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PhD Research and Training proposal

1. EXCELLENCE (4 pages max)

1.1. Pre-proposal's context, positioning and objective(s)

Bones, like many biological materials, are complex architectural composites with several length scales among the elementary building blocks. Through an intricate hierarchical arrangement, a hard mineral phase (carbonated hydroxyapatite, cAp) and a softer organic matrix (type I collagen), as well as water, ions and macromolecules, are efficiently combined at the nanoscale to achieve outstanding mechanical performance, see Fig.1. Identification of the organization and morphology of the mineral phase is still challenging due to the limitations of electron microscopy imaging techniques. It is generally accepted that individual collagen molecules assemble into quarter-staggered arrays to form collagen fibrils, creating overlap and gap zones that produce the characteristic 67 nm periodic banding. These fibrils are mineralized, with cAp crystals being deposited in the gap zones (intra-fibrillar mineralization) and around them (extra-fibrillar mineralization) [5,18].

In mineralized collagen fibrils (MCFs), the interfaces between cAp and collagen (mineral-collagen interfaces, MICs) and between collagen bands (collagen-collagen interfaces, CCIs) are responsible for load transfer from the collagenous matrix to the mineral reinforcement embedded in it and inside the collagenous matrix. A key aspect of this project is the modeling of the contact at these interfaces, which is thought to be not perfect and to play a dominant role in the mechanical behavior of MCFs. Contact modelling in biological architectural materials such as bone or nacre has already been shown to lead to more accurate predictions of their toughness and to a better agreement with experimental data, see for example [1,7,17]. Up to the knowledge of the project's proponents, contact effects in MCFs have been so far exclusively modeled by using cohesive interface models [7,17,20]. These models are typically applied on a bidimensional unit cell, where cAp is localized between collagen bands and cohesive traction-separation laws are imposed at the CCIs and MCIs. The results of these studies are encouraging and should continue to be explored to theoretically identify the primary mechanisms responsible for nanoscale bone toughness and to better reproduce experimental tensile test data on animal and human bone samples. About the importance of further investigation of contact modeling in MCFs, we quote the author of a recent review: *''The existing models can provide reasonable agreement with experiments, but improved predictive performance awaits incorporation of realistic interfaces ''*[18].

The aim of the present project is to improve MCFs modelling by incorporating some contact models proposed by Lebon et al., which incorporate multiphysics and damaging effects arising from a smaller scale [2,3,12–16]. So far, these contact models have been proposed to simulate the load transfer behavior and damage accumulation in structural adhesive, by describing them as imperfect interfaces that incorporate a microstructure of defects evolving under loading. The starting point of the development of these imperfect interface models assumes that the contact between two adherents is realized by an adhesive substance that is micro-cracked and undergoes a degradation process, see Figure 2. The micro-cracks are modelled using a Kachanov-type material description and different constitutive behaviours have been considered for the material constituting the adhesive substance: linear elastic and soft [2,13], linear elastic and hard [12,14], linear elastic with rugosity effects [3], non-linear elastic [14] and multiphysics [15,16]. The method for generating an imperfect contact model is based on an asymptotic analysis carried out on a composite consisting of two surrounding media (adherents) connected by a thin interphase of the adhesive substance. The interphase thickness depends on a small parameter ε and the results calculated at the lowest order in ε of the asymptotic analysis define an original and non-trivial interface model which includes the mechanical properties (elasticity, damage, multiphysics, etc.) of the adhesive.

The versatility of the asymptotic method used in [2,3,12–16] is expected to be particularly advantageous in the MICs and CCIs modeling, because of the possibility of incorporating the principal types of interfacial bonding that are thought to occur at these interfaces, such as molecular entanglement, intermolecular interactions and mechanical interlocking, see Figure 3 [18]. For example, mechanical interlocking could be considered by adding

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rugosity effects, cf. [3]. Intermolecular interactions are typically described by means of an interaction energy, which could be considered in an asymptotic analysis based on a variational formulation, cf. [13].

