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# Sonoporation: using ultrasound for targeted drug delivery

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Clinical diagnostic (B-mode) ultrasound imaging has been in use since 1951. In the past few years its potential for therapeutic uses has been expanding; for example in physiotherapy, high-intensity focused ultrasound for surgery, aesthetic facial rejuvenation and ultrasound-enhanced thrombolysis.

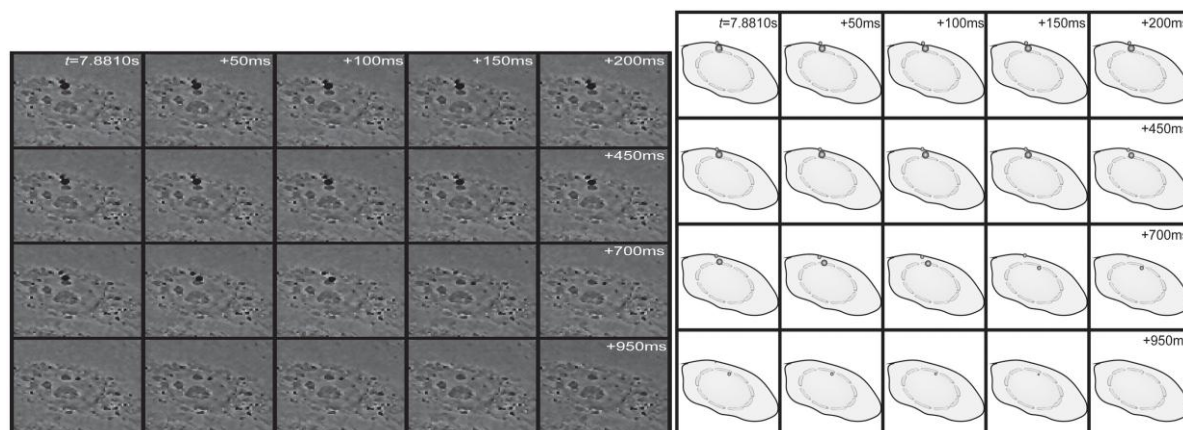
In medical diagnostics ultrasound contrast agents are commonly added to the blood stream in ultrasonic imaging: contrast-enhanced ultrasound (CEUS). They consist of microscopically small bubbles (microbubbles) encapsulated by elastic shells. During an ultrasound cycle microbubbles oscillate, *i.e.*, they expand and subsequently contract. Depending on their elastic properties, on the local conditions, and on the acoustic settings, they move in the direction of the sound field, coalesce with other microbubbles, fragment, jet, cluster, release their contents, and dissolve in the surrounding liquid. Taking advantage of these behaviours we explored the use of using encapsulated microbubbles as possible vehicles for targeted drug delivery. Such a non-invasive, localised, side-effect-free method would revolutionise drug delivery as we know it.

This increased uptake has been attributed to the formation of transient porosities in the cell membrane that have diameters up to 0.1  $\mu\text{m}$ , *i.e.*, big enough for the transport of drugs into the cell. The pores reseal themselves within one minute. The ultrasound-assisted transient permeabilization of a cell membrane is called sonoporation. Understanding the physics underlying sonoporation is of uttermost importance for the development of ultrasound-activated therapeutic agents.

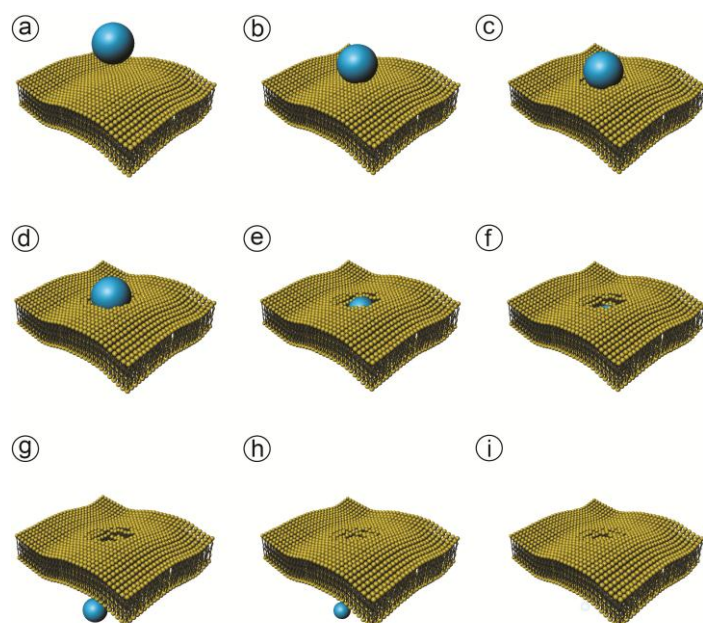
We designed a setup consisting of a state-of-the-art 6.6MHz ultrasound transducer and a custom made sonication chamber combined with a confocal fluorescent microscope and high-speed camera to allow for simultaneous sonication and optical observation. Cervical cancer cells were cultivated in an OptiCell<sup>TM</sup> chamber and placed in the sonication chamber. Fluorescent MicroMarker microbubbles were inserted into the OptiCell<sup>TM</sup> chamber and subsequently sonicated at an MI=0.2.

