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In situ measurement and modeling of biomechanical response of human cadaveric soft tissues for physics-based surgical simulation

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Abstract
Background Development of a laparoscopic surgery simulator that delivers high-fidelity visual and haptic (force) feedback, based on the physical models of soft tissues, requires the use of empirical data on the mechanical behavior of intra-abdominal organs under the action of external forces. As experiments on live human patients present significant risks, the use of cadavers presents an alternative. We present techniques of measuring and modeling the mechanical response of human cadaveric tissue for the purpose of developing a realistic model. The major contribution of this paper is the development of physics-based models of soft tissues that range from linear elastic models to nonlinear viscoelastic models which are efficient for application within the framework of a real-time surgery simulator.

Methods To investigate the in situ mechanical, static, and dynamic properties of intra-abdominal organs, we have developed a high-precision instrument by retrofitting a robotic device from Sensable Technologies (position resolution of 0.03 mm) with a six-axis Nano 17 force-torque sensor from ATI Industrial Automation (force resolution of 1/1,280 N along each axis), and used it to apply precise displacement stimuli and record the force response of liver and stomach of ten fresh human cadavers.

Results The mean elastic modulus of liver and stomach is estimated as 5.9359 kPa and 1.9119 kPa, respectively over the range of indentation depths tested. We have also obtained the parameters of a quasilinear viscoelastic (QLV) model to represent the nonlinear viscoelastic behavior of the cadaver stomach and liver over a range of indentation depths and speeds. The models are found to have an excellent goodness of fit (with $R^2 > 0.99$).

Conclusions The data and models presented in this paper together with additional ones based on the principles presented in this paper would result in realistic physics-based surgical simulators.

Keywords Surgical simulation · Soft tissue · Biomechanical properties · Human cadaver · Indentation experiments

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Laparoscopic surgery is demanding in terms of the surgeon's skills due to poor depth perception, restricted field of view, limited hand–eye coordination, and diminished haptic cues [1]. Surgeons therefore have a learning curve and require repetitive practice to reach a proficient skill level.

Virtual-reality-based surgical simulators have emerged as promising tools to develop and assess laparoscopic dexterity among surgical residents [2–5]. Just as flight simulators are used to train pilots, it has been proposed to apply virtual-reality-based systems to select, train, credential, and retrain physicians in the art and science of their craft. In such a system, human users interact with virtual three-dimensional models of organs using their sense of vision as well as actively manipulate them using their sense of touch. It has been shown that trainees benefit from use of simulators [6]. In training residents these systems allow well-planned and detailed exposure to even rare situations. In addition, they offer the possibility of recording the trainee's actions for objective evaluation and customizing the training program to each trainee.

Development of surgical skills during training involves memory of tactile experience [7–9]. A recent study [10] involving 30 surgical residents at the Shapiro Simulations and Skills Center at Beth Israel Deaconess Medical Center in Boston showed that on average subjects performed 36% faster and 97% more accurately with force feedback than without, even when cognitively loaded. Hence realistic force feedback from virtual deformable organs is important for the success of surgical simulators. It is therefore important to incorporate the correct mechanics of the soft tissues being operated on. Surgical simulators that do not incorporate this and are purely based on computer graphics simulations are glorified video games with limited training value. Development of any realistic physics-based surgical simulator therefore requires experimental determination and modeling of the mechanics of soft tissue response.

Measurement of soft tissue mechanical properties is an established research area [11, 12]. The major challenge in this field is that biological soft tissues exhibit complex mechanical behavior including nonlinear, inhomogeneous, anisotropic, and rate-dependent response. For surgical simulation, ideally it is necessary to measure, and then model the in vivo mechanical response of the soft tissues operated on. However, current efforts are either aimed at obtaining ex vivo properties [13–16], which are grossly different from in vivo conditions [17–22], or utilizing animal models such as pigs [17] and which have fundamental differences in anatomy and tissue consistency compared to humans.

In ex vivo techniques, tissue samples are excised from the organ of interest and tested with devices and procedures similar to those used for engineering materials. However, the act of excision alters tissue conditions drastically due to factors such as temperature, hydration, break-down of proteins, and loss of blood supply. Moreover, the boundary conditions of the sample are different from in vivo states.

While in vivo measurement of soft tissue properties is most desirable, invasive experiments on live human patients involves significant risks. Noninvasive methods such as ultrasound [23] or magnetic resonance imaging (MRI) elastography [24] are alternatives, but due to the very low amplitude of the interrogating signals, only linear elastic parameters may be measured. Besides, techniques such as ultrasound employ high excitation frequencies that are irrelevant for surgical explorations. Since large deformations are involved in surgery and the human motor responses are only in the range of a few tens of Hertz [25], noninvasive techniques are subject to major limitations.

