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Elastography: general principles and clinical applications

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1. Introduction

Elastography visualizes differences in the biomechanical properties of normal and diseased tissues (Sarvazyan et al. 1995; Krouskop et al. 1998; Samani et al. 2007; Parker et al. 2011). Elastography was developed in the late 1980s to early 1990s to improve ultrasonic imaging (Lerner and Parker 1987; Lerner et al. 1988; Ophir et al. 1991; O'Donnell et al. 1994), but the success of ultrasonic elastography has inspired investigators to develop analogues based on magnetic resonance imaging (Muthupillai et al. 1995; Bishop et al. 2000; Sinkus et al. 2000; Weaver et al. 2001), and optical coherence tomography (Khalil et al. 2005; Kirkpatrick et al. 2006; Ko et al. 2006). In this chapter, we will focus on ultrasonic techniques with a brief reference to approaches based on magnetic resonance imaging.

The general principle of elastography can be summarized as follows: (1) perturb the tissue using a quasi-static, harmonic, or transient mechanical source; (2) measure the resulting mechanical response (displacement, strain or amplitude and phase of vibration); and (3) infer the biomechanical properties of the underlying tissue by applying either a simplified or continuum mechanical model to the measured mechanical response (Manduca et al. 1998; Ophir et al. 2000; Bamber et al. 2002; Greenleaf et al. 2003; Parker et al. 2011). In this chapter, we will describe (a) the general principles of quasi-static, harmonic, and transient elastography (see Fig. 1)—the most popular approaches to elastography and (b) the physics of elastography—the underlying equations of motion that governs the motion in each approach. We also provide examples of clinical applications of each approach.

2. The physics of elastography

Like conventional medical imaging modalities, forward and the inverse problems are encountered in elastography. The former problem is concerned with predicting the mechanical response of a material with known biomechanical properties and external boundary conditions. Understanding this problem and devising accurate theoretical models to solve it has been an effective strategy in developing and optimizing the performance of ultrasound displacement estimation methods. The latter problem is concerned with estimating the biomechanical properties non-invasively using the forward model and knowledge of the mechanical response, and external boundary conditions. A comprehensive review of methods that have been developed to solve the inverse problem is given in (Doyley 2012), therefore, in this section we will focus only on the forward problem.

The forward elastography problem can be described by the following system of partial differential equations (PDEs) given in compact form (Timoshenko and Goodier 1970; Fung 1981):

$$\nabla \cdot [\sigma_{ij}] = \beta_i, \quad (1)$$

where σ_{ij} is the three-dimensional stress tensor (i.e., a vector of vectors), β_i is the deforming force, and ∇ is the del operator. Using the assumption that soft tissues exhibit linear elastic behavior, then the strain tensor (ε) may be related to the stress tensor (σ) as follows (Landau et al. 1986):

$$\sigma_{ij} = C_{ijkl} \varepsilon_{kl}, \quad (2)$$

where the tensor C is a rank-four tensor consisting of 21 independent elastic constants (Fung 1981; Ophir et al. 1999; Greenleaf et al. 2003). However, under the assumption that soft tissues exhibit isotropic mechanical behavior then only two independent constants, λ and μ (lambda and shear modulus), are required. The relationship between stress and strain for linear isotropic elastic materials is given by:

$$\sigma_{ij} = 2\mu \varepsilon_{ij} + \lambda \delta_{ij} \Theta, \quad (3)$$

where $\Theta = \nabla \cdot \mathbf{u} = \varepsilon_{11} + \varepsilon_{22} + \varepsilon_{33}$ is the compressibility relation, δ is the Kronecker delta, and the components of the strain tensor are defined as:

$$\varepsilon_{ij} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \quad (4)$$

Lamé constants (i.e., λ and μ) are related to Young's modulus (E) and Poisson's ratio (ν), as follows (Timoshenko and Goodier 1970; Fung 1981):

$$\mu = \frac{E}{2(1+\nu)}, \quad \lambda = \frac{\nu E}{(1+\nu)(1-2\nu)} \quad (5)$$

