Appel A Projets I : formulaire de candidature

Il n'est pas indispensable d'utiliser le présent formulaire pour soumettre un projet. Toutefois pour faciliter le travail des rapporteurs, merci de respecter l'architecture générale de ce document pour votre réponse.

Nom du correspondant : Philippe LASAYGUES

Nom du projet : (THEOS) Theranostic ultrasound perspectives for pediatric bone diseases

Résumé du projet (5 lignes en anglais) :

Control and monitoring of the child skeleton growth are crucial for early diagnosis and therapy follow-up of pediatric bone pathologies. Today, it is a priority to better understand the biomechanical behavior of child bones in order to develop a dedicated diagnostic device associated with new therapeutic perspectives. Relevant research subjects are thus proposed: evaluation of mechanical characterization of child bone quality, development of a high-resolution parametric ultrasound modality, and the use of ultrasound stimulation as therapeutic treatment.

Volet(s) complémentaires demandé(s) : X Collaboration internationale ☐ ~~Pédagogie~~

Préambule : Nous présentons le projet dans son intégralité, tel qu'il est soutenu par le consortium. A noter toutefois que les tâches no1&3 sont celles concernées en priorité par cet appel. En effet, inviter le Pr Diego Garzón-Alvarado à venir travailler à Marseille est une opportunité que nous souhaitons saisir sur la période des 16 mois impartis. Meysam Majnooni, doctorant ED353, travaille actuellement sur ces 2 tâches, et ce serait très intéressant qu'il puisse bénéficier de cette collaboration. La tâche 2 relève plus partiellement de cet appel. Actuellement Luis Espinosa, chercheur post-doctorant (Labex MEC 2020) travaille sur l'imagerie, et un sujet de thèse a été déposé auprès de l'ED353. Une collaboration existe également depuis plusieurs années avec le Pr Flavio Prieto qui se poursuit.

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Scientific content (3 pages maxi)

Scientific context

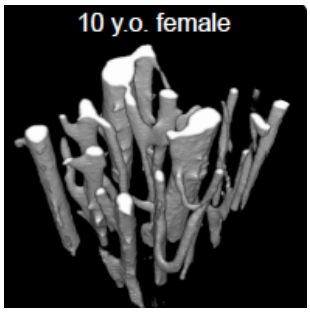
Control and monitoring of the children skeleton growth are crucial for early diagnosis and therapy follow-up of pediatric bone pathologies. An unconsolidated fracture, or a physical activity resumption too fast (after an osteogenesis apparatus treatment for example) can have short-term consequences (temporary disability of activity, school, sports or leisure) and long-term consequences (physical disabilities). Certain idiopathic juvenile diseases, cancer, genetic disorders, osteogenesis imperfecta..., need to be better diagnosed and monitored. Current treatments have side effects: chemical reactions, metabolic effects, or mechanical effects (surgery). All of these elements today require a better knowledge of the mechanical behaviors of child bones through a multi-physics approach, in medical, biomechanical, biochemical, acoustic, image and signal processing fields, which could lead to the development of new diagnostic device associated to new therapeutic perspectives. This is the aim of the project which brings together teams specialized in their field of expertise.

Program

New relevant axes of research are therefore proposed in this project: evaluation of morphological and mechanical parameters of child bone quality in *in vivo* configurations (task no1), development of an ultrasound imaging diagnosis modality, with better resolution and parametrization of the bone lesion area (task no2), and the use of low-intensity ultrasound stimulation as therapeutic treatment of this lesion (task no3).

Task no1: Characterization of the child cortical bone as a two-level porosity material

There is currently a growing interest in child bone health, firstly because children are concerned by specific infantile osteopathologies (such as tumors, non-union fractures, osteogenesis apparatus treatment, physis pathologies) and secondly because bone health during childhood will be of a great importance for bone health in adulthood. Therefore, the mechanical characterization of the child bones and of their skeleton development is a key issue. The development of relevant biomechanical models of bone growth are critical needs for the medical community. For pediatricians, radiologists and orthopedic surgeons, knowledge of the impact of a pathology on child bone quality remains a major goal in order to anticipate the evolution of diseases, to guide their diagnoses and thus to define an optimal therapeutic strategy. Furthermore, a relevant morphological and mechanical characterization of growing bone is a key element to develop effective and adapted devices of child bone disease diagnosis (task no2) and therapy (task no3).