A variety of techniques have been developed to investigate the force–displacement response of soft tissues. A number of groups have developed instruments that apply normal indentation to the tissue [26–28]. Surgical instruments have been modified [29, 30], equipping them with force and position sensors, as well as motors for system controls, to measure the response of tissue grasping. Two groups have developed tissue aspiration techniques [31, 32], in which a tube is placed against tissue and then the pressure within the tube is lowered after a seal is achieved. A disadvantage of such suction techniques is that they assume the conditions to be axisymmetric and hence are incapable of considering anisotropy. In vivo material properties of organs have also been measured using modified laparoscopic instruments [33]. Torres-Moreno [34] measured the moduli at several different levels of indentation on extremal tissues of amputated limbs of live patients to demonstrate the nonlinear dependence of the soft tissue properties on indentation depth. However, accurate in vivo measurements of intra-abdominal organs require the organs to be accessible to the testing machine, which poses significant risk to the patient.

The use of fresh human cadavers [15, 16] is a risk-free alternative to live human experiments. Cadavers are widely used in surgical education. Excellent gift programs make them relatively easy to procure and they pose minimal hazards. Of course, depending on the time elapsed after death, cadaver tissue loses the elasticity and consistency characteristic of live human patients. Hence the use of fresh, unfrozen cadavers is essential. An important observation is that fresh human cadaver tissue properties are much closer to in vivo mechanical properties of humans than pig tissues, e.g., the mean elastic modulus of in vivo healthy human liver can be calculated to be around 7 kPa from the shear modulus data obtained in [35] using nuclear magnetic resonance (NMR) elastography (assuming a Poisson's ratio of 0.5), while our estimate based on fresh human cadavers reported in this paper is 5.9359 kPa (a difference of 16%) compared with 12.88 kPa for pig liver [20] (difference of 84%).

After the soft tissue properties are measured they may be used with computational techniques such as the point-associated finite-field approach [36], which we have developed as a promising new technique for real-time surgical simulation. This technique has been applied to the simulation of nonlinear [37] as well as viscoelastic [38] response of soft tissues. Such a "virtual cadaver" model will replace the use of real cadavers, which are in short supply compared with the number of surgical trainees, offer limited training to a relatively small number of individuals at a time, and in which exposure to rare medical situations cannot be predetermined.

We report results of in situ experiments performed on fresh human cadavers to measure mechanical properties of intra-abdominal organs such as the liver and the stomach. These experiments were carried out at the US Surgical cadaver facility in Norwood, CT and the Albany Medical College.

The organization of the paper is as follows. We first describe the experimental protocol, discuss the results, and then present linear and nonlinear mechanical models before presenting some conclusions.

Materials and methods

For performing in situ force–displacement experiments on internal organs, we modified a robotic device, the Phantom Premium 1.0 from Sensable Technologies (Fig. 1). This device is used to deliver precise displacement stimuli and is fitted with a six-axis force sensor from ATI Industrial Automation (Nano 17) to measure reaction forces. The transducer has a force resolution of 0.78 mN along each orthogonal axis and a bandwidth of 10 kHz. The Phantom has a nominal position resolution of 30 μm, a maximum force of 8.5 N, and bandwidth exceeding the typical motion frequencies in actual surgery. Flat-faced cylindrical indenters were fitted to the tip of the force sensor to apply the displacement stimuli without introducing significant contact nonlinearities due to change in contact area during deformation. Reaction force and tool displacement data samples were time-coded and recorded 1,000 times per second using custom software. Phantom control and data acquisition were performed using a 2 GHz Pentium IV PC.

Fresh, unfrozen cadavers, obtained within 48 h after death, were used for the experiments. The cadavers were placed in supine position on the surgical table. Unlike in actual surgery, the stomach was not insufflated. A midline incision was performed to open the abdomen and expose the intra-abdominal organs. The Phantom was placed on a rigid stand next to the table, which was adjusted such that the indenter was normal to the organ surface. The indenter was then lowered in small increments until it was visually determined to be barely in contact with the organ surface when the stimuli were delivered and the force measurement started.

It is important to consider the effect of preconditioning on tissue elasticity measurements. When cyclic loading/unloading tests are performed on soft tissues, hysteresis of tissue force–displacement curves occurs [9], indicative of viscoelastic behavior. The response is not repeatable for the initial few cycles (Fig. 2). It is therefore necessary to first precondition the tissue prior to actual measurements. To precondition the tissue, cyclic loading was applied for 1 min at 2 Hz before actual data recording commenced.