The stress tensor is eliminated from the equilibrium equations (i.e., equation (2)) using equation (3). The strain components are then expressed in terms of displacements using equation (4). The resulting equations (i.e., the Navier-Stokes equations) are given by:

$$\nabla \cdot \mu \nabla \mathbf{u} + \nabla(\lambda + \mu) \nabla \cdot \mathbf{u} = \rho \frac{\partial^2 \mathbf{u}}{\partial t^2}, \quad (6)$$

where ρ is the density of the material, $\mathbf{u}$ is the displacement vector, and t is time. For quasi-static deformations, equation (6) reduces to:

$$\nabla \cdot \mu \nabla \mathbf{u} + \nabla(\lambda + \mu) \nabla \cdot \mathbf{u} = 0 \quad (7)$$

For harmonic deformations, the time-independent (steady-state) equations in the frequency domain give (Sinkus et al. 2000; Van Houten et al. 2001):

$$\nabla \cdot \mu \nabla \mathbf{u} + \nabla(\lambda + \mu) \nabla \cdot \mathbf{u} = \rho \omega^2 \mathbf{u}, \quad (8)$$

where ω is the angular frequency of the sinusoidal excitation. For transient deformations, the wave equation is derived by differentiating equation (6) with respect to x, y, z , which gives the following result (Timoshenko and Goodier 1970):

$$\nabla^2 \Delta = \frac{1}{c_1^2} \frac{\partial^2 \Delta}{\partial t^2} \quad (9)$$

where $\nabla \cdot \mathbf{u} = \Delta$, and the velocity of the propagating compressional wave, c_1 , is given by:

$$c_1 = \sqrt{\frac{\lambda + 2\mu}{\rho}} \quad (10)$$

The wave equation for the propagating shear wave is given by:

$$\nabla^2 \zeta = \frac{1}{c_2^2} \frac{\partial^2 \zeta}{\partial t^2} \quad (11)$$

where $\zeta = \nabla \cdot \mathbf{u}/2$ is the rotational vector, and the shear-wave velocity, c_2 , is given by:

$$c_2 = \sqrt{\frac{\mu}{\rho}} \quad (12)$$

Analytical methods have been used to solve the governing equations for quasi-static, harmonic, and transient elastographic imaging methods (Love 1929; Sumi et al. 1995; Kallel et al. 1996; Bilgen and Insana 1998) for simple geometries and boundary conditions. However, numerical methods — namely, the finite-element method — are used to solve the governing equations for all three approaches to elastography on irregular domains and for heterogeneous elasticity distributions (Parker et al. 1990; Ponnekanti et al. 1994; Konofagou et al. 1996; Hall et al. 1997; Samani et al. 2001; Van Houten et al. 2001; Miga 2003; McLaughlin and Renzi 2006; Bringham et al. 2007).

3. Approaches to elastography

3.1 Quasi-static elastography

Quasi-static elastography visualizes the strain induced within tissue using either an external or internal source. A small motion is induced within the tissue (typically on the order of 2% of the axial dimension) with a quasi-static mechanical source. The axial component of the internal tissue displacement is measured by performing cross correlation analysis on pre- and post-deformed radio-frequency (RF) echo frames (Ophir et al. 1991; O'Donnell et al. 1994; Bamber and Bush 1995) and strain is estimated by spatially differentiating the axial displacements. In quasi-static elastography, soft tissues are typically viewed as a series of one-dimensional springs that are arranged in a simple fashion. For this simple mechanical model, the measured strain (ε) is related to the internal stress (σ) as follows (Hooke's Law):

$$\sigma = k\varepsilon \quad (13)$$

where k is the Young's modulus (or stiffness) of the tissue. No method can measure the internal stress distribution *in vivo*; consequently, the internal stress distribution is assumed to be constant (i.e., $\sigma \approx 1$); an approximate estimate of Young's modulus is computed from the reciprocal of the measured strain. The disadvantage of computing modulus elastograms in this manner is that it doesn't account for stress decay or stress concentration; consequently,

quasi-static elastograms typically contain target-hardening artifacts (Ponnekanti et al. 1994; Konofagou et al. 1996), as illustrated in Fig. 2.

