

# The resonance frequency of SonoVue™

as observed by high-speed optical imaging

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**Abstract**—The resonance frequencies of individual SonoVue™ contrast agent bubbles were measured optically by recording the radius-time curves of a *single* microbubble at 24 different frequencies. For these experiments the Brandaaris 128 fast framing camera was operated in a special segmented mode. The resonance frequencies found for SonoVue™ microbubbles are in good agreement with the modified Herring model for coated bubbles indicating that the shell is only slightly affecting the resonance frequency of this class of contrast bubbles.

*contrast agents, resonance frequency, high-speed imaging*

## I. INTRODUCTION

An ultrasound contrast agent (UCA) is a liquid containing small, encapsulated microbubbles. A general property is its size distribution as measured e.g. with a coulter counter, resulting in mean size and the range. For SonoVue™ (Bracco) e.g. the mean diameter is 3 micrometer, while 95 % of the bubbles are smaller than 10 micrometer. Acoustic characterization is done on a representative sample of the UCA, containing many microbubbles, resulting in e.g. scattering and attenuation properties as function of the frequency. From this data e.g. the resonance behavior of the sample can be deduced. As the sample contains many microbubbles no direct conclusion can be drawn for individual bubbles. In this proceeding a method is proposed to characterize individual bubbles in a contrast agent under a microscope and with a fast framing camera.

## II. THEORY

To predict the behavior of microbubbles, several theoretical models have been proposed. First of all, in 1917, Lord Rayleigh [1] studied cavitation bubbles around ship propellers. Minnaert [2] in 1933 performed a theoretical study of the sound emission of bubbles. Combined with some experiments, he explained the characteristic resonance frequency. In the early 1950's Plesset and Noltingk and Neppiras introduced more sophisticated models for oscillating bubbles, followed by refinements in the late 1950's (Keller, Gilmore, Herring, Trilling) and the 1980's by Keller and Miksis and Prosperetti.

Encapsulated microbubbles were first modeled by De Jong et al. [3] in 1992 and De Jong and Hoff [4] in 1993, incorporating experimentally determined elasticity and friction parameters into the Rayleigh-Plesset model. Church [5] used linear visco-elastic constitutive equations to describe the shell.

A recent addition to the list of models for contrast agent dynamics is developed by Morgan et al. [6]. The model is based on the modified Herring equation. Incorporating the shell properties, the model is described by the following equation:

$$\begin{aligned} \rho R \ddot{R} + \frac{3}{2} \rho \dot{R}^2 = & \left( p_0 + \frac{2\sigma}{R_0} + \frac{2\chi}{R_0} \right) \left( \frac{R_0}{R} \right)^{3\gamma} \left( 1 - \frac{3\gamma}{c} \dot{R} \right) \\ & - \frac{4\mu \dot{R}}{R} - \frac{2\sigma}{R_0} \left( 1 - \frac{1}{c} \dot{R} \right) - \frac{2\chi}{R} \left( \frac{R_0}{R} \right)^2 \left( 1 - \frac{3}{c} \dot{R} \right) \\ & - 12\mu_{sh} \varepsilon \frac{\dot{R}}{R(R-\varepsilon)} - (p_0 + P(t)) \end{aligned} \quad (1)$$

where  $R$ ,  $\dot{R}$ , and  $\ddot{R}$  represent the radius, velocity and acceleration of the bubble wall,  $\sigma$  the surface tension,  $\mu$  the viscosity,  $p_0$  the ambient pressure and  $P = P_a \sin \alpha t$  the applied acoustic field. Typical shell parameters here are the shell elasticity  $\chi = 0$  to 4 N/m, the shell viscosity  $\mu_{sh} = 0$  to 8 Pa·s and the shell thickness  $\varepsilon = 1$  nm.

The resonance frequency of coated bubbles  $\omega_0$  can be derived from Eq. 1 numerically, however for small-amplitudes,  $R(t) = R_0(1 + \varepsilon(t))$  with  $\varepsilon(t)$  a small disturbance on the radius, an analytical expression can be derived:

$$\omega_0^2 = \frac{1}{\rho R_0^2} 3\gamma p_0 + \frac{1}{\rho R_0^2} (3\gamma - 1) \frac{2\sigma}{R_0} + \frac{1}{\rho R_0^2} (\gamma - 1) \frac{6\chi}{R_0}. \quad (2)$$

The first two terms are the same found for the expression for the resonance frequency of free gas bubbles. The additional third term accounts for the shell effects. In Fig. 3 the resonance is plotted for free gas bubbles and for encapsulated bubbles with a shell elasticity  $\chi = 0.26$  N/m, the surface tension  $\sigma = 0.051$  N/m and the polytropic gas exponent  $\gamma = 1.07$ .

