MARIE SKLODOWSKA-CURIE ACTIONS

Co-funding of regional, national and international programmes (COFUND)

DOC2AMU PROJECT 2017 CALL FOR APPLICATIONS

Imaging of bone diseases in children using Ultrasonic Computed Tomography

1. DESCRIPTION OF THE PHD THESIS PROJECT

1.1 OBJECTIVES OF THE PROJECT BASED ON THE CURRENT STATE OF THE ART

For children bone pathologies (tumours, non-union fractures, distraction), the development of ultrasonic imaging modality and protocols is an important challenge to provide an alternative to conventional modalities such as X-ray radiology or MRI which are limited in case of children's examination due to radiation problem, to the often required anaesthesia, or to some behaviour disturbances [1]. Furthermore, ultrasounds could be used as therapeutic vector in the context of bone repair, leading to a theranostic issue. The locks associated with the in vivo configuration are numerous: accessibility of anatomical sites, attenuation due to soft tissue resolution, paired bones. For several years, the **"Waves and Imaging" Group of The Laboratory of Mechanics and Acoustics (LMA-CNRS)** has been studying the ultrasonic computed tomography (analogous to echography for the physics of wave propagation and with the X-ray tomography for the inverse problem) [2] of children bone tissues. An experimental device was developed and tested in academic configurations [3] (Figure 1). To take into account the important parameters of the in vivo theranostic process and to integrate them into the device and the associated protocol, we use a multiphysics modelling with finite element methods [4] developed by the **Biomechanics Group of the Institute of Movement Sciences (ISM)**. This model allows to interpret more accurately the experimental results and guide the development of the prototype to clinical application.

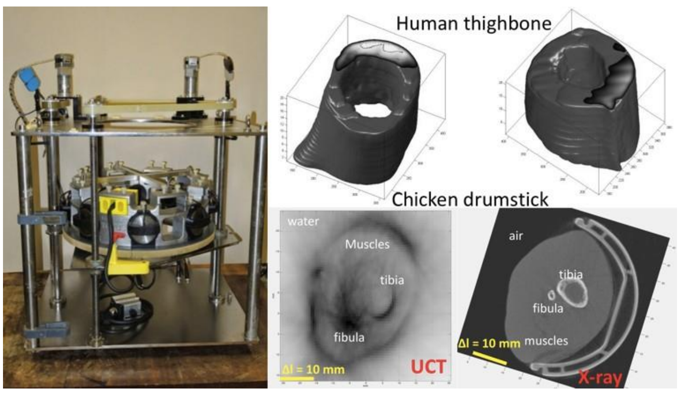

Figure 1: Ultrasonic Computed Tomography of cortical bone. (left) experimental device; (right) Examples of in vitro results

The main objective of the Ph-D thesis, is to develop a real prototype of predictive analysis and diagnosis of the paediatric skeleton coupled with a therapeutic unit of bone repair stimulation. Tasks are based on combining numerical (***task no1***) and experimental (***task no3***) tests in order to optimize the signal processing and to solve the inverse problem (***task no2***). The work will begin with academic models and then the in-vivo parameters will be gradually integrated to achieve a realistic clinical model (***task no4***). The morphology of the complete anatomical structure (skin, muscle, bone) will be take into account.

1.2 METHODOLOGY

(Task no1) Numerical modelling is of prime interest to tackle multiphysics issues. The simulation of ultrasonic waves propagation through biological tissues is an efficient way to gain insight into bone characterization [5] and imaging but also to understand the potential therapeutic effects of ultrasounds on bone healing [6]. In this project, a numerical model is developed on commercial finite element software *Comsol Multiphysics* in order to simulate the experimental set up (task 3 & 4). The goal is to optimize the device configuration and the ultrasonic parameters. The numerical model could also provide a better understanding of the signals recorded in the experimental setup and improve the signal processing and the interpretation of the data.
After validating this model on in vitro testing, it could integrate all the complexity of the in vivo configuration to extrapolate the in-vitro results to clinical applications: soft tissues, paired bone etc. Moreover, the numerical modelling task is a big issue to understand the therapeutic effects of ultrasounds. It should take into account the theranostic aspect of ultrasonic propagation through bone. This is challenging because although they are clinically observed. The therapeutic effects of ultrasound on bone healing are still misunderstood, and the physical mechanisms implied remain unclear [7]. Couple diagnosis (characterization and imaging) and therapy with the same modality is the grail for clinicians. But to do so, we need to couple several parameters and physics and the numerical modelling is an unmissable tool to achieve this goal.