Despite this limitation, several groups have obtained good elastograms in applications where accurate quantification of Young's modulus is not essential. For example, Fig. 3 shows the results of a case study, where quasi-static elastography was performed on a 73 year old female with a Phylloides tumor in the upper outer quadrant of her left breast. Phylloides tumors are rare variants of fibroadenoma, with a rich stromal component and more cellularity. They grow quickly, developing macroscopically lobulated internal structures and they may reach a large size, visibly altering the breast profile. Sonography generally shows a solid, moderately hypoechoic nodule, with smooth borders and good sound transmission (Rizzatto et al. 1993). Inhomogeneous structures may be present because of small internal fluid areas. These appearances are non-specific and sonography is not currently able to distinguish between benign and malignant cases, nor can it make a differential diagnosis between fibroadenoma and Phylloides tumors.

In the sonogram shown in Fig. 3, the tumor covers most of the field of view, with the capsule of the anterior margin visible close to the top of the image and the posterior margin visible at the bottom left. Within the tumor the appearance is heterogeneous on a large scale, with macroscopic lobules separated by echogenic boundaries that are probably fibrous in nature. The strain elastogram (Fig. 3b) confirms this appearance, but shows it much more clearly with greater contrast than the sonogram (Fig. 3a). The capsule at the top of the image is seen to be stiffer than either the subcutaneous fat (anterior) or the tumor tissue (below). The macroscopic lobules within the tumor are very clearly defined as relatively soft regions separated by stiff septa, which is also consistent with the septa being of a fibrous nature.

Direct and iterative inversion schemes have been developed to make quasi-static elastograms more quantitative. These techniques compute the Young's or shear modulus from the measured displacement or strain using the forward elasticity model described in equation (7). Direct inversion schemes use a linear system of equations that are derived by rearranging the PDEs that describe the forward elastography problem (Skovoroda and Aglyamov 1995; Sumi et al. 1995; Bishop et al. 2000).

$$(\partial_{yy} - \partial_{xx})(\varepsilon_{xy}\mu) + \partial_{xy}(\varepsilon_{xy}\mu) = 0 \quad (14)$$

Equation (14) contains high-order derivatives that amplify measurement noise, which compromises the quality of ensuing modulus elastograms as demonstrated in Fig. 4.

Iterative inversion techniques (Doyley et al. 1996; Kallel and Bertrand 1996) overcome this issue by considering the inverse problem as a parameter-optimization task, where the goal is to find the Young's modulus that minimizes the error between measured displacement or strain fields, and those computed by solving the forward elastography problem. The matrix solution at the $(k + 1)$ iteration that has the general form:

$$\mu^{k+1} = \Delta\mu^k + \left[J(\mu^k)^T J(\mu^k) + \rho I \right]^{-1} J(\mu^k)^T (u_m - u\{\mu^k\}), \quad (15)$$

where $\Delta\mu^k$ is a vector of shear modulus updates at all coordinates in the reconstruction field and J is the Jacobian, or sensitivity, matrix. The Hessian matrix, $[J(\mu^k)^T J(\mu^k)]$, is ill-conditioned. Therefore, to stabilize performance in the presence of measurement noise, the matrix is regularized using one of three variational methods: the Tikhonov (Kallel and Bertrand 1996), the Marquardt (Doyley et al. 2000), or the total variational method (Jiang et

al. 2009; Richards et al. 2009). Fig. 5 shows an example of modulus elastograms computed with the iterative inversion approach.

The contrast-to-noise ratio of the modulus elastogram is better than that of the strain elastogram, which improved the detection of the boundary between the ablated region and normal tissue to enable accurate determination of the size of the thermal zone.

3.2 Harmonic elastography based on local frequency estimation

In harmonic elastography (Lerner and Parker 1987; Lerner et al. 1988; Parker et al. 1990; Yamakoshi et al. 1990; Muthupillai et al. 1995), low-frequency acoustic waves (typically < 1 kHz) are transmitted within the tissue using a sinusoidal mechanical source. The phase and amplitude of the propagating waves are visualized using either color Doppler imaging (Lerner et al. 1990; Parker et al. 1990; Yamakoshi et al. 1990)— see Fig. 6— or phase-contrast MRI (Muthupillai et al. 1995; Sinkus et al. 2000; Weaver et al. 2001).

