t_c-\tau)/\rho_{c,i}}\ \dot{\boldsymbol{E}}_{\boldsymbol{c}}\, d\tau \\ &+ \int_0^{t_s} \sum_{i=1}^{2} \left[A_{s,i} + B_{s,i}(I_2^c - 3)\right] e^{-(t_s-\tau)/\rho_{s,i}}\ \dot{\boldsymbol{E}}_{\boldsymbol{s}}\, d\tau\end{aligned} \tag{2.9}$$

where, the subscripts “c” and “s” represent the variables defined for compression and torsional shear, respectively. We used two different deformation modes and hence, two time scales, since the duration of the compression and torsion experiments are different in our experiments. The strain rate functions for compression ($\dot{\boldsymbol{E}}_{\boldsymbol{c}}$) and torsion ($\dot{\boldsymbol{E}}_{\boldsymbol{s}}$) are given as

$$\dot{\boldsymbol{E}}_{\boldsymbol{c}} = \begin{bmatrix} -\frac{\dot{\lambda}}{2\lambda^2} & 0 & 0 \\ 0 & -\frac{\dot{\lambda}}{2\lambda^2} & \frac{\gamma\dot{\lambda}}{4\sqrt{\lambda}} \\ 0 & \frac{\gamma\dot{\lambda}}{4\sqrt{\lambda}} & \frac{1}{2}(2\lambda\,\dot{\lambda}\,\gamma^2 + 2\lambda\dot{\lambda}) \end{bmatrix} \tag{2.10}$$

$$\dot{\boldsymbol{E}}_{\boldsymbol{s}} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & \frac{1}{2}\sqrt{\lambda}\dot{\gamma} \\ 0 & \frac{1}{2}\sqrt{\lambda}\,\dot{\gamma} & \gamma\lambda^2\dot{\gamma} \end{bmatrix} \tag{2.11}$$

where, $\dot{\lambda}$ and $\dot{\gamma}$ are the stretch (or strain) and shear rates, respectively.

2.3.3 Hyper-Viscoelasticity

The total stress response of the liver tissue under combined loading of compression and torsion is given as

$$\boldsymbol{\sigma^t} = \boldsymbol{\sigma^e} + \boldsymbol{\sigma^v} \tag{2.12}$$

The total hydrostatic pressure, $p = p_e + p_v$, is determined by means of the equilibrium equation, $div\ \boldsymbol{\sigma^t} = 0$, and using traction free boundary conditions as suggested by Ciarletta and Destrade [17]. Finally, the normal force (*NF*) during compression and the torque (*T*) during torsion can be calculated using the components of the stress tensor as:

$$NF = 2\pi \int_0^R r\, \sigma_{33}^t\, dr \tag{2.13}$$

$$T = 2\pi \int_0^R \sigma_{23}^t\, r^2\, dr \tag{2.14}$$

Chapter 3

RESULTS

In order to determine the optimum material parameters of the proposed hyper-viscoelastic model, the experimental data obtained from the compression and the dynamic shear loading experiments are used simultaneously along with an optimization scheme utilizing the least-square approach (see Figure 3.1). Hence, the goal of the optimization is to estimate the material coefficients of the model $(\mu, A_{c,1}, A_{c,2}, A_{s,1}, A_{s,2}, B_{c,1}, B_{c,2}, B_{s,1}, B_{s,2}, \rho_{c,1}, \rho_{c,2}, \rho_{s,1}, \rho_{s,2})$ by minimizing the error between the experimental data and the corresponding values generated by the model. The material parameters estimated by the optimization process are tabulated in Table 3.1.