Over the past several years, multi-physical and multiscale studies focused only on healthy child bone samples have been established as reference database. Recently, an evaluation of stiffness coefficients in the three orthogonal bone axes has been done giving some indication of how bone anisotropy is related to age (1). High-resolution X-ray images enable to characterize the vascular pores network in healthy child bone and to relate morphometric parameters to mechanical properties (2,3). Nevertheless, the characterization of bone as an *ex vivo* material at mesoscopic or microscopic scales is not sufficient, we need to consider the mechanical behavior of bone in the *in vivo* conditions and to identify the relevant morphological and mechanical parameters related to it. In particular, we have to study more precisely the

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contribution of the soft tissues around the bone (periosteum, muscle) and the fluid inside the pore networks (vascular and lacuno-canalicular) of cortical bone. The child cortical bone is a complex material with two-level porosity network: the vascular porosity (Haversian and Volkmann canals around 100µm) and the lacuno-canalicular network (1 to 10µm pores). The presence of fluid in this two-level porosity induces a viscoelastic behavior of the bone tissue under an ultrasound wave stress. In modelling, the vascular porosity is, generally, taken into account in terms of volume fraction without considering the spatial distribution or the shape or the organization of the pores (3). Previous numerical studies show that the morphometric parameters are critical to investigate the mechanical behavior of the bone (4). The evaluation of the bone tissue permeability at lacuno-canalicular level remains a tricky, fundamental question, and an open question. It is noteworthy that the lacuno-canalicular network is the place where are the osteocytes which are regarded as the pivotal cells orchestrating the biomechanical regulation of bone mass and structure. They are considered as the mechanosensory cells responsible of bone remodeling under mechanical loading (4,5). Consequently, the characterization of the lacuno-canalicular porosity is an important step to analyze and understand the therapeutic effect of ultrasonic wave on bone regeneration (task no3).

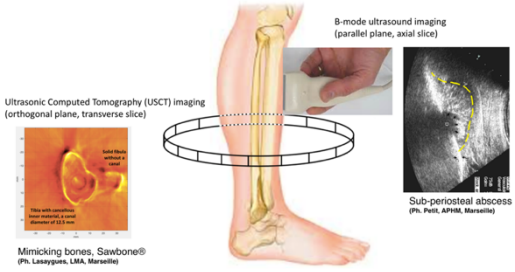
Therefore, in this task, we want to improve the parametric and morphometric analysis of the child bone and obtain detailed information into lacuno-canalicular porosity and permeability. In this sense, we propose to develop the project with mathematical and computational modeling, acoustic and biomechanical experiments, using the µCT platform of the Federation Fabri de Peiresc, and the instrumented *in situ* tensile and compression test device (application made in CPER 2021).

Relevant original points of interest:

- Multi-scale behavioral law (macro- to nanoscale, lacuno-canalicular network modelling);
- Porosity and permeability, fluid-solid interaction;

Task no2: USCT vs. B-mode Ultrasound ("echography")

For child bone pathologies, the development of ultrasound imaging modalities is an important challenge in order to provide an alternative to conventional modalities such as X-ray which have to be limited due to their radiation risk, or magnetic resonance imaging, a major tool but which requires more frequent anesthesia (6), and gives poor cortical information. Nowadays, the B-mode ultrasound is the first-line examination for the diagnosis of many child diseases, due to its efficiency without harmful effects. However, B-mode ultrasound has difficulty to penetrate bone and, therefore, can only see the outer surface of bony structures, and not what lies within them. The image is not quantitative; the grayscale levels are not linked to any significant physical parameters of the organs, such as speed of sound or attenuation. The Quantitative UltraSound (QUS) method can be used to assess the qualitative characteristics of bone tissue but skeletal sites are limited only to peripheral calcaneus, phalanges, or patella (7). For several years, tests of bone imaging have been conducted using the ultrasonic computed tomography (USCT) which is mainly used for soft tissue imaging, and an dedicated experimental device was develop at LMA. However, commonly used soft tissue approximation methods do not provide quantitative images for bone imaging because of the high impedance contrast between the echogenic structures and the surrounding soft tissue (8). We have



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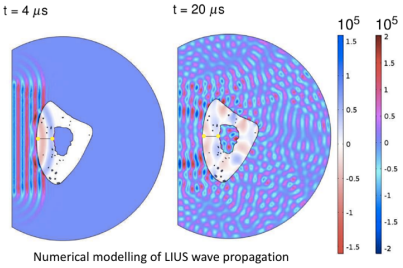
suggested a numerical non-linear inversion algorithm (9) (*cf postodocral fellow, Labex MEC 2020*). To be further, locks associated with an *in vivo* configuration must be removed: the number of transducers, the power and the intensity of the wave, the image resolution and the contrast in the deep zone, the accessibility of non-peripheral skeletal sites, or in between the two leg and arm bones, and the muscle and soft tissue effect in term of wave dispersion and attenuation.

