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Theoretical microbubble dynamics in a viscoelastic medium at capillary breaching thresholds

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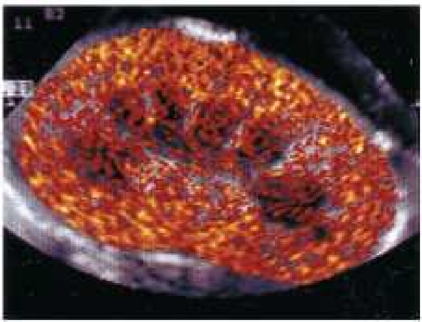
Introduction: Contrast-enhanced ultrasound

- Sonography: acoustic scattering of ultrasound waves at material interfaces for diagnostic imaging.

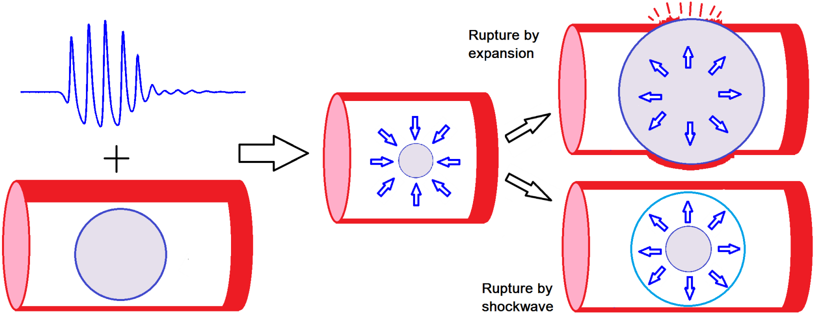
- Contrast-enhanced ultrasound (CEUS): gas-filled microbubbles act as additional interfaces for improved contrast. (Averkiou *et al.* , 2003)
    - Applications: imaging blood perfusion, measuring flow rate in heart, etc.



(Wei *et al.* , 2001)

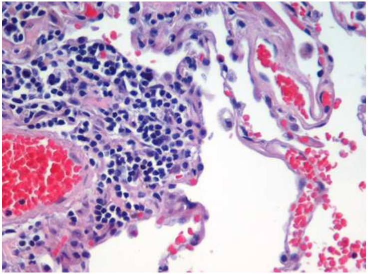
Motivation: bioeffects

- CEUS has been shown to cause negative bioeffects, as evidenced by bleeding, including cardiomyocyte death and capillary rupture.
- Bioeffect thresholds and injury mechanisms remain unknown (Barnett *et al.* , 1994).
  - Shockwaves, release of free radicals, re-entrant jets, bubble expansions, etc...



IC threshold vs. bioeffects threshold

- Bioeffects have been previously attributed to inertial cavitation (IC) (Holland & Apfel, 1990).
- Historically, thresholds for IC of air bubbles in water have been considered as possible bioeffects thresholds (Yang & Church, 2005).
  - $R_{max}/R_0 = 2$ (Apfel & Holland, 1991; Noltingk & Neppiras, 1950)
  - $T_{max} = 5000$ K (Flynn & Church, 1988)
- Tissue is viscoelastic and may have different IC thresholds.
- Through a combined experimental and numerical approach we show that:
  - Cavitation dynamics depends on media.
  - Bioeffects can be related to measures of cavitation.



(Grumelli *et al.* , 2004)