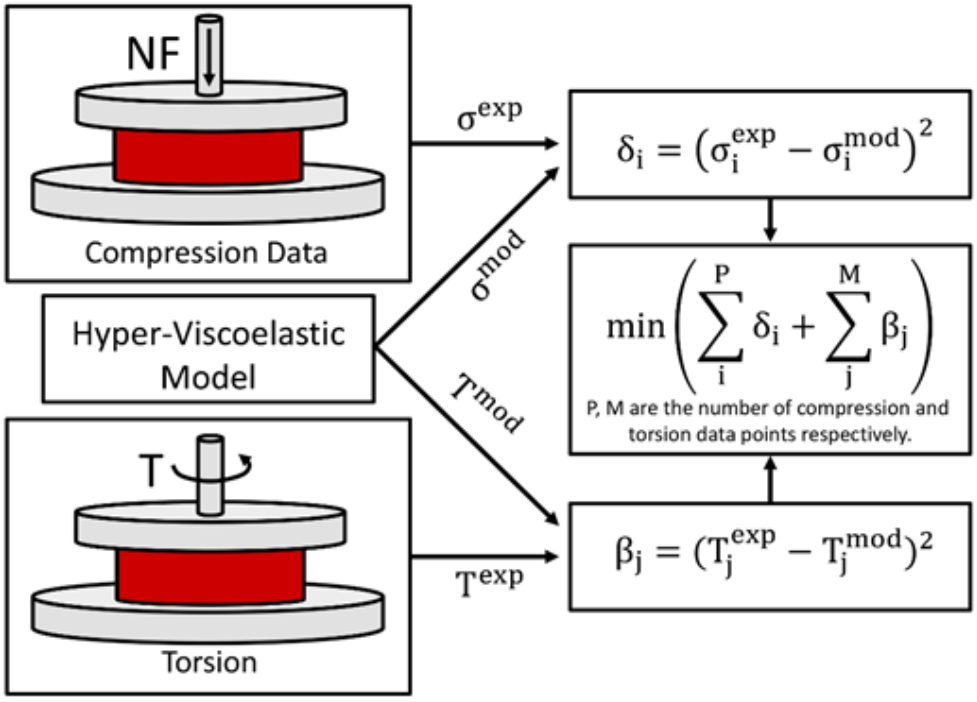

Figure 3.1: The optimization scheme for the estimation of the material parameters of the hyper-viscoelastic model.

Table 3.1: The material parameters of the hyper-viscoelastic model estimated by the optimization.

Parameter	**Value**	**Parameter**	**Value**
μ [Pa]	2.67E2	$B_{s,1}$ [Pa]	1.56E1
$A_{c,1}$ [Pa]	1.53E-8	$B_{s,2}$ [Pa]	9.16E1
$A_{c,2}$ [Pa]	8.78E-8	$\rho_{c,1}$ [s]	5.01E-1
$A_{s,1}$ [Pa]	2.00E-3	$\rho_{c,2}$ [s]	3.92E1
$A_{s,2}$ [Pa]	8.74E1	$\rho_{s,1}$ [s]	8.28E5
$B_{c,1}$ [Pa]	2.09E6	$\rho_{s,2}$ [s]	7.85E-2
$B_{c,2}$ [Pa]	3.61E5		

The normal force-strain response of the bovine liver for different loading rates is given in Figure 3.2. The markers and error bars represent the mean (average of 3 animals) experimental data and the standard deviations from the mean values, respectively. The solid curves show the corresponding model output ($R^2 > 0.98$). As shown in the figure, the stress response is highly nonlinear, which becomes more prominent with the loading rate.

