

ACCREDITATION TO SUPERVISE RESEARCH (HABILITATION A DIRIGER DES RECHERCHES - HDR)

presented by: **Pierre-Yves ROHAN**
Defense: 23 September 2022

Biomechanics of soft tissue injuries resulting from mechanical interaction with external medical devices

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ACKNOWLEDGEMENTS

I want to acknowledge all the members of the HDR committee and, especially, the courtesy of the reviewers who agreed to examine my manuscript.

I owe a lot to the students who have walked a little path with me. I have learnt a lot from you and this manuscript exists only and solely because of you: *Aurélien MACRON, Nolwenn FOUGERON, Stéphane URCUN, Thomas LAVIGNE, Alexandre SEGAIN, Maher ABOU KARAM*,... I also owe a lot to my mentors: *Karol MILLER, Adam WITTEK, Stéphane AVRIL, Pierre BADEL, Yohan PAYAN, Stéphane BORDAS, Stébastien LAPORTE* and especially *Sylvain PERSOHN, Xavier BONNET* and *Hélène PILLET*. Because of you I understand why science needs strong mentors.

I also want to extend my warmest gratitude to all the colleagues of the IBHGC. Special dedication to the *team resto*, the *team course*, the *team Belette* and the *team musique*, Special thanks to *Marine SOUQ* and *Sylvain PERSOHN* for boosting the good mood and for making this research lab a nurturing, collaborative and caring environment.

Finally, a very special thank you to Dina and Léo who make my day so much better.



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SUMMARY IN FRENCH

La prévention des lésions superficielles et profondes dans les tissus mous biologiques lors de l'interaction physique entre une personne et un dispositif médical mécanique est un enjeu majeur. Les défis existent encore aujourd'hui car il est essentiel que les chargements mécaniques transmis aux tissus mous superficiels et profonds soient maintenus dans des plages d'intensité qui garantissent la **viabilité tissulaire**. Les personnes à mobilité réduite sont particulièrement exposées. Pour ces personnes, les dispositifs d'assistance tels que les prothèses et les Fauteuils Roulant Manuels permettent de mener une vie saine, productive, indépendante et digne.

La modélisation biomécanique a été identifiée comme un outil potentiel pour aider les cliniciens dans les processus actuels d'évaluation des risques et, également, les industriels dans leur processus de conception. Depuis mon entrée dans le monde de la recherche académique, j'ai eu l'occasion de mettre en application la méthode des éléments finis (MEF) non-linéaire pour évaluer la transmission des efforts lors de l'interaction physique entre une personne et un dispositif médical mécanique (**Partie 1**). Les applications visent **1/** l'évaluation du risque lésionnel lors de l'interaction physique entre une personne et un dispositif médical mécanique (**risques de lésions cutanées** et d'inconfort liés à des surpressions résultant d'une orthèse/prothèse mal adaptée [Sections [2.4](#), [3.3](#)] et **risque d'escarres** en position assise ou couchée sur des surfaces d'appui [Sections [2.5](#), [2.6](#), [2.7](#), [2.9](#), [3.1](#), [3.2](#)]) **2/** l'aide à la gestion des troubles chroniques des tissus mous (prise en charge des varices de jambe [Section [2.2](#)]) et **3/** l'aide à la planification chirurgicale (non abordé dans ce manuscrit).

Cependant, un certain nombre de verrous scientifiques doivent être levés pour comprendre les déterminants mécaniques de l'apparition de lésions dans les tissus mous lors d'un contact prolongé avec un dispositif externe et pour envisager l'intégration de tels outils, d'une part, dans le parcours de soins pour être en mesure de renforcer la prévention des escarres sur le plan clinique et, d'autre part, dans le milieu industriel, pour l'aide à la conception de ces dispositifs externes. Le verrou majeur réside dans le fait que les **lésions tissulaires sont régies par un certain nombre de processus biologiques et physiques couplés qui se produisent à différentes échelles spatiales et ont souvent des caractéristiques temporelles très différentes**. Donc, la connaissance de l'état mécanique statique local (localisation de lésion) ne suffit pas à elle seule à prédire l'apparition et l'évolution des lésions tissulaires.

Pour progresser dans la représentativité de ces jumeaux numériques de l'être humain et pour assoir leur pertinence clinique, mon projet de recherche est formulé en trois axes principaux pour les années à venir (**Partie 2**).

Premièrement, d'un point de vue clinique, **la durée de la sollicitation mécanique** joue un rôle crucial dans l'apparition des escarres (Coleman 13; Coleman 14). L'étude de référence étant celle de Reswick et Rogers (Reswick 76) qui a établi, en 1976, une courbe de risque de survenue d'escarre sur la base d'observations sur 980 sujets sains et patients. L'étude, plus récente de Swisher et collaborateurs montre également que l'endommagement tissulaire induite par un chargement externe et quantifiable à l'histologie, est un phénomène réversible jusqu'à un certain seuil (Swisher 15). Ainsi, l'étude de l'évolution temporelle de la réponse mécanique et, en particulier, de la **dégradation progressive des tissus mous en fonction du chargement**, est essentielle pour comprendre et prévenir la formation d'escarres. Les tentatives de caractérisation de la dépendance temporelle des tissus mous supposent généralement une formulation viscoélastique et ignorent la nature poreuse du milieu (les tissus mous étant perfusés par le sang et par le fluide interstitiel, il peut être assimilé à un milieu poreux à double-porosité). Le premier objectif (détaillé dans le **chapitre 5**) vise donc à explorer, à l'aide d'une approche mixte expérimentale-numérique, le lien entre réponse mécanique et microcirculation 1/ *ex vivo* à travers des essais classiques de laboratoire (traction/compression), *in vivo* dans un modèle animal et, en routine clinique, dans une population à risque (personnes âgées). Ce travail permettra de poser les bases pour étudier la **dégradation progressive des tissus mous** lors du couplage entre la réponse mécanique et la réponse biologique (et plus particulièrement avec la biochimie de l'oxygène).

Deuxièmement, d'un point de vue plus fondamental, c'est une dérégulation de la réponse inflammatoire cellulaire et les mécanismes métaboliques qui jouent un rôle clé dans l'apparition de la nécrose. Le deuxième objectif (détaillé dans le **chapitre 6**) vise donc à explorer ce processus biologique complexe. Plus précisément, en utilisant une approche mixte expérimentale-numérique, l'objectif est d'étudier la cascade d'événements reliant réponse mécanique, ischémie, **inflammation**, **nécrose** et **cicatrisation** dans les tissus mous biologiques dans un modèle animal et, en routine clinique, dans une population à risque (personnes âgées). Ce travail permettra de mieux comprendre la dynamique inflammatoire chez les personnes qui développent une escarre. Ce travail permettra également d'étudier les traitements potentiels *in silico*.

Troisièmement, les études de faisabilité du déploiement de tels dispositifs en milieu clinique et industriel et les études pré-cliniques et l'évaluation clinique de l'efficacité de l'approche biomécanique est la finalité à long terme visé pour avoir un impact. Le troisième objectif (détaillé dans le **chapitre 7**) vise donc à proposer une méthodologie pour rendre l'utilisation de tels modèles multi-échelles et multiphysiques compatibles à la routine clinique afin de pouvoir amorcer les études de faisabilité.

What is the biomechanics of soft tissue? In a foreword for the journal Biomechanics and Modeling in Mechanobiology, Y.C. Fung suggests that biomechanics is the "middle name" between biological structure and function. Hence, the biomechanics of soft tissue seeks to explain the function of soft tissues on the basis of their structure and their mechanics. Understanding, and thus controlling better the mechanics in relation to the structure of any soft biological tissue, how mechanical information is transduced by the cells, and how changes in the cellular and molecular structure of tissues thereby affect tissue function, is a central research goal in soft tissue mechanics.

HOLZAPFEL, G.A., 2017. **COMPUTATIONAL BIOMECHANICS OF SOFT BIOLOGICAL TISSUES: ARTERIAL WALLS, HEARTS WALLS, AND LIGAMENTS**, IN ENCYCLOPEDIA OF COMPUTATIONAL MECHANICS SECOND EDITION (EDS E. STEIN, R. BORST AND T.J.R. HUGHES)

Despite the broad research on the modeling of tissue damage, there is still no clear understanding of what "damage" of a soft biological tissue is from the microstructural point of view. Conventional macroscopic indicators, as known from damage in engineered materials, may not predict damage in biological tissues appropriately and accurately enough. In addition, tissues are living materials, so that damage may trigger a process of health restoration called healing. A better understanding of the damage mechanism in soft biological tissues is critical to the characterization of tissue injury, including its implications on biological (physiological/pathological) responses, and the damage modeling in computational simulations.

HOLZAPFEL, G.A., FEREIDONNEZHAD, B., 2017. **CHAPTER 5 - MODELING OF DAMAGE IN SOFT BIOLOGICAL TISSUES**, IN: PAYAN, Y., OHAYON, J. (EDS.), BIOMECHANICS OF LIVING ORGANS. ACADEMIC PRESS, OXFORD, PP. 101-123.

General Introduction

CHAPTER 1

GENERAL INTRODUCTION

With a continuous increasing craze towards technologies that can repair or enhance the human body, the question of the adaptation of mechanical device interfaces to human limbs is a challenge that now has become crucial. One of the most important bottlenecks is to simultaneously ensure optimal biomechanical function/performance and, at the same time, fulfill comfort and safety constraints. Exoskeletons and assistive robots are iconic examples of these mechanical devices. Yet, the underlying challenge extends to all the situations where a person is in contact with a mechanical system that share a mechanical interface with the human body. This include, for example, immobilized persons supported on a bed or in a wheelchair, amputees wearing a prosthesis, and individuals with orthoses or functional medical devices attached to the skin. This can result in soft tissue damage, particularly in at-risk persons such as the elderly and those with comorbidities such as diabetes..

The research work that I have carried out so far has focused on modelling and simulating the transmission of mechanical loads in biological soft tissue during the mechanical interaction with external devices from a structural mechanics perspective (**Part 1**). The clinical and industrial motivations were **1/** the evaluation of the risk of chronic wounds and skin breakdown as we interact with the environment around us (more specifically the risk of superficial tissue injury resulting from sub-optimally fitted orthosis/prosthesis [sections 2.4, 3.3] and the risk of deep tissue injury when lying or sitting on support surfaces [Sections 2.5, 2.6, 2.7, 2.9, 3.1, 3.2]) **2/** to assist in the management of soft tissue injuries (varicose veins [Section 2.2]) and **3/** to assist in surgery planning (not included in the manuscript).

Challenges still exist today because there is a **subject specific tolerance to mechanical loading** (Traa 19). Investigations conducted by the group of Cees Oomens at Eindhoven University of Technology at different length and time scales (from the single cell scale (Bouten 99; Bouten 03b; Peeters 03) to the tissue scale (Bosboom 01; Bosboom 03; Stekelenburg 06b; Stekelenburg 06a; Stekelenburg 07; Ceelen 08; van Nierop 10; Loerakker 10; Loerakker 11; Nelissen 18; Traa 19)) have shown that **soft tissue injury is, fundamentally, a multi-scale and multi-physics process** (Oomens 14). Cell deformation triggers a variety of effects, such as volume changes and cytoskeletal reorganization, which may be involved in early tissue breakdown. Furthermore, and more importantly, wound initiation depends, in large part, on how cells sense and respond to chemo-mechanical stimuli (Gefen 16; Turner 14), It has been shown that signaling cascades coordinate how cells change their local Extra-Cellular Matrix to maintain homeostasis and any disruption triggers **inflammatory disorders**. This is consistent with clinical results showing that many factors other than the magnitude of loading affect an **individual load tolerance**,

such as their age, level of mobility, nutritional status, and degree of tissue perfusion (Coleman 13). To be **clinically relevant**, computational models should therefore be designed to predict the transmission of loads throughout the different length and time scales and be able to capture the main **interactions between mechanical response and biological response** and explicitly **incorporate chemo-bio-mechanical couplings**.

In order to progress in the clinical relevance of Digital Twins in the context of soft tissue injury prevention, the focused research project is formulated in three main areas for the coming years (**Part 2**).

First, the mechanical characterization of the **time-dependent mechanical behavior up to damage** of soft tissues under prolonged loading is an important challenge because it has been established that it is the progressive tissue damage that determines pressure ulcer development, not the instantaneous local deformation itself. In the literature, attempts to characterize the time-dependence of soft tissues generally assume a viscoelastic formulation and typically ignore the porous nature of the medium ((Van Loocke 09; Simms 12; Wheatley 15)). Yet, soft tissues can be assimilated to a hierarchical reactive bi-compartment porous medium: the extracellular matrix constitutes the solid scaffold; blood is in the vascular porosity whereas the extra-vascular porous compartment is saturated by two cell phases and interstitial fluid (mixture of water and nutrient species). The first objective of the focused research project (**chapter 5**) will be to **link the damage process during prolonged loading with ischemia/reperfusion and mechanical deformation** in **1/** an animal model, **2/** in human skin substitutes and, **3/** in clinical routine, in at risk persons.

Second, from a more fundamental perspective, the pathogenesis of Pressure Ulcer involves the activation of the acute inflammatory response, a cascade of events mediated by a set of specialized cells (e.g. platelets, mast cells, macrophages, and neutrophils) and molecules (inflammatory cytokines, free radicals, and Damage-Associated Molecular Pattern molecules) in stressed or damaged tissue (Houwing 00; Peirce 01; Ziraldo 15). The inflammatory response can either heal the tissue, or become self-maintaining inflammation that causes tissue damage (Ziraldo 15). The second objective of the focused research project (detailed in **chapter 6**) will be to investigate the primary determinant of soft tissue damage (detailed in **chapter 6**). More specifically, the aim will be to study the cascade of events linking mechanical response, ischemia, and inflammation, and wound healing in biological soft tissues in an animal model and, in a routine clinical setting, in a population at risk (individuals). This work will provide a better understanding of the inflammatory dynamics in people who develop a pressure ulcer. This work will also allow the study of potential treatments *in silico*.

Third, the feasibility studies of the deployment of such devices in clinical and industrial settings and pre-clinical studies and **clinical evaluation** of the efficacy of the biomedical approach is the long-term goal. The third objective (detailed in the text of the chapter "Clinical Project") is therefore to propose a methodology to make the use of such multi-scale and multiphysical models compatible with clinical routine so that feasibility studies can be initiated.

Nota Bene. Throughout the manuscript, the reader will be referred to associated publication listed in the publication list given in **chapter 11** to go further. The following convention will be used : [P] for Journal publications, [BC] for Book Chapters, [IT] for Invited Talks, [CP] for Conference Proceedings in journals with peer-review and [CA] for Conference Abstracts without peer-review.

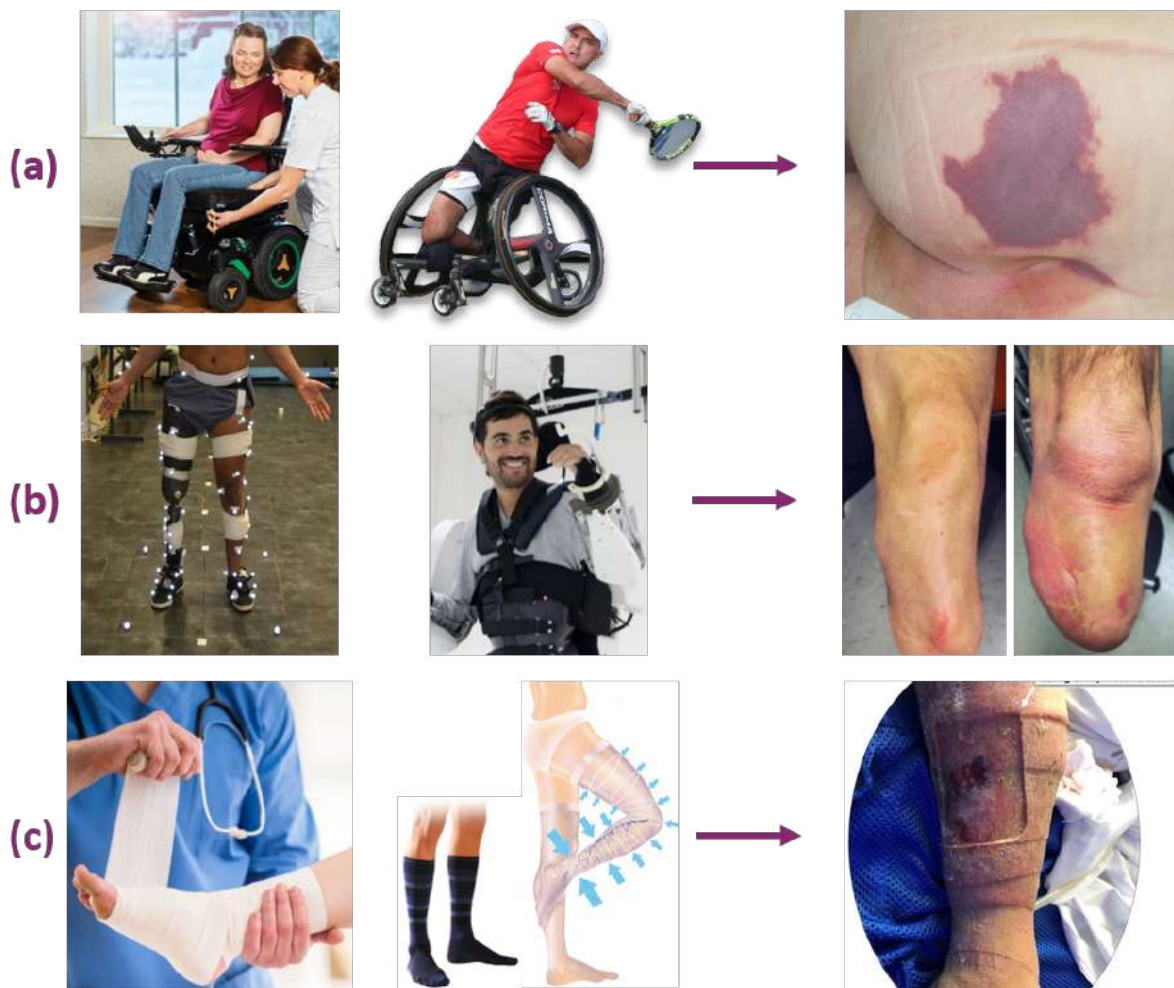
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Part I

Characterization of soft tissue behaviour and injury risks during device/human interactions: A structural mechanics approach

Characterization of device/human interactions

Injury risk



THE RESEARCH WORK THAT I HAVE CARRIED OUT SO FAR HAS FOCUSED ON THE MODELLING AND SIMULATION OF THE MECHANICAL RESPONSE OF BIOLOGICAL SOFT TISSUE SUBMITTED TO EXTERNAL MECHANICAL LOADING AS A RESULT OF MECHANICAL INTERACTION WITH EXTERNAL DEVICES. THE CLINICAL AND INDUSTRIAL MOTIVATIONS ARE (A) THE EVALUATION OF THE RISK OF CHRONIC WOUNDS AND SKIN BREAKDOWN AS WE INTERACT WITH THE ENVIRONMENT AROUND US (RISK OF PRESSURE ULCERS WHEN LYING OR SITTING ON SUPPORT SURFACES [SECTIONS 2.5, 2.6, 5.3, 3.2]), (B) RISK OF SKIN BREAKDOWN RESULTING FROM SUB-OPTIMALLY FITTED ORTHOSIS/PROSTHESIS [SECTIONS 2.4, 3.3]) (C) TO ASSIST IN THE MANAGEMENT OF SOFT TISSUE INJURIES (VARICOSE VEINS [SECTION 2.2]). SOURCE IMAGE (C) **A WOUND DRESSING THAT IS OVERLY STIFF AND/OR INAPPROPRIATELY APPLIED CAN DO MORE HARM THAN GOOD!**

CHAPTER 2

IMPACT OF THE TRANSMISSION OF LOADS IN BIOLOGICAL SOFT TISSUES ON TISSUE VIABILITY: SUMMARY OF THE WORK CONDUCTED SO FAR

2.1 Research question (hypothesis)

Biological soft tissues have unique hierarchical architectures and an extremely efficient deformation ability that allow them to play diverse mechanical roles (Sharabi 22) **as we interact with the environment around us**. Skeletal muscle, for example, is a multiphasic tissue, composed of the extracellular matrix (ECM), muscle fibers, and saturating fluid allowing it, on one hand, to generate and transmit tremendous amounts of forces (Fitts 91), and also, on the other hand, to distribute load (Simms 12) during conditions such as bed rest, prosthesis fitting, and high rate impacts such as those from athletic events or automotive accidents. Likewise, the sole of the foot has a specialised structure that enables it to tolerate the mechanical forces of ambulation (Boyle 19).

Excessive mechanical loads resulting from the mechanical interaction between the human body and external devices can lead to superficial and deep tissue injuries. **Superficial soft tissue injuries** such as tears (LeBlanc 11), blisters (Knapik 95) and superficial pressure ulcers (Bouten 03a) may appear when the skin surface is exposed to high surface pressure and/or shear loads. Skin load tolerance is highly site specific (Coleman 14) and reflects the function of the anatomical location (Boyle 19). For example, plantar skin can tolerate repeated pressures and shear stresses as high as 1000 kPa (Lieberman 10) without injury, while a small fraction of this loads (1/200th) is sufficient to injure other parts of the body, such as the heel (Hoogendoorn 17).

Deep tissue injuries generally occur during prolonged exposure to mechanical loads that are **lower than those needed to rupture or physically damage the skin** (Bouten 03a), for example, when patients interact with medical devices (Black 10) and support surfaces (McInnes 15). Deep tissue injuries are pressure ulcers which initiate in the subcutaneous tissues and extend through a bottom-up pathway. Once deep tissue injuries are visual at skin level, serious irreversible tissue damage has already occurred. It is estimated that nearly one in five hospitalized patients develop pressure ulcers in European Union

hospitals (Vanderwee 07), with critically ill, immobilised and neuropathic patients most at risk. It leads to great expenditures for healthcare systems and society (Demarré 15) but are generally preventable. Symptoms such as pain, discomfort, exudate, and odor can occur, which can further restrict mobility and daily activities as well as lead to disturbed sleep and a general reduced quality of life. Patient's psychological well-being can be affected by feelings of anxiety, worry, and dependence. This can lead to social isolation and the inability to participate in activities.

One difficulty in preventing soft tissue injury has been quantifying the load tolerance of soft tissues. In mechanical engineering, **damage accumulation in materials** is a consequence of micro-defect evolution, which may lead to degradation of mechanical properties up to failure. Despite the broad research on the modelling of tissue damage (the reader is referred to the excellent book chapter of Gerhard Holzapfel and Behrooz Fereidoonzhad (Holzapfel 17) for more details), **there is still no clear understanding of what "damage" of a soft biological tissue is** from a microstructural point of view. This part of the manuscript (**Part I**) **focuses on the evaluation of the mechanical loads in situ** as we interact with the environment around us.

Moreover, when soft tissue injury prevention **fails** as a result of non-adherence, various comorbidities, or gaps in care, it can result in chronic, non-healing wounds that subject the patient to significant discomfort and distress. It has been estimated, for example, that a single diabetic ulcer carries a cost of nearly US\$ 50,000 (Paquette 02) and chronic wounds as a whole cost the medical system over US\$ 25 billion per year, with the number of patients affected growing yearly from 6.5 million, given the increasing prevalence of diabetes and other chronic diseases that may affect wound healing (Brem 07). It is no surprise, then, that wound healing has received a great deal of attention from the scientific community (Han 17; Rodrigues 19; Cañedo-Dorantes 19; Hanna 97). Wound healing is also a huge commercial enterprise, with the market for wound care products exceeding US\$ 15 billion and treating wound scarring another US\$ 12 billion (Sen 09). For this reason I have also chosen to **include the work I did during my PhD thesis** ([section2.2]) because of its relevance to the topics discussed in this part.

Part I of the manuscript focuses on the evaluation of the mechanical loads *in situ* as we interact with the environment around us. It is assumed, in this part, that conventional macroscopic indicators, as known from damage in engineered materials, can predict damage in biological tissues.

2.2 PhD Thesis (2010-2013): Mechanical response of leg veins to Medical Elastic Compression



10/2010 - 12/2013 Supervisors: **Stéphane AVRIL** & Pierre BADEL [P1, P2, P3]
Industrial Collaboration: **SIGVARIS**

Medical Compression Stockings (MCS) are considered as a mainstay in the treatment options for patients suffering from lower leg deep venous insufficiency (Gloviczki 11) (figure 2.1(d)). They have been shown to be very effective in (i) preventing and managing Deep Venous Thrombosis (Bouman 14), post-thrombotic syndrome (van der Velden 14) and ulcers of the leg (Dolibog 14), (ii) improving abnormal venous return (Lattimer 14) and (iii) improving muscle calf pumping function (Mosti 14). Traditionally, the benefit of compression therapy in deep veins is attributed to a narrowing of the deep veins and, as a result, to a prevention of blood pooling in veins. This, however, has never been conclusively demonstrated. As a matter of fact, conflicting results have been reported which call into question this hypothesis (Mayberry 91) and which highlight the need to address the key question of whether or not the benefits of action of MCS are correlated to a decrease in the vein luminal cross-sectional area.

The purpose of this PhD work was therefore to study transmission of pressure in the soft tissues of the lower leg during external compression with and without muscle activation to improve our understanding of the main biomechanical parameters affecting the response of lower leg deep veins to external compression.

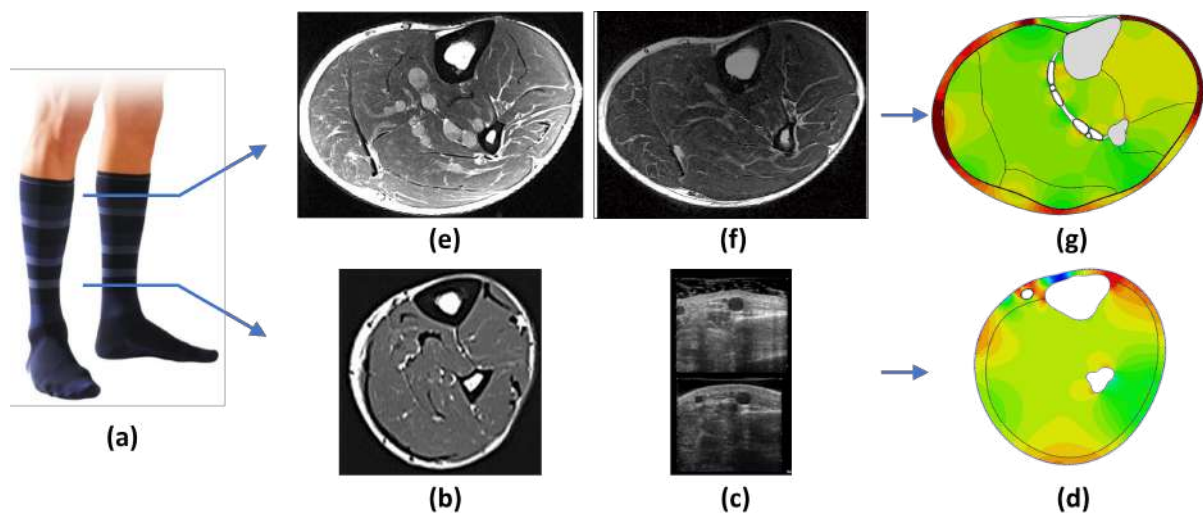


Figure 2.1: (a) **Sigvaris MCS** (b) MRI slice of a patient with a varicose vein in supine position (c) Ultrasound data of the same patient with and without wearing a 15-20 mmHg MCS in standing position (d) Hydrostatic pressure in the soft tissues during elastic compression (e) MR image of a patient in supine position (f) MR image of a patient in supine position wearing a 15-20 mmHg and with muscle contraction. Hydrostatic pressure in the soft tissues during elastic compression.

