Microbubble – microvessel interactions and their influence on UmTDD: Simulation study

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Introduction

Ultrasound-mediated Targeted Drug Delivery (UmTDD) is a rapidly advancing field with great potential for localised treatment of many diseases. Microbubbles (µBs) are used as the target objects and are ensonified to oscillate and produce bioeffects. Even though physics of µB oscillations have been thoroughly studied [1-3], the impact of confinement within microvessels on their behaviour is non-trivial [2,3].

The size of gas-filled micro-bubble contrast agents has both an impact on bubble distributions within the body and dictates the resonance frequency when driven acoustically. Upon exposure to low-amplitude acoustic fields, µBs are known to spherically oscillate at small amplitudes. As oscillations increase in amplitude, approximation of expansion as being symmetric becomes increasingly inaccurate, eventually leading to µB rupture at sufficiently large peak negative pressures. This ability to selectively direct or amplify acoustic energy through µB oscillation is the basis for their use in localised therapeutic applications.

Understanding the existence and extent of µB-cell interaction becomes a determining factor within the complex microvasculature-fluid system. Thus, it becomes essential to better understand the influence of small blood vessels on µB flow and oscillation under a driving acoustic field in order to exploit UmTDD as a clinically applicable technology.

It is well known that real physical systems at equilibrium become nonlinear when driven at large amplitudes, which has consequences on the effective resonance frequency of the system. Changes in external acoustic pressure will create µB resonance frequency shifts, having a direct effect on their oscillation amplitude. Hence, these effects must be taken into account experimentally when studying UmTDD applicability. Furthermore, µBs enclosed within capillary networks suffer an extra degree of hydrostatic and mechanical damping due to confinement and vessel-wall effects respectively which lead to a shift in their resonance frequency, invalidating the assumption of using the Minnaert frequency during these treatments. In addition, the continuous interaction with the capillary wall will produce a further shift of the resonance frequency, as high- and low-pressure regions are created around the µB.

In this work, we study how the resonance frequency of contrast agent µBs is modified as a function of two key parameters: relative radius between capillary and µB, and µB proximity to the vessel wall. We use acoustic-pressure amplitude values relevant for UmTDD treatments, which have been reported to be from hundreds of kPa to a few MPa [4,5], to ensure we are operating in a regime of maximised µB oscillation. The obtained results help us to better understand the key parameters influencing UmTDD efficiency and allow us to develop a platform in which we can directly study key parameters related to its efficacy and potential.

Methods

Micro-bubble oscillation is modelled using two-phase flow in the finite element analysis (FEA) software COMSOL Multiphysics©. We theoretically assess the resonance frequency shift µBs undergo within blood capillaries and how it is influenced by µB position and size relative to blood capillary diameter. These studies included µB radii from 0.5 to 4 µm within 5 µm radius capillaries. Before studying the influence of µB relative size and position, µB behaviour in an infinite fluid domain was studied and validated against Rayleigh-Plesset behaviour.

Results

FEA COMSOL simulation has proven to be a good tool to obtain an approximate behaviour of µBs when confined within blood vessels. Prior to the study, the µBs were checked to follow the ideal gas law, as well as the Rayleigh-Plesset behaviour when acoustically driven in an infinite volume of fluid. These two previous studies were run to ensure data reliability (Fig. 1) and validated the use of a 2D system to optimize computation time while keeping data accuracy.

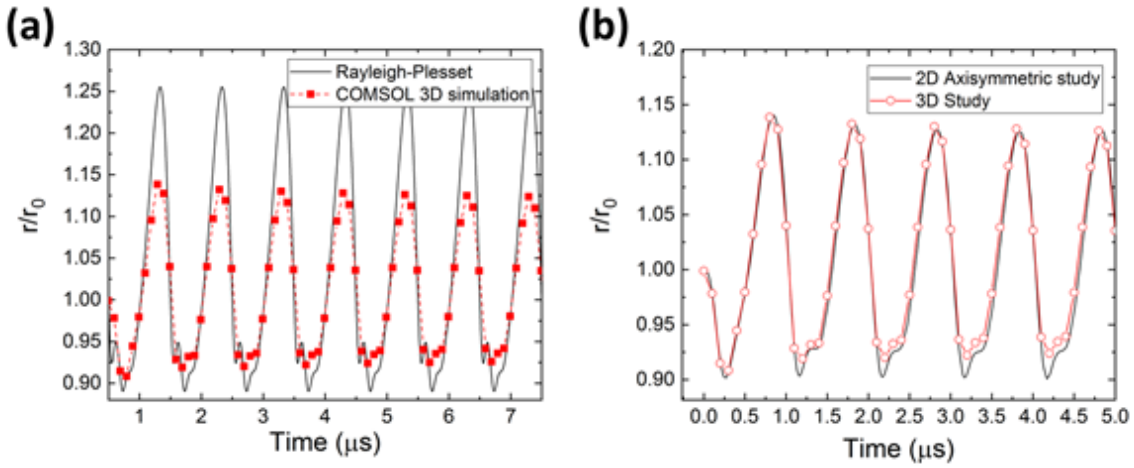

Fig. 1: Data validation. (a) shows the comparison between COMSOL results obtained from 3D geometries and the results obtained from solving the Rayleigh-Plesset equation. (b) Shows a comparison between COMSOL results obtained from simulations using 3D and 2D-axisymmetric geometries.

