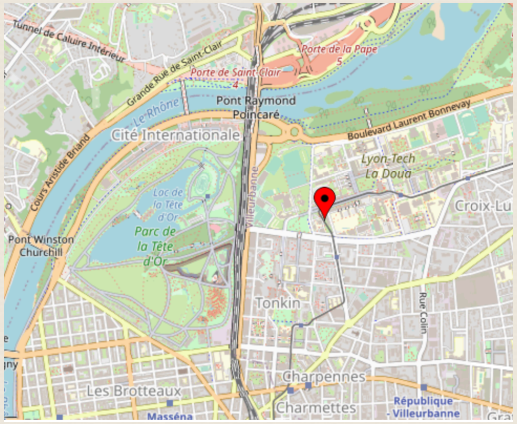
BONITOS symposium gathers leading experts in bone tissue from all the disciplines (biology, biomechanics, mathematics,...) into one place. To discuss bones in all its research approaches, we propose a hybrid symposium between European and US fellows and expect to initiate international collaborations. We are very proud to create the first edition of this kind, and hopefully followed by many others in the next years.

Welcome to BONITOS 2021 !

HOW TO REACH THE PLACE



Salle Séminaire 2, Braconnier Building
University of Lyon, Campus de la Doua

Map: https://www.univ-lyon1.fr/campus/plan-des-campus/batiment-braconnier#.YTiEqtMzb00

Entrance:
from the back of the building (side closer than the tram stop) below the emergency exit stairs

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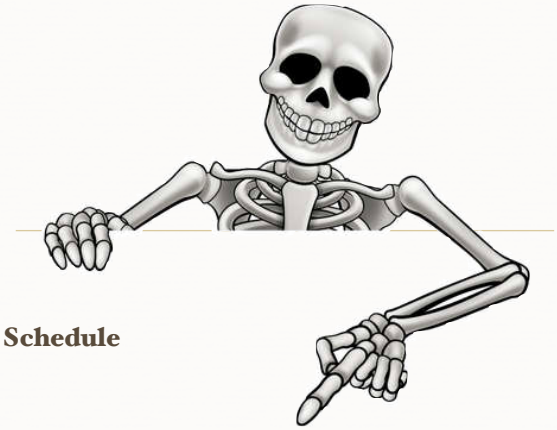
BONITOS 2021

September 17th, 2021

University Claude Bernard Lyon 1
Lyon, France



Schedule

9:00	**Opening talk**	**J.P. Berteau**
9:15	Talk 1	H. Follet
9:45	Talk 2	I. Fiedler
10:15	Talk 3	J. P. Berteau
10:45	**Coffee Break**	
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15:30	Talk 9	C. Alcevedo

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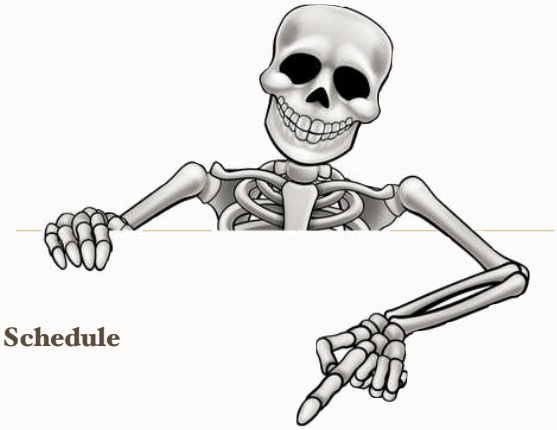
TITLES

