Ultrasound Stimulated Vibrometry for Measuring Viscoelastic Tissue Properties

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Vibrometry with Ultrasound

- Background- What is the Problem?
  Tissue stiffness vs disease
- Rationale for measurement- noninvasive, quick, inexpensive, simple, quantitative
- Significance- early diagnosis, almost real time.
- Approach- use stress application to measure strain response. Stress/strain results.
- Introduction-ultrasound radiation force methods are now growing rapidly and will remap ultrasound methods.

Vibrometry with Ultrasound

- **Where Does Radiation Force Come From?**
  - **Nonlinear terms in second order wave equation.**
- **What Tissue Properties are Accessible with the Method?**
  - **Elastic and viscous moduli**
- **What approaches have been tried?**
  - **External stress, impulse, vibration- internal stress, impulse, harmonic**
- **Why vibrometry? Wave equation is local, harmonic**
- **How does it work? Initiate shear wave, measure wavelength**
- **Results- Phantoms, tissue,**
- **Applications, homogeneous, liver (MRE), kidney, Lesions?**
- **Conclusions**
  - **Quantitative, simple, fast, add to commercial scanners.**

Palpation and Disease

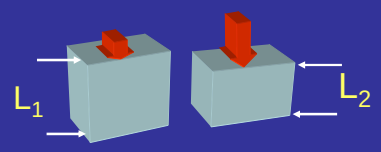
- Many disease processes are associated with changes in tissue stiffness
- Palpation is a common tool for disease detection through the evaluation of stiffness
  - Clinical- and self-breast exam
  - Testicular exam
  - Digital rectal (prostate) exam
- Palpation is most sensitive to tumors that are large and close to the skin surface

Lets stop and look at fundamental linear viscoelastic mechanics

- What is the required to evaluate a linear homogeneous viscoelastic material?
- What do models like Voigt and Maxwell have to do with the characterization?

Primer on stiffness
Stress and Strain

Stress = σ = force/unit area

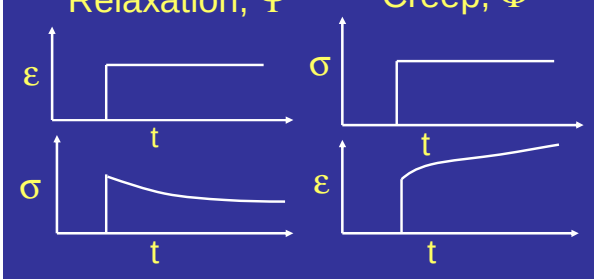


Strain = $\varepsilon = (L_1 - L_2)/L_1$

Modulus $E = \sigma/\varepsilon$ (force/area)

Relaxation and Creep (linear, viscoelastic, homogeneous)

Relaxation, Ψ | Creep, Φ



Creep Compliance Φ, and Relaxation Function Ψ

$$\epsilon(t) = \int_{-\infty}^{\infty} dt'\, \Phi(t-t')\dot{\sigma}(t'), \quad \sigma(t) = \int_{-\infty}^{\infty} dt'\, \Psi(t-t')\dot{\epsilon}(t'),$$

$\varepsilon(t) = Strain$ $\sigma(t) = Stress$ $\Phi(t), \Psi(t) = Green\ functions$

$$\Phi(\tau) = 0, \ \Psi(\tau) = 0, \quad \tau < 0$$

$$\phi(\omega)\psi(\omega) = -1/\omega^2,$$

T. Yamamoto [1] and T. Minato [1]

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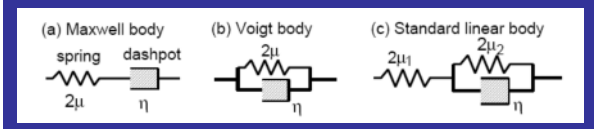
Models for linear viscoelastic materials



T. Yamamoto [1] and T. Minato [1]
[1] *Department of Earth and Planetary Science, Nagoya University, Nagoya 464-8602, Japan*

Table 1. Green's functions and their Fourier transforms for the viscoelastic models

