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Low Intensity Pulsed Ultrasound Stimulation of Cancer Cells: Experimental Set-Up and Digital Twin to Study Mechanotransduction

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1. Introduction

Ultrasound (US) based modalities are widely used in biomedical applications for both diagnostic and therapeutic purposes, as they are non-invasive and non-ionizing. Low intensity pulsed ultrasound (LIPUS) is a non-destructive technique that aims to mechanically stimulate the cells to elicit biological response through a process known as mechanotransduction. While LIPUS stimulation has largely been studied for tissue regeneration, recent studies have demonstrated its potential to inhibit tumor proliferation and migration, in addition to enhance drug delivery (Calero et al., 2025; Wood and Sehgal, 2015). This approach could be envisioned as a complementary strategy for the treatment of cancers that have a poor response to traditional modalities, including intracranial cancers. To develop relevant LIPUS-based therapies in oncology, it is essential to understand how US interacts with tumor cells and the tumor microenvironment (TME) to trigger mechanotransduction.

In-vitro studies are therefore essential to correlate US parameters and mechanisms with cellular responses. To this end, an experimental set-up was designed to perform LIPUS stimulation on glioblastoma (GB) spheroids – which is the most common cerebral cancer in adults.

This work presents an experimental set-up for LIPUS stimulation and its digital twin. To characterize the mechanical constraints induced by US on cells, it is necessary to control the acoustic dose delivered to the GB spheroids. In order to validate the model, numerical estimations of acoustic pressure were compared with experimental measurements. With further development, this digital twin will become a key tool for investigating the effects of LIPUS on cancer spheroids.

2. Materials and methods

2.1 LIPUS stimulation set-up

The GB spheroids (U251) (diameter < 1mm) are cultured in 200 µL of cell medium in a 96-wells plate (Greiner Bio-One, Austria) with an incurvated bottom.

LIPUS stimulation is performed using an immersion 1 MHz-transducer (Imasonic, France) with a 13 mm diameter driven by a waveform generator (TTI, UK) coupled with a power amplifier (KMP Electronic Bulgaria).

A 3D-printed support was specifically designed to hold the bottom of the well at h = 28 mm from the front face of the transducer (beginning of the far field). A water filled balloon was used as a coupling medium (Figure 1a) in order to allow wave propagation from the transducer to the well.

2.2 LIPUS signal

The LIPUS signal consisted of 1 MHz bursts with a duration τ = 200 μs, amplitude V_{pp} = 125 mV and a pulse repetition period (PRP) of 1 ms.

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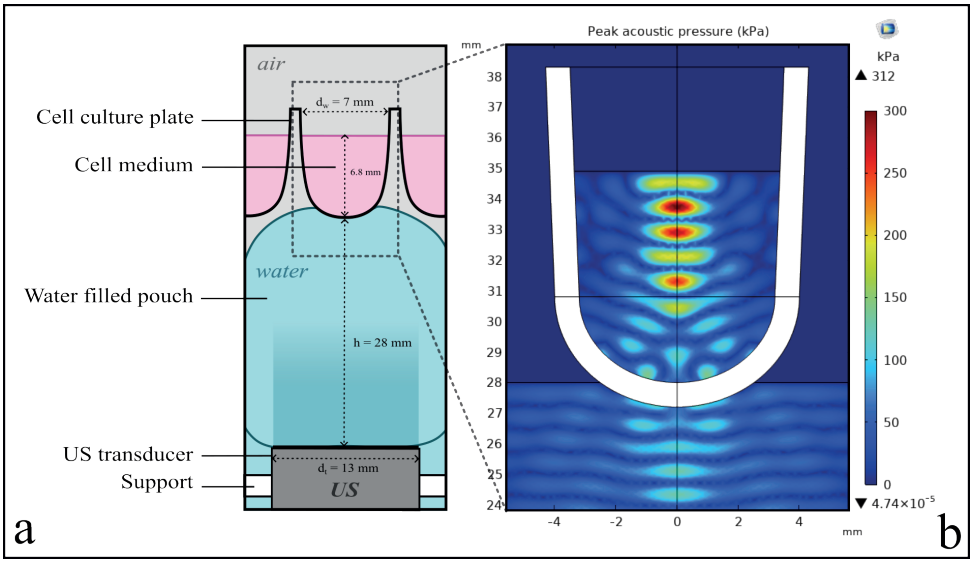

Figure 1. a. Diagram of the in-vitro LIPUS stimulation set-up. b. Peak acoustic pressure field in the fluid domain obtained using the digital twin on COMSOL Multiphysics® for the LIPUS signal (Incident pressure p_i equal 57 kPa).

