Dynamic Material Properties of Human and Animal Livers

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Abstract Accurate characterization of the mechanical properties of soft tissues is important for diagnosing medical pathologies and developing solutions for them. With the recent advances in technologies leading to the development of surgical simulators, medical robots, and computer-assisted surgical planning systems, this topic has gained even more importance. However, most of the earlier research studies conducted with animal and human livers have focused on the investigation of static (strain-dependent) material properties. The number of studies investigating the dynamic material properties (time and frequency-dependent) of animal and human livers are much less than the ones investigating the static material properties. In fact, there is almost no data available in the literature showing the variation in dynamic material properties of healthy or diseased human liver as a function of excitation frequency.

1 Motivation

Soft organ tissues exhibit complex nonlinear, anisotropic, non-homogeneous, time, and rate-dependent behavior. Fung [1] has revealed that nonlinear stress–strain relationship is common for soft tissues but the degrees are different for different tissues. Since soft organs are composed of different materials, like elastin and collagen, in different combinations, soft tissue properties are both coordinate and direction dependent. Time and rate dependent behavior is also common and explained by viscoelasticity.

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While strain-dependent material properties have been investigated extensively, less attention has been paid to the dynamic material properties. However, the dynamic response of soft tissues to periodic or impact loading is important in many areas of biomechanics and biomedical engineering. For example, frequency-dependent mechanical properties play a crucial role when investigating the mechanisms of organ injury that result from high-speed impact such as car accident. The propagation speed and radius of the impact wave depends on the dynamic material properties of the organ. Similarly, when designing prosthetic devices for lower-body amputates, it is important to know how the soft tissue responds to the periodic impacts coming from the ground.

2 Measurement Methods

In most of the earlier studies focusing on dynamic material properties, either time- or frequency-dependent material properties have been measured via stress relaxation and dynamic loading experiments, respectively. The current methods of acquiring the dynamic material properties of soft tissues involve the use of mechanical indenters, rotational rheometers, and medical imaging techniques.

The time-dependent viscoelastic material properties of soft tissues are typically characterized by ramp and hold experiments in biomechanics literature. When a soft organ tissue is subjected to a ramp and hold strain, the stress response at that strain decreases exponentially with time, reaching to a steady state value. This is explained by the phenomena of stress relaxation under constant strain (Fig. 1) and can be characterized by a time-dependent relaxation modulus, $\mathrm{E_R(t)} = \sigma(\mathrm{t})/\varepsilon_0$.

If, for example, a Generalized Maxwell Solid model (a parallel connection of N Maxwell arms and a spring as shown in Fig. 2) is used for modeling the linear viscoelastic behavior of a soft tissue, then the time-dependent relaxation modulus of the tissue can be obtained analytically from its stress response to a constant strain input as

$$E_R(t) = E_0\left[1 - \sum_{j=1}^{N} \alpha_j\right] + E_0 \sum_{j=1}^{N} \alpha_j e^{-t/\tau_j} \tag{1}$$

This representation is also known as the Prony series. Here, E_0 is the short-term elastic modulus, $\alpha_\mathrm{j} = E_j/E_0$ is the relative modulus and $\tau_j = b_j/E_j$ is the time constant, where b_j represents the damping coefficient and N is the number of terms (i.e. Maxwell arms) used in the model. Note that the long term modulus, which determines the steady state response, is related to the short term modulus through the relative moduli, $E_\infty = E_0(1 - \sum_{j=1}^{N} \alpha_j)$. The number of Maxwell arms (N) and the material coefficients E_0, α_j, and τ_j can be estimated by fitting Prony series to the experimental data acquired by the stress relaxation experiment.