Model	Green's function	Fourier transform
Maxwell	$\Phi(t) = \frac{t+\tau}{2\mu\tau}$	$\phi(\omega) = -\frac{1-i\omega\tau}{2\mu\tau\omega^2}$
	$\Psi(t) = 2\mu e^{-t/\tau}$	$\psi(\omega) = \frac{2\mu\tau}{1-i\omega\tau}$
Voigt	$\Phi(t) = \frac{1-e^{-t/\tau}}{2\mu}$	$\phi(\omega) = \frac{i}{2\mu\omega(1-i\omega\tau)}$
	$\Psi(t) = 2\mu[\theta(t) + \tau\delta(t)]$ 1)	$\psi(\omega) = \frac{2i\mu(1-i\omega\tau)}{\omega}$
Standard linear	$\Phi(t) = \frac{1}{2\mu_2}\left(1 + \frac{\mu_2}{\mu_1} - e^{-t/\tau_2}\right)$	$\phi(\omega) = \frac{1}{2\mu_2}\left[-\left(1+\frac{\mu_2}{\mu_1}\right)\frac{1}{i\omega} - \frac{\tau_2}{1-i\omega\tau_2}\right]$
	$\Psi(t) = \frac{2\mu_1}{\mu_1+\mu_2}(\mu_2 + \mu_1 e^{-t/\tau_{12}})$ 2)	$\psi(\omega) = \frac{2\mu_1}{\mu_1+\mu_2}\left(-\frac{\mu_2}{i\omega} + \frac{\mu_1\tau_{12}}{1-i\omega\tau_{12}}\right)$ 2)

$\eta = 2\mu\tau$

Note: 1) $\theta(t)$ is the step function, and $\delta(t)$ is the δ function. 2) $\tau_{12} = \eta/2(\mu_1+\mu_2)$. 3) The expressions of $\Phi(t)$ and $\Psi(t)$ are those for $t > 0$. $\Phi(t)$ and $\Psi(t)$ should be zero for $t < 0$. See eq. (2).

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Requirements for tissue stiffness measurement technique

- Non invasive
- Quantitative
- Simple
- Fast
- Repeatable
- Accurate

Background

Example: Liver Cirrhosis

- **Causes:**
  - Sustain wound healing to chronic liver injury
  - Viral; autoimmune; drug induced; cholestatic; metabolic diseases
- **Prevalence:**
  - Hundreds of millions worldwide
  - 900,000 in USA (number increasing)
- **Risk (50% 5 year mortality):**
  - Hepatic failure
  - Primary liver cancer

Limitation of Liver Biopsy

- Pain (French survey)
- Complications
  - Hospitalization: 1~5%
  - Mortality 1/1,000~1/10,000
- Low reproducibility
  - Inter-observer variability: ~20%

Need for Noninvasive Alternative

- Fibrosis is reversible
- Risk and cost of unnecessary biopsy
  - $2,200
  - HCV: ~25%
- New treatment development (tracking)
  - Establish effectiveness
  - Optimize dosing

One approach is to use Magnetic Resonance Elastography: MRE#

- Vibrate tissue from the surface of the body
- Cause shear wave propagation within the tissue
- Measure wave speed
- Deduce stiffness from the wave equation.

#Muthupillai, R., D. J. Lomas, P. J. Rossman, J. F. Greenleaf, A. Manduca, and R. L. Ehman: **Magnetic resonance elastography by direct visualization of propagating acoustic strain waves**. *Science* 269:1854-1857, September 29, 1995.

Wave equation

$$\partial_t^{\,2}\phi - c_s^2\nabla^2\phi = 0$$

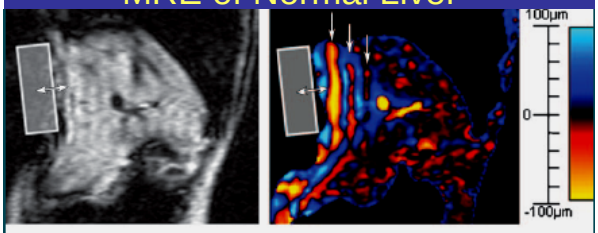
$$c_s^2 = \partial_t^2\phi / \nabla^2\phi$$

$$c_s(\omega) = \sqrt{\frac{2\left(\mu^2 + \omega^2\eta^2\right)}{\rho\left(\mu + \sqrt{\mu^2 + \omega^2\eta^2}\right)}} \qquad \text{(Voigt)}$$

$$\mu = storage, \quad \rho = density$$

$$\eta = loss, \quad \omega = 2\pi f$$

MRE of Normal Liver

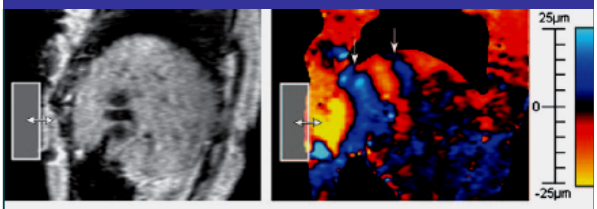


a. b.