(Task no2) Ultrasonic Computed Tomography (USCT) has been proposed as a tool to provide quantitative images of the speed-of-sound in the cross-section of long bones with a millimetric resolution [8], allowing accurate assessment of cortical thickness. The main difficulty of USCT of bones is the large impedance contrast between hard bones and the surrounding soft tissues. In that context, ray-based and first order Born approximation methods commonly used in USCT of soft tissues [9] fail to provide quantitative images, except adapted, but time cost consuming, algorithms such as, for example, Compound USCT [10]. Iterative approaches based on high-order approximations have been proposed to address the non-linear inverse problem for high contrast targets [11]. Our group applied one of such iterative methods, called distorted Born diffraction tomography (DBDT), to bone mimicking phantoms and obtained fairly accurate estimates of the geometry and wave velocity [12]. The distorted Born method is time consuming, and the forward problem model assumes a constant tissue density. In this thesis, we want to exploit the potential of an inversion method used in geophysics, by the **"Acoustics underwater, seismic and seismology" group** of the LMA. The inversion algorithm is a non-linear iterative algorithm based on the Full Waveform Inversion (FWI) principle [13]–[15]. The objective is to simultaneously reconstruct the velocities of compression and shear wave in the bone without any assumption of spatial constancy of tissue density.

(Task no3 & no4) Once the requisite degree of accuracy will be obtained, it will be possible to start experiments on children’s bone using the **ultrasonic scanner**. The methods developed in the previous tasks will be tested using bone mimicking phantoms as well as real human and animal bones, with a non-canonical homogeneous shape. Results will be compared with classical X-ray tomography scan. To implement the numerical processing codes, it will be necessary to synthesis a waveform usable to adapt the time and frequency signatures of the transmitted signal, and then improving the development of the device.

1.3 WORK PLAN

Tasks	Year 1		Year 2		Year 3	
Months	6	12	18	24	30	36
Task 1: Modelling analysis of interaction wave/bone						
Task 2: Inverse problem and imaging						
Task 3: Experimental developments and signal processing						
Task 4: Clinical validation tests						

1.4 SUPERVISORS AND RESEARCH GROUPS DESCRIPTION

The project of the Ph-D thesis is a part of a major research program on characterization and imaging of bone tissue in children (AAP ANR 2017, Healthcare technologies, Medical Imaging), involving several national and international laboratories: LMA, ISM, IUSTI Marseille, LVA-INSA, Lyos-INSERM et LabTau-INSERM Lyon), Children's Hospital APHM and CERIMED, Charité University, Germany, University of Monastir, Tunisia.

- ***Philippe Lasaygues*** (IRHC, HDR), which will be the thesis Supervisor and the Project Coordinator, is working at the Laboratory of Mechanics and Acoustics (LMA), Marseille. LMA is a research unit of the CNRS (UPR 7051) attached to the Institute for Engineering and Systems Sciences (INSIS), to Aix-Marseille University (AMU) and Central Marseille. The research on medical field of the "Wave & Imaging" team is focused on the ultrasonic characterization and imaging of biological medium/material such as hard (bones) and soft (cells, blood, breast) tissues. Some of researchers in the "Wave & Imaging" team, have interests in numerical study of acoustic or seismic wave propagation in complex media, with associated effects related to strong local heterogeneities and/or steep topography. LMA is one of the four laboratories involved in the Research Federation Fabri de Peiresc FR 3515) and supports the mechanical characterization platform (micro-tomography, thermal imaging, ultrasonic imaging, mechanical engineering and modelling). The laboratory is a main partner of CERIMED since its creation. LMA is involved, for example, in the ClearPEM Sonic project [16]–[19], in the NOVUSBIO project (A*MIDEX grants), and in the DHU-Imaging project (A*MIDEX grants). LMA is involved in France Life Imaging.

