Tracking the deformation of a tissue phantom induced by ultrasound-driven bubble oscillations

M Tinguely, O K Matar, V Garbin
Department of Chemical Engineering, Imperial College London, London SW7 2AZ, United Kingdom
E-mail: m.tinguely@imperial.ac.uk

Abstract. Microbubbles are used as contrast agents in ultrasound medical imaging. Once the microbubbles are injected into the body, they flow through the vascular system, confined by viscoelastic boundaries. The proximity of the boundaries affects the dynamics of the bubbles in ultrasound, in a manner that depends on the boundary’s viscoelastic properties. Experiments on violently collapsing bubbles have revealed the dynamics of deformation of blood vessel walls. However, the deformation field induced by a bubble undergoing small-amplitude oscillations, relevant for ultrasound imaging, is difficult to access in experiment, and has not been reported yet. We present an experimental method to measure the deformation field induced by a bubble oscillating inside a microchannel within a tissue phantom. We use high-speed video microscopy to track the displacement of tracer particles embedded in the phantom, along with the dynamics of the bubble.

1. Introduction
Microbubbles have gained a lot of interest in the biomedical field for their ability to enhance contrast in ultrasound imaging, and for their potential to promote the uptake of drugs at ultrasound-targeted locations in the body [1]. Once the microbubbles are injected into a patient’s body, they flow through the vascular system, confined by viscoelastic walls. This configuration is quite different from the classical problem of a bubble near a rigid boundary or a free surface [2] because both the geometric confinement and the viscoelastic properties of the walls have to be taken into account to accurately predict the dynamics of the bubble, and the effect on the deformation of walls. Experiments on the growth and collapse of a microbubble inside a blood vessel show vessel distension and invagination [3]. Numerical simulations have investigated similar configurations to predict the bubble dynamics, and the displacement and the stress induced on the surface of the vessel wall [4, 5, 6]. These phenomena are strongly dependent on the properties of the confining walls. To accurately model the interaction of ultrasound-driven bubbles inside vessels with confining walls, it is crucial to characterize the deformation of the surrounding tissue induced by the bubble dynamics. Experimental investigations, however, usually only report the deformation of the solid surface [7, 8].

We present a method to measure the deformation of both the surface and the bulk of a tissue phantom induced by an oscillating bubble. We use side-view and bottom-view high-speed video microscopy to track the displacement of particles embedded in the bulk of the tissue phantom. The ultrasound-driven bubble oscillates in a microchannel inside the phantom, in order to mimic a vessel within a tissue. Our setup allows extracting the deformation of the
phantom as a function of time in horizontal and vertical cross-section of the phantom, providing information to reconstruct the local deformation in four dimensions, \((x, y, z, t)\).

2. Methods

**Preparation of tissue phantoms** - We used agarose gel as tissue phantom. The viscoelastic properties are controlled by tuning the concentration of the gels. We can thus mimic different tissues by producing gels with the corresponding properties [9]. To produce a gel, a solution of agarose powder (A9539, Sigma Aldrich) was dissolved in water, heated to 95°C, and stirred for 30 min. Tracer particles for particle image velocimetry (9-13 µm hollow glass spheres, 110P8, LaVision GmbH) were then added to the solution. The solution was poured into a mold where we previously positioned a square capillary (8290, CM Scientific, 1.2×1.2×5 mm) on two spacers to create the channel inside the gel. The solution was left to cool and set for 24 hours at room temperature. The gel was removed from the mold, and the capillary was gently removed from the gel, leaving an empty channel inside the gel. The gel sample was 40 mm long, 20 mm wide, and 7 mm thick, and the bottom of the 1.2×1.2×40 mm long channel ran 2 mm above the bottom of the gel sample (see fig. 1). We present results for a gel with an agarose concentration of 2% w/v. The shear modulus \(G = 43 \pm 2\) kPa was measured from a creep test using a stress-controlled rotational rheometer (Discovery HR-1, TA Instruments).

**Experimental setup** - Figure 1 shows the experimental setup. A piezoelectric transducer (Physik Instrumente, P-121.05) was glued on the bottom surface of a glass dish placed on the stage of an inverted microscope (Olympus, IX71). The gel sample was positioned on the bottom of the dish with the direction of the channel along the \(x\) axis, and submerged in ultrapure water. A 45° mirror was placed in water for side-view imaging. The objective could be placed either below the channel, or below the mirror for respectively bottom-view and side-view visualizations in transmission mode. The deformation of the channel by the oscillating bubble was imaged at 4× magnification and recorded using a high-speed camera (Photron, FASTCAM SA5) at 60,000 frames per second. A waveform generator (Agilent, 33220A), and a power amplifier (T&C Power Conversion, AG 1021) actuated the piezoelectric transducer. The amplitude of the pressure oscillations inside the channel was recorded with a hydrophone (RP acoustics, PVDF RP 33 s). We measured the pressure amplitude by positioning the hydrophone tip inside the channel, through the gel, after the experiments. Nitrogen microbubbles of controlled size were generated with a co-flowing microfluidic device [10]. By moving the outlet of the device, we were able to inject only one bubble into the channel. We present results for a bubble having a radius \(a = 350\) µm. We applied a single ultrasound burst of 10 cycles at 10 kHz. For a peak-to-

![Figure 1](image-url)

Figure 1: Schematic of the experimental setup and definition of the coordinate system. The black dash lines represent the optical path. (a) \((x, z)\) plane, with microscope objective below the bubble for bottom-view visualizations. (b) \((y, z)\) plane, with microscope objective below the mirror for side-view visualizations.
peak pressure amplitude of 60 kPa, the maximum amplitude of oscillations of the bubble was \( \Delta a = (a_{\text{max}} - a_{\text{min}})/2a_0 = 5\% \) of the initial radius. Due to the confinement, the bubble slightly deviated from a spherical shape towards an ellipsoid during the oscillations. The deviation from spherical shape remained small: the maximum deformation parameter, \( D = |d_1 - d_2|/(d_1 + d_2) \), where \( d_1 \) and \( d_2 \) are the major and minor axis of the ellipsoid in the vertical plane through the center of the bubble, did not exceed 2.3 \%.