Figure 6: MR elastographic wave images of a 21-year-old healthy volunteer (transcostal approach, 20-mm orthogonal plane). Rectangle indicates position of driver. Double-headed arrows indicate vibrational motion of driver. (a) Magnitude image. (b) Corresponding Zs phase-difference image shows shear waves (single-headed arrows) propagating in liver.

Ehman R. L. et al.

MRE of Cirrhotic Liver



a. b.

Figure 7: MR elastographic wave images of a 60-year-old patient (transcostal approach, 20° oblique plane). Rectangle indicates position of driver. Double-headed arrows indicate vibrational motion of driver. (a) Magnitude image. (b) Corresponding Zs phase-difference image shows shear waves (single-headed arrows) in liver. Wavelength is large, which indicates high liver stiffness. On the basis of wavelength measurements, mean liver stiffness was 19.2kPa Results of liver biopsy performed 4 months earlier showed cirrhosis.

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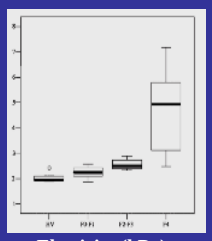
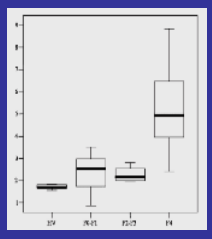
In Vivo Study by MRE



Elasticity (kPa)



Viscosity (Pa*s)

L. Huwart et al., Liver fibrosis: non-invasive assessment with MR elastography, NMR in Biomedicine, 19:173-179, 2006.

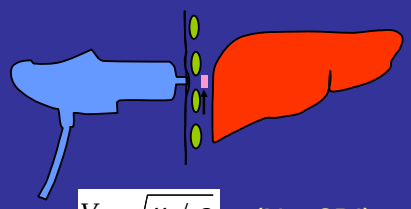
MR Elastography for Fibrosis Staging

- Slow (>20 minutes)
- Expensive
- Precise, accurate

Ultrasound Elastography for Fibrosis Staging

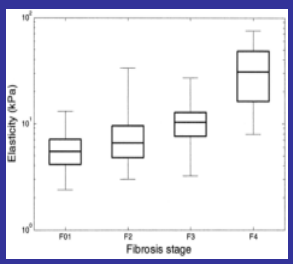
- Fibroscan™ (Echosens, Paris)
- Sonoelasticity
- Supersonic Imagine™
- Elastography
- ARFI
- SDUV

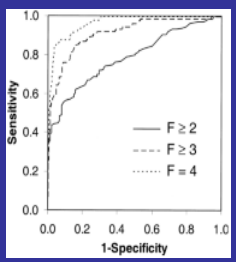
Ultrasound-based Fibroscan™



$V = \sqrt{\mu / \rho}$ (Not 2D!)

