Elastography Phantoms Based on Hydrogels from Agar, Gelatin and Their Mixtures

Timothy J Hall
Medical Physics Department
University of Wisconsin

2012.Aug.6
QIBA Ultrasound

Outline

- What are Agar and Gelatin
  - Basis for many commercial ultrasound phantoms
- Compressional wave properties
- Multi-modality properties
- Visco-elastic properties
  - Elastic properties
  - Viscous loss properties
  - Temporal stability
    - Long-term storage
  - Reproducibility

Hydrogels for Ultrasound Phantoms

- Agar (aka agar-agar)
  - A gelatinous derivative from red algae
    - Mostly a linear polysaccharide agarose
    - Also a mixture of small molecules (agaropectin)
  - Melts at 85°C; congeals at 32-40°C
- Gelatin
  - Derived from collagen
    - Generally boiling and drying animal hides
  - Commonly used in foods
    - Jello, marshmallows, some yogurt, jellybeans, etc.
  - Melting and congealing temperatures depends on molecular length
    - Below 37°C without additives

Hydrogels for Ultrasound Phantoms

- There is a long history demonstrating utility of agar- and gelatin-based hydrogels in ultrasound phantoms
  - Medical Physics 5(5):391-394, 1978
  - IEEE Trans Nuc Sci NS-27(3): 1176-1182, 1980
  - Radiology 134:517-520, 1980
  - Medical Physics 7(1): 43-50, 1980
  - Medical Physics 9(5): 703-710, 1982
  - Ultrasound Med Biol 8(3): 277-287, 1982
  - Ultrasound Med Biol 8(4): 381-392, 1982
  - J Clin Ultrasound 10(3): 91-100, 1982
  - Medical Physics 9(6): 848-855, 1982
  - Ultrasonic Imaging 6(3): 342-347, 1984
  - Medical Physics 17(3): 380-390, 1990
  - Ultrasound Med Biol 25(5): 831-838, 1999
  - Many more…

Hydrogels for Ultrasound Phantoms

- These materials can be manufactured to have a wide range of acoustic properties
- Nearly independent control over attenuation, sound speed, scattering properties
  - Attenuation:
    - Magnitude ~0.1—1.5dB/cm-MHz
    - Frequency dependence $f^1 - f^{1.5}$
  - Sound speed ~1450—1700m/s
  - B/A (mimic the range of soft tissues)
  - Scattering properties: "you name it"

Hydrogels for Ultrasound Phantoms

- Specifically, there is even a paper that reports the use of these materials to mimic the acoustic properties of liver
  - Medical Physics 9(5): 703-710, 1982
- For elasticity imaging applications, this level of mimicking likely isn't necessary

Hydrogels for Ultrasound Phantoms

- These materials can also be used for multi-modality phantoms
  - X-ray
    - Radiology 142(30):755 -757, 1982
  - Microwave
    - Phys Med Biol 50(18): 4245-4258, 2005
  - MRI
    - Medical Physics 12(4): 516-516, 1985
    - Medical Physics 25(7): 1145-1156, 1998
    - Neurosurg 45(6): 1423-1429, 1999

Hydrogels for Ultrasound Phantoms

- We have LOTS of experience with these materials. We know:
  - Agar doesn't bond to agar
  - Agar doesn't bond to gelatin
  - Gelatin DOES bond to gelatin
    - Its basically animal hide glue (which bonds to itself)!