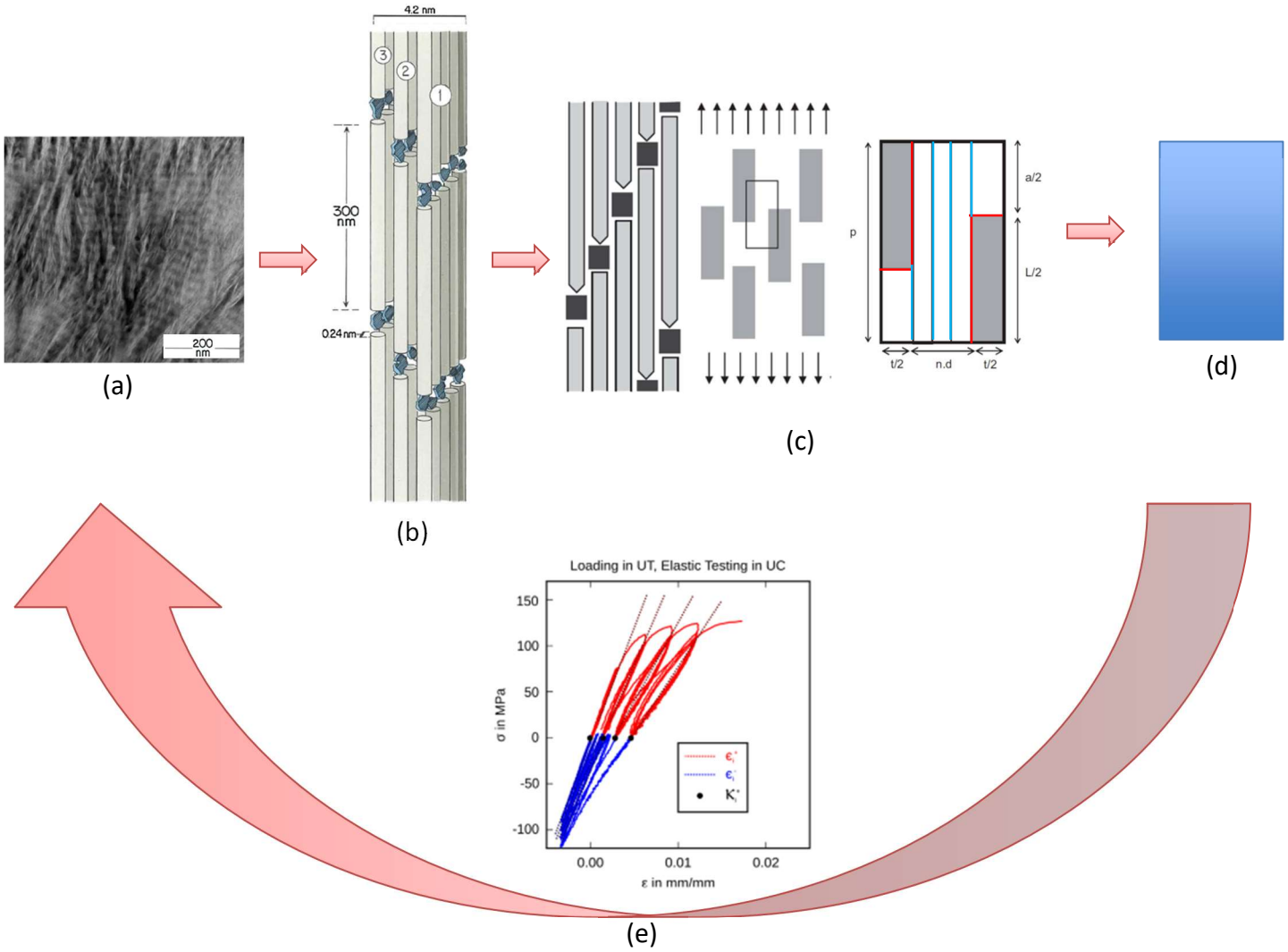

Figure 1. Hierarchical structure of bones and scheme of the research methodology: a) banding pattern observed in osteonal lamellae (source of the image:[5]); b) 3D literature model for arrays of mineralized collagen fibril, showing collagen molecules (white columns) and cAp minerals (in gray) nucleated in the collagen gaps [18]; c) 2D model leading to a simplified 2D representation, with collagen in white and cAp in gray [17]. In this representation, we propose that the unit cell incorporates contact effects (red and blue lines) at the collagen-mineral interface and at the collagen-collagen interface; d) equivalent material obtained after multiscale asymptotic homogenization; e) experimental validation of the equivalent material model with literature data (source of the stress-strain diagram: [6]).

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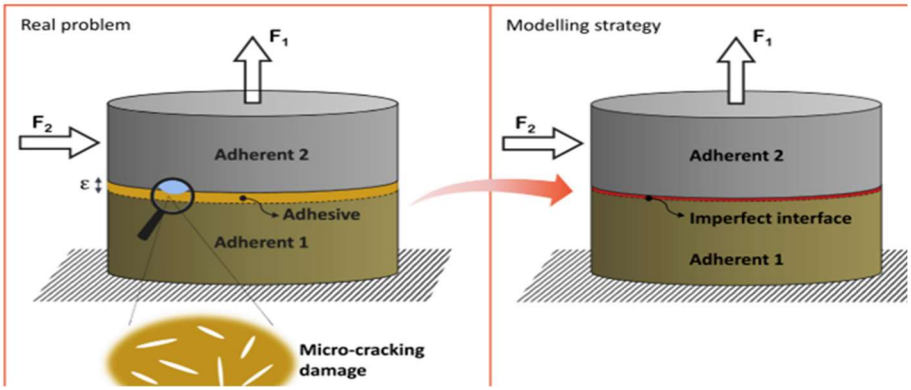

Figure 2. Scheme of the imperfect interface modeling strategy [12].