- ***Cécile Baron*** (CR1), which will be the thesis co-Supervisor, is working at the Institute of Movement Sciences (ISM). ISM is a mixed research unit (UMR 7287) shared between the CNRS and the Aix-Marseille University. It is attached to the Institute of Biological Sciences (INSB). The ISM is a member of the Star Carnot Institute. It collaborates with more than a hundred national and international partners and with 4 competitiveness clusters. The Interdisciplinary Group in Osteo-articular and Cardiovascular Biomechanics (GIBoc) gathers clinicians, engineers and biologists to understand and repair the living. It is a multidisciplinary team with transversal skills to develop new ways of research on multiscale biomechanics from cells, to tissues and organs.

2. 3I DIMENSIONS AND OTHER ASPECTS OF THE PROJECT

2.1 INTERDISCIPLINARY DIMENSION

They are several scientific and technological contributions of this project. The experimental implementation of numerical modelling applied to ultrasound diagnosis and therapy *(**carried out by C. Baron, ISM**)*, and/or inversion algorithms adapted to ultrasonic computed tomography *(**carried out by P. Lasaygues, LMA**)* of children's bones are limited, and very few articles are published. The consortium LMA/ISM, associated with others national and international laboratories, is one of the first groups to publish results on the characterization of children's bone tissues. In this project, the idea of using skills of geophysicists is particularly relevant. For geophysicists, it is the opportunity to validate their modelling and inversion approaches on small-scale experimental cases, and on living, heterogeneous and anisotropic materials. For the biomedical and biomechanical engineering communities, it is possible to achieve a parametrization of the properties (elasticity matrix) of the bone tissues, and to propose a complete quantitative image that can be clinically compare to a bone elasto-tomography procedure. Communities complement each other.

The doctoral candidate will benefit from the knowledge of both main laboratories, LMA (medical and geophysical skills) and ISM (biomechanical skills), and will actively participate in the life of both laboratories.

2.2 INTERSECTORAL DIMENSION:

Clinical partners

The Marseille Public University Hospital (**Assistance Publique – Hopitaux de Marseille, APHM**) and the **CERIMED** (Centre Européen de Recherche en Imagerie Médicale) will be involved in the project as Intersectoral partners.

- ***Prof. Petit Philippe*** *(PU-PH), Head of the Department of Paediatric and Prenatal Radiology, "Timone" Children-Hospital APHM. Prof Philippe PETIT is associated with the project of children's bone imaging, since the beginning of the research program carried out by the consortium (LMA/ISM). He regularly acts as an expert for validation experiments on animal or human models.*
- ***Prof. Gorincour Guillaume*** *(PU-PH), CERIMED, Laboratory of Interventional and Experimental Imaging, INSERM EA4264. Prof Guillaume GORINCOUR will conduct the animal validation tests in the framework of DHU-Imaging (**Prof. Eric Guedj**) in which the LMA and ISM are involved.*

Comparative tests based on clinical ultrasound and X-ray imaging devices and preclinical experiments on animal and human models will be carried out by the doctoral candidate at CERIMED and APHM, respecting the favourable opinion of the hospital convention (CPP).

Impact and benefits of the project

The project will lead to important results: progress towards the development of a biomechanical model and elastic constitutive relations in case of bone diseases; progress towards the diagnostic of specific child's bone pathologies, using the USCT device, and adapted solutions for therapy in case of bone healing and cancer. Challenges of this project will induce substantial developments in scientific, technological and clinical domains, and the consortium brings a major contribution to the prevention of children's bone diseases. The number of identified osseous diseases will increase due to a better knowledge of the mechanisms of children's bone modelling. Such advances will allow a better clinical management of patients. The social and financial impact of this research project is that the use of ultrasounds in the case of children clinical exam is unquestionably beneficial. Ultrasonic wave is a form of mechanical energy, not electrical energy or ionizing, not invasive and not painful. Ultrasonic-based device is a reduced cost exam related to the investment of the device. USCT could be viewed as a further examination for the conventional echography, without any risk to the patient and the person accompanying such as the parents. Today the device is a demonstrator. Results in academic configurations match predictions and the proof of concept is established. The component and the hardware modules were drafted and validated in laboratory environment. Regarding the economic model, the project is in a level of TRL 3-4 (Technology Readiness Level). The goal of this thesis is to upgrade the device to validate it in a more relevant clinical environment (i.e. TRL 5-6). Furthermore, the technological challenge is to extend the development by combining ultrasonic imaging and therapy on a single device. An economic positioning study of the project will target industrial partners and future phases for technological transfer (partnership with the SATT Sud-Est).