Hydrogels for Ultrasound Phantoms

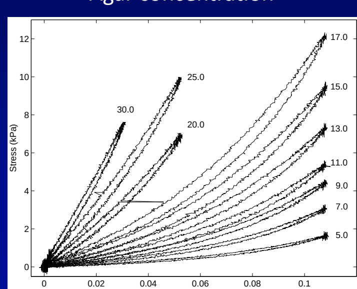
- We have LOTS of experience with these materials. We know:
  - Young's modulus is proportional to (roughly) the square of the gel concentration
  - For 0-30% strain, stress-strain is linear in gelatin and nonlinear in agar

IEEE UFFC 44(6): 1355-1365, 1997
Phys Med Biol 55: 2679-2692, 2010

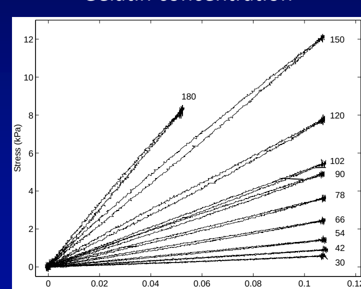
Hydrogels for Ultrasound Phantoms

- Without additives, gelatin and agar are nearly completely elastic (little viscous loss) at low frequencies (below 100Hz)

Agar concentration



Gelatin concentration



IEEE UFFC 44(6): 1355-1365, 1997
Phys Med Biol 55: 2679-2692, 2010

Hydrogels for Ultrasound Phantoms

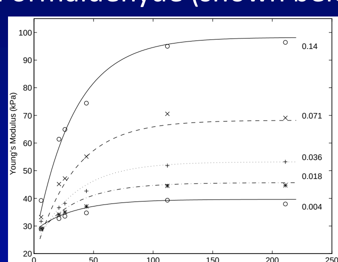
- With additives (i.e., formaldehyde, paraldehyde, glutaraldehyde) the melting point of gelatin is raised well above 50^{o}C

- These additives also provide one of many mechanisms for controlling the modulus of the gel

IEEE UFFC 44(6): 1355-1365, 1997

Hydrogels for Ultrasound Phantoms

- Addition of formaldehyde, paraldehyde, glutaraldehyde also accelerates the congealing process
  – Formaldehyde (shown below) being the slowest



Young's modulus of 90g/L 275 Bloom gelatin with different formaldehyde concentrations

Stiffness v. time is predictable

IEEE UFFC 44(6): 1355-1365, 1997

Hydrogels for Ultrasound Phantoms

- Simple materials have been shown to be highly reproducible
  - About 5% standard deviation in elastic moduli among sets of 5 samples manufactured independently

IEEE UFFC 44(6): 1355-1365, 1997

Hydrogels for Ultrasound Phantoms

- Mixtures of agar and gelatin have nonlinear elastic properties and components bond to each other
  - Gelatin in the mixture bonds to gelatin of the other component part (targets in a background)

Phys Med Biol 55:2679-2692, 2010
Phys Med Biol 57(15):4787-4804, 2012

Hydrogels for Ultrasound Phantoms

- Dispersions of oil droplets in agar, gelatin or agar-gelatin mixtures
  - Lower elastic modulus
  - Lower sound speed
  - Mimic fatty tissues

Ultrasonic Imaging 25: 17-38, 2003
Ultrasound Med Biol 32(2): 261-270, 2006
Ultrasound Med Biol 32(6): 857-874, 2006
Phys Med Biol 55:2679-2692, 2010
Phys Med Biol 57(15):4787-4804, 2012

Hydrogels for Ultrasound Phantoms

- Acoustic and elastic properties of these materials are (macroscopically) uniform throughout
  - To the extent that we've been able to measure them
    - Expect wave propagation phenomena to change within a wavelength of a boundary!

Hydrogels for Ultrasound Phantoms

- Elastic properties of composite phantoms are predictable based on the independently measured elastic properties of component materials
  – Contrast in strain images is predictable within about 2dB for hyperelastic deformations of nonlinear elastic media

Phys Med Biol 57(15):4787-4804, 2012

Hydrogels for Ultrasound Phantoms

- All the materials described so far in this presentation are essentially lossless
  – Nearly completely elastic
  – Nondispersive

- Many tissues (including liver) exhibit viscous loss

Modeling Complex Mechanics

The complex shear wave number k:

$k = (2\pi f)(\rho_o/G)^{1/2} = 2\pi f/c_s - i\alpha$

$G \equiv$ complex shear modulus at frequency f
$G \equiv G' + iG''$

-- $G' \equiv$ shear storage modulus
-- $G'' \equiv$ shear loss modulus

$\rho_o \equiv$ mass density

c_s = shear wave speed (frequency dependent)

