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Experimental setup for synchronous optical and acoustical observation of contrast microbubbles

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ABSTRACT:

In clinical ultrasound, blood cells cannot be differentiated from surrounding tissue. A contrast agent has been added to the blood that helps to differentiate between blood and other tissue types. Ultrasound contrast agents consist of low-solubility gas microbubbles encapsulated by a stabilizing shell. With mean diameters below 6 μm , these microbubbles are small enough to pass through the lung capillaries. To improve the predictability of the dynamic behavior of contrast agents, we observe contrast microbubbles under insonification. Our experimental setup has been designed for simultaneous optical and acoustical observations of ultrasound contrast agents. The optical part was calibrated using a microelectronic device as a calibration object. Our first result is the observation of ultrasound-induced disruption of a thick-shelled agent.

INTRODUCTION:

Ultrasonic imaging is a relatively cheap, reliable diagnostic technique. In clinical ultrasound, blood cells cannot be differentiated from surrounding tissue, due to the low acoustic impedance difference between blood cells and their surroundings. A contrast agent has been added to the blood that helps to differentiate between blood and other tissue types, which consist of low-solubility gas microbubbles encapsulated by a stabilizing shell, small enough to pass through the lung capillaries. The resonance frequencies of ultrasound contrast agent microbubbles lie within the clinical diagnostic range. Agents can be designed to specifically target a receptor system [1], thus facilitating ultrasonic molecular imaging [2]. Ultrasonic contrast-enhanced imaging applications depend on the detectability of microbubbles. The detectability in turn depends on the ultrasonic pulsing scheme, which in turn depends on the predictability of the contrast microbubble behavior. A bubble in a sound field can be considered a simple forced damped harmonic oscillator. However, physical parameters such as the mass of the bubble-liquid system, the mechanical resistance, and the stiffness of the system are dependent of the bubble radius.

Therefore, the spherically symmetric oscillating behavior of ultrasound contrast agent microbubbles has been described with more complicated models based on the Rayleigh-Plesset equation, modified for the presence of a shell [3, 4]. To improve the predictability of the dynamic behavior of contrast agents, we observe contrast microbubbles under insonification.

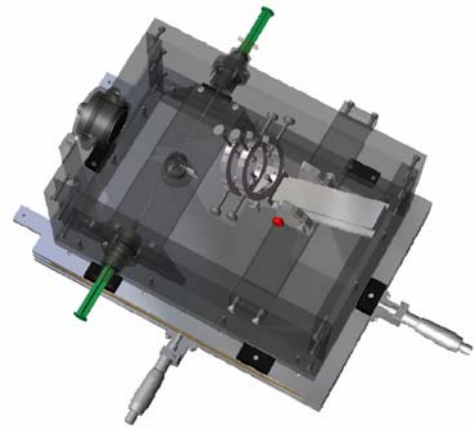


Figure 1: Top view of experimental setup container on top of x - y -table. The capillary, attached to the syringes, is spanning the full width.

EXPERIMENTAL SETUP:

The experimental setup has been designed for simultaneous optical and acoustical observations of ultrasound contrast agents. The measurements are done in a Perspex container filled with deionized water, which stands on top of a custom-built micron-adjustable x - y -table (*cf.* Figure 1). A single-element transducer can be mounted to the side of the container. Also, there is a holder for conventional array transducers of commercial echo machines. To circumvent attenuation effects of the microbubbles between the transducer surfaces and the acoustic foci, the contrast agent is inserted through a syringe into a CUPROPHAN[®] RC55 cellulose capillary (Membrana GmbH, Wuppertal) with a 200 μm inner diameter and an 8 μm wall thickness. This capillary spans the full width of the container. The central part of the capillary has been illuminated from below by a DC21 40,000 footcandle fiber optic continuous light source (StockerYale, Inc., Salem, NH, USA). On top of the capillary, focused at the capillary, there is a LUMPlanFL 60 \times high numerical aperture (NA=0.90) water immersion objective lens

(Olympus Deutschland GmbH, Hamburg) with a 2 mm working distance. The microscopic system is a customized BXFM-F unit (Olympus), with two eye-pieces and two separate camera outlets. The spherical foci of our single-element transducers with center frequencies between 0.5 and 10 MHz coincide with the optical focus (*cf.* Figure 2), allowing for simultaneous optical and acoustical interrogation (*cf.* Figure 3).

