Estimation of Contrast Agent Concentration using Spectrum Analysis
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Abstract: A theoretical model was formulated to calculate the calibrated power spectrum of ultrasonic contrast agents. This method incorporates the scattering coefficient from an encapsulated bubble and includes the effects of realistic focused beams. Analytical calculations and experimental studies were conducted for Albunex® over the frequency range used in medical ultrasound. Our results show that contrast agent concentration can be estimated from the slope and intercept, which are measured using linear regression. [Work supported in part by NIH Grant RO1-EY01212 and RO1-EY10369]

INTRODUCTION

Ultrasonic contrast agents such as Albunex®, can greatly enhance the echogenicity of blood for improved imaging of blood flow. The quantification of blood flow using contrast agents depends on the particle concentration of these agents. Our study aimed at obtaining concentration information, and ultimately quantifying blood flow by analyzing the power spectrum of backscatter from these agents. It also examined means to monitor changes in particle radius induced by low frequency ultrasound.

CALIBRATED POWER SPECTRUM OF CONTRAST AGENTS

We have expanded the calibrated power spectrum analysis method developed by Lizzi¹ et al. to study the ultrasonic backscattering properties from contrast agents. By considering scattering² from encapsulated bubbles, we relate the spectral features of the power spectra to contrast agent characteristics including concentration and size. Our model³ calculates the power spectrum of backscatter from Albunex® particles near the focal plane of a focused transducer (aperture a, focal length r), assuming that the particles are spatially distributed in a random manner and neglecting intervening attenuation. The calibrated power spectrum expressed in dB is

\[ S_{ab}(f) = 10 \log \left( \frac{0.036a^2L}{r^2} \right) + 10 \log (C_r) + 10 \log (\sigma(f, R)n(R)dR), \]  

where \( \sigma(f, R) \) is the scattering cross section for a contrast agent particle of radius R at frequency f and L is the analysis gate length. \( C_r \) is the total concentration, \( n(R) \) is the size distribution function, and \( C_r n(R)dR \) represents the number of particles with equilibrium radii between R and R+dR within a unit volume. Spectral features such as slope and intercept can be measured by applying linear regression analysis to equation 1 over the frequency band being analyzed. We have shown that the intercept is related to known system factors (a, r, L) and \( C_r \), and \( n(R) \). The slope only depends on \( n(R) \).

CALCULATIONS AND EXPERIMENTAL RESULTS FOR ALBUNEX®

Theoretical calculations of calibrated power spectra for Albunex® were performed. Experimental results were obtained from the digitized backscatter RF data received by a focused transducer.¹

![Power spectra of Albunex® at concentrations of 1) 2.5×10⁷/ml and 2) 2.0×10⁷/ml](image)

Figure 1: power spectra of Albunex® at concentrations of 1) 2.5×10⁷/ml and 2) 2.0×10⁷/ml
Figure 1 shows the power spectra were obtained from rf data from Albunex® solutions measured with focused transducers of center frequency of 7.5 MHz. For concentrations of $2.5 \times 10^7 / \text{ml}$ and $2.0 \times 10^7 / \text{ml}$, linear regression intercepts are -34.0 and -35.2 dB respectively. Using the parameters for Albunex® in equation 1, we obtained concentration estimates of $1.8 \times 10^7 / \text{ml}$ and $1.4 \times 10^7 / \text{ml}$, which are comparable with the experimental values.

We also used our method to examine changes in R induced by a low frequency ultrasound. At frequencies above resonance, we have shown previously that intercept can be approximated as

$$
\bar{T} = 10 \log(0.03 a^2 L / r^2) + 10 \log(C_r) + 10 \log(4 \pi < R^2 >).
$$

(2)

Therefore intercept depends on $C_r <R^2>$, the product of concentration and the mean square radius of the particles. $<R^2>$ can be calculated when the size distribution is known; concentration can then be obtained from intercept. However, contrast agent particles may exhibit different size distributions due to filtering or breakage and the direct measurement of size distribution may not be possible, such as in the *in vivo* rabbit eye, an animal model we used to study contrast agents.

We have developed a dual frequency band technique and conducted experiments to monitor the change of intercept values due to change of $<R^2>$ with Albunex® solutions. In our method, a composite signal was constructed using a short (~0.5 μs) high frequency (10 MHz) pulse and a longer (~6 μs) low frequency pulse (0.5 MHz). The phase between these two signals is electronically controlled so that the high frequency pulse can be placed at any interval during the low frequency pressure cycle. When transmitted through solution of contrast agent, the low frequency ultrasound causes the bubbles to change size due to oscillation; the high frequency backscatter will be affected due to that size change. Figure 2 shows the high frequency rf data received before, during, and after the low frequency pulse; here, the high frequency pulse is placed at maximum negative pressure of the low frequency signal, using low pressure levels that cause minimum breakage. Our results demonstrated noticeable increase in rf signals during the low frequency pulse, corresponding with increased size of Albunex bubbles.

![Figure 2: Rf data received before, during, and after the low frequency ultrasound](image)

**CONCLUSIONS AND SUMMARY**

We have formulated a calibrated power spectrum analysis to study ultrasonic contrast agents. Our results demonstrate that concentration information can be extracted from spectral intercept using this method. Our dual-frequency-band method provides a potential to monitor changes in bubble size. Further studies are being conducted to obtain quantitative information from the dual-frequency-band experiments.

**REFERENCES**