Incorporating these physical and possible chemical effects leading to changes in the mechanical and structural properties on bone into an *ad hoc* contact model would lead to an original description of MICs, based on an interpretation of phenomena that is thought to occur at a scale smaller than that of the interface. Integrating the resulting contact model into a homogenization scheme (cf. Figure 1d) is expected to provide insights into deformation and relaxation mechanisms across scales and have a better predictive capacity than a phenomenological approach based on the cohesive interface model. Recently, the multiscale asymptotic homogenization technique has shown its potential in describing the effective elastic properties of hierarchical composites [8,10,11]. This technique is very advantageous because it uses multiple scale expansions of the fields to exploit the scale separation between the characteristic lengths of the local structures and those of the whole material.

In summary, for the present project we propose a mathematical and computational methodology based on multiscale homogenization involving the following steps:

1. define the multiscale problem: given the (3D or 2D) microstructure representation (as in Figure 1b or Figure 1c), this steps involves the identification of a realistic contact model, the choice of the unit cell, where homogenized (effective) properties are to be determined, and the introduction of a small parameter ε representing the ratio of nanoscale features (e.g., interface thickness) to the microscale structure;
2. define the scales characterizing the system, for instance, the scale of the interface, an intermediate scale where details of the local structure are identified, and a coarse scale characterizing the whole composite;
3. smooth out the microstructural variations via the asymptotic homogenization steps (Figure 1d): representation of the relevant fields and individual constituent overall properties in terms of the defined scales; series expansions of the solution in terms of the asymptotic parameters; intermediate scale periodicity; upscaling to determine the coarse scale equations for the lowest order component of the elastic displacement field;
4. validation of the homogenized material model with the experimental data available in the scientific literature, Figure 1e.

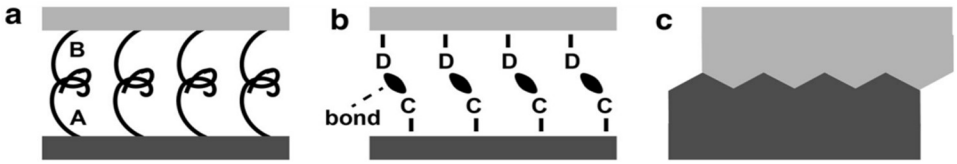

Figure 3. Schematics of interfacial bonding types between cAp (dark gray) and collagen (light gray): a) molecular entanglement; b) intermolecular interactions; c) mechanical interlocking of cAp and collagen (source of the images: [18]).

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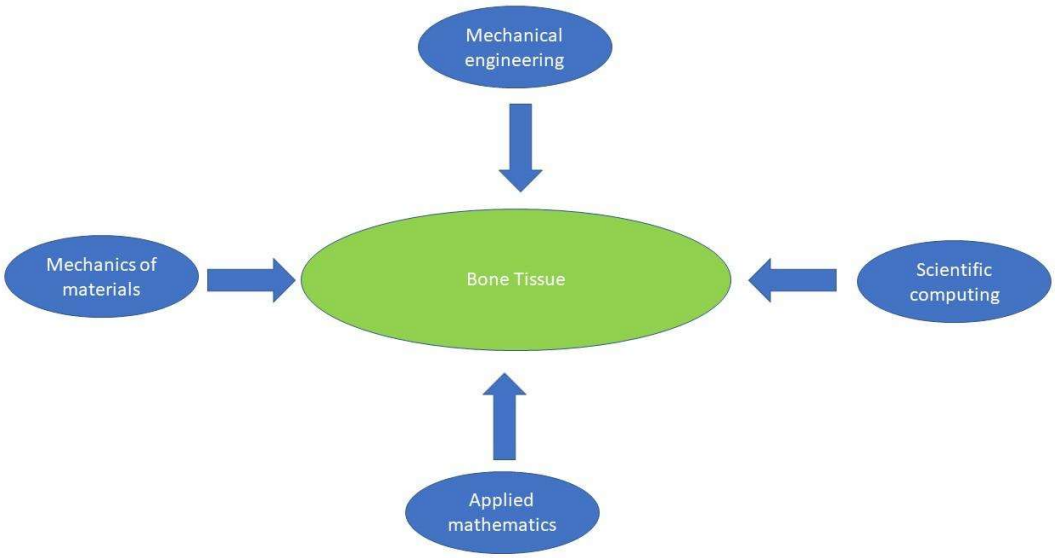
1.2. Interdisciplinary dimension of the project

The proposed international project (Aix-Marseille University-CIVIS, Glasgow University-CIVIS, Ferrara University, Composites Expertise Solution) is clearly interdisciplinary, involving specialists in solids mechanics, materials, engineering, industrial expertise, biomechanics, scientific computing and applied mathematics. The members of the consortium have a large expertise in these disciplines.