Assuming that shear waves propagate with plane-wavefronts, then an approximate estimate of the local shear modulus (μ) may be computed from local estimates of the wavelength as follows:

$$v_{shear} = \sqrt{\frac{\mu}{\rho}} \quad (16)$$

where v_{shear} is the velocity of the shear wave, and ρ is the density of the tissue. In a homogeneous tissue, shear modulus can be estimated from local estimates of instantaneous frequency (Manduca et al. 2001; Wu et al. 2006). Although shear modulus estimated using this approach is insensitive to measurement noise, the spatial resolution of the ensuing modulus elastograms is limited. A further weakness of the approach is that the plane-wave approximation breaks down in complex organs such as the breast and brain, when waves reflected from internal tissue boundaries interfere constructively and destructively.

Like quasi-static elastography, solving the inverse elastography problem also improves the performance of harmonic elastography. Fig. 7 shows a representative example of an elastogram obtained from a health volunteer by solving the inverse harmonic elastography problem. The resolution of the elastograms was sufficiently high to visualize fibroglandular tissue from the adipose tissue (Van Houten et al. 2003; Doyley et al. 2004).

3.3 Transient elastography based on arrival time estimation

A major limitation of harmonic elastography is that shear waves attenuate rapidly as they propagate within soft tissues, which limits the depth of penetration. The transient approach to elastography overcomes this limitation by using the acoustic radiation force (ARF) of an ultrasound transducer to perturb tissue locally (Sarvazyan et al. 1998; Nightingale et al. 2003; McAleavey et al. 2009). This elastographic imaging method uses an ultrasound scanner with an ultra-high frame rate (i.e., 10,000 fps) to track the propagation of shear waves. As in harmonic elastography, local estimates of shear modulus are estimated from local estimates of wavelength. However, the reflections of shear waves at internal tissue boundaries make it difficult to measure shear wave velocity— this limitation can be overcome by computing wave speeds directly from the arrival times as discussed in Ji et al. (2003). Figure 8 shows an example of shear wave elastograms obtained from a breast cancer patients using a commercially available transient elastography system.

4. The future of elastography

Soft tissues display several biomechanical properties, including viscosity and nonlinearity, which may improve the diagnostic value of elastography when visualized alone or in combination with shear modulus. For example, clinicians could use mechanical nonlinearity to differentiate between benign and malignant breast tumors (Krouskop et al. 1998). Furthermore, there is mounting evidence that other mechanical parameters, namely viscosity (Sinkus et al. 2005b; Qiu et al. 2008) and anisotropy (Sinkus et al. 2005a) could also differentiate between benign and malignant tissues – similar claims have also been made for shear modulus (Sinkus et al. 2005a). Not only can these mechanical parameters discriminate between different tissue types, but they may provide value in other clinical areas, including brain imaging (Sack et al. 2009; Hamhaber et al. 2010), distinguishing the mechanical properties of active and passive muscle groups (Asbach et al. 2008; Hoyt et al. 2008; Perrinez et al. 2009), characterizing blood clots (Schmitt et al. 2007), and diagnosing edema (Righetti et al. 2007). Several investigators are actively developing techniques to visualize different mechanical properties using quasi-static, harmonic, and transient elastographic imaging approaches.

4.1 Viscoelasticity

In most approaches to elastography, the mechanical behavior of soft tissues is modeled using the theory of linear elasticity (Hooke's law), which is an appropriate model for linear elastic materials (i.e., Hookian materials). However, it is well known that most materials, including soft tissues, deviate from Hooke's law in various ways. Materials that exhibit both fluid-like and elastic (i.e., viscoelastic) mechanical behavior deviate from Hooke's law (Fung 1981). For viscoelastic materials, the relationship between stress and strain is dependent on time. Viscoelastic materials display three unique mechanical behaviors: (1) strain increases with time when stress (externally applied load) is sustained over a period of time, a phenomenon that is known as viscoelastic creep; (2) stress decreases with time when strain is held constant, a phenomenon known as viscoelastic relaxation; (3) during cyclic loading, mechanical energy is dissipated in the form of heat, a phenomenon known as hysteresis.

