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
Let's stop and look at fundamental linear viscoelastic mechanics

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

Primer on stiffness

\[ \text{Stress} = \sigma = \frac{\text{force}}{\text{unit area}} \]

\[ \text{Strain} = \varepsilon = \frac{L_1 - L_2}{L_1} \]

Modulus \( E = \frac{\sigma}{\varepsilon} \) (force/area)

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Relaxation and Creep (linear, viscoelastic, homogeneous)

Relaxation, \( \Psi \)  
\[ \varepsilon(t) = \int_{-\infty}^{t} \Phi(\tau) \dot{\varepsilon}(\tau) d\tau, \quad \sigma(t) = \int_{-\infty}^{t} \Psi(t - \tau) \dot{\sigma}(\tau) d\tau. \]

\( \dot{\varepsilon}(t) = \text{Strain}, \quad \dot{\sigma}(t) = \text{Stress}, \quad \Phi(t), \Psi(t) = \text{Green functions} \)

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

\[ \Phi(\omega) = -\frac{1}{\omega^2}, \quad \Psi(\omega) = 0 \]

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Creep Compliance \( \Phi \), and Relaxation Function \( \Psi \)

T. Taniguchi, \( ^1 \) and Y. Kashiwagi, \( ^2 \)

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Models for linear viscoelastic materials

(a) Maxwell body

(b) Voigt body

(c) Standard linear body

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

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Green’s function</th>
<th>Fourier transform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxwell</td>
<td>( f(t) = \frac{1}{2\mu} t )</td>
<td>( \phi(\omega) = \frac{1}{2\mu \omega} )</td>
</tr>
<tr>
<td>Voigt</td>
<td>( f(t) = \frac{1}{2\mu} (1 - \frac{t}{\tau}) )</td>
<td>( \phi(\omega) = \frac{2\mu}{\lambda^2} )</td>
</tr>
<tr>
<td>Standard linear</td>
<td>( f(t) = \frac{1}{2\mu} \left( 1 - \frac{t}{\tau} - e^{-\frac{t}{\tau}} \right) )</td>
<td>( \phi(\omega) = \frac{2\mu(1 - \frac{\tau}{\lambda})}{\lambda^2} )</td>
</tr>
</tbody>
</table>

Note: 1) \( \theta(t) \) is the step function, and \( f(t) \) is the force function. 2) \( \tau = \frac{\lambda^2}{\mu^2} + \frac{\mu}{\lambda} \). 3) The expressions of \( f(t) \) and \( \phi(\omega) \) are true for \( t > 0 \). \( f(t) \) and \( \phi(\omega) \) should be zero for \( t < 0 \). See eq. (2).
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.

Wave equation
\[ \partial_t^2 \phi - c_s^2 \nabla^2 \phi = 0 \]

\[ c_s^2 = \frac{\partial_t^2 \phi}{\nabla^2 \phi} \]

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

\[ \mu = \text{storage}, \quad \rho = \text{density} \]
\[ \eta = \text{loss}, \quad \omega = 2\pi \]

In Vivo Study by MRE

Ehman R. L. et al.

MR Elastography for Fibrosis Staging

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

Ehman R. L. et al.
Ultrasound Elastography for Fibrosis Staging

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

In Vivo Study by Fibroscan™


Ultrasound-based Fibroscan™

\[ v = \sqrt{\frac{\mu}{\rho}} \] (Not 2D!)

Sonoelastography

Display (b)
Microcomposites
Timing generator
Converter
Toshiba SSA-210
Ultrasonic transducer array
Mechanical vibrator
Small reflectors
Liver
So no elastographic 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.

Sonoeasticity

Supersonic Shear Imaging

Mathias Fink, University Paris VII, France

Inverse Problem in heterogeneous medium
Supersonic Imaging (SSI)

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

**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 modification.

**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].

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Where does the radiation stress come from?