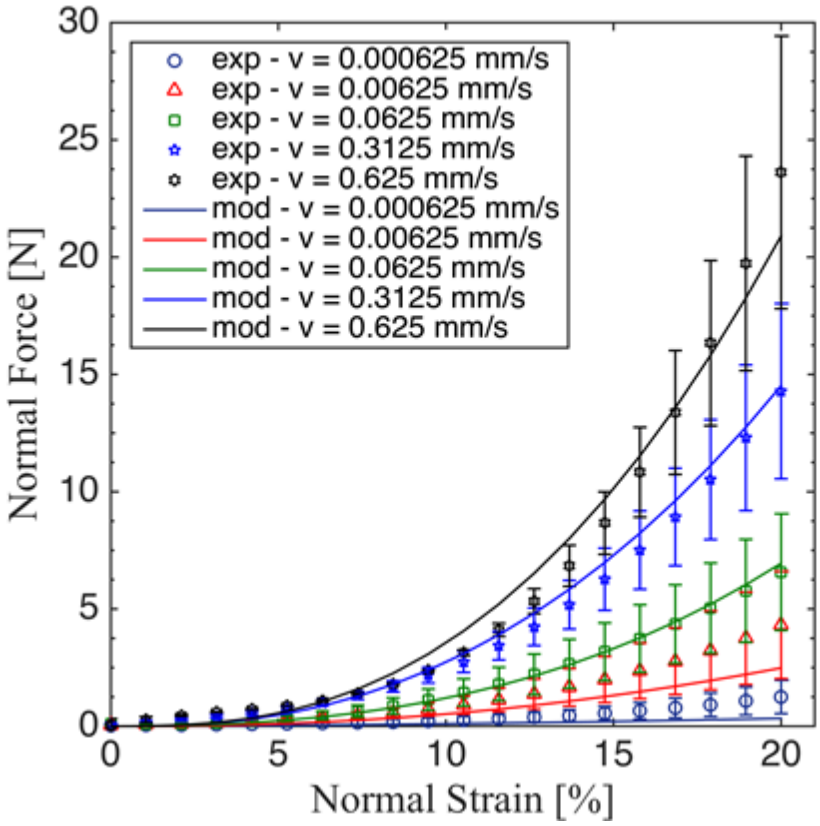

Figure 3.2: The normal force-strain response of bovine liver for different compression rates. The markers and the solid curves represent the mean experimental data and the model output, respectively.

The average torque response of the liver samples as a function of frequency for compressive pre-strains of ε = 1%, 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5% and 20%, applied at compression rate of v = 0.000625 mm/s, is shown in Figure 3.3. The markers and solid curves represent the mean experimental data and model output ($R^2 > 0.91$), respectively. As shown in the figure, the magnitude of torque response increases with the frequency and the compressive pre-strain. This plot clearly shows the effect of compression on the shear response of the soft tissue.

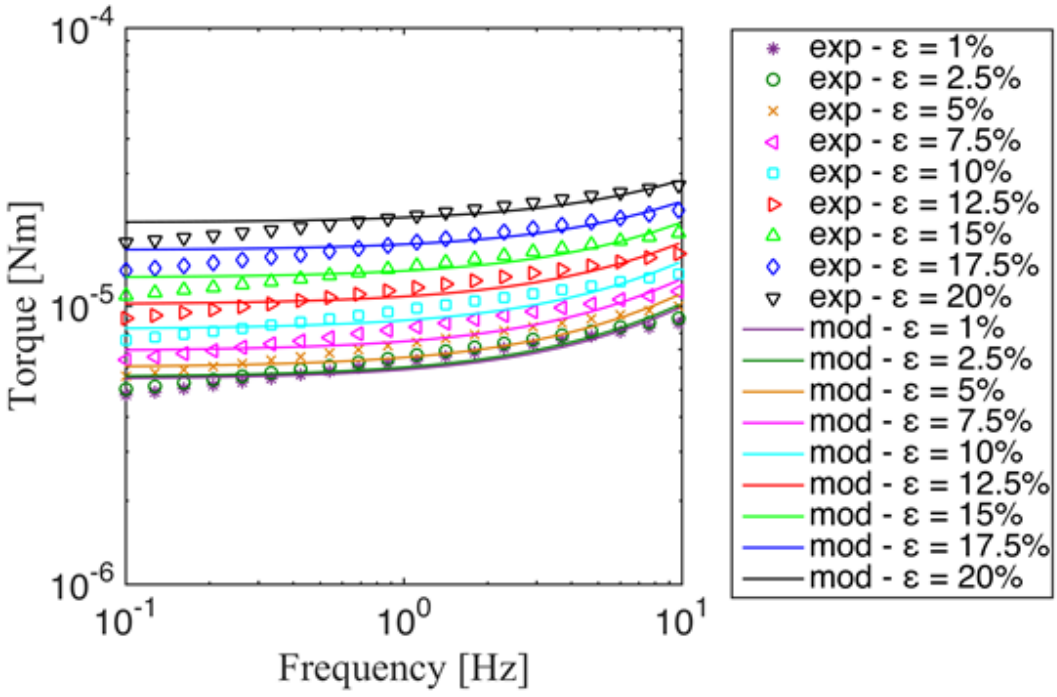

Figure 3.3: The torque response of bovine liver for different compressive pre-strains at quasi-static compression rate of v = 0.000625 mm/s. The markers and the solid curves represent the mean experimental data and the model output, respectively.

Also, using the torque response and the physical dimensions of the tissue samples, the mean (average of 3 animals) values for storage and loss (shear) moduli at ω = 0.1 Hz, 1 Hz and 10 Hz are calculated for different compressive pre-strains and tabulated in Table 3.2, Table 3.3 and Table 3.4 respectively. At low frequency (ω = 0.1 Hz), the storage and loss moduli of the samples vary between G_S = 306–945 Pa and G_L = 56-150 Pa, respectively. When the frequency of stimulation is reached to 10 Hz, the storage and loss moduli of the samples vary between G_S = 658-2148 Pa and G_L = 60-363 Pa, respectively. The results show that the storage and loss shear moduli of bovine liver increase as a function of compressive frequency and pre-strain.