Several investigators are actively developing elastographic imaging methods to visualize the mechanical parameters that characterize linear viscoelastic materials (i.e., viscosity, shear modulus, Poisson's ratio). For example, Asbach et al. (2008) developed a multifrequency method to measure the viscoelastic properties of normal liver tissue versus diseased liver tissue taken from patients with grade 3 and 4 liver fibrosis. They computed the shear modulus and viscosity variations within the tissue by fitting a Maxwell rheological model to the measured data and solving the linear viscoelastic wave equation in the frequency domain. They observed that fibrotic liver tissue had a higher viscosity (14.4 ± 6.6 Pa s) and elastic modulus ($\mu_1 = 2.91 \pm 0.84$ kPa and $\mu_2 = 4.83 \pm 1.77$ kPa) than normal liver tissue. Their results revealed that although liver tissue is dispersive, it appeared as non-dispersive between the frequency range of 25 — 50 Hz. Catheline et al. (2004) computed the shear modulus (μ) and viscosity (η) by fitting the measured speed of sound and attenuation equation to Voigt's and Maxwell's rheological models. They observed that the recovered shear modulus values were independent of the rheological model employed, but viscosity values were highly dependent on the models employed.

Sinkus et al. (2005b) developed a direct-inversion scheme to visualize the mechanical properties of viscoelastic materials, in which a curl operation was performed on the time-harmonic displacement field $\mathbf{u}(\mathbf{x}, t) = \mathbf{u}(\mathbf{x}, t)e^{i\omega t}$ to remove the displacement contribution of the compressional wave. They derived the governing equation that describes the motion incurred in an isotropic, viscoelastic medium by computing the curl of the PDEs that

describe the motion incurred by both transverse and compressional shear waves. The resulting PDEs for transverse waves are given in compact form by:

$$\rho \partial_t^2 \mathbf{u} = \mu \nabla^2 \mathbf{u} + \eta \partial_t \nabla^2 \mathbf{u} \quad (17)$$

Sinkus et al. (2005b) developed a direct-inversion scheme from equation (17), in which μ and η were the unknowns. They evaluated the inversion scheme using (a) computer simulations, (b) phantom studies, and (c) patient studies. Their simulation studies revealed that the proposed algorithm could accurately recover shear modulus and viscosity from ideal displacement data. However, with noisy displacements, a good estimate of shear modulus was obtained only when the shear modulus of the simulated tissue was less than 8 kPa. The inversion scheme overestimated the shear modulus values when actual stiffness of the tissue was larger than 8 kPa. A similar effect was observed when estimating viscosity, albeit much earlier (i.e., the algorithm provided good estimates of viscosity when $\mu < 5$ kPa). Although the shear modulus affected the bias in the viscosity measurement, the authors demonstrated that the converse did not occur; i.e., the viscosity did not affect the bias in shear modulus. Despite these issues, their phantom studies revealed that inclusions were discernible in both μ and η elastograms, and the viscosity values agreed with previously reported values for gelatin (0.21 Pa s). The patient studies revealed that the shear modulus values of malignant breast tumors were noticeably higher than those of benign fibroadenomas, but there was no significant difference observed in the viscosity of the tumor types, a result that would appear to contradict those reported in (Qiu et al. 2008).

4.2 Non-linearity

When soft tissues deform by a small amount (an infinitesimal deformation), their geometry in the undeformed and deformed states is similar, and thus the deformation is characterized using engineering strain. To characterize finite deformation, we first have to define a reference configuration, which is the geometry of the tissue under investigation in either the deformed or undeformed state. The Green-Lagrangian strain is defined as:

$$\varepsilon_{ij} = \frac{1}{2} \left[\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} + \frac{\partial u_k}{\partial x_i} \frac{\partial u_k}{\partial x_j} \right] \quad (19)$$

The nonlinear term is neglected when the magnitude of the spatial derivative is small, to produce the linear strain tensor as defined in equation (3). The relationship between stress and strain is nonlinear even for linearly elastic material when it is undergoing finite deformations. Consequently, Skovoroda et al. (1999) proposed a direct-inversion scheme to reconstruct the shear modulus distribution of a linear elastic material that is undergoing finite deformation.