TALK 1:	Experiment on ex-vivo vertebrae for numeric model evaluation: bone metastasis cases	**H. Follet**	Université Claude Bernard Lyon 1, Inserm, Lyon , France
TALK 2:	Bone quality in zebrafish models of skeletal activity and disease	**I. Fiedler**	University Medical Center Hamburg-Eppendorf, Germany
TALK 3:	Osteoarthritis Progression : a challenge for both clinicians and biomechanicians	**J. P. Berteau**	The College of Staten Island at the City University of New York, USA
TALK 4:	Failure load prediction of metastatic femur: mechanical characterization and finite element modelling	**A. Levillain**	Université Claude Bernard Lyon 1, Inserm, Lyon , France
TALK 5:	Theoretical Evidence of Bone Genetic Regulatory Network Inhibition during Bone Mineralization	**L. Pujo-Menjouet**	Université Claude Bernard Lyon 1 Lyon , France
TALK 6:	Effect of mechanical forces on bone development	**S. Shefelbine**	Northeastern University, Boston, USA
TALK 7:	The Effect of Helium Ion Radiation on Bone Material Properties	**A. Lau**	The College of New Jersey, USA
TALK 8:	Structure-Function Relationship of Trabecular	**L. Cardoso**	The City College at the City University of New York, USA
TALK 9:	Dynamic Imaging technique to capture bone damage evolution in bone fragility associated with high collagen glycations	**C. Acevedo**	University of Utah, USA



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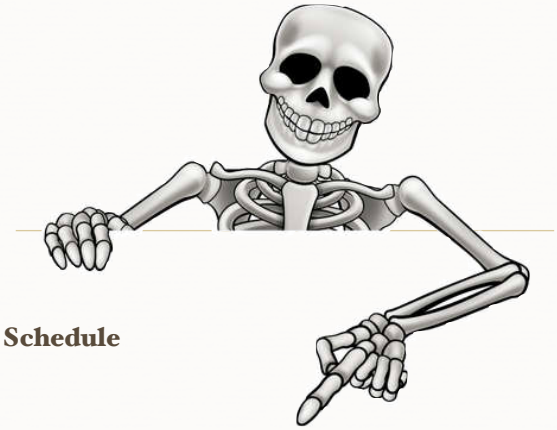
ABSTRACTS

TALK 1: Osteolytic metastases located in the vertebrae reduce the strength and enhance the risk of pathological vertebral fractures. This risk can be predicted by means of validated finite element models. The aim of this study was to conduct experiments based on previous validated protocols to evaluate finite element models. Twelve lumbar vertebral bodies (L1) were prepared by removing the cortical endplates and creating the defects that represent osteolytic metastases. Defects were created by drilling without cortical involvement and had a size around 30%. Vertebral bodies were scanned using a clinical QCT (Quantitative Computed Tomography) before and after defect creation for 3D reconstruction. The specimens were tested under compression loading until failure. Digital image correlation was used to assess strain fields, qualitatively and quantitatively, in the anterior wall of the vertebral body. Mean failure load was 3.26 kN (range 1.25-7.67 kN) and stiffness was 9.67 kN/mm (range 3.12 – 21.43 kN/mm). A linear correlation was found between failure load and stiffness with a coefficient r 2 = 0.95. At failure, mean values of von Mises strains and minimal principal strains (compressive) was 1.53% (range 0.51 – 2.55 %) and -1.43% (range -2.34 – -0.35 %) respectively. Failure loads and stiffnesses were consistent with the literature considering similar experiments. These data as well as those needed to build patient-specific models will be shared with the scientific community in order to evaluate different models on the same dataset.

TALK 2: The zebrafish (*Danio rerio*) is a teleost (bony fish) which has gained increasing interest in the field of musculoskeletal health. Based on its genetic similarity with humans (~70% of all genes and ~80% of disease-related genes) it serves as a valuable model organism allowing to perform large-scale functional and interventional studies to assess the various factors of bone quality. Many bone diseases are characterized by alterations in skeletal morphology and an increase in fracture risk, which often originates from lower length scales of the bone material, e.g. at the mineral and collagen phase. For instance, the *Chihuahua* zebrafish model of human classical dominant osteogenesis imperfecta is characterized by deformed vertebrae and increased fracture risk at the whole bone level which we could link to reduced mineral and collagen maturity assessed with vibrational spectroscopy, as well as to a reduced elastic modulus assessed with nanoindentation. In a wild type zebrafish model of exercise, we found an increase in bone formation and mineralization assessed with histology and quantitative backscattered electron microscopy. Interestingly, both models also showed alterations in the muscle fiber morphology analyzed with histology and microCT, highlighting the value of zebrafish to study effects of disease and treatment on the musculoskeletal system.