Industrial partners

CR PACA brings together several businesses in the ultrasonic area, potentially concerned by the aim of this project. For example, Supersonic Imaging Inc., company based in Aix-en-Provence, develops the Aixplorer® device used by the LMA for elastography-based measures. In the same way, the **Eurosonic-Mistras Inc**. (**David Marlot**), based in Vitrolles, is working with the LMA to develop new devices (ANAÏS and TON'US) for ultrasonic computed tomography of children's bones [3], and breasts [20].

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

2.2 INTERNATIONAL DIMENSION:

The so-formed LMA/ISM group is working with international teams. The consortium is co-working with the team of the ***Prof. Laurence H. Le***, Department of Radiology and Diagnostic Imaging, and ***Dr. Rui Zheng***, Department of Surgery, University of Alberta, Edmonton, CA [21]–[23]. These teams are involved in basic and clinical research utilizing ultrasonic and mechanical techniques to study and image bone tissues. The consortium is also co-working with The ***Prof. Kay Raum***, Center for Regenerative Therapies (BCRT), Charité University, Berlin, Germany [24]. The main goal of this group is to combine numerical modelling, acoustical and biomechanical competences of musculoskeletal tissues to evaluate normal, pathological, and healing conditions and to utilize the elastic interaction of waves with matter to stimulate healing. The LMA is co-working with the ***Dr. Wajih Elhadj Youssef***, Laboratory of Electronics and Micro-electronics, University of Monastir, Tunisia (*Project IMERA 2017, "COSTOS-P2"*). This laboratory is mainly specializing in the development of real-time electronic systems, and is interested in ultra-fast image processing methods.

3. RECENT PUBLICATIONS

[1] P. Petit *et al.*, “Rate of Abnormal Osteoarticular Radiographic Findings in Pediatric Patients,” *Am. J. Roentgenol.*, vol. 176, no. 4, pp. 987–990, Apr. 2001.

[2] P. Lasaygues, R. Guillermin, and J.-P. Lefebvre, “Ultrasonic Computed Tomography,” in *Bone Quantitative Ultrasound*, P. Laugier and G. Haïat, Eds. Dordrecht: Springer Netherlands, 2011, pp. 441–459.

[3] P. Lasaygues *et al.*, “Advanced Ultrasonic Tomograph of Children’s Bones,” in *Acoustical Imaging*, vol. 31, A. Nowicki, J. Litniewski, and T. Kujawska, Eds. Dordrecht: Springer Netherlands, 2012, pp. 31–38.

[4] C. Baron, “Using the Gradient of Human Cortical Bone Properties to Determine Age-Related Bone Changes Via Ultrasonic Guided Waves,” *Ultrasound Med. Biol.*, vol. 38, no. 6, pp. 972–981, Jun. 2012.

[5] C. Baron and S. Naili, “Propagation d’ondes élastiques au sein d’un guide d’ondes élastiques anisotrope à gradient unidirectionnel sous chargement fluide,” *Comptes Rendus Mécanique*, vol. 336, no. 9, pp. 722–730, Sep. 2008.

[6] C. Baron, C. Guivier-Curien, V.-H. Nguyen, and S. Naili, “How to understand effects of LIPUS on bone healing? A multiscale computational study,” *22nd Congr. Eur. Soc. Biomech.*, 2016.

[7] F. Padilla, R. Puts, L. Vico, and K. Raum, “Stimulation of bone repair with ultrasound: A review of the possible mechanic effects,” *Ultrasonics*, vol. 54, no. 5, pp. 1125–1145, Jul. 2014.