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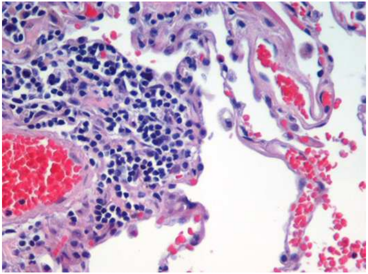
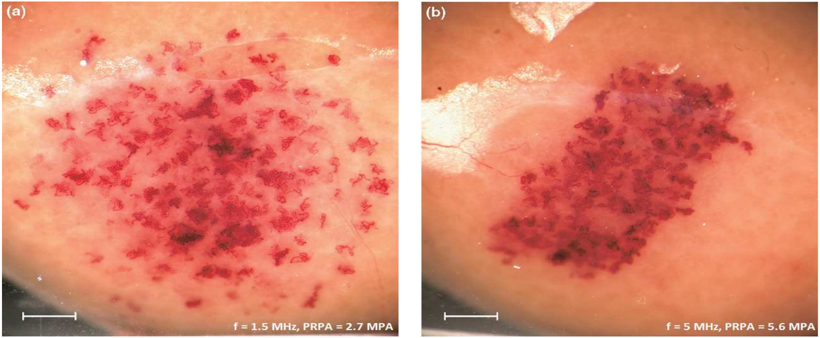


(Grumelli *et al.* , 2004)

Experimental Approach

Bioeffects thresholds for CEUS in vivo were determined experimentally (Miller *et al.* , 2008).

- Rats were given a 10 $\mu L/kg/min$ infusion of US contrast agent solution and subjected to CEUS.
- For pulses of 1.5 - 7.5 MHz, the threshold amplitudes corresponding to glomerular capillary hemorrhage (GCH) were determined.
- Experimental pulse waveforms were used in cavitation simulations.



The Keller-Miksis Equation

$$\left(1-\frac{\dot R}{Ma}\right)R\ddot R+\frac{3}{2}\left(1-\frac{\dot R}{3Ma}\right)\dot R^2=\frac{R}{Ma}\left(\left(Eu+\frac{2}{We}\right)\frac{3\gamma}{R^{3\gamma+1}}\dot R+\frac{2\dot R}{WeR^2}+3\dot S\right)$$

$$\left(1+\frac{\dot R}{Ma}\right)\left[\left(Eu+\frac{2}{We}\right)\frac{1}{R^{3\gamma}}-\frac{2}{WeR}+3S-Eu-p_\infty-\frac{R}{Ma}\dot p_\infty\right]$$

Standard Linear Solid model for stress, $\tau_{rr}(R)$, $S(R)=\int_{R=1}^{\infty}\frac{\tau_{rr}(r)}{r}\,dr$

$$S+De\dot S+De\frac{\dot R}{R}\tau_{rr}=\frac{4}{9Ca}\left(1-\frac{1}{R^3}\right)-\frac{4}{3Re}\left(\frac{\dot R}{R}\right)$$

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Parameter:	Dimensional		Dimensionless
Elasticity	$G=5,100,1000\quad(kPa)$	$\mapsto$	$Ca=c^2\rho/G=20,1,0.1$
Relaxation Time	$t_c=0-1\ (s)$	$\mapsto$	$De=\lambda c/R_0=0-10^7$
Initial Radius	$R(0)=0.1-2\ (\mu m)$		
Adiabatic Index			$\gamma=1.33,1.4$

Note: $R_0=1\ \mu m$, $c=\sqrt{p_{atm}/\rho}$, $We=\rho R_0c^2/s$, $Re=\rho R_0c/\mu$, $Ma=c_0/c$, $Eu=1$

(Holland & Apfel, 1990; Yang & Church, 2005; Hua & Johnsen, 2012)

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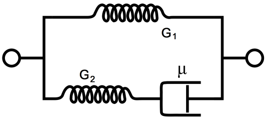

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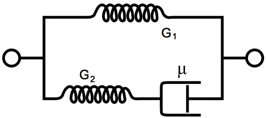

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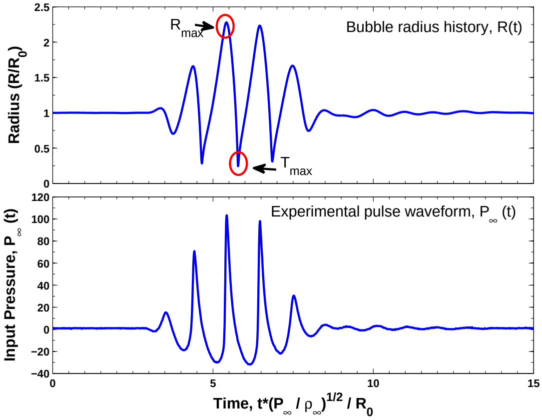
Studying the bubble response

Given the input signal from the ultrasound experiments, the bubble response was simulated for a variety of conditions.