The indentation tests comprised (a) ramp-and-hold tests and (b) sinusoidal indentations. In the ramp-and-hold tests the indenter was driven to various depths (1–8 mm) at various velocities (1–8 mm/s) and held at each depth for 60 s. A 3-min interval followed each trial to allow the tissue to relax. Each test was performed for a maximum of five trials. In the sinusoidal experiments, low-frequency sinusoidal indentation stimuli (0.2–3 Hz) were delivered

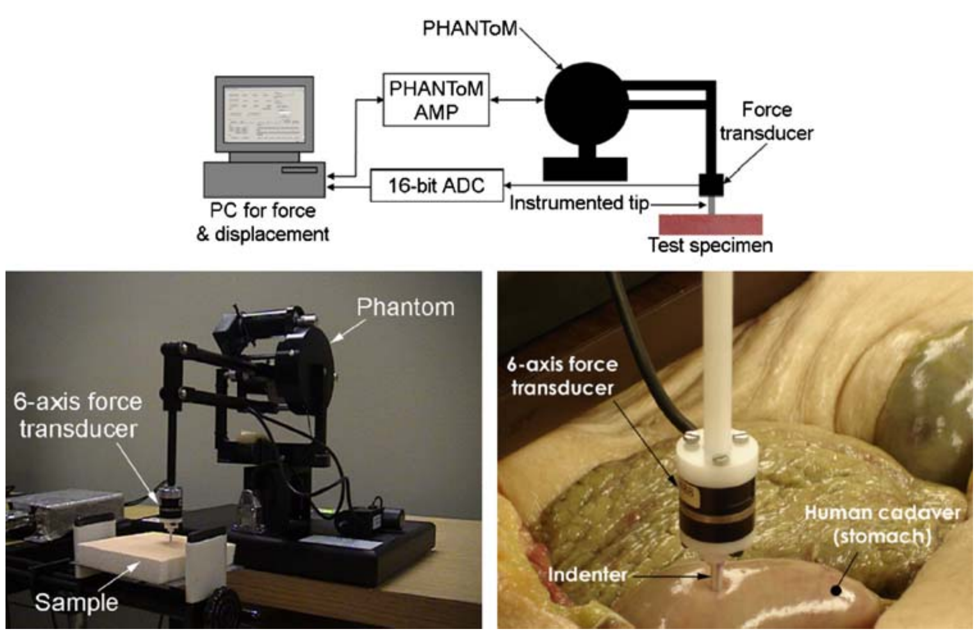
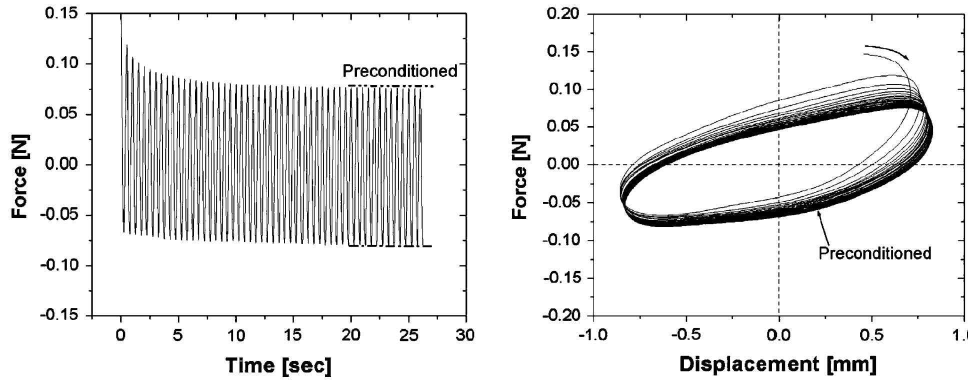


Fig. 1 Experiment setup for in situ indentation experiments on cadaver stomach and liver (upper: schematic diagram, lower: actual setup)

Fig. 2 Preconditioning of tissue



with various amplitudes (0.5–1 mm) superimposed on a pre-indentation of 4 mm to ensure that the indenter stayed in contact with the organ over the entire application of the load.

An obvious feature of the raw data is the high-frequency noise components. Data analysis was performed using MATLAB® (Mathworks, Inc.) with noise removed using a unit-gain, zero-phase, low-pass, numerical Butterworth filter.

Results

Results of the ramp-and-hold indentation experiments on the liver and stomach of human cadavers are plotted in Fig. 3. The steady-state forces, defined as the average force values between 38 and 40 s after the initiation of the ramp, as functions of indentation depth are plotted with corresponding standard deviations in Fig. 4. The choice of this time interval to measure the "steady-state" force is justified since waiting for force relaxation beyond that period of time is not relevant for the purpose of surgery simulation. These curves clearly indicate the nonlinear behavior of the tissue.

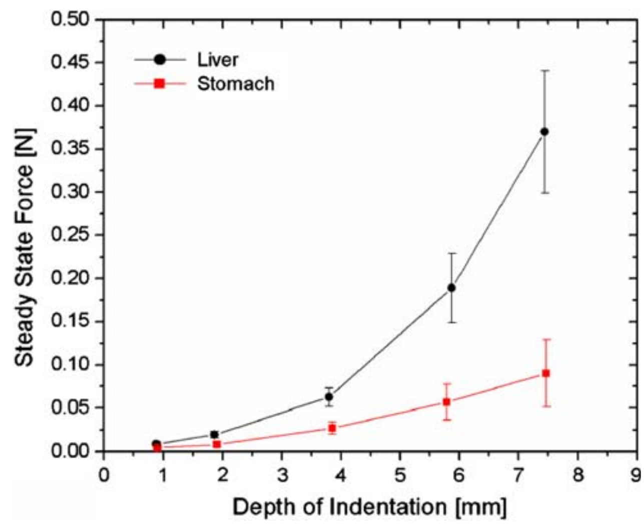
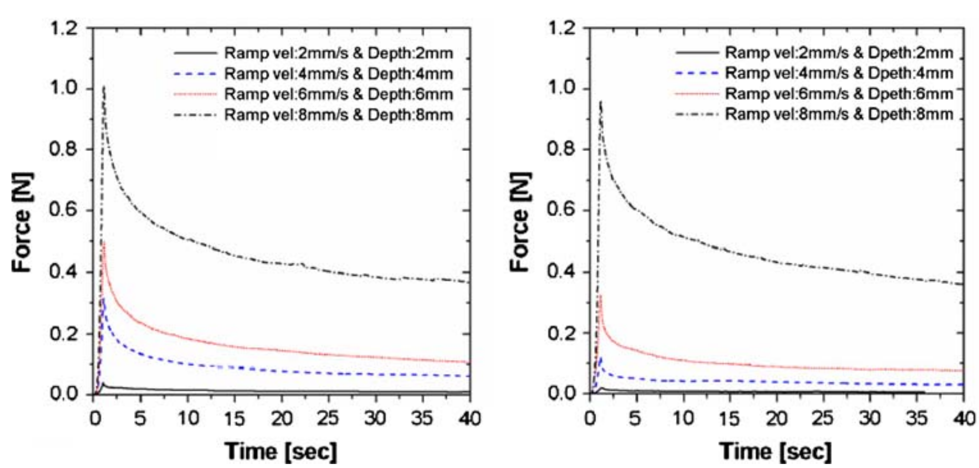


Fig. 4 Mean steady-state force versus depth of indentation with standard deviation

Figure 5A shows an example of the response of the cadaver stomach to sinusoidal excitation. When the response force is plotted as a function of displacement, pronounced hysteresis is observed [9] (Fig. 5B). This hysteresis is a consequence of the viscoelastic nature of the

Fig. 3 Force response of the liver (left) and stomach (right) to ramp-and-hold indentation stimuli



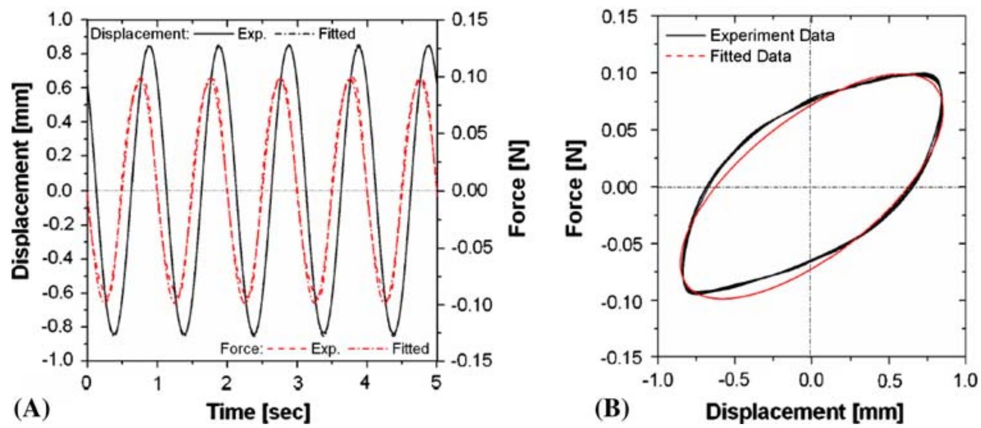


Fig. 5 The force–time and force–displacement responses of the stomach to sinusoidal indentation at 1.0 Hz

material, and the nonzero area enclosed by the curve represents loss of energy due to viscous damping.

In order to quantify the viscoelasticity of the tissues, we estimated the dynamic stiffness (the amplitude ratio of response force to input displacement) and damping properties (the phase lag between force and input), extracted by fitting of the experiment data using MATLAB. Denoting the measured deformation and force by $\delta_m(t)$ and $F_m(t)$ respectively:

$$\begin{aligned} \delta_m(t) &= \delta \cos(\omega t) \\ F_m(t) &= F \cos(\omega t + \theta) \end{aligned} \tag{1}$$

where $\omega(= 2\pi f)$ represents the excitation frequency, δ and F are the amplitudes of displacement and force respectively, θ is the phase angle between the displacement and force. Then, the apparent dynamic stiffness (F/δ) and loss factor ($\tan\theta$) can be determined.