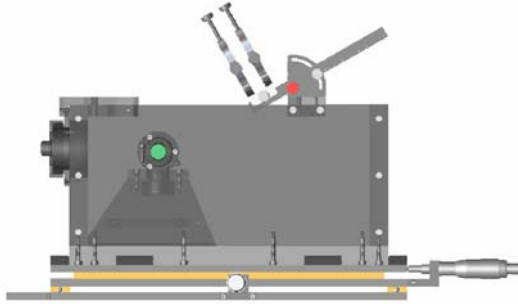


Figure 2: Side-view of experimental setup container.

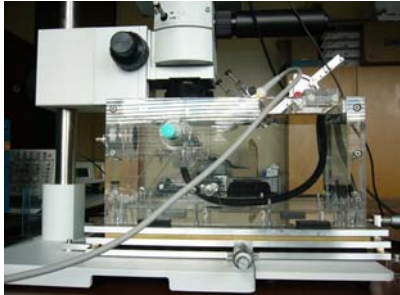


Figure 3: Photograph of experimental setup during operation.

CALIBRATION:

We used a microelectronic device with a $6.1\ \mu\text{m}$ wire width (*cf.* Figure 4), recorded with a WAT-902DM monochrome CCD camera (Watec Co., Ltd., Tsuruoka-Shi, Yamagata-Ken, Japan).

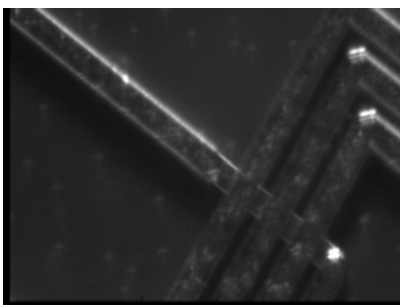


Figure 4: Photograph through microscopic system of microelectronic device with $6.1\ \mu\text{m}$ wire width. The frame corresponds to a $94.4 \times 70.8\ \mu\text{m}^2$ area.

FIRST RESULT:

Thick-shelled bubbles have demonstrated gas release during a high-amplitude ultrasonic cycle [5,

6]. The increased pressure difference between inside and outside of the bubble during the expansion phase of the wave causes the shell to be stretched across a critical deformation, resulting into its mechanical cracking. The released bubble has an oscillation amplitude much higher than an encapsulated bubble of the same size. Figure 5 shows Quantison™ (Upperton Ltd, Nottingham, UK) microbubbles subjected to pulsed ultrasound from a commercial echo machine, operating at a 3 MHz center frequency and a mechanical index $MI=1.5$. Clearly, one bubble demonstrates disruption. The released bubble has been observed to dissolve in subsequent frames.

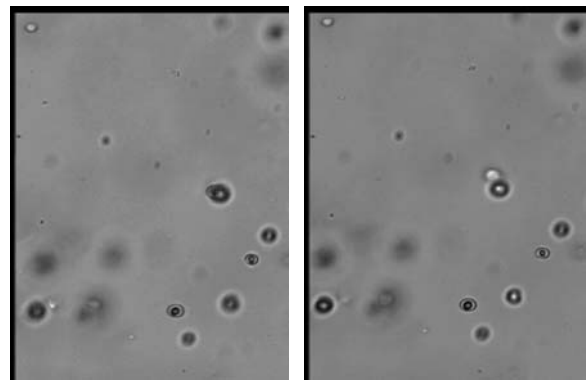


Figure 5: Quantison™ microbubbles subjected to pulsed ultrasound from a commercial echo machine, operating at a 3 MHz center frequency and a mechanical index $MI=1.5$. Inter-frame time is 100 ms. The frame corresponds to a $94.4 \times 70.8\ \mu\text{m}^2$ area.

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