First, a patient-specific Finite-Element model of the human leg with varicose vein was developed in (Rohan 13) to model the stress distribution in and around a vein wall in order to determine the biomechanical response of varicose veins to compression treatment (figure 2.1(d)). Because experimental data

on the mechanical properties of healthy superficial veins and varicose veins are scarce in literature, ultrasound images of *in vivo* varicose veins were acquired and analysed to extract the material constants using Finite Element Model Updating (figure 2.1(c)). Results showed that external compression is effective in decreasing the trans-mural pressure, thereby having a positive effect in the control and treatment of vein-related diseases. A 2D FE biomechanical model of the lower leg was then developed to study the response of the main deep veins to both elastic compression and muscle contraction (figure 2.1(g)) from MRI data (figure 2.1(e-f)) in (Rohan 14). The numerical results confirmed those of clinical studies showing that, in the standing position, it is mainly muscle activation that is responsible for narrowing deep veins luminal diameter, not the interface pressure applied by commercially available MCS which is insufficient to have a significant impact.

In short, results obtained show that MCS are effective in reducing the vein luminal diameter of lower leg superficial veins but, suprisingly, have virtually no effect on lower leg deep veins in the upright position. Interestingly, some studies also reported that, irrespective of the effects on the luminal diameter, MCS lead to an increase in the blood flow in deep veins (Downie 08). These observations suggest that, by increasing the pressure in the deep soft tissues of the leg, MCS contribute to emptying the blood present in the micro-circulation. Lower leg deep veins therefore carry more blood during external compression (due to an increased venous blood flow) but do not see their luminal diameter decreased, as observed clinically. It is envisaged to investigate in the near future the response of the deep micro-circulation to external compression.

Investigating the mechanisms giving rise to vein tortuosity [P2]

The mechanisms giving rise to vein tortuosity, which is often associated with varicosis, are poorly understood. Recent works suggest that significant biological changes in the wall of varicose veins may precede the mechanical aspects of the disease. To test this hypothesis, a Finite Element model was developed during my PhD in (Badel 13) based on previous experimental work on vein buckling. The model was then used to evaluate the effect of alterations of the mechanical behavior of the wall on tortuosity onset and severity. The results showed that increasing anisotropy towards the circumferential direction promotes tortuosity. An increase in wall stiffness tends to decrease the level of tortuosity but interestingly, if the vein segment is little or not stretched such increase will not prevent, or it will even promote, the onset of tortuosity. These results provide additional arguments supporting the hypothesis of tortuosity being the consequence of biologically-induced changes in the varicose vein wall.

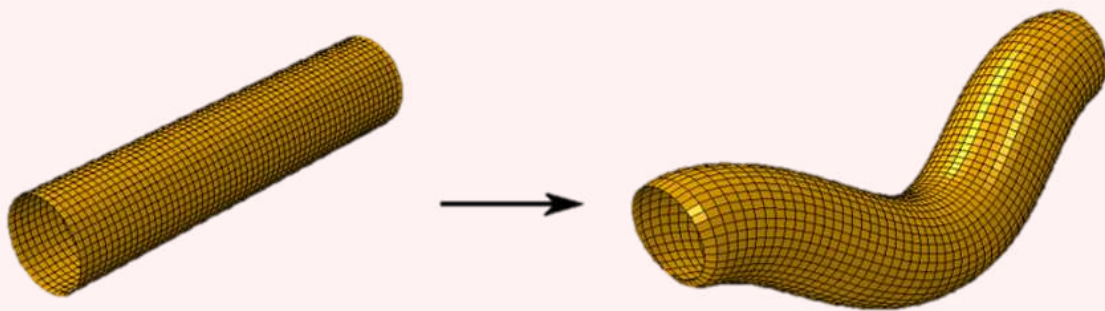


Figure 2.2: A numerical Finite Element model was developed to reproduce the phenomenon of tortuosity forming via a buckling mechanism.

2.3 Synthesis of challenges: Elaborating subject-specific FE models is a long and tedious task

Nonlinear Finite Element Analysis remains a method of choice for soft tissue biomechanics. However, the **extraction of clinically relevant data from such finite element simulations** remains a challenging task for the whole community (the reader is referred, for example, to the very relevant editorial of (Viceconti 05) published in *Journal of Clinical Biomechanics*). Several initiatives and guidelines have been proposed in the literature for establishing the credibility of biomechanical models developed in academia especially when results are to be transferred to a patient (Anderson 07; Henninger 09; Erdemir 12; Burkhart 13; Hicks 15; Viceconti 20; Oefner 21). These studies have emphasized that **verification, validation and uncertainty quantification** are a major requirement prior to the clinical interpretation of numerical predictions. These guidelines have also advocated the necessity to move from reporting standards to model sharing to increase the **reproducibility, reusability, and accountability** of models (Erdemir 12). It has also been highlighted in the literature that a fundamental element in model credibility is its **applicability**, which is how far from the conditions under which the model has been validated, the predictions remain credible. This is an important point because even when a model has been validated by means of controlled laboratory experiments, the conditions are only partially representative of a specific patient and situation.

In practice, the main challenges for the implementation of Nonlinear Finite Element Analysis in everyday clinical practice is the **development of reliable and affordable techniques for the subject specific modelling** of the patient **anatomy, *in vivo* boundary conditions and loads and constitutive parameters**. Although the ability to use any modelling technique in the clinic is mainly determined by its ease of use, its non-invasive nature and low cost, the potential to actually enhance clinical practice is determined to a great extent by the accuracy and relevance of the information it can provide (Behforootan 17). The following provides an overview of different challenges to investigate their applicability in a clinical setting and where applicable, the first steps taken in my research to contribute to overcome these.

- ⇒ **Subject specific modelling of the patient anatomy and Finite Element discretisation:** Several studies in the literature have demonstrated that the mechanical response of soft tissues (in terms of stress and strain localization) is highly sensitive to the simplifications made in the representation of the anatomy (the reader is referred, for example, to the sensitivity analysis of (Luboz 14a)). To incorporate highly accurate and clinically relevant representations of the anatomy, authors rely on medical images such as Magnetic Resonance Imaging (MRI) (Linder-Ganz 07; Al-Dirini 16; Levy 17; Moerman 16), Computer Tomography (CT) (Luboz 18) or, to a lesser extent, Ultrasound Imaging (US) (Chatzistergos 15). Nevertheless, patient-specific models are currently employed in small-sized clinical applications, mostly because the generation of each model is a time-demanding operation requiring manual intervention by specialized operators (several hours (Modenese 18) to days (Cohen 99)).

My contributions to the field have been: **1/** during my post-doctoral research at the **TIMC-IMAG** laboratory, I participated to the development of an automatic atlas-based method that generates subject-specific FE meshes via a 3D registration guided by Magnetic Resonance images (Bijar 15). I have also participated to the evaluation of the performance of mixed element meshes as an alternative to all-tetrahedral or all-hexahedral meshing for the

analysis of problems involving nearly incompressible materials at large strains (Rohan 16). As a complementary work, I also worked on the implementation of a recovery-based error indicator developed by for non-linear problems (Oral presentation, CMBBE 2014 figure 2.3 below). **2/** Since I joined the IBHGC, I have participated to the development of a method for the 3D reconstruction of the foot from low-dose biplanar radiographs (Rohan 18) and on the fast and automatic generation of all-hexahedral subject-specific FE models of the pelvis (Fougeron 18) and knee joint (Lahkar 21) from low-dose biplanar radiographs and associated 3D reconstructions. **3/** I have also had the opportunity of developing a collaboration with a Franz CHOULY, Michel DUPREZ, Stéphane BORDAS and Arnaud LEJEUNE on the implementation of a posteriori error estimates based on the Dual Weighted Residual technique to quantify the FE discretization errors and to optimize the FE mesh (Duprez 20). This is work in progress.

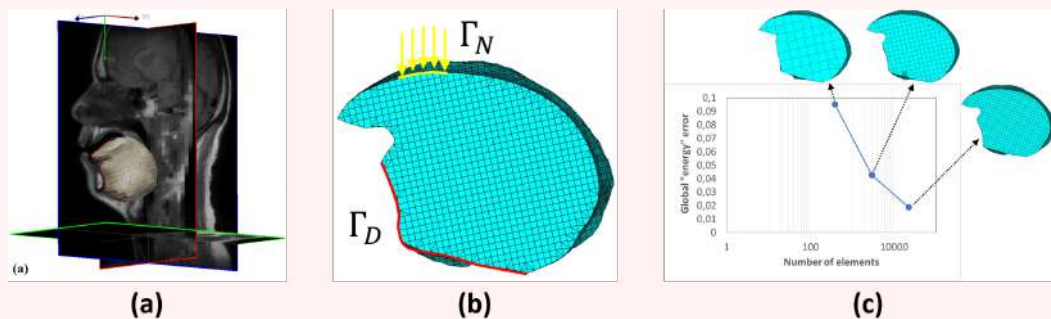


Figure 2.3: (a) Patient-specific biomechanical models of the tongue build from MRI (Bijar 15) (b) Boundary Conditions (c) Evolution of the recovery-based error indicator as a function of the FE mesh.

The question of subject specific modelling of the patient anatomy and Finite Element discretisation is a challenging problem and will be discussed throughout this manuscript.

⇒ **Constitutive modelling and calibration:** Given the inter-individual variability of the mechanical properties, a personalized assessment of the constitutive parameters *in vivo* is paramount in order to feed models that can accurately predict the finite-strain behavior of biological soft tissues. For simplicity, soft tissues are frequently assumed to behave as hyperelastic materials (the reader is referred to the book edited by Yohan PAYAN and Jacques OHAYON (Payan 17) for an extensive overview of the state-of-the-art in terms of characterization of the mechanical properties of soft tissues), and therefore described with the constitutive theory of finite elasticity for which nonlinear continuum mechanics provide the fundamental framework.

However, **personalisation of material properties is a highly challenging bottleneck** for the whole community. One way to evaluate the *in vivo* mechanical behaviour of soft tissues is to submit them to a well defined mechanical boundary condition and monitor the resulting tissue deformations. This allows to characterize experimentally the *in vivo* force-displacement (Malinauskas 89; Moerman 13; Sadler 18), *in vivo* inflation pressure-stretch (Tian 12; van Disseldorp 20) or *in vivo* aspiration pressure-volume (Kappert 21) data from which constitutive parameters can be estimated either using an inverse methodology (Vavourakis 15; Sengeh 16; Frauziols 16) or the Virtual Fields Method (Avril 08; Avril 10; Mei 19). As an alternative, Magnetic Resonance Elas-

tography (Mariappan 10; Debernard 11; Nelissen 19) and (ultrasound) Shear Wave Elastography (Gennisson 03; Blank 22) shows great promise for the non-invasive characterization of the stiffness of musculoskeletal tissues. Compared to the results obtained using traditional tensile tests, promising results have been obtained in N=4 swine muscle samples (Eby 13) and in N=14 cadaveric achilles tendons (Haen 17).

To address the issues associated with the *in vivo* passive mechanical properties of deep soft tissues, I have had the opportunity of working on a method combining freehand Ultrasound-Based indentation and inverse Finite Element modelling for the identification of hyperelastic material properties of thigh soft tissues (Fougeron 20).

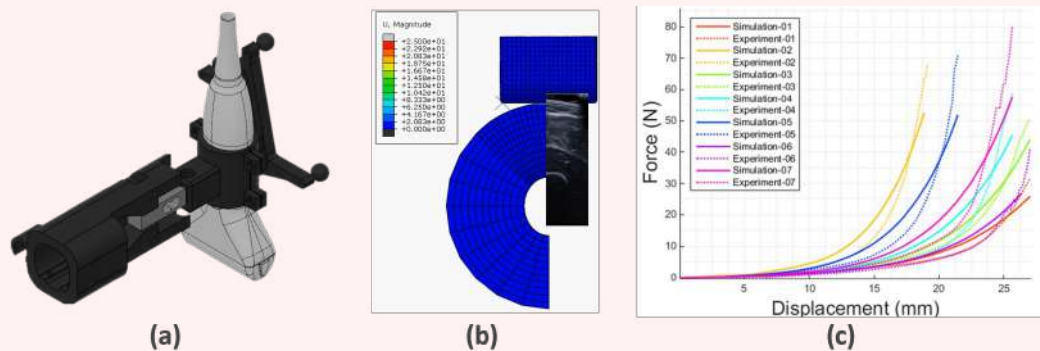


Figure 2.4: (a) Custom US-based freehand indenter conceived by combining a 200 N force sensor with a linear US probe (b) FE model and US image (c) Comparison of experimental and numerical force-displacement curves for N=8 participants.

One key challenge remains. Tissues and organs are prestrained and residually stressed *in vivo*. It follows that the reference undeformed configuration that can be obtained using medical imaging is not stress-free. The estimation of the stress-free reference state is an active area of research (Rajagopal 07; Pierce 15; Mîra 17; Rausch 17; Wang 18; Gamage 17) that won't be covered in the manuscript. But it is important to stress this limitation because the prediction of large deformations is a non-linear problem, making it necessary to calculate the stress-free reference state in order to provide reliable predictions of deformations under a variety of loading conditions.

⇒ **Boundary conditions:** Of all the sources of uncertainties, boundary and loading conditions are generally considered as being the most influential parameters (the reader is referred, for example, to the sensitivity analysis conducted in (Akrami 17) showing that predictions of peak plantar pressures during gait are moderately sensitive to material properties, Ground Reaction and muscle forces, but significantly sensitive to foot orientation). Unsurprisingly, they are also the most difficult to evaluate and to model and will be discussed throughout this manuscript.

Accounting for the patient needs and, in particular, person-environment relationships, is also an important factor for ensuring patient satisfaction and consequently successful rehabilitation. Indeed, acceptance rates and user satisfaction are not only dependent on technical aspects, but also to a great extent on social and psychological factors. There is often considerable unconsciousness among the actors (engineers, users, occupational therapists, health care professionals, politicians, researchers) that hinders communication, exchange of concepts, knowledge, and meaning. There is a need to incorporate user engagement into design processes for prosthetic limbs.

2.4 PhD **Nolwenn FOUGERON** (2017-2020): residual limb / prosthetic socket interaction



09/2017- 12/2020 Nolwenn FOUGERON H el ene PILLET (30%), Xavier BON- NET (35%), Pierre-Yves ROHAN (35%) [P20, P27, CP7]
Industrial Collaboration: PROTEOR

Prostheses and orthoses enable people with physical impairments or functional limitations to live healthy, productive, independent, dignified lives and to participate in education, the labour market and social life. The current design and manufacture of Prosthetic and Orthotic device interfaces is dominated by hand-forming of thermoplastic materials on the plaster obtained via subtraction manufacturing techniques to allow for adaptation of the geometry to every user. This manual and iterative process is necessary to target optimal load transfer and ensure a good socket fit. At the same time, the process is highly dependent on the skill and experience of the prosthetist, as well as patient feedback with no quantitative prediction of fit prior to the manufacture of the socket (Paterno 18).

Sub-optimally fitted orthosis/prosthesis can lead to pain and, potentially, to dermatologic problems such as contact dermatitis (Lyon 00) and keratosis (Ibbotson 94) and in serious cases, internal tissue strain and ischemia can lead to deep tissue injury (Bouten 03a). Estimates suggest that up to 50% of people with lower limb amputation, and especially transfemoral amputation, do not regularly use their prosthesis, primarily due to socket fitting problems causing socket discomfort and skin problems (Meulenbelt 07; Meulenbelt 09). The incidence of skin disorders, especially in the lower-limb, is substantial (Lyon 00) resulting from the requirement to transmit elevated compressive and shear forces between the prosthesis and residual limb. The consequences of mis-adaptation of the prosthetic are obviously also economical and design and manufacturing processes are a key factor of the competitiveness in this domain.

Biomechanical modelling has been identified as a potential tool to assist the prosthetist in their design process. Current developments aiming at coupling a FEA solver with a CAD package (Colombo 16; Colombo 13; Goh 05) often seek to limit the request of clinical input, which could be a cause of current failure of the approach. It is essential to be able to adapt local modifications in sensitive regions associated with soft tissue injury or neuroma. Such an approach limiting the request of clinical input also neglects important psychological aspects during the socket fitting process which are important for a successful rehabilitation (Pezzin 04).

In the literature, several research groups have proposed to incorporate FEA into prosthesis fitting and socket fit assessment (Colombo 16; Colombo 13; Goh 05; Zhang 00). The pioneer work for incorporating numerical predictions into the CAD/CAM-based prosthesis fitting approach was made in the 1980s by Krouskop et al. (Krouskop 87). Several teams have since proposed socket design and manufacturing processes based on the finite element method (Colombo 11; Jamaludin 19). No direct experimental validation of the underlying relationships between socket design and load transfer predicted by the model has been performed, and such validation evidence must be obtained prior to any clinical evaluation. On the modelling point of view, several limits have also been identified from the review of the literature. Most of the time, the residual limb model only included the representation of the femoral bone in soft

tissue (with generic mechanical properties) submitted to static loads that are poorly representative of the mechanical actions really imposed during locomotor activities such as gait.

In the PhD work of Nolwenn FOUGERON, PROTEOR and the IBHGC have proposed a methodology for modelling the interaction between the residual limb and the socket based on the combination of a subject-specific Finite Element model and a subject-specific MusculoSkeletal model (Fougeron 22) (Figure 2.5). With regard to the literature, this is the first approach for the evaluation of pressures at the interface that have integrated the personalization of the material properties of soft tissues (based on the procedure we proposed in (Fougeron 20)) and a more realistic modelling of the coxo-femoral joint. Indeed, in the case of transfemoral amputee, the modelling of the femoral bone is not sufficient and load transmission through the pelvic that are made possible through the ischial part of the bone that is in regard of a dedicated support on the socket (ischial support, figure 2.5(b)) must be taken into account. In the mentioned work, a musculo-skeletal modelling of the coxo-femoral joint including the estimation of muscular forces and the consideration of the mechanical action implied by the presence of the ischiatic support have been combined with the finite element framework. Nevertheless, the results obtained with the finite element model still need to be validated experimentally in order to decide the relevance of the proposed approach.

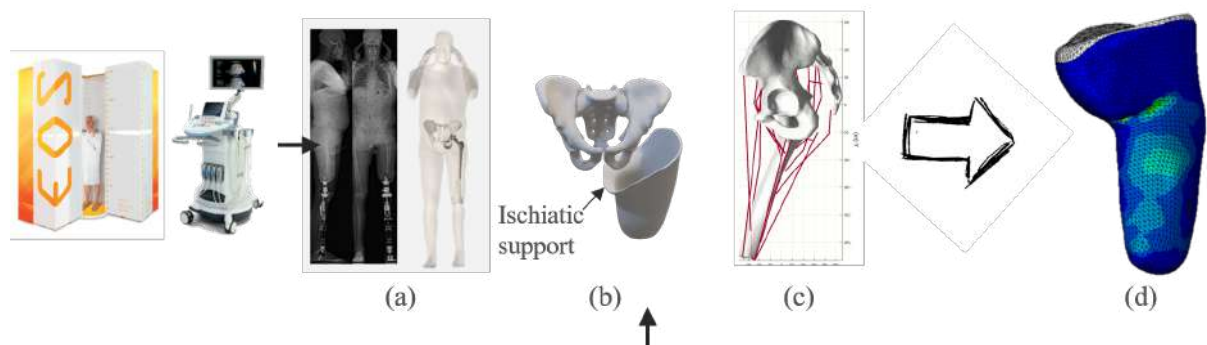


Figure 2.5: (a) The personalized geometry was defined using bi-planar X-ray imaging. Soft tissues material properties were estimated using a custom-made setup. (b) 3D optical scanner was used to acquire the ischial containment socket geometry (characterized by the ischiatic support enveloping the ischium). (c) The boundary conditions were defined using a static optimization of a MSK model (d) The developed model was used to evaluate interface pressure.

In this work, a model of the lower limb musculoskeletal system representing muscle geometry using a series of line segments was coupled with a Finite Element Model to estimate interface loads (pressure). The mechanical action implied by the presence of the ischiatic support was accounted by a reduction of the net hip abduction moment. This mainly resulted in a reduction of the force developed by the main hip abductor muscle, the gluteus medius. The associated peak pressures were 71 kPa, 63 kPa and 67 kPa, respectively for a reduction of the net hip moment by 0 %, 50 % and 100 %. The differences estimated were small compared to the differences in muscular forces. These small changes may be explained by the simplification of the muscles modelling. A volumetric representation of the muscles as proposed by (Ramasamy 18) may provide better insights into the impact of the muscular activation on the interface pressure. .

2.5 PhD Aurélien MACRON (2016-2019): Preventing sitting-acquired pressure ulcers



11/2015- Aurélien Hélène PILLET (50%) [P11, P12, P13, P18, CP4]
 03/2019 MACRON Pierre-Yves ROHAN (50%)
 Collaboration: CEA list

Pressure Ulcers (PUs) have been defined in the 2019 Clinical Practice Guideline (CPG) published jointly by the European Pressure Ulcer Advisory Panel (EPUAP), the National Pressure Injury Advisory Panel (NPIAP), and the Pan Pacific Pressure Injury Alliance (PPPIA) as *"localized injuries to the skin and underlying soft tissue that form during prolonged exposure to mechanical loads"* (Kottner 19)). It is a complication primarily related to the care and treatment of individuals who have difficulty moving or changing positions. Symptoms such as pain, discomfort, exudate, and odor can occur, which can further restrict mobility and daily activities as well as lead to disturbed sleep and a general reduced quality of life. Patient's psychological well-being can be affected by feelings of anxiety, worry, and dependence. This can lead to social isolation and the inability to participate in activities. In long term care or hospitalized patients, the prevalence ranges between 9 % (Moore 11) and 15 % (Børsting 17) and is most frequently observed over the sacrum or the heel. Two thirds of PU are observed in patients above 70 years of age (Agrawal 12). It leads to great expenditures for healthcare systems and society (Allman 99) but are generally preventable. As the population ages, and the incidence of chronic diseases increases, this trend is expected to rise markedly.

Prevention of pressure ulcers currently relies on labor-intensive vigilance in nursing care (Ayello 08; Wong 11; Reddy 06). Patients are manually turned nearly every hour to relieve pressure, and high-risk areas are visually inspected for pressure ulcers (Ayello 08). In many hospital and community settings, risk assessment scores, regular skin assessment and clinical judgments are used to develop an individualized prevention plan for the specific patient. However, interpretation and the development of these individualized prevention strategies is limited by the extremely large range of descriptors that contribute to PU development and the complex interplay between them (see Coleman et al (Coleman 13) for a systematic review). To assist the clinician in developing such individualized prevention plans, new integrative approaches allowing an improved risk assessment that encompasses and bridges the gap between the clinical, physiological, and mechanobiological factors are needed.

Several European projects, such as IASIS (FP7-SME), PUMA (FP7-SME) and its continuation i-LiveRest (H2020-EU), developed control system based on smart textiles (measuring impedance, pressure, temperature and humidity for the most recent project) to detect early signs of tissue damage. These projects are very promising and could be used to alert nursing staff when a threshold is exceeded. Despite all efforts however, no universally applicable diagnostic tool has been identified to date. In light of the progress being made in the fields of mechanobiology and the identification of biomarkers associated with the early development of pressure ulcers, it is very likely that the current lack of effectiveness of technological approaches for the identification of the risks originates from the fact that they are not built upon our current understanding of the damage cascade caused by exposure to sustained deformations and the resulting inflammation and ischaemia.

The development of digital models represents a viable paradigm for future technology for the reason that they have the potential to explain soft tissue injury risk factors. In particular, by combining an

animal model of Deep Tissue Injury (DTI) with computational modelling, it has been shown that direct deformation damage was only apparent when a certain strain threshold was exceeded (Ceelen 08). In humans, computational modelling of load-bearing soft tissue has shown that bony prominences induce substantial stress concentrations, which explains why these areas are vulnerable to ulceration (Chow 78; Dabnichki 94; Luboz 14b; Oomens 03; Levy 13; Levy 14; Linder-Ganz 07; Linder-Ganz 08a; Linder-Ganz 08b; Sopher 10; Al-Dirini 16; Levy 17; Luboz 18; Moerman 16; Zeevi 17) have been proposed based on either MRI (most of the studies) or CT-Scan data (Luboz 18). These studies have considerably advanced the analysis and understanding of the potential internal risks of the seated individual, and provided tools to assess PU risk based upon anatomy (Gefen 11; Luboz 18; Oomens 13)

Yet, in all these studies, only 4 different tissue types are considered for FE modelling: bone, muscle tissue, fat tissue and skin, although, in the particular case of MRI, muscle groups, tendon, fat pads and ligament borders are visible. This approach, although computationally efficient, fails to take advantage of the capacity of MRI to differentiate between the individual soft tissue structures. In addition, the representation of a realistic unloaded sitting position is jeopardized by the experimental limitations of MRIs and CT-scans: Long acquisition times of MR imaging prevent a prolonged unloaded sitting configuration without resorting to devices such as: rubber tires (Linder-Ganz 07), inclined plane (Al-Dirini 16) and thigh and arms supports (Call 17) while the confinement of the scanner limits the acquisition to the lying position only.

In the PhD of Aurélien MACRON, a methodology combining low-dose biplanar X-ray images (EOS imaging, Paris, France), B-mode ultrasound images and optical scanner acquisitions in a non-weight-bearing sitting posture has been proposed as an alternative to MRI-based/CT-scan-based assessment for the fast generation of patient-specific FE models of the buttock and applied to 6 healthy subjects (Macron 18) (figure 2.7). All the subjects had clusters of muscle tissue enduring compressive and maximal shear strain above the thresholds defined in the literature (Ceelen 08; Loerakker 11). In agreement with previous results reported in the literature (Linder-Ganz 07), our results showed that the maximal tissue strains and stresses occurred in the muscle layer at the bone interface.

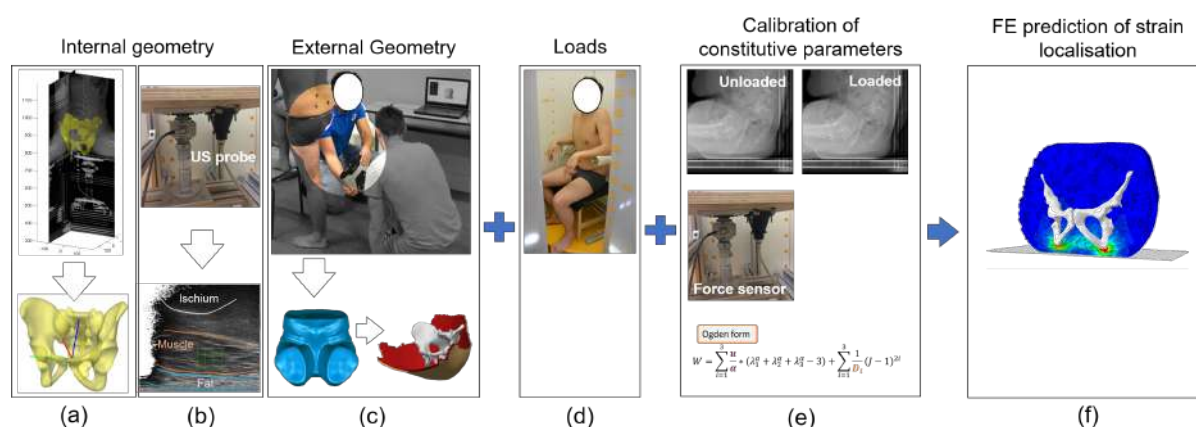


Figure 2.6: Main steps of the model construction and analysis: (a) bi-planar X-ray radiographs and associated 3D reconstruction of the pelvis (b) US video clips of the subdermal and simultaneous measurement of the load (c) Optical scan of the external shape (d) experimental vertical force measured in the loaded sitting position (e) Calibration of constitutive parameters based on experimental force-displacement data (f) Distribution of the principal Log shear strain predicted by the FE model for subject 1 of (Macron 18).