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After several seconds microbubbles were seen to enter the cancer cells and subsequently dissolve (*cf.* Figure 1). This was verified by analysing the high-speed photography and by 3D scanning for the microbubble fluorescence. Figure 2 shows a 3D schematic representation of the microbubble penetrating the cell membrane and dissolving. The cell cytotoxicity after sonoporation was negligible.



**Figure 1 – High-speed photographic (left) and schematic (right) sequence showing two microbubbles entering and dissolving in a HeLa cancer cell.**



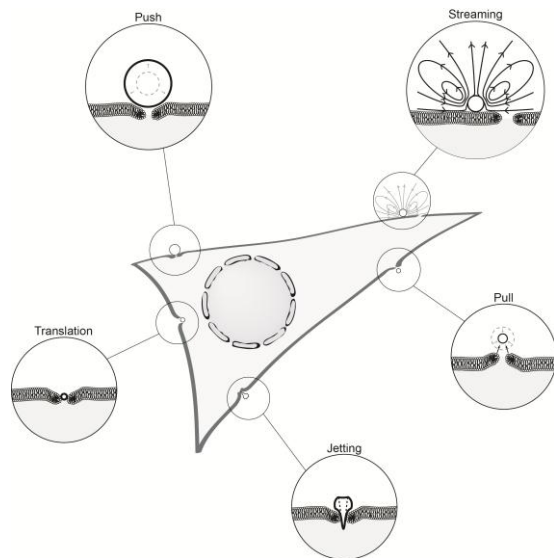
**Figure 2 – Schematic representation of a lipid-encapsulated microbubble translating into a cell owing to radiation forces (frames a-g) and subsequently dissolving (frames h-i).**

This method is the first method ever observed that could allow a therapeutic load to be delivered directly into a cell. Current sonoporation hypotheses, summarised in Figure 3, can generate pores in the cells but require a separate drug delivery method.

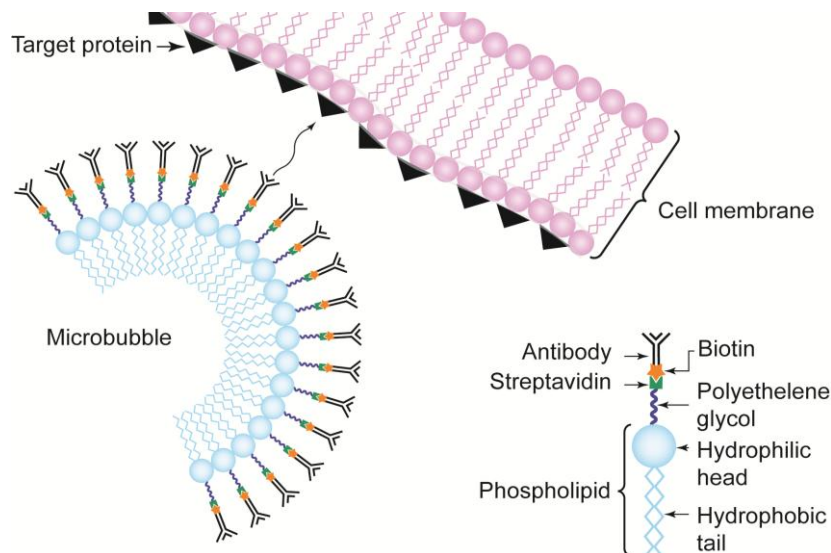
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The next steps in non-invasive ultrasound enhanced drug delivery would be to manufacture targeted microbubble that would be targeted to specific cells allowing double targeting. This would be achieved by attaching specific antibodies to the microbubble shell (*cf.* Figure 4).

In conclusion, in current clinical settings, four non-exclusive mechanisms are plausible for the physical explanation for sonoporation with the aid of ultrasound contrast agent microbubbles with microbubble translation being very promising for its ability to deliver the drug load directly into cells.



**Figure 3 – Schematic representation of the five physical mechanisms supposedly involved in sonoporation.**



**Figure 4 – Schematic illustration showing the multi-block structure of microbubbles necessary to target specific cells.**

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Notes: