Constitutive Modeling of Human Liver Based on in Vivo Measurements

Edoardo Mazza¹, Patrick Grau¹, Marc Hollenstein¹, and Michael Bajka²

¹ Institute of Mechanical Systems,
Department of Mechanical and Process Engineering,
ETH, 8092 Zurich, Switzerland

Edoardo.Mazza@imes.mavt.ethz.ch

² Clinic of Gynecology, Dept OB/GYN,
University Hospital, 8091 Zurich, Switzerland

Abstract. In vivo aspiration experiments on human livers are analyzed and material parameters for a non-linear-viscoelastic constitutive model are determined. A novel procedure is applied for the inverse analysis that accounts for the initial tissue deformation in the experiment and for the non-homogeneity of liver tissue. A numerical model is used consisting of a surface layer (capsule) and an underlying non-linear-viscoelastic solid (parenchyma). The capsule is modeled as hyperelastic membrane using data from measurements on bovine and human tissue. In a two step optimization procedure the set of constitutive model parameters for the “average” response of liver parenchyma is obtained. The proposed model is in line with literature values of high strain rate elastic modulus obtained from dynamic elastography. The model can be used to predict the nonlinear, time dependent behavior of human liver in computer simulations related to surgery training and planning.

Keywords: Liver, mechanical behavior, constitutive model, inverse analysis.

1 Introduction

Computer simulation of minimally invasive hepatic surgery and computer based systems for surgical training and planning require mathematical models of liver’s mechanical behavior, in order to provide realistic haptic feedback and to predict organ deformation, [1, 2]. Evaluation of tissue’s mechanical response might also lead to an improvement of diagnostic procedures. As an example, intra-operative ultrasonography is combined with palpation to detect liver tumors, [3]. Recent studies have applied dynamic magnetic resonance elastography for the detection of liver fibrosis [4, 5], confirming the diagnostic potential of mechanical parameters. Knowledge of the mechanical behavior of human liver might also contribute to improvements in radiation therapy. 4D CT or MRI is used for evaluation of organ displacement due to respiratory motion, [6], and a-priori knowledge on the mechanical behavior of the liver could improve the predictive capabilities of the algorithms used for tumor localization.

For all the above mentioned clinical applications constitutive models are required that describe the nonlinear elastic, time and loading history dependent response of soft

tissue. Formulations of these models and determination of the constitutive model parameters require corresponding experiments. The measurements must be characterized by well defined kinematic and kinetic boundary conditions, so to allow the inverse problem to be solved. Data from ex vivo experiments (see, e.g., [7-9]) are often inappropriate for mechanical modeling since the properties of a living organ can change after removal from its natural milieu with e.g. an intact blood perfusion. This motivates the development of experimental techniques for in vivo mechanical testing of soft biological tissue. Account on the state of the art in measuring the deformation behavior of soft biological tissue, in particular liver, is given in [16]. A few works shall be mentioned here: In [10] a motorized endoscopic grasper is used for in vivo experiments on porcine liver. [11] and [12] present indentation tests on animal organs in vivo. The influence of liver perfusion on its mechanical behavior has been demonstrated by Kerdok et al, [13]. Carter et al. [14] performed intra-operative in vivo experiments on human liver. They used an indentation device and reported a value of approximately 270 kPa for the linear elastic modulus of human liver. In contrast, dynamic elastography experiments on human liver, [4, 5], indicate that the linear elastic modulus of healthy human liver is in the range of 6 kPa.

In vivo mechanical experiments on human liver were recently performed during open surgery using the so called “aspiration device”, [15, 16]. In [15] mechanical characterization was combined with histological evaluation of liver tissue biopsies obtained from the resected liver at the site of mechanical testing. This procedure enabled a quantitative analysis of the correlation between mechanical response and tissue microstructure of normal and diseased liver. Constitutive models for human liver were derived in [16] based on data from 23 measurements on 6 healthy organs.

Two main factors affect the liver model presented in [16] and lead to a significant discrepancy with respect to the data reported in [4, 5]: (i) the liver was modeled as a homogeneous deformable solid, without consideration of the mechanical resistance of Glisson’s capsule (the connective tissue layer that covers the organ); (ii) the initial deformation of the liver tissue (due to the compressive force required to ensure a good initial contact between aspiration device and liver) was not considered for the inverse problem solution. In the present paper we solve the inverse problem for the in vivo experiments from [16] applying a novel modeling approach that accounts for the initial tissue deformation and for the macroscopic non-homogeneity of the liver.

2 Experiments

2.1 Aspiration Device and Measurement Procedure

A brief description of the aspiration device is given here. Further information on the device, on the design of each component, on the image analysis procedure, on the control algorithms, and on the sterilization process are reported in [17]. The working principle of the device is illustrated in Fig. 1 and is based upon the pipette aspiration technique. The device consists of a tube in which the internal pressure can be controlled according to a desired profile. The tube is closed on one extremity by a disc containing the circular opening for tissue aspiration. The experiment is performed by

(i) gently pushing the tube against the tissue to ensure a tight initial contact, and (ii) creating a (time variable) vacuum inside the tube so that the tissue is sucked through the aspiration hole (with a diameter of 10 mm). An optical fiber, which is connected to an external source of light, provides the illumination in the inner part of the tube. The images of the side-view are reflected by a mirror and are captured by a digital camera. The grabbed images are analyzed off-line in order to extract the profiles of the deformed tissue. The duration of the loading and unloading cycle is about 15 seconds and the magnitude of the vacuum is selected in order to avoid tissue damage due to excessive deformation. Time histories of measured pressure and tissue profile (Fig. 2) constitute the input data used to determine the mechanical properties of the tissue.

Fig. 1. A: Sketch of the aspiration device and camera view. B: Example of an image grabbed by the digital camera on a liver tissue with the highest point of the profile (P) indicated. C: in vivo experiment on human liver.

Experiments were conducted during open abdominal surgical interventions. Patients undergoing abdominal surgery (for other reasons than a liver pathology) were asked on the day before surgery and gave their informed consent. Tests were performed at the very beginning of the surgical procedure, i.e. just after the opening of the abdomen with the liver in situ and perfused, and before any other surgical step. The surgeon placed the tip of the device on the liver surface trying to keep a constant and gentle contact force between the device and the tissue in the course of the measurement. Further information on the test protocol as well as on advantages and limitations of the aspiration technique is reported in [16].

2.2 Measurement Results

Tissue deformation upon application of the negative pressure cycle is represented through the displacement history of the highest point of the profile (point P, Fig. 1). Data for all measurements on six healthy livers can be found in [16]. Fig. 2 shows the measured pressure and average displacement history. The average curve is calculated over all measurements on the six organs. The average initial displacement is approximately 1.3 mm and is due to the compressive force exerted when pushing the tube against the tissue.

Fig. 2. Left: Applied negative pressure history. Right: Average displacement history of point P.

3 Data Analysis and Discussion

Due to non-linearity in geometry and material response and to the complex geometry of the experiment, a numerical calculation is required for determining the constitutive model parameters from the experimental data. The experiment is simulated by an axisymmetric finite element (FE) model as described in [17]. This assumption implies an isotropic response of the tissue. The material parameters are determined iteratively from the comparison of calculated and measured displacement of the point P. The program Abaqus 6.6 has been used for the inverse FE analysis.

