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Piezoelectric micromachined ultrasound transducers (PMUTs) for acoustic positioning of suspended microtissues

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Introduction

Three-dimensional (3D) microscale *in vitro* culture models (microtissues) have become conventional drug development and regenerative medicine platforms. The physical manipulation of microtissues is instrumental throughout the whole microtissue use cycle. Existing techniques for handling are based on manual pipetting, which has limited precision and is time consuming. To unlock the full potential of microtissue technology, there is a pressing need to develop effective tools for controlled manipulation and positioning of such large and heterogenous biological entities, which we aim to address using acoustic manipulation. In this study, sound pressure fields generated by elastic membranes, which are actuated by piezoelectric thin-film transducers, are studied numerically. Strong trapping regions are formed 500 µm above the membranes and are shown to trap 200 µm microtissues. High trapping strength is achieved by mechanical decoupling between the membranes and the substrate.

Acoustic manipulation of microtissues

Acoustophoresis has been recently proposed as a label-free and biocompatible technique to manipulate and position microtissues. [1-2] Acoustophoresis uses non-contact forces arising from sound pressure fields to control the motion and the position of objects suspended in a fluid. In most techniques, acoustic standing waves are produced, creating pressure nodes toward which biological samples are pulled and trapped. Typically, acoustic waves are generated by bulk transducers made of lead zirconate titanate or interdigital transducers made of lithium niobate. In this study, we propose an innovative acoustic platform that leverages the power of piezoelectric micromachined ultrasound transducers (PMUT) to position suspended microtissues in 3D space. PMUTs are widely used in acoustic imaging and sensing, but only a few studies used them in acoustofluidic [3].

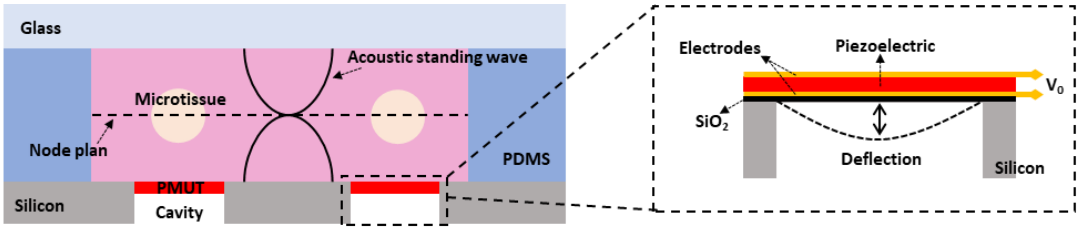

Figure 1: Schematic view showing the acoustofluidic positioning device.

PMUT-based acoustofluidic platform

A PMUT is a membrane composed of a passive elastic layer, usually silicon, and a piezoelectric layer such as aluminum nitride. PMUTs allow the miniaturization of high-resolution ultrasonic transducer arrays while offering good acoustic matching. The flexural vibrations of the membrane, which are caused by lateral strains generated from the piezoelectric effect, produce the acoustic waves. The resonance frequency of PMUTs depends on several parameters, including the density, flexural rigidity, and geometry of the membrane, therefore offering a large design space.

We envision a platform composed of a silicon chip containing an array of PMUTs with on top an acoustofluidic chamber with PDMS walls and a glass lid. A schematic of the platform is depicted in Fig. 1. The glass lid reflects the acoustic waves generated by the transducers and creates vertical standing waves in the chamber. PDMS has a very high transmission factor; therefore, the acoustic waves are expected to travel outside the chamber. This way, we can reduce the interference pattern's complexity and produce standing waves uniquely along the thickness direction. The height of the chamber was designed considering the resonance frequency of

the PMUTs to generate acoustic nodes in the middle of the chamber. This configuration would levitate the microtissues into the same plane and arrange them in an array defined by the sound pressure profile generated by a specific PMUT array design.