[8] P. Lasaygues, “Assessing the cortical thickness of long bone shafts in children, using two-dimensional ultrasonic diffraction tomography,” *Ultrasound Med. Biol.*, vol. 32, no. 8, pp. 1215–1227, Aug. 2006.

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[10] P. Lasaygues, E. Ouedraogo, J.-P. Lefebvre, M. Gindre, M. Talmant, and P. Laugier, “Progress towards in vitro quantitative imaging of human femur using compound quantitative ultrasonic tomography,” *Phys. Med. Biol.*, vol. 50, no. 11, pp. 2633–2649, Jun. 2005.

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[12] P. Lasaygues, R. Guillermin, and J.-P. Lefebvre, “Distorted Born diffraction tomography applied to inverting ultrasonic field scattered by noncircular infinite elastic tube,” *Ultrason. Imaging*, vol. 28, no. 4, pp. 211–229, Oct. 2006.

[13] D. Komatitsch and R. Martin, “An unsplit convolutional perfectly matched layer improved at grazing incidence for the seismic wave equation,” *GEOPHYSICS*, vol. 72, no. 5, pp. SM155–SM167, Sep. 2007.

[14] V. Monteiller, S. Chevrot, D. Komatitsch, and Y. Wang, “Three-dimensional full waveform inversion of short-period teleseismic wavefields based upon the SEM-DSM hybrid method,” *Geophys. J. Int.*, vol. 202, no. 2, pp. 811–827, May 2015.

[15] J. Tromp, D. Komatitsch, and Q. Liu, “Spectral-Element and Adjoint Methods in Seismology,” *Communications in Computational Physics*, pp. 1–32, 2008.

[16] G. Cucciati *et al.*, “Development of ClearPEM-Sonic, a multimodal mammography system for PET and Ultrasound,” *J. Instrum.*, vol. 9, no. 03, pp. C03008–C03008, Mar. 2014.

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[18] Jun Dang *et al.*, “Development of an Anthropomorphic Breast Phantom for Combined PET, B-Mode Ultrasound and Elastographic Imaging,” *IEEE Trans. Nucl. Sci.*, vol. 58, no. 3, pp. 660–667, Jun. 2011.
[19] M. Pizzichemi *et al.*, “157: ClearPEM-Sonic: a multimodal PET-ultrasound mammography system,” *Radiother. Oncol.*, vol. 110, pp. S76–S77, Feb. 2014.
[20] J. Rouyer, S. Mensah, E. Franceschini, P. Lasaygues, and J.-P. Lefebvre, “Conformal ultrasound imaging system for anatomical breast inspection,” *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 59, no. 7, pp. 1457–1469, Jul. 2012.
[21] K. Metwally, E. Lefevre, C. Baron, R. Zheng, M. Pithioux, and P. Lasaygues, “Measuring mass density and ultrasonic wave velocity: A wavelet-based method applied in ultrasonic reflection mode,” *Ultrasonics*, Sep. 2015.
[22] R. Zheng and P. Lasaygues, “Simultaneous assessment of bone thickness and velocity for ultrasonic computed tomography using transmission-echo method,” 2013, pp. 2084–2087.
[23] R. Zheng, E. Lefevre, C. Baron, and P. Lasaygues, “Thin bone sample assessment using ultrasonic transmitted signals based on wavelet processing method,” in *2013 International Congress on Ultrasonics*, Singapore, 2013, pp. 1–5.
[24] Q. Leguillette, J.-P. Berteau, C. Baron, and R. Kay, “Mechanical and structural characterization of the spinal entheses: a multimodal approach,” Julius Wolff Institute, Berlin, Germany, Master Thesis, 2012.

4. EXPECTED PROFILE OF THE CANDIDATE

Suitable candidates will have a M.Sc. (Master of Research) or equivalent degree, from a reputable University or Engineering School and have strong interests in conducting research in the areas of biomechanical and/or acoustical applications, with theoretical, numerical and experimental aspects. Previous experience in medical field is advisable but not required.

We are looking for highly motivated students who can tackle scientific problems on biomechanics and ultrasonic systems-oriented approaches. We offer excellent research facilities, interdisciplinary scientific training, and a comprehensive complementary training programme in an international environment. Candidates will have excellent written and verbal communication skills, ability to work harmoniously in a collaborative research team, and to present a large autonomy in the work, responsibilities, dynamism and availability. Good knowledge of spoken French or English as well of written English is required.