Confined µBs suffer a non-negligible decrease of their resonance frequency when compared with their correpsonding Minnaert frequencies (Fig. 2). However, when the confinement effects are insignificant, µBs re-gain their Minnaert frequency. This resonance frequency shift is due to an increase in the damping of the system, as both the surrounding fluid and the solid vessel wall contribute to it. This result could be hugely beneficial for the development of UmTDD technology for medical applications, as resonance freqeuncy shifts up to 44.2%, suggest that a greater response of the µBs would occur at its confined resonance frequency than at their Minnaert frequency.

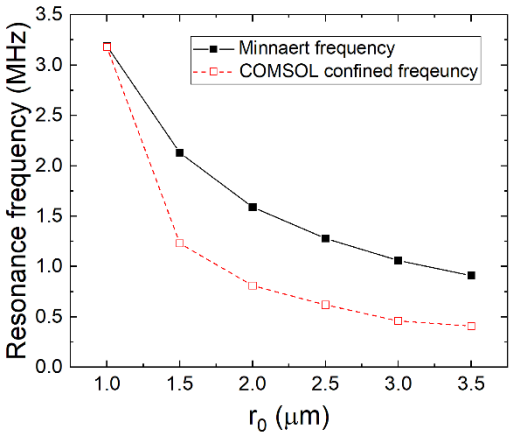

Fig. 2: Comparison between the resonance frequency of micro-bubbles when surrounded by an infinite volume of liquid (Minnaert frequency, as shown by the empty squares connected with a red-dashed line) and when confined within a blood vessel. When a 1 µm radius bubble is confined within a large enough vessel, the Minnaert frequency is recovered. As the bubble becomes highly confined, deviation from the Minnaert frequency becomes larger.

Proximity of the µBs to the vessel wall was studied in COMSOL to see how the different positions can influence the resonance frequency of the system (Fig. 3, where 0 represents the centre of the vessel). From

Fig. 3 it can be observed that as µB size increases, the resonance frequency shift decreases. Our resonance frequency study is limited to µB oscillations no larger than the internal diameter of the vessel, which was observed to take place from 2.5 µm radius bubbles upward. Hence, for radii above this value, a proper study of the resonance frequency of the system cannot be performed as oscillation amplitude exceeds the confinement of the vessel. It can be further observed from Fig. 3 that the maximum frequency shift as a function of µB position is of 120 kHz.

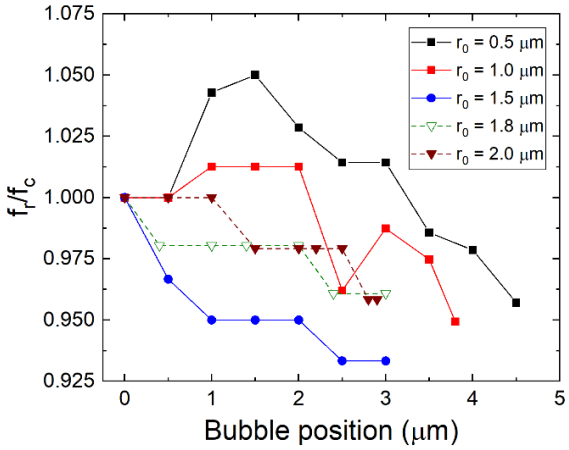

Fig. 3: Resonance frequency shift for different micro-bubble sizes as they approach the vessel wall. Their resonance frequency has been normalised to their resonance frequency when placed at the centre of the vessel (f_c).

Conclusions

In this work, we show that µB confinement and proximity to vessel wall are key factors to take into consideration to develop UmTDD protocols, as they have both been observed have an effect on the resonance frequency of the system. We have proved that simulation using COMSOL is an appropriate tool as it provides good agreement between theoretical and simulated results. Whereas confinement effects have been observed to produce a dramatic shift of the resonance frequency of the system (44% shift with respect to Minnaert frequency), proximity to vessel wall was observed to produce maximum frequency shifts of 120 kHz (representing maximum shifts of an 8.22%), becoming unimportant for UmTDD given the wide bandwidth of the used transducers.

The next step is to experimentally validate these results by using 3D-printed micro-channels using tissue-mimicking materials. These will be filled with blood-mimicking fluid altogether with 2-8 µm µBs, and the full system will be acoustically stimulated using several ultasonic frequencies that will allow determining the resonance frequency of the system by recording the µBs oscillation using high-speed camera technology and by adequately treating the obtained data.

References

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