The first order acoustic wave equation

\[ \partial_t^2 \Psi - c^2 \Delta \Psi = 0 \]

\[ \nu = \nabla \Psi \]
\[ \nu = \text{Wavefield velocity} \]
\[ \gamma = \text{Specific heat ratio} \]
\[ c = \text{Phase velocity} \]


The acoustic wave equation to second order describes radiation pressure

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

\( \nu = \text{Wavefield velocity} \quad \nu = \nabla \Phi + \nabla \Psi \)
\( \gamma = \text{Specific heat ratio} \quad \Phi = \Phi_1 + \Phi_2 \)
\( c = \text{Phase velocity} \quad \sin \alpha \sin \nu = \frac{1}{2} \left[ \cos (\mu - \nu) - \cos (\mu + \nu) \right] \]
\( \sin^2 \mu = \frac{1 - \cos (2\alpha)}{2} \)


Proposed Method (SDUV)

- Device independent (beam shape, Tx)
- Depends only on local \( \mu \) and \( \eta \) (Voigt model)
- Independent of ultrasound intensity

\[ c_i = \frac{2(\nu^2 + \sigma^2 \eta^2)}{\rho (\mu \pm \sqrt{\mu^2 + \sigma^2 \eta^2})} \]
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

**Dispersion along (a) and across (b)**

- **Along:** $m_1 = 29$ kPa, $m_2 = 9.9$ Pa*s
- **Across:** $m_1 = 12$ kPa, $m_2 = 5.7$ Pa*s

Vibration frequency (Hz)

Shear wave speed (m/s)

Rabbit Liver Results

**Dispersion in healthy rabbit liver**

- **LMS fit:** $m_1 = 1.6$ kPa, $m_2 = 0.76$ Pa*s

Vibration frequency (Hz)

Shear wave speed (m/s)

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
- Water
- Pressure Measurement Point
- Impact Load
- Velocity Measurement Point
- Constitutive Behavior
  - (Orthotropic Shell)
  - Circumferential Elastic Modulus
  - Longitudinal Elastic Modulus
  - Shear Modulus

Forward Solution with FEM

- Given $\{p(x,t)\}_{i=1,2,...,n}$
  - Measured acoustic pressure in fluids at points in the fluid
- Let $M$ be a matrix of material parameters such as elasticity, viscosity, etc.
- Define an error functional as
  $$ E(\hat{\alpha}) = \left( \sum_{i=1}^{n} \left[ p_i^m(\hat{\alpha}) - p_i(x,t) \right] \right)^2 $$
- Then, solve this optimization problem.
  $$ \text{minimize} \left[ E(\hat{\alpha}) \right] $$

Inverse Problem Formulation

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

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The SMARS Algorithm

1. Start
2. Random Search
   - Randomly generate test solutions
   - Evaluate solutions with numerical model
   - Determine if current solution is optimal
3. Surrogate Model
   - Randomly generate additional test solutions
   - Evaluate additional test solutions
   - Determine if current solution is optimal
4. Yes
5. Stop
6. No
7. Randomly generate additional test solutions
8. Evaluate additional test solutions
9. Determine if current solution is optimal
10. Yes
11. Stop
12. No

Sensitivity Experiment and Inverse Solution

Vessel
- Diameter: 50mm
- Thickness: 1mm
- Length: 10cm
- 5kHz Impact

Constitutive Behavior (Orthotropic Shell)

<table>
<thead>
<tr>
<th>E_c</th>
<th>E_L</th>
<th>ν_c</th>
<th>ν_L</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.85x10^6</td>
<td>1.16x10^6</td>
<td>3.94x10^5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Acoustic Pressure Sensitivity Response

Circumferential Elastic Modulus
Longitudinal Elastic Modulus
In-Plane Shear Modulus

In-Plane Shear Modulus

Vessel Surface Velocity Sensitivity Response

Circumferential Elastic Modulus
Longitudinal Elastic Modulus
In-Plane Shear Modulus

In-Plane Shear Modulus
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.
Liver Elastography with Ultrasound

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

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?