Modeling of ultrasound propagation through contrast agents

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Abstract — **In the past years many advances have been made in the detection of ultrasound contrast agents (UCA) by exploiting their nonlinear behavior. However, little attention has been paid to the nonlinear distortion of ultrasound (US) waves propagating through contrast media. The aim of this study is to model the nonlinear propagation of low pressure US waves through contrast media. The Burgers' equation (approximated to the second order) is used to model the nonlinear US propagation. In addition, the results are compared to a numerical approximation of forward scattering, combining the linear-wave and modified Rayleigh-Plesset Noltingk Neppiras and Poritsky (RPNNP) equations. Measurements are performed for the model validation. Using a single element transducer, a Hanning-windowed 20 cycle US pulse was transmitted through water. An acoustically transparent tube (22 mm diameter) was positioned in the transducer focus containing different UCA concentrations up to 0.2%. All measurements were performed with an US mechanical index of 0.1 to prevent bubble collapse. The adopted frequency range was 0.5 to 3.5 MHz, which is around the UCA resonance frequency. The waves were measured by a hydrophone placed in line with the transducer. For low concentrations of UCA, the propagation of US waves can be described using the Burgers' equation. For higher concentrations and frequencies close to the UCA resonance frequency a phase shift arises in the measurements which can be predicted by combining the modified RPNNP and the linear-wave equations.**

Keywords — **Nonlinear propagation, ultrasound imaging, ultrasound contrast agent.**

I. Introduction

Contrast ultrasound (US) imaging is a growing field with large potential for accurate delineation of physiological cavities as well as for quantification of perfusion, aimed at detection of both ischemic regions and cancer. Ultrasound contrast agents (UCA) are a dispersion of microbubbles of gas enclosed in a biocompatible shell, with a diameter in the range of 1 μm to 10 μm (of the order of red blood cells). When UCAs are exposed to an external oscillating pressure field, the microbubbles backscatter nonlinearly the received waves introducing higher harmonics [1, 2].

Visualization and quantification of UCA is usually accomplished by dedicated imaging modes. In the past years, several improvements have been made to increase the contrast to tissue ratio (CTR), which is a quality measure of contrast enhanced images. In fact, while UCAs have a nonlinear behavior, tissue has an approximately linear behavior. This difference is exploited by several contrast enhancement imaging modes. For example, harmonic imaging is a method where the US scanner extracts and processes only the second harmonic of the received signal [3]. This procedure can also be applied to subharmonic, ultraharmonic, and superharmonic frequencies because at these frequencies the UCA backscatter is large in comparison with the contribution of tissue [4]. Together with the selection of specific frequency bandwidths, special pulse schemes can also be adopted to preferably detect the nonlinear response of UCA with respect to the linear response of tissue. Well known UCA-enhancement schemes are the power and phase modulation schemes [3]. While contrast detection is enhanced by exploiting its nonlinear behavior, little attention has been paid to the nonlinear distortion of US waves propagating through UCA.

The aim of this study is to model and quantify the nonlinear behavior of low pressure US waves propagating through UCA. The obtained insight could permit to predict and simulate the nonlinear propagation of US waves through UCA, possibly resulting in the design of improved contrast imaging modes. This will eventually lead to improvement of the diagnostic applications of US contrast imaging.

Using a test setup consisting of a single element transducer and a hydrophone, the nonlinear propagation of US waves through UCA is measured. The contrast agent used in this study is Luminity™ (Bristol-Myers Squibb). Luminity™ consists of phospholipid-encapsulated octafluoropropane microspheres. It belongs to the third generation UCAs, which are composed of high-molecular-weight gases, less diffusible than air, stabilized with an outer layer of protein, lipids or synthetic polymers. These measurements are simulated using the Burgers' equation for low concentrations of UCA. For higher concentrations, this model is not suitable and the modified Rayleigh-Plesset Noltingk Neppiras and Poritsky (RPNNP) equation is used to approximate the nonlinear behavior of UCAs [5].

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II. MATERIALS AND METHODS

Nonlinear propagation of US through a homogeneous medium can be described by the Burgers' equation [2]. In this study, the Burgers' equation is used to model the nonlinear distortion of US waves caused by low-concentration UCA.

An alternative approach for the characterization of US propagation through UCA consists of a numerical approximation of the forward scattering phenomenon, combining the linear-wave and the modified RPNNP equations. The description of US propagation as a forward scattering process through the bubble dispersion is a more accurate representation of the underlying physical phenomena, however, only numerical approximations can be obtained.