α = shear wave attenuation constant

Complex Mechanics in Soft Tissues

- loss factor $\equiv \tan\delta \equiv G''/G'$
  - where δ is the angle by which displacement lags shear force
- G'' and $\tan\delta$ can be substantial in soft tissues:
  - Klatt, et al: $G' \approx$ 2-3kPa and $\tan\delta \approx 0.35$ in normal *in vivo* liver tissue at 25-62Hz
  - Sinkus et al: $G' \approx$ 1kPa and $\tan\delta \approx 0.25$ in normal *in vivo* breast tissue at 65Hz
  - Arbogast and Margulies: $G' \approx$ 1.5kPa and $\tan\delta$ perhaps 0.5 in *in vitro* porcine brainstem

Complex Mechanics in Soft Tissues

TRADE-OFF BETWEEN RESOLUTION AND ATTENUATION

Freq. (Hz)	Storage modulus G' (kPa)	Loss factor G"/G' = 1/4 λ (cm)	Loss factor G"/G' = 1/4 $x_{1/e}$ (cm)	Loss factor G"/G' = 1/2 λ (cm)	Loss factor G"/G' = 1/2 $x_{1/e}$ (cm)
50	1	2.0	2.6	2.2	1.5
100	2	1.4	1.9	1.5	1.0
200	3	0.89	1.15	0.94	0.63
300	4	0.68	0.88	0.72	0.49

Hydrogels for Lossy Elastography Phantoms

- Start with Low loss tissue-mimicking (TM) materials
  - Ultrasound Med & Biol vol. 32, 2006
- Add a high molecular weight polysaccharide to produce high loss
  - Others have tried this also
    - Gallippi, et al.
- Measure complex shear moduli with instrument to be described later (next meeting?)

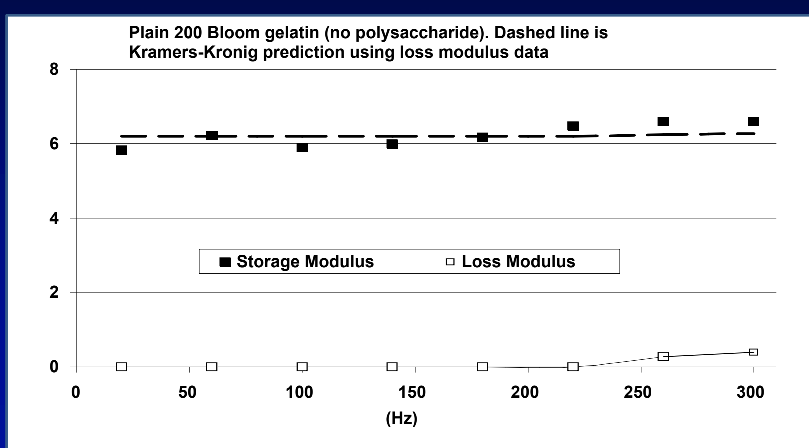
Hydrogels for Lossy Elastography Phantoms

- Verify plausible results using Kramers-Kronig relations
  - Mathematical relationship between real and imaginary parts of any physically-realizable system
  - Allows prediction of one part (e.g. the Real part) from knowledge of the other (Imaginary) part

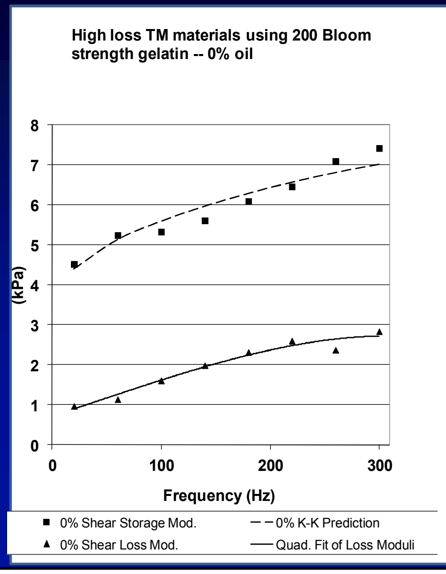
- Again, more on this later (next meeting?)