**Particle tracking** - The gel deformation was measured by tracking the displacement of the tracer particles with sub-pixel accuracy. The positions of the particles were determined in each frame to obtain trajectories. First, the positions of the particles were obtained with accuracy of

![Diagram](image)

**Figure 2:** (a) Schematic of the experiment showing the planes where the visualizations were recorded. The microscope objective is placed either below the bubble (H) or below the mirror (V) for bottom-view or side-view visualization. (b) Trajectories of tracer particles from a side-view high-speed movie of the vertical plane V1 through the center of the bubble. The white dashed lines represent the horizontal planes H1, H2, and H3. (c) Trajectories of tracer particles from a bottom-view high-speed movie of the horizontal plane H1 containing the top surface of the channel. (d) Trajectories of tracer particles from a bottom-view high-speed movie of the horizontal plane H2 through the center of the bubble. (e) Trajectories of tracer particles from a bottom-view high-speed movie of the horizontal plane H3 containing the bottom surface of the channel. In (b-e), the particle displacement is magnified by a factor of 50 for clarity, and the color changes with the distance from the bubble.
one pixel by finding the local maxima from binarized images [11]. The grayscale values of the pixels in the original image were then used to improve the accuracy. For each particle position obtained from the first step, we calculated the center of mass of the particle using as weight the brightness of the pixels within a radius of 4 pixels.

3. Results
We present four visualizations, shown in fig. 2 (b)-(e), which reveal the deformation field in the horizontal planes containing the top and the bottom of the channel: H1 and H3, respectively, and in the vertical and the horizontal planes through the center of the bubble: V1 and H2, respectively. Because of buoyancy, the bubble is in contact with the top wall of the channel, but does not touch the other walls. The trajectories within the top planes H1 (c) and the bottom plane H3 (e) are mostly radial, centered at the (x,y) position of the center of the bubble. In contrast, within the planes passing through the center of the bubble, V1 (b) and H2 (d), the particles describe elliptic trajectories. The deformation occurs on all four walls, with a larger amplitude of deformation for the wall that is in contact with the bubble. The high spatial and temporal resolution of these measurements enable us to track the deformation induced by the localized oscillating pressure applied by the bubble on the top wall, but also the complex deformation field induced by the fluid flow generated by the volumetric oscillations of the bubble. A quantitative analysis of the deformation field in the phantom will be the subject of future work. Using this setup we have recently investigated the deformation induced by a bubble oscillating near a planar viscoelastic surface [12].

4. Conclusion
We presented an experimental method to measure the deformation induced by an oscillating bubble in a channel inside a tissue phantom. Using high-speed video microscopy, we tracked the displacement of tracer particles embedded in the phantom, and extracted the deformation field on the surface of the channel and in the bulk. Accurate measurements of the deformation field will help develop models to predict the effect of viscoelastic confinement on the dynamics of bubbles for different geometries.

Acknowledgments
M. T. acknowledges support from the Swiss National Science Foundation under grant P2ELP2_151953. O. K. M. acknowledges support from the Engineering and Physical Sciences Research Council (UK) through the MEMPHIS Programme Grant (EP/K003976/1).

References
[1] Ferrara K, Pollard R and Borden M 2007 Annual Review of Biomedical Engineering 9 415–447
[2] Blake J R and Gibson D C 1987 Annual Review of Fluid Mechanics 19 99–123
[3] Chen H, Kreider W, Brayman A A, Bailey M R and Matula T J 2011 Physical review letters 106 034301
[4] Hay T A, Ilinskii Y A, Zabolotskaya E A and Hamilton M F 2012 The Journal of the Acoustical Society of America 132 124–137
[5] Coralic V and Colonius T 2013 European Journal of Mechanics-B/Fluids 40 64–74
[6] Hosseinkhah N, Chen H, Matula T, Burns P and Hynynen K 2013 The Journal of the Acoustical Society of America 134 1875–1885
[7] Van Wamel A, Kooiman K, Harteveld M, Emmer M, Ten Cate F J, Vershuis M and De Jong N 2006 Journal of controlled release 112 149–155
[8] Yoshida K, Nakatani S, Tsukamoto A, Ushida T and Watanabe Y 2008 Japanese Journal of Applied Physics 47 4290
[9] Duck F A 1990 Physical properties of tissues: a comprehensive reference book (Academic Press)
[10] Benson B R, Stone H A and Prud’homme R K 2013 Lab on a chip 13 4507–4511
[11] Crocker J C and Grier D G 1996 Journal of colloid and interface science 179 298–310
[12] Tinguely M, Hennessy M G, Pommella A, Matar O K and Garbin V 2015 submitted