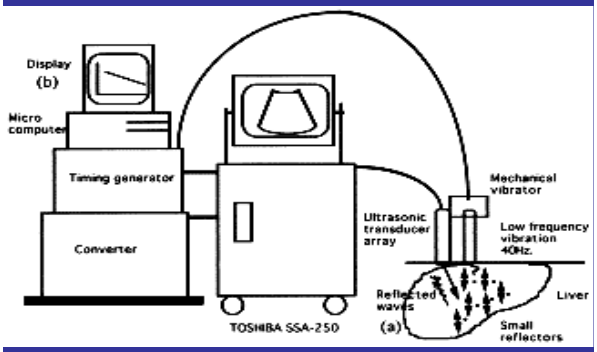
In Vivo Study by Fibroscan™



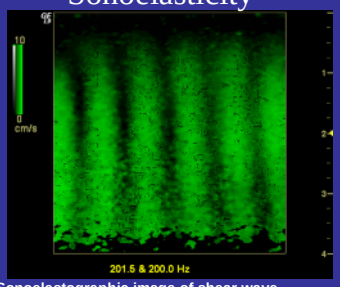


M. Ziol et al., Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C , Hepatology, 41:48-54, 2005.

Sonoelasticity



Sonoelasticity

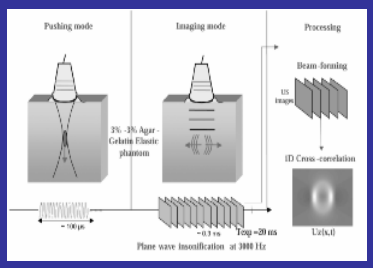


Sonoelastographic image of shear wave interference patterns induced in a tissue-mimicking phantom using externally applied mechanical vibration.

Robert M. Lerner, M.D. and Kevin J. Parker, Ph.D.

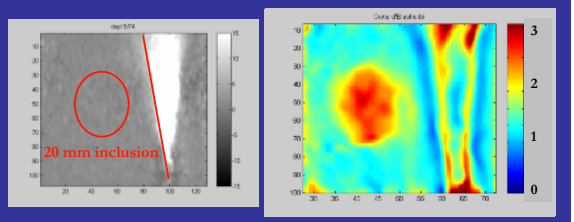
Images copyright University of Rochester

Supersonic Shear Imaging



Mathias Fink, University Paris VII, France

Inverse Problem in heterogeneous medium :Supersonic Imaging (SSI)



- Fink et. al.

Review So Far

- Tissue elasticity is widely seen as important in disease detection, and perhaps in diagnosis.
- Many methods are being developed including ultrasound methods.
- Ultrasound radiation stress is used to produce strain in tissue in several of these methods.

Goal of last half of presentation

- To present two methods of quantitative tissue elastic property measurement
- The first is Shearwave Dispersion Ultrasonic Vibrometry (SDUV)
- The second is Surrogate Model Accelerated Random Search

- John C. Brigham, W. Aquino, F. Mitri, J.F. Greenleaf, and M. Fatemi. Inverse Estimation of Viscoelastic Material Models for Solids Immersed in Fluids using Acoustic Emissions. Journal of Applied Physics 101, (2007).
- John C. Brigham and W. Aquino (2007) Surrogate Model Accelerated Random Search (SMARS) Algorithm for Optimization with Costly Objective Functions. Computer Methods in Applied Mechanics and Engineering, in review.

Significance of Ultrasound Radiation Force Method

- Stiffness measurement can be made using modern ultrasound system
- Simple modifications required
- Shear wave equation has local support under appropriate conditions
- Both storage and loss moduli can be measured.
- Noninvasive, simple, fast, accurate.

Approach

- Use ultrasound radiation pressure to provide stress in tissue
- Use ultrasound pulse echo methods to measure resulting strain
- Calculate elasticity and viscosity of tissue from stress/strain relationships through models
- Use methods that can be applied to modern ultrasound scanners as a software modification with little hardware modificaiton.

Quantitative Measurements of tissue properties

- Propagate harmonic or pulse shear wave from radiation force site on vessel wall or within tissue.
- Measure phase velocity dispersion of the freely propagating wave.
- Solve for complex shear modulus given relevant model [INVERSE PROBLEM].

Were does the radiation stress come from?

The first order acoustic wave equation

$$\partial_t^2 \Psi - c^2 \Delta \Psi = 0$$

$$\upsilon = \nabla \Psi$$

$\upsilon = Wavefield \quad velocity$

$\gamma = Specific \quad heat \quad ratio$

$c = Phase \quad velocity$

Allison Malcolm et al ASME, Chicago, 2006.