Outline:

- Gas content
- Tissue Properties
  - Elasticity
  - Relaxation
- Experimental parameters
  - Pulse amplitude
  - Bubble size
  - Pulse frequency



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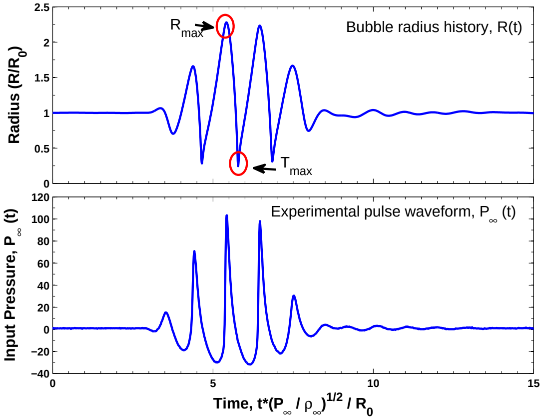

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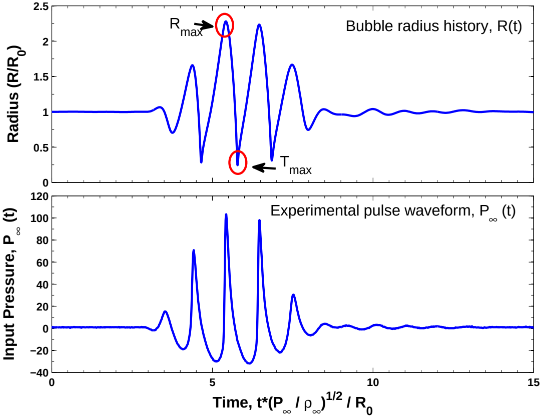

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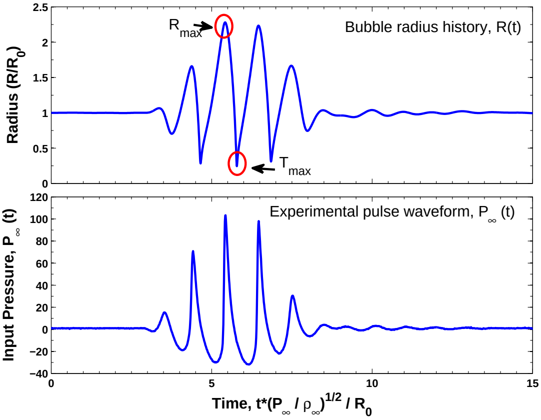
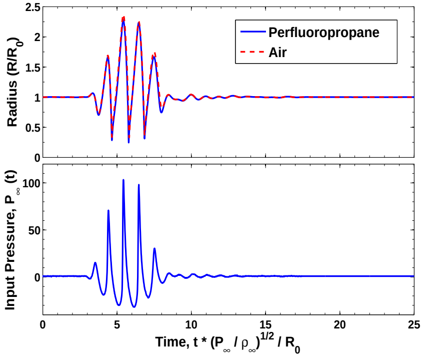
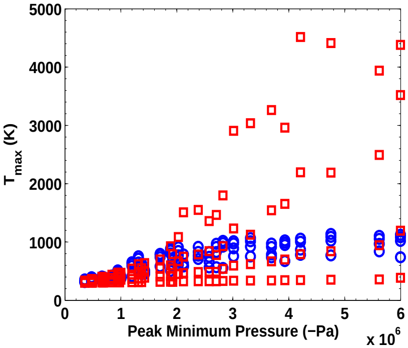