Figure 6 shows the frequency responses of the tissues excited at 0.2, 0.5, 0.8, 1, 2, and 3 Hz with 1-mm amplitude. It was found that, in general, the liver is stiffer than the stomach, whereas the loss factor of stomach is higher than that of liver. The stiffness and viscoelastic properties of liver and stomach are relatively constant over the investigated frequency range. As is usual for biological tissues, there was significant variability in the response between cadavers.

The experimental data was used to develop mathematical models of the tissues which could be used in virtual reality-based surgical simulators. First we will discuss the development of linear elastic models in which the primary quantity to evaluate is the Young's modulus, as soft tissues are essentially incompressible. However, the experimental results clearly indicate that nonlinearity is an important factor (Fig. 4). We have developed powerful algorithms to simulate the behavior of linear elastic soft tissues in real time [36], which essentially scale linearly with the number of unknowns. However, nonlinear response modeling is far more complex since the problem has to be solved iteratively and is therefore time consuming. Hence the choice of the model that captures the essential physics without being computationally expensive is of paramount importance in surgery simulation. We have developed methods to incorporate nonlinear response of soft tissues in our simulations [37].

Viscoelasticity is another important trait of soft tissue biomechanics. In our experiments, we observed that the force response is clearly strain rate dependent and, when the indenter was held at a constant depth of indentation, the force on the indenter relaxed with time (Fig. 3).

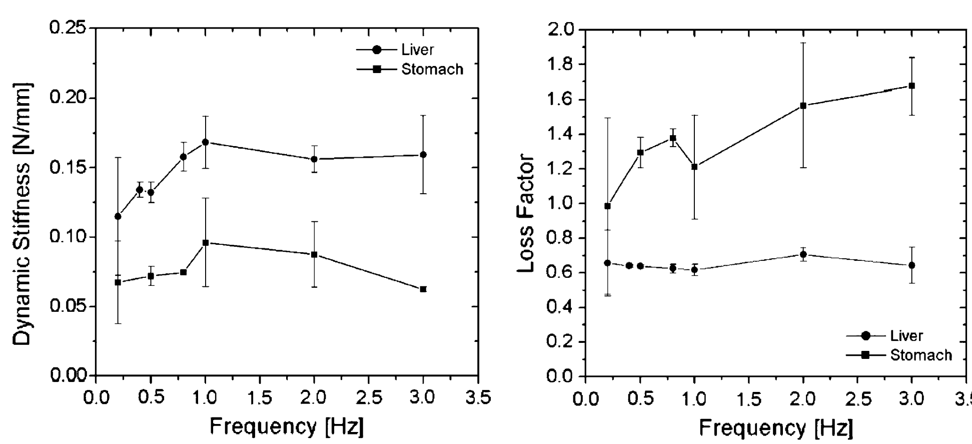


Fig. 6 Dynamic stiffness and loss factor from sinusoidal indentation at 0.2, 0.5, 0.8, 1, 2, and 3 Hz indentations with 1-mm amplitude on liver and stomach

Corresponding to sinusoidal stimuli, the force–indentation depth plot was clearly hysteretic, indicating energy dissipation (Fig. 5B). Fung [1, 11] proposed a quasilinear viscoelastic (QLV) theory to describe the load–deformation viscoelastic relationship of biological soft tissues. In this theory, the load response of the tissue to an applied deformation history was expressed in terms of a convolution integral of a reduced relaxation function and a nonlinear elastic function. We have developed a QLV model to represent the nonlinear and time-dependent behavior of soft tissues.

The effective Young's modulus, E, describes the approximate linear elastic response of the tissue. We utilized the described ramp-and-hold indentation experiments described to compute the effective Young's moduli of human liver and stomach tissue assuming incompressible behavior, i.e., a Poisson's ratio of 0.5. The assumption of linear elasticity depends on the use of small deformations, relative to the characteristic dimensions of the organ. The effective elastic Young's modulus, E, corresponding to an indentation depth of δ may be calculated using the formula [39]:

$$E = \frac{3P}{8a\delta} \tag{2}$$

where P is the reaction force and a is the diameter of a right circular frictionless punch indenter applied to an elastic isotropic half-space.

Table 1 lists the effective elastic modulus of liver and stomach of human cadaver from the ramp-and-hold indentation experiments. The mean elastic modulus of liver and stomach are estimated to be 5.9359 kPa and 1.9119 kPa, respectively, over the range of indentation depths tested. The effective modulus increases with increasing indentation depth indicates nonlinear tissue response. A very simple piecewise linear model will be able to utilize such a table to generate the reaction forces corresponding to different depths of indentation. However for large deformations, a fully nonlinear model is advantageous.