The acoustic wave equation to second order describes radiation pressure

$$\partial_t^2 \Psi - c^2 \Delta \Psi = \partial_t \left[|\nabla \Phi|^2 + \frac{\gamma - 1}{2c^2} (\partial_t \Phi)^2 \right]$$

$\upsilon = Wavefield \quad velocity$

$\gamma = Specific \quad heat \quad ratio$

$c = Phase \quad velocity$

$$\upsilon = \nabla \Phi + \nabla \Psi$$

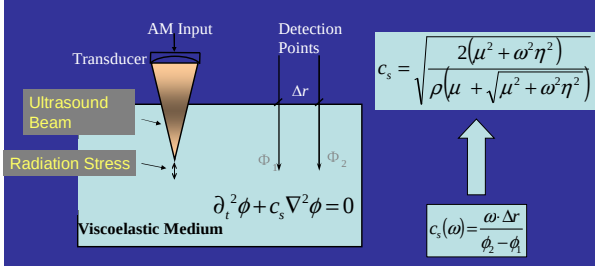
$$\Phi = \Phi_1 + \Phi_2$$

$$\sin u \sin v = \frac{1}{2}[\cos(u - v) - \cos(u + v)]$$

$$\sin^2 u = \frac{1 - \cos(2u)}{2}$$

Allison Malcolm et al ASME, Chicago, 2006.

Proposed Method (SDUV)



$$\partial_t^2 \phi + c_s \nabla^2 \phi = 0$$

$$c_s = \sqrt{\frac{2(\mu^2 + \omega^2 \eta^2)}{\rho(\mu + \sqrt{\mu^2 + \omega^2 \eta^2})}}$$

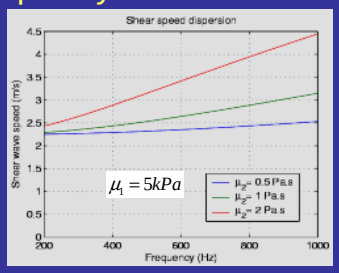
$$c_s(\omega) = \frac{\omega \cdot \Delta r}{\phi_2 - \phi_1}$$

Depends only on local μ and η (Voigt model)
Device independent (beam shape, Tx)
Independent of ultrasound intensity

Advantages of SDUV

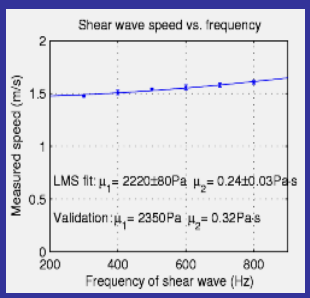
- Shearwave Dispersion Ultrasound Vibrometry –SDUV
- Truly quantitative
- Elasticity & viscosity
- Applicable to ascites patients
- "Virtual biopsy" can be guided by 2D B-scan

Shear Speed Varies with Frequency and with Viscosity

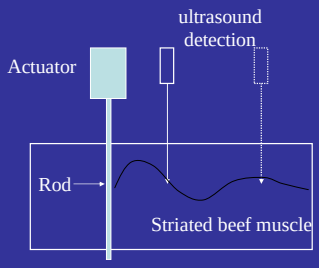


Therefore the viscosity must be measured to avoid bias.

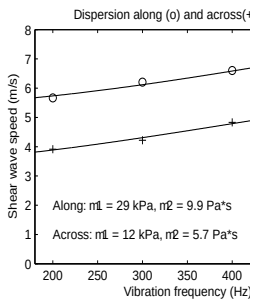
Test of Accuracy



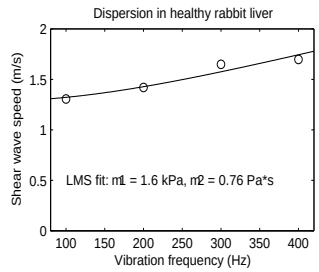
In Vitro Measurement in Beef



Results



Rabbit Liver Results



Review

- Linear viscoelastic tissues are characterized by a Green function.
- The use of a model allows fitting for viscous and elastic terms.
- Vibrometry allows the shear wave equation to be used to calculate shear wave speed and dispersion.
- Voigt model provides fit to speed dispersion for viscous and elastic moduli.

Can we make quantitative measurements of moduli in vessels?