Both models are used in this study to estimate the nonlinear behavior of US waves when propagating through contrast media. To validate the simulations, a measurement setup is built to measure the nonlinear propagation of US waves through different UCA concentrations.

A. Nonlinear propagation of ultrasound

US waves are acoustic waves in the frequency range ($f=\omega/2\pi$) above the audible range. Therefore, the basic principles and equations of acoustics can be used to characterize the acoustic field of US. According to [2], the wave equation can be described using the partial differential equation for a non-viscous plane wave propagation in one spatial dimension given as

$$\frac{\partial^2 P(x,t)}{\partial x^2} = \frac{1}{v^2}\frac{\partial^2 P(x,t)}{\partial t^2}, \tag{1}$$

where x and v denote the propagation axis and the propagation velocity, respectively. The acoustic pressure P of an US wave can be described by the solution of the wave equation

$$P(t,x) = P_A e^{j(\omega t - kx)}, \tag{2}$$

where P_A is the amplitude of the pressure wave and k is the wave number. The combined effects of dissipation and nonlinearity caused by the propagation of the US wave through UCA on progressive plane waves can be described by the Burgers' equation [2] given as

$$\frac{\partial P}{\partial x} - \frac{\delta}{2c_0^3}\frac{\partial^2 P}{\partial \tau^2} = \frac{\beta P}{\rho_0 c_0^3}\frac{\partial P}{\partial \tau}. \tag{3}$$

Here δ is the diffusivity of US, c_0 is the speed of sound, ρ_0 is the ambient density, and $\tau = t - x/c_0$ is the retarded time frame variable of an observer traveling with the wave front. The right term in equation (3) describes the nonlinear behavior of propagating US. The coefficient of nonlinearity β is defined as $\beta=1+B(2A)^{-1}$, with B/A being the nonlinearity coefficient as defined in [2]. Taking $\beta = 0$ results in an equation for diffusivity and taking $\delta = 0$ results in an equation which represents the nonlinear behavior of a propagating US wave. A measure of the level of nonlinearity relative to that of dissipation is given by the Gol'dberg number, which is defined as

$$\Gamma = \frac{\beta \varepsilon k}{\alpha}, \tag{4}$$

where $\alpha=\delta\omega^2(2c_0^3)^{-1}$ is the small signal absorption coefficient and $\varepsilon = P_0(\rho_0 c_0^2)^{-1}$ is the acoustic Mach number [2]. Since gas bubbles insonated by a pressure wave tend to oscillate in diameter, the backscatter of the contrast agent consists of the radiation by the bubble oscillation. This oscillation of a spherically shelled bubble with radius R can be modeled as a spring-mass system with equilibrium radius R_0 [2]. The modified RPNNP equation, combined with the linear-wave equations, is used to predict the oscillation of a single bubble [5]. The RPNNP equation is formulated as

$$\begin{aligned} \rho_0 R\ddot{R} + \frac{3}{2}\rho_0 \dot{R}^2 = P_{g0}\left(\frac{R_0}{R}\right)^{3\kappa} + P_v - P_0 - \frac{2\sigma}{R} \\ -2S_p\left(\frac{1}{R_0} - \frac{1}{R}\right) - \delta_t \omega \rho_0 R\dot{R} - P_{ac}(t), \end{aligned} \tag{5}$$

where P_{g0} is the initial gas pressure inside the bubble and δ_t is the total damping coefficient that combines radiation damping, viscosity damping, thermal damping and shell friction damping. S_p is the bubble shell elasticity parameter, σ is the surface tension at the bubble shell, κ is the polytropic state coefficient of the gas inside the bubble and P_v denotes the vapor pressure of the liquid. At time $t > 0$, a pressure P_{ac} is superimposed on the constant hydrostatic/equilibrium pressure P_0.

Assuming that the main source of nonlinearity is the nonlinear oscillation of insonated bubbles, the model for propagation of US waves though UCA can be described by the linear-wave equation for inhomogeneous medium given as

$$\frac{\partial^2 P}{\partial x^2} - \frac{1}{c_0^2}\frac{\partial^2 P}{\partial t^2} = -\rho_0 N \frac{\partial^2 V}{\partial t^2}, \tag{6}$$

where V is the volume of a single bubble and N the number of diluted bubbles per liter liquid [7]. The volume change of a spherical microbubble during oscillation can be described as

$$\frac{\partial^2 V}{\partial t^2} = \frac{4\pi}{3}\frac{\partial^2 R}{\partial t^2} = 4\pi\left(2R\dot{R}^2 + R^2\ddot{R}\right). \tag{7}$$

B. Simulations

The propagation of an US wave through nonlinear media can be simulated using the Burgers' equation (3). This is shown in Fig. 1 for different propagation distances; the solid, dotted and dashed curves represent an US wave propagating through a nonlinear medium for increasing distance from the transducer.

When either the attenuation or the nonlinearity is zero, an exact solution for the Burgers' equation can be derived. Otherwise, the solution has to be approximated. For a single frequency source, an approximated solution of the Burgers' equation is given by Hamilton [2] as

$$P(x,\tau) = \sum_{n=1}^{\infty} b_n(x)\sin(n\omega_0\tau), \tag{8}$$

where b_n are the Fourier coefficients representing the spectral amplitudes of the n-th harmonic. In case the attenuation exceeds the nonlinearity ($\Gamma < 1$), the first two spectral coefficients can be approximated as

$$\begin{aligned} b_1 &= e^{-\alpha x} - \frac{1}{32}\Gamma^2 e^{-\alpha x}(1-e^{-2\alpha x})^2 + O(\Gamma^4), \\ b_2 &= \frac{1}{4}\Gamma(e^{-2\alpha x} - e^{-4\alpha x}) + O(\Gamma^3). \end{aligned} \tag{9}$$

Equation (9) is suitable to derive the nonlinearity coefficient β by using a curve fit of the approximated solution (8) on the experimental measurements. In fact, this curve fitting gives the spectral coefficients b_n from which Γ can be extracted.

An analytical solution for equation (6) cannot be obtained, therefore it is solved numerically by discretizing $P(x,t)$ and $R(x,t)$ and map them to a spatial and temporal grid. Hence, equation (6) can be solved numerically using

$$\begin{aligned} P_{i,j} = {} & 2P_{i,j-1} - P_{i,j-2} + {c_0}^2 \Delta t^2 \frac{P_{i+1,j-1} - 2P_{i,j-1} + P_{i-1,j-1}}{\Delta x^2} \\ & + 4\pi\rho_0 {c_0}^2 \Delta t^2 \left[2R\dot{R}^2 + R^2\ddot{R}\right]_{i,j-1}, \end{aligned} \tag{10}$$

where $P_{i,j}$ and $R_{i,j}$ are the discretized pressure and bubble radius, respectively, at each point in space i and time j. Δt and Δx are the temporal and spatial step sizes. The US wave propagation is then simulated by alternately solving equation (10) to obtain P_{ac} and substituting this into equation (5) for each time step i to calculate the bubble radius and its derivatives [8].

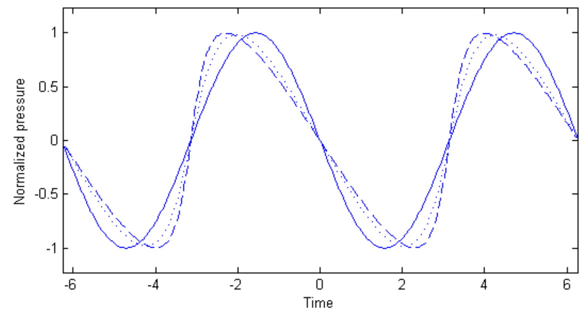

Fig. 1 Simulated propagation of an US wave using the Burgers' equation.

C. Measurement setup

To validate the models, a measurement setup is built for the measurement of the nonlinear distortion of an US wave propagating through different dilutions of UCA (Fig. 2). This setup consists of a large tank filled with water. A single element US transducer (Panametrics V360) with a nominal resonance frequency of 2.25 MHz ± 0.5 MHz is mounted fixed through the wall of the tank. An Hanning-windowed pulse of 20 sine cycles is designed using Labview® (National Instruments) and uploaded to a waveform generator (Agilent 33220A). The waveform is amplified using a RF power amplifier (ENI 240L) before it is transmitted to the transducer.

Acoustically transparent tubes (SpectraPor) containing different UCA concentrations are placed at the transducer focus D to have the maximal pressure in the contrast agent dilution. The diameter of these tubes is 22 mm. The focal distance, defined as $D = r^2/\lambda$ with r the diameter of the transducer and λ the US wavelength, is equivalent to the transition between the Fresnel and the Fraunhofer field [6]. The UCA in the tubes consists of a dilution of Luminity™ in saline with concentrations up to 0.2%. Aligned with the transducer, a hydrophone (Onda HGL-0400) with a bandwidth of 250 kHz to 20 MHz is used to measure the US waves that passed through the tube. The hydrophone is coupled to an amplifier (Onda AH-2010-025) and a National Instruments A/D-interface (NI-5122). The data acquisition is programmed in Labview®.

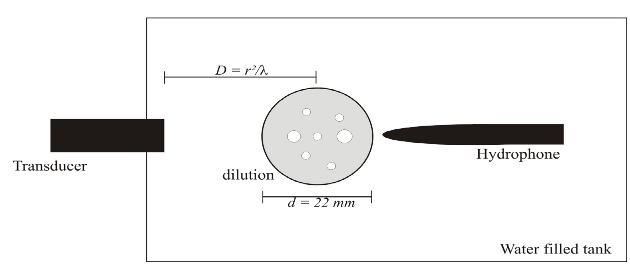

Fig. 2 Schematic overview of the measurement setup.

All measurements are performed with a low US mechanical index of 0.1 at the transducer focus to avoid bubble collapse. The frequency range is 0.5 – 3.5 MHz with steps of 0.5 MHz, which is around the resonance frequency of Luminity™.

III. Results

From the measurements it can be seen that for increasing UCA concentration, the nonlinearity of the US wave increases. Furthermore, for frequencies close to the microbubble resonance (2-2.5 MHz) and UCA concentrations above 75 μL/L, a phase shift arises in the second harmonic of the US wave. This is shown in Fig. 3 for high UCA concentrations (300 μL/L) at a frequency close to the microbubble resonance frequency (2.5 MHz).

Using the Burgers' equation, the US wave propagation is simulated for different propagation distances as shown in Fig. 1. Using equation (9), the ratio of nonlinearity Γ can be determined from a given US wave with an accuracy of 5% when the nonlinearity is in the range of $0.3<\Gamma<1$. The Burgers' equation is not suitable to simulate the phase shift in the second harmonic as raised in the measurements. However, the combination of the modified RPNNP and the linear-wave equations can be used to predict the US wave propagation around the resonance frequency (2-3 MHz) and for higher UCA concentrations (>75 μL/L). This is shown in Fig. 4, however, the position of the phase shift does not correspond to the measurements.

IV. Discussion and conclusions

The ratio of nonlinearity (β) can be estimated for UCA concentrations up to 75 μL/L using the approximated solution of the Burgers' equation for $\Gamma<1$. Further research will be done to extend this to a larger range of nonlinearity.

Close to the UCA resonance frequency (2-3 MHz), the measurements show a phase shift in the second harmonic of the US wave for concentrations higher than 75 μL/L. The Burgers' equation is not suitable to simulate this phase shift, but using the combination of the modified RPNNP and the linear-wave equations, the US wave propagation behavior can be simulated. However, the phase shift is not properly positioned yet. Further research will be done to make a more accurate prediction.

In general, the results show that the Burgers' equation provides an accurate description of the nonlinear propagation of US waves through UCA for concentrations up to 75 μL/L. For higher concentrations and for frequencies around the UCA resonance frequency (2-2.5 MHz), the combination of the modified RPNNP and the linear-wave equations can provide a better prediction of the nonlinear propagation of US waves through UCA.

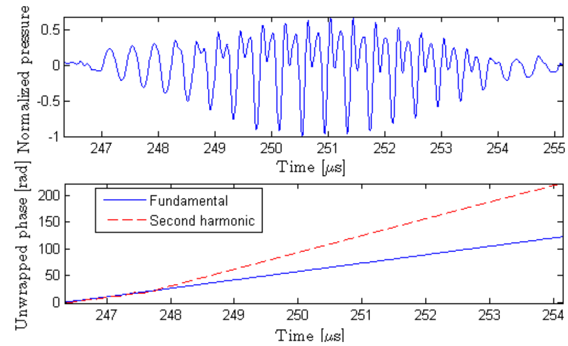

Fig. 3 Normalized pressure and unwrapped phase for an US wave at 2.5 MHz and high concentration Luminity™ (300 μL/L).

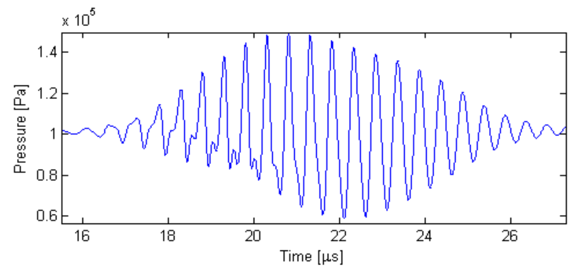

Fig. 4 Simulated propagation using the combination of the modified RPNNP and the linear-wave equations.

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