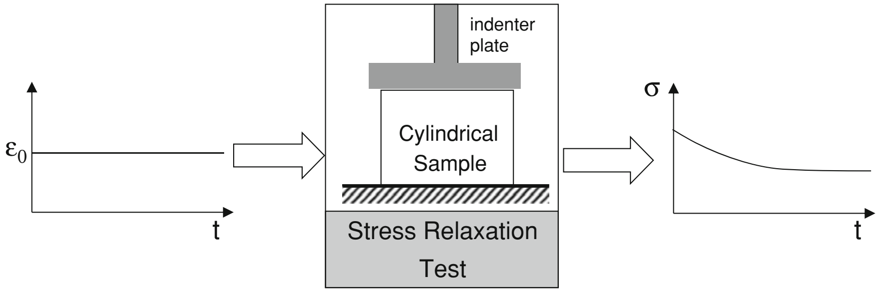

Fig. 1 Stress relaxation test

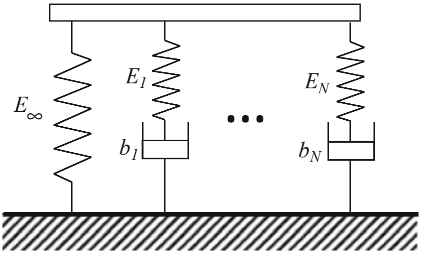

Fig. 2 Generalized Maxwell solid

In order to characterize the frequency-dependent viscoelastic material properties of soft tissues, the most common method is the dynamic loading test: small periodic strains at varying frequencies are applied to the tissue sample and the stress response is recorded (Fig. 3).

The input and the output signals are both periodic in time domain and can be represented as

$$\begin{aligned} \varepsilon(t) &= \varepsilon_0\, Sin\,(\omega t) \\ \sigma(t) &= \sigma_0\, Sin\,(\omega t + \delta) = \sigma_0[Sin(\omega t)Cos(\delta) + Cos(\omega t)Sin(\delta)] \end{aligned} \tag{2}$$

Here, ε_0 and σ_0 are the amplitudes of the strain and the stress signals respectively, ω is the frequency of the signals, and δ is the phase angle between strain and stress signals. If the phase angle is 0°, then the tested material is purely elastic, if it is 90°, then it is purely viscous, and if it is between 0 and 90°, then it is viscoelastic.

Because of the viscoelastic nature of soft tissues, two stress components can be obtained from the measurements at each frequency: one with amplitude $\sigma_0 Cos(\delta)$ and in-phase with the applied strain (elastic response) and the other with amplitude $\sigma_0 Sin(\delta)$and 90° out-of-phase with the applied strain (viscous response). Now, if we take the ratio of the stress to the applied strain, then, two elastic moduli, one in-phase and the other 90° out-of-phase with the applied strain, can be calculated at each frequency. These two moduli form the so-called complex modulus, $E^*(\omega)$, with the in-phase modulus, also known as the storage modulus, $E_S(\omega)$, being its real part and the out-of-phase modulus, also known as the loss modulus, $E_L(\omega)$ being its imaginary part.

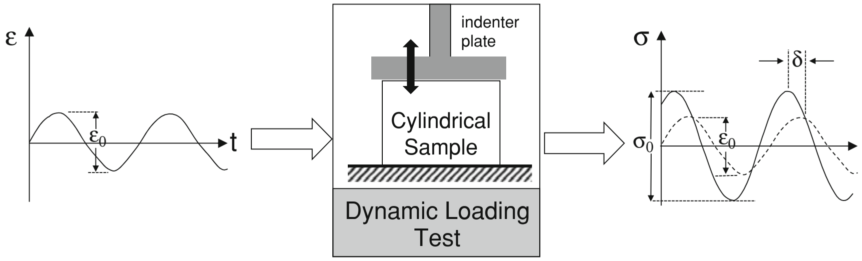

Fig. 3 Dynamic loading test

$$E^*(\omega) = E_S(\omega) + jE_L(\omega) \tag{3}$$

The storage and loss moduli define the energy storage and dissipation capacity of the soft tissue, respectively. Moreover, the ratio of the loss modulus to the storage modulus at each frequency is equal to the tangent of the phase angle at that frequency and defined as the loss factor

$$\eta(\omega) = \frac{E_L(\omega)}{E_S(\omega)} \tag{4}$$

If the loss factor is smaller than one, then the material shows more elastic behavior. On the other hand, if the loss factor is greater than one, the viscous behavior dominates the response. For soft tissues, the loss factor is typically smaller than one.