Numerical study

The platform's performance was numerically studied using a commercial FEM software (COMSOL Multiphysics). The chamber walls were set as perfect matching layers and the lid was considered a hard wall boundary to capture the behavior of PDMS and glass, respectively. The 1 mm diameter PMUTs consist of an elastic silicon membrane (80 µm thickness) and a piezoelectric actuator in aluminum nitride (1 µm thickness). Fig. 4A shows Gor'kov minima that form 500 µm above the PMUTs. These regions serve as strong acoustic traps for microtissues. The pitch between the PMUTs was found to strongly influence the intensity and the location of the potential minima. For example, by increasing the pitch from 1250 µm to 1500 µm, we could double the number of minima from two to four. The potential gradient along the vertical direction also increased, strengthening the trap. Figure 4A also shows that the transducers on the edges are less efficient in generating potential minima; thereby, particles might not be captured in this area. This effect is hypothesized to arise from the asymmetric environment of the edge transducers, which have only one neighbor, influencing the interference pattern. The impact of the edge effect can be minimized by optimizing the platform's design to generate a high potential gradient (e.g., with a 1500 µm pitch). These results show that the interference pattern of the acoustic waves is highly sensitive to small variations in the platform's design. Consequently, optimizing the design using FEM software is an important and cost-effective step in developing the platform. Current simulations indicate that the most promising layout possesses a pitch of 1500 µm.

Additionally, the simulations have shown that acoustic forces required for the levitation of 200 µm diameter microtissues could be generated by making trenches around the PMUTs. The trenches mechanically decouple the edges of the PMUTs from the silicon substrate, resulting in larger deflection than clamped membranes (Fig. 4B). Acoustic pressure is proportional to the deflection. Thus, the mechanical decoupling of the membranes also increases the strength of the acoustic traps. In the simulation, the trenches' effect was modeled by anchoring the membrane (fixed constraint condition) from a ring at its bottom, while the anchorage is made from the sides for a clamped membrane. The acoustic force was calculated based on the Gor'kov theory. For microtissues of 200 µm diameter, the z component of the maximal acoustic force, $F_{ac,z}$=35 nN, is about 9x larger than the sum of gravitation and Archimedes force, F_g=4 nN, showing the potential of the platform to levitate big particles in acoustic traps.

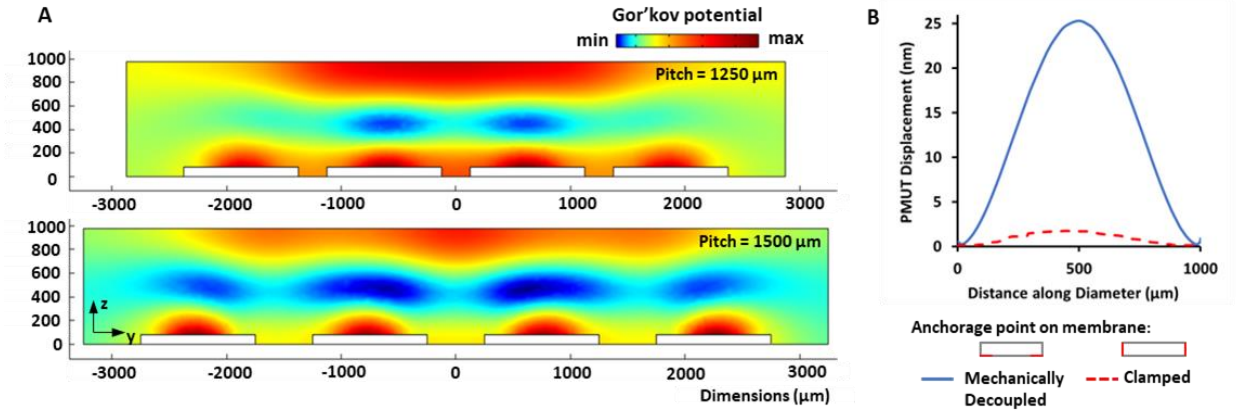

Figure 2: A) Gor'kov potential generated by 4 PMUTs at f_{res}= 777 kHz and V = 50 V with two different pitches. Color indicates the intensity of the potential. **B)** Deformation along the diameter of the membrane for clamped and mechanically decoupled PMUTs excited in the fundamental vibrational mode. A schematic of the anchorage is depicted for a clamped and mechanically decoupled membrane.

Conclusion

The numerical assessment of the platform showed that sufficient acoustic power is generated to levitate 200 µm diameter microtissues. The generation of high acoustic power in a minimally invasive fashion makes this technology a promising candidate for controlled positioning and manipulation of microtissues. Particularly, the technique would find applications in end-point analysis such as micro-histology, in which positioning several microtissues on the same plane is critical. Transducers are currently in fabrication and will be characterized. Additionally, the platform's accuracy and speed of positioning will be tested with microtissues of different sizes.

References

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