Abstract

In this work, we present a theoretical and experimental study of the evolution with frequency of the nonlinear coefficient $\beta$ of contrast agents. The “effective” attenuation, phase velocity and nonlinear coefficient of the contrast agent are calculated considering the encapsulating shell properties and the size distribution of gas bubbles. With a volume fraction of gas of $10^{-3}$, value as high as 250 was found near the lower resonance for the fraction of gas of $10^{-5}$. Variation of the nonlinear response of contrast agents have been reported [2, 3], and in each case at only one acoustic nonlinearity parameter for contrast agents are known to evolve with frequency, as shown for example by de Jong et al. [4]. Nevertheless, to our knowledge the nonlinear coefficient frequency evolution has not been yet measured.

In this paper, the theoretical approach used in Russian literature for nonlinear propagation in bubbly mixture like contrast agents. Then, experimental measurements of linear parameters (attenuation and phase velocity) of the studied contrast agent [1].

Introduction

Contrast agents have been found useful in many ultrasonic imaging applications such as blood flow visualisation. Most of the manufactured ultrasonic contrast agents are liquids with encapsulated gas microbubbles. Generally, the properties of the solid shell encapsulating the gas are determined by acoustic measurement of linear parameter (attenuation and phase velocity) and nonlinear parameter, in the frequency range 1 to 10 MHz, are presented for two different contrast agents: Sonasoid® and Sonovue®.

Theoretical background

Nonlinear waves in contrast agent mixture

A contrast agent mixture is a liquid with distributed encapsulated gas bubbles. It is characterised by a volume gas content $z$. In the case of low bubbles concentration ($z << 1$), the nonlinear wave equation in a contrast agent mixture can be expressed approximately by [5]:

$$\nabla^2 p' - \frac{1}{c_0^2} \frac{\partial^2 p'}{\partial t^2} + \rho_0 \frac{\partial^2 z'}{\partial t^2} = -\frac{\beta}{\rho_0 c_0^4} \frac{\partial^2 p}{\partial t^2}$$

where $p'$ and $z'$ are respectively the pressure and volume gas content variations, and $\beta = 1 + B/2A$ is the coefficient of nonlinearity of the fluid.

Nonlinear bubble dynamic

To obtain a closed system of equations it is necessary to relate the single-bubble volume to the pressure. To describe the behaviour of a contrast agent bubble, we assume that it maintain it spherical shape. Church [6] has obtained the nonlinear equation of motion for a gas bubble enclosed in a solid, incompressible, viscoelastic shell, given in the thin shell approximation by [1]:

$$RR + \frac{3}{2}R^2 = \frac{1}{P_0} \left[ p' \left( \frac{R_0}{R} \right) - p_0(t) \right]$$

where $R_0$ and $R$ are the equilibrium shell thickness, $p_{eq}$ is the equilibrium pressure in the gas inside the bubble, $p_0(t)$ is the pressure in the liquid far from the bubble, $\kappa$ is the polytropic exponent of the gas, $G_S$ is the shear modulus of the shell, and $\mu_t$ and $\mu_s$ are the shear viscosity of the liquid and the shell, respectively. In term of volume displacement $V = 4/3 \pi R^3$, the nonlinear bubble dynamic equation reads:

$$\frac{d}{dt} \left[ \frac{\ddot{V}}{V} \right] - \frac{p_0}{4\kappa c_0^2} = p_0 \left( \frac{V(t)}{V} \right)^\kappa - p_0(t)$$

$4 V \left[ \mu_t d_{s0} V \right] + \mu_s \left[ 12 G_S d_{s0} \left( \frac{V}{V_0} \left( 1 - \left( \frac{V}{V_0} \right)^\kappa \right) \right) \right] - 4 V \left[ \mu_t d_{s0} V \right] + \mu_s \left[ 12 G_S d_{s0} \left( \frac{V_0}{V} \left( 1 - \left( \frac{V}{V_0} \right)^\kappa \right) \right) \right]$$
where \( V_0 = V(R_0) \) is the equilibrium volume, and 
\( a = \rho_s \left( \frac{1}{4\pi} \right)^{2/3} \left( \frac{1}{3} \right)^{1/3}. \) Here a radiation damping has
been added by a term of the form 
\( -\frac{\rho_s}{4\pi c_0} \). A second order perturbation approach with 
\( V = V_0 + v \) yields:
\[
\ddot{v} + 2(\beta_1 + \beta_2) \dot{v} + \omega_0^2 v + \frac{R_0 v}{\varepsilon} = -\varepsilon \dot{v} + (\alpha + d) \dot{v}^2 + \beta_1 (2v \dot{v} + v^2) + (12 \beta_1 + 24 \beta_2) \beta_1 \dot{v} \dot{v}^2
\]
where we have introduced the following notation:
\( \omega_0^2 = \omega_0^2 + \alpha_0^2 \) with \( \alpha_0^2 = 3\kappa \rho_s \rho / \rho_c R_0^4 \) and 
\( \alpha_0^2 = 12G_s d c / \rho_c R_0^4 \), \( \alpha = 3\beta_1 (\kappa + 1) \alpha_0^2 \), \( d = 10 \beta_1 \omega_0^2 \), 
\( \beta_1 = 1/8\pi R_0^3 \), \( \varepsilon = 4\pi R_0^3 / \rho_1 \). \( \beta_1 = 6\mu_s d c / \rho_c R_0^4 \) and 
\( \beta_2 = 2\mu_1 / \rho_c R_0^3 \) are the solid and fluid viscosity 
damping terms, respectively. \( \alpha_0 \) and \( \alpha_0^2 \) are the resonant cyclic frequency of the encapsulated and 
free bubble, respectively, and \( \alpha_0 \) is the shell 
contribution.