If a Generalized Maxwell Solid model is used again for modeling the frequency response behavior of a linear viscoelastic soft tissue, then the storage and loss moduli can be written in terms of the viscoelastic material coefficients as

$$E_S(\omega) = E_0\left[1 - \sum_{j=1}^{N} \alpha_j\right] + E_0 \sum_{j=1}^{N} \frac{\alpha_j \tau_j^2 \omega^2}{(1 + \tau_j^2 \omega^2)} \tag{5a}$$

$$E_L(\omega) = E_0 \sum_{j=1}^{N} \frac{\alpha_j \tau_j \omega}{(1 + \tau_j^2 \omega^2)} \tag{5b}$$

The viscoelastic material coefficients can be estimated via curve fitting the model to the experimental data of storage and loss moduli.

3 Review of the Literature

Liu and Bilston [7] investigated the linear viscoelastic properties of bovine liver using a generalized Maxwell model and conducted three types of experiments (a) shear strain sweep oscillation, (b) shear stress relaxation, and (c) shear oscillation.

The shear stress and strain were calculated based on the torsional load. In strain sweep oscillation experiments, the liver tissue was subjected to a sinusoidal angular torsion at a fixed frequency of 1, 5, or 20 Hz using a strain controlled rheometer. The strain amplitudes were gradually increased from 0.06 to 1.5% while the storage and loss moduli of the bovine liver were measured. In stress relaxation experiment, sudden torsional shear strain was applied to liver tissue for 0.02 s and the shear relaxation modulus was measured over 3000 s. Finally, in shear oscillation experiments performed in the range of 0.006–20 Hz, the storage and loss moduli were measured again. The results show that the shear relaxation modulus of bovine liver reaches to steady state around 0.6 kPa. The results of the oscillatory shear experiments show that the storage modulus of bovine liver increases from 1 to 6 kPa with increasing frequency while the loss modulus increases to a peak value of 1 kPa at about 1 Hz and then decreases to 0.4 kPa as the frequency reaches to 20 Hz. Kruse et al. [6] utilized magnetic resonance elastography (MRE) and estimated the average shear modulus of porcine liver as 2.7 kPa for five different animals at six different wave frequencies ranging from 75 to 300 Hz. Kiss et al. [5] performed in vitro experiments with canine liver tissue to characterize its viscoelastic response. They measured the storage and the loss moduli of the liver tissue for the frequencies ranging from 0.1 to 400 Hz by applying cyclic stimuli to the tissue. The resulting moduli spectra were then fitted to a modified Kelvin–Voigt model, which was called as the Kelvin–Voigt fractional derivative model (KVFD) by the authors. They show that there is an excellent agreement between the experimental data and the KVFD model; particularly at frequencies less than 100 Hz. Valtorta and Mazza [19] developed a torsional resonator to characterize the dynamic material properties of bovine and porcine livers. By controlling the vibration amplitude, shear strains of less than 0.2% were induced in the tissue. The experiments were performed at different eigenfrequencies of the torsional oscillator and the complex shear moduli of bovine and porcine livers were characterized in the range of 1–10 kHz. The results of the in vitro experiments on porcine liver show that the magnitude of complex shear modulus varies between 5 and 50 kPa depending on whether the data collected from the external surface or the internal section of the liver (as reported by the authors, the former leads to considerably larger shear stiffness due to the presence of the stiff capsula). The shear modulus of the bovine liver is shown to vary between 15 and 30 kPa. Samur et al. [15] developed a robotic indenter to measure the strain and time-dependent material properties of pig liver during a laparoscopic surgery. Using the robotic indenter, force versus displacement and force versus time responses of pig liver under static and dynamic loading conditions were successfully measured to characterize its material properties in three consecutive steps (Figs. 4a, b). First, the effective elastic modulus of pig liver was estimated as 10–15 kPa from the force versus displacement data of static indentations based on the small deformation assumption (Fig. 4c). Then, the stress relaxation function, relating the variation of stress with respect to time, was determined from the force versus time response data via curve fitting (Fig. 4d). Finally, an inverse finite element solution was developed using ANSYS finite

