Ultrasound stimulation of bone regeneration: better understanding for better care

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Bone is a living material capable of regenerating to adapt itself to the mechanical stresses of its environment through the process of bone (re)modelling. Unfortunately, despite its amazing healing capacity, 5 to 10% of fractures show delayed or non-union fractures.

Who doesn't know anyone who has suffered a bone fracture? The causes of a bone fracture can be very different in nature: trauma, stress (fatigue fracture), idiopathic or congenital bone diseases and disorders, bone metastases, therapeutic treatments such as prostheses implant, bone lengthening or tumor resection. Although the field of bone regeneration has made great advances in recent decades, coupling personalized diagnosis and optimal treatment of bone fracture remains a challenge due to the large number of variables to be taken into account. **In-silico models can help to better understand this complexity and thus improve the understanding of bone regeneration processes.**

Ultrasound in medical applications is best known for diagnostic devices such as B-mode imaging. The advantages of ultrasound imaging compared to conventional medical imaging modalities such as X-ray or MRI are numerous: non-invasive, non-destructive, non-irradiating, non-ionizing, low-cost and portable devices that can be used at the bedside. These characteristics take on a particular resonance in the case of pediatric care. But ultrasound can also be a therapeutic vector.

Ultrasound stimulation of bone regeneration (USBR), initially controversial, is now recognized by the scientific and medical communities. The first clinical observation of the effect of ultrasound on bone healing was reported in the 1950s (Corradi and Cozzolino, 1953). Since the 1980s, USBR has contributed to a number of scientific publications: cell culture (Fung 2014; Puts 2016), animal model (Duarte 1983, Pilla 1990, Azuma 2001), clinical study (Malizos 2006), which has aroused controversy and today has a consensus in its favour. In 1994, the Food and Drug Administration approved the use of ultrasound stimulation in medical and paramedical fracture treatment protocols, and a device based on this principle is sold by Bioventus (Exogen®). **However, the underlying multiphysical processes remain poorly understood** (Padilla 2014).

In parallel with studies that focus on understanding biological processes in response to USBR (from cell to organ), there are many works on bone mechanotransduction. Mechanotransduction is the translation of a mechanical stimulus into a biological response. The mechanotransduction of bone associated with bone repair is complex, multi-scale and multi-physics. The impossibility of conducting in-vivo experiments reinforces the need to develop theoretical and numerical models such as the one described in this project.

The project proposes to create a bridge between these two communities, that of mechanics and that of biologists and clinicians by developing a finite element (FE) numerical model under Comsol Multiphysics simulating the ultrasound stimulation of a human bone in a configuration close to the in-vivo configuration. Bone is a multi-component, multi-scale tissue and interaction with ultrasound requires a "tissue to cell" model.

The thesis work is divided into 2 issues:

1 - Morphometric and physical characterization of double cortical porosity - The bone is considered here as a medium with 2 porosity levels: vascular (Ø~100 µm) and lacuno-canalicular (Ø~100nm - 10 µm). One of the key parameters of Biot modeling is the permeability of the poroelastic medium. To date, the experimental measurement of the permeability of the lacuno-canalicular network (LCN) is inaccessible. Therefore, LCN permeability is estimated by theoretical or experimental approaches coupled with numerical/analytical models and ranges from 10^{-17} to 10^{-25} m2 (Cardoso 2013).
Recent advances in X-ray imaging provide a better estimate of LCN morphometry in 3D giving access to a realistic estimate of the flow. Thanks to these investigation ways, the aim is to assess LCN permeability of the cortical bone which will feed the digital model.

2 - Estimation of the mechanical effects induced by ultrasound (US) on bone cells - This part of the study concerns 2 scales and several physics using an FE model (Comsol Multiphysics). Ultrasound stimulation is generated at **the bone tissue level considered as a poroelastic medium** and the study target is the biological response pilot bone cell, at the **microscopic scale**.

A better understanding of the US stimulation mechanisms on bone remodeling makes it possible to envisage various applications: aid in the treatment of fractures, optimization of callotasis treatment (bone elongation), treatment of bone metastases, aid in peri-prosthetic healing, etc.

References
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Candidate Profil
The candidate will have a solid background in fluid and solid mechanics and numerical modelling skills. Knowledge in biomechanics and/or acoustics will be a bonus. The proposed topic is an open and exciting one that requires tenacity and initiative.

Applications
Applications will be sent by e-mail to Cécile Baron (cecile.baron@univ-amu.fr) and Carine Guivier-Curien (carine.guivier@univ-amu.fr) and will include M2 transcripts, a CV, a letter of motivation and any letters of recommendation.

This thesis is proposed in the framework of the inter-ED AMU call for projects (https://college-doctoral.univ-amu.fr/fr/appel-a-projet-inter-ed). The results of the awarding of the 6 doctoral contracts will be notified at the beginning of June following the hearings of the 12 pre-selected projects.