Hydrogels for Lossy Elastography Phantoms

Start with lossless materials

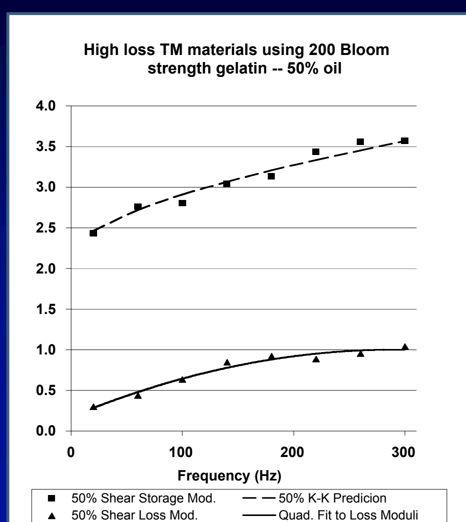


Hydrogels for Lossy Elastography Phantoms



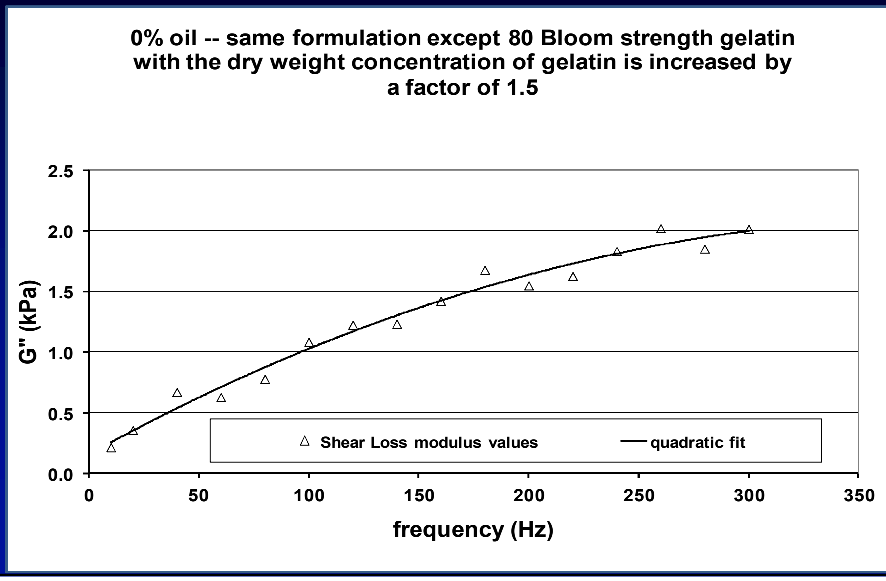
Add the high molecular weight polysaccharide