2.3 Digital twin

The digital twin was developed using a finite element (FE) method on COMSOL Multiphysics®. The *Acoustic Propagation in Fluids* module (coupling medium and cell medium) and the *Solid Mechanics* module (cell culture plate), were used to simulate the propagation of the US waves in time domain.

This model was validated using experimental pressure measurements taken with a 0.5 mm needle hydrophone (Precision Acoustics Ltd, UK) placed in a well that was completely submerged in water using the method described in Majnooni et al. (2023). This allows us to determine the value of the incident pressure p_i to be input into the digital twin.

3. Results and discussion

The model (Figure 1b) was developed based on the configuration of the experimental set-up including air/medium interface and the water balloon. The figure shows the peak acoustic pressure distribution in the well for our LIPUS signal for an incident pressure p_i = 57 kPa. Although this model is still under development, it is expected to become an essential tool to better understand the US-induced mechanisms. Through parametric studies, it will enable quantification of the acoustic dose delivered to the cells for different sets of US parameters (τ, V_{pp}, PRP). To enhance the model's relevance in the context of in-vitro studies on biological material, the GB spheroid component will be integrated inside the well using its mechanical properties measured by atomic force microscopy (AFM) nanoindentation (Rico et al., 2008). The digital twin will allow the quantification of the mechanical stress at the spheroid scale, which cannot be accessed experimentally.

In parallel, LIPUS stimulation of fluorescent GB spheroids will be carried out to identify the US parameters that induce anti-tumorous effects, assessed through fluorescence measurements. By combining these in vitro experiments with FE-simulations from our model, we aim to identify the physical mechanisms that trigger mechanotransduction. Moreover, correlating the information of the mechanical properties of the spheroids to their response to LIPUS treatment will provide a better understanding of the interaction of US with cells.

In this context, the digital twin will guide the selection of US parameters to generate controlled stimuli in different cell models and induce mechanotransduction. This approach can then be translated to more realistic biological models, such as tumor spheroids grafted onto normal brain tissue slices (*i.e.* organotypic models) (Piris et al., 2023).

4. Conclusions

This work presents an in-vitro setup designed to study the effects of LIPUS stimulation on GB spheroids, complemented by the development of a digital twin to

better understand US-induced mechanotransduction. These approaches are part of a broader framework to evaluate how LIPUS stimulation can be translated into cancer therapy.

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Contributor Role

Conceptualization, EP, CB; Resources, MC, ED, PL, CB; Methodology, MB, YG, PL, CB; Software, MB, YG, PL, CB; Validation, PP, MC, EP, PL, CB; Formal analysis, MB, PP, YG, MC, PL, EP, CB; Investigation, MC, PL, EP, CB; Data curation, MB, PL, CB; Writing – original draft preparation, MB, PL, CB; Writing – review, MB, PP, YG, MC, PL, EP, CB; Supervision, PL, CB; Project administration, PL, CB; Funding acquisition, MC, EP, PL, CB.

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References

Calero, A., Fernández-Marcelo, T., Sury, P. *et al.* (2025). Migration and invasion of cancer stem cells are prevented by low-intensity pulsed ultrasound therapy. *Cancer Cell Int, 25*, 212. https://doi.org/10.1186/s12935-025-03854-3

Majnooni, M., Lasaygues, P., Long, V., Scimeca, J.-C., Momier, D., Rico, F., Buzhinsky, N., Guivier-Curien, C., & Baron C. (2022). Monitoring of in-vitro ultrasonic stimulation of cells by numerical modelling. *Ultrasonics, 124*, 106714. https://doi.org/10.1016/j.ultras.2022.106714

Piris, P., et al. (2023) Conditional generation of free radicals by selective activation of alkoxyamines: towards more effective and less toxic targeting of brain tumors. *Chem Sci., 14* (29), 7988–7998. https://doi.org/10.1039/d3sc01315d

Rico, F., Wojcikiewicz, E. P., & Moy, V. T. (2008). Atomic force microscopy studies of the mechanical properties of living cells. In *Applied Scanning Probe Methods IX: Characterization* (pp. 89–109). Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-540-74083-4_4

Wood, A., & Sehgal, C. (2015). A review of low-intensity ultrasound for cancer therapy. *Ultrasound in Medicine and Biology, 41*(4), 905–928. https://doi.org/10.1016/j.ultrasmedbio.2014.11.019