TALK 3: Subchondral bone (SB) alterations are major biomarkers of osteoarthritis (OA) progression and are more and more used by clinicians to detect OA. Although they are well described in late stage OA, the first SB biomechanical and compositional alterations are not well described. In our latest experiments, we induced Post Traumatic OA (PTOA) in C57Bl6 mice right knee and investigated 40 mice (n=13 control group [CL] and n=27 PTOA group) by using Gait Analysis, Histomorphometry, Atomic Force Microscopic Nanoindentation, and Raman Spectroscopy.. While no difference was observed regarding collagen or mineral-related compositional RS properties, we depicted higher crystallinity in the medial condyle compared to the lateral condyle in the PTOA groups that was not observed in the control group. For instance, the lateral condyle decreases in degree of mineralization, decreases in crystal size and present a lower stiffness. Our study reveals a novel set of data about an intermediate stage of PTOA progression where SB nanoscopic stiffness decreases while degree of mineralization is not severely altered yet. This can help clinician to diagnose OA sooner by using SB alterations.



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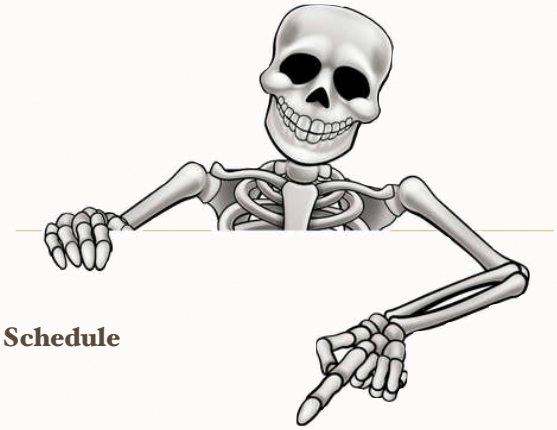
TALK 4: Femur metastases are associated with severe skeletal complications, including bone fracture. Current clinical scores, such as Mirels', poorly estimate the risk of fracture. The strength of tumoral bone segments can be assessed using patient-specific finite element models, but their accuracy is hampered by several limitations, including a lack of knowledge of metastatic bone mechanical properties. Therefore, the aim of this study is to characterize the local mechanical properties of bone metastases and primary tumor tissues for comparison. Creep-indentation tests were performed on human metastatic bone and primary tumor (breast, kidney, thyroid) samples obtained after surgery, using Atomic Force Microscopy. The elastic modulus and elastic fraction were calculated using Hertz and Maxwell models, respectively. The elastic modulus of metastatic tissue was of the same order of magnitude as that of tumor tissue, with mean values ranging between 1 and 10 kPa, and was much lower than the elastic modulus of bone tissue (around 10-20 GPa). Bone metastasis mechanical properties were heterogeneous, with an increase in the elastic modulus toward bone tissue. This new knowledge of bone metastasis mechanical properties will allow the refinement of our finite element model of metastatic femurs, to improve the failure load prediction.

TALK 5: The Bone self-assembly process is monitored by the bone Genetic Regulatory Network (GRN) and consists in building a collagen matrix and mineralizing it. The goal of this paper was to capture the behavior of the bone GRN. Our hypothesis was to model the direct interactions between the genes of (i) transcription factors and (ii) proteins. To do so, we provided a literature review of the bone GRN, and proposed a system of nonlinear differential equations modeling the interactions through Michaelis-Menten and Hill functions. Compared to empirical data, the two best systems (among 12^4 = 20, 736 possibilities) used factors of inhibition from the start of the activation of each genes which reveal negative indirect interactions. We suggest that the inhibition comes from negative feedback loops or micro-RNAs located inside of the nucleus. This first mathematical model of the bone GRN demonstrates a necessary inhibition process during Bone self-assembly.