The time dependent nonlinear elastic behavior of liver tissue is modeled here with the quasilinear viscoelastic (QLV) model, [18]. This model comprises hyperelastic equations and a viscoelastic dissipative component. The reduced polynomial form is used here for the strain energy potential U :

$$U = \sum_n C_{n0} (J^{-\frac{2}{3}} (\lambda_1^2 + \lambda_2^2 + \lambda_3^2) - 3)^n + \frac{K_0}{2} (J - 1)^2 \quad (1)$$

C_{n0} are material parameters, λ_i are the so called principal stretch ratios and $J = \lambda_1 \lambda_2 \lambda_3$ is the determinant of the deformation gradient tensor. For the bulk modulus a constant value of $K_0 = 10^7 \text{ N/m}^2$ is used (quasi-incompressible behavior). The time dependence of the mechanical response is described by assuming time dependent coefficients C_{n0} in U through the relaxation function $g(t)$:

$$g(t) = 1 - \sum_{k=1}^2 g_k \left(1 - \exp\left(-\frac{t}{t_k}\right) \right) \quad (2)$$

where g_k and t_k characterize the relaxation behavior. For liver parenchyma ($n=1,2$; $k=1,2$) a total number of 6 parameters have to be determined from the experiments.

Numerical values for these parameters were given in [16] and are reported in Table 1. These values were obtained through an inverse procedure in which (i) the initial deformation of the liver was neglected, and (ii) the liver was modeled as consisting of a homogeneous material (no differentiation of capsule and parenchyma). The present analysis improves as compared to [16] in these two important points.

In order to consider the influence of Glisson's capsule, a 2 material model is used for the calculations: a layer of elements (thickness: 40 μm) with constitutive equations representative of the mechanical behavior of the capsule are defined at the upper surface of the axisymmetric FE model (Fig. 3). Model parameters for the capsule are reported in Table 1. These parameters were not determined based on the *in vivo* liver measurements. In fact, the information provided by the aspiration test is not sufficient to uniquely define the mechanical properties of capsule and parenchyma. Since the capsule is expected to be less dependent on the biochemical environment, its properties were determined based on *ex vivo* tests. Data from equibiaxial tests on bovine liver capsule were used, corrected based on the comparison of the uniaxial response of bovine and human capsules (see [19, 21, 22]).

The inverse procedure thus delivers the constitutive model parameters for liver parenchyma. Fig. 3 illustrates the novel procedure applied to account for the initial deformation of the liver as resulting from the compressive force exerted by the surgeon. Note that the compressive force is not known, but the initial deformation is measured in each experiment. The inverse procedure consists of 2 steps: (i) a preliminary "indentation" step (simulating the initial tissue compression) followed by (ii) the aspiration phase. The material parameter set is used in (i) and the indentation depth "d" is iteratively adjusted to obtain the measured initial displacement z_0 of the point P (first optimization loop); the aspiration phase is then simulated and the discrepancy between measured and calculated displacement history of P evaluated. Based on these results, the new parameter set is defined for the next iteration (second optimization loop). The Nelder-Mead Simplex Search Method (implemented in Matlab 7, function *fminsearch*, [20]) is used for the optimization procedure. This method allows rapid convergence to the "best fit" parameter set (few hours with standard hardware and software implementation), which however correspond to a local minimum of the objective function. Uniqueness of the obtained material parameters of parenchyma can thus not be ensured. On the other hand, simpler material models (with $k=1$ or $n=1$, see equation 1 and 2) clearly failed to predict the measured time history of P.

The procedure also delivers the value of the applied compressive force. The influence of FE mesh density, friction coefficient between aspiration device and liver, and far field boundary conditions has been studied in [21], with calculations and experiments. It was shown that the latter can affect the material parameters identification to some extent, and this influence increases with larger compressive force applied initially on the liver (indentation step). The material parameters corresponding to the measured average liver response are reported in Table 1. Using these constitutive equations and material constants, the correspondence of measured and calculated displacement histories of point P is excellent, as shown in Fig. 4. The calculated

initial compressive force is approximately 8 N, note that the weight of the instrument corresponds to a force of approximately 12 N.

Fig. 4 illustrates the behavior obtained for uniaxial stress loading conditions using the constitutive model parameters reported in Table 1. The curves for the so called “instantaneous” response are shown for liver parenchyma as obtained from the procedure proposed in this paper, and compared with the corresponding curves for the livermodel from [16]. As expected, the new model predicts a much more compliant behavior. The corresponding instantaneous small strain modulus of parenchyma is

Fig. 3. Inverse procedure for identification of material parameters of liver parenchyma. The FE model is shown and the kinetic and kinematic boundary conditions are indicated.