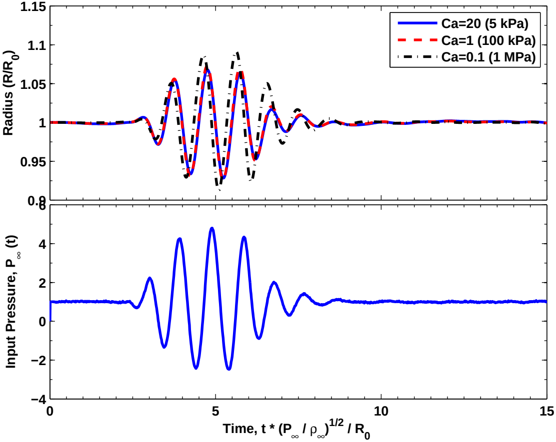
Effects of gas content





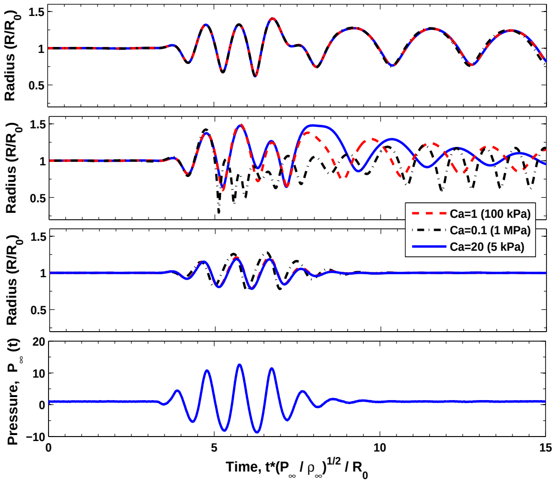
- Gas content has a negligible effect on the bubble dynamics.
- Adiabatic index ($\gamma_{PFP} = 1.13$, $\gamma_{air} = 1.4$) has a large impact on maximum temperatures.

Effects of elasticity (Voigt model)



- Microbubbles in most elastic tissue (1 MPA) show largest oscillations (Hua & Johnsen, 2012).
- Nearly identical bubble dynamics seen in less elastic tissues (5 and 100 kPa).

Effects of stress relaxation and elasticity (SLS model)



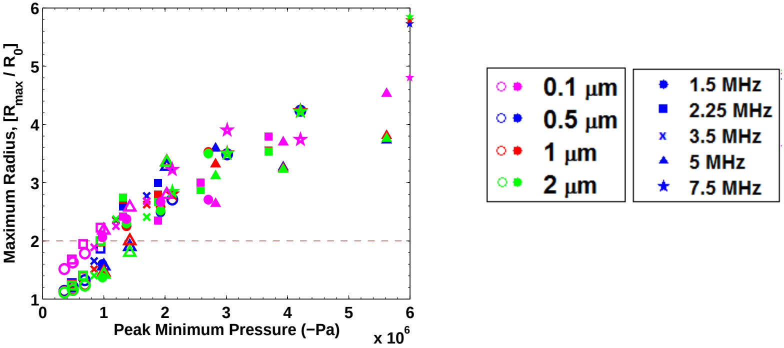
Slower relaxation
$\lambda = 100\mu s,\ De = 1000$

Faster relaxation
$\lambda = 0.1\mu s,\ De = 1$

No relaxation
$\lambda = 0s,\ De = 0$

- Relaxation affects bubble dynamics (R_{max}, R_{min}), damping, and dependence on elasticity at intermediate values of relaxation time.
- Change in elasticity seems insignificant in quickly relaxing media.