To investigate the ability of a local model of the region beneath the ischium to capture the internal response of the buttock soft tissues predicted by a complete 3D FE model from a limited number of parameters, a simplified model was developed based on data compatible with daily clinical routine (Macron 20). This study highlighted that the local mechanical environment within soft tissues is very sensitive (in the statistical sense i.e. variance-based sensitivity analysis) to the geometry of bony prominences and the relative thickness of the different soft tissue elements. Of particular interest, the sensitivity analysis showed that the maximum shear strain in the muscle tissue was very sensitive (29 %) to the radius of curvature of the ischium in the plane perpendicular to the shortest radius of curvature. These results are in line with other results in the literature supporting the widely accepted idea that bone geometry will affect internal stresses and strains occurring under bony prominences.

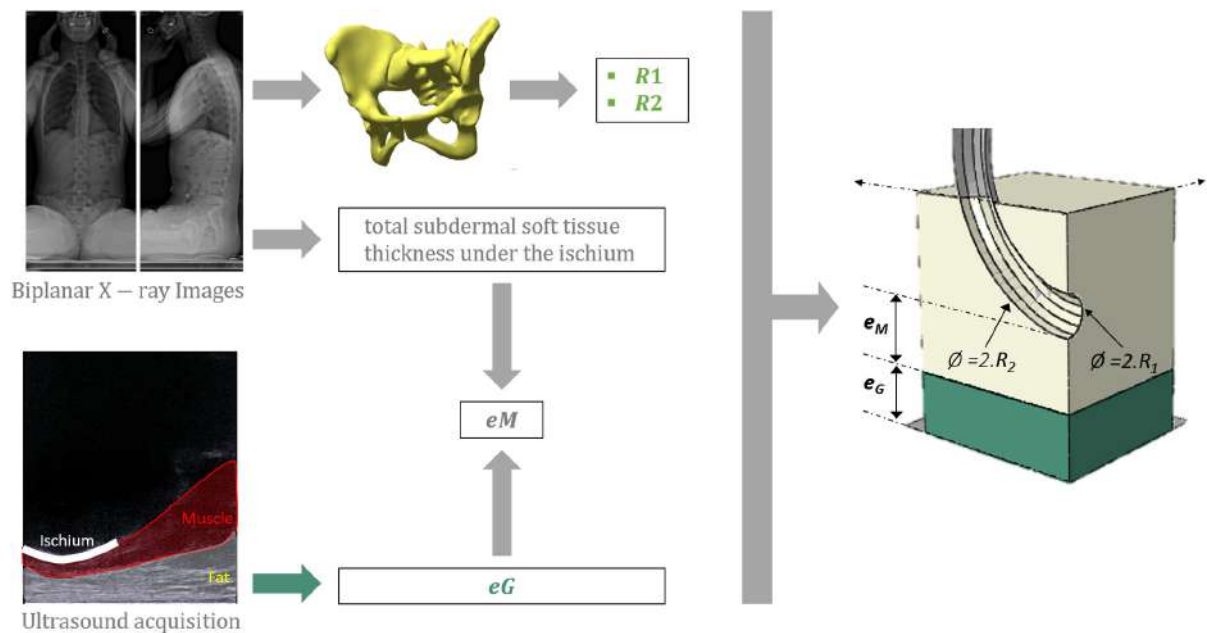


Figure 2.7: Local FE model geometry generated from the 4 geometric parameters R_1 , R_2 , e_F , e_M extracted from the ultrasound and bi-planar x-ray images. The ischial tuberosity is represented by a torus generated by the revolution of a circle of radius R_1 (minor radius) around a portion of a circle of radius R_2 (major radius). e_M and e_F are used to define the muscle and fat thicknesses.

The analysis of the ultrasound videos allowed to observe the complex behaviour of this tissue layer during the loading. In particular, it was observed that the gluteus maximus and hamstring muscles did not always remain underneath the IT, but instead, in certain subjects, slid out of plane, leaving the IT on the fat tissue. This observation is close to previous reported results (Call 17). Sonenblum et al., for example, observed that the gluteus maximus had a posterior and lateral displacement between simulated unloaded and loaded sittings in an MRI (Sonenblum 15; Sonenblum 13). This contributes to the decrease of the thickness of soft tissue muscle under the ischial tuberosity. These results should be further investigated because it clearly shows that the assumptions commonly made by teams developing finite element model of the buttock are strong and do not allow to replicate the experimental ground truth.

2.6 PhD Ekaterina MUKHINA (2019-2022): Sacrum soft tissue response under compression



09/2019- Ekaterina **Yohan PAYAN** (40%), Nathanael CONNNESSON [**P25**, **CP6**]
11/2022 MUKHINA (30%), **Pierre-Yves ROHAN** (30%)

The experimental quantification of soft tissue displacements and associated strain fields of soft tissues under compression an important question for pressure ulcer prevention research. As highlighted in the previous section, research in pressure ulcer prevention over the past 20 years has sought to explain soft tissue injury risk factors in terms of the local stress-strain response of soft tissues. Of particular interest are the series of experiments performed at the Eindhoven University of Technology ([Ceelen 08](#); [Loerakker 11](#); [Stekelenburg 06b](#); [van Nierop 10](#); [Traa 19](#)) involving indentation of the tibialis anterior muscle of Brown-Norway rat. These lead to the identification of a damage threshold for murine skeletal muscle tissue. Using dedicated organ-scale Finite Element models, it was shown that direct deformation damage was apparent only when a given maximum Green-Lagrange shear strain threshold was exceeded ([Ceelen 08](#)), and that the damaged area was correlated to the magnitude of the elastic strain energy applied ([Loerakker 10](#)).

To estimate experimentally soft tissue motion under external mechanical loading *in vivo*, many studies proposed to combine Magnetic Resonance (MR) imaging with Digital Image Correlation (DIC) ([Trebbs 21](#); [Tavana 20](#)) (for a review of the major developments on measurement techniques for the estimation of the displacement fields via Digital Volume Correlation (DVC) the reader is referred to the recent work of ([Buljac 18](#))). Although MRI is a potential tool for the quantitative evaluation of soft tissue displacements, it has important drawbacks such as high costs, a confined environment and the requirement for the patient to not move for long periods in positions that can be uncomfortable.

B-mode ultrasound (US) imaging is commonly available at a bedside in clinical environment and does not require long acquisition time, in contrast to MRI. Moreover, US imaging has been shown to be promising for the quantification of soft tissue motion using DIC ([Gemisson 13](#); [Slane 14](#); [Chimenti 16](#); [Affagard 15](#)). From the perspective of PU prevention, B-mode US imaging has also shown promising results in the assessment of risk factors associated with anatomical features ([Swaine 18](#); [Akins 16](#); [Macron 20](#); [Karam 22](#)). One strong hypothesis however, is the assumption that tissue displacement is contained in the US imaging plane. Previous results obtained in the PhD of Aurélien Macron showed that soft tissue displacement during sitting, estimated using US imaging combined with Digital Image Correlation in two perpendicular planes, was as important in the frontal and sagittal planes ([Doridam 18](#)). As a result, tracking muscle features using 2D image registration techniques in each plane would introduce biases. This is a major limitation for the use of 2D US imaging as practical and clinically relevant alternative to MRI-based assessment of soft tissue motion under mechanical loading.

The objective of the PhD of Ekaterina MUKHINA was to characterize the out-of-plane displacement using a custom-made MR-compatible setup under a realistic US transducer loading. The sacrum was chosen as a target because of the high prevalence of PUs at this location and ease of access for experimentation. A custom-made MR-compatible setup was designed and assembled with the objective of applying a controlled external compressive force with only a vertical load (i.e. with no shearing load) on the

sacrum via a US-like indenter throughout the MRI acquisitions (Figure 2.8). 3D MRI acquisitions were performed at the IRMaGe research platform (Univ. Grenoble Alpes) in 5 configurations: one unloaded and 4 loaded in decreasing order of loads from 1.2 kg to 400g by steps of 200g or 400g.

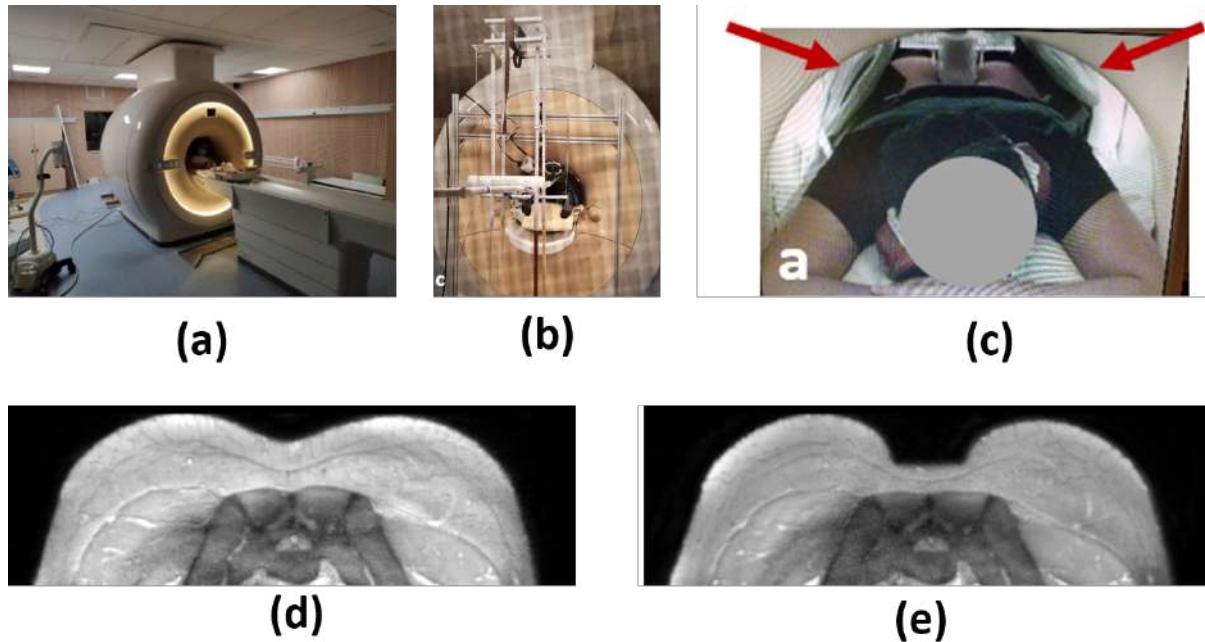


Figure 2.8: a) Front view of the IRMaGe research platform (Univ. Grenoble Alpes) b) rear view showing the custom-made MR-compatible setup allowing to hold a 3D-printed copy of the SL10-2 linear probe perpendicular to sacrum skin surface and allowing the transmission of a controlled external compressive force with only a vertical component (i.e. with no shearing component on the skin) c) Participant lying in the MR scanner with two antennas (red arrows) placed on either side of the pelvis; d) transverse slice of the unloaded configuration at the region of indentation. e) transverse slice of the loaded (1200 g) configuration at the region of indentation.

Preliminary results obtained on N=1 healthy volunteer confirm that, for the chosen loads, the out-of-plane movement cannot be considered negligible. The ratios between the out-of-plane and in-plane displacements were higher than 0.6 for more than half of the voxels for all load cases. To further explore the results obtained in this campaign, a FE model of the indentation is under analysis.

EPUAP funding for the development of a simplified framework for generating *in silico* models from freehand Ultrasound for monitoring internal tissue strains for the prevention of PUs



Funding: 10 k€

An EPUAP Research Project Collaboration Funding has been secured (collaboration with Yohan PAYAN and Bethany KEENAN) to further investigate the feasibility and clinical relevance of a simplified framework for generating *in silico* models from freehand Ultrasound for monitoring internal tissue strains for the prevention of PUs.

2.7 PhD Alexandre SEGAIN (2021-2024): High Fidelity modelling of buttock soft tissues



09/2021- Alexandre H el ene PILLET (40%), Giuseppe SCIUM E (30%), Pierre-Yves
09/2024 SEGAIN ROHAN (30%), Collaboration: Bethany KEENAN

The development of accurate and realistic models that can be used to predict the mechanical response of soft tissues in compression (and especially in the sitting position for the prevention of wheelchair-acquired pressure ulcers) is a challenging problem due to the heterogeneous three-dimensional structural organisation (anatomy) of the skin/subcutaneous complex (figures 2.9(b-c), adapted from (Herlin 15)). The interaction between the components (skin, superficial and deep adipose tissues) and connective arrangements (1/ dense fibrous septa that cross link these layers to form a Retaining Connective Network 2/ thin septa that separate the adipose tissue lobules) and the mobility of the components are responsible for important variation between soft tissue behaviors.

The impact on the inter-individual variation of buttock soft tissue deformation during sitting has been observed *in vivo* using MRI imaging. For example, Sonenblum et al. (Sonenblum 15) showed that, in a population of 4 able-bodied and 3 Spinal Cord Injured subjects, 5 out of 7 had fat tissue beneath the IT in the sitting position (the Gluteus Maximus being positioned more laterally and posteriorly to the Ischial Tuberosity (IT); figure 2.9(a) adapted from (Sonenblum 15)). This observation is inconsistent with the assumption dominating the literature that, during sitting, the IT compresses a bilayered material composed of muscle and fat tied at the interface (Linder-Ganz 07). Computational models are generally based on this assumption (Chow 78; Dabnichki 94; Linder-Ganz 07; Oomens 13; Levy 14; Moerman 16; Luboz 18; Macron 18) and, therefore, the validity of the stress and strain numerical estimations can be questioned. No direct experimental validation has been performed to date. Such validation evidence must be obtained prior to any clinical evaluation.

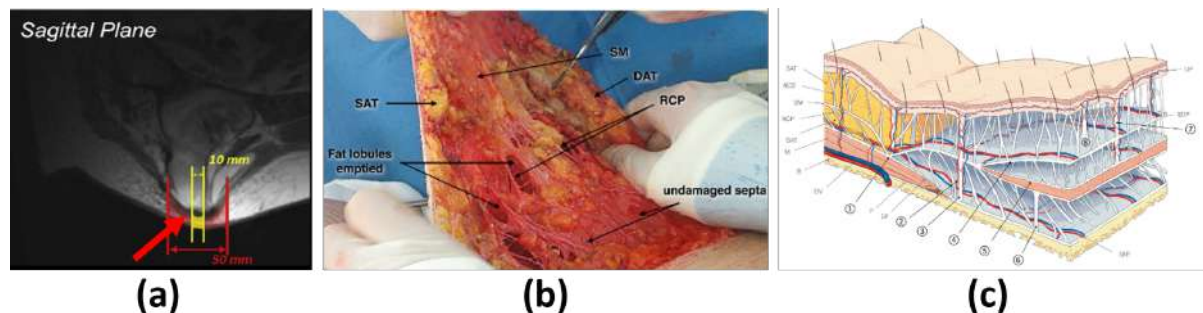


Figure 2.9: a) (top) MRI slice of weight-bearing individual in seated position (Linder-Ganz 07) (bottom) associated FE model predicting strain localization in muscle tissue. b) MRI slice of weight-bearing individual in seated position (Sonenblum 15) c) Intra-operative picture of a thigh dermo-lipectomy adapted from (Herlin 15) showing the difference between superficial fascia, fat lobules, dense fibrous septa and membranes of septa. d) Generic model of the skin/subcutaneous tissue complex (Herlin 15).

The objective of the PhD of Alexandre SEGAIN is to develop methods to experimentally characterize the strain distribution in buttock soft tissue during sitting to investigate the impact of the internal mobility of the skin/subcutaneous complex on strain localization. This work is currently in progress.

2.8 COLLABORATION David RYCKELYNCK: Real-time prediction of strain localization

A major barrier to the clinical translation of risk assessment tools based on FE modelling is the prohibitive cost of preparing and running complex non-linear models. Computation time can be reduced in several ways: improving the algorithms (Bui 18; Courtecuisse 14; Joldes 10), by reducing the complexity of the model (Linder-Ganz 08b; Portnoy 06; Yarnitzky 06) or by using parallel computing (Joldes 10). As an alternative, there is a growing interest in the community for the use of Machine Learning techniques to challenge the real-time simulation of biological soft tissues mechanical response under hyperelasticity assumptions and real-time constraints (the reader is referred to (Cueto 14) for a recent review on the existing literature on real-time simulation in the field of computational surgery).

From the perspective of PU prevention research, promising results have been reported using projection-based Model Order Reduction, which consists in restricting the search of the solution to a low-dimensional space spanned by a reduced-order basis. This reduced-order basis is inferred from a set of pre-computed high-fidelity solutions, using linear dimensionality reduction techniques. (Luboz 18) used Proper Orthogonal Decompositions (POD) of the pressure and strain fields coupled with a machine learning method to evaluate biological tissue stains in a patient-specific Finite Element (FE) model interactively (<1s) for any pressure field measured below the buttocks. More recently, (Niroomandi 20) proposed to use a Proper Orthogonal Decomposition with Interpolation (PODI) to interactively compute the response of a patient-specific Finite Element Model to specific muscle activations (0.1s versus 12h for the high-fidelity solutions computed using ArtiSynth). In both cases, the study was based on the morphology of a single male subject.

However, as highlighted in the literature, conventional ROM methods may incur in severe limitations when dealing with nonlinear parametrized PDEs, as these are strongly anchored to the assumption of modal linear superimposition they are based on. Projection-based model order reduction using local subspaces have been proposed as a promising alternative (Amsallem 12; Amsallem 16). A general framework for projection-based Model Order Reduction assisted by Deep Neural Networks called dictionary-based ROM-nets was recently proposed by (Daniel 20; Ryckelynck 21). It consists in using Deep Learning techniques to recommend a suitable local Reduced-Order Model from a dictionary. The dictionary of local reduced-order models is constructed from a clustering of simplified simulations enabling the identification of the subspaces in which the solutions evolve for different input variables.

The objective of this collaborative work with David RYCKELYNCK was to apply the dictionary-based ROM-nets previously developed (Daniel 20; Ryckelynck 21) for the assessment of subject-specific in vivo sub-dermal soft tissue strains and stresses in the ischial regions during sitting.

The dictionary-based ROM was developed based on the full-order models of 16 subjects (9 men and 7 women) developed in (Macron 18; Macron 20). First, because of the limited training data available, a data augmentation scheme was proposed using a three-step procedure : a sub-modelling technique was first employed to prune the high-fidelity models; a Statistical Shape Model was then built using by applying a Principal Component Analysis on the landmark coordinates of the 10 submodels (figure 2.10); to finish, 100 synthetic data were generated around each training data in a radius set at $D_0/4$ around the mean vector shape where D_0 is the minimum of the distance matrix between all the reduced coordinates

between subjects. Second, a dictionary was defined as a collection of all the representative subjects identified using the K-medoid clustering of the training dataset. To solve the clustering problem, a mechanical dissimilarity matrix was defined as the projection error of the mechanical strain to evaluate the distance between the Digital Twins in the ambient space. Finally, a Decision Tree Classifier, acting as a model selector, was trained with a database of 707 labelled Finite Element models. The 202 validation data and the 6 unseen test data were used to evaluate the classification performance of the trained Decision Tree Classifier.

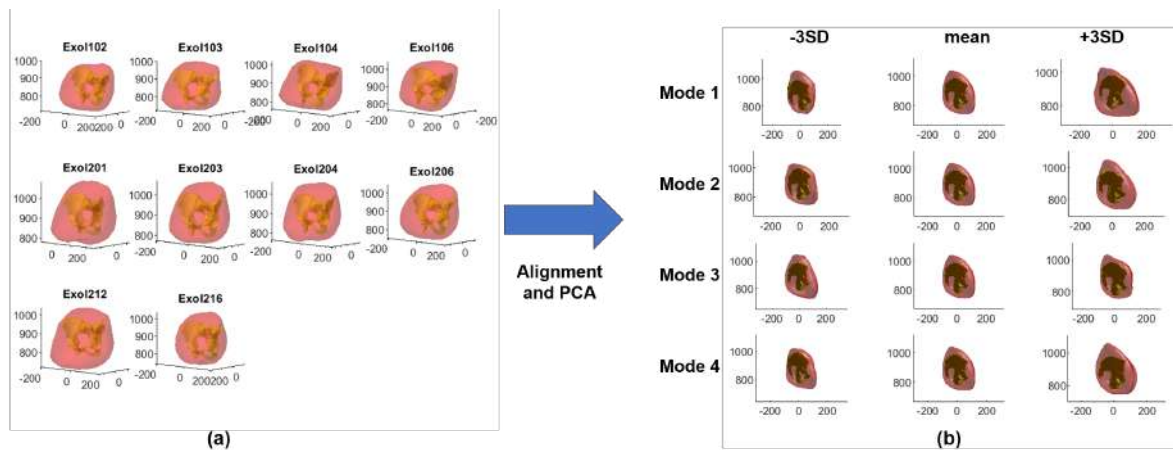


Figure 2.10: Geometrical modes computed for the setting of a common ambient space for morphological variabilities between digital twins and also for data augmentation. (a) training data (b) modes of variation 1-4 showing significant anatomical differences observed at 3 standard deviations (SD) from the mean shape

The performance of the dictionary-based ROM was satisfactory (accuracy of 100% on the training data; accuracy, precision, recall and F1-score of, respectively, 83%, 100%, 83% and 90% on the unseen test data). The computation of the strain field by the Decision Tree Classifier requires 0.1 second compared to 20 minutes for the submodel and about 8 hours for the high-fidelity model. The projection error, computed as the difference between the strain field predicted by the dictionary based reduced model with only 4 modes of variation for the unseen testing data and those obtained using the full scale simulation, was 9%.

The implementation of the dictionary-based ROM-nets was validated in this contribution. Results show that a robust model can be trained to predict and estimate mechanical response. They also highlight the potential of dictionary-based ROM-nets for providing real-time estimations of strains within soft tissues undergoing compression. As it is the case with Machine Learning techniques, the prediction accuracy of the proposed approach is expected to improve significantly as the training data increases. This work represents an important step towards the introduction of mechanical-based assessment tools in clinical routine.

2.9 COLLABORATION Bethany KEENAN: Heel soft tissue response under compression

The methodology combining low-dose biplanar X-ray images (EOS imaging, Paris, France), B-mode ultrasound images and optical scanner acquisitions previously proposed in (Macron 18) was adapted, in this collaborative work with Bethany KEENAN for the assessment of subject-specific in vivo sub-dermal soft tissue strains and stresses in the heel.

Prevention of pressure ulcer in the heel is an important topic because several studies have shown that nearly 30% of pressure ulcers occur on the heels and associated regions of the lower limb heel (Vanderwee 07; VanGilder 17). There is little protective subcutaneous tissue within the heel, making it vulnerable to pressure, friction and shear forces. The current clinical practice emphasizes the decrease of mechanical loads by providing support surfaces to relieve points of high interface pressure. However, treatment interventions based on this principle may not be effective. A biomechanical approach to evaluate the soft tissue injury risk is a potential solution towards a personalised estimate of this risk.

In this collaborative work, a T2-MRI scan of the foot was captured in both an unloaded and loaded configuration for one female volunteer in supine (figure 2.11(a)). Bones and soft tissues were segmented and saved. Biplanar X-ray images and US video clips of the same participant were acquired simultaneously in 6 configurations: unloaded, loaded, 60°abduction, 60°adduction, 90°dorsiflexion and 30°plantarflexion 2.11(d-e)). A custom setup was conceived to hold an US probe below the heel in the EOS cabin (figure 2.11(b-c)). Pressure measurements were also acquired using a Zebris FDM pressure platform. The bone 3D reconstruction from MRI data were imported into the EOS biplanar radiographs such that each bone could be repositioned in the loaded configuration according to the bone contours in the radiograph. A 3D FE foot model was then developed. Generic constitutive parameters were assumed from the literature (Neo-Hookean and Ogden constitutive laws). The loading conditions were then simulated by applying a gravity load to the FE model in the reference undeformed configuration. The vertical displacement of the calcaneus, the log strain in the soft tissues and the contact pressure were extracted for analysis. The impact of assuming generic materials constitutive parameters on the mechanical response was assessed by comparing the FE-based prediction to the experimental data. This work is currently in progress.

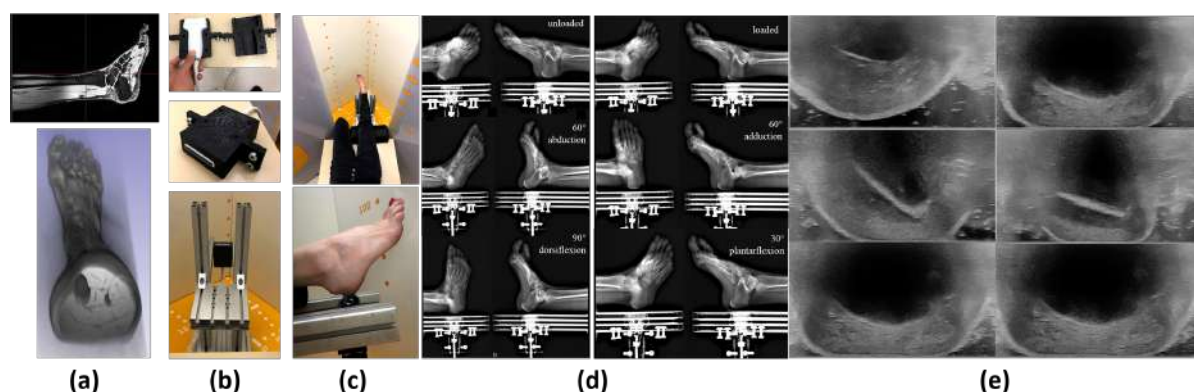


Figure 2.11: a) MRI scan in loaded configuration b) custom setup to hold US probe in the EOS cabin c) subject positioned in the EOS cabin with the US probe positioned under the heel d) biplanar X-ray images acquired in 6 configurations. Associated US video clips.

CHAPTER 3

POTENTIAL SOCIETAL AND ECONOMIC VALUE: ONGOING CLINICAL AND INDUSTRIAL COLLABORATIONS

This sections addresses the question of the potential societal and economic impact of the publicly funded research conducted so far with the support of the IBHGC and ENSAM.

3.1 Clinical translation: Can biomechanical modelling contribute to go beyond existing clinical assessment paradigms?

Clinical translation is challenging. So far, the research work conducted in the field of pressure ulcer prevention at the IBHGC has been made in a population of healthy volunteers and has not been related to the actual onset of injury. If tools have been developed for accelerating computational procedures for monitoring strains within soft tissues undergoing compression in the context of Pressure Ulcer prevention [cf section 5.6], they are limited in their clinical application because they require input data that are challenging to obtain with sufficient spatial resolution in patients - even at a single time point \hat{a} and thus are typically restricted to single case examples, limiting their generalizability.