Hydrogels for Lossy Elastography Phantoms

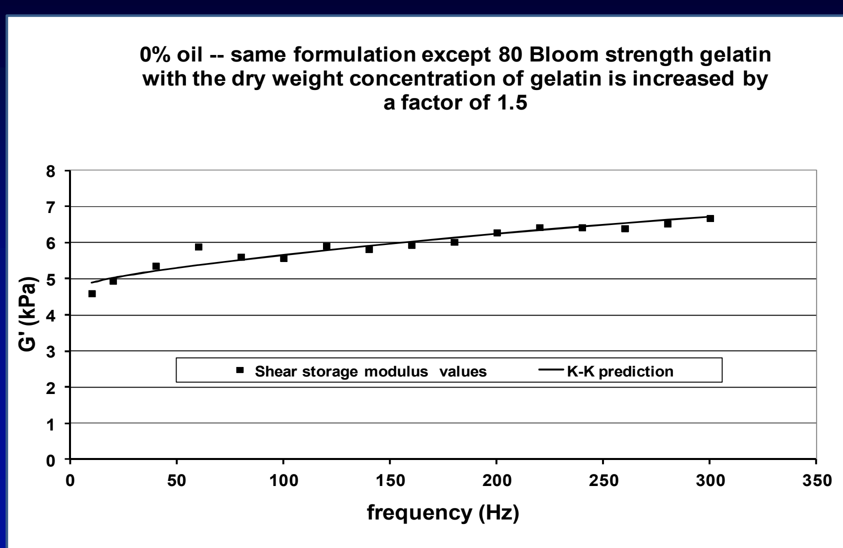


Add oil dispersion to the gel mixture

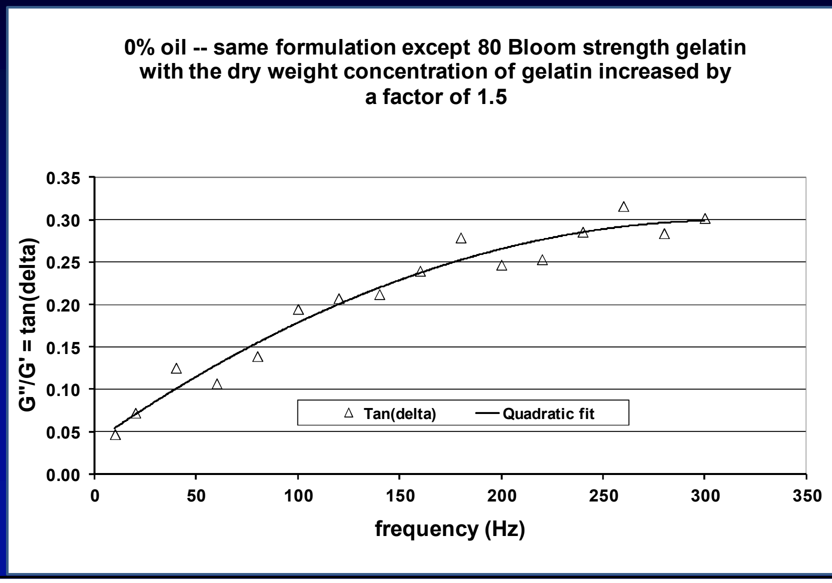
Hydrogels for Lossy Elastography Phantoms



Hydrogels for Lossy Elastography Phantoms



Hydrogels for Lossy Elastography Phantoms



Hydrogels for Lossy Elastography Phantoms

US and NMR properties at 22°C

TM Material identity	T_1 (ms)	T_2 (ms)	US speed (m/s)	US atten. coeff.÷freq. (dB/cm/MHz)			
				2.5 MHz	4.5 MHz	6.0 MHz	8.0 MHz
0% oil	161	34	1662	0.46	0.47	0.47	0.52
50% oil	174	52	1542	0.59	0.76	1.02	1.36
70% oil	178	61	1507	0.62	0.67	0.74	0.83

Hydrogels for Ultrasound Phantoms

- Storage
  - Agar phantoms can be stored for MANY years in water-alcohol solution
  - Gelatin will swell if stored in a water-alcohol bath
  - Gelatin phantoms seem most stable when stored in an oil bath
    - Mineral oil is a good choice
    - Long-term stability depends on composition
      - Months of stability, at least

Summary

- Hydrogels have long history as tissue-mimicking ultrasound phantoms
  - More than 15yrs of development and testing as elastography phantom materials
- Nearly independent control over all compressional and shear wave properties
- Small-strain shear properties range from <<1kPa to >1MPa
- Elastic nonlinearity at least similar to breast tissues
- Tan δ values similar to liver are achievable

Summary

- Phantom material development still underway
- Active area of research in our lab
- Many variables to investigate
  - Polysaccharide type
  - Gel component concentrations
  - Cross linking agent (e.g. formaldehyde) concentration
- Long-term stability needs to be documented