The Institute of Cancer Research

Progress in quantitative elastography for cancer medicine

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Apologies for any omissions!
Palpation, an ancient diagnostic technique

- Hippocrates: for battle injuries, if the bone is not visible palpate to locate weapon mark, determine whether bone is denuded of flesh and, for head injuries, whether the cranium underneath is strong or weak.

- Egypt ~1900BC: palpation mentioned in the Edwin Smith Papyrus.

- Still valuable, both by doctors and in “self examination” techniques

- Limited to a few accessible tissues and organs

- Interpretation of information is highly subjective
Ultrasound elastography

- Mechanical "palpation" images that are related to a broad range of tissue viscoelastic parameters, obtained by processing time-varying echo data to extract the spatial and temporal variation of a stress-induced tissue displacement or strain.

- Principle of (most current) Elastography: Consider only the stiffness according to Hook’s law, and use ultrasound to image the tissue strain that results from an externally applied stress. Ignore what happens to the internal stress.

- Related to work that dates back to the 1970s in France and Belgium.
Methods for ultrasound elastography

Method of applying stress:
- static / dynamic source, step / vibrational / impulse, transducer displacement / separate source / acoustic radiation force, shear / compressional source, applied displacement / force, constrained mechanical / hand-induced motion, large displacement / small / incremental
- surface loading / deep loading (radiation force)

Signal measurement:
- displacement / strain / other
- Doppler / speckle decorrelation / speckle tracking / RF tracking / texture change / frequency shifting (plus hybrids, spatial / frequency domain implementation of tracking)
- Other variables: tracking interpolation techniques, 1D / 2D / 3D data, displacement vector components, steered beams, decorrelation minimisation or correction methods, strain estimators

Strain Imaging

- Image a region of interest by conventional ultrasound => “undeformed image”
- Gently press on the skin surface and image again => “deformed image”
- Compare structures in the two (RF) images => displacement image
- Calculate the difference in displacement from one axial position to the next => axial strain image, or “elastogram” (Ophir et al, 1991)
Ultrasound echo tracking

Before compression

RF echo voltage

After compression

RF echo voltage

$x_1 = 5\,\text{cm}$

$y_1$

$x_2 = 7\,\text{cm}$

$y_2$

$x_3 = 9\,\text{cm}$

$y_3$

Time / axial distance (x) ➔

Adapted from J Civale, PhD thesis, University of London, 2007
Real-time freehand strain imaging

- Systems from various companies:
  - Hitachi, Siemens, Medison, Ultrasonix, Toshiba, Zonare

- Various real-time algorithms:
  - Zero phase root seeking
  - Combined RF + envelope autocorrelation
  - 2-D correlation tracking
  - Doppler (TD strain rate imaging)

- Promising results from trials in test clinics around the world
Typical elastographic (left) and echographic (right) appearance of a malignant breast tumour
Methods for assessing tissue elasticity

- Manual palpation
- Visual relative motion assessment during a dynamic ultrasound examination
- Measurement/imaging of displacement, strain, etc.
- Quantitative reconstruction of mechanical characteristics

Increasing system complexity but decreasing complexity of image interpretation.
Freehand strain images (elastograms) of a stiff spherical inclusion
Contrast and diameter required for visual detection of elastic lesions

Young’s Modulus contrast threshold

Lesion size (speckle area^{1/2})

Visual relative motion assessment

Axial strain imaging

Quantitative elastography

- Absolute values of mechanical characteristics
  - Improved differential diagnosis, i.e. tissue characterisation (where have we heard this before?).
  - Ability to pool data in multi-centre studies.
  - Early assessment of onset of various conditions, monitoring of response to treatment.
  - Potential for thermal dosimetry.

- Reliable relative values may be sufficient for some applications, where there is a calibration control.

- “Cleaning up” elastograms: a by-product of having to account for boundary conditions.

- Improve contrast resolution by separating variables.
Quantitative elastography: potential / challenges

- Quantity imaged / measured:
  - Young’s modulus
  - Non-linearity
  - Viscosity
  - Hysteresis
  - Anisotropy
  - Poisson’s ratio
  - Porosity and permeability
  - Mechanical discontinuities / low friction boundaries

- Current approach: to study, experimentally and theoretically, the relative importance of a number of mechanical characteristics in a variety of situations.
Use of a calibrated elastic stand-off

**Interests:**
- Potential for an objective non-invasive imaging method for assessing and monitoring the severity and treatment of breast fibrosis?
- Quantitative diffuse tissue stiffness measurements using freehand ultrasound strain imaging?

Compliant, gelatine or PVA gel pad of measured elastic modulus, loaded with acoustic scatterers \(\rightarrow\) measure of applied stress profile at tissue surface.

First-order correction to strain image data for non-uniform stress fields, by a column-wise reference to the strain in the overlying region of the standoff, defined with the aid of registered B-mode images.

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Trans-abdominal strain ratios for liver fibrosis

Sufficient standardisation possible for useful combination with aspartate transaminase–to–platelet ratio index

Source: Friedrich-Rust M et al. AJR, 188:758, 2008
Quantitative stiffness imaging

Forward problem

Inverse problem

Strain Image

Stiffness Image

Simple iterative reconstruction

\[ E(x, y, z) = E^n(x, y, z) \]

\[ \phi(E) = \| U(E) - b \|^2 \]

\[ E_{n+1} = E_n + E_{\text{new}} \]

Single lesion reconstruction

Strain image

Relative Young’s modulus image

Relative reconstruction of phantom containing 3 lesions

Sonogram

Strain image

Relative Young’s modulus image
**Imaging ionising radiation dose**

- **The need:** to measure absorbed dose distributions in 3D
  - verify complex 3D treatment plans (conformal radiotherapy)
  - study effects of motion, and of motion correction strategies

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**Graph:**

- **Elastic modulus [kPa]:**
  - Batch 1
  - Batch 2
  - Batch 3
  - Batch 4

**Dose [Gy]:**

- **Relative dose:** MRI
  - (slippery top and bottom)
- **EI**
  - (slippery top and sticky bottom)

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Other approaches to Young’s/shear modulus determination
MR elastography

- Fully 3D
- Quantitative
- Registered with MR images
- Vibration frequency variable (study viscous effects)
- Directionally sensitive (study anisotropy)
- Many research groups
- Commercial versions
- All the practical cost, availability, slow acquisition, and convenience disadvantages of MR

Image of breast phantom showing standing wave pattern for 100 KHz vibrations

Image reconstruction from data on the left, showing shear stiffness in kPa.

$$c_s = \sqrt{\frac{E}{3\rho}}$$

Ultrasound to measure shear wave speed

CW shear excitation, either with 2 interfering sources to generate “crawling waves”, or with a single source and an oscillating ultrasound probe (as below) to stroboscopically sample the shear propagation.

\[ c_s = \sqrt{\frac{E}{3\rho}} \]

K. Parker et al. University of Rochester
Modulus imaging by travelling shear wave inversion – tissue surface impulse excitation

Localised transient displacement from a focused radiation force impulse

**Force applied for duration of 1 ms**

**Displacement distribution after 3 ms**
System from “Supersonic Imagine”
Liver:
Showing shear speed dispersion due to viscosity

Muller M et al. UMB;35:219, 2009
Other elasticity parameters under study
Tissue porosity and permeability

- Soft tissues contain free fluid in the interstitium and microvasculature, which flows when the tissue is compressed →
  - soft tissue is poroelastic (e.g. brain, cartilage, malignant tumours, oedematous tissues)

- Disease changes fluid properties in tissue (oedema, hydrocephalus, cancer)

- Permeability is important for drug access to cells

- Use of poroelastic theory to interpret strain images obtained using elastographic techniques:
  - New information
  - Prevent misinterpretations caused by applying traditional linear elastic assumptions
Poro-elastic Materials

- Two-phase poroelastic material:
  - solid phase or “matrix” (porous, permeable, elastic)
  - liquid phase (incompressible)

For example:

Adapted from
Gibson & Ashby (2002)
Relevance to Elastography

When compressed, the solid matrix deforms and the pore fluid flows. Mechanical behaviour described by Biot (1941):

\[ \nabla^2 \varepsilon = \frac{1}{H_A k} \frac{\partial \varepsilon}{\partial t} \]

where \( \varepsilon \) = volumetric strain
\( H_A = \) aggregate elastic modulus
\( k = \) permeability
\( t = \) time

Thus, compression-induced fluid flow causes a time-dependent spatially-varying strain similar to heat conduction

Since strain is directly affected by fluid flow:
- Fluid flow could influence elastograms
- Strain imaging could be used to detect compression-induced fluid flow.
Elastography of a porous cylinder

Soya-bean gel (tofu)

- Elastographic techniques can be used to image the slow fluid flow that is due to a sustained compression – including the direction of flow
- Imaging of quantities related to modulus, permeability and Poisson’s ratio by fitting to the spatio-temporal dependence of volumetric strain

Parametric Images for porous media

Product of Young’s modulus and permeability

\( H_k \times 10^{-7} \text{ Pa m}^4 \text{ N}^{-1} \text{ s}^{-1} \)

\[ 1.15(\pm 0.21) \times 10^{-7} \text{ m}^2 \text{s}^{-1} \]

Poisson’s ratio

\[ \nu \]

\[ 0.095(\pm 0.0251) \]

Lymphoedema Trial

B-mode
‘traditional’ elastography
end-of-ramp

changes during sustained compression

-15% -10% -5% 0%

50s 150s 275s 400s

-10% 0% 10% 20%

Need for volumetric strain - example

Finite element model

(Finite element model)

Axial strain (first 7 s)

Volumetric strain (first 7 s)
Modelling inhomogeneous and multi-compartmental poroelastic tissue

- Generalised theory to included a vascular compartment, and allow fluid exchange between the interstitium and the local microvasculature, i.e. now have $E_s$, $\nu_s$, $k$ and $\chi$ (microvascular filtration coefficient).

- Inclusion of simulated tumours - higher than normal values of $E_s$, $k$ and $\chi$ (from the high density and leaky walls of microvessels associated with angiogenesis).

- Results suggest: (a) fluid drainage into local microvasculature should be the dominant flow-related stress/strain relaxation mechanism, (b) strain relaxation should be on the order of 5–10 s, (c) should be measurable by elastography.

Surface tensile strain for skin and subcutis

Fixed foot
Motor driven
RF data acquisition
Computer for processing

Tensile Strain Images

Echo Image:

- Strain propagates through to the fat layer
- Slip boundary properties may be used for diagnosis

Anisotropy (in normal skin)

Conclusion

- Considerable opportunity to extract new and quantitative information on tissue characteristics – promising opportunities for inverse problem solving
- Ongoing work - 3D measurement of displacement/strain for quantification of mechanical properties

Images courtesy of J. Lindop, G.Treece and A.Gee, University of Cambridge