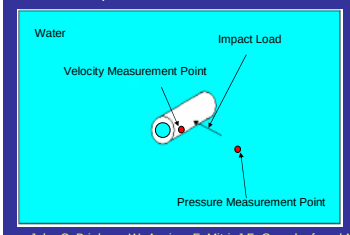
- Very complex (smaller than the shear wavelength)
- Excite modes of vibration in vessels.
- Measure response to force
- Estimate material properties given appropriate model using a forward/inverse FEM feedback approach (SMARS)

The Surrogate-Model Accelerated Random Search (SMARS) Algorithm

- Combines random search algorithm with surrogate model method of optimization
  - Random Search: Stochastic Global Search
  - Surrogate-Model: Efficient Local Search
- Locate global solutions with limited function evaluations
- General applicability and ease of implementation
- Easy parallelization

Simulated Experiment (forward problem)

Vessel
Outside Diameter=5mm
Thickness=1mm
Length=10cm
5kHz Impact



Constitutive Behavior (Orthotropic Shell)

$$\begin{Bmatrix} \sigma_C(t) \\ \sigma_L(t) \\ \sigma_S(t) \end{Bmatrix} = \begin{bmatrix} Q_{11} & Q_{12} & 0 \\ Q_{21} & Q_{22} & 0 \\ 0 & 0 & Q_{33} \end{bmatrix} \begin{Bmatrix} \varepsilon_C(t) \\ \varepsilon_L(t) \\ 2\varepsilon_S(t) \end{Bmatrix}$$

$$Q_{11} = \frac{E_C}{1-\nu_{CL}\nu_{CL}}, Q_{12} = Q_{21} = \frac{\nu_{LC}E_C}{1-\nu_{LC}\nu_{CL}},$$

$$Q_{22} = \frac{E_L}{1-\nu_{CL}\nu_{LC}}, Q_{33} = G$$

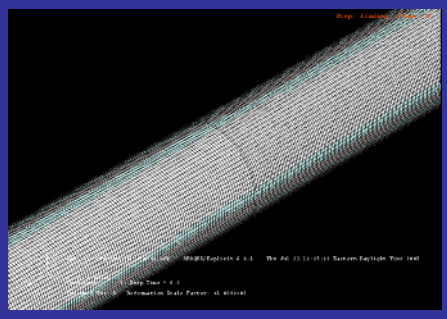
$E_C \equiv$ Circumferential Elastic Modulus

$E_L \equiv$ Longitudinal Elastic Modulus

$G \equiv$ In-Plane Shear Modulus

- John C. Brigham, W. Aquino, F. Mitri, J.F. Greenleaf, and M. Fatemi. Inverse Estimation of Viscoelastic Material Models for Solids Immersed in Fluids using Acoustic Emissions. Journal of Applied Physics 101, (2007).

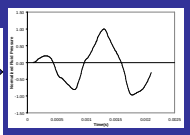
Forward Solution with FEM



Inverse Problem Formulation

Given $\left| p^{\exp}\left(\vec{x}_j, t\right) \right| \; j = 1, 2, \ldots, n$

(Measured acoustic pressure in time at n points in the fluid)



Let $\vec{\alpha} \in \mathbb{R}^m$ be a vector of material parameters such as elasticity, viscosity, etc.

Define an error functional as

$$E(\vec{\alpha}) = \left(\int_{t_1}^{t_2} \sum_{j=1}^{n} \left[\left| p^{\exp}\left(\vec{x}_j, t\right) \right| - p^{FE}\left(\vec{x}_j, t, \vec{\alpha}\right) \right]^2 d\omega \right)^{\frac{1}{2}}$$

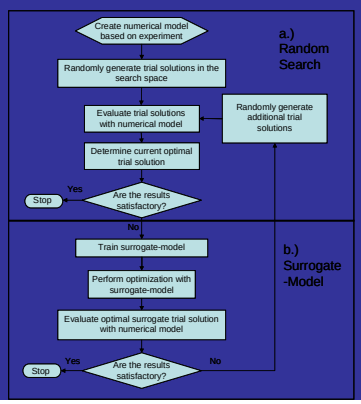
Then, solve this optimization problem.

$$\underset{\vec{\alpha} \in \mathbb{R}^m}{\text{minimize}} \left\{ E(\vec{\alpha}) \right\}$$

- Global search capabilities
- Unaffected by non-convex error surface
- Tolerant to noise and imprecision in experimental data
- Minimize calculations of expensive numerical analysis

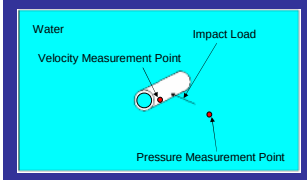
- John C. Brigham, W. Aquino, F. Mitri, J.F. Greenleaf, and M. Fatemi. Inverse Estimation of Viscoelastic Material Models for Solids Immersed in Fluids using Acoustic Emissions. Journal of Applied Physics 101, (2007).

