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Sonoporation

Using ultrasound for targeted drug delivery

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Introduction

Sonoporation is the transient permeabilisation and resealing of a cell membrane with the help of ultrasound and/or an ultrasound contrast agent.

Ultrasound contrast agents consist of elastic shelled gas-filled microbubbles. These are used to enhance the echogenicity of blood in ultrasound diagnostics. In a specific ultrasound field these microbubbles oscillate. This oscillation creates cell membrane permeabilisation allowing increased uptake of drugs.

As ultrasound can be focused, the cell membrane stimulation can be targeted, for example malignant tumors.

Our work focused on understanding the biophysical mechanisms behind sonoporation in order to improve its efficiency.

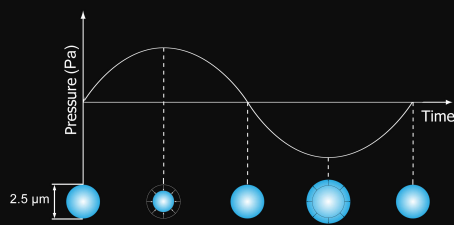


Fig. 1 - Microbubble oscillation in an ultrasound field.

Methods

We sonicated HeLa cancer cells in the presence of fluorescent labeled Micro-Marker. An MI of 0.2 at 6.6MHz was used, well within the clinical diagnostic range. We recorded the behaviour of the microbubbles using a high-speed camera and a confocal microscope (Fig.2). After sonication a z-stack was performed in order to precisely locate the microbubbles.

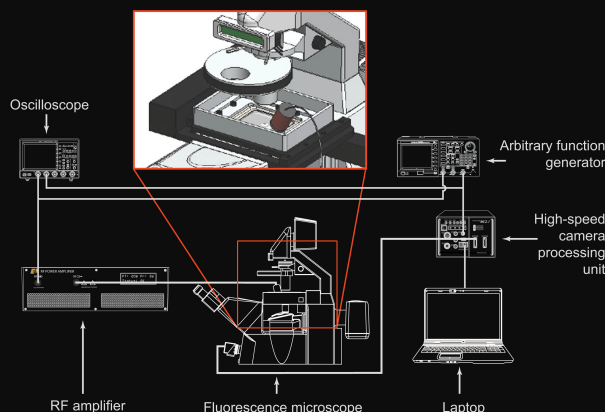


Fig. 2 - Schematic illustration showing configuration for simultaneous high-speed photography and fluorescent imaging.

Results

Within several seconds of sonication, microbubbles were observed to be attracted to cells and subsequently penetrate the cell membrane (Fig. 3). The z-stack proved that the bubble had entered the cell and subsequently dissolved (Fig. 4).

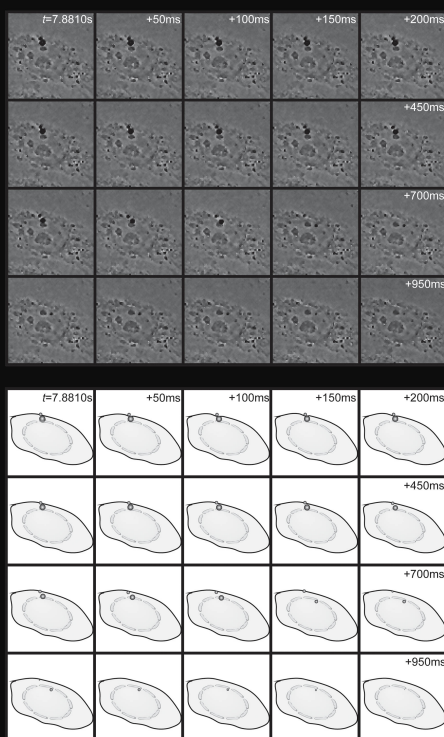


Fig. 3 - Microbubble entering cell recorded using a high-speed camera (top) and schematic representation (bottom). Each frame corresponds to 37 x 37 (μm)².

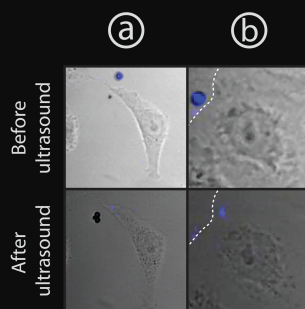


Fig. 4 - Location of fluorescence in two HeLa cells before and after sonoporation. After sonication fluorescence was located in the center of the cell.

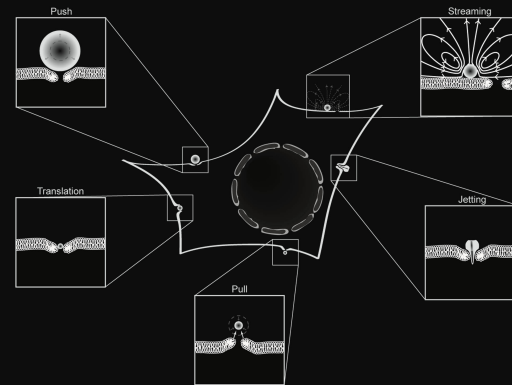


Fig. 5 - Schematic representation of 5 of the phenomena involved in sonoporation.

Conclusions

It has been demonstrated that lipid-shelled microbubbles can be forced to enter cells at a low MI. Hence, if a therapeutic load is added to the bubble, ultrasound guided delivery could be facilitated at diagnostic settings. In addition, these results may have implications for the safety regulations on the use of ultrasound contrast agents for diagnostic imaging.