We have shown in (Macron 20) that computer simulations are very sensitive (in the statistical sense i.e. variance-based sensitivity analysis) to the geometry of bony prominences and the relative thickness of the different soft tissue elements. If the relationship between morphological geometrical parameters and tissue viability were established, then non-invasive, bed-side applicable imaging techniques such as B-mode ultrasound, ultrasound elastography and ultrasound-based indentation could represent a promising alternative for screening at-risk geometrical predispositions. This represents an active area of research (Akins 16). Recent research has focused on characterizing the intrinsic individual biomechanical risk factors and their evolution in vulnerable subpopulations (related to weight loss/gain, disuse-induced muscle atrophy and fat infiltration in post-spinal cord injury; and declining structural capacities associated with ageing). The use of shear wave elastography has also been investigated as a means for the mechanical characterization of early (subclinical) changes in tissue integrity eventually leading to PUs in animal models (Deprez 11) and healthy volunteers (Schäfer 15). However, the predictive value of these diagnostic imaging techniques and their link to tissue damage requires further evaluation.

A first attempt to adapt existing measurement procedures and test protocols to make them feasible for bedside testing requirements was made in the Master's Thesis of Maher ABOU KARAM ([P25], collaboration with Yohan PAYAN and Nathanael CONNNESSON). The aim was to evaluate the use of B-mode US and SWE in the assessment of bone geometry, tissue morphology and tissue stiffness in the context of sacral Pressure Ulcer prevention in the elderly. A protocol was developed (Karam 22) (see figure 3.1 for the list of parameters) and was tested for reliability on a group of 19 healthy young subjects by two operators: a physician and an engineer. Afterwards, the protocol was tested on a group of 11 healthy older people by the physician only.

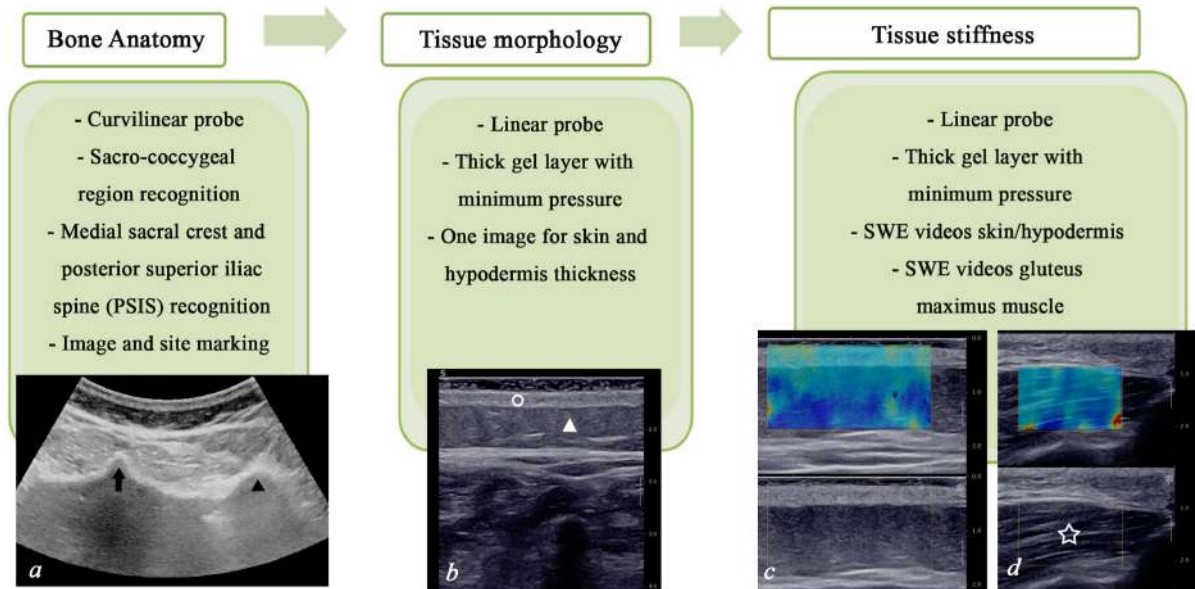


Figure 3.1: US acquisition protocol of the sacral region in the transverse view. a) bone morphology assessed with a curvilinear probe in B-mode (SuperCurved C6-1X) b) skin and adipose tissue morphology was assessed with a linear probe (SuperLinear L10-2) (b); skin (c), adipose tissue (c) and gluteus maximus muscle tissue stiffness(d) were estimated with US- Shear Wave Elastography.

ICC showed poor to good reliability except for skin SWE and hypodermis thickness. No significant differences were observed between the young and older group except for the muscle Shear Wave Speed (2.11 +/- 0.27 m/s vs 1.70 +/- 0.17 m/s respectively). This is the first protocol combining US and SWE that can be proposed on a large scale in nursing homes. Reliability however was unsatisfactory for many parameters despite efforts to standardize the protocol. Further studies are needed to improve reliability.

Clinical contacts



To investigate the potential clinical benefit of biomechanical approaches to inform patient decision making, contact has already been established with **Emilie LEBLONG**, Physical medicine and rehabilitation physician at the Pôle Saint-Hélier, **Marie-Line GAUBERT-DAHAN**, geriatrician and **head of the Geriatric rehabilitation department** of the Intercommunal Hospital Group Le Raincy Montfermeil and **Agnès HARTEMANN** head of the diabetes department of Pitié-Salpêtrière Hospital in Paris.

3.2 ANR PhotoBooth of Ageing (not funded): Detection of frailty syndrome

The biomechanical characterization of soft tissues to evaluate the soft tissue injury risk could potentially also be useful in exploring early detection of frailty syndrome in older adults. Frailty is a geriatric syndrome characterized by decreased functional and physiological reserves leading to increased vulnerability for adverse health outcomes triggered by minor stress events. Between a quarter and half of people older than 85 years are estimated to be frail, and these people have a substantially increased risk of falls, disability, long-term care, and death. Comprehensive geriatric assessment is currently the internationally established method to assess elderly people in clinical practice. However, the practical limitations of the assessment is the time and expertise needed and the ability to reach the people in general population. The development of simple, valid, accurate, and reliable methods to detect frailty are lacking and represent a significant challenge to the community.

The PhotoBooth of Ageing project aims at developing a first proof of concept of its long-term vision of a frailty interventional study (figure 3.2) to address three main challenges: 1/ Provide objective measurements of several dimensions of frailty phenotype 2/ Go to the contact of the general population 3/ Address the acceptability and stigmatization issues at the different stages of the research. In this first phase, the project will develop active sensing technologies that are adequate to auto-evaluate the whole spectrum of the frailty dimensions (sensory, mobility, nutrition, cognition). The participative approach will provide the best acceptability of the technological solutions and the project will also address the recruitment flaws in elderly population. The experimentation will rely on a pharmacy network to reach as many older adults as possible. Such advances in the measurement of biological aging and definition of biomarkers have the potential to inform on individuals' risk early in the aging-course and to inform timely preventive strategies, contributing to a healthy aging even in late ages.

The work is currently in progress and gathers the complementarity skills of multiple stakeholders: **Karine PERES**, epidemiologist of ageing and frailty, INSERM-Université de Bordeaux; **Hélène SAUZEON**, human factor approaches for older adults, INSERM-Université de Bordeaux; **Pierre Louis BERNARD**, functional evaluation and ageing, EUROMOV DHM (Université de Montpellier); **Isabelle MARC**, functional vision and hearing, EUROMOV DHM (Institut Mines-Télécom) and **Ludovic SAINT-BAUZEL**, assistive robotics for elderly, ISIR-Sorbonne Université.

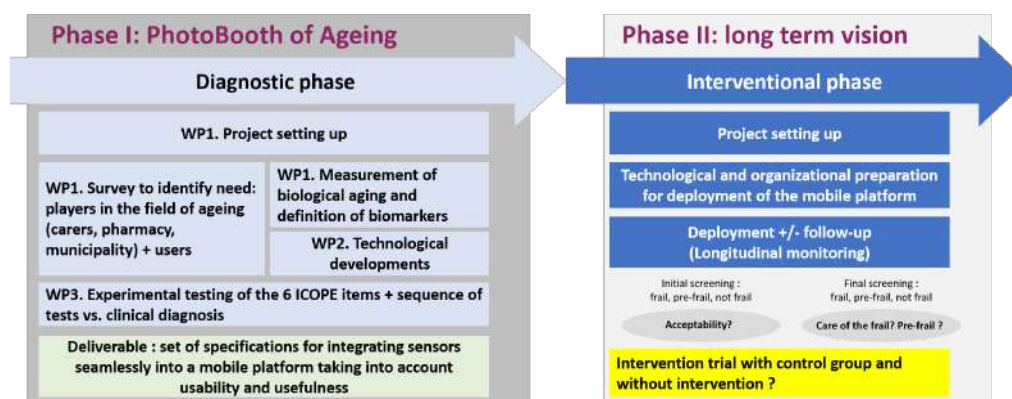


Figure 3.2: Outline of PhotoBooth of Ageing project.

3.3 PROTEOR: Human/Orthopaedic device interfaces



The introduction of the digital chain in the Orthopaedic field, from data acquisition to the production of external mechanical devices represents a major challenge for the industry. For more than 15 years, **PROTEOR** has been engaged in a process of collaborative research with the IBHGC with a continuous implication in several joint research programs. In particular, in the previous PhD work of Nolwenn FOUGERON [cf section 2.4], **PROTEOR** and the IBHGC initiated an original methodology for modelling the interaction between the residual limb and the socket combining subject-specific finite element and subject-specific musculoskeletal modelling. This is ongoing work.

3.4 PERMOBIL: Linking product performance to clinical outcomes



PERMOBIL commercialises a family of products that are leaders in advanced rehabilitation technology. Amongst these, **PERMOBIL** commercialises wheelchair cushions frequently prescribed for wheelchair users considered at risk for pressure ulcers. The efficacy of wheelchair cushions has been demonstrated: they have been shown to decrease sitting pressure (Reenalda 09; Geyer 01), to decrease sitting asymmetry (Kim 13), to decrease internal tissue strains (Levy 14; Shoham 15), and most importantly, to decrease sitting acquired pressure injury incidence (Brienza 10; Geyer 01) (based on clinical studies). But, choosing between the many varieties of skin protection cushions to best meet a specific patient's needs remains a challenge.

The International Organization for Standardization (ISO) specifies a variety of methodologies for testing the performance and efficacy of wheelchair cushions and which allow to quantify various metric of cushion performance such as shape compliance. Yet, none relates to soft tissue deformation, which is implicated in all physiological pathways to pressure ulcer onset including direct deformation damage, as well as ischemia secondary to deformation of blood vessels and impaired lymphatic drainage To better inform seating evaluation and recommendation for proper protection, the relationship between external loading and deformation should be further investigated.

The objective of this collaborative work which has just started is to adapt existing methods developed at the IBHGC for the assessment of subject-specific *in vivo* sub-dermal soft tissue strains and stresses in the ischial regions during sitting to related product performance and clinical outcomes .

CHAPTER 4

LIMITS OF CURRENT APPROACHES FOR PREDICTING SOFT TISSUE DAMAGE INITIATION

Over the past 20 years, research has sought to explain soft tissue injury risk factors in terms of 1/ the interface pressure/shear as a potential tool to inform on the risk of **superficial** soft tissue injuries such as tears, blisters and superficial pressure ulcers (Krouskop 87; Zhang 00; Goh 05; Colombo 11; Colombo 13; Colombo 16; Jamaludin 19) and 2/ soft tissue strain localization as a potential tool to inform on the risk of **deep** soft tissue injuries (Chow 78; Dabnichki 94; Oomens 03; Linder-Ganz 07; Linder-Ganz 08a; Linder-Ganz 08b; Sopher 10; Gefen 11; Levy 13; Oomens 13; Luboz 14b; Levy 14; Moerman 16; Zeevi 17; Levy 17; Al-Dirini 16; Luboz 18). However **the results obtained with finite element modelling still need to be validated experimentally**. From the perspective of the Stump-Socket Interaction, as far as I am aware of, **only two studies have focused on the experimental validation** of the prediction of transfemoral (above knee) amputation models (Colombo 16; Jamaludin 19) and none has been performed in terms of favourable prediction accuracy and systematic experimental validation. Likewise, from the perspective of Pressure Ulcer prevention research, recent MRI investigations focusing on the deformation of the seated buttocks have observed little or no gluteus maximus muscle present under the peak of the ischial tuberosity (Sonenblum 13; Sonenblum 15; Call 17; Sonenblum 18). These findings suggest that finite element models depicting considerable muscle coverage are not consistent with actual anatomy. More importantly, **none of the Finite Element models have been validated in terms of strain localization** (quantity of interest according to the series of experiments performed at the Eindhoven University of Technology (Stekelenburg 06b; Ceelen 08; van Nierop 10; Loerakker 11; Traa 19)). For the prediction of both superficial and deep tissue injuries, such validation evidences must be obtained prior to any clinical evaluation and relies on the capacity to assess experimental data in the clinical environment. Furthermore, given the large inter- and intra-individual loading and anatomic variability, the development of appropriate measurement methods to obtain reliable model input data including accurate description of the material properties, geometrical data, loading characteristics, and boundary and interface interaction conditions is a key challenge.

Challenge #1: The results obtained with FEA still need to be validated experimentally. The development of appropriate measurement methods is a key perspective work.

Moreover, studies in the literature are generally conducted with the assumption of quasi-static loading and response. Yet, the knowledge of the local mechanical condition alone is not sufficient to predict tissue damage initiation. **It is the progressive tissue damage that determines ulcer development, not the instantaneous strain localization itself** (Swisher 15). There currently exists no clinically relevant method to detect progressive tissue damage to indicate whether a patient is at imminent risk of developing an ulcer. However, based on the results produced in the literature that, from an electrical perspective, cells (and tissue) can be represented as conductive centre (cytoplasm) embedded in a conductive medium (extracellular fluid), separated by a relatively non-conductive barrier (cell membrane) (Valentinuzzi 96; Markx 99; Patel 08; Lukaski 13), many researchers are actively conducting clinical trials¹⁹ and are patenting impedance-based wound monitoring devices (Xu 14; Fan 14; Honda 14). In (Swisher 15), Swisher et al. hypothesized that pressure ulcers may be able to be detected and diagnosed based on the changes in electrical impedance caused by the loss of cellular integrity or cell death following an ischaemia/reperfusion event. Using impedance spectroscopy across flexible electrode arrays *in vivo* on a rat model, they found that the frequency spectra of impedance measurements were correlated in a robust way with the state of the underlying tissue across multiple animals and wound types (see figure 4.1 below). These results highlight that the loading history (and associated mechanical response) is a major determinant of tissue damage. It follows that the biomechanical investigation of the time-dependent stress-strain mechanical behaviour of soft tissues, and in particular, of skeletal muscle tissue, is essential to improve the understanding of the onset of DTI and therefore would allow a better prevention.

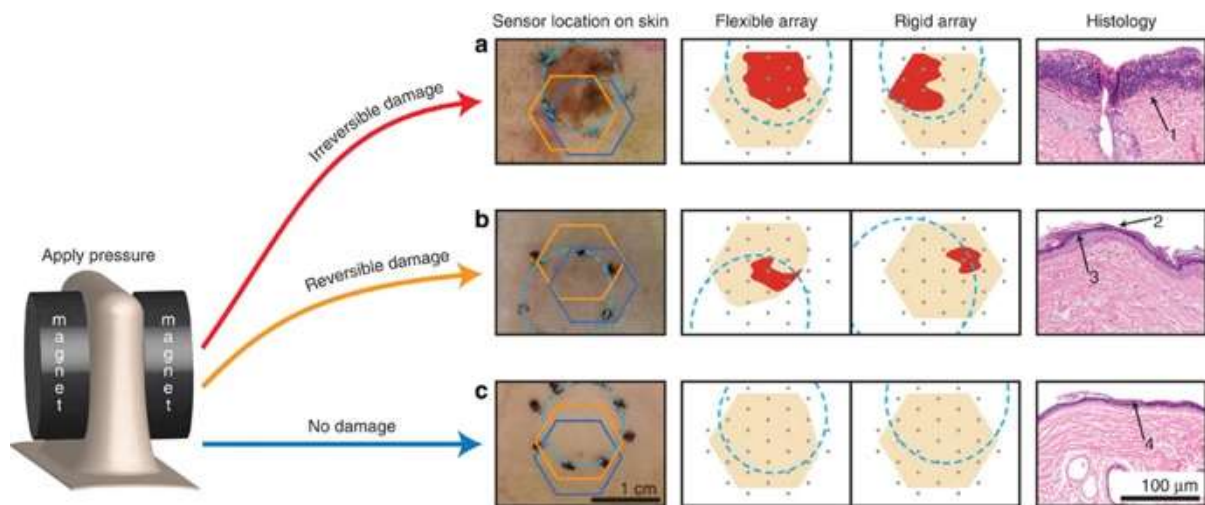


Figure 4.1: Adapted from (Swisher 15). The authors used magnets to create a pressure ulcer model on rats *in vivo*. Depending on the amount of pressure, the duration of treatment and animal-to-animal variation, the authors observed either: (a) irreversible damage both visually and electrically; (b) reversible damage electrically but not visually; (c) no damage visually or electrically (c). Histological analysis indicated loss of epidermis (1) and ulceration when there was irreversible tissue damage, hyperkeratosis (2) and hypergranulosis (3) when the damage was measurable but reversible, and focal hyperkeratosis (4) in the scenario where no damage is detected.

Challenge #2: Biomechanical investigation of the time-dependent stress-strain mechanical behaviour of soft tissues is essential to improve the understanding of the onset of DTI.

One of the most remarkable differences between classical engineering materials and living matter is the

ability of the latter to remodel in response to diverse stimuli. The mechanical behaviour of living matter is therefor **governed not only by an elastic or viscoelastic/poroelastic response to loading but also by the complex interplay between chemical-biological-mechanical factors.** Understanding and predicting the very strong link between mechanical response and biological processes (in particular, oxygen biochemistry and inflammatory cytokine biology) and how their interactions vary from subpopulation to subpopulation (it is known, for example, that some subjects at risk for pressure ulcers have no neurovascular capacity of the skin resulting in a lack of coupling between skin mechanical sensitivity and skin vasodilation (Fromy 12)) is an important step. This step is necessary in order to shed light on the relative importance of the parameters proven to be determinant in the development of pressure ulcers.

Challenge #3: The interplay between chemical-biological-mechanical factors is key to understand and eventually predict the initiation and propagation of soft tissue damage.

Finally, the implementation of non-destructive, non-invasive and, above all, valid means of characterization for real-life trials in clinical routine is an essential challenge to be met in order to be able to feed these models with relevant longitudinal and individual data.

Challenge #4: Development of innovative procedures to establish synergy between individual and temporal patient data and digital models.

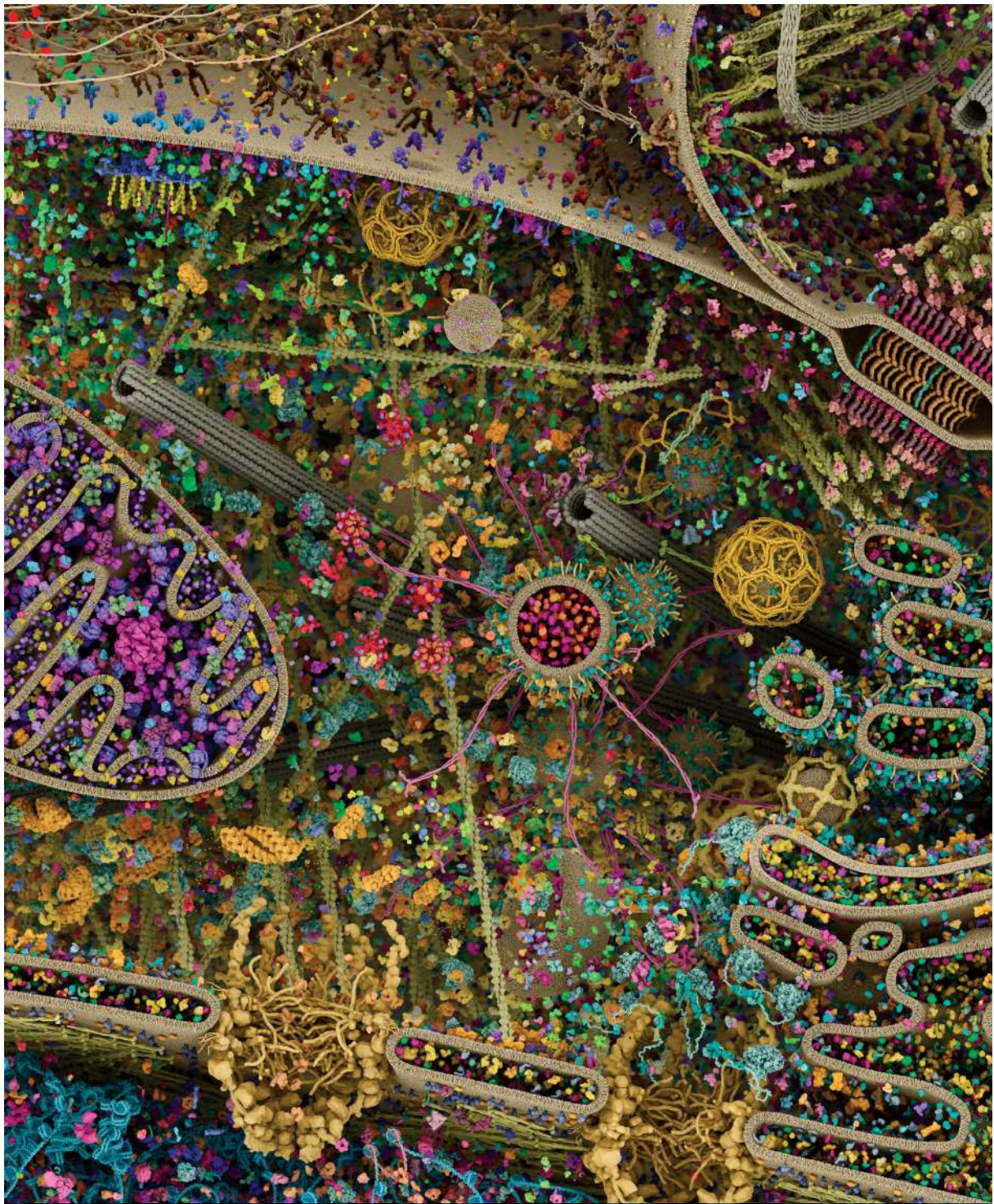
More than the strain localization it is the interplay interplay between chemical-biological-mechanical factors that needs to be clarified

Soft tissue injury is essentially a multi-scale and multi-physics process. The interplay between chemical-biological-mechanical factors is therefore key to understand and eventually predict the initiation and propagation of soft tissue damage. Existing histopathologic data (Bouten 01a; de Berg 95; Bouten 03a) suggest a cellular origin to pressure ulcer initiation and development. Indeed cell deformation triggers a variety of effects which may be involved in early tissue breakdown. Furthermore, and more importantly, wound initiation depend, in large part, on how cells sense and respond to chemo-mechanical stimuli (see Gefen et al.(Gefen 16) for a review of the mechano-biology of chronic wounds and Turner et al. (Turner 14) for a review on the role of the main cytokine and chemokine cell signaling molecules, and how disruption of these pathways triggers inflammatory disorders). These observations clearly emphasizes the importance of explicitly including cell-level behaviors in tissue-level models for predicting initiation of soft tissue injury

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Part II

Focused research project:
Mechanobiology of soft tissue injury



The Cellular Landscape

Created for Cell Signaling Technology by Digizyme, and inspired by the stunning art of David Goodsell, this 3D rendering of a eukaryotic cell is modeled using X-ray, nuclear magnetic resonance (NMR), and cryo-electron microscopy datasets for all of its molecular actors. It is an attempt to recapitulate the myriad pathways involved in signal transduction, protein synthesis, endocytosis, vesicular transport, cell-cell adhesion, apoptosis, and other processes. Although dilute in its concentration relative to a real cell, this rendering is also an attempt to visualize the great complexity and beauty of the cell's molecular choreography. Explore: www.cst-science.com/cellularlandscapes



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3D RENDERING OF THE MYRIAD PATHWAYS INVOLVED IN SIGNAL TRANSDUCTION, PROTEIN SYNTHESIS, ENDOCYTOSIS, VESICULAR TRANSPORT, CELL-CELL ADHESION, APOPTOSIS, AND OTHER PROCESSES IN A CELL. ADAPTED FROM CELL SIGNALING TECHNOLOGY, INC..

CHAPTER 5

TESTING SOFT TISSUE RESPONSE IN EXTREME CONDITIONS OF ISCHEMIA AND MECHANICAL DEFORMATION TO LINK DAMAGE WITH HYPOXIA

5.1 Research question (hypothesis)

To investigate the relationships between mechanical loading, the pathophysiological response to external mechanical loading and tissue breakdown, a hierarchical approach has been proposed by the group of Cees Oomens at Eindhoven University of Technology (summarised in figure 5.1 below), in which the effects of external mechanical loading have been studied in different, yet complementary, length and time scales with increasing complexity. They developed *in vitro* models, ranging from the single cell (**micrometer** scale, figure 5.1(a)) (Bouten 99; Bouten 03b; Peeters 03) to cell-matrix constructs (**millimeter** scale, figure 5.1(b)) (Bouten 01b; Breuls 03; Gawlitta 07b; Gawlitta 07a) to study the relationship between cell deformation and cell damage, as well as the influence of the surrounding extracellular matrix. They developed animal models (figure 5.1(c)) (Bosboom 01; Bosboom 03; Stekelenburg 06b; Stekelenburg 06a; Stekelenburg 07; Ceelen 08; van Nierop 10; Loerakker 10; Loerakker 11; Nelissen 18; Traa 19) to investigate the role of tissue (re) perfusion and lymph flow. They also conducted research on human subjects (figure 5.1(d)) (Soetens 19a; Soetens 19b) to investigate inflammatory processes.

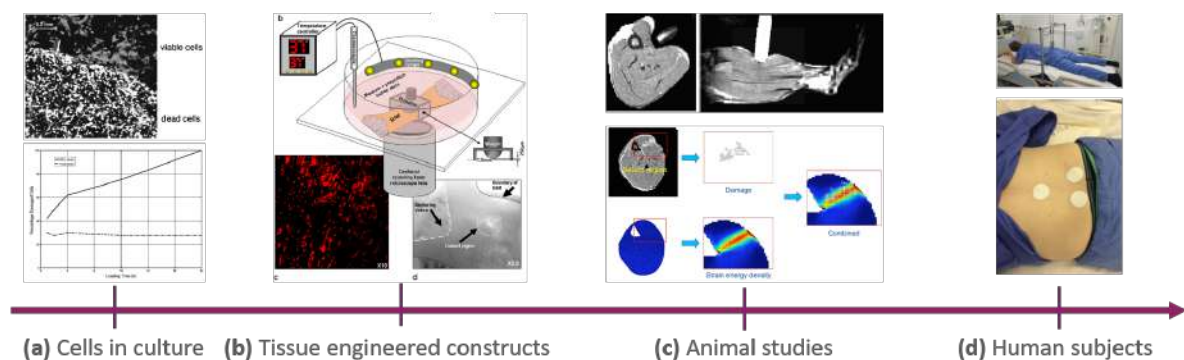


Figure 5.1: Hierarchical approach developed at Eindhoven University of Technology. Inspired from [Dan Bader's Vaedictory lecture](#) (January 24 2020 at Eindhoven University of Technology).

