PHD PROJECT	Understanding articular cartilage through image-guided multi-scale mechanical analysis (CartiMMage)
INSTITUTION	University of Montpellier, France
RESEARCH UNIT	Laboratory of Mechanics and Civil Engineering (LMGC), CNRS – 860 rue Saint Priest
GRADUATE SCHOOL	ED 166 - Information, structures and systems (I2S)
PHD SUPERVISOR	Patrick Cañadas
PHD CO-SUPERVISORS	Cristina Cavinato, Simon Le Floc'h

- **Summary of the project:**

In order to understand the response of articular cartilage (AC) to mechanical loads, it is important to investigate the micro-mechanisms of deformations and stresses that occur within the tissue during movement, as well as the mechano-biological role of the cells that make up the tissue. The study of load response of tissue components in healthy and pathological conditions such as osteoarthritis is challenging because the methods currently used are highly selective at the spatial scale. The present project addresses these challenges through a multiscale experimental mechanical approach guided by imaging. A numerical model, informed by experimental data, will confirm the deformation micro-mechanisms and fill the gaps in understanding the multiscale properties of the tissue. This project is part of a collaboration between experts in biomechanics and biologists and rheumatologists specialized in AC models.

- **Location:**

The main research site will be the Laboratory of Mechanics and Civil Engineering (LMGC) at the University of Montpellier (Saint-Priest Campus) with decentralization towards the laboratories of the Institute of Regenerative Medicine and Biotherapies (IRMB, INSERM/UM, CHU Montpellier, France).

- **Profile:**

The candidate should be highly motivated and passionate about scientific research, with strong analytical and problem-solving skills. The candidate should have a master's or engineering degree in (bio)mechanics, materials science, bioengineering, or a related field, as well as a solid understanding of principles in structural mechanics and materials. Prior knowledge in imaging, experimental techniques, and/or finite element numerical modeling would be appreciated. Additionally, the candidate should be able to effectively communicate their research results, both in writing and orally, in both French and English.

- **Detailed description:**

During joint movement, the AC performs various functions, including the transmission of mechanical stresses and shock absorption while continuously maintaining a lubricated surface. The mechanobiological activity of AC cells under mechanical stimulation, maintains the tissue's homeostatic balance. Therefore, the detection of microscopic stresses by cells is a crucial point in determining the regeneration cycles under normal loading conditions, predicting injuries, and the progression of diseases such as osteoarthritis [1]. The determination of stress levels necessary for cell activation is therefore crucial, for example, for the development of regenerative bioreactors for AC or for understanding the development of degenerative diseases. However, little is still

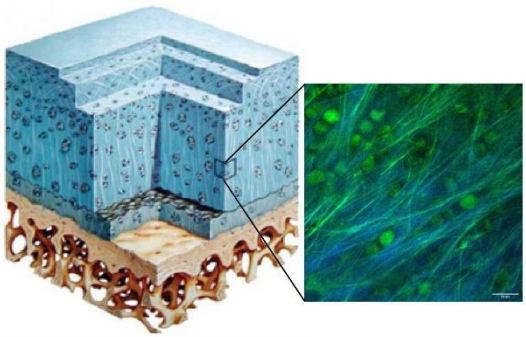

Figure 1 Architectural layout of articular cartilage (left) and microstructure observed by multiphoton microscopy (right). Adapted from Landínez-Parra et al. [2] and Chernyatinskiy et al. [3].

known about these mechanisms. The well-established collaboration between the biologists of the IRMB 'Biology of Mesenchymal Stem Cells and Cartilage Therapies' group and the 'Biomechanics of interactions and organization of tissues and cells' (BIOTIC) team of the LMGC has so far allowed the study of AC development through *ex vivo* models and numerical models of mechanically stimulated cartilage micropellets. [4,5]. This collaboration is evolving towards the characterization of increasingly complex materials using biomimetic scaffolds printed in 3D [6]. However, these scaffolds still have limitations in their ability to achieve stiffness and rupture strains comparable to those of native tissues. An advancement that will consolidate this collaboration is the use of multiscale mechanical characterization techniques coupled with imaging, which has so far been a missing link in understanding the differences between synthetic constructs and native tissues.

In this project, the direct consideration of cells, ECM and the components that connect them, as well as the fluid phase, will allow for the analysis of differences in mechanical properties observed at both millimeter and microscopic scales of this complex biological tissue, which is a potential mechanical activator of cellular activity. This requires a meticulous coupling of experimental studies with imaging-guided mechanical tests and reproducible with modern high-resolution microscopy techniques, and multi-scale numerical and theoretical modeling of mechanical behavior.

The first phase of the project will rely on the use of reproducible and consistent macroscopic compression mechanical tests [7], in order to characterize the time-dependent and independent behavior of volumes of murine tibial plateau models, guided by imaging. Images will be acquired at the milli- and micro-meter level through the coupling of high-resolution cameras and multiphoton microscopy, which will enable acquisition of the 3D microstructure as a function of loading state. Atomic force microscopy (AFM) microindentation tests will then characterize the specific microscopic mechanical response of the components of the CA. Special attention will be given to defining the mechanical results at the tissue scale and for each determinant microcomponent, namely heterogeneity, anisotropy, nonlinearity, as well as tissue permeability. In parallel, the microstructural and immunohistochemical properties of tissue components will be stated [8].

The second phase will be based on the development of a numerical mechanical model of growth and remodeling informed by our multi-scale experimental observations. Recent analyses have highlighted the importance of treating the AC as a composite material composed of at least two phases, solid and fluid, with appropriate constitutive descriptions [9]. To secure the modeling approach, we will begin with a visco-poro-hyperelastic constitutive model without an explicit fiber network, and then evolve towards visco-poro-hyperelastic models reinforced by fibers. A stress-adapted mixing approach for the AC and implemented in FEM will be completed by integrating hyperelastic laws whose parameters have been estimated using previous multi-scale tests. Finally, we will add a multi-scale approach to the model through a homogenization procedure previously used for soft tissues with wavy fibers [10]; in this approach, the microstructural elements in the cell's nearby environment can be explicitly taken into account. We will pay particular attention to leaving the possibility of gradually introducing terms describing cellular activity in the formulation for opening up to future projects that are more specialized in the mechanobiology of the AC [11].

- **Application:**

  To apply, please send your CV, cover letter, and transcript of grades to patrick.canadas@umontpellier.fr and cristina.cavinato@umontpellier.fr by **May 8th, 2023**. We also welcome letters of recommendation in support of your application.

- **Administrative aspects**: The PhD student is linked by state-approved agreements to University of Montpellier. This PhD is funded for 36 months, starting in Fall 2023 (Gross monthly salary ~ 2100 €/month).

- **Références :**

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