Table 1. Material parameters for the QLV model

	$C_{10}(t=0, \text{ kPa})$	$C_{20}(t=0, \text{ kPa})$	$C_{30}(t=0, \text{ Pa})$	g_1	$t_1 \text{ (sec.)}$	g_2	$t_2 \text{ (sec.)}$
Liver, [16]	9.8	26.3	-	0.51	0.58	0.15	6.89
Capsule	122.2	168.2	0.05	0	-	0	-
Parenchyma	1.0	6.5	-	0.46	0.55	0.27	2.66

Fig. 4. Left: instantaneous uniaxial response for liver parenchyma (continuous line) and for homogeneous liver model (dotted line, from [16]). Right: comparison of measured (dotted line) and “best-fit” FE calculation (continuous line, corresponding to the parameters indicated in Table1).

approximately 6 kPa. This value coincides with the elastic modulus obtained for liver parenchyma in [4, 5] using dynamic elastography. This correspondence supports the validity of the proposed model and the novel inverse procedure for analysis of the aspiration experiments. The modulus values of liver parenchyma from this work, [4] and [5] are approximately 50 times smaller as compared with the human liver modulus reported in [14]. This difference is attributed to an oversimplified mechanical analysis of the indentation tests in [14] that assimilates the indentation experiment to a uniaxial test.

4 Conclusions

Intraoperative mechanical measurements on human livers were analyzed in this paper. A novel procedure has been presented for the inverse analysis of the aspiration experiment. Consideration of the initial compressive force and differentiation between Glisson's capsule and parenchyma in the FE calculations led to a new set of material parameters for constitutive modeling of human liver. The proposed model is in line with observations from dynamic elastography. The model equations can be used for predicting the nonlinear, time dependent response of human liver in computer simulations related to clinical applications, such as hepatic surgery training and planning or tumor localization in radiation treatment.

The following problems related to the aspiration experiments and the inverse analysis proposed in this paper require further investigations in future work: (i) the mechanical model of human Glisson's capsule is based on few (non patient specific) uniaxial measurements on human tissue, (ii) the calculated deformation history in the aspiration experiment depends strongly on the capsule behavior and to much less extent on the model parameters of parenchyma, (iii) the far field boundary conditions influence to some degree the tissue response to the initial compression, (iv) this compressive force varies during the aspiration phase (due to respiratory motion).

Future analysis will also consider biphasic models to describe the flow of fluids within the parenchyma during mechanical loading, thus leading to a compressible behavior of liver tissue.

Acknowledgments

This work was supported by the CO-ME/NCCR research network of the Swiss National Science Foundation. The work of S. Klosterkemper and A. Blaser is gratefully acknowledged.

References

1. Picinbono, G., Delingette, H., Ayache, N.: Non-linear anisotropic elasticity for real-time surgery simulation. *Graphical Models* 65(5), 305–321 (2003)
2. Schwartz, J., Denninger, M., Rancourt, D., Moisan, C., Laurendeau, D.: Modelling liver tissue using a visco-elastic model for surgery simulation. *Med. Image An.* 9, 103–112 (2005)