Table 1 Effective elastic modulus of liver and stomach from human cadaver experiments

Indentation depth (mm)	Liver		Stomach	
	Mean (kPa)	Standard deviation (kPa)	Mean (kPa)	Standard deviation (kPa)
1	2.4847	0.5590	1.2529	0.2882
2	2.6116	0.5189	1.0829	0.2780
4	4.1113	0.6901	1.7537	0.4678
6	8.0462	1.7087	2.4569	0.8779
8	12.4256	2.3887	3.0133	1.3060

The radius of indenter "a" is 1.5 mm

The nonlinear time- and history-dependent viscoelastic behavior of soft biological tissues is captured by the quasilinear viscoelastic (QLV) model of Fung [11]. This model has been successfully applied to the modeling of various soft tissues including ligament/tendon [40] and pig aortic valve [41]. The QLV theory assumes that the material response can be separated into a strain- and a time-dependent component that can be determined separately from experiments. The force response of a material to a step input is given by the relaxation function of that material, $R(t)$. In Fung's QLV theory, the relaxation function for a quasilinear viscoelastic material takes the form:

$$R(\delta, t) = G(t) \cdot F^e(\delta), \tag{3}$$

where $G(t)$ is the reduced relaxation function normalized by the peak force and $F^e(\delta)$ is called the instantaneous elastic response function, which may be nonlinear.

The force response of a quasilinear viscoelastic material at time t is:

$$F(t) = \int_{-\infty}^{t} G(t-\tau) \frac{\partial F^e(\delta(\tau))}{\partial \delta} \frac{\partial \delta(\tau)}{\partial \tau} d\tau \tag{4}$$

where $\partial F^e/\partial \delta$ is the instantaneous response of the material and $\partial \delta/\partial \tau$ is the input deformation, or strain history. This equation signifies that the force response will vary as a function of time even if the input deformation is constant over a significant period of time. Obtaining $F^e(\delta)$ and $G(t)$ precisely requires experimental data from an instantaneously applied step. In practice, a step function is replaced by a ramp with a finite rise time. We have determined the parameters of the QLV model by the instantaneous assumption approach. This approach is based on curve-fitting the equations describing the elastic response and reduced relaxation function separately to the force–displacement or stress–strain curve obtained during loading and the normalized and time-shifted relaxation data from static stress relaxation experiments.

The first step is to determine the viscoelastic parameters. Using the force–displacement curves such as those in Fig. 3, and invoking the correspondence principle [42] it is straightforward to determine the parameters of the following Prony series expansion of the reduced relaxation function of the tissue:

$$G(t) = G_0 \left(1 - \sum_{i=1}^{2} \bar{g}_i^p \left(1 - \exp\left(-\frac{t}{\tau_i}\right)\right)\right) \tag{5}$$

where $G_0 (= G(0))$ is the initial value of the rigidity, $\bar{g}_i^p$ is the i^{th} Prony series parameter, and τ_i is the corresponding Prony retardation time constants that are to be obtained by fitting experimental data. An appropriate choice of how many time constants is adequate may be made considering the fact that the most important frequency range relevant for surgery simulation is 0.01–10 Hz. We chose a second-order linear solid model ($n = 2$) in this work. However, such a model is not unique.

Using the above model and the experimental data, we can find $\bar{g}_i^p$ and τ_i by a nonlinear least-square optimization technique such as the Levenberg–Marquardt algorithm [43] implemented in MATLAB®. In the Levenberg–Marquardt method, the use of which which is well known for parameter identification problems, global convergence towards a stationary point of the objective function is obtained using stabilization of the Gauss–Newton method through a regularization term.

The parameter identification problem can be stated as the minimization of a function $f(x)$ that is a sum of the squares of the difference between the experimental data and the response obtained from the mathematical model. In our case, the compared quantities are the response from the mathematical model for viscoelastic response and the associated experimental data. Therefore, we minimize the following objective function:

$$f(p) = \frac{1}{2}||r(p)||^2 = \frac{1}{2}\sum_{i=1}^{m}\left(G_i^{Model}(p) - f_i^{EXP}\right)^2 = \frac{1}{2}\sum_{i=1}^{m} r_i(p)^2 \quad (6)$$

where $f_i^{EXP}(i = 1\ldots m)$ is the experimental data normalized by the peak force at the tip of the indenter, $G_i^{Model}(i = 1\ldots m)$ is the response predicted by the mathematical model (5), p is the vector of parameters to be identified, i.e., $p = [\bar{g}_1^p \quad \bar{g}_1^p \quad \tau_1 \quad \tau_2]^T$, m is the number of experimental points, and n is the number of parameters.

Table 2 lists the estimated Prony series parameters from selected experiments. Figure 7 shows that the reaction forces obtained from the fitted model agree with the observed behavior of the liver (Fig. 7A) and stomach (Fig. 7B) under various loading conditions. Reduced relaxation functions that are curve-fit to a second-order Prony series were found to have excellent goodness of fit ($R^2 > 0.99$).