The SMARS Algorithm



Sensitivity Experiment and Inverse Solution

Vessel
Outside Diameter=5mm
Thickness=1mm
Length=10cm
5kHz Impact



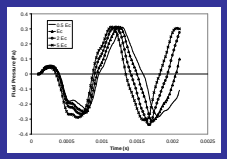
Constitutive Behavior (Orthotropic Shell)

$$\begin{Bmatrix}\sigma_C(t)\\ \sigma_L(t)\\ \sigma_S(t)\end{Bmatrix} = \begin{bmatrix}\frac{E_C^2}{E_C - E_L\nu_{CL}^2} & \frac{E_C E_L \nu_{CL}}{E_C - E_L\nu_{CL}^2} & 0\\ \frac{E_C E_L \nu_{CL}}{E_C - E_L\nu_{CL}^2} & \frac{E_C E_L}{E_C - E_L\nu_{CL}^2} & 0\\ 0 & 0 & 2G\end{bmatrix}\begin{Bmatrix}\varepsilon_C(t)\\ \varepsilon_L(t)\\ \varepsilon_S(t)\end{Bmatrix}$$

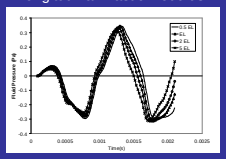
E_C = Circumferential Elastic Modulus
E_L = Longitudinal Elastic Modulus
G = In-Plane Shear Modulus
ν_{CL} = Orthotropic Poisson's Ratio

Acoustic Pressure Sensitivity Response

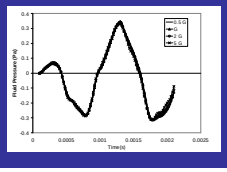
Circumferential Elastic Modulus



Longitudinal Elastic Modulus



In-Plane Shear Modulus

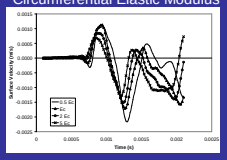


Inverse solution

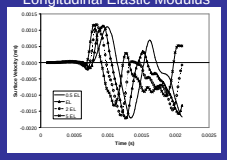
	E_C (Pa)	E_L (Pa)
Target	$5.45\text{x}10^6$	$1.09\text{x}10^6$
Mean	$5.50\text{x}10^6$	$1.16\text{x}10^6$
Std Dev	$4.88\text{x}10^5$	$3.43\text{x}10^5$

Vessel Surface Velocity Sensitivity Response

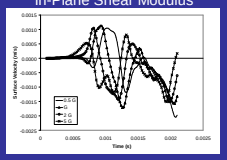
Circumferential Elastic Modulus



Longitudinal Elastic Modulus



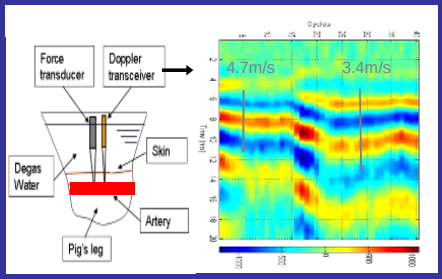
In-Plane Shear Modulus



Inverse solution

	E_C (Pa)	E_L (Pa)	G(Pa)
Target	$5.45\text{x}10^6$	$1.09\text{x}10^6$	$3.78\text{x}10^5$
Mean	$4.85\text{x}10^6$	$1.07\text{x}10^6$	$3.94\text{x}10^5$
Std Dev	$4.94\text{x}10^4$	$2.86\text{x}10^3$	$1.34\text{x}10^3$

Effect of nitroglycerine on pulse wave speed in pig femoral artery



Review 1

- Radiation Stress comes from the second order terms of the wave equation for acoustic waves.
- Motion within tissue can be produced at a remote location with radiation force by focusing ultrasound at that location.
- Harmonic motion produced by AM modulated ultrasound can induce a shear wave in the tissue.
- The shear wave has local support, so measurement of the wave speed and dispersion gives the storage and loss moduli of the tissue.

Review 2

- Radiation force can be used to induce motion in complex structures such as vessels.
- Complexities such as anisotropy, and inhomogeneity may require FEM or other modeling in an iterative loop to solve for material properties of complex structures from their response to radiation stress.