Table 3.2: The storage and loss (shear) moduli of bovine liver at 0.1 Hz for different compressive pre-strains.

Compressive Pre-strain (ε)	Storage Modulus [Pa]	Loss Modulus [Pa]
1%	306±14	56±5
2.5%	320±11	57±4
5%	354±9	63±4
7.5%	400±10	70±4
10%	460±9	79±4
12.5%	541±10	91±4
15%	639±27	105±5
17.5%	768±36	125±6
20%	945±60	150±5

Table 3.3: The storage and loss (shear) moduli of bovine liver at 1 Hz for different compressive pre-strains.

Compressive Pre-strain (ε)	Storage Modulus [Pa]	Loss Modulus [Pa]
1%	440±29	94±10
2.5%	460±24	98±7
5%	513±22	108±8
7.5%	584±20	119±8
10%	681±17	135±7
12.5%	813±10	155±5
15%	980±30	180±6
17.5%	1195±37	211±6
20%	1497±82	251±8

Table 3.4: The storage and loss (shear) moduli of bovine liver at 10 Hz for different compressive pre-strains.

Compressive Pre-strain (ε)	Storage Modulus [Pa]	Loss Modulus [Pa]
1%	658±61	60±15
2.5%	678±30	70±31
5%	726±56	80±4
7.5%	867±44	119±21
10%	1047±36	131±9
12.5%	1221±57	173±19
15%	1411±63	237±28
17.5%	1729±83	296±22
20%	2148±167	363±7

Finally, the "true" dynamic shear response of bovine liver for zero pre-compression ($\varepsilon = 0$) is estimated by the proposed hyper-viscoelastic model. With respect to the true response, the mean relative error (MRE) in the dynamic shear response of bovine liver samples, measured at different compressive pre-strains, is calculated and plotted in Figure 3.4 and tabulated in Table 3.5. The figure shows that there is a cubic relation between the MRE and the compressive pre-strain. The statistical differences between the dynamic shear responses of bovine liver measured at different compressive pre-strains and the "true" dynamic shear response corresponding to zero compressive strain are investigated by paired t-tests (Bonferroni correction is applied). The dynamic shear moduli of bovine liver measured at compressive pre-strains higher than $\varepsilon = 2.5\%$ is found to be statistically different than its true shear moduli estimated for zero compressive strain ($p < 0.05$).