Effects of pulse amplitude



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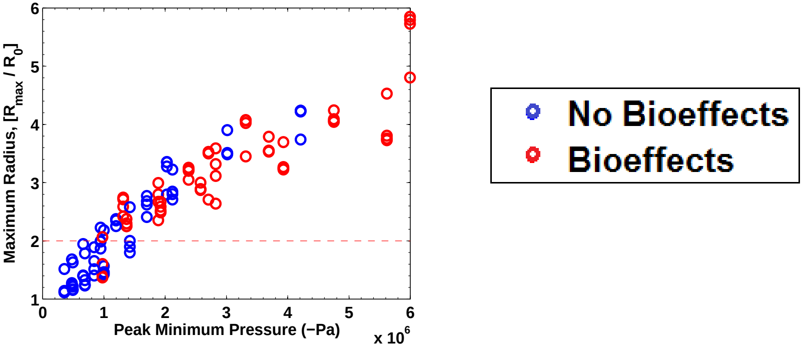

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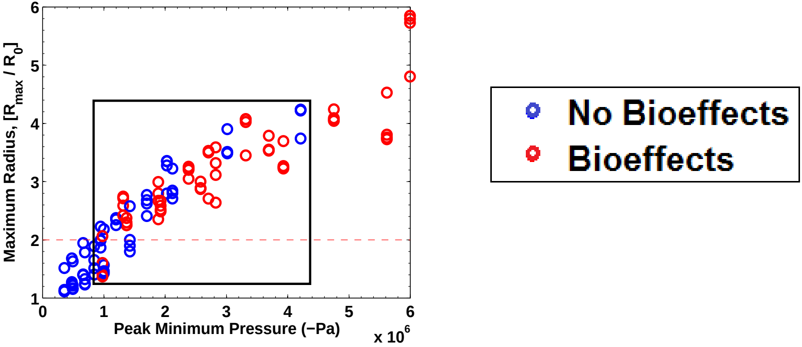

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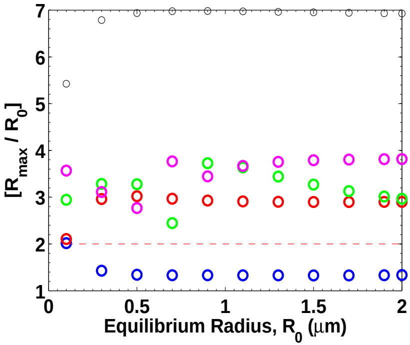
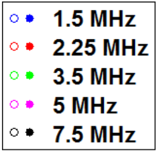
Effects of equilibrium radius, R_0, at bioeffects threshold

Water case





- Actual bubble size distribution is unknown.
- Sensitivity to bubble size is weak in tissue.

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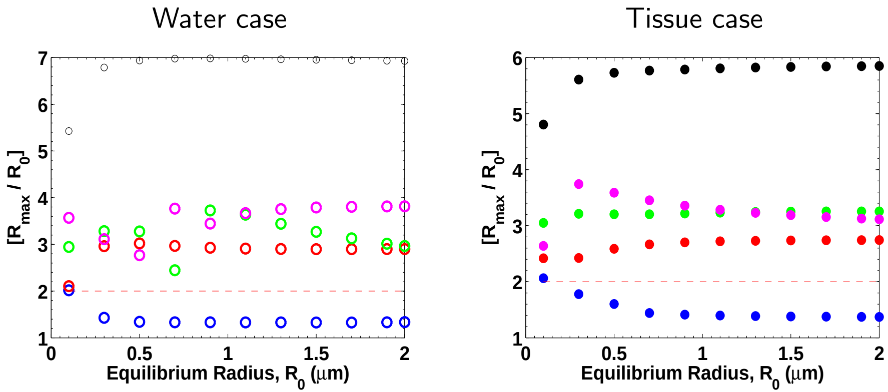