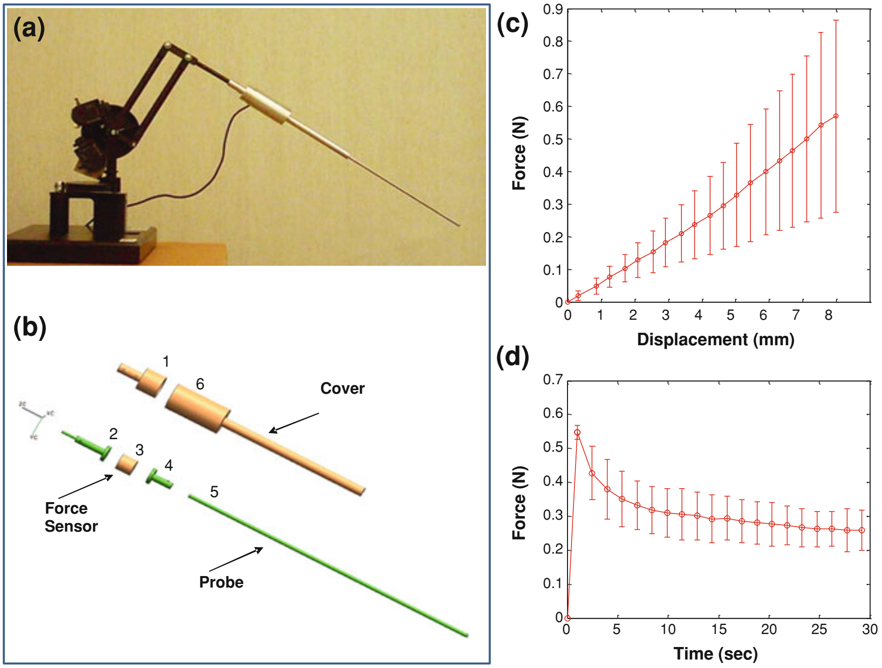

Fig. 4 **a** Our robotic indenter **b** and its components. The indenter is inserted into the abdominal cavities of 3 pigs through a surgical trocar for collecting displacement and force data **c** The average force response of 3 pigs as a function of indentation depth (strain rate is 0.2 mm/s) **d** The average force relaxation response of 3 pigs for the indentation depth of 4 mm and strain rate of 4 mm/s [15]

element package to estimate the optimum values of hyper-viscoelastic material properties of pig liver through optimization iterations (Fig. 5). To implement the inverse solution, a finite element model of liver tissue was constructed from axisymmetric 2D finite elements having homogeneous, isotropic, hyper-viscoelastic and nearly incompressible material properties. The hyperelastic behavior of pig liver was modeled using Mooney-Rivlin strain-energy function and the viscoelastic behavior was modeled using Generalized Maxwell Solid with N = 2. The initial estimates of hyperelastic and viscoelastic material coefficients used in the optimization iterations were obtained independently from the experimental data of static indentation and stress relaxation experiments, respectively. The optimization algorithm minimized the error function defined as $Error = \sum_{j=1}^{M} \left(F_j^{\mathrm{EXP}} - F_j^{\mathrm{FEM}}\right)^2$ where, M represented the number of data samples, F_j^{EXP} was the experimental force value of the j th sample, and F_j^{FEM} was the force value obtained from the finite element solution at the corresponding time step. The solution was iterated until the magnitude of error was less than some force threshold.