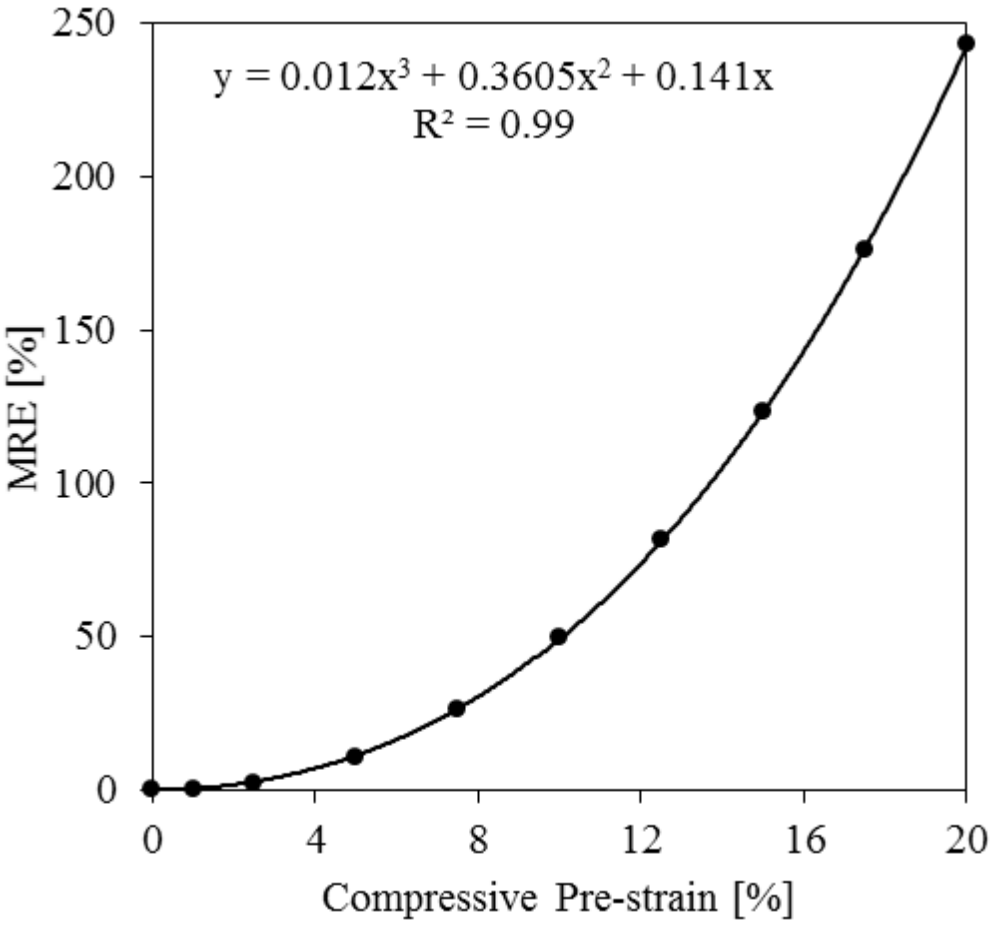

Figure 3.4: The mean relative error (MRE) made in the measurement of dynamic shear modulus of bovine liver as a function of compressive pre-strain.

Table 3.5: The mean relative error (MRE) in dynamic shear modulus of bovine liver measured at different compressive pre-strains. The frequency of stimulation varies between 0.1 and 10 Hz.

$MRE_{\varepsilon=1\%}$	0.2%
$MRE_{\varepsilon=2.5\%}$	2.3%
$MRE_{\varepsilon=5\%}$	11.0%
$MRE_{\varepsilon=7.5\%}$	26.6%
$MRE_{\varepsilon=10\%}$	49.9%
$MRE_{\varepsilon=12.5\%}$	81.7%
$MRE_{\varepsilon=15\%}$	123.3%
$MRE_{\varepsilon=17.5\%}$	176.4%
$MRE_{\varepsilon=20\%}$	243.1%

Chapter 4

DISCUSSION

The compression experiments show the rate-dependent hyperelastic behavior of liver tissue. The proposed hyper-viscoelastic model fit well to the experimental force-strain curves obtained for different compression rates. If the small strain assumption is used, the static linear elastic modulus of the bovine liver can be estimated as $E = 3\,\mu = 801$ Pa (assuming that the liver tissue is homogenous, isotropic, and incompressible). This value is in agreement with linear elastic modulus estimated for bovine liver (ranges between E = 1600-33600 Pa as a function of preservation period varying from 5 to 53 h) in Yarpuzlu et al. [11], (as $E \sim$ 5000 Pa for the preservation period of 1-4 h) in Ocal et al. [18], (between E = 400 Pa and E = 700 Pa using an ultrasound device and between E = 300 Pa and E = 1600 Pa using a mechanical tensile testing device) in Chen et al. [19], shear modulus estimated for bovine liver (G = 600 Pa) in Liu and Bilston [4], (G = 3400 Pa) in Sapin-de Brosses et al. [20], linear elastic modulus for pig liver ($E \sim$ 10000 Pa) in Ottensmeyer [21], Kruse et al. [22], Tay et al. [23], Samur et al. [16] and elastic modulus for human liver ($E \sim$ 20000 Pa) in Nava et al. [24].

The results of the dynamic shear loading experiments show that the shear modulus of bovine liver increases with frequency, compressive pre-strain, and the rate of compression. We observed that the storage and loss shear modulus of bovine liver ranges between G_S = 306-2148 Pa, and G_L = 56-363 Pa respectively, measured at temperature of 24°C, for the torsional shear strain of 0.5%, frequency varying between 0.1 Hz to 10 Hz, and the