5. SUPERVISORS’ PROFILES

Philippe Lasaygues was born in Saint-Etienne, France, in 1965. He received a Ph.D. degrees in Acoustic from the University of Aix-Marseille II, Marseille France, in 1992. He is working for the French National Centre for Scientific Research (CNRS) at the Laboratory of Mechanics and Acoustics (LMA), Marseille, France, as Senior Research Engineer (IRHC). He is heading the "Ultrasonic" platform of the LMA and of the AMU education platform on ultrasounds (IUT St Jérôme). His interests include ultrasounds, ultrasonic imaging and tomography, bio-engineering, medical applications, signal processing and experimental developments. He is involved in several research programs as coordinator with French partners and International partners. He has been also coordinator for industrial programs. He was proposal coordinator of an ANR’s projects *“BioGMID – Biological Growth Medium Integrity Diagnoses using bi-modality tomographies”, (2007-2010)* and *"MALICE - Multiscale AnaLysIs of Children's bonE growth: both advanced ultrasonic cross-sectional imaging and biomechanics model"* (2012 – 2016), and main partner for 3 others ANR's projects (SMART-US, 2019-2014, AVENTURE, 2013-2017, CUMBA, 2016 - 2020). He has supervised and co-supervised, 9 PhD students (0 actually supervised), 4 Postdoctoral fellows, and 68 Training courses & master's degree. Every year, he carries out several expert surveys in the domain of acoustics, ultrasounds, medical imaging, non-destructive testing, signal processing, for regional, national and international councils, and/or editorial boards. He is currently member of the Scientific Board of the National Research Centre. Currently, he is member of the Institute of Electrical & Electronic Engineers (IEEE), of the European Acoustics Association (EAA - Board of the TC-ULT - Technical Committee on Ultrasound), and of French Acoustical Society (SFA - French Acoustical Society - Board of the GAPSUS - Physical acoustics, Underwater acoustics, Ultrasonic group).

- *3 Keynote lectures; 2 Invited papers; 4 Chapters in book; 37 Refereed Journal Articles; 91 Non-refereed journal articles & Congress; 22 Seminars (international & national); Web of Science, h-index = 7.*

- (recent) Honour thesis - **DIONG M. Lamine** (2015 - Statistical optimization algorithms applied to inverse problems in electromagnetism and acoustical imaging), currently in post-doctoral position, ISAE, Toulouse, **ARCINIEGAS Andrés** (2014 - Ultrasonic computed tomography of standing trees), currently in post-doctoral position, SATIES Lab., Cergy-Pontoise - **BERTEAU Jean-Philippe** (2011 - Children Bone characterization), currently Assistant Professor, CUNY Graduate Center, New-York, USA.

Cécile Baron was born in Paris in 1979. She received a Ph.D. degrees in Mechanics from the University of Bordeaux I, Bordeaux France, in 2005. She has been assistant professor at Pierre and Marie Curie University in Paris at The Jean Le Rond d'Alembert Institute. Since 2010, she has been working for the French National Centre for Scientific Research (CNRS) at the Institute of Movement Sciences, Marseille, France, as Researcher (CR1). She is a specialist in semi-analytical methods and simulation of elastic wave propagation in heterogeneous media. She has been interested in biomechanics and ultrasonic characterization of bone quality since 2006. She followed her research on bone characterization considering bone tissue as a functionally graded material and focused on children bone characterization. On this topic, she got involved in two ANR's projects "BioGMID – Biological Growth Medium Integrity Diagnoses using bi-modality tomographies", (2007-2010) and "MALICE - Multiscale AnaLysIs of Children's bonE growth: both advanced ultrasonic cross-sectional imaging and biomechanics model" (2012 – 2016). She participated in the supervision of two PhD students and she is currently co-supervisor of a thesis (HERMES grants from AMU).

- *1 scholar book, 1 chapter of book, 13 refereed journal articles, 16 seminars (international & national); Web of Science, h-index = 5.*