To determine the nonlinear elastic response, the loading portion of a relaxation response was used (Fig. 8). One way

Table 2 Prony series parameters and relaxation time constants from the normalized force data on liver and stomach of human cadaver

	Depth (mm)	$\bar{g}_1^p$	$\bar{g}_2^p$	τ_1 (s)	τ_2 (s)	R^2
Liver	2	0.3788	0.3849	0.2309	9.4601	0.9985
	4	0.4422	0.3558	0.6696	8.8517	0.9994
	6	0.4235	0.3575	0.6927	10.9220	0.9994
	8	0.3182	0.3234	0.6958	11.0834	0.9998
Stomach	2	0.4743	0.2730	0.7195	12.4827	0.9969
	4	0.5372	0.2345	0.2816	9.4699	0.9986
	6	0.4301	0.3262	0.3223	7.4916	0.9996
	8	0.2960	0.3364	0.7384	13.2608	0.9998

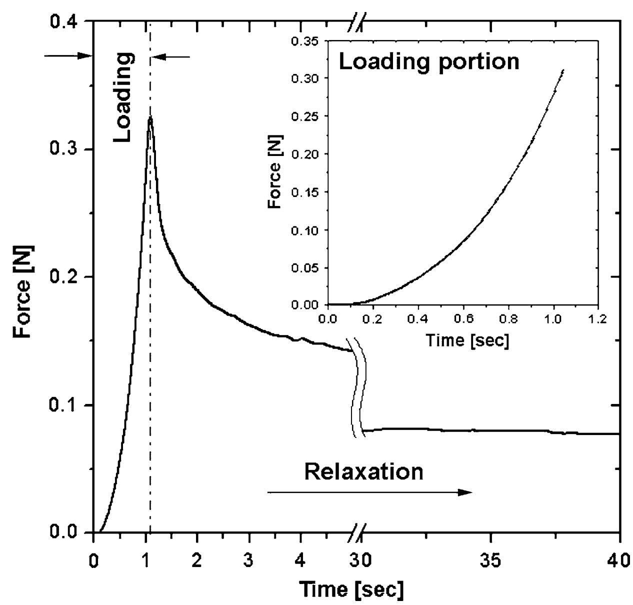


Fig. 8 Loading and relaxation response of the cadaver stomach to a 6-mm ramp indentation

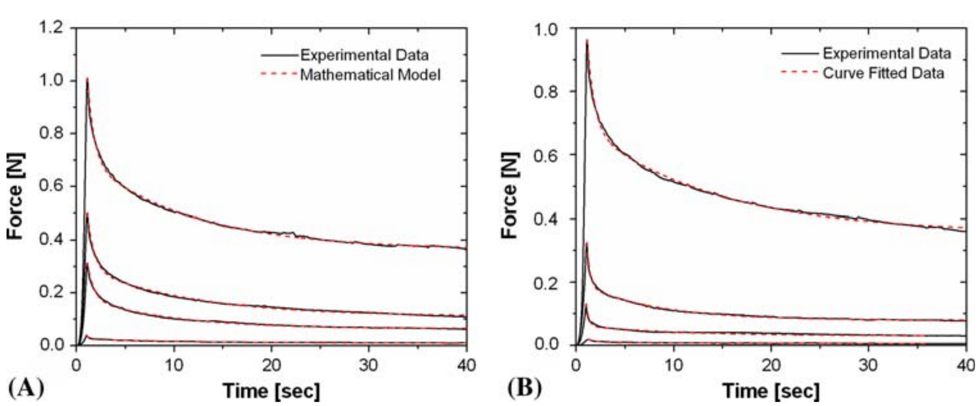


Fig. 7 Response to ramp-and-hold indentation on (**A**) liver and (**B**) stomach of human cadaver and model prediction using second-order Prony series expansion

