PHD POSITION

INTERACTION OF ULTRASOUND WITH 3D MICRO-ENVIRONMENT OF BONE CELLS: EXPERIMENTAL AND NUMERICAL STUDIES

Lab	Institut de Recherche sur les Phénomènes Hors Equilibre, **IRPHé**, UMR7342, Marseille, France https://irphe.univ-amu.fr/en
Duration	36 months starting from **sept./oct. 2023**
Skills	(bio)mechanics, acousto-µfluidics, computational modelling
Key words	In vitro ultrasound stimulation ; mechanotransduction; acoustic streaming ; multiscale; porous media; Finite Element model ; experimental models.
Funding	ANR project INVICT-US - **2150 € / month** (gross salary)
Supervisors	Cécile **Baron,** CR CNRS (HDR), and Carine **Guivier-Curien,** MCF AMU (HDR)

Context and preliminary work

Bone tissue is a complex biological tissue, capable of adapting to its mechanical environment by optimizing its structure, a process known as bone remodeling. Ultrasound stimulation (UStim) of bone regeneration was discovered in the 1950s and has been widely studied since. However, the underlying mechanotransduction mechanisms (translation of mechanical stimuli into biological response) remain poorly identified and this lack of knowledge fuels controversy, preventing the development of efficient and optimized therapeutic tools [1].

The characterization and quantification of mechanical stresses induced by ultrasound stimulation on bone cells (osteocytes) is essential to understand these mechanisms.

To gain insight into this multiscale and multiphysics issue, the development of an *in vitro* model is a first key-step. An *in vitro* UStim experimental set-up has been tested on 2D cell cultures (i.e. inside cell culture dishes) [2]. This experimental set-up is coupled to an equivalent Finite Element (FE) model in order to monitor and tune the acoustic dose delivered to the cells and thus provide a relevant interpretation of future biological results [3]. However, *in vivo*, osteocytes are not in a 2D configuration. They are surrounded by a fluid (called pericellular matrix) inside a complex 3D lacuno-canalicular network embedded in the extra-cellular matrix (ECM). This 3D micro-environment affects the interaction of UStim with cells and must be taken into account in both the experimental and FE models. To this aim, a commercial porous 3D scaffold (Alvetex™) has been implemented in the previous experimental set-up and an innovative BioMIM scaffold will be developed in the context of the ANR project INVICT-US.

The next step is to identify and quantify the mechanical stresses induced by ultrasound stimulation on the osteocytes and to understand the hydrodynamic phenomena that cause them. In this aim, the parallel development of a computational twin model is essential. It will give access to mechanical forces applied on the on the osteocytes, data inaccessible experimentally, which can be correlated to the experimental biological response.

Objectives

The objective of this PhD project is to to advance in the understanding of the mechanotransduction of bone cells stimulated by ultrasound, by experimentally and numerically modeling the interaction of ultrasound waves with their three-dimensional mechanical microenvironment.

One of the challenge is to identify the hydrodynamic phenomena inside this 3D micro-environment, such as acoustic streaming, likely to be involved in bone cells mechanotransduction induced by ultrasound waves (Fig. 1). These investigations will concern I) theoretical studies on microfluidics channels coupled with µPIV experiments; ii) experimental and numerical measurements related to the *in vitro* set-up integrating the biomimetic scaffold and iii) a numerical study using a finite-element model representing a realistic lacuno-canalicular network.

This subject is part of a larger project in collaboration with biologists to correlate the biological response of stimulated osteocytes to identified mechanical constraints.

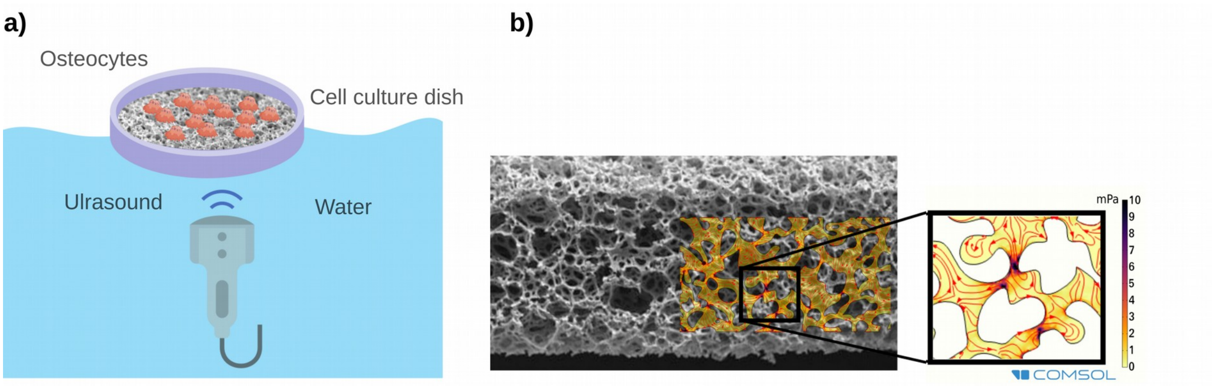

Figure 1: a) In vitro UStim of cells seeded in the 3D porous scaffold. b) Streaming velocities and fluid shear stress inside the 3D porous scaffold (Alvetex).

Profile

The candidate must have academic knowledge and/or experience in one or more disciplinary areas related to the subject: (bio)mechanics of fluids and solids, acoustics. FE modeling skills combined with a strong interest in experimental development is an essential asset to allow a quick handling of the implemented means. He/she will have to show synthesis, communication, rigor and methodology to be able to invest in the various aspects of the work requested.

How to apply ?

Please send a CV, cover letter and Master (M2) results to cecile.baron@univ-amu.fr; carine.guivier@univ-amu.fr. You can join some recommendation letters.

[1] F. Padilla, *et al.*, "Stimulation of bone repair with ultrasound: a review of the possible mechanic effects," *Ultrasonics*, vol. 54, no. 5, pp. 1125–1145, Jul. 2014, doi: 10.1016/j.ultras.2014.01.004.

[2] M., Majnooni *et al.*, "Anti-reflection cover to control acoustic intensity in in vitro low-intensity ultrasound stimulation of cells," *Acta Acust.*, vol. 6, 2022, doi: 10.1051/aacus/2022007.

[3] Majnooni, M. *et al.*, "Monitoring of In vitro ultrasonic stimulation of cells by numerical modeling," *Ultrasonics*, vol. 124, p. 106714, 2022, doi: 10.1016/j.ultras.2022.106714.