Some materials exhibit nonlinear material properties that are typically described using a strain energy density function. Among the strain energy functions proposed in the literature, the most widely used for modeling tissues are (a) the Neo-Hookean hyperelastic model, and (b) the Neo-Hookean model with an exponential term. Oberai et al. (2009) used a different model, the Veronda-Westman strain energy density function, to describe the finite displacement of a hyperelastic solid that is undergoing finite deformation, which is defined by:

$$W = \mu_0 \left(\frac{e^{\gamma(I_1-3)} - 1}{\gamma} - \frac{I_2 - 3}{2} \right) \quad (20)$$

where the terms I_1 and I_2 are the first and second invariants of the Cauchy-Green strain tensor, μ_0 is the shear modulus, and γ denotes the nonlinearity. For the nonlinear case, they proposed an iterative inversion approach to reconstruct a nonlinear parameter, and the shear modulus at zero strain.

Using data obtained from volunteer breast cancer patients, one with a benign fibroadenoma tumor and the other with an invasive ductal carcinoma (IDC), they observed that for the fibroadenoma case, the tumor was visible in modulus elastograms that had been computed using small strain and large strain (12%), although the contrast of the elastograms computed at large strain (7:1) was lower than that computed at smaller strain (10:1). The fibroadenoma tumor was not visible in nonlinear parameter elastograms. The inclusion in the patient with IDC was discernible in shear modulus elastograms recovered using small and large strains. However, the stiffness contrast of the modulus elastograms recovered at both small and large strains were comparable, and the IDC tumor was visible in nonlinear parameter elastograms. This result is one of several that has demonstrated the clinical value of nonlinear elastographic imaging. Specifically, elastography can characterize the nonlinear behavior of soft tissues and may be used to differentiate between benign and malignant tumors.

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- Like conventional medical imaging modalities, forward and the inverse problems are encountered in elastography.
- Quasi-static elastography visualizes the strain induced within tissue using either an external or internal source.
- Direct and iterative inversion schemes have been developed to make quasi-static elastograms more quantitative.
- Soft tissues display several biomechanical properties, including viscosity and nonlinearity, which may improve the diagnostic value of elastography when visualized alone or in combination with shear modulus.
- Elastography can characterize the nonlinear behavior of soft tissues and may be used to differentiate between benign and malignant tumors.

Figure 1. Schematic representation of current approaches to elastographic imaging: quasi-static elastography (left), harmonic elastography (middle), and transient elastography (right).

Figure 2. Sonogram (a) and strain (b) elastograms obtained from a phantom containing a single 10 mm diameter inclusion whose modulus contrast was approximately 6.03 dB

Figure 3. Sonographic (a) and elastographic (b) images of Phylloides breast tumor. Courtesy of Dr. Jeff Bamber at the Institute of Cancer Research in London.

Figure 4.

Modulus elastograms computed from ideal axial and lateral strain estimates (a) and (b) strain estimates that were corrupted with 4% additive white noise. The simulated phantom contained an inclusion with a Gaussian modulus distribution that had a peak contrast of 4:1. Courtesy of Dr. P. Barbone, Boston University Department of Mechanical and Aeronautical Engineering.

Figure 5. Sonogram (a), strain elastogram (b), and modulus elastogram (c) of RF ex vivo ablated bovine liver. Courtesy of Drs. T. J. Hall, T. Varghese, and J. Jiang (University of Wisconsin-Madison).

Figure 6.

In vivo porcine liver with a thermal lesion. The sonogram (a) shows a lesion (yellow arrow) with indistinct boundaries. The sonoelastogram (b) demonstrates a vibration deficit indicating a hard lesion. Red arrows point to boundary of the liver.

Figure 7. Montage of MR magnitude images (A) and shear modulus elastograms (B) recovered from a healthy volunteer using the subzone inversion scheme. Courtesy of Drs. J. B. Weaver and K. D. Paulsen, Dartmouth College, Thayer School of Engineering.

Figure 8.

Comparison B-scan, compression elastography, and transient shear wave images of a breast with pathology confirmed invasive ductal carcinoma. The maximum diameter on the longitudinal axis on B-mode was 17 mm, whereas both elastographic techniques indicated a larger footprint of the cancer. (Courtesy of Dr. W. Svensson, Imperial College, London).