TALK 6: The skeletal system adapts readily to changes in mechanical load, allowing bone to alter shape and structure in response to its mechanical environment. In this talk Dr. Shefelbine will show a snapshot of her current work in which she uses experiments, imaging and computational modeling to probe the link between mechanics and bone growth. Her lab uses salamander limb regeneration to understand the role of mechanical loading in joint development. Blocking the ability of cells to detect mechanical signals results in altered joint morphology. Computer simulations of growth dependent on mechanical stresses can predict the altered morphology. Her lab is currently using computational modeling to understand clinical growth pathologies, such as bone deformities in cerebral palsy and femoroacteabular impingement in elite adolescent athletes. Understanding the mechanical causes of altered growth will aid in developing effective therapies.



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TALK 7: Exposure to ionizing radiation is known to have degenerative effects on bone health. Declines to both microstructural and material properties of bone impact overall bone strength and fracture risk. There are limited studies investigating the material property changes in bone after exposure to radiation. This study investigates the time course of bone material property changes in rats exposed to Helium-4 radiation. Rats were exposed to a single, whole-body dose (0, 5, or 25 cGy) of Helium-4 radiation. Bone material properties were assessed at 7, 30, 90, and 180-day time points after radiation exposure using spherical micro-indentation of the femoral cortical bone. No statistically significant differences were observed at 7 or 30-days after exposure to either 5 or 25cGy doses when compared to sham controls. At 90-days post exposure, 25cGy of Helium-4 radiation caused a statistically significant decline in the bone instantaneous shear moduli (-33%) and the relaxed shear moduli (-32%). This decline was followed by a recovery to baseline levels by 180-days after exposure. Future work could investigate the time course for alterations in bone turnover as well as systemic hormonal changes caused by radiation exposure, which could lead to potential pathways for radioprotective countermeasures.

TALK 8: Trabecular bone adapts its bone mass, porosity, microarchitecture and tissue composition in response to its mechanical environment through a well-orchestrated bone remodeling process. Such adaptation mechanism in young individuals makes bone mechanically competent to resist low-trauma fractures; however, a high resorption and low bone formation imbalance in the elderly leads to bone loss, the advent of osteoporosis and fragility fractures. A major determinant of bone mechanical function is its mass density, which is generally assessed by a Bone Mineral Density (BMD) measurement using Dual Energy X-ray Absorptiometry. However, BMD measurements lack both sensitivity and specificity to effectively identify patients with decreased bone strength and at risk of fracture. Indeed, other factors, including bone microarchitecture and tissue composition, are critical for better predicting fracture risk. In this talk, I will present a summary of our studies on the structure-function relationship in trabecular bone using ultrasound wave propagation in porous media. In particular, we demonstrated that the spatial distribution of trabecular bone mass (i.e. fabric and porosity), when combined with bone tissue mineral density, is able to describe the directional-dependent variability of the anisotropic elastic and yield behavior of trabecular bone better than BMD alone.

TALK 9: The objective of this work is to understand bone failure mechanisms under fracture resistance experiment (i.e., toughness test) in fragility fractures involving degradation of collagen by glycation to mimic human bone aging or type 2 diabetes effects. With short acquisition and high-resolution imaging, dynamic synchrotron radiation micro-computed tomography (SRμT) is well suited for *in situ* mechanical testing to monitor 3D micro-crack evolution and to determine the stress/strain fields via DVC based on osteocyte lacunae displacement in real-time loading. However, the high levels of radiation exposure associated with synchrotron imaging compromises the mechanical and fracture properties in bone. To address this issue, we developed a novel method combining SRμT at beamline 8.3.2 of the ALS and machine learning to image *in situ* tissue deformation and crack growth. This method consists of acquiring low-quality scans at a reduced radiation dose (and reduced signal-to-noise ratio) reconstructed with convolutional neural network to recover the signal level and reduce the noise. This technique was used heat treated bovine bone samples to induce different levels of collagen damage. This will improve our ability to assess and prevent fracture risk in population with fragility diseases, and offers new possibilities to lower the radiation dose in medical imaging.