This multiscale strategy using cell culture and animal studies lead to the conclusion that there are at least **two damage mechanisms** which play an important role in PU development: (i) **mechanically induced capillary occlusions** that lead to low oxygen concentration in the tissue triggering a cascade of inflammatory signals that culminate in ulceration (Kosiak 61; Gawlitta 07c; Loerakker 10; Loerakker 11; Sree 19). This process can occur even for very small strain intensities and takes several hours (2-4h) before the first signs of cell damage can be detected (Breuls 03; Loerakker 10; Stekelenburg 06b; Stekelenburg 07). (ii) **direct (shear) cell deformation** (Bouten 03b; Peeters 03; Bosboom 03; Stekelenburg 07; Ceelen 08; van Nierop 10; Loerakker 10; Loerakker 11; Nelissen 18; Traa 19) observed only when a given maximum Green-Lagrange shear strain threshold was exceeded (Ceelen 08). The damaged area has been shown to be correlated to the magnitude of the elastic strain energy applied (Loerakker 10). The processes by which this fast-occurring damage develops are not entirely clear, although it probably involves damage to the cell membrane and re-organisation of internal cell structures (for more information, the reader is also referred to the review paper of Gefen and Weihs (Gefen 16)).

As proposed in (Bouten 05), to be clinically relevant, computational models should be designed to predict the interplay both 1/ between external and internal mechanical conditions within soft tissues at different length and time scales and also 2/ between the mechanical response and cellular activities. In this way, relationships between cellular activities at the micro-scale can be extrapolated to the level of bulk tissue to give clinically relevant predictions on tissue breakdown.

In a previous collaborative work with **Giuseppe SCIUME** (University of Bordeaux) and **Stéphane BORDAS** (University of Luxembourg) (co-supervision of the PhD thesis of **Stéphane URCUN**), a reactive multiphase poromechanical model initially developed by Sciumè et al. (Sciumè 13; Sciumè 14) (figure 5.2 (a)) was adapted 1/ to investigate the influence of hypoxia and mechanical inhibition on tumor growth (Urcun 21) (figure 5.2(b)) (Urcun 21) 2/ to model the growth of a non-operable glioblastoma. Building upon this work, the objective of this chapter is to develop a reactive multiphase porous model linking mechanical deformation, tissue hypoxia and tissue damage.

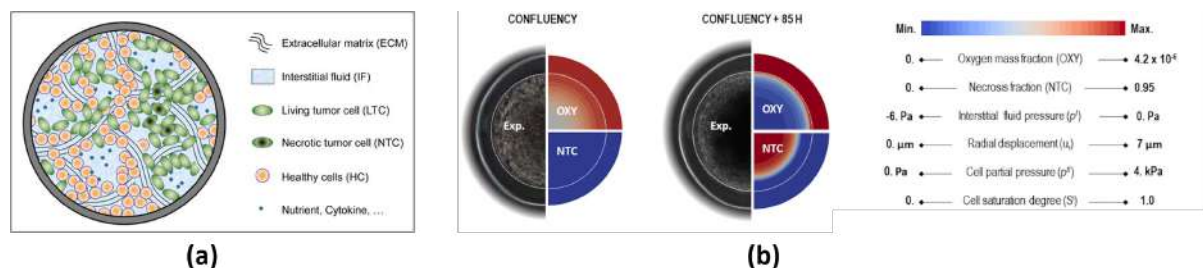


Figure 5.2: (a) Multiphase system within a Representative Elementary Volume. Image source: (Sciumè 13) (b) Numerical simulation of the *in vitro* experiment of (Alessandri 13) and evaluation of model prediction. Image source: (Urcun 21).

In this chapter, we focus on the interactions at the tissue scale and investigate the relative importance of mechanically induced ischemia and direct cell deformation. The **objective is to develop a reactive multiphase porous model linking mechanical deformation, tissue hypoxia and tissue damage.**

5.2 MSc Thomas LAVIGNE (2020-2021): Poromechanical modelling of skeletal muscle



10/2020- Thomas Collaboration with Benjamin WHEATLEY, [P26]
09/2021 LAVIGNE Giuseppe SCIUMÈ and Stéphane BORDAS

The first step is to develop a poromechanical model of soft tissues behaviour. In this section, we restrict our analysis to skeletal muscle tissue although the procedure is easily transferable to adipose tissue, fascia and skin.

In the literature, attempts to characterize the time-dependence of skeletal muscle tissue generally assume a viscoelastic formulation and typically ignore the bi-phasic nature of the tissue (Van Looke 09; Simms 12; Wheatley 15). In the case of viscoelasticity, the underlying physical mechanisms that give rise to the time dependent stress-strain behavior are not known. Yet, it is known that skeletal muscles are composed of a porous solid matrix (muscle fibers and extracellular matrix) filled with fluid (approximately 75% bound and free fluid (Sjogaard 82)). The overall mechanical behavior of these tissues depends not only on the solid matrix deformation, but also on the movement of the fluid in and out of the pores during the deformation. As a result, many research teams have proposed using poroelastic constitutive models as an alternative to visco-elastic models to capture the history-dependent response of soft tissues under static and dynamics loading (Gimmich 19; Argoubi 96; Peyrounette 18; Siddique 17; Hosseini-Farid 20; Franceschini 06; Urcun 22).

In a recent study, Anurag VAIDYA and Benjamin WHEATLEY (Bucknell University, USA) tested porcine Tibialis Anterior (TA) muscle samples under fast and slow Confined/Unconfined compression (Vaidya 20). Briefly, thirty-one cylindrical muscle porcine samples (average height 7.0 mm and average radius 3.2 mm) were compressed in an impermeable steel well, using a uniaxial tabletop Instron 3366 tensile testing system equipped with an Al₂O₃ porous plunger (figure 5.3 (a)). Specimens were strained to 15 % at two different strain rates: a fast compression at 15 %/s (N=16 cylinders) and a slow compression at 1.5 %/s (N=15 cylinders). They were maintained at this strain level during 400 s. All tests were completed under transverse compression to simulate the most common uniaxial physiological loading orientation.

In the Master's thesis of Thomas LAVIGNE, and in collaboration with Benjamin WHEATLEY, a poroelastic Finite Element model (figure 5.3 (b)) was developed in the general purpose Finite Element software ABAQUS (ABAQUS, 2019) to explore the capability of poroelasticity to reproduce the apparent viscoelastic behaviour of passive muscle tissue under Confined Compression (Lavigne 22). An inverse analysis was performed to fit a quasi-incompressible, isotropic, poroelastic constitutive model to reproduce the experimental mechanical response (stress relaxation). The results of the one-to-one sample calibration on the N=31 samples are given in figure 5.3 (c) below. The calibration procedure allowed to approximate the slope between 350 s and 400 s with a poro-elastic model for all the samples. Also, the peak stress was mostly recovered by the poroelastic model (N = 25/31 for which the difference between the peak stress assessed experimentally and that predicted by the simulation is lower than 5%).

The strength of the poroelastic model assumed in this study is mainly its fewer number of variables compared to more complex constitutive models employed in the literature to capture the temporal evolution of muscle tissue such as, for example, the visco-hyper-elastic model assumed in (Vaidya 20) with 18 parameters to calibrate (versus 6 parameters in the present study: the Young's modulus and Poisson's ratio of the drained solid matrix, the void ratio and hydraulic permeability of the sample, and the soil grain's and fluid's bulk moduli).

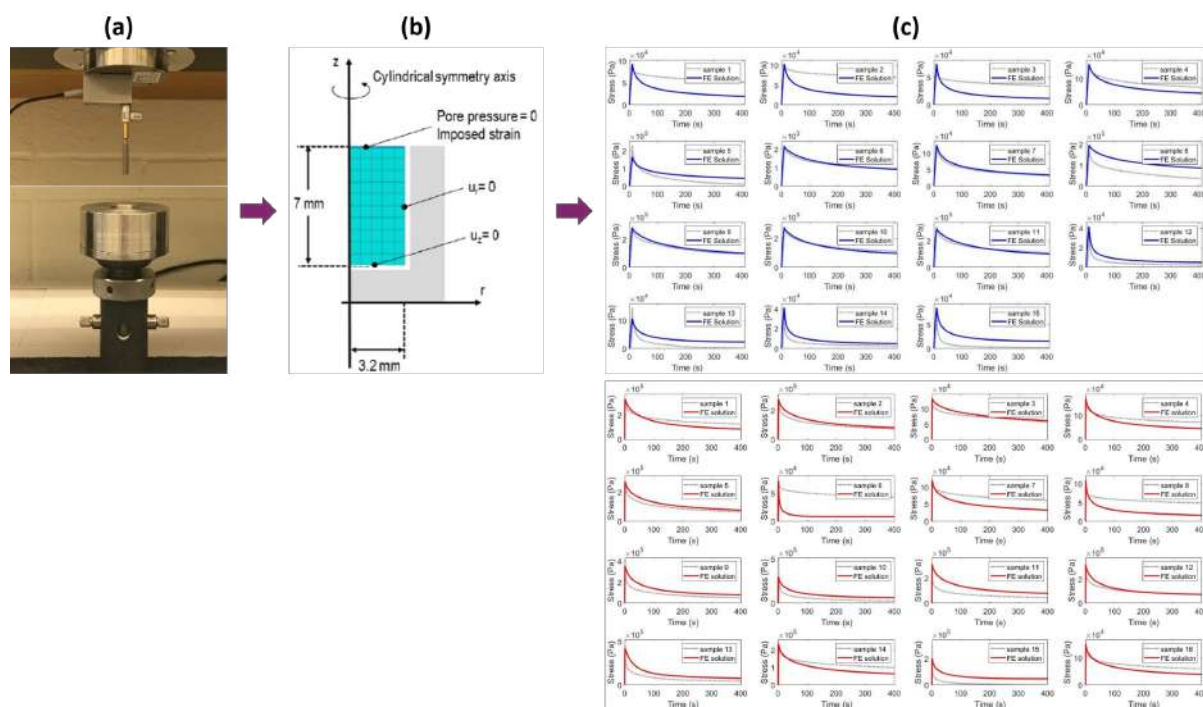


Figure 5.3: (a) Experimental set up for confined compression (b) Schematic representation of the finite element model (c) Results of the one-to-one calibration carried out on the $N = 15$ samples (blue curves) for the slow strain-rate loading condition and on the $N = 16$ samples (red) for the fast strain-rate loading condition. The reader is referred to (Lavigne 22) for more details.

Poroelectricity represents a promising approach for investigating the mechanisms responsible for the onset of Pressure Ulcers

Numerous problems of relevance in biomechanics, have at their core, the presence of a deformable solid matrix which experiences flow-induced strain. Although a fluid-structure interaction (FSI) problem, the number and range of fluid passages is generally so vast that the direct approach of a deterministically defined boundary between fluid and solid is impossible to apply. In these cases, homogenisation and statistical treatment of the material-fluid system is possibly the only way forward. A prominent technique of this type is that of poroelasticity. Results obtained in this work support the idea that poroelasticity is capable of reproducing the apparent viscoelastic behaviour of passive muscle tissue under confined compression. Poroelasticity also represents a promising approach for getting insights into the mechanisms of PU onset because it allow to integrate multiscale, multiphysics data to probe biologically relevant phenomena at a smaller scale and embed the relevant mechanisms at the larger scale.

5.3 PhD thesis Thomas LAVIGNE (coming soon !): Reactive multiphasic porous model linking mechanical deformation, tissue hypoxia and tissue damage



10/2022- Thomas Pierre-Yves ROHAN (35%), Giuseppe SCIUMÈ (35%)
10/2025 LAVIGNE Stéphane BORDAS (30%); Collaboration: Bérèngère FROMY

The scientific objective of this PhD project will be to establish relationships between the progressive tissue damage, local mechanical deformation and tissue hypoxia when soft tissues are exposed to prolonged external loads. The reactive multiphase poromechanical model initially developed by Sciumè et al. (Sciumè 13; Sciumè 14; Urcun 21) will be adapted to link mechanical deformation, tissue hypoxia and tissue damage. To build the model and to evaluate its clinical validity in predicting onset of soft tissue injury, an experimental animal study will be conducted in collaboration with (and supervised by) Bérèngère FROMY, co-leader of the SKIN (SKin functional INtegrity) research group at the LBTI (Laboratoire de Biologie Tissulaire et Ingénierie thérapeutique). The experimental protocols previously developed by Fromy et al. (Fromy 12; Fromy 10) will be adapted. The PhD thesis will be structured in 3 Work Packages (figure 5.4 below).

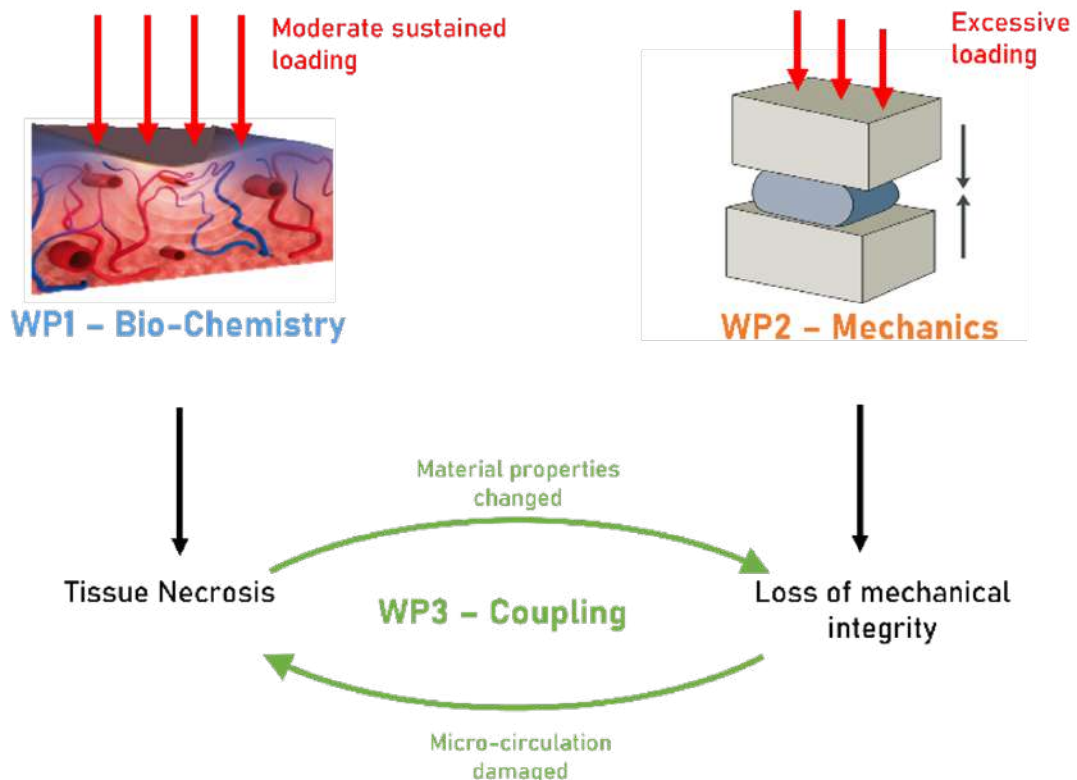


Figure 5.4: The PhD thesis will be structured in 3 Work Packages: [WP1] will focus on the effect of hypoxia alone when the tissue is submitted to moderate sustained loadings on tissue damage onset and progression, [WP2] will study the effect of high intensity mechanical loadings on tissue damage onset and progression and [WP3] will study the relative impact and interactions between both phenomenon.

All animal experiments will be submitted to Lyon Animal Ethical Committee (CECCAP) for prior approval before being sent to the French National Ethic Committee. In accordance with the provisions of European Directive 2010/63/UE, the study will comply with the "3 R's" standards for housing and cares. Depilated healthy mice (C57BL6) will be anesthetized. **Exploration of healthy soft tissue structure** will be done by performing: Magnetic Resonance Imaging (MRI) of bone and soft tissue, structural mapping of skin at the cellular level down to a depth of 500 μm *in vivo* using the Line-field confocal optical coherence tomography (Dubois 18) and Shear Wave Speed (SWS) measurement. **Characterization of healthy skin** will be done by: Challenging skin blood flow under low and high pressure application, evaluating the neurovascular status of the skin, assessing micro-circulation using Laser Doppler flowmeter and Laser Speckle Contrast Imaging and measuring skin oxygenation using transcutaneous pressure of oxygen (tcPO₂). **Characterization of the compression-induced damage** will be performed by loading the soft tissue with an MR-compatible device (inspired from (Stekelenburg 06a)) and, using a T2-weighted MRI sequence, the damage initiation and its subsequent temporal progression will be monitored. Two loading regimes will be investigated: moderate sustained loading and high intensity mechanical loading. The mice will then undergo prolonged pressure application to induce pressure ulcers using a patented protocol adapted from (Fromy 12) using 2 magnets. After mouse euthanasia, skin lesion areas will be harvested at maximum wound size for histology, and rheology assessment.

Based on the experimental results obtained, [WP1] will focus on the effect of skin hypoxia alone when the tissue is submitted to moderate sustained loading. A porous bi-compartment Finite Element (FE) model will be developed to simulate skin micro-circulation : One compartment for blood (vascular porosity representing microvascular volume fraction), one compartment for interstitial fluid (extravascular porosity representative of the intercellular interstitium). Oxygen transport in the vessels and oxygen exchanges between the two porous compartments will be modelled through a mass conservation equation for the oxygen species in the blood and one for the oxygen in the interstitial fluid. The model will be calibrated and (cross) validated based on the experimental data. [WP2] will study the effect of high intensity mechanical loadings on tissue damage. A simplified, porous mono-compartment Finite Element (FE) model will be developed to simulate the response of soft tissues to external loading over short time scales. [WP3] will study the interplay between the two damage mechanisms. The feasibility and relevance of calibrating a Perzyna-type elastic-viscoplastic (Perzyna 66; Perzyna 71; Heeres 02) constitutive models to reproduce the temporal evolution of damage will be investigated.

There have been a few attempts in the literature to test the relationship between applied pressure, soft tissue mechanical properties and architecture and tissue hypoxia. Sree et al. (Sree 19) for example employed a computational homogenization approach (FE²) to link vasculature collapse at the microscopic scale with oxygen diffusion at the tissue scale. They showed that vessel orientation distribution is the single most important factor leading to vessel collapse for noninteracting vessels and also that pure shear does not result in a significant reduction of blood vessel volume fraction. However, these results remain to be confronted to experimental evidences. Moreover, the huge number of vessels in the soft tissues - tens of billions - prevents any modelling approach with an explicit architectural representation down to the scale of the capillaries at clinically relevant scales. Alternative approaches, such as porous media mechanics represent an interesting alternative.

5.4 Collaboration Benjamin WHEATLEY and Eric MONTEIRO: Multilevel FE modelling of fluid pressurization

In the Master’s thesis work of Thomas LAVIGNE ([section 5.2]) it has been assumed that the drained solid phase was quasi-incompressible and linear elastic. The assumption of a quasi-incompressible drained solid phase seems reasonable because muscle fibres may exhibit nearly incompressible behaviour as fluid-filled structures with no fluid transport across the cell boundary. There is evidence that this is the case (Sleboda 17). However, **if the drained solid phase had been assumed to be highly compressible, this would lead to a different set of calibrated constitutive poro-elastic parameters** (the reader is referred to Appendix E of (Lavigne 22)) strongly suggesting that further experimental and theoretical investigations are needed to shed more light on the mechanical behaviour of the drained solid scaffold.

In addition to the Confined/Unconfined compression tests performed on porcine Tibialis Anterior muscle samples (Vaidya 20), Benjamin WHEATLEY has also conducted semi-confined compression experiments associated with intramuscular pressure measurements with fiber optic pressure microsensors to determine the role of fluid pressurization in skeletal muscle compressive stiffness. Preliminary testing (unpublished data from Benjamin WHEATLEY) shows a strong relationship between tissue stress and fluid pressurization in muscle tissue, suggesting that fluid plays an important role in compressive muscle mechanics. Adopting a multilevel finite element approach as previously proposed in (Breuls 02), a collaborative work has been initiated with Benjamin WHEATLEY and Eric MONTEIRO to develop a model to predict Intramuscular pressure in muscle tissue subjected to macroscopic external loads. A schematic representation of the flow chart of the Multilevel Finite Element approach, inspired from (Breuls 02), is given in figure 5.5 below.

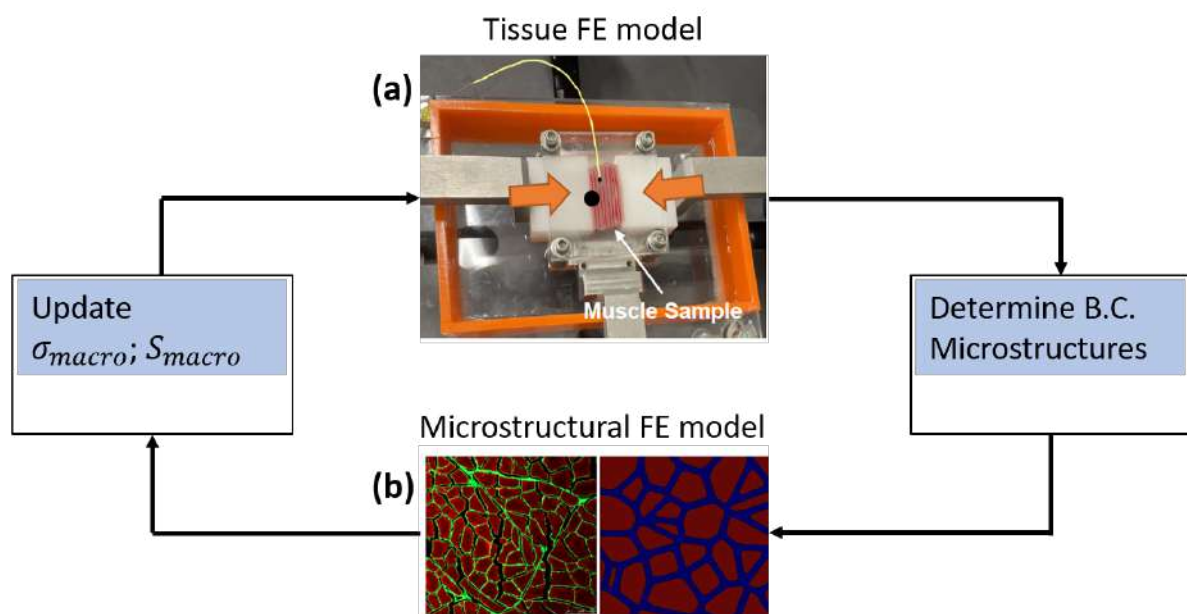


Figure 5.5: Flow chart of the Multilevel Finite Element approach inspired from (Breuls 02). (a) Compression Set-up. The fiber optic pressure microsensor is outlined with the yellow line. (b) histological section of muscle tissue and example of a histology-based microstructural finite element model.

A collection of 2D microstructural FE models will be generated from histological images taken at different locations of the tissue sample. The pore space will be filled and associated to Interstitial fluid. Boundary conditions will be inferred from the macroscopic deformation tensors. A fluid-structure interaction problems will be solved with co-simulation in ABAQUS to determine Interstitial fluid pressure and Solid scaffold solid stress. The macroscopic stresses and tangent stiffness matrices will be returned from the microscopic models to the macroscopic integration points.

This work currently in progress will enable to develop a more accurate description of the transmission of loads across a wide range of scales. It will constitute an important database against which different assumptions and modelling simplifications will be tested. This will allow to gain insight into what is the most relevant simplified framework to determine Interstitial fluid pressure and Solid scaffold solid stress.

5.5 Collaboration Benjamin WHEATLEY and Giuseppe SCIUMÈ: In situ characterization of loaded muscle samples via synchrotron X-ray tomography

In parallel, a second collaborative work that has been initiated with Benjamin WHEATLEY and Giuseppe SCIUMÈ to prepare an application to image skeletal muscle tissue under compression at the European Synchrotron Radiation Facility (ESRF). The objective is to obtain quantitative experimental estimations of the magnitude and distribution of mechanical strain at the microscopic level in skeletal muscle tissue under compression. Contrarily to Magnetic resonance Imaging and Ultrasound imaging which allow probing soft tissues at macroscopic scales but imposes limits on both the spatial and temporal resolution, synchrotron X-ray tomography yields greater spatial resolution. Combined with digital volume correlation (DVC), it could be used to realize full-field tissue-level strain measurements (Giuliani 17; Madi 19). Preliminary investigations are currently in progress to image bovine muscle tissue samples on the μ -CT system present at the IBHGC.

5.6 Collaboration Bérengère FROMY and Marie-Line DAHAN: Clinical evaluation of the coupling between mechanical response and microcirculation in vulnerable individuals

This collaborative project aims to explore experimentally, in a clinical context, the link between mechanical response and microcirculation in a population at risk. The objective is to study the physical/biological phenomena involved in the appearance of tissue lesions and to understand how this interaction participates in the initiation of pressure sores in biological soft tissue. The project will focus in particular on the development of pressure sores in the elderly. This population is particularly at risk for tissue damage, which represents a global medical, social and economic problem for health care systems. A better understanding of the changes that occur with aging seems crucial to reduce the incidence of pressure ulcers in the elderly, since the best treatment is prevention.

This work requires the definition of specific methods allowing the risk assessment in conditions as close as possible to the clinical routine and with a reduced time to invest by the subject. Preliminary work has been initiated by each of the project partners, for the characterization of geometry, material properties and local deformation on the one hand (Doridam 18; Fougeron 18; Fougeron 22) and for the

microvascular characterization of the skin using laser Doppler and transcutaneous oxygen pressure on the other hand (Fromy 10). However, the definition, evaluation, and implementation of the different characterization methods still remains largely to be investigated and is the major challenge of this work.