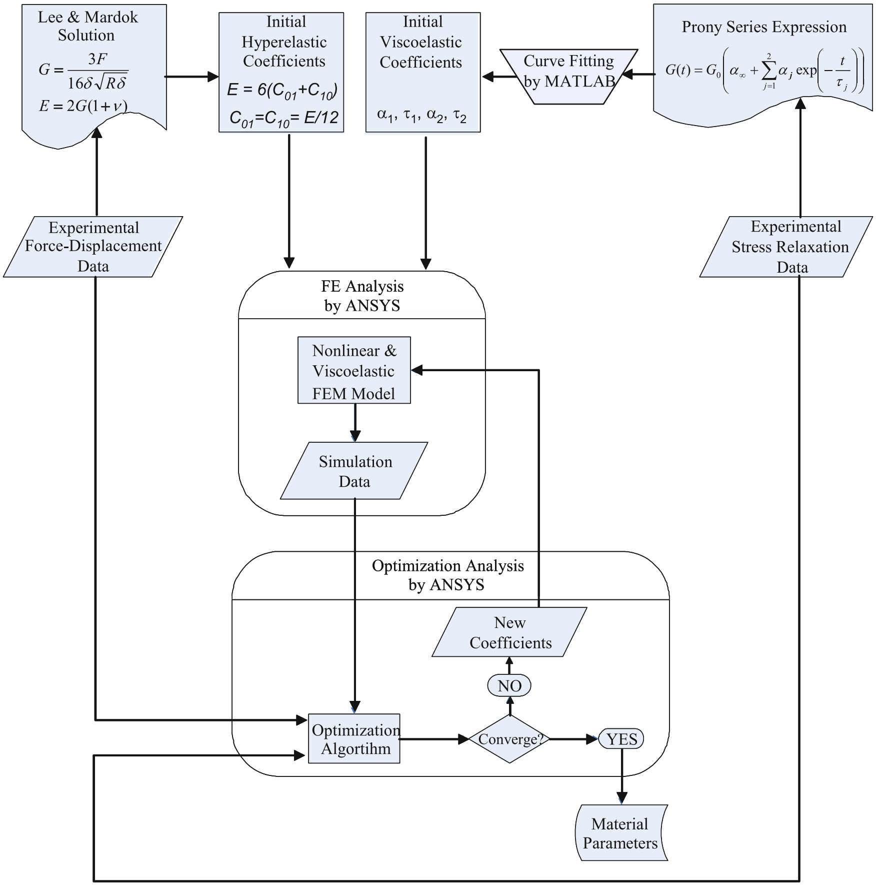

Fig. 5 The flow chart of our inverse finite element solution for estimating the hyper-viscoelastic material coefficients of pig liver [15]

Zhang et al. [20] characterized the frequency-dependent viscoelastic properties of fresh veal liver using two independent methods: crawling wave estimator (CRE) and the mechanical measurement (MM). In CRE method, the liver samples were placed between piezoelectric shear wave sources and the resulting crawling wave movies were captured using ultrasound scanners to estimate the elastic modulus in frequency range from 80 to 280 Hz. In MM method, stress relaxation experiments were performed with a mechanical compression device and the complex elastic modulus was obtained from time domain response via Fourier transform for the same frequency range. The results of the experiments showed that the magnitude of the complex elastic modulus of veal liver varied from 10 to 40 kPa and increased with frequency in the tested range.

Compared to the animal studies, the number of studies investigating the dynamic material properties of human liver and pathologies through biomechanical

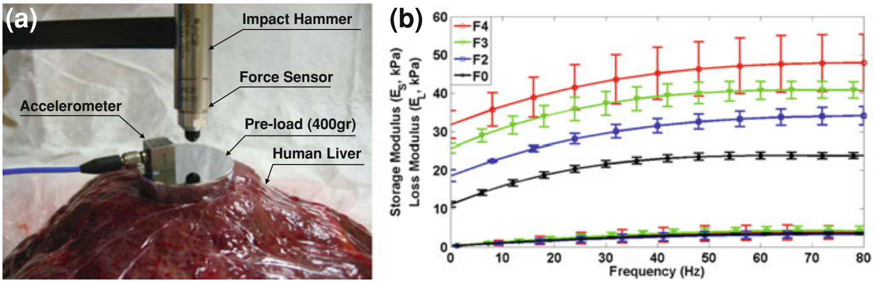

Fig. 6 **a** The dynamic material properties of human liver were measured as a function of frequency by an impact hammer. **b** The storage (*upper curves*) and loss (*lower curves*) moduli of human liver as a function of frequency for different levels of fibrosis [13]

