Developing a Test Method for Acoustic Characterization of an Ultrasound Contrast Agent

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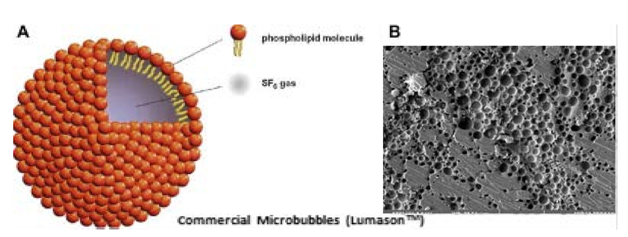
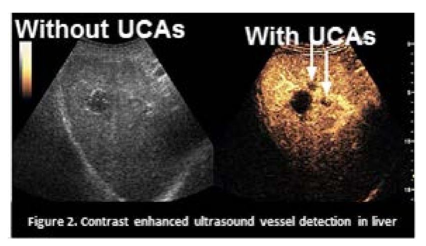
BACKGROUND/ABSTRACT

Lumason™ (sulfur hexafluoride lipid type-A microsphere suspension) is an ultrasound contrast agent (UCA) used for improving ultrasonography in the liver and urinary tract. The effectiveness of UCAs has been correlated with certain acoustic properties, such as attenuation and backscatter. To better quantify the overall effectiveness of Lumason™, an analysis of the effect of these properties on ultrasonography is necessary.





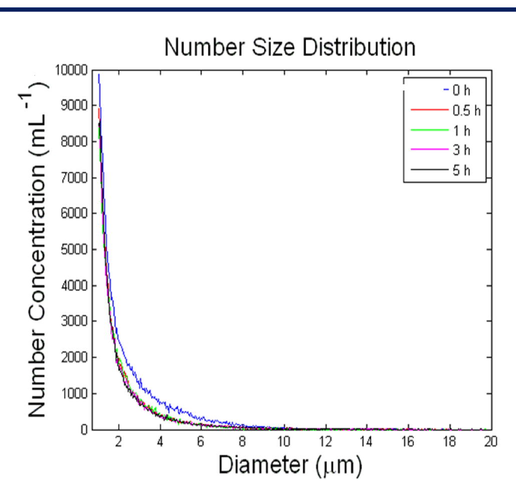
OBJECTIVES

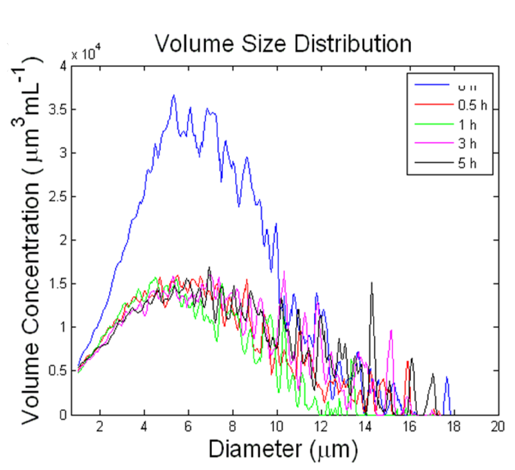
- Facilitate regulatory review of generic UCA development
  - Characterize various acoustic properties
    - Volume and size distribution
    - Attenuation and backscatter coefficient (BSC)
  - Derive theoretical backscattering analysis
    - Compare to experimental results

SIZE DISTRIBUTION

Volume-weighted concentration is more sensitive to changes in the bubble size distribution of a sealed vial over time.