The project can be divided into 4 main tasks:

1. Applying for approval and authorization of the French Ethics Committee (CPP). This project includes experiments involving human subjects. According to the Loi Jardé (Ordonnance 2016-800 of 16/06/2016), all experiments involving human subjects require a preliminary validation by an ethical comity. The first step will consist in writing the protocol, Applying for approval and authorization of the French Ethics. The promotor will be the Groupe Hospitalier Intercommunal Le Raincy-Montfermeil. The investigator will be Marie-Line DAHAN.
2. Recrutement: In this prospective study, data will be collected from the 2 groups of patients paired in terms of BMI and sex-ratio. **1/** at-risk old persons (60-75 yo and braden scale lower than 12) N=50 **2/** general population (young healthy volunteers) N=50
3. Measurements: This project will focus on the heel for two main reasons. First, it is one of the most common sites of pressure ulcer development. Second, it is an anatomical area with a thin layer of soft tissue (which will facilitate data collection and interpretation) and is also easily accessible (unlike other pressure ulcer-prone areas such as the sacrum or ischium). The following measurements will be collected : **1/** Functional exploration of the cutaneous microcirculation **2/** B-mode ultrasound imaging for the quantification of soft tissue thickness and calcaneum geometry **3/** B-mode ultrasound imaging for the quantification of localized soft tissue strains under the weight of the foot. **4/** Ultrasound Shear Wave Elastography **5/** Transcutaneous oxygen pressure (TcPO₂) **6/** Line-field confocal optical coherence tomography (LC-OCT) for the real time assessment of skin structures with a resolution close to that obtained by conventional histology

5.7 Limitations

The underlying mechanism by which tissue-scale strain and ischemia lead to cell apoptosis involves a complex cascade of cellular signaling pathways. Compression-induced ischemia, for example, renders the tissue hypoxic, i.e., causes a drop in partial oxygen pressure. In response to hypoxia, native cells release chemo-tactic signals, which attract neutrophils and macrophages (?). Subsequently, neutrophils infiltrate the tissue and release tumor necrosis factor alpha (TNF α), which leads to cell death. Cell necrosis, in turn, releases damage associated molecular patterns (DAMPs) which further recruit neutrophils, initiating a perpetual cycle of inflammation that eventually leads to cytokine-induced edema and, ultimately, ulcer formation. Integrating biological signalling network is therefore paramount to assess the interplay between chemical-biological-mechanical factors. This is a key challenge to understand and eventually predict the initiation and propagation of soft tissue damage

CHAPTER 6

FROM TISSUE-SCALE BEHAVIOUR TO CELL MECHANO-SENSING

6.1 Research question (hypothesis)

Soft tissue injury initiation depend, in large part, on how cells sense and respond to chemo-mechanical stimuli (the reader is referred to Gefen et al.(Gefen 16) for a review of the mechano-biology of chronic wounds and Turner et al.(Turner 14) for a review on the role of the main cytokine and chemokine cell signaling molecules). It is well documented that **mechanical loads at the tissue level are transmitted to cells in their local extracellular matrix (ECM) and transformed into chemical signals through the process of mechano-transduction** (Wang 06). Signaling cascades inside cells and also between cells coordinate how cells change their local ECM to maintain homeostasis (Humphrey 14). Under a normal physiological framework, inflammation is necessary for the systematic immunity including tissue repair and regeneration as well as returning to homeostasis. Inflammatory cellular response and metabolic mechanisms play key roles in the well-orchestrated tissue regeneration. If this response is deregulated, it becomes chronic, which in turn causes improper repair and autoimmune disorders, ultimately leading to tissue necrosis.

In the particular case of **pressure ulcer pathogenesis**, the inflammatory response consists of a highly conserved cascade of events mediated by a set of specialized cells (platelets, white blood cells, macrophages, and neutrophils) and molecules (inflammatory cytokines, free radicals, and Damage-Associated Molecular Pattern molecules) that delimit stressed or damaged tissue, and alert and recruit other cells and molecules (Houwing 00; Peirce 01; Ziraldo 15). The inflammatory response can either restore the tissue to equilibrium (healing) and resolve, or become self-maintaining inflammation that causes and is caused by ancillary tissue damage. This excessive inflammation prevents the body from initiating wound healing and can lead to PU incidence (Vodovotz 10). The dynamic interplay of the inflammatory and healing cascades determines the ultimate success or failure of the healing process.

Several computational **biological** models (mostly Agent-Based Models) of inflammation have been proposed in the context of pressure ulcer initiation by the group of Yoram Vodovotz of the University of Pittsburgh (Mi 07; Vodovotz 13; Solovyev 13; Ziraldo 15) and have provided very useful insights into the pathogenesis and effective treatment of pressure ulcers. In (Solovyev 13), a hybrid model combining an Agent-Based Model (ABM) skin/muscle injury, inflammation, and ulcer formation and an Ordinary Differential Equation-based (ODE) model of reactive hyperemia was developed (see figure 6.1) and

calibrated in N=12 volunteers (N=6 subjects with spinal cord injury and N=6 subjects without any neurological deficits). The response to a medium-scale pressure on the skin with different frequencies, estimated that the risk of initiation and progression of pressure ulcer was more important in spinal cord injured volunteers.

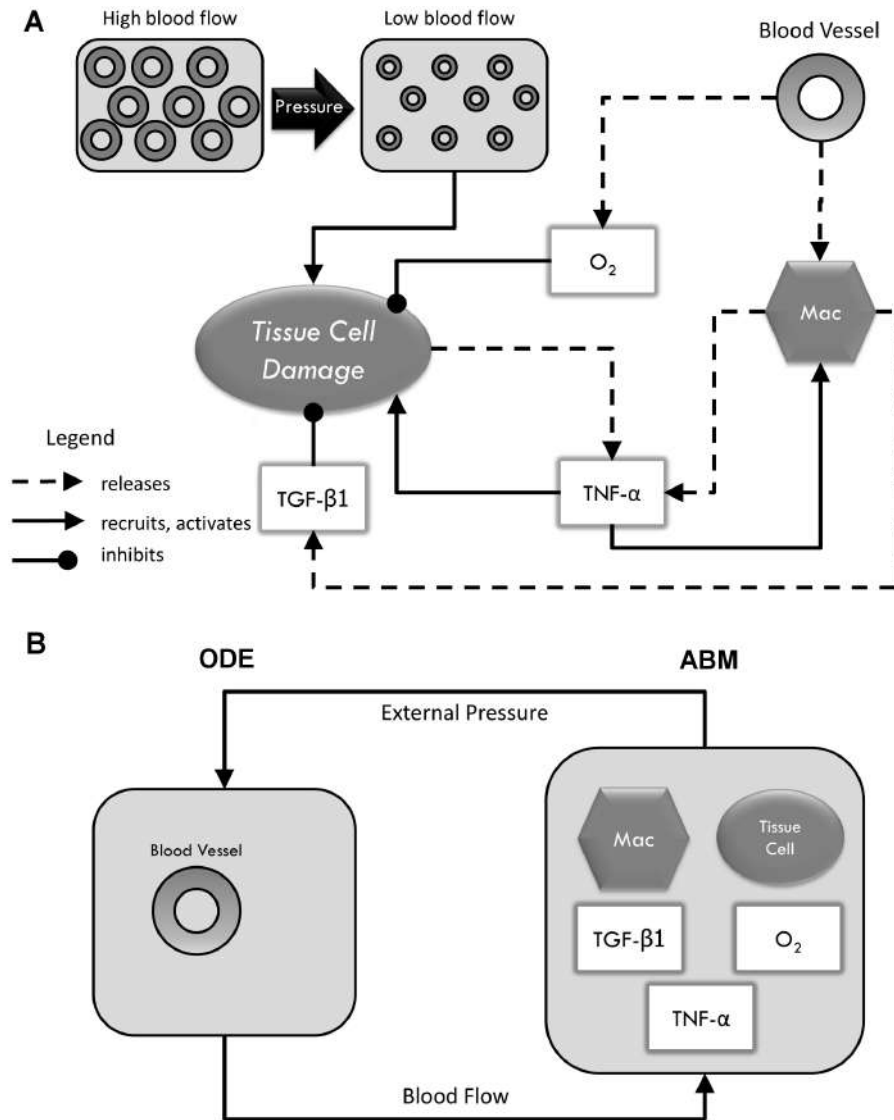


Figure 6.1: Adapted from (Solovyev 13). Components of the coupled Ordinary Differential Equation-Agent-Based Model model of pressure ulcer formation developed in (Solovyev 13). Panel (A) shows interactions between main components of the model. Panel (B) demonstrates the connection between Ordinary Differential Equation and Agent-Based Model portions of the model.

Agent-based models have emerged as a promising approach for elucidating complex biological systems, including inflammation and wound healing. Further work is needed to characterize and **understand the relationship between the progressive tissue damage accumulation, local mechanical deformation, tissue hypoxia, inflammation regulatory network and cytokine-induced edema.**

6.2 Linking progressive tissue damage accumulation, mechanical deformation, hypoxia, inflammation and cytokine-induced edema in soft tissue under compression

The expression of inflammatory mediators (tumor necrosis factor (TNF)- α) can be visualised in rat models (? ? ?) and detected in plasma and urine in clinical routine (?) and can be correlated to apoptosis. Building upon the protocols already developed, the objective is to **develop methods to characterize experimentally and model the coupling between mechanical response and biological response** both at the cell-scale and at the tissue scale (in collaboration with **Bérenghère FROMY** and **Giuseppe SCIUMÈ**). This is an important step to better understand the relationship between the progressive tissue damage accumulation, local mechanical deformation, tissue hypoxia, inflammation regulatory network and cytokine-induced edema in soft tissue under prolonged compression loading. This is also important to guide the development of clinically relevant models that can inform patient decision making and allow the development of an individualized prevention plan.

The experimental approach will consist in characterizing the mechanical, physiological and biological response of mice skin during the compression of the animal Tibialis Anterior muscle with a custom loading device to induce pressure ulcers using an adaptation of a patented protocol. This will be conducted in collaboration with (and supervised by) **Bérenghère FROMY**, co-leader of the SKIN (SKin functional INtegrity) research group at the **LBTI (Laboratoire de Biologie Tissulaire et Ingénierie thérapeutique)**. Experiments will also be conducted in **human skin substitutes to bridge the gap between animal research and clinical research.**

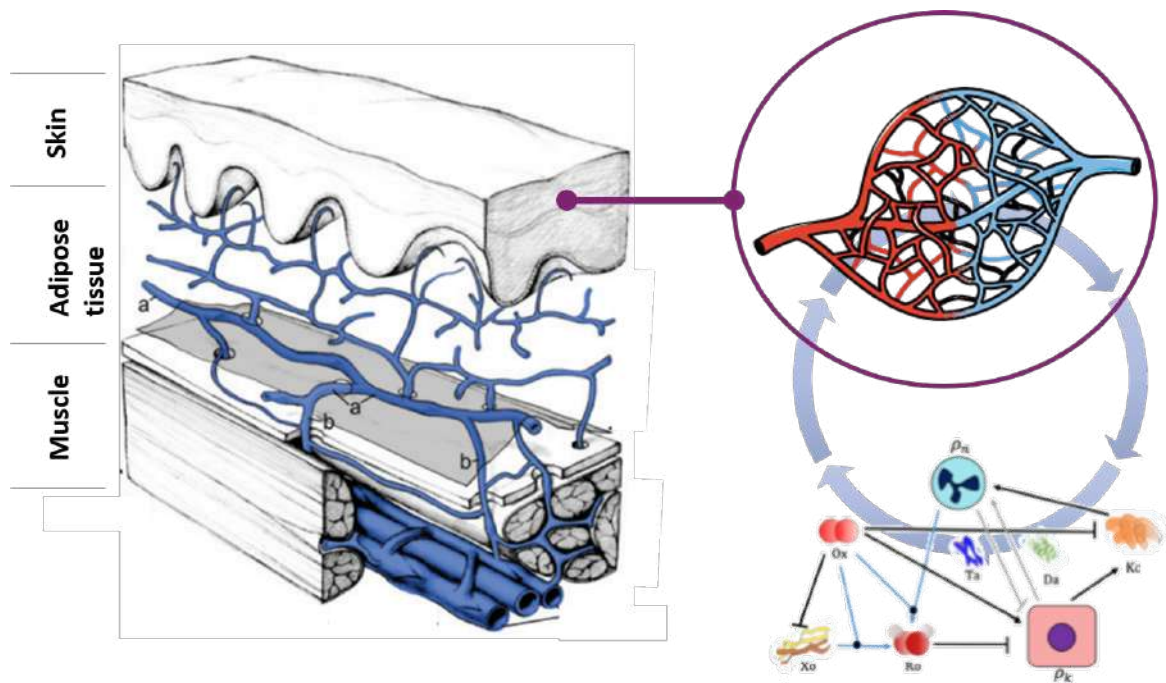


Figure 6.2: Schematic representation of the multiscale mechanobiological model coupling linking mechanical deformation, tissue hypoxia and inflammation regulatory network involved in PU formation. Image sources: The Vein Book (Partsch 07)(left), Servier medical art (right top) (Sree 19) (right bottom).

The numerical part will, first, involve developing a high fidelity multiscale mechano-biological model coupling linking mechanical deformation, tissue hypoxia and inflammation regulatory network involved in PU formation. It will consist of a vascularized multiphase reactive continuum including two porous compartments: one saturated by cells and interstitial fluid and a second filled with blood (providing nutrients and oxygen). The model will be founded on the Thermodynamically Constrained Averaging Theory (Gray 05). This will allow to model ischemia, the resulting tissue hypoxia and inflammatory response. Level set methods will also be used to model the evolution of cytokine-induced edema. **The experiments performed on small animal models will be reproduced numerically and will be split into training set and validation set.** Then, from the high-resolution multiscale mechanobiological simulations, a macroscopic tissue damage law will be developed. This will be cast into low-fidelity digital model linking mechanical deformation, tissue hypoxia and inflammation regulatory network to a tissue-scale Finite Element model that is rich enough to translate the tissue-scale and cell-scale processes that are important for PU initiation. Uncertainty quantification will be performed to assess the predictive value of the model and to evaluate the possibility of simplifications to reduce the number of parameters needed as input.

As a perspective work, as suggested by the group of Yoram Vodovotz of the University of Pittsburgh (Solovyev 13; Ziraldo 15), the model could be easily transferred to clinics wherein **1/** the perfusion part of the model could be calibrated to data related to blood flow following experimental pressure responses in non-injured human subjects and the damage part of the model could be calibrated to clinical images of wounds collected in patients in clinical routine.

CHAPTER 7

BUILDING A TECHNOLOGY DEMONSTRATOR TO MAKE A STEP TOWARDS PARTICIPATORY RESEARCH

Digital tools have shown great potential to enhance health services' capacity to achieve the goals of the triple aim (**enhance patient experience, improve health outcomes, and control or reduce costs**), but their actual impact remains variable. As frequently highlighted in the literature, it is increasingly understood that it is not sufficient to just **push a new technological development into the clinical world** and hope that it is adopted. Their actual implementation in clinical setting represents a challenging perspective. For example, Pressure Ulcer preventive care is only one of the many responsibilities and tasks that healthcare workers need to undertake within patient care. The development of approaches that are practical, easy to use, and accurate need to be addressed, together with the demonstration that the patient can benefit from it. **Accounting for the patient needs** is also an important factor for ensuring patient satisfaction and consequently successful prevention plans. Indeed, acceptance rates and user satisfaction are not only dependent on technical aspects, but also to a great extent on social and psychological factors. There is often considerable unconsciousness among the actors (engineers, users, occupational therapists, health care professionals, politicians, researchers) that hinders communication, exchange of concepts, knowledge, and meaning.

As a first step to make the **connection to the clinical setting** and to initiate a **participatory approach** with the user, the **objective of this third area of research is to to develop a technology demonstrator of the proposed multi-scale multi-physics digital twin on an open-source software platform routinely used in translational medicine and clinical practice to provide a practical and usable tool**. The developments will rely on **3D Slicer**, an open-source software platform for medical data processing and visualization, which have been tested by physicians in real situations, among others at the Brigham and Women's Hospital. The platform and the leveraged products are routinely used in translational medicine and clinical practice, and can be considered as a standard *de facto* on its field .

The objective is to create a custom application (extension of **3D Slicer**) integrating the prediction model and **developing a simple tablet-friendly interface**. Starting from the model that will be developed in section 6.2 linking progressive tissue damage accumulation, mechanical deformation, hypoxia, inflammation and cytokine-induced edema in soft tissue under compression (figure 7.1 left), the workflow will consist in constructing a data-driven digital model i.e. a "hybrid" computational workflow that combines equation-based modelling and data-driven algorithms in a single tool, able to provide detailed process insight within a reasonable time-frame, usable in clinical practice for the physical-to-virtual connection (figure 7.1 middle). The approach hinges on a robust stochastic model and parameter identification methodology which has been developed in the Legato Team since the **ERC RealTcut** project of **Stéphane BORDAS** (*FP7-ERC-2011-StG-279578: Towards real time multiscale simulation of cutting in non-linear materials with applications to surgical simulation and computer guided surgery*). The virtual-to-physical connection consists in developing a risk score based on the multi-physics field predictions and which triggers both actions intended to reducing or redistributing interface pressures and an alert to the clinical team to adapt the preventive strategies. Finally CMake's external projects module will be used to download, configure, and compile the model libraries as part of Slicer's build process. Special attention will be paid to designing measures that ensure compliance with data privacy laws like GDPR (figure 7.1 right)

By developing a set of 'digital case studies' simulating patient outcomes, the proposed technology demonstrator will also serve as a support to the development of clinical guidelines, educational modules and medical/clinical training aids. This will serve as a basis for stimulating the emergence of an EU innovation eco-system around the technological paradigm.

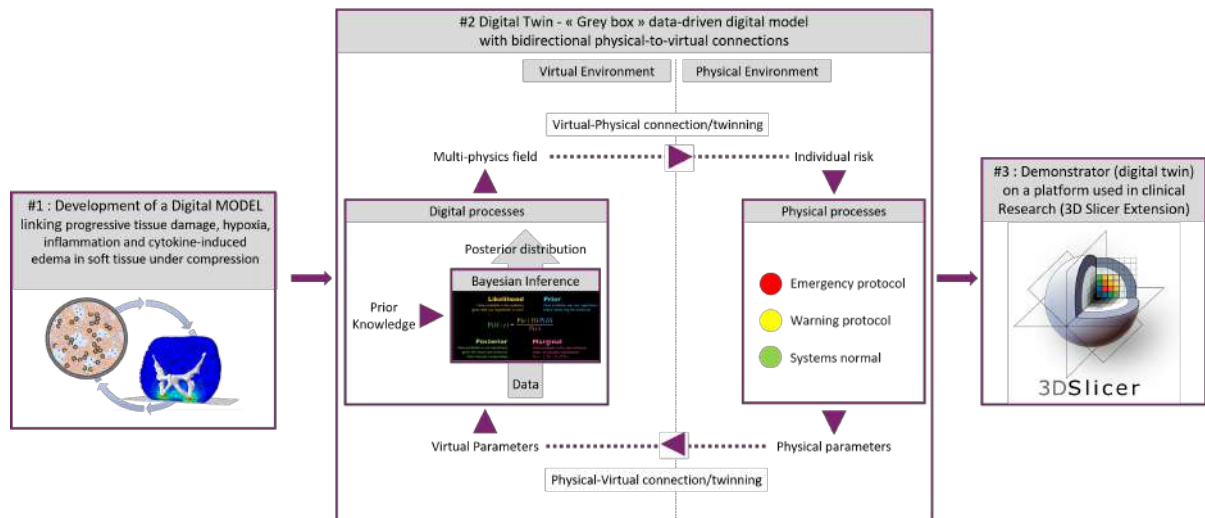


Figure 7.1: **Left**: Model that will be developed in section 6.2 linking progressive tissue damage accumulation, mechanical deformation, hypoxia, inflammation and cytokine-induced edema in soft tissue under compression. **Middle**: data-driven digital model integrating machine learning and multiscale modelling. **Right**: CMake's external projects module will be used to download, configure, and compile the model libraries as part of Slicer's build process.

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General Conclusion

CHAPTER 8

GENERAL CONCLUSION AND PERSPECTIVES

The objective of this manuscript was to put into perspective the scientific work I have been conducting so far from the perspective of the research questions addressed, methodologies developed and contributions to the field ([Decree of 23 November 1988 on the habilitation to conduct research](#)) and to outline the focused research project I will pursue during the coming years.

In chapter 2, I have presented the most important part of my research activity conducted so far on the modelling and the simulation of the transmission of mechanical loads in biological soft tissue during the mechanical interaction with external devices **from a structural mechanics perspective**. Elaborating such personalized non-linear Finite Element models is a long and tedious task for the whole community (section 2.3). Currently, the main challenge, lies in the **validation of the relationship between external mechanical load and the mechanical quantities of interest** for the prediction of soft tissue injury risk (interface pressure/shear for superficial tissue damage; tissue strain for deep tissue injury). Such validation evidences must be obtained prior to any clinical evaluation. Such validation evidence is also important to guide the development of clinically relevant models that can inform patient decision making and allow the development of an individualized prevention plan (what is the level of complexity required for the model, what is the level of penalization required, etc). Building upon the environment of the IBHGC, **I intend to focus my attention in the coming years to the validation of non-linear Finite Element models for estimating the risk of soft tissue injury**.

Such an approach, however, is limited for the prediction of soft tissue damage initiation because many factors other than the magnitude of loading affect an **individual load tolerance**. Soft tissue injury is, fundamentally, **a multi-scale and multi-physics process** and there is a need to **understand the relationship between the progressive tissue damage accumulation, local mechanical deformation, tissue hypoxia, inflammation regulatory network and cytokine-induced edema**. There is also a need to investigate to what extent models need to be complex (or, rather, to what extent they can be simplified) in order to be able to robustly predict the onset of superficial or deep tissue damage following the exposure to prolonged external loads in a clinical setting.

In order to progress in the clinical relevance of Digital Twins in the context of soft tissue injury prevention, I have tried to outline the scientific issues that I intend to address in the short and medium

term, by giving some initial methodological elements illustrated by preliminary work in **Part 2** of the manuscript. Briefly, the scientific issues will focus on characterizing experimentally and modelling the very strong link between mechanical response and biological processes (in particular, **oxygen biochemistry** and **inflammatory cytokine biology**) and their relative role in the development of soft tissue injury. Despite **the pioneer work of the group of Cees Oomens at Eindhoven University of Technology** (section 5.1), this is a field that has been little addressed and more should be done not only to **better understand the basic mechanobiological mechanisms that drive soft tissue damage** but also, and most importantly, to **overcome the barriers to the clinical translation of risk assessment tools** based on FE modelling.

As frequently highlighted in the literature, it is increasingly understood that it is not sufficient to just **push a new technological development into the clinical world** and hope that it is adopted. Their actual implementation in clinical setting represents a challenging perspective. The development of approaches that are practical, easy to use, and accurate need to be addressed, together with the demonstration that the patient can benefit from it. **Accounting for the patient needs** is also an important factor for ensuring patient satisfaction and consequently successful prevention plans. Indeed, acceptance rates and user satisfaction are not only dependent on technical aspects, but also to a great extent on social and psychological factors. There is often considerable unconsciousness among the actors (engineers, users, occupational therapists, health care professionals, politicians, researchers) that hinders communication, exchange of concepts, knowledge, and meaning. There is a need to incorporate user engagement into design processes for prosthetic limbs. These are also important aspects that I have already started to integrate within my research and that I will continue to investigate.

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Part III

Administrative requirements

CHAPTER 9

CURRICULUM VITAE

9.1 Curriculum Vitae

PERSONAL INFORMATION

ROHAN Christian Pierre-Yves

Date of birth: 18/10/1986

Nationality: French

ORCID ID: [0000-0001-6171-7724](https://orcid.org/0000-0001-6171-7724)

Scopus Author Identifier: [55920714100](https://scopus.com/authid/detail.uri?authorid=55920714100)

Google Scholar Profile : https://scholar.google.com/citations?user=IG_9-3AAAAAJ&hl=en

Personal website: <https://sites.google.com/site/cpyrohan/>

ACCADEMIC POSITIONS

- 2014-present Assistant Professor at [École Nationale Supérieure d'Arts et Métiers \(ENSAM\)](#) in Paris, France, at [Institut de Biomécanique Humaine Georges Charpak \(IBHGC\)](#)
- 2013-2014 Postdoctoral position, research on computer-guided surgery of the tongue. Computer Assisted Medical Interventions team, [TIMC-IMAG](#) laboratory, Grenoble, France. Supervisors: [Yohan PAYAN](#) and [Pascal PERRIER](#)

EDUCATION

- 2010 - 2013 PhD in mechanical engineering, [École Nationale Supérieure des Mines, Saint-Étienne](#), France, "*Biomechanical response of lower leg veins to Medical Elastic Compression*". PhD Supervisor: [Stéphane AVRIL](#) (ERC-2014-CoG-BIOLOCHANICS). Co-advisor: Pierre BADEL (ERC-2014-StG-AArteMIS). Industrial Collaboration: [SIGVARIS](#).
- 2009 - 2010 Double Degree Master's programme, [ENSEIRB-MATMECA/IPB](#) engineering degree and Master of Science in Mechanical engineering of the University of Science and Technology Bordeaux-1, Bordeaux, France

Research internship (02/2010 - 09/2010) at the ISML, [University Of Western Australia](#) (Perth, Australia) on "*Galerkin Meshless method for modeling soft tissue damage*". Supervisors: [Karol MILLER](#) and [Adam WITTEK](#).

AWARDS

- 2021 **Young Researcher Award of the "Société de Biomécanique"** (society for French-speaking biomechanical engineers)
- 2019 Research and doctoral supervision award ("Prime d'encadrement doctoral et de recherche") awarded by the Ministry of Higher Education and Research.

INTERNATIONAL SCIENTIFIC RESPONSIBILITIES

- 2021-2023 Chair of the *"Research Committee"* of the European Pressure Ulcer Advisory Panel (EPUAP) <https://www.epuap.org/organisation/#executiveboard>
- 2022 Guest editor for a Special Issue of **Clinical Biomechanics** on "Biomechanics of Breast Tissues and its Clinical Applications"

INTERNATIONAL TRAINING AND NETWORKING

- 2022 **Cruciblist for the European Crucible 2022**

ORGANIZATION OF INTERNATIONAL SCIENTIFIC MEETINGS

- 2023 Organizing committee of the 18th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering (CMBBE2023) Paris, France.
- 2022 Co-moderator (with **Yohan PAYAN**) of the *Breast Biomechanics in Health and Disease* session of the *Organ Biomechanics* Track at the 9th World Congress of Biomechanics (WCB2022), <https://www.wcb2022.com/programModer.asp>, Taipei, Taiwan.
- 2022 Co-chair of the *"Biomechanics Committee"* of the 25th French Mechanics Congress, <https://cfm2022.fr/themes-scientifiques/s2-biomecanique>, Nantes, France.
- 2015 Organizing committee of the 40th edition of the Congress of the Société de Biomécanique (SB2015), <https://sb2015-paris.sciencesconf.org/>, Paris, France.
- 2013 Organizing committee of the Euromech colloquia *534-Advanced experimental approaches and inverse problems in tissue biomechanics*, <https://euromech.org/colloquia/2012/534>, Saint-Etienne, France.