measurements are very limited. Most of the earlier studies have focused on the characterization of static and viscoelastic material properties of animal [2, 4, 14, 15, 18] and human livers [10], but not their frequency-dependent properties. Saraf et al. [17] investigated the dynamic response of human liver in hydrostatic compression and simple shear using the Kolsky bar technique at high strain rates ranging from 300 to 5000 s^{-1}. This technique involves the use of two elastic pistons with a disk-shaped material sample inserted between their ends. A pressure wave is generated by applying an impact at the free end of one of the pistons. By measuring the difference of vibrations at the extremities of the structure, the mechanical properties of the sample can be obtained. Using this approach, Saraf et al. [17] measured the bulk and the shear moduli of human liver under dynamic loading as 280 kPa and 37–340 kPa (depending on the strain rate), respectively. Mazza et al. [9] conducted in vivo and ex vivo experiments with ten human subjects having some liver pathology. Static mechanical properties of human liver were measured at multiple locations using an intra-operative aspiration device. Most of the tests were performed on diseased liver segments undergoing subsequent resection. Measurements were performed by the surgeon on the normally perfused liver in vivo and on the resected specimen ex vivo. The relationship between mechanical parameters and various pathologic conditions affecting the tissue samples was quantified. The fibrotic tissue is found to be three times stiffer than the normal tissue. Later, Nava et al. [10] performed aspiration experiments on healthy human liver with the same device. They estimated the long term and instantaneous linear elastic modulus of human liver as 20 and 60 kPa respectively. Ozcan et al. [13] measured the frequency-dependent dynamic material properties of a human liver using an impact hammer. The procedure involves a light impact force applied to the tested liver by a hand-held hammer. The results of the experiments conducted with 15 human livers harvested from the patients having some form of liver disease showed that the proposed approach could successfully differentiate the level of fibrosis in human liver. The storage moduli of the livers having no fibrosis (F0) and that of the cirrhotic livers (F4) was observed to vary from 10 to 20 kPa and 20 to 50 kPa for the frequency range of 0–80 Hz, respectively (Fig. 6).

4 Discussion

In earlier studies focusing on dynamic viscoelastic material properties of soft tissues have typically relied on the experimental data collected from one type of experiment only. Either relaxation or dynamic loading experiments are performed to model time- or frequency-dependent material properties of the soft tissues being tested, respectively. However, due to the nature of these experiments, the information that can be extracted from each one is different though a conversion from time to frequency domain or vice versa is possible through Laplace transformations. Ocal et al. [11] showed that a better fit to viscoelastic tissue model can be achieved if the results of both experiments are taken into account in the analysis (Fig. 7). For this purpose, they first measured the storage and loss moduli of bovine liver as a function of excitation frequency using an impact hammer. Second, its time-dependent relaxation modulus was measured separately through ramp and hold experiments performed by a compression device. Third, a Maxwell solid model that successfully imitates the frequency- and time-dependent dynamic responses of bovine liver was developed to estimate the viscoelastic material coefficients by minimizing the error between the experimental data and the corresponding values generated by the model.