compressive pre-strain varying from ε = 1% to ε = 20%. These results are compatible with those of the earlier studies. Liu and Bilston [4] found the shear storage and loss moduli of the bovine liver under ε = 5% compressive pre-strain at 37°C temperature to vary between G_S =1000-7000 Pa and G_L = 300-1000 Pa, respectively for the torsional shear strain of γ = 0.11% and the frequency range of ω = 0.006-20 Hz. Valtorta and Mazza [25] used a torsional resonator to characterize the complex shear modulus of bovine liver under 0.2 Pa vacuum pressure for the frequency range of 1–10 kHz at the ambient temperature. The results of the experiments suggested that the magnitude of the complex shear modulus of the liver varies between $|G^*|$ = 5000-20000 Pa. Wex et al. [6] performed strain (ω = 1 Hz, γ = 0.0001-1%), stress (ω = 1 Hz, τ = 0.1-100 Pa), and frequency sweeps (ω = 0.1-10 Hz, γ = 0.001%) and relaxation experiments (ω = 1 Hz, τ = 1 Pa, for 600 s) on porcine liver using a rheometer under a constant pre-load of 0.6 N. The magnitude of the complex shear modulus was reported to vary between $|G^*|$ = 564-1004 Pa and $|G^*|$ = 470-578 Pa under frequency sweep for the post-mortem period of 1 h and 20-27 h, respectively. Ayyildiz et al. [1] performed amplitude sweep test (ω = 20 Hz, γ = 0.1-2%), and frequency sweep test (ω = 0.1-20 Hz, γ =1%) on bovine liver tissue under ε = 5% pre-strain as a function of preservation solution and period. The LVR of the bovine liver samples was determined as γ_{LVR} = 1%. The storage modulus of the samples stored in Ringer, HTK and UW solutions varied between G_S = 361-2084 Pa, G_S = 262-701 Pa and G_S = 266-2073 Pa, respectively. Also, the loss modulus of the samples stored in Ringer, HTK and UW solutions measured as G_L = 78-675 Pa, G_L = 51-187 Pa, and G_L = 64-815 Pa, respectively. Klatt et al. [3] conducted rheological experiments with bovine liver samples in the frequency range of ω = 2.5-62.5 Hz and at γ = 0.3% torsional shear strain and 1°C temperature. The storage and loss moduli were varied between G_S = 1000-3000 Pa and G_L = 400-1270 Pa, respectively. Kruse et al. [22] measured the magnitude of the complex shear modulus of the porcine liver at 37°C as $|G^*|$ = 3000 Pa at 100 Hz and as $|G^*|$=5000 Pa at ω = 300 Hz by using the MRE method. Sapin-de Brosses et al. [20]

measured the magnitude of complex shear modulus of bovine liver as $|G^*| = 3400 \pm 500$ Pa by Supersonic shear imaging technique for the frequency range of ω = 150-200 Hz at a temperature of 25°C and for post-mortem period of 0-48 h. Riek et al. [26] used MRE technique to examine the dynamic mechanical properties of bovine liver tissue at a temperature of 17-19°C for the frequency range of ω = 100-800 Hz and post-mortem period of 0-2 h. The authors reported the storage and loss moduli of bovine liver tissue as G_S = 1420-4910 Pa and G_L = 740-1620 Pa, respectively.

The dynamic elastic moduli of animal and human livers have been also investigated in the literature. The results of these studies can be compared to those reported above when the relation between linear elastic and shear moduli ($E = 3\,\mu$) is used. Ocal et al. [18] measured the elastic storage and loss moduli of the bovine liver at the room temperature as E_S = 5000-80000 Pa and E_L = 1000-13000 Pa, respectively for the frequency range of ω = 0-80 Hz and post-mortem period of 1-48 h. Kiss et al. [2] applied cyclic stimuli (ω = 0.1-400 Hz) to the canine liver tissue in the normal direction within 72 h of post-mortem time at 21°C and estimated the storage and loss modulus as E_S = 4000-10000 Pa and E_L = 800-10000 Pa, respectively. Ozcan et al. [27] performed impact hammer experiments on fresh human livers harvested from the patients having some form of liver disease and found that the storage moduli of the livers having no fibrosis (F0) and that of the cirrhotic livers (F4) varied from E_S = 10000-20000 Pa and E_L = 0-5000 Pa for the frequency range of ω = 0–80 Hz, respectively.