Second harmonic propagation in contrast agents

Consider first a transducer emitting a harmonic wave. Assuming that the energy of the second 
harmonic created in the medium is small, nonlinear 
effects do not influence the amplitude of the primary 
wave. In this case, the problem can be solved by the 
perturbation method. Combining Eqs. (1) and (4) the 
following Helmoltz type equations are obtained up to 
second order:
\[
\begin{align*}
\left( \nabla^2 + \frac{\omega_0^2}{c_0^2} \right) p_1 &= 0 \quad (5) \\
\left( \nabla^2 + \frac{4\omega_0^2}{c_0^2} \right) p_2 &= \frac{2\beta_2(\omega_0^2)}{\rho_c R_0^4} \rho_1 p_1^2 \quad (6)
\end{align*}
\]
with the complex propagation velocity \( c_m \) given by:
\[
1 = \frac{1}{c_m^2} = \frac{1}{c_0^2} + \int_{R_m}^{R_c} \rho_n(R_0) \varepsilon \left( \omega_0^2 - (m \omega_0^2)^2 + j \delta_0 (m \omega_0^2) \right)^{-1} dR_0 \quad (7)
\]
and the nonlinear coefficient of the contrast agent:
\[
\beta_2(\omega) = \beta \left( \kappa n(R_0) \varepsilon \rho_1 c_0^3 \left[ \alpha + d - 3\beta_1 \omega_0^2 + j2\omega_0 \beta_1 (\beta_1 + 2\beta_2) \right] \right) dR_0 \quad (8)
\]
where we have introduced the dimensionless damping constant:
\[
\delta_0(\omega) = \frac{2\beta_1}{m \omega_0} + \frac{2\beta_2}{m \omega_0} + \frac{2\beta_{rad}}{m \omega_0} \quad (9)
\]

with:
\[
\beta_{rad} = \frac{R_0 (m \omega_0^2)^2}{2 \omega_0} \quad (10)
\]
So, a contrast agent mixture is an attenuating and disperse 
medium, with a nonlinear coefficient 
depending on frequency. Introducing the liquid 
and the encapsulated gas bubble compressibility, 
\( K_l = \rho_s c_0^2 / \rho_c R_0^4 \) and 
\( K_b = \omega_0 \rho_c R_0^4 / \beta \) respectively, 
the nonlinear coefficient could be written, in the low 
frequency limit \((2 \omega_0 << \omega)\) for a uniform radius 
mixture, as:
\[
\beta_2 = \beta + \frac{K_l}{K_b} \left[ \frac{5 \omega_0^2}{3 \omega_0^2} + \frac{\kappa + 1}{2} \omega_0^2 \right] \quad (11)
\]
Eqn (11) is equivalent to the nonlinear coefficient 
obtained, in the low volume concentration, by 
the mixture law introduced by Apfel [7] and corrected 
by Everbach et al. [8] defining the nonlinear coefficient 
\( \beta_{se} \) of the encapsulated gas by:
\[
\beta_{se} = \frac{5 \omega_0^2}{3 \omega_0^2} + \frac{\kappa + 1}{2} \omega_0^2 \quad (12)
\]
In the case of a free gas bubble eqn (12) corresponds 
to the usually defined nonlinear coefficient of a gas. 
This mixture effect induces an increase of the 
nonlinear coefficient of a bubbly liquid by several 
orders of magnitude than the nonlinear coefficient 
of liquids or gas.

In the high frequency limit \((\omega >> \omega_0)\) the nonlinear 
parameter of the contrast agent mixture tends to 
the nonlinear coefficient of the surrounding fluid. So, the 
enhanced nonlinearity introduced by the contrast 
agent bubbles is pronounced only in the frequency 
range near or lower their resonance frequency.