Moreover, most of the earlier studies on human or animal liver have utilized the dynamic loading test for the characterization of frequency-dependent material properties. However, one drawback of the dynamic loading test is that the measurements have to be made at each frequency within the range of frequencies of interest, which may not be practical for measuring, for example, live tissue properties of human liver in place since the time interval for data collection is typically limited due to the adverse effect of the subject's breathing on the measurements. Furthermore, the collected data can be erroneous for the same reason. Faster and more practical methods are desired for the dynamical characterization of soft organ tissues. Here, it is also important to emphasize that most tissue experiments conducted in the past have been in vitro studies and the experimental data has been collected from the excised and well-shaped tissue samples. However, material properties of soft tissues change in time and the results obtained from in vitro measurements can be misleading. The results obtained by Ottensmeyer et al. [12] and Ocal et al. [11] show that the soft tissues become stiffer and more viscous in time (Fig. 8). Unfortunately, the existing commercial measurement devices and approaches are typically designed to work with small samples of known geometry in a laboratory environment. New devices and measurement approaches are necessary for in vivo experiments to determine the live dynamic material properties of organs in place. Since in vivo measurements are performed on the whole organ rather than well-shaped tissue samples, the extraction of material properties is more challenging. If the cross-sectional area and the length of the sample are known in advance, the dynamic material properties can be easily estimated from the measured data. Otherwise, either the effective values of cross-sectional area and length are required to estimate the dynamic material properties

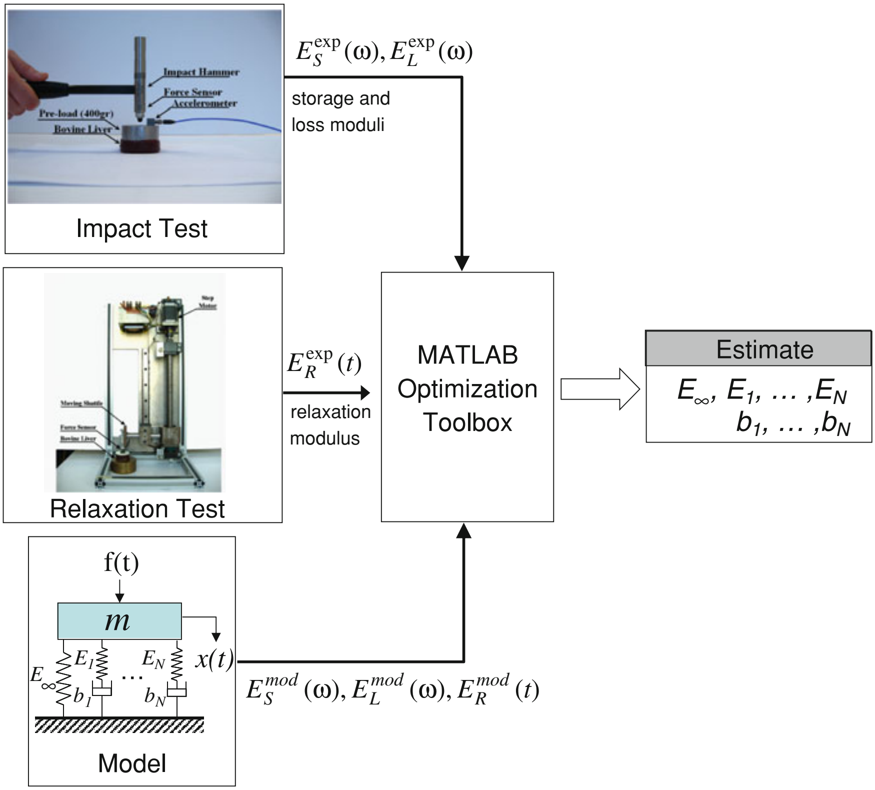

Fig. 7 The flow-chart of the optimization process followed for estimating the viscoelastic material coefficients of soft organ tissues [11]

of organ tissue [13] or the inverse FE analysis must be performed to estimate the properties from the measured data [3, 15]. During the inverse analysis, the assumptions made about the organ geometry, stress distribution, contact mechanics, and boundary conditions affect the estimation of material properties.