The differences in the measurement devices, measurement methods, and the measured subjects (human, porcine, bovine, canine) contribute significantly to the discrepancies in the results of the studies reported above. Another reason for the discrepancy could be the effect of measurement conditions. The environmental conditions such as temperature and humidity affect the material properties of the soft tissue. The storage and loss moduli of the liver tissue were shown to reduce with increasing temperatures (Geerligs et al. [28], Kiss et al. [29], Klatt

et al. [3]). Nicolle and Palierne [10] reported that dehydration of tissue samples leads to overestimation of shear modulus. Similarly, the biological state of the tissue samples, sample preservation method and solution are also significant factors affecting the outcomes of the measurements. Garo et al. [7] and Ayyildiz et al. [1] independently showed a significant increase in dynamic shear moduli of brain and liver tissues for post-mortem interval longer than 6 h and 11 h, respectively. Ayyildiz et al. [1] demonstrated that the type of chemical solution used for the preservation of the tissue samples has an influence on the estimation of dynamic shear moduli. In addition, the sample preparation process also has a significant impact on the measured material properties. Hollenstein et al. [30], Umale et al. [31] reported that the liver tissue feels softer when the Glisson's capsule is removed during the sample preparation. Hrapko et al. [8] showed that obtaining tissue samples from different cutting planes cause variations in shear properties due to the anisotropy. There are also inherent difficulties in material characterization of soft tissues using a rheometer, which may affect the outcome of the measurements. For example, to prevent slippage between the plates of the rheometer and sample, a sand paper is typically attached to the plates or the sample is glued to the plates. Nicolle and Palierne [10] compare the use of sandpaper versus adhesive in rheological measurements and conclude that both methods have drawbacks.

There are limited number of studies in the literature investigating the effect of compression and compression rate on the dynamic material properties of liver tissue. Hrapko et al. [8] used a rotational rheometer to perform dynamic frequency tests to investigate the effect of compression on shear response. The authors showed that the magnitude of the complex shear modulus of brain tissue is 11.6-21.5% higher than those measured without pre-compression (ω = 1-10 Hz) for the compression forces varying between 5-10 mN. Tan et al. [5] investigated the effect of the pre-strain on the viscoelastic behavior of the liver tissue at 2-6 h post mortem time. The authors conducted amplitude sweep experiments at a frequency of ω = 1 Hz and shear strain value varying between γ = 0.005% and 2%. The

storage and loss moduli of liver tissue were reported to vary between G_S = 350-450 Pa and G_L = 70-90 Pa, respectively for the pre compressive strain varying between ε = 1-20%. DeWall et al. [31] used dynamic compression testing to quantify the viscoelastic properties of 16 human liver samples for a frequency range of ω =1-30 Hz under a compression strain of ε = 2%, a compression pre-strain varying from ε = 1 to 6%, and for a post-mortem period of 0-2 h. The elastic storage and loss moduli of the healthy human liver were observed to increase with pre-compression and varied between E_S = 2000-6000 Pa and E_L = 500-2000 Pa, respectively. Nicolle et al. [12] performed rheological experiments on porcine liver samples at 37°C in the frequency range of ω = 0.1-4 Hz under strain rates of 0.0151, 0.133, and 0.7 s^{-1} and for the post-mortem period of 0-24 h. The storage and loss moduli of the samples were measured as G_S = 800-1100 Pa and G_L = 150-300 Pa, respectively.

Chapter 5

CONCLUSION

In order to perform reliable rheological measurements, some amount of compressive pre-strain should be applied on the sample to prevent slippage and maximize grip between the sample and the plates of a rheometer. This work investigates the effect of normal compression on the characterization of the shear properties of bovine liver tissue. The methodology proposed in this study applies not only to rheological characterization of soft tissues, but also viscoelastic solids in other domains, such as rubber and cheese. Though the effect of compressive pre-strain on the dynamic shear moduli of viscoelastic materials during rheological measurements has been already acknowledged in a few studies in the literature, no systematic study, including experimentation and theoretical modeling, has been conducted to fully investigate this effect in depth. In this regard, our study is the first to look into this research problem in the domain of soft tissue mechanics, but the results of the study can be easily generalized to the other domains such as elastomers, food products, and construction engineering.

As reported in this study, the pre-compression has a significant effect on the dynamic shear modulus of soft tissue measured by a rheometer. Our study shows that dynamic shear moduli of bovine liver measured at compressive pre-strains higher than $\varepsilon > 2.5\%$ are statistically different than its true shear moduli, estimated by the model for zero compressive strain ($p < 0.05$). In fact, the results suggest that a mean relative error reaches to 243.1% in the measurement of dynamic shear moduli of bovine liver under the compressive pre-strain

of ε = 20% (ω = 1-10 Hz). Therefore, for liver tissue, we suggest applying compressive pre-strains not higher than 2.5% in order to avoid over-estimation of shear material properties. If it is not possible to collect rheological data at lower pre-strains due to contact problems and slippage, then we recommend applying a correction to the measured vales using the relation given in Figure 3.4.

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