Modeling low-intensity ultrasound mechanotherapy impact in tumor dynamics

Mechanotherapy represents an emerging frontier in cancer treatment, harnessing the power of mechanical forces to selectively target and eradicate cancer cells. The underlying principle behind this approach lies in the observation that cancer cells exhibit increased sensitivity to mechanical stimuli, which is perceived and translated into biochemical signals in a process known as mechanotransduction.

Low-intensity ultrasound (LIUS) has emerged as a potential therapy in this context. However, the precise mechanisms of its action and the diverse responses elicited by different frequencies, energies, and configurations of LIUS remain incompletely understood. Ongoing biological studies are aimed at unraveling the underlying mechanisms. Nevertheless, biological experiments are costly and time-consuming.

To address this challenge, we present a mathematical model of LIUS mechanotherapy and its impact on cancer progression at two different scales: i) slow-time scale t in which growth, migration, and poroelastic rearrangements occur, and ii) fast-time scale t_u representing ultrasound propagation through the tumor. To couple the slow-time and fast-time scales, the model incorporates a mechanotransduction function that operates during ultrasonic time intervals and induces tumor dynamics response upon surpassing a specific stress threshold.

The self-developed computational model is solved using finite element analysis in a two-dimensional plane strain setting. While many parameters are sourced from literature, the mechanotransduction parameters are derived from preliminary experimental data involving in vitro ultrasound treatment of melanoma cancer stem cell spheroids. To replicate the in vitro experiments (see Figure 1) and calibrate the mechanotransduction parameters, the model undergoes training by simplifying the degrees of freedom.

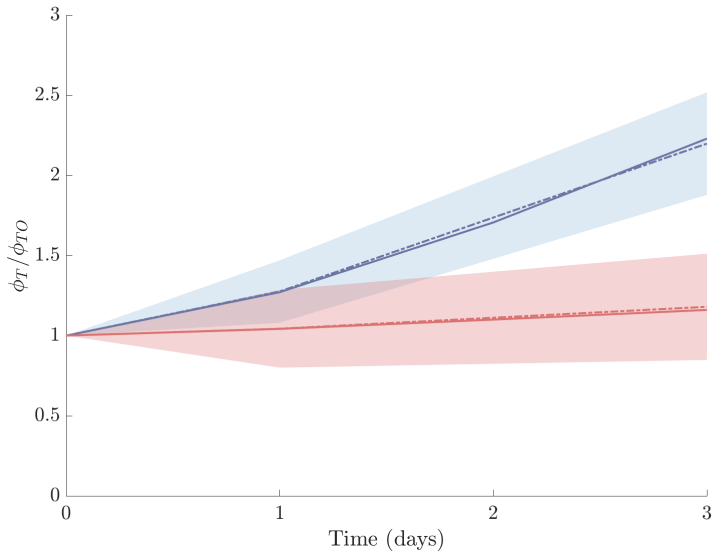

Figure 1. Computational modeling can reproduce LIUS mechanotherapy in vitro*, suggesting a reduction of cell viability for sonicated spheroids (red lines) at f = 5MHz, A = 1.5kPa, in comparison with non-sonicated spheroids (blue lines).*

Then, we propose to apply LIUS to a previously validated model to evaluate the complete system of equations. Numerical results (see Figure 2) suggest that the proliferation of healthy cells ($\emptyset_H$) remains selectively activated while tumor cells ($\emptyset_T$) diminish proliferation, allowing for modeling selective therapy. Furthermore, we observe ultrasound diffraction through the tumor, with shadow zones where the ultrasound does not act through the difference of existing viscosities between the tumor and the medium.

In the absence of movement, the presence of zones with different stress levels may lead to instabilities. The tumor phase then grows by breaking the initial tumor symmetry, leading to a concentration of cells at points of lower stress, as depicted in Figure 2. This stress is transmitted to the ECM phase ($\emptyset_M$), which in turn deregulates its growth.

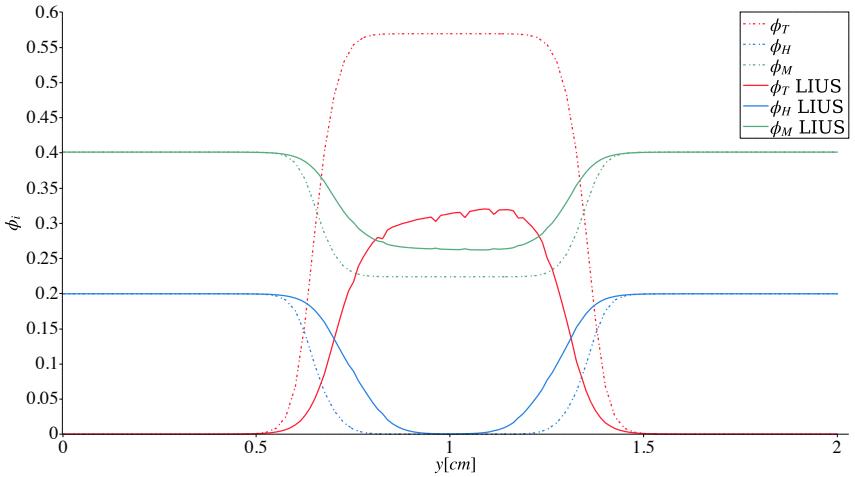

Figure 2. Selective therapy and patterns*. LIUS selectively reduces the proliferation of the tumor cell phase, causing patterns in low-stress areas while the healthy phase remains unaltered. Results at time t = 21days.*

These observations shed light on why some experimental studies have reported the continued proliferation of cells. Tumor cells may proliferate in shadow zones where the threshold stress is heterogeneously reached, resulting in no significant difference in total cell count compared to the control. However, the spatial distribution of cells could be a critical factor for investigation.

If migration is allowed, the system is able to dissipate and homogenize differences in growth or stress while tumor cells migrate in the predetermined direction of ultrasound propagation regulating patterns internally due to cross-diffusion process.

In summary, our multiscale model provides a promising approach for exploring the effects of LIUS mechanotherapy on cancer cells. With further development and experimentation, this approach could provide a novel complement treatment option for cancer that is less aggressive, more effective, and more cost-efficient than current therapies.