Effects of nonlinear ultrasound propagation through varying contrast-agent concentrations

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Introduction: Several methods are being developed for quantitative contrast echography. These methods aim at the assessment of perfusion defects or alterations, caused for instance by the presence of ischemic or cancerous tissue [1, 2]. In order to extract quantitative data from contrast echography, the concentration of the diluted ultrasound contrast agent (UCA) must be accurately measured. To this end, the sensitivity to UCA of ultrasound (US) imaging techniques has been increasingly improved in the past decade by the introduction of several dedicated contrast-enhancement imaging modes, often referred to as harmonic modes, which exploit the nonlinear behaviour of the UCA microbubbles [3].

A common measure for the performance of these imaging modes is the contrast-to-tissue ratio (CTR), which is the ratio between the acoustic backscatter coming from UCA and tissue [4]. The determination of the CTR is usually based on independent measurements of the backscatter from UCA and tissue, while the interaction between the two systems is not considered. In this study, the nonlinear distortion of US propagating through varying concentrations of Definity® UCA (Bristol-Myers Squibb) is measured and modeled. The implications on contrast imaging are also discussed and quantified.

Methodology: For the analysis of nonlinear distortion, a narrow-band US signal was transmitted by a single element circular transducer. After passing through a latex tube filled with different concentrations of UCA, the distorted pressure wave was measured using a calibrated hydrophone (Onda HGL-0400). Two different US sequences were used: a ten period sinusoidal wave was used for the analysis of the harmonic content of the distorted US wave, while a sequence of three pulses of 2 periods, the first and third pulse having half amplitude, was used to determine the implications on power modulation contrast detection modes.

All measurements were performed with a low Mechanical Index (MI) of 0.1 (measured in the centre of the UCA dilutions, corresponding also to the transducer focal distance) and contrast concentrations up to 36μL/L. The concentration is defined in terms of gas volume per liquid volume. The investigated concentration interval is suitable for quantitative measurements because it provides, based on dedicated measurements performed by commercial scanners (Sonos 5500 and iE33, Philips Medical Systems), an approximately linear relationship between UCA concentration and backscattered acoustic intensity. Two

US frequencies, 1 and 2 MHz, respectively below and close to the resonance frequency of Definity® UCA, were used.

The measured US signals were fitted by a nonlinear model derived from the Burgers equation (approximated to the second order) and describing the nonlinear sound propagation through a homogenous medium [5]. The results were also compared to numerical simulations of the combined linear-wave and modified Rayleigh-Plesset equations as described by Zabolotskaya and Soluyan [5, 6, 7]. This approach considers the bubble dynamics as the main source of nonlinearity.

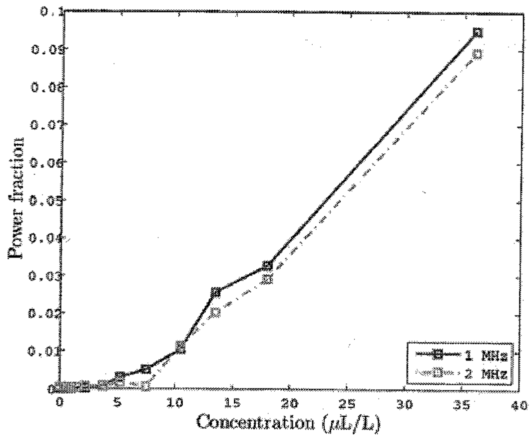
Additional in vitro measurements were made to quantify the effects of US nonlinear propagation through UCA on the signal coming from a tissue mimicking phantom (ATS Laboratories) in ultra-harmonic, second harmonic, and power modulation mode by a Sonos 5500 and an iE33 US scanner. Software Q-Lab (Philips Medical Systems) was used for the acoustic quantification.

Results: The measurements showed an average increase of US distortion for increasing UCA concentration at both the investigated frequencies. This distortion can be measured as the fraction of the total power that is transferred to the second harmonic (Fig. 1). The increase of other harmonics (sub-, ultra- and super-harmonic) was less significant. An increase of the attenuation for increasing UCA concentrations was also found. Despite the attenuation, the power modulation measurements revealed an increased energy for increasing concentrations within the investigated range.

The Burgers model fits showed a high correlation coefficient (larger than 0.97 for all concentrations) at 1 MHz. Based on the Burgers model, the nonlinearity coefficient β was also estimated [5]. For the considered range of concentrations, $\beta \in (0, 100)$. For the measurements at 2 MHz (closer to resonance frequency), the Burgers model could not provide accurate fits. In fact, at this frequency the bubble dynamics seems to be the dominant contribution to the US distortion. Therefore, the numerical simulations integrating the linear-wave and the modified Rayleigh-Plesset equations were adopted to predict the US distortion. The power-spectrum prediction was satisfactory. Obviously, accurate parameter estimations, such as by the Burgers model, cannot be obtained by numerical simulations.

Figure 2 shows two distorted waves at 1 and 2 MHz. The typical saw-shaped curve, explained by classic nonlinear propagation theory and well predicted by the Burgers model, is clearly recognizable at 1 MHz. At 2 MHz, the saw-shaped distortion is replaced by an asymmetry between compression and rarefaction, which is clearly related to the dynamics of coated bubbles. The distortion increases for increasing UCA concentration.

The in vitro measurements by the commercial scanners confirmed the increasing US distortion for increasing UCA concentrations. This effect was especially noticeable for ultra-harmonic imaging.



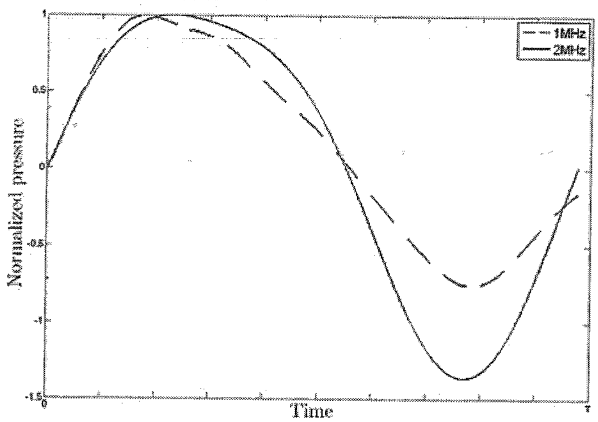


Fig. 1. Second harmonic power fraction.

Fig. 2. Distorted US wave, 13.5 $^{\mu L}/_{L}$ Definity®.

Conclusions: The nonlinear distortion of US propagating through UCA dilutions was investigated for different concentrations of Definity®. For the measurements performed at 1 MHz, below resonance, the presented analysis by the Burgers model provides a suitable approach for quantification of the nonlinear distortion. Instead, the Burgers equation is not suitable for modelling nonlinear distortion of US propagating at 2 MHz. As this frequency is closer to the resonance frequency of the adopted UCA, models incorporating the nonlinear bubble dynamics are likely to provide better results.

In general, as confirmed by our measurements with commercial scanners, the US distortion increases for increasing UCA concentration. Therefore, attention should be paid to the nonlinear propagation of US through contrast when evaluating contrast enhancement modes. In particular, the CTR can be negatively affected by the effects of nonlinear propagation through UCA.

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