OUTSIDE EXAMINATOR IN PhD EVALUATION COMMITTEE

- 2022 Outside examiner in the PhD defense of Mechanical engineering of Juan Deyo MAEZTU-REDIN. Thesis title: *"Mechanics of hydrogel fibers and of their assemblies for the design of biological tissue substitutes with high resistance"*
- 2021 Outside examiner in the PhD defense of Mechanical engineering of Elaheh ELYASI. Thesis title: *"Biomechanical modeling of the knee joint for computer assisted medical interventions"*
- 2019 Outside examiner in the PhD defense of Mechanical engineering of Venkat Siva Radha Krishna AYYALASOMAYAJULA. Thesis title: *"3-D reconstruction of micro-scale mechanical state of the abdominal aortic aneurysm wall"*

IMPLICATION IN ENSAM

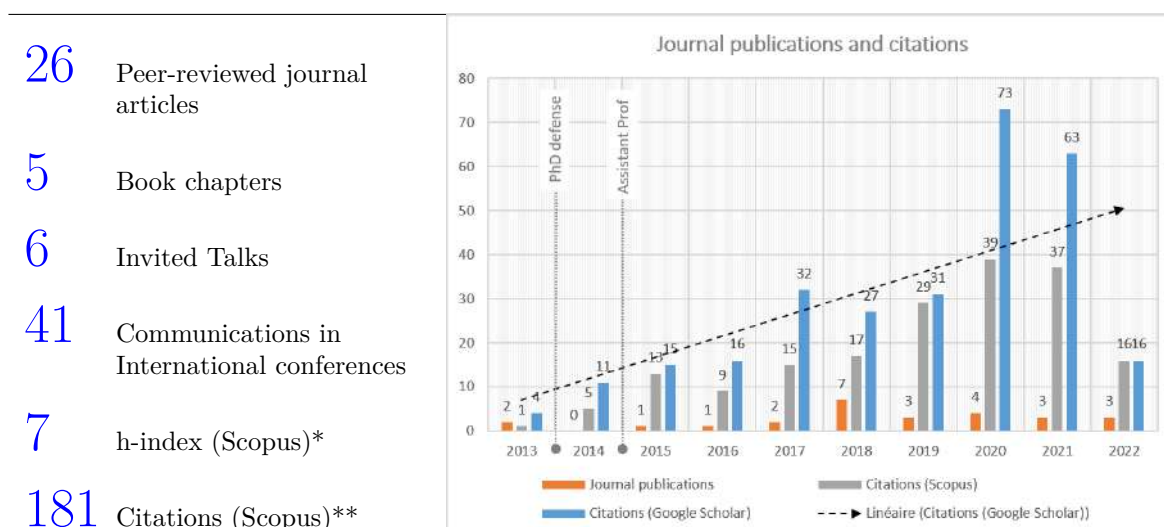
Sept 2022-	Academic coordinator in charge of the ENSAM exchange programme with the USA
2021-present	Member of the Arts et Métiers High Performance Computing Center Cassiopee 's Scientific and Users committee.
2021-present	co-chair (with H�el�ene PILLET and Yannick TILLIER) the "Health Science" subtrack of the BioMechanics (BioMECH) track of the Biomedical Engineering Paris Master�s programme
2020-present	Scientific animation of weekly seminars at Institut de Biom�canique Humaine Georges Charpak (IBHGC)

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

2014-present	Soci�t� de Biom�canique
2014-2020	European Society of Biomechanics
2018-present	European Pressure Ulcer Advisory Panel Executive Board (2021-2024)
2022-present	Association Francaise de M�canique
2022-present	International Society for Porous Media

SCIENTIFIC PRODUCTION

Table 9.1 below summarizes the scientific production (journal publications and citations according to both Scopus and Google citations). For the complete list of publications, the reader is referred to Appendix 11 (section 11.1 for journal publications (P), section 11.2 for book chapters (BC), section 11.3 for invited talks (IT), section 11.4 for conference proceedings (CP) in journals with peer-review and section 11.5 for conference abstracts (CA) without peer-review (CP)). The link to the different communications is also available from my personal website <https://sites.google.com/site/cpyrohan/>




Last update : 01/03/2022 | * h-index (Google Citation): 10 | ** Citations (Google Citation): 288

Table 9.1: Scientific publications and citations according to both Scopus and Google citations.




9.2 Co-Supervision

CO-SUPERVISION OF POSTDOCTORAL FELLOWS



	09/2016- 12/2017	Jamie FRAME	Rachele ALLENA (40%), Laurent CORTE (30%), Pierre-Yves ROHAN (30%)	[P10, P14, CA12]
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CO-SUPERVISION OF GRADUATE (PhD) STUDENTS






Upcoming PhD students (funding secured for Jérôme HADDAD and PhD candidate on ANR IMPRINT)

	09/2022- 09/2025	Thomas LAVIGNE	Pierre-Yves ROHAN (35%), Giuseppe SCIUMÈ (35%) Stéphane BORDAS (30%)	
	09/2022- 09/2025	Jérôme HADDAD	Pierre-Yves ROHAN (25%), Agnès HARTEMANN (25%), Georges HA VAN (25%), Antoine PERRIER (25%)	
	09/2022- 09/2025	To be recruited on ANR IMPRINT PROJECT 3.3	Hélène PILLET (30%), Xavier BONNET (35%), Pierre-Yves ROHAN (35%)	

Current PhD students

	09/2021- 09/2024	Alexandre SEGAIN	Hélène PILLET (40%), Giuseppe SCIUMÈ (30%), Pierre-Yves ROHAN (30%)	
	09/2019- 11/2022	Ekaterina MUKHINA	Yohan PAYAN (40%), Nathanael CONNNESSON (30%), Pierre-Yves ROHAN (30%)	[P25, CP6, CA23, CA27]

Past PhD Students

	11/2018- 03/2022	Stéphane URCUN	Wafa SKALLI (25%), Stéphane BORDAS (25%), Giuseppe SCIUMÈ (25%), Pierre-Yves ROHAN (25%)	[P26, P23, CP8, CA32, CA25, CA24]
	09/2017- 12/2020	Nolwenn FOUGERON	Hélène PILLET (30%), Xavier BONNET (35%), Pierre-Yves ROHAN (35%)	[P20, BC5, CP7, CA30, CA26, CA21, CA18]
	09/2017- 12/2020	Bhriгу LAHKAR	Wafa SKALLI (35%), Patricia THOREUX (35%), Pierre-Yves ROHAN (30%)	[P22, P21, CA22, CA17]
	11/2015- 03/2019	Aurélien MACRON	Hélène PILLET (50%) Pierre-Yves ROHAN (50%)	[P18, P13, P12, P11, CP4, CA20, CA16, CA15, CA14, CA11, CA9]
	09/2014- 12/2017	Virginie RAMPAL	Wafa SKALLI (35%), Philippe WICART (35%), Pierre-Yves ROHAN (30%)	[P19, P8, P7, CA7]

CO-SUPERVISION OF UNDERGRADUATE STUDENTS

As part of the **Biomedical Engineering Paris Master's programme**, I co-supervise 1 to 2 research project students each year : Theo NANICHE (2022), Pauline ALGOURDIN (2022), Léa CHALANQUI (2022), Pierre MARTINOT (2022), Thomas LAVIGNE (2021) [P26, CP8, A32], Maher ABOU KARAM (2021) [P25], Fabien TATIN (2021), Guillaume REBEYRAT (2020), Audrey BERRIOT (2020) [BC5], Nicolas RUYSSSEN (2019), Mohammed Javad SADEGHINIA (2018) [P13], Jennifer DORIDAM (2018) [P13], Zahrasadat MAHDIANSADR (2017), Mikael FONSECA (2017) [P13], Bhriugu LAHKAR (2017) [A13], Nolwenn FOUGERON (2017) P11, CA16], Etienne LEMERCIER (2016), Stan DURAND (2016) [P15], Mayra MORA ESPINOSA (2016), Rebekah SAKSIK (2016) [P8], Guillaume SAUTIERE (2015) [CA4], Leopold ROBICHON (2015) [CA5].

As part of collaborations, I have also co-supervised the M1 research internship of Manon BLAISE (2018, Collaboration with **Franz CHOULY** of the Laboratoire de Mathématiques de Besançon, Université Bourgogne Franche-Comté) and the M2 research internships of Marie VIOLLEAU (2018, collaboration with Eric Monteiro of the Laboratoire PIMM - ENSAM Paris).

REVIEWING ACTIVITIES

Table 9.2 below summarises my participation to peer review processes. Part of these have been verified and recorded on **publon website**.





	IEEE Transactions on Biomedical Engineering (IF: 4.538) N=3		Annals of Biomedical Engineering (IF: 3.934) N=3
	Sensors (IF: 3.576) N=2		Journal of Tissue Viability (IF: 2.932) N=3
	Journal of Elasticity (IF: 2.085) N=1		Journal of Biomechanics (IF: 2.712) N=2
	International Journal for Numerical Methods in Biomedical Engineering (IF: 2.747) N=4		Medical & Biological Engineering & Computing (IF: 2.602) N=3
	Clinical Biomechanics (IF: 1.624) N=1		Computer Methods in Biomechanics and Biomedical Engineering (IF: 1.763) N=2
	Scientific reports - Nature (IF: 4.380) N=2		Journal of Medical Imaging (IF: 4.7) N=1

Table 9.2: Summary of peer review participation. Last update : 01/03/2022. IF: Impact Factor.

TEACHING ACTIVITIES

Table 9.3 summarizes the teaching activities I realised since I joined the IBHGC. The hours indicated below correspond to the equivalent in terms of hours of tutorials ("Heures Equivalent TD", HETD). For a more detailed description, the reader is referred to Appendix 10.

2020-2021	326 h
2019-2020	276 h
2018-2019	348 h
2017-2018	408 h
2016-2017	437 h
2015-2016	460 h
2014-2015	283 h

Table 9.3: Summary of teaching activities since I joined the IBHGC in 2014.

Since 2021, I co-chair (with H el ene PILLET and Yannick TILLIER) the "Health Science" subtrack of the **BioMechanics (BioMECH)** track of the **Biomedical Engineering Paris Master's programme**.

INDUSTRIAL CONTRACTS AND SUBCONTRACTING

2022-2023	LIGA2BIO	Functional evaluation of Anterior Cruciate Ligament grafts in pre-clinical animal models	PI: Pierre-Yves ROHAN
2022	Clinical request	Biomechanical evaluation of humeral component sizing on humeral bone mechanical response	PI: Pierre-Yves ROHAN and Claudio VERGARI
2020-2022	ANR LIGAGEL 2	Functional evaluation of Anterior Cruciate Ligament grafts in pre-clinical animal models	PI: Pierre-Yves ROHAN
2017	GTX Medical	Preliminary Finite Element Analyses	PI: Pierre-Yves ROHAN
2014-2016	ANR LIGAGEL 1	Functional evaluation of Anterior Cruciate Ligament autografts in pre-clinical animal models	PI: H�el�ene PILLET

9.3 Grants

RESEARCH GRANTS AND FUNDINGS

2022-2023	Travel grant	INSIS PEPS on <i>Computer-Assisted Surgery and Prevention with Calculation Adaptation</i> . PI: Michel DUPREZ	face-to-face meetings
2022-2025	Funding of 1 PhD	ANR IMPRINT <i>Individualized Manufacturing from fully digital PRocesses : human / orthopaedic device INTerfaces</i> . PI: H�elene PILLET and Laurine CALISTRI	Co-supervision of 1 PhD (To be recruited)
2022-2025	Funding of equipment and 1 MSc	Institut Carnot ARTS AD-DICT <i>Structural materials Aging and Damage study using high resolution DIC Technique Applications to an elastomer and to the intervertebral disc</i> . PI: Halim HADDAD	Co-supervision of 1 MSc (To be recruited)
2020-2022	10 k�	EPUAP research project collaboration funding on the <i>preliminary evaluation of the clinical relevance of generating biomechanical models from freehand Ultrasound for monitoring internal tissue strains for the prevention of Pressure Ulcers</i> . PI: Pierre-Yves ROHAN	MRI acquisitions and face-to-face meetings
2018-2022	Funding of 1 PhD	H2020-MSCA-ITN-2018 STINTS: Skin Tissue Integrity under Shear on the <i>Experimental and numerical approaches to biomechanical modelling of gluteal soft tissue</i> . PI: Yohan PAYAN	Co-supervision of 1 PhD (E. MUKHINA)
2018-2021	Funding of 1 PhD	ENSAM "R�seau sant�" <i>Mechano-biology of tumor growth with the aim of clinical application, a reactive multiphase poromechanical approach</i> . PI: Wafa SKALLI and St�phane BORDAS	Co-supervision of 1 PhD (S. URCUN)
2016-2019	Funding of 1 PhD	Fondation Arts et M�tiers <i>Contribution to modelling the human-machine mechanical interface in the full-body exoskeleton EMY developed by CEA LIST</i> . PI: H�elene PILLET	Co-supervision of 1 PhD (A. MACRON)
2016-2018	40 k�	Fondation de l'Avenir funding on the <i>Development of a monitoring tool of the subdermal soft tissue deformation for the prevention of pressure ulcers</i> . PI: H�elene PILLET	Co-supervision of 3 MSc (J. DORIDAM, M. J. SADEGHINIA, N. FOUGERON)
2016-2017	Funding of 1 Post-Doc	"Coup de pouce" funded by the F�d�ration Francilienne de M�canique, <i>Modelling the osseointegration of hydrogel implants</i> . PI: Rachele ALLENA	Co-supervision of 1 Post-Doc (J. FRAME)
2014-2016	Travel grant	R�gion Bourgogne-Franche-Comt� funding on <i>Mathematical models and numerical methods for non-linear elasticity and multiphysics couplings</i> . PI: Franz CHOULY	face-to-face meetings

9.4 Synthesis: Narrative CV

To align with the principles of the [Declaration on Research Assessment \(DORA\)](#) that research (and researchers) should be more fairly evaluated on the scientific vision, appropriate experience, and contributions to science and society, instead of solely metrics, journal names, and other information that does not fully represent the potential, value and impact of a research (and researchers), a narrative CV is proposed in this section to support a broader and more nuanced evaluation.

I started my training in research during my final year project in 2010 at the [University Of Western Australia](#) (Australia). I had the pleasure of working for 6 months on the development of an algorithm based on the "*Galerkin Meshless method for modeling soft tissue damage*" under the supervision of [Karol MILLER](#) and [Adam WITTEK](#). Following this first very positive experience, I continued with a PhD thesis at the École Nationale Supérieure des Mines, Saint-Étienne in working in the development of methods to evaluate the "*biomechanical response of lower leg veins to Medical Elastic Compression*" under the supervision of [Stéphane AVRIL](#) and Pierre BADEL (ERC-2014-StG-AArteMIS) and in collaboration with [SIGVARIS](#), the market leader of the manufacture of medical compression garments. Followed a one year of postdoctoral research at the [TIMC-IMAG](#) laboratory of University Grenoble Alpes in France on the *development of a biomechanical model of the oral cavity for preoperative planning of tongue operations* under the supervision of [Yohan PAYAN](#) and [Pascal PERRIER](#). These two experiences in the academic research environment were periods of personal fulfilment and confirmed that laboratory research corresponded to my expectations.

I was recruited in October 2014 at the [Institut de Biomécanique Humaine Georges Charpak](#) (IBHGC) of [Arts et Métiers](#) as an assistant professor in biomechanics. Very quickly I became interested in the problem of prevention of biological soft tissue injuries. In the framework of Aurélien MACRON's PhD thesis (2016-2019), we proposed an original method for the fast generation of patient-specific Finite Element models of the buttock [[P12](#), [P18](#)] which received the [Journal of Clinical Biomechanics Award](#) during the 2018 EPUAP conference. In the PhD work of Nolwenn FOUGERON (2017-2020) an original methodology was proposed for modelling the interaction between the residual limb and the socket for characterizing the transmission of mechanical loads and for investigating the consequences for tissue viability and integrity [[P20](#)] (CIFRE fellowship, collaboration with [PROTEOR](#), the French leader in Prosthetic and Orthotic).

I am currently pursuing this research towards the development of personalized multi-scale multi-physics model of the subcutaneous tissues response during interactions with support surfaces. The *objective is to develop new modelling philosophies and methodologies to achieve forward-multi-physics simulations explicitly including cell-level behaviors in tissue-level models for predicting initiation of soft tissue injury and, expressly, the onset of Stage I Pressure Ulcer following the exposure of the skin to prolonged external loads at the skin interface*. In that context, I recently co-supervised the PhD thesis of Stéphane URCUN (Collaboration with [Giuseppe SCIUMÈ](#) and [Stéphane BORDAS](#)) on the *development of methods for the simulation of tumor growth using a reactive multiphase poromechanical approach* [[P26](#), [P23](#)] and the Postdoc of Jamie FRAME [[P10](#), [P14](#)] (collaboration with [Rachele ALLENA](#) and [Laurent CORTE](#)) on the development of a mechano-biological model of multi-tissue evolution in bone for the simulation of the osseointegration of hydrogel implants. The IBHGC also joined the European H2020 Integrated Training Network project *STINTS (Skin Tissue Integrity under Shear)* and, in that context, I currently co-supervise (with [Yohan PAYAN](#) and Nathanael CONNNESSON) the PhD thesis of MUKHINA on the *Experimental and numerical approaches to biomechanical modelling of gluteal*

soft tissue [P25]. In an attempt to foster the development of computational models from data that can be obtained in clinical routine (US-based computer models), we applied and recently obtained an **EPUAP research project collaboration** funding on the *preliminary evaluation of the clinical relevance of generating biomechanical models from freehand Ultrasound for monitoring internal tissue strains for the prevention of Pressure Ulcers* (collaboration with **Yohan PAYAN** and **Bethany KEENAN**).

Interacting with the clinical partners opened my eyes on the importance of doing research with the patient as the central focus. This was a very inspiring and I would like to be more involved in the development of education framework that will incorporate the key topics related to pressure ulcers and the promotion of international research collaborations and internationally excellent research. As part of this motivation, I recently applied for and now chair (2021-2023) the **Research Committee** of the **European Pressure Ulcer Advisory Panel (EPUAP)**. The EPUAP was created in London in December 1996 to lead and support all European countries in the efforts to prevent and treat pressure ulcers. As chair of the Research Committee, my role is to provide the Executive Board of EPUAP with independent advice on issues relating to the development and delivery of a research strategy which promotes international research collaborations and internationally excellent research.

CHAPTER 10

TEACHING

10.1 BME-Paris Master's programme

[Introduction to Solid Mechanics \(Moodle link\)](#)

Course Supervisor: Pierre-Yves ROHAN

This module introduces students to solid mechanics: continuous description of a solid, definition of strain and stress tensors, equilibrium, constitutive relation, principle of minimum potential energy and complimentary potential energy, principle of virtual work, beam model and relation with the 3D model. The theory is currently applied to the quantification of the shear plane tissue motion using ultrasound imaging and Digital Image Correlation (figure 10.1 below).

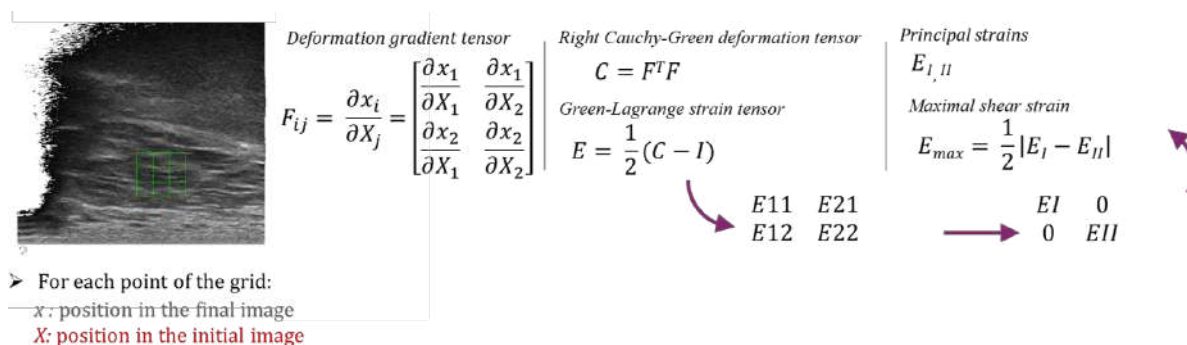


Figure 10.1: Practical application of the theory to quantification of the in-plane tissue motion using ultrasound imaging and Digital Image Correlation based on the data collected in [P13].

[Statistics, Methodology & Literature Review \(Moodle link\)](#)

Course Supervisors: Floren COLLOUD and Pierre-Yves ROHAN

The main objective is to introduce research methodology so that students can communicate science efficiently both orally and written (publications, master's thesis, conference, etc). The module consists of two main sections. The first section introduces the purpose, processes and methodologies of research projects. It aims at increasing their knowledge of academic standard practices (using bibliography tools, writing a research introduction and presenting scientific work orally). The second section focuses on basic statistical tools for quantitative research and more specifically on statistical hypothesis testing, with practicals using R programming language.

Introduction to Modeling and Simulation in Biomechanics (Linear FEM) (Moodle link)

Course Supervisor: Pierre-Yves ROHAN

The objective is to summarize modern and effective Finite Element procedures for the linear analyses of static problems with applications in biomechanics. The material that will be discussed includes the basic finite element formulations (Principle of Virtual Work, local balance of momentum, etc), the effective implementation of these formulations in computer programs (MATLAB and ABAQUS), and recommendations on the actual use of the methods in engineering practice. The prerequisite of the lecture is Continuum mechanics (linear elasticity). The theory is applied to the design and analysis of a prosthesis hip joint in plexiglass ("birefringent" material) using the ABAQUS (figure ??). The FE results are evaluated against compression tests inspired from the ASTM F2996 - 13 standard.

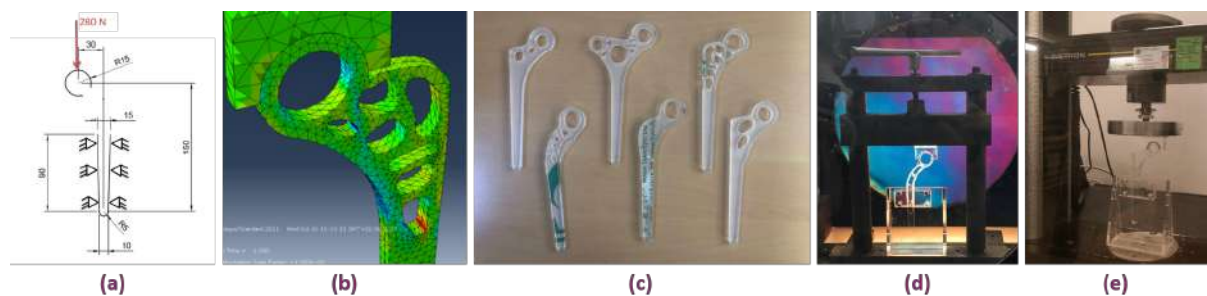


Figure 10.2: (a) Geometrical constraints and boundary conditions to be satisfied (b) Finite Element Analysis (c) prototyping of the solutions using machining of plexiglass (d) Photoelasticimetry for mapping experimental strain fields (e) compression tests inspired from the ASTM F2996 - 13 standard.

Advanced course on Modeling and Simulation in Biomechanics (Non-linear FEM) (Moodle link)

Course Supervisors: Wafa Skalli and Pierre-Yves ROHAN

The objectives of the Non-Linear computational biomechanics course aim to present the basic principle of virtual work equation and the incremental solution approach for the nonlinear finite element analysis of solids and structures (incremental stress and strain decompositions in the total Lagrangian form of the principle of virtual work (figure 10.3(a)), Solution of Nonlinear Static Dynamic FE Equations, mixed u/p formulation, Contact Non-Linearities). The theory will be applied to simulate the nonlinear static response of buttock soft tissue during quasi-static compression 10.3(b-c)).

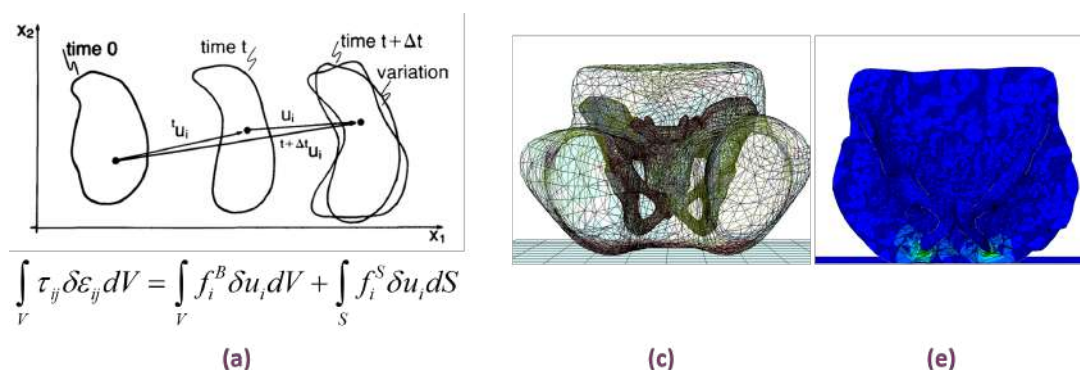


Figure 10.3: (a) Continuum mechanics Total and Updated Lagrangian formulation (b) simulation of the nonlinear static response of buttock soft tissue during quasi-static compression based on the data collected in [P12]

Mechanical behavior of biological tissues ([Moodle link](#))

Course Supervisors: Floren COLLOU and Pierre-Yves ROHAN

The aim of mechanics of biological tissues is to provide a deeper understanding of tissue structure and function by considering the mechanics of both soft and hard tissues. This involves experimental, microstructural, continuum mechanical and computational approaches. The lectures will discuss the composition and structure of biological tissues to explain and justify the mechanical properties. Experimental methods and issues specific to biological tissues will be taught. Finally, methods for identification of parameters for mechanical models will be introduced. In particular, a practical work will be conducted to characterise the 3D material response of porcine jugular vein (10.4) by means of Strain-Energy Density Functions following the principle of pseudo-elasticity introduced and based on experimental Inflation/extension test data.

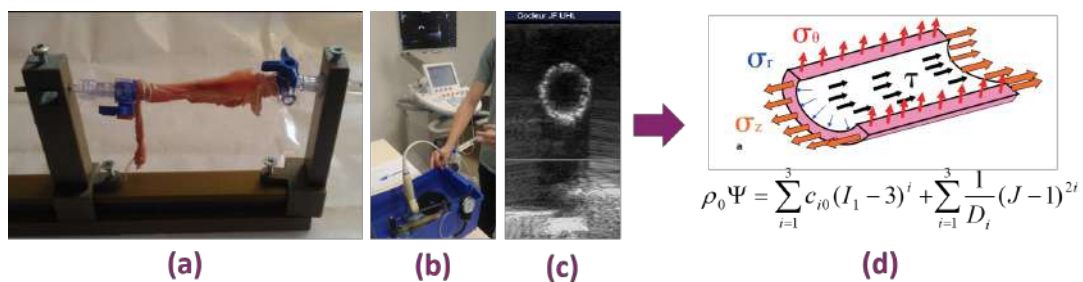


Figure 10.4: (a-b) Custom-made 3D printed setup. Close-up on vein sample and global view (c) Ultrasound image (d) Inverse problem. The goal is to compute the parameters C_{10} , C_{20} , C_{30} of the Yeoh Strain Energy Density Function from experimental data

Mechanics of Complex Materials and modelling ([Moodle link](#))

Course Supervisors: Yannick TILLIER and Pierre-Yves ROHAN

The objective is to present the nonlinear theory of continuum mechanics required for the modeling of the elastic properties of soft biological tissues, with particular reference to the fiber structure of such tissues. The theory will be applied to the calibration of anisotropic hyperelastic material model parameters of aortic Valve leaflets with experimental data obtained from ex vivo biaxial tests (practical session figure 10.5). Recent developments aiming at the characterization of the microstructure of Intervertebral Disc tissue and skin tissue will also be explored.

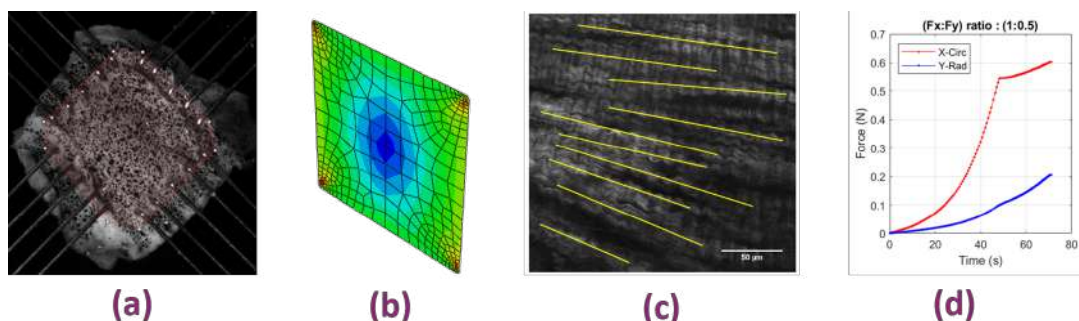


Figure 10.5: (a) Experimental measurements acquired during the PhD work of Colin LAVILLE ([Laville 17](#)). Sample mounted on the biaxial tensile device with speckle pattern (b) Numerical model of rectangular membrane submitted to biaxial conditions provided (c) Local fiber orientations and dispersion obtained from confocal microscopy in ([Laville 17](#)) (d) Response predicted by the FE model.