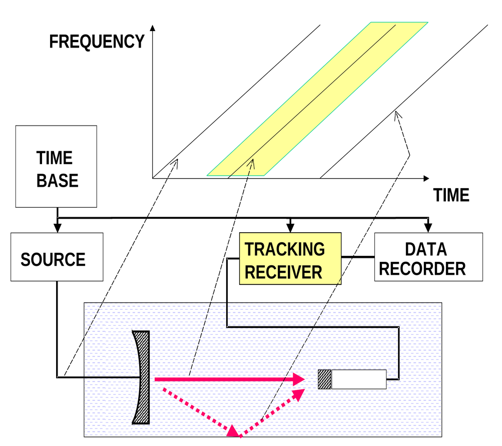
Multisizer™ 4 Coulter Counter



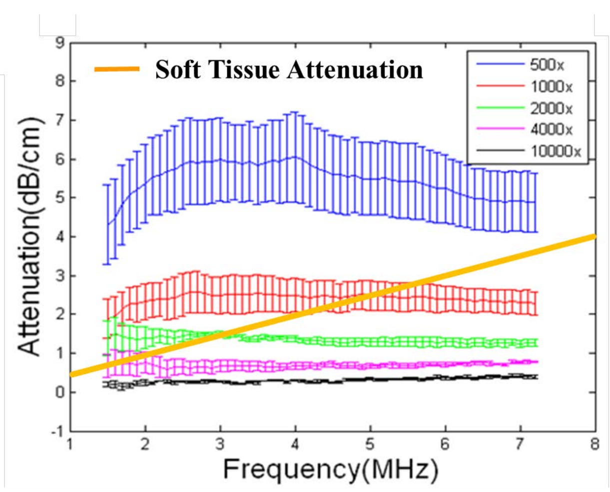


ATTENUATION

Time Delay Spectrometry



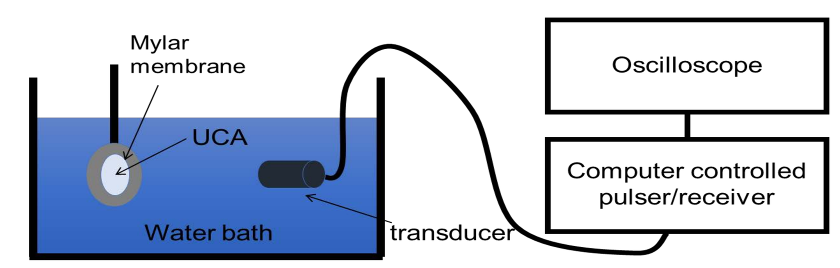
$[\alpha]_{Soft\ Tissue} = 0.5 \cdot [f]^1$



Higher concentrations (smaller dilution factors) yield a **higher attenuation** coefficient.

BACKSCATTER COEFFICIENT (BSC)