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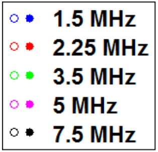
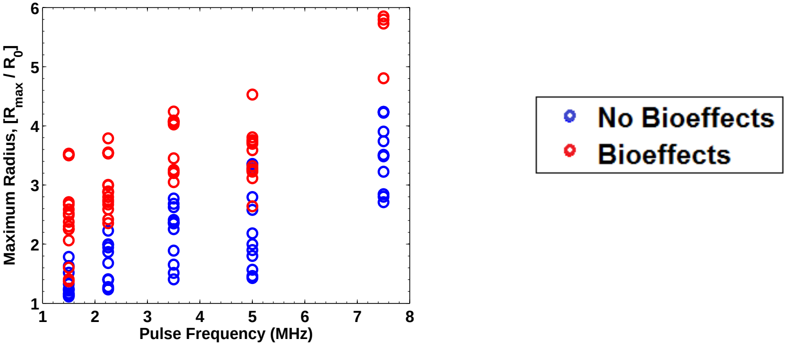
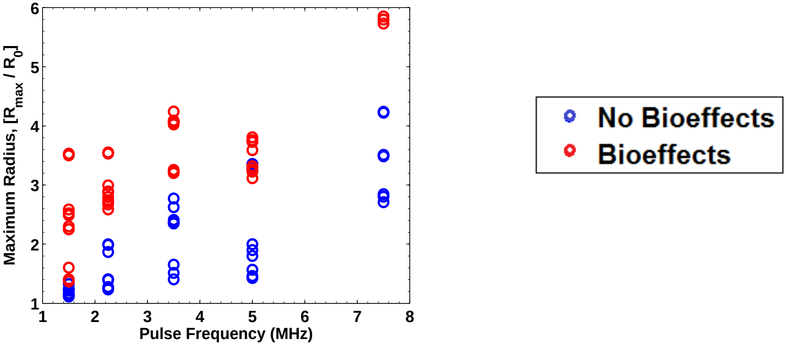


Effects of pulse frequency



- At a given frequency, the bioeffects threshold shows a strong correlation to cavitation dynamics

Effects of pulse frequency



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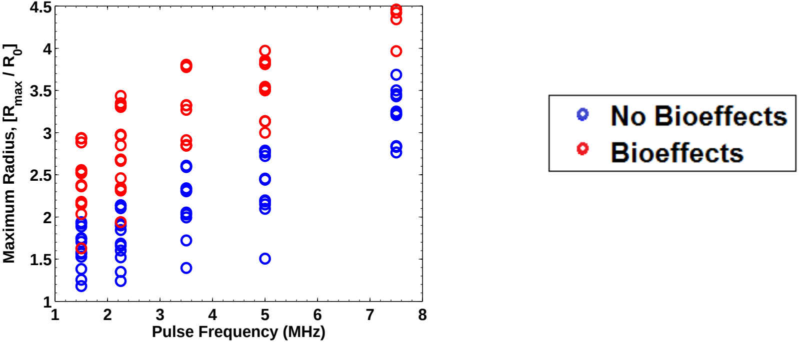
- Most of the outlying data points correspond to $0.1\mu m$ bubbles.

Effects of pulse frequency



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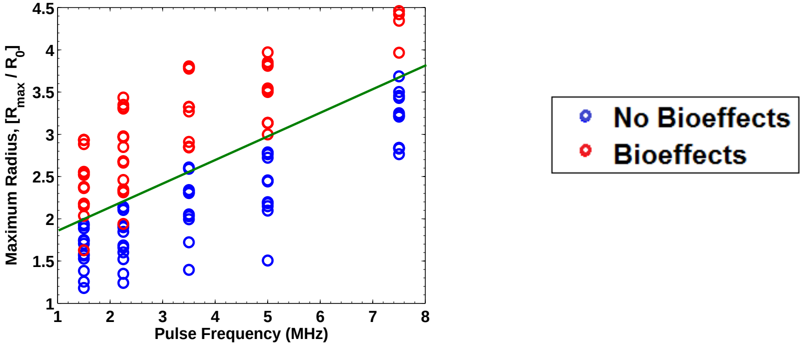

