Controlled Cavitation and Sonoporation in Microfluidics

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CONTROLLED CAVITATION AND SONOPORATION IN MICROFLUIDICS

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INTRODUCTION

Cavitation – the growth and collapse of mostly empty bubbles – is commonly attributed to large scale or very rapid flows, e.g. at ship propellors or at fuel injection nozzles. Cavitation is very aggressive to materials and one reason is its ability to focus fluid flows to very small scales; the bubbles concentrate the energy from the fluid during their shrinkage. Only recently the attention from largely free cavitation bubbles has shifted towards the study of more confined bubbles [1–5]. Here we report on an experiment to exploit cavitation in microfluidic systems or so called lab-on-a-chip devices for flow handling and biological cell manipulation. In microfluidics generally due to the small scales low Reynolds number flows are observed. Yet, cavitation bubble-induced flows allow to reach a high Reynolds number regime also on these small scales. By exploiting this rarely studied flow regime new techniques for liquid and cell handling become feasible. Here, we will report first on the effect of a channel wall on the bubble dynamics and then present an application for cell handling and membrane poration.

EXPERIMENTAL SETUP

A single and well controlled cavitation bubble is generated with an expanded beam from a pulsed and frequency-doubled Nd:YAG laser (Solo PIV, New Wave, USA) focused into a light absorbing liquid (water or cell growth medium supplemented with Direct Red 81 or Trypan Blue, respectively). The energies of the laser pulses are in the range $5-50\,\mu$J and have a duration of 6 ns. The focus of the laser beam and the image plane of the 40x objective of the inverted microscope superimpose, thus allow to take in-focus images with a high-speed camera (up to 1 million frames/s, HPV-1, Shimadzu Corp., Japan) of the bubble outline. A filter block reflects only the green laser light and lets pass all other wavelengths for proper illumination with a fiber lamp. The microfluidic chambers are first designed with a CAD software, transfered onto a lithographic mask, and then etched into a silicon wafer. The microsystems are then fabricated from a polymeric material PDMS (polydimethylsiloxane, Sylguard 184, Dow Corning, USA) using conventional molding technique and bonded to a glass cover slip or polypropylene foil.

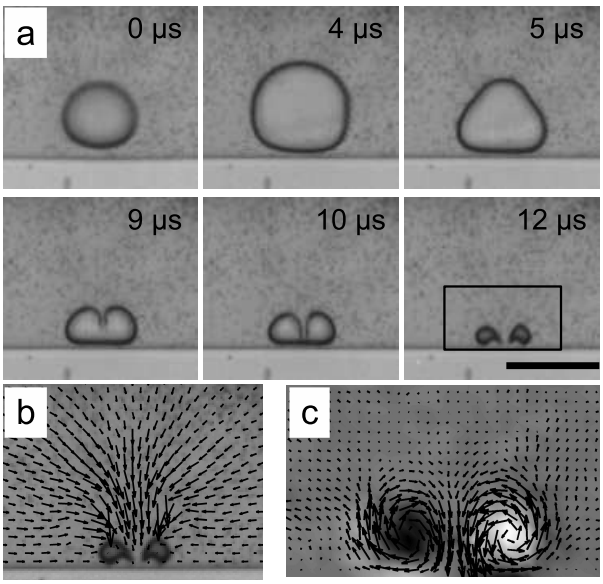

Figure 1. PLANAR BUBBLE DYNAMICS CLOSE TO A CHANNEL WALL. (a) SELECTED FRAMES FROM A HIGH-SPEED RECORDING DEPICTING THE FORMATION OF A LIQUID JET TOWARDS THE WALL. THE SCALE BAR IS $150\,\mu$m IN LENGTH. (b) VELOCITY FIELD OF THE FLOW AFTER THE BUBBLE HAS SPLIT UP DUE TO THE IMPACTING JET FLOW. THE LONGEST VELOCITY VECTOR CORRESPONDS TO 7.4 m/s. (c) VORTICITY PLOT AVERAGED OVER THE TIME INTERVAL $t \in [24\,\mu\text{s}; 64\,\mu\text{s}]$ AFTER BUBBLE CREATION.