Relevant original points of interest

- Numerical modelling of US/Organ interaction effect of the soft tissues (periosteum, muscle);
- Signal and image processing in the case of adjacent bone (tibia and fibula)

Task no3: Therapeutic perspectives

Ultrasonic waves can be used as a therapeutic vector in the context of bone repair. Understanding the mechanisms induced by ultrasonic wave propagation at the different scales of bone tissue, from the organs to the cells, would make it possible to take into account the main parameters of the therapeutic process and to integrate them into a protocol associated with diagnosis. Nowadays, clinical ultrasonic therapy modalities are mainly high-intensity focused ultrasound, not usable to (children) bones because of the high intensities of radiation. Osteo-articular diseases cause a disruption of the bone (re)modeling, generating weak bones leading to serious skeletal events (fractures, spinal compression). One solution could be to resort to low-intensity ultrasonic stimulation (*LIUS*). In this case, low-intensity US waves interact with tissue and cells, producing mechanical effects that promote bone regeneration. Little is known about the mechanotransduction induced by *LIUS*. In this task, we want to understand the process that drives bone regeneration, and in particular the mechanotransduction processes (10). How does the organ translate ultrasonic stress into cellular biological reaction? A first component of the project involves the development of a multi-physical, multiscale numerical modeling that integrates (*A*) wave propagation and its interaction with bone as a poro-elastic material, with soft tissues represented by viscous fluids, and the biological fluids such as marrow and blood; (*B*) fluid/structure interactions at the cellular scale. The *LIUS* method must be optimized to define the frequency, the power and/or the intensity of the ultrasonic wave to be applied to improve bone repair (11,12). This requires the implementation of cell culture protocols associated with an ultrasonic transmitted device. Understanding the ultrasonic mechanical and piezo-electric effects on biological tissues would be a major scientific breakthrough. If the ultrasonic parameters (frequency, intensity, power) useful for *LIUS* therapy can be controlled and coupled with an ultrasonic imaging system, a pediatric theranostic tool could be proposed.



Numerical modelling of LIUS wave propagation

Relevant original points of interest

- Modelling of US/tissues/organs, US/cells interactions;
- Modelling of fluid-solid interactions and ultrasonic effects (frequency, intensity, power)

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Expected benefits

Impact and benefits: The social and financial impact is that the use of ultrasounds in children clinical exam is unquestionably beneficial. Ultrasounds are not ionizing, not invasive and not painful, and the exam is low costs. USCT could be viewed as a further examination for the conventional B-mode ultrasound. Today a device exists as a demonstrator (TRL 1-3), and results in academic configurations match predictions. One goal of this project is to upgrade the device to validate it in a more relevant clinical environment (TRL 3-4). Furthermore, the technological challenge is to extend the development by combining ultrasonic imaging and therapy on a single device.

Industrial partners: An economic positioning study of the project will target industrial partners and future phases for technological transfer (partnership with the SATT Sud-Est). The Eurosonic-Mistras Inc., based in Vitrolles, is working with the LMA to develop the USCT device adapted to child bones (13).

Publications: As far as scientific communication is concerned, the original research brought out by this projet should lead to rank journal publications. Results will also be presented in international conferences gathering ultrasounds and acoustics, and biomechanical and bioengineering communities.

Perspectives: The same consortium will apply for the 2020 French-Colombian ECOS-North call for projects (exclusively for missions in France and Colombia, primarily for students). In 2020, the consortium plan to submit an application in the ANR calls for projects. A first unsuccessful application in 2018 highlighted the limitations of the biomechanical model taken into account, both in imaging and therapy. Upgraded the modeling is the main objective of this new project and collaboration between our laboratories is the best way to achieve it. We will associate the experimental platform (US, μCT) with mathematical and numerical modeling. To our knowledge, we are the only consortium to propose this multi-physical and multi-modal approach on child bones.

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