## III. EXPERIMENTAL SETUP

The experimental setup is schematically drawn in Fig. 1. SonoVue™ contrast bubbles, supplied by Bracco Research SA, Geneva, Switzerland, were led through a capillary fiber inside a small water-filled container. A broadband single element transducer was mounted at 75 mm from the capillary. An Olympus microscope with a 60x high resolution water-



Figure 1. Experimental setup.

immersed objective and a 2x magnifier produced an image of the contrast bubbles. The image was then relayed to a high speed framing camera (Brandaris 128 [7]), resolving the insonified microbubble dynamics. An arbitrary waveform generator, a Tektronix AWG 520, was used to produce waveforms. An ENI A-500 amplifier was used to amplify the waveforms.

In order to find the resonance frequency of the individual bubbles the bubbles were subjected to a frequency scan with a start frequency of 1.5 MHz and a final frequency of 5 MHz. The step size was 160 kHz. The bubbles were investigated with sequential bursts of 8 cycles and the acoustic pressure was 130 kPa. The pressure generated with the broadband single element transducer was calibrated to be equal for all frequencies. To make sure that the bubble oscillations would remain in the linear regime, the pressure was kept at 130 kPa. The oscillations of the individual bubbles were recorded with the fast framing camera. The camera was operated in a segmented mode where the conventional single acquisition of 128 frames was replaced by recording 4 segments of 32 frames each. As the camera houses memory space for 6 conventional acquisitions this procedure resulted in the recording of 24 sets of 32 frames. The camera was operated at a framing rate of 15 million frames per second and the full frequency scan took less than 1 second. From the images the radius- time (R-t) curves for each individual bubble were measured for each frequency component. From these R-t curves the maximum radius excursion  $R_{max}$  was determined and normalized to the resting radius  $R_0$ .

IV. RESULTS

Fig. 2 shows a result of a frequency scan for Sonovue™ contrast agent microbubbles. Here the relative bubble radius excursion, defined as the ratio of  $R_{max}$  over  $R_0$  is plotted as a function of the frequency. As seen from the figure, the large bubble of 4.0 µm has its resonance frequency at 1.6 MHz. The 3.2 µm bubble has a resonance frequency of 2.1 MHz. The smaller bubble of 2.6 µm is on resonance at a frequency of 3.1 MHz.

The frequency for which the maximum relative radius excursion  $R_{max}/R_0$  was observed was taken as the resonance frequency for that particular bubble. These data are included in Fig. 3 together with the Rayleigh-Plesset model for free gas bubbles and the modified Herring model for contrast bubbles. The resonance frequencies found for SonoVue™ microbubbles are in good agreement with the modified Herring model for coated bubbles. This would mean that the shell is only slightly

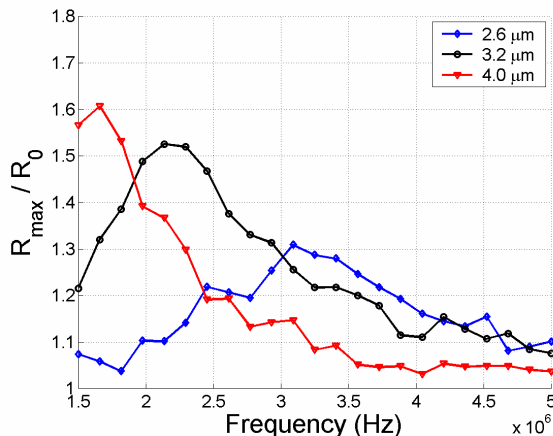


Figure 2.  $R_{max}/R_0$  as a function of the frequency for 3 typical bubbles. The legend shows bubble diameters.

affecting the resonance frequency of this class of contrast bubbles.

V. CONCLUSIONS

A method was developed to determine the resonance frequency of individual contrast agents. With this method the resonance frequency was determined for several coated microbubbles. The measured resonance frequency is in good agreement with the modified Herring model for contrast bubbles. For SonoVue™, this would mean that the shell is only slightly affecting the resonance frequency.

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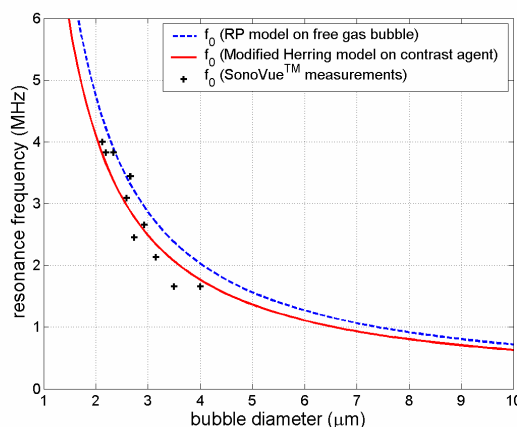


Figure 3. Resonance frequency as function of diameter. For the contrast bubble model, the shell elasticity  $\chi$  is here taken 0.26 N/m.

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