BUBBLE DYNAMICS CLOSE TO A BOUNDARY

It is well known that a bubble collapsing at some stand-off distance from an infinite boundary develops an *inertia driven* flow focusing phenomena. The proximity of the boundary disturbs the radial flow, e.g. it causes a faster inflow from the wall-distant part of the bubble interface. There flow becomes focused and a jet flow directed towards the rigid boundary is generated. This jet flow travels through the bubble center, penetrates the lower bubble interface, and impacts onto the boundary where it creates a long lasting vortex ring. Figure 1 a) depicts the stages of a bubble expanding and shrinking now within a microfludic device at a channel boundary, see bright lower border. During shrinkage the bubble obtains a triangular shape. The top part of the bubble interface flips towards the boundary between $t = 5\,\mu$s and $t = 9\,\mu$s and thereby creates a jet with a tip diameter of approx. $8\,\mu$m. It impacts with a velocity of roughly 25 m/s onto the boundary. Later the two tiny remains of the bubbles become entrained in two counter-rotating vortex rings. An averaged flow field over $40\,\mu$s after the jet impact is depicted in Fig. 1c. Tracing the maximum of the vorticity $c = \nabla \times \underline{u}(x,y)$ within this time interval we find a decrease (not shown) from $10^5\,\text{s}^{-1}$ to $3 \cdot 10^4\,\text{s}^{-1}$. Thus, the center of the vortex rotates with an initial rotation rate of more the 10.000 rotations/s, which is sufficient to mix fluid within a time-interval of a few microseconds.

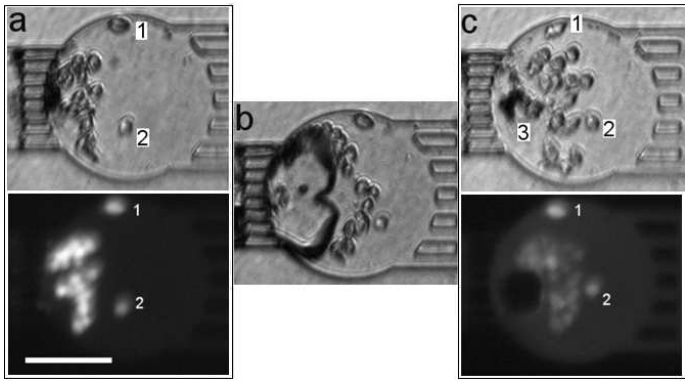

Figure 2. (a) THE CIRCULAR CHAMBER CONTAINS 19 VIABLE AND CALCEIN-AM LOADED HL 60 CELLS. FRAME (b) DEPICTS THE BUBBLE WITH A JET FLOW TOWARDS THE LEFT GRID STRUCTURE. (c) TOP: BRIGHT FIELD PICTURES 10 min LATER; THE CELLS LABELED 1 AND 2 ARE ONLY SLIGHTLY DISPLACED. THE DARK STAINED CELLS CLOSE TO LABEL 3 ARE DEAD CELLS (c) BOTTOM: FLUORESCENCE PICTURE 85 s AFTER THE CAVITATION EVENT: THE MEAN INTENSITY VALUE OF THE CELLS MARKED 1 AND 2 HAVE DECREASED BY LESS THAN 3% WHEREAS THE CELLS CLOSER TO THE BUBBLE SHOW A DROP IN INTENSITY BY A FACTOR OF 2.5. THE SCALE BAR IS $100\,\mu$m IN LENGTH.

CELL MEMBRANE PORATION

Now suspension cells (human leukemia or HL60 cells) are exposed to a cavitation bubble. We are interested in the temporary rupture of the cell membrane. Therefore, the cells are loaded in advance with a fluorescent marker, Calcein-AM. This allows to use the fluorescence intensity inside the cell and that of the surrounding liquid as an indicatar for dye release, thus to probe for a transient opening of the cell membrane.

Figure 2 shows the effect of the bubble on cell positions during and after a single bubble oscillation in a specially designed microchamber: the cells closest to the center of the bubble (label 3 in Fig. 2c) are displaced farthest from their initial position while cells labeled 1 & 2 in Fig. 2a and c have only slightly moved. The bubble pulsation also exhibits a jet flow towards the left grid structure, Fig. 2b. It is also very interesting to compare the fluorescence emission of the cells as shown in the bottom row of Fig. 2a and c. Clearly, the cells close to the bubble experience a remarkable reduction of the intensity whereas cells labeled 1 & 2 seem to be unaffected. Additionally, the level of background fluorescence increases, which can be explained with a leakage of Calcein from the cells upon poration.

Laser-induced sonoporation in microfluidics is a novel and very advantageous method for viable or permanent poration (not shown here) of cells. By adjusting the laser spot with respect to the cells selective and viable drug delivery can be achieved. Additionally, no wiring is necessary and any optical accessible area on the microfluidic device can be addressed.

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