10.2 ENSAM "Bioengineering" Expertise

ENSAM "Bioengineering" Expertise ([ENSAM link](#))

Course Supervisor: Xavier BONNET

The objective of this lecture is to train ENSAM engineers in the field of health technologies and prepare future engineers to be able to formalize the problems specific to the fields of biomechanics and the professional environment specific to medical devices. The lectures will cover 1/ a presentation of the medical device industry sector 2/ Kinematic and kinetic analysis of motion 3/ Mechanical modeling of the human body 4/ Bio materials 5/ Biomechanical injury and traumatology 6/ Anatomy 7/ Medical imaging and geometric modeling. These lectures will be applied during practical exercises, carried out using the IBHGC's equipment. The courses will also be put into practice during the realization of mini-projects, carried out in partnership with industrialists who have proposed the problem: design of prostheses, exoskeletons or evaluation systems.



Figure 10.6: Design and 3D printing of a Polycentric Prosthetic Knee Joint

10.3 ENSAM Apprenticeship programme

Introduction to Statistics

Course Supervisors: Xavier BONNET and Pierre-Yves ROHAN

The goal of this course is to introduce the basic concepts that allow us to understand and formulate a statistical inference problem. The lectures aim to provide the tools to solve the most standard problems in statistics (in its classical approach). At the end of this course, students should be comfortable with fundamental statistical concepts (sampling, point estimation, interval estimation and hypothesis testing). These concepts will be illustrated in the following classical applications: ANOVA, linear regression, Chi-square tests. The goal is not to turn students into future statisticians but to give them a technical and intuitive understanding of (basic) statistical analysis applied to engineering.

CHAPTER 11

PUBLICATION LIST

Last update of the citation metrics : 01/02/2022. The following prefixes are used P : Journal publications, BC : Book Chapters, IT : Invited Talks, CP : Conference Proceedings in journals with peer-review, CA : Conference Abstracts without peer-review.

11.1 Peer-reviewed journal articles

2022

- [P27] *Impact of the ischial support in ischial containment socket on the stump-socket interaction: a finite element study*, Nolwenn Fougeron, **Pierre-Yves Rohan**, Jean-Loic Rose, Xavier Bonnet, H el ene Pillet, Medical Engineering and Physics, accepted, Volume n/a, pp n/a
#Citations (scopus) = 0
- [P26] *Numerical investigation of the time-dependent stress-strain mechanical behaviour of skeletal muscle tissue in the context of Pressure Ulcer prevention*, Thomas Lavigne, Giuseppe Scium e, Sebastien Laporte, H el ene Pillet, St ephane Urcun, Benjamin Wheatley, **Pierre-Yves Rohan**, Journal of Clinical Biomechanics, March 2022, Volume 93, pp n/a
#Citations (scopus) = 0
- [P25] *Reliability of B-mode Ultrasound and shear wave elastography in evaluating sacral bone and soft tissue characteristics in young adults with clinical feasibility in elderly*, Maher Abou Karam, Ekaterina Mukhina, Nils Daras, Isabelle Rivals, H el ene Pillet, Wafa Skalli, Nathana el Connesson, Yohan Payan, **Pierre-Yves Rohan**, Journal of Tissue Viability, February 2022, Volume n/a, pp n/a,
#Citations (scopus) = 0
- [P24] *Cortex tissue relaxation and slow to medium load rates dependency can be captured by a two-phase flow poroelastic model*, St ephane Urcun, **Pierre-Yves Rohan**, St ephane P. A. Bordas, Giuseppe Scium e, Journal of the Mechanical Behavior of Biomedical Materials, February 2022, Volume 126, pp n/a
#Citations (scopus) = 0

2021

- [P23] *Digital twinning of Cellular Capsule Technology: emerging outcomes from the perspective of porous media mechanics*, St ephane Urcun, **Pierre-Yves Rohan**, Wafa Skalli, Pierre Nassoy, St ephane P. A. Bordas, Giuseppe Scium e, July 2021, PLoS ONE, Volume 16(7):e0254512
#Citations (scopus) = 0

- [P22] *Development and evaluation of a new methodology for Soft Tissue Artifact compensation in the lower limb*, Bhrigu K. Lahkar, **Pierre-Yves Rohan**, Ayman Assi, H el ene Pillet, Xavier Bonnet, Patricia Thoreux, Wafa Skalli, Journal of Biomechanics, June 2021, Volume 122:110464
#Citations (scopus) = 0
- [P21] *Development and evaluation of a new procedure for subject-specific tensioning of finite element knee ligaments*, Bhrigu K. Lahkar, **Pierre-Yves Rohan**, H el ene Pillet, Patricia Thoreux, Wafa Skalli, Computer Methods in Biomechanics and Biomedical Engineering, January 2021, Volume 24(11), pp 1195-1205,
#Citations (scopus) = 1
- 2020
- [P20] *Combining Freehand Ultrasound-Based Indentation and Inverse Finite Element Modelling for the Identification of Hyperelastic Material Properties of Thigh Soft Tissues*, Nolwenn Fougeron, **Pierre-Yves Rohan**, Diane Hearing, Jean-Lo ic Rose, Xavier Bonnet, H el ene Pillet, Journal of Biomechanical Engineering, September 2020, Volume 142(9):091004
#Citations (scopus) = 2
- [P19] *Combined 3D analysis of morphology and function of the clubfoot lower-limb: a preliminary study*, Virginie Rampal, **Pierre-Yves Rohan**, H el ene Pillet, Aurore Bonnet-Lebrun, Mickael Fonseca, Eric Desailly, Philippe Wicart, Wafa Skalli, Orthopaedics and Traumatology: Surgery and Research, November 2020, Volume 106(7), Pages 1333-1337
#Citations (scopus) = 1
- [P18] *Is a simplified Finite Element model of the gluteus region able to capture the mechanical response of the internal soft tissues under compression?* Aur elien Macron, H el ene Pillet, Jennifer Doridam, Isabelle Rivals, Mohammad Javad Sadeghinia, Alexandre Verney, **Pierre-Yves Rohan**, Clinical Biomechanics, January 2020, Volume 71, Pages 92-100
#Citations (scopus) = 0
- [P17] *Quantifying discretization errors for soft-tissue simulation in computer assisted surgery: a preliminary study*, Michel Duprez; St ephane Bordas; Marek Bucki; Huu Phuoc Bui; Franz Chouly; Vanessa Lleras; Claudio Lobos; Alexei Lozinski; **Pierre-Yves Rohan**; Satyendra Tomar, Applied Mathematical Modelling, January 2020, Volume 77(1), Pages 709-723
#Citations (scopus) = 12
- 2019
- [P16] *Microstructural characterization of annulus fibrosus by ultrasonography: a feasibility study with an in vivo and in vitro approach*, Tristan Langlais, Pierre Desprairies, Raphael Pietton, **Pierre-Yves Rohan**, Jean Dubouset, Judith R. Meakin, Peter C. Winlove, Raphael Vialle, Wafa Skalli, Claudio Vergari, Biomechanics and Modeling in Mechanobiology, June 2019, Volume 18, Pages 1979-1986
#Citations (scopus) = 2
- [P15] *Passive wrist stiffness: The influence of handedness (link broken)*, Stan Durand, **Pierre-Yves Rohan**, Taya Hamilton, Wafa Skalli, Hermano Igo Krebs, IEEE Transactions on Biomedical Engineering, Volume 66(3), March 2019, Pages 656-665
#Citations (scopus) = 5
- [P14] *A mechano-biological model of multi-tissue evolution in bone*, Jamie Frame, **Pierre-Yves Rohan**, Laurent Cort e, Rachele Allena, Continuum Mechanics and Thermodynamics, Volume 31(1), January 2019, Pages 1-31
#Citations (scopus) = 4
- 2018
- [P13] *Feasibility of sub-dermal soft tissue deformation assessed using B-mode ultrasound for pressure ulcer prevention*, Jennifer Doridam, Aurelien Macron, Claudio Vergari, Alexandre Verney, **Pierre-Yves Rohan**, H el ene Pillet, Journal of Tissue Viability, Volume 27(4), November 2018, Pages 238-243
#Citations (scopus) = 2

- [P12] *Development and evaluation of a new methodology for the fast generation of patient-specific Finite Element models of the buttock for sitting-acquired Deep Tissue Injury prevention*, Aurélien Macron, Hélène Pillet, Jennifer Doridam, Alexandre Verney, **Pierre-Yves Rohan**, Journal of Biomechanics, Volume 79, October 2018, Pages 173-180
#Citations (scopus) = 4
- [P11] *Subject Specific Finite Element Mesh Generation of the Pelvis from Bi-Planar X-ray Images: Application to 120 clinical cases*, Nolwenn Fougeron, **Pierre-Yves Rohan**, Aurelien Macron, Christophe Travert, Hélène Pillet, Wafa Skalli, Computer Methods in Biomechanics and Biomedical Engineering, Volume 21(5), July 2018, pages 408-412
#Citations (scopus) = 0
- [P10] *Optimal bone structure is dependent on the interplay between mechanics and cellular activities*, Jamie Frame, **Pierre-Yves Rohan**, Laurent Corté, Rachele Allena, Mechanics Research Communications, Volume 92, September 2018, Pages 43-48
#Citations (scopus) = 2
- [P9] *3D reconstruction of foot in the weight-bearing position from bi-planar X-ray radiographs: Evaluation of accuracy and reliability*, **Pierre-Yves Rohan**, Antoine Perrier, Mira Ramanoudjame, Jerome Hausselle, Henri Lelièvre, Raphael Seringe, Wafa Skalli, Philippe Wicart, Journal of Foot and Ankle Surgery, Volume 57(5), October 2018, Pages 931-937
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- [P8] *Assessing 3D paediatric foot morphology using low-dose biplanar radiography: Parameter reproducibility and preliminary values*, Virginie Rampal, **Pierre-Yves Rohan**, Rebekah Saksik, Philippe Wicart, Wafa Skalli, Orthopaedics and Traumatology: Surgery and Research, Volume 104(7), November 2018, Pages 1083-1089
#Citations (scopus) = 0
- [P7] *Lower-Limb Lengths and Angles in Children Older than Six Years: Reliability and Reference Values by EOS Stereoradiography*, Virginie Rampal, **Pierre-Yves Rohan**, Ayman Assi, Ismat Ghanem, Olivier Rosello, Anne-Laure Simon, Elodie Gaumetou, Valerie Merzoug, Wafa Skalli, Philippe Wicart, Orthopaedics and Traumatology: Surgery and Research, Volume 104(3), May 2018, Pages 389-395
#Citations (scopus) = 7
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- [P6] *Three-dimensional reconstruction using stereoradiography for evaluating adult spinal deformity: a reproducibility study*, Emmanuelle Ferrero, Renaud Lafage, Shaleen Vira, **Pierre-Yves Rohan**, Jonathan Oren, Edward Delsole, Pierre Guigui, Frank Schwab, Virginie Lafage, Wafa Skalli, European Spine Journal, Volume 26 (8), August 2017, Pages 2112-2120
#Citations (scopus) = 11
- [P5] *Finite element models of the human tongue: a mixed-element mesh approach*, **Pierre-Yves Rohan**, Claudio Lobos, Mohammad Ali Nazari, Pascal Perrier, Yohan Payan, Computer Methods in Biomechanics and Biomedical Engineering: Imaging and Visualization, 5:6, March 2016, 390-400
#Citations (scopus) = 4
- 2016
- [P4] *Atlas-Based Automatic Generation of Subject-Specific Finite Element Tongue Meshes*, Ahmad Bijar, **Pierre-Yves Rohan**, Pascal Perrier, Yohan Payan, Annals of biomedical engineering 44 (1), January 2016, Pages 16-34
#Citations (scopus) = 13
- 2015
- [P3] *Prediction of the biomechanical effects of compression therapy on deep veins using finite element modelling*, **Pierre-Yves Rohan**, Pierre Badel, Bertrand Lun, Didier Rastel, Stephane Avril, Annals of biomedical engineering 43 (2), February 2015, Pages 314-324
#Citations (scopus) = 22
- 2013

- [P2] *Finite Element simulation of buckling-induced vein tortuosity and influence of the wall constitutive properties*, Pierre Badel, **Pierre-Yves Rohan**, Stéphane Avril, Journal of the Mechanical Behavior of Biomedical Materials; Volume 26, October 2013, Pages 119â126
#Citations (scopus) = 13
- [P1] *Biomechanical response of varicose veins to elastic compression: A numerical study*, **Pierre-Yves Rohan**, Pierre Badel, Bertrand Lun, Didier Rastel, Stéphane Avril, Journal of biomechanics; Volume 46, Issue 3, February 2013, Pages 599â603
#Citations (scopus) = 27

11.2 Book chapters

- [BC5] *Evaluation of the agreement between Ultrasound-based and bi-planar X-Ray radiography-based assessment of the geometrical features of the Ischial Tuberosity in the context of the prevention of seating-related pressure injury*, Audrey Berriot, Nolwenn Fougeron, Xavier Bonnet, H el ene Pillet, **Pierre-Yves Rohan**, In: Joldes G., Doyle B., Wittek A., Nielsen P., Miller K. (eds) Computational Biomechanics for Medicine. Springer, 2020, accepted
#Citations (scopus) = 0
- [BC4] *Biomechanics of Living Organs: Hyperelastic Constitutive Laws for Finite Element Modeling : Chapter 22 Spine*, S ebastien Laporte, Maxim Van den Abbeele, **Pierre-Yves Rohan**, Clayton Adam, Philippe Rouch, Wafa Skalli, In Biomechanics of Living Organs, edited by Yohan Payan and Jacques Ohayon, Academic Press, Oxford, 2017, Pages 471-495
#Citations (scopus) = 1
- [BC3] *Role of Ligaments in the Knee Joint Kinematic Behavior: Development and Validation of a Finite Element Model*, Fran cois Germain, **Pierre-Yves Rohan**, Goulven Rochcongar, Philippe Rouch, Patricia Thoreux, H el ene Pillet, Wafa Skalli, In: Joldes G., Doyle B., Wittek A., Nielsen P., Miller K. (eds) Computational Biomechanics for Medicine. Springer, 2016, 15-26
#Citations (scopus) = 5
- [BC2] *Patient-specific computational models: Tools for improving the efficiency of Medical Compression Stockings*, Laura Dubuis, **Pierre-Yves Rohan**, S ebastien Avril, Pierre Badel, Johan Debayle, In: Wittek A., Miller K., Nielsen P. (eds) Computational Biomechanics for Medicine. Springer, New York, NY, 2013, 25-37
#Citations (scopus) = 3
- [BC1] *Patient-Specific Modeling of Leg Compression in the Treatment of Venous Deficiency*, S ebastien Avril, Pierre Badel, Laura Dubuis, **Pierre-Yves Rohan**, Johan Debayle, Serge Couzan, Jean-Fran cois Pouget, In: Gefen A. (eds) Patient-Specific Modeling in Tomorrow's Medicine. Studies in Mechanobiology, Tissue Engineering and Biomaterials, Springer, Berlin, Heidelberg, 2012, Vol 9, 217-238
#Citations (scopus) = 7

11.3 Invited Talks

- [IT6] *Finite Element modelling, tissue characterization and inverse Methods to understand the pathways of skin integrity (programme)*, **Pierre-Yves Rohan**, DRIVEN workshop organised as satellite event during the SOFA Week 2021 , Nov 2021.
- [IT5] *Tissue Characterisation and poroelastic modelling for Pressure Ulcer Prevention (twitter)*, **Pierre-Yves Rohan**, 46 eme congr es de la "Soci et e de Biom ecanique", Young Investigator Award, 2021, Oct 2021.
- [IT4] *Synergy between machine learning and multiscale modeling : state of the art and opportunities for (youtube video)*, **Pierre-Yves Rohan**, European Pressure Ulcer Advisory Panel2021 Virtual Meeting, 18 - 19 October 2021, Virtual Event

- [IT3] [State of the art in modelling individual risk of injury in the context of Pressure Ulcer prevention \(youtube video\)](#), **Pierre-Yves Rohan**, National Institute on Disability and Rehabilitation, November 2020
- [IT2] Modelling and innovations for pressure ulcer prevention, **Pierre-Yves Rohan**, Expert Training Day organized by the Société Française de l'escarres, June 2020
- [IT1] Prevention of injury risks through the modelling of human beings in their environment and in their interactions with this environment, **Pierre-Yves Rohan**, Workshop and round table research and innovation: St Hélier 2030 project, June 6 2019

11.4 Conference proceedings in journals with peer-review

- [CP8] [The possible role of poro-elasticity in the apparent viscoelastic behaviour of passive muscle: a case study](#), Thomas Lavigne, Giuseppe Sciumè, Sébastien Laporte, Hélène Pillet, Stéphane Urcun, **Pierre-Yves Rohan**, Computer Methods in Biomechanics and Biomedical Engineering ([pages 320-322 of the pdf](#))
- [CP7] [Prediction of muscle forces in residual limb during walking: comparison of transfemoral and Gritti-Stokes amputations](#), Nolwenn Fougeron, Xavier Bonnet, Brieuc Panhelleux, Jean-Loic Rose, **Pierre-Yves Rohan**, Hélène Pillet, Computer Methods in Biomechanics and Biomedical Engineering, accepted
- [CP6] [Calibration of the fat and muscle hyperelastic material parameters for the assessment of the internal tissue deformation in relation to pressure ulcer prevention](#), Ekaterina Mukhina, **Pierre-Yves Rohan**, Nathanael Connesson, Yohan Payan, Computer Methods in Biomechanics and Biomedical Engineering, accepted
- [CP5] [Femoral residuum/socket kinematics using fusion between 3D motion capture and stereo radiography](#), Brieuc Panhelleux, Nolwenn Fourgeron, Nicolas Ruysen, **Pierre-Yves Rohan**, Xavier Bonnet, Hélène Pillet, Computer Methods in Biomechanics and Biomedical Engineering, Volume 22 (Supp 1), October 2019, Pages S245-S247
- [CP4] [Subject specific hexahedral Finite Element mesh generation of the pelvis from bi-Planar X-ray images](#), Nolwenn Fougeron, Aurelien Macron, Hélène Pillet, Wafa Skalli, **Pierre-Yves Rohan**, Computer Methods in Biomechanics and Biomedical Engineering, Volume 20 (Supp 1), October 2017, Pages S75-S76
- [CP3] [Speech biomechanics: What have we learned and modeled since Joseph Perkell's tongue model In 1974?](#) Pascal Perrier, Yohan Payan, Mohammad Ali Nazari, Nicolas Hermant, **Pierre-Yves Rohan**, Claudio Lobos, Ahamad Bijar, The Journal of the Acoustical Society of America, 2016, 139 (4), 2193-2193
- [CP2] [Finite element modelling of nearly incompressible materials and volumetric locking: a case study](#), **Pierre-Yves Rohan**, Claudio Lobos, Mohammad Ali Nazari, Pascal Perrier, Yohan Payan, Computer methods in biomechanics and biomedical engineering, Volume 17 (sup1), July 2014, Pages 192-193
- [CP1] [Patient-specific modelling of the calf muscle under elastic compression using magnetic resonance imaging and ultrasound](#), Fanny Frauziols, **Pierre-Yves Rohan**, Pierre Badel, Stéphane Avril, Jerome Molimard, Laurent Navarro, Computer methods in biomechanics and biomedical engineering; Volume 16 (Supp 1), August 2013, Pages 332-333

11.5 Conference abstracts without peer-review

- [CA33] [Influence of seated posture on the mechanical response of the internal soft tissues of the gluteus region: Implications for pressure ulcer prevention in adult wheelchair users \(dropbox link\)](#), Bethany Keenan, Valentin Chaplet, Hélène Pillet and **Pierre-Yves Rohan**, 22nd Annual Meeting of the European Pressure Ulcer Advisory Panel, 14 - 16 September 2022, Prague, Czech Republic

- [CA32] [Modelling the apparent viscoelastic behaviour of passive muscle tissue under confined compression using a poroelastic framework \(dropbox link\)](#), Thomas Lavigne, Giuseppe Sciumè, Sébastien Laporte, Hélène Pillet, Stéphane Urcun, **Pierre-Yves Rohan**, 9th World Congress of Biomechanics, July 10-14 2022, Taipei.
- [CA31] [A mixed numerical-experimental approach to evaluate the internal soft tissue response of the heel \(dropbox link\)](#), Bethany Keenan and **Pierre-Yves Rohan**, EUROMECH Colloquium 627, Current challenges in soft tissue mechanics, 6 April à 8 April 2022, Frankfurt, Germany
- [CA30] [Finite element modeling as a tool for predicting pressures at the interface between the residual limb and the femoral socket: comparison of integrated ischium and quadrilateral sockets \(dropbox link\)](#), Nolwenn Fougeron, **Pierre-Yves Rohan**, Jean-Loïc Rose, Xavier Bonnet, Hélène Pillet, ISPO-France 2021, November 4 - 5 2021, Lyon, France
- [CA29] [A wear model to predict reconstructed ACL resistance in vivo and applications to surgery planning in sheep \(book of abstracts\)](#), Deyo Maeztu-Redin, Julien Caroux, **Pierre-Yves Rohan**, Hélène Pillet, Alexia Cermolacce, Julien Trinka, Mathieu Manassero, Véronique Viateau, Laurent Corté, Congres 2021 de l'association Française pour le developpement des biomateriaux (BIOMAT), October 19 - 22 octobre 2021, Bourg Saint-Maurice, France
- [CA28] [A wear model to predict in-vivo damage of ACL grafts \(online abstracts\)](#), Deyo Maeztu-Redin, Julien Caroux, **Pierre-Yves Rohan**, Hélène Pillet, Alexia Cermolacce, Julien Trinka, Mathieu Manassero, Véronique Viateau, Laurent Corté, 31st Conference of the European Society for Biomaterials (ESB2021) together with 43rd Annual Congress of the Iberian Society of Biomechanics and Biomaterials (SIBB) in Porto, Portugal, September 5-9, 2021.
- [CA27] [In vivo experimental characterization of the biomechanical response of sacral soft tissues under compression using both B-mode Ultrasound and MRI : premiliminary assessment on 2 healthy volunteers \(book of abstracts\)](#), Ekaterina Mukhina, **Pierre-Yves Rohan**, Nathanael Connesson, Yohan Payan, European Pressure Ulcer Advisory Panel2021 Virtual Meeting, 18 - 19 October 2021, Virtual Event
- [CA26] [Feasibility of using Freehand Ultrasound imaging to measure anatomical features of the Ischial Tuberosity to improve the design of assistive and rehabilitation devices : US-based versus EOS-based assessment \(book of abstracts\)](#), Audrey Berriot, Andrea Reano, Nolwenn Fougeron, Xavier Bonnet, Hélène Pillet, **Pierre-Yves Rohan**, European Pressure Ulcer Advisory Panel2021 Virtual Meeting, 18 - 19 October 2021, Virtual Event
- [CA25] Multiphase Reactive Poromechanics Modeling Of Non-Operable Glioblastoma IDH Wild Type, Stéphane Urcun, Giuseppe Sciume, **Pierre-Yves Rohan**, Davide Baroli, Ruairidh Howells, Vincent Lubrano, Wafa Skalli, Stephane P.A. Bordas, 16th U.S. National Congress on Computational Mechanics (USNCCM), July 25-29, 2021, Virtual Event
- [CA24] [Brain tissue poro-mechanical modeling: clinical data assimilation and growth simulation of non-operable gliomas \(dropbox link\)](#), Stéphane Urcun, Giuseppe Sciume, **Pierre-Yves Rohan**, Davide Baroli, Ruairidh Howells, Vincent Lubrano, Wafa Skalli, Stephane P.A. Bordas, 14th World Congress on Computational Mechanics (WCCM), ECCOMAS Congress 2020, 19â24 July 2020, Paris, France
- [CA23] [Feasibility of using 2D ultrasound data for building a personalized numerical model of the sacral region for the evaluation of the subject-specific risk of sacral pressure \(book of abstracts\)](#), Ekaterina Mukhina, **Pierre-Yves Rohan**, Nathanael Connesson, Yohan Payan, European Pressure Ulcer Advisory Panel 2020 Virtual Meeting, September 24 2020, Virtual Event
- [CA22] [Contribution to the development of subject specific finite element based musculoskeletal model of the lower limb based on the combination of biplanar x-ray images and gait trials: a comprehensive roadmap \(dropbox link\)](#), Bhrigu k. Lahkar, **Pierre-Yves Rohan**, Hélène Pillet, Patricia Thoreux, Wafa Skalli, CAMS-Knee Workshop 2020, February 4-7 2020, Zurich, Switzerland
- [CA21] [Investigation of the in vivo passive mechanical properties of thigh soft tissues in healthy volunteers using a custom-made freehand ultrasound-based indentation setup \(book of abstracts\)](#), Nolwenn Fougeron, Xavier Bonnet, D Haering, J-L Rose, Hélène Pillet, **Pierre-Yves Rohan**, 21st Annual Meeting of the European Pressure Ulcer Advisory Panel, September 18-20 2019, Lyon, France

- [CA20] Investigation of the buttock soft tissue stiffness at the ischial tuberosity in healthy volunteers using an ultrasound instrumented chair set-up (book of abstracts), Mohammad Javad Sadeghinia, Aurélien Macron, Johan Combe, Xavier Bonnet, H el ene Pillet, **Pierre-Yves Rohan**, 21st Annual Meeting of the European Pressure Ulcer Advisory Panel, September 18-20 2019, Lyon, France
- [CA19] Feasibility of lumbar disc lamellar measurement with in-vivo ultrasonography (book of abstracts), Claudio Vergari, Tristan Langlais, Pierre Desprairies, Raphael Pietton, **Pierre-Yves Rohan**, Jean Dubousset, Judith R. Meakin, Peter C. Winlove, Raphael Vialle, Wafa Skalli, 25th Congress of the European Society of Biomechanics, July 7 - 10 2019, Vienna, Austria
- [CA18] In Vivo Identification of the Mechanical Properties of the Thigh Tissues from Freehand Ultrasound for the Numerical Investigation of loads at the Socket/Residual Limb Interface of Amputee People (dropbox link), Nolwenn Fougeron, Xavier Bonnet, Jean-Loic Rose, **Pierre-Yves Rohan**, H el ene Pillet, 16th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering and the 4th Conference on Imaging and Visualization (CMBBE2019) , August 14-16 2019, New-York, USA
- [CA17] Impact of personalisation of geometry on the passive kinematic response of the knee joint in Flexion-Extension (dropbox link), Bhrigu Lahkar, **Pierre-Yves Rohan**, H el ene Pillet, Patricia Thoreux, Wafa Skalli, 16th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering and the 4th Conference on Imaging and (CMBBE2019), August 14-16 2019, New-York, USA
- [CA16] All-Hex Finite Element Mesh Generation of Soft Tissues of the pelvic region using Polycut for the assessment of the subdermal soft tissue strains responsible for the onset of Deep Tissue Pressure Ulcers (dropbox link), Nolwenn Fougeron, Fran cois Girinon, Aur elien Macron, H el ene Pillet, **Pierre-Yves Rohan**, 8th World Congress of Biomechanics, July 8-12 2018, Dublin
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