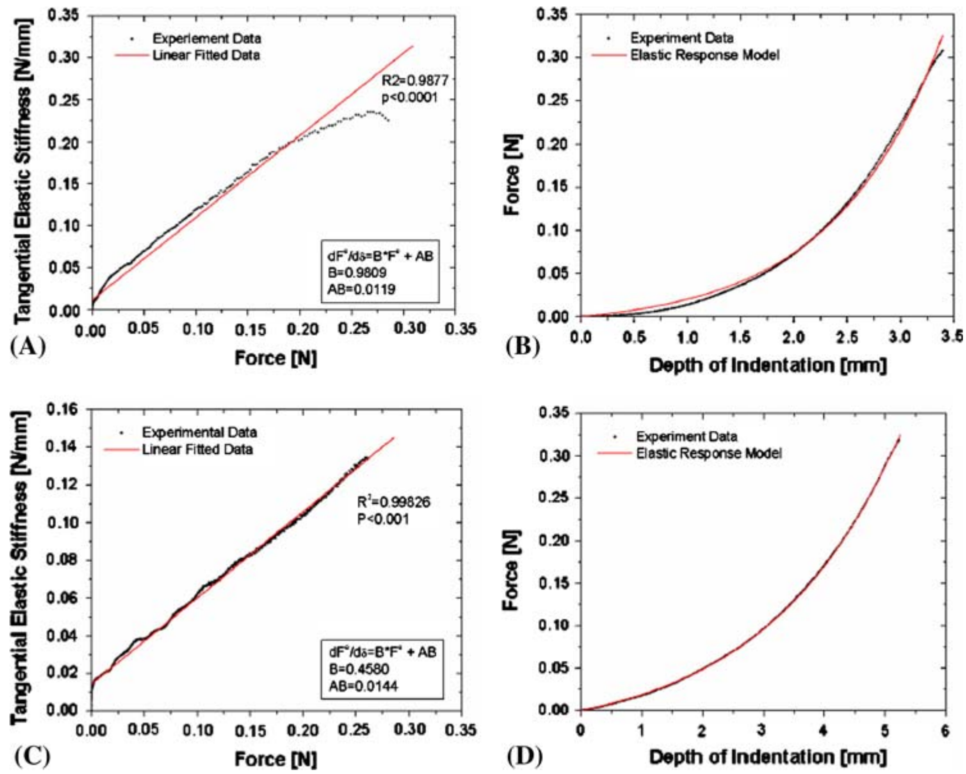


Fig. 9 Model for elastic response of liver (**A**, **B**) and stomach (**C**, **D**): (**A**, **C**) Tangential elastic stiffness–force curve (**B**, **D**) experimental data and mathematical model for elastic response

to characterize the elastic response of a hyperelastic medium is to invoke the existence of a strain-energy function, *W*. For example, if a body is elastically isotropic, the strain-energy function must be a function of the strain invariants. Well-known examples of strain-energy functions are those due to Rivlin [44], Ogden [45], and Yeoh [46].

However, the use of such an elastic potential implies that the stress in the body is obtained by taking derivatives of the potential with respect to the strains, which is computationally expensive during surgery simulation. Hence we follow a more empirical approach. From Fig. 9 we observe that the force–displacement relationship is of the following form [47].

$$F^e(\delta) = A(e^{B\delta} - 1), \tag{7}$$

where A and B are constants. Since

$$\begin{aligned}\frac{\partial F^e(\delta)}{\partial \delta} &= ABe^{B\delta} = ABe^{B\delta} - AB + AB \\ &= B\left[A(e^{B\delta} - 1)\right] + AB = BF^e + AB,\end{aligned} \tag{8}$$

we conclude that B and the product AB are the rate of change of the slope of the force–displacement curve and the initial slope of the curve, respectively.

Note that the slope of the force–displacement curve is linearly related to the force. When the force is zero or near zero, the product AB governs the slope of the force–displacement curve. We take the derivative of the force with respect to the indentation depth to obtain the elastic response of the soft tissue. Figure 9A and C shows the tangential elastic stiffness ($dF^e/d\delta$) with respect to the force for cadaver liver and stomach. Experimental data show that the change of force with respect to indentation depth is proportional to the force for low values of the force. The estimated parameters for Eq. 7 are $A = 0.0121$ N (0.0315 N) and $B = 0.9809$ (0.4580) for liver (stomach).

Discussion

The development of realistic physics-based surgical simulators has significant implications in improving how surgeons are trained to perform minimally invasive surgery. Better trained surgeons will translate into fewer operating room errors, less patient morbidity, and vastly improved patient outcomes, resulting in faster healing, shorter hospital stays, and reduced postsurgical complications and treatment costs, benefiting stakeholders such as payers (employers, health maintenance organizations, Medicare), providers (integrated practices, hospitals, individual physicians), and patients. However, the development of such a realistic surgical simulator that enables the trainee to touch, feel, and manipulate virtual tissues and organs through surgical tool handles used in actual surgery, while seeing high-quality images as in real surgery, is a complex procedure that calls for significant research in the area of novel computational technology as well as the measurement and modeling of soft tissue response of intra-abdominal organs. In this paper, we have developed a measurement system for obtaining the mechanical response of intra-abdominal organs by performing in situ experiments on livers and stomachs in fresh human cadavers. Mathematical models have been developed based on these experiments which can be directly used in physics-based surgery simulators.

First, we estimated the effective elastic properties. The parameters of the quasilinear viscoelasticity model were then determined. Key assumptions in our approach are that the organs are incompressible, homogeneous, and isotropic, and that the deformations are relatively small compared with the characteristic dimensions of the organ. For solid organs such as the liver, these assumptions are realistic. However for hollow organs such as the stomach with multiple layers it might seem that anisotropy would be important. In [48], however, the results of ex vivo testing of cadaver and surgically removed stomachs indicate very little quantitative difference between axial and transverse mechanical behavior. However, we would like to verify this in our future studies. In addition to anisotropy, we would like to investigate the behavior of non-preconditioned tissue. The data and models presented in this paper together with additional ones based on the techniques presented here are expected to result in realistic physics-based surgical simulators.

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