Compared to the animal studies, the number of in vivo studies on humans is very limited due to the obvious reasons. If a mechanical device to be used for the measurement of material properties, minimum damage must be made on the organ tissue. There are currently two approaches (see [15] for details): (a) free-form measurements and (b) robotic measurements. A “free-form” measurement typically involves the use of a hand-held probe equipped with position and force sensors. Major benefit of using a hand-held probe over a robotic arm is safety. Since the operator manually derives the probe, unexpected and risky movements are unlikely to happen. However, there are two problems with this design. First, the measurements are made manually and not repeatable. The second difficulty is the identification of a reference point for the displacement measurements. On the other hand, if a robotic arm is used for the same measurements, the problems

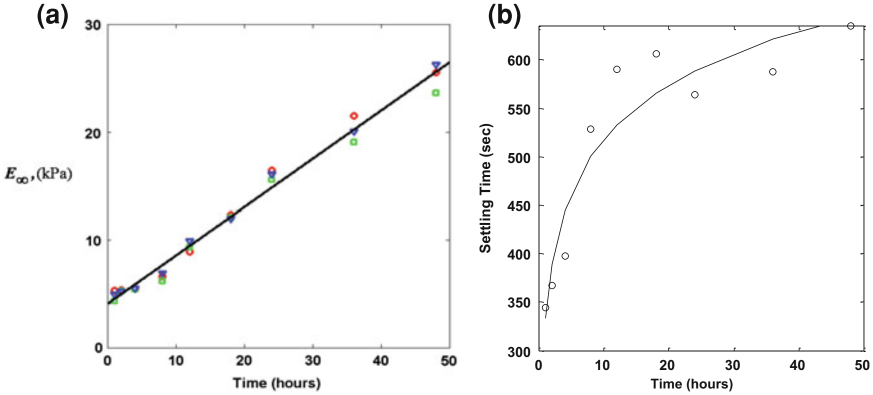

Fig. 8 **a** The variation in the long-term (steady state) elastic modulus of bovine liver as a function of preservation period for 3 different animals. **b** The variation in the settling (i.e. relaxation) time of bovine liver as a function of preservation period [11]

related to the actuation and position sensing can be solved. More controlled indentations can be performed on tissue surface by a pre-programmed robotic arm and an indenter attached to the arm. In addition, a robotic arm can be programmed to generate different types of stimuli. Thus, dependency to a user is eliminated and repeatability is achieved. Besides, the tip coordinates of the indenter can be acquired using encoders of the robotic arm with respect to the fixed coordinate frame. Other issues that must be considered in the measurement of live tissue properties inside human body are sterilization, safety, and compatibility with the surgical devices and environment. Sterilization of instruments in hospitals is carried out using steam under pressure, liquid or gaseous chemicals, or dry heat. Steam and ethylene oxide (gaseous) sterilization are performed at temperatures around 130 and 50°C, respectively. On the other hand, liquid sterilization is performed at room temperature but takes longer time. Most of the standard sterilization techniques can easily damage the components of a measurement system since the sensors and actuators are typically sensitive to heat and humidity. Therefore, the design must enable the parts to be easily assembled and disassembled for sterilization. Safety is another important concern. Some safety measures must be taken such that unexpected and risky movements must be avoided to prevent damaging tissue. The measurement device must shut down itself automatically if anomalies are detected.

In summary, there are limited number of studies and data on the dynamic (in particular, frequency-dependent) material properties of healthy and diseased animal and human livers. Moreover, there is a large variation in tissue properties of the liver measured by different research groups. While a part of this variation is due to the differences in measurement devices, techniques, and site, it is also known that tissue properties vary within the same species depending on the age, weight, and gender. It is still an open question how these variations will be integrated into the biomechanical models of liver. Also, most of the existing data has been collected invasively through mechanical measurement devices, which limits their usage in human studies. Alternative medical imaging techniques based on transient ultrasound elastography [16] and Magnetic Resonance Elastography, MRE [8] have been developed to quantify dynamic material properties non-invasively. In both approaches, the measurements are performed externally without having any direct contact with the actual liver tissue. As a result, there are still open questions about the accuracy and the validity of these approaches. Moreover, the liver elasticity values reported in these studies are typically measured at a certain frequency rather than a range of frequencies as in the case of dynamic loading test.

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