Figure 1 : Nonlinear coefficient vs. Frequency for a 
solution containing uniform radius \( R_0 = 1.2 \) \( \mu \) free gas 
bubbles (solid line), uniform radius \( R_0 = 1.2 \) \( \mu \) encapsulated 
Sonazoid® gas bubbles (dashed line), and a real radii 
distribution of Sonazoid® gas bubbles 
(dotted line) with a volume fraction \( z = 10^{-5} \).
The influence of the bubble encapsulation on the nonlinear coefficient is displayed in Fig. 1: the resonance frequencies ($\omega = \omega_1$ and $\omega = \omega_2/2$) are less pronounced in mixture with encapsulated bubbles due to the enhancement of the bubble oscillation attenuation, and shifted to higher frequencies. In Fig. 2 it is shown that bigger bubbles induce higher nonlinear coefficient. This fact is confirmed in Fig 1, where the nonlinear coefficient maximum is shifted toward a smaller frequency for a real distribution Sonazoid® mixture.

**Experimental technique**

*Insert–substitution nonlinear coefficient measurement*

A second harmonic insert-substitution method was employed to measure the nonlinearity parameter of contrast agents as a function of frequency, in the range from 1 to 10 MHz. The principle of the method, as depicted on Fig. 3, is to measure the ratio of the second harmonic pressure amplitude $p_2/p_{2\text{ref}}$, where $p_2$ and $p_{2\text{ref}}$ are the pressure amplitudes of the second harmonic waves in the sample with unknown nonlinear coefficient $\beta$ and in a reference medium with a known nonlinear coefficient $\beta_{\text{ref}}$, respectively. For nonlinear parameter measurement of contrast agent, the reference medium chosen is Isoton II the saline aqueous solution in which the contrast agent bubbles are injected.

![Figure 3 : Second harmonic insertion – substitution principle.](image)

**Experimental set-up**

The experimental system for measuring the acoustic nonlinearity coefficient $\beta$ of contrast agents at different frequencies is shown in Fig. 4. A function generator (HP 3314A, Hewlett Packard, Santa Clara, CA) produce a 50 mV amplitude sinusoidal burst signal during 20 μs, with a frequency varying between 1 and 20 MHz with a 0.5 MHz step. This signal is amplified by a 55 dB power amplifier (ENI A150, Rochester, NY) before transmission to a planar 10 MHz, 0.25” diameter PZT transducer (ISL-1002-HR, Technisonic, Fairfield, CT). The transmitted wave, which do not exceed 55 kPa, is received by a 15 MHz, 0.25” diameter wideband PZT transducer (ISL-1502-HR, Technisonic, Fairfield, CT) at a distance $d$ (between 1 and 2 cm). The received signal is directly sampled by a digital oscilloscope (LeCroy 9430, Chestnut Ridge, NY), and saved on a computer via a GPIB link. In order to increase the signal to noise ratio a 128 averaging is used.

**Experimental results and discussion**

First, 0.06 ml of Sonazoid solution initially at $z = 3 \times 10^{-3}$ has been injected in 22 ml of Isoton, giving a Sonazoid® mixture at $z = 9 \times 10^{-4}$. Attenuation and phase velocity measured just after injection, and 15 min and 30 min after, are shown in Fig. 5a-b. The measures obtained just after injection are in good agreement with thus presented by Hoff [6]. Fig. 5 clearly shows a widening and a frequency shift of the resonance with time. Moreover, attenuation and dispersion become less and less important. This demonstrates an evolution of the bubbles distribution, probably linked to the disappearance of the bigger bubbles. In Fig. 5c, the nonlinear parameter measured,
The high nonlinear coefficient dispersion predicted theoretically is confirmed. In the frequency range 1 to 10 MHz the nonlinear coefficient changes more than one order of magnitude. Moreover, the measured nonlinear coefficient peaks near or less the half resonance frequency. Nevertheless, just after injection, an unexpected maximum of the nonlinear coefficient appears near the 6 MHz resonance frequency.

Same measurements are shown in Fig. 6 for SonoVue® with an initial volume fraction of 4.5 \(10^{-6}\), at times \(t_1=0\) (solid line), \(t_2=15\) min (dashed line), \(t_3=30\) min (dotted line), and \(t_3=45\) min (dash-dotted line) after bubbles injection.

### Conclusion

The nonlinear coefficient evolution with frequency of contrast agents has been studied theoretically and experimentally. For the first time, the dispersion of the nonlinear coefficient in contrast agents has been measured. It has been shown that it peaks near or less the half resonance frequency. This parameter combined with attenuation can give more information about microbubbles size distribution.

### References