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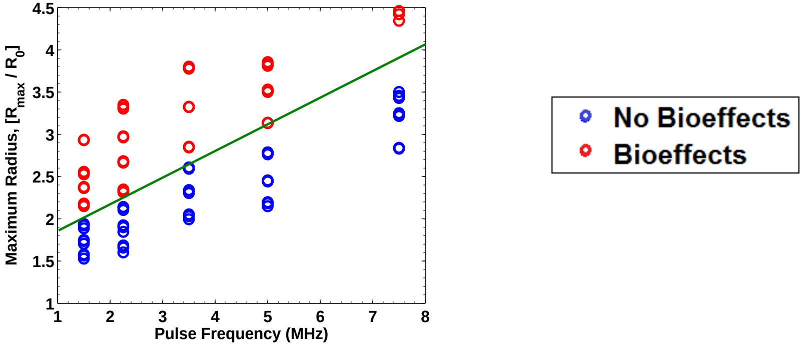

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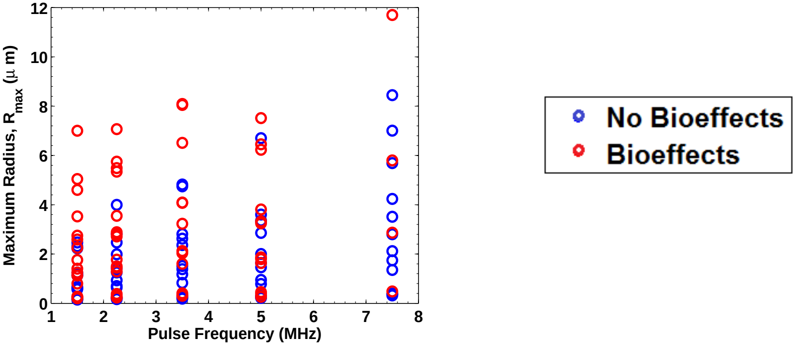

- There is no obvious correlation between R_{max} and bioeffects. Allen & Roy (2000)

Summary and conclusions

- Poorly characterized mechanical properties (stiffness, relaxation) strongly affect the bubble dynamics.
    - Gas content affects the temperature only.
- There is no clear relationship between peak minimum pressure and cavitation-related bioeffects.
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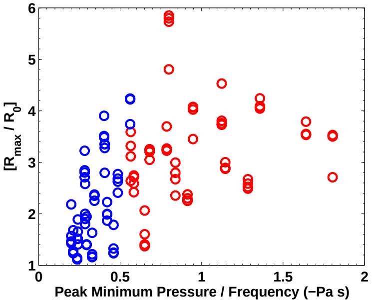

- Future work:
  - A full solution of equations of motion to investigate injury mechanisms
  - Investigate p/f as a possible bioeffects threshold.

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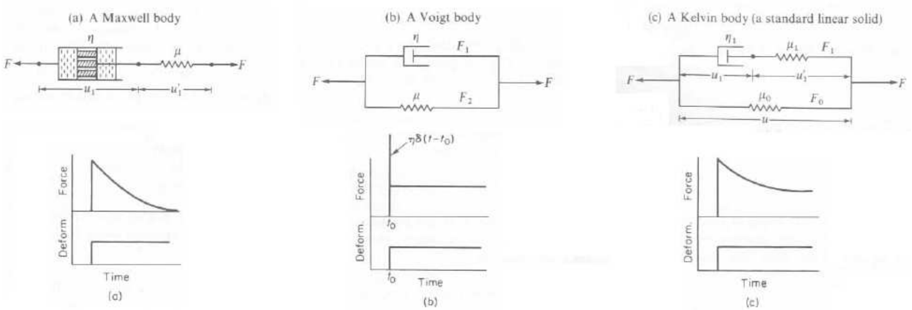
Viscoelastic models



From Fung (1993)

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