3. Knol, J.A., Marn, C.S., Francis, I.R., Rubin, J.M., Bromberg, J., Chang, A.E.: Comparison of dynamic infusion and delayed CT, intraoperative ultrasound, and palpation in the diagnosis of liver metastases. *American Journal of Surgery* 165(1), 81–88 (1993)
4. Huwart, L., Peeters, F., Sinkus, R., Annet, L., Salameh, N., ter Beek, L.C., Horsmans, Y., Van Beers, B.E.: Liver fibrosis: non-invasive assessment with MR elastography. *Nmr In Biomedicine* 19(2), 173–179 (2006)
5. Rouvière, O., Yin, M., Dresner, M.A., Rossman, P.J., Burgart, L.J., Fidler, J.L., Ehman, R.L.: MR elastography of the liver: Preliminary results. *Radiology* 240(2), 440–448 (2006)
6. Von Siebenthal, M., Székely, G., Lomax, A.J., Cattin, P.C.: Systematic errors in respiratory gating due to intrafraction deformations of the liver. *Med. Phys.* 34(9), 3620–3629 (2007)
7. Miller, K.: Method of testing very soft biological tissues in compression. *Journal of Biomechanics* 38, 153–158 (2005)
8. Snedeker, J., Bajka, M., Hug, J.M., Székely, G., Niederer, P.: The creation of a high-fidelity finite element model of the kidney for use in trauma research. *Journal of Visualization and Computer Animation* 13, 53–64 (2002)
9. Zheng, Y.P., Li, Z.M., Choi, A.P.C., Lu, M.H., Chen, X., Huang, Q.H.: Ultrasound palpation sensor for tissue thickness and elasticity measurement - Assessment of transverse carpal ligament. *Ultrasonics* 44(Suppl. 1), E313-E317 (2006)
10. Brown, J.D., Rosen, J., Kim, Y.S., Chang, L., Sinanan, M., Hannaford, B.: In-Vivo and In-Situ Compressive Properties of Porcine Abdominal Soft Tissues. In: *Medicine Meets Virtual Reality 11. Studies in Health Technology and Informatics*, vol. (94), pp. 26–32. IOS Press, Amsterdam (2003)
11. Ottensmeyer, M.P.: TeMPeST I-D: An instrument for measuring solid organ soft tissue properties. *Experimental Techniques* 26, 48–50 (2002)
12. Samur, E., Sedef, M., Basdogan, C., Avtan, L., Duzgun, O.: A robotic indenter for minimally invasive measurement and characterization of soft tissue response, *Med. Med. Image An.* 11, 361–373 (2007)
13. Kerdok, A., Ottensmeyer, M., Howe, R.: Effects of perfusion on the viscoelastic characteristics of liver. *Journal of Biomechanics* 39(12), 2221–2231 (2006)
14. Carter, F.J., Frank, T.G., Davies, P.J., McLean, D., Cuschieri, A.: Measurement and modelling of the compliance of human and porcine organs. *Med. Image An.* 5, 231–236 (2001)
15. Mazza, E., Nava, A., Hahnloser, D., Jochum, W., Bajka, M.: The mechanical response of human liver and its relation to histology: An in vivo study. *Med. Image An.* 11, 663–672 (2007)
16. Nava, A., Mazza, E., Furrer, M., Villiger, P., Reinhart, W.H.: In vivo mechanical characterization of human liver, *Med. Med. Image An.* 12, 203–216 (2008)
17. Nava, A.: *Vivo Characterization of the Mechanical Response of Soft Human Tissue*, ETH Zurich Diss. no.17060 (2007)
18. Fung, Y.C.: *Biomechanics*, 2nd edn. Mechanical properties of living tissues. Springer, New York (1993)
19. Hollenstein, M., Nava, A., Valtorta, D., Snedeker, J.G., Mazza, E.: Mechanical Characterization of the Liver Capsule and Parenchyma. In: Harders, M., Székely, G. (eds.) *ISBMS 2006. LNCS*, vol. 4072, pp. 150–158. Springer, Heidelberg (2006)
20. Nelder, J., Mead, R.: A simplex method for function minimization. *Computer Journal* 7, 308–313 (1965)
21. Grau, P.: Analysis of in vivo aspiration experiment on human liver and comparison with the indentation experiment, Master Student Project, ZfM report Nr. 2008-2 (2008)
22. Klosterkemper, S.: Enhanced Finite Element Characterization of Soft Tissues and Internal Organs, Master Student Project, ZfM report Nr. 2008-1 (2007)