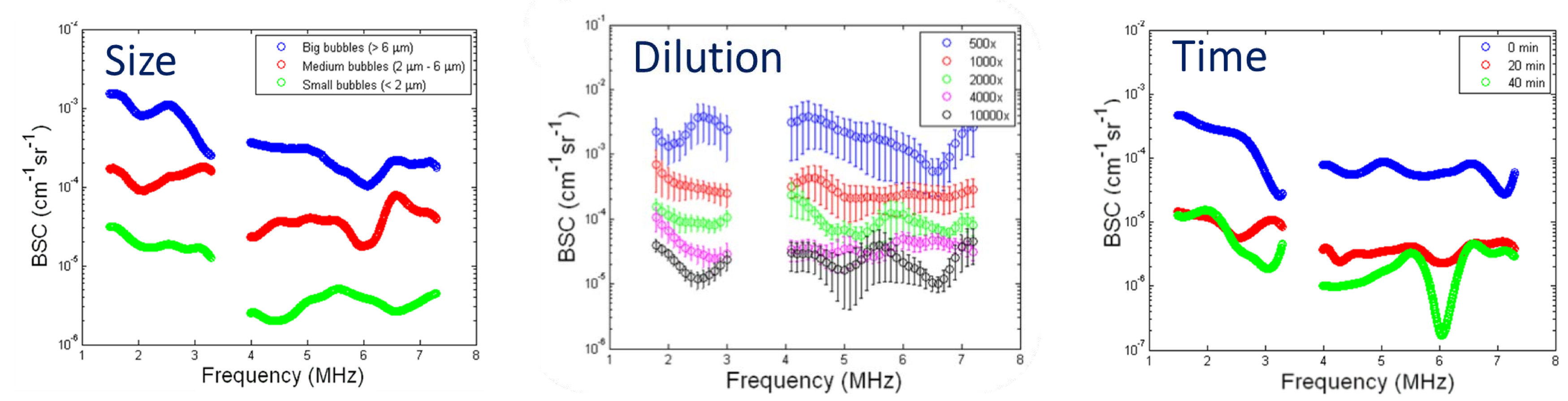
BSC Measurement Setup



$$BSC = 2.17\,\frac{z_0{}^2\Gamma^2}{A_0\Delta z}\left|\frac{P_{bsc}}{P_{ref}}\right| A_\propto$$

$$A_\propto = e^{4\alpha_0(f)x_0}\,\frac{4[\alpha(f)L]^2}{(1-e^{-2\alpha(f)L})^2}$$

(Leithem et al. 2012)



BSC DERIVATION

$$n(f) = \frac{1}{4\pi}\sum_r n(r)\cdot\sigma_{sc}(f,r) \quad \text{\_\_\_\_\_\_ (1)}$$

$$\sigma_{sc}(f,r) = \frac{4\pi r^2}{\left[\left(\left(\frac{f_R(r)}{f}\right)^2-1\right)^2+\delta^2(r,f)\right]} \quad \text{\_\_\_\_\_\_ (2)}$$

$$f_R(r) = \frac{1}{2\pi}\sqrt{\frac{3\gamma P_o}{\rho r^2}+\frac{2S_p}{\rho r^3}} \quad \text{\_\_\_\_\_\_ (3)}$$

$$\delta(r,f) = 4\frac{\zeta}{\rho r^2\omega}+kr+\frac{S_f}{4\pi r^3\rho\omega} \quad \text{\_\_\_\_\_\_ (4)}$$

(Gorce et al. 2000) (Medwin et al. 1977) (Jong et al. 1992)

$\boldsymbol{n(f)}$ is the backscatter coefficient (BSC)

$\boldsymbol{n(r)}$ is the number-weight size

$\boldsymbol{\sigma_{sc}(f,r)}$ is the scattering cross section of a microbubble.

$\boldsymbol{f_R(r)}$ is the resonance frequency of a microbubble

$\boldsymbol{\delta(r,f)}$ is energy loss through bubble oscillation

$$n(f) = \frac{1}{4\pi}\sum_r n(r)\cdot\frac{4\pi r^2}{\left[\left(\left(\frac{1}{2\pi f}\sqrt{\frac{3\gamma P_o}{\rho r^2}+\frac{2S_p}{\rho r^3}}\right)^2-1\right)^2+\left(4\frac{\zeta}{\omega\rho r^2}+kr+\frac{S_f}{4\pi r^3\rho\omega}\right)^2\right]}$$

$$= \sum_r n(r)\cdot\frac{r^2}{\left[\frac{1}{r^6}\left(\underbrace{\left(\frac{S_p{}^2}{4\pi^4\rho^2 f^4}\right)}_{A}+\underbrace{\left(\frac{S_f{}^2}{64\pi^4\rho^2 f^2}\right)}_{B}\right)+\frac{1}{r^5}\left(\underbrace{\left(\frac{3\gamma P_o S_p}{4\pi^4\rho^2 f^4}\right)}_{C}+\underbrace{\left(\frac{\zeta S_f}{2\pi^3\rho^2 f^2}\right)}_{D}\right)+\underbrace{\cdots}_{etc.}\right]}$$