Conclusions

- SDUV obtains quantitative measurements of elastic and viscous shear moduli in isotropic homogeneous tissues, tested *in vitro* not yet *in vivo*.
- SMARS obtains quantitative measurements in anisotropic, elastic shells, so far only tested in fluid and in simulation.

Acknowledgements

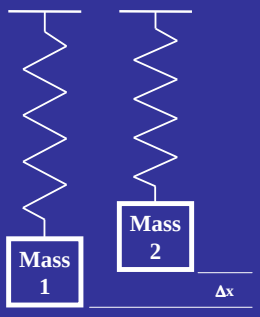
- National Institute of Biomedical Imaging and Bioengineering grants EB2167 and EB2640.
- Randy Kinnick, experiments
- Cristina Pislaru MD, animal experiments
- Dr Chen, Zheng, and Greenleaf have patents and patents pending on some of these approaches.

Mayo Ultrasound Laboratory 2/07

Thank You

Elasticity Theory in 1-D

-Hooke's Law



$$\Delta F = k\,\Delta x$$

Spring Constant k

Tim Hall

Liver Elastography with Ultrasound

Real-Time Elastography for Noninvasive Assessment of Liver Fibrosis in Chronic Viral Hepatitis

Mireen Friedrich-Rust[1]
Mei-Fang Ong[1]
Eva Herrmann[1]
Volker Dries[2]
Panagiotis Samaras[1]
Stefan Zeuzem[1]
Christoph Sarrazin[1]

AJR:188, March 2007

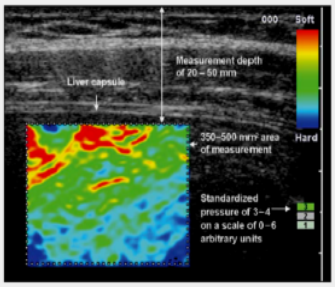


Fig. 1—Tissue elasticity distribution represented as color-coded images over conventional B-mode image. Image presents example of 34-year-old healthy female subject.

Elastography Measurements of Liver Stiffness in Humans

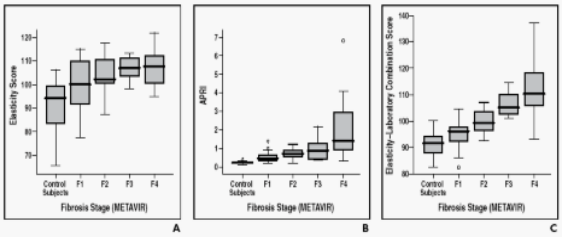


Fig. 2—Box plots show correlation between noninvasive tests and histologic results from liver biopsy. Top and bottom of boxes represent first and third quartiles, respectively. Length of box represents interquartile range within which 50% of values are located. Thick line through each box represents median. Error bars mark minimum and maximum values (range). Small circles represent outliers.
A, Real-time elastography. Skewed data for control subjects might be explained by inhomogeneous group of patients, whereas skewed data for fibrosis stage F2 can be explained by small number of patients in this group.
B, Aspartate transaminase–to–platelet ratio index (APRI). Skewed data are equalized when using log scale for APRI score.
C, Elasticity–laboratory combination values for each fibrosis stage.

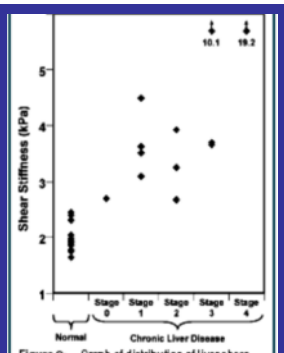


Figure 8: Graph of distribution of liver shear stiffness in 12 healthy volunteers and 12 patients with chronic liver disease and varying degrees of liver fibrosis proved with biopsy results.

Olivier Rouvière, Meng Yin, M. Alex Dresner, Phillip J. Rossman, Lawrence J. Burgart, Jeff L. Fidler, and Richard L. Ehman
MR Elastography of the Liver: Preliminary Results
Radiology 2006; 240: 440-448.

Can we do this in complex tissue?

- Homogeneous, isotropic liver is one thing but vessels are much more complicated.
- Need to confine excitation to only specific modes and then solve simplified model.
- Can we use FEM to help?