Set each term equal to:

$$C = \left(\frac{3\gamma P_o S_p}{4\pi^4\rho^2 f^4}\right) \text{ and } D = \left(\frac{\zeta S_f}{2\pi^3\rho^2 f^2}\right)$$

$$\frac{C}{D} = \frac{\left(\frac{3\gamma P_o S_p}{4\pi^4\rho^2 f^4}\right)}{\left(\frac{\zeta S_f}{2\pi^3\rho^2 f^2}\right)} = \left(\frac{3\gamma P_o S_p}{2\pi f^2\zeta S_f}\right) = \left(\frac{S_p}{S_f * f}\right) * \left(\frac{3\gamma P_o}{2\pi\zeta f}\right) \sim 1 * \left(\frac{10^5}{10^{-3} * 10^6}\right) \sim \left(\frac{10^5}{10^3}\right) >> 1$$

→ C governs the equation, can disregard D term

Repeat steps for all terms to simplify entire expression

Assumptions and measured parameters

$\boldsymbol{S_p} \triangleq S_f * f$

$\rightarrow S_p{}^2 \triangleq f^2 S_f{}^2$

$\mathbf{r} \triangleq 10^{-6}$

$\boldsymbol{f} \sim 10^6$

$\boldsymbol{\zeta} \sim 10^{-3}$

$\boldsymbol{\rho} \sim 10^3$

$\boldsymbol{\gamma P_o} \sim 10^5$

$(\boldsymbol{\gamma} \sim 1.1072\ for\ SF_6)$

(Harfield et al. 2016)

Simplified Expression $\quad n(f) = \sum_r n(r)\cdot r^6\,\frac{2\pi\rho f}{16\zeta^2}$

Averaging measured number-weighted concentration of Lumason in 2000x, $n(r) \propto r^{-2.72}$: $\quad n(f) = \sum_r r^{3.28}\,\frac{2\pi\rho f}{16\zeta^2}$

BSC DERIVATION (CONT.)

Assuming $V \propto r^3$ then $V^{1.09} \propto r^{3.28}$:

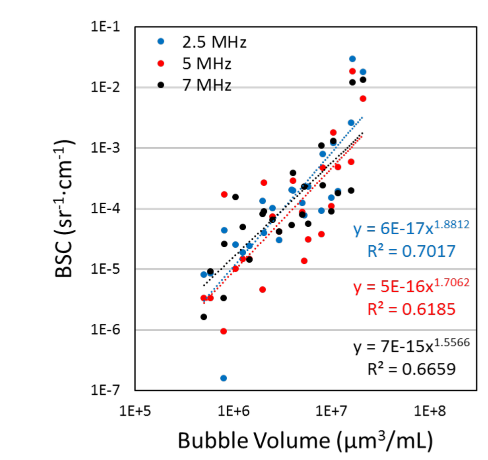
$$\therefore\ n(f) \propto \sum_V \boldsymbol{V^{1.09}}\,\frac{2\pi\rho f}{16\zeta^2}$$

This demonstrates a BSC dependence on volume density (other values are constant for a particular UCA measurement).

The average fitting value of measured BSC at 2.5, 5, and 7 MHz:

$V_{total}{}^{1.71}$

In macroscopic view: $\boldsymbol{V_{total}{}^{1.71} \approx \sum_V V^{1.71}}$



Theoretical	Experimental
$\eta(f) \propto \sum_V V^{1.09}$	$\eta(f) \propto \sum_V V^{1.71}$

The experimental and theoretical results are comparable.

CONCLUSION

- Size distribution, attenuation coefficient and backscatter coefficient are characterized for Lumason™ UCA.
- Variation in bubble concentration (500x-10000x) caused a significant difference in acoustic properties (BSC, attenuation) of Lumason™.
- The derivation of the backscatter performance corroborated the experimental results that volume-weighted concentration are more sensitive than number-weighted concentration for BSC evaluation.
- BSC is a key parameter and better indication for engineering equivalence of Lumason™ contrast agent.
- This study will facilitate development and regulatory review of generic ultrasound contrast agents.

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