- Mechanical engineering (F. Lebon, Aix-Marseille University, Y.H. Grunewald, Composites Expertise Solution, R. Rizzoni, Ferrara University)
- Mechanics of Materials (R. Rizzoni, Ferrara University, F. Lebon, Aix-Marseille University)
- Biomechanics (R. Penta and A. Ramirez Torres, Glasgow University)
- Scientific computing (F. Lebon, Aix-Marseille University, R. Penta and A. Ramirez Torres, Glasgow University)
- Applied Mathematics (R. Penta and A. Ramirez Torres, Glasgow University)
- Industrial expertise (Y.H. Grunewald, Composites Expertise Solution)

The aim of the project is to gain a better understanding of the mechanical behavior of healthy and possibly diseased bones in order to provide better tools and treatments in the future. This subject clearly falls within the field of biomechanics. In particular, knowledge of biomechanics will enable the results of literature tests to be analyzed. The tools of engineering mechanics and mechanics of materials are essential for finely modelling the behavior of materials. These tools require considerable knowledge of applied mathematics, in particular asymptotic theory and homogenization in the case we are interested in. Scientific computing is needed to validate the models. All these areas are essential if we are to predict the behavior of bone tissue. Lastly, knowledge of the industrial environment will enable the candidate to better understand the needs in this field. The interdisciplinary approach proposed here is highly original. Works in the literature are often limited to one or two fields of expertise. It should also be noted that the consortium's experts in biomechanics have numerous contacts with the medical world, and the Marseille partner can benefit from the interdisciplinary nature of its university, in particular through the university institutes.



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2. IMPACT (2 pages max)

2.1. Expected impact of the project on the candidate's career

The project will enable the PhD student to become a recognized researcher in the fields of biomechanics, applied mathematics and solid mechanics, particularly with regard to the mechanical behavior of complex media. The innovative procedures developed as part of the project will give him/her a unique opportunity to broaden his/her knowledge and improve his/her career prospects. The results obtained during the PhD will also be of great benefit to society by providing a better understanding of the behavior of bone tissue. These are important benefits according to the societal objective in the field of health put forward in the call for projects. This will also give the applicant a high potential for attracting funding for future research.

By promoting the project's developments as explained in the project, it will be possible to create a network of researchers and develop professional contacts with whom to collaborate after the end of the grant, thanks also to the interdisciplinary nature of the project. In addition, the collaborations established as part of this project will enable the researcher to become firmly integrated into the European research landscape.

During the fellowship, the candidate will strengthen his or her leadership, management and knowledge transfer skills by working closely with other members of the laboratories.

In addition, the involvement of an industrial partner as a tutor (socio-economic mentor) will also provide greater insight into this field.

Winning this fellowship such as the Marie-Curie IF Action will enable him/her to move to the forefront of research specializing in biomechanics and to apply for prestigious fellowships such as the ERC, a permanent research position or an industrial position after the fellowship. For example, thanks to the management and teaching skills he/she has acquired, he/she will have the scientific and professional maturity needed to take up a position as assistant professor in structural engineering and head of a research group.

2.2. Expected impact for the thematic axis

The targeted theme is 'Health and well-being'.

Although AMU already has extensive knowledge in this field through its research centers, institutes and collaborations with clinicians at APHM (Assistance Publique des Hôpitaux de Marseille), this research will benefit knowledge in the thematic area and, in the longer term, patients.

It is well known that knowledge of the mechanical behavior of biological tissues and how it changes with age is fundamental to the development and implementation of therapeutic treatments. Osteoporosis, in particular, is a disease of bone metabolism responsible for increased fragility, leading to a higher risk of fracture. It is constantly on the increase with the ageing of the population and, according to WHO estimates, there will be almost 6.3 million femoral neck fractures worldwide by 2050. The aim of this work, which is to assess the mechanical behavior of bone tissue from the nanoscopic to the macroscopic scale, using an approach that combines mechanics, mathematics and a numerical approach, could lead to significant advances in knowledge. The success of this project would represent a major advance in our understanding of pathologies with expected benefits in terms of diagnostic management, prognosis assessment, evaluation of medical treatments and surgical approach.

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2.3. Dissemination, exploitation and communication activities planned

The type of outreach activities could range from an Internet presence, press articles and participating in events to presenting science, research and innovation activities to citizens, including to students from primary and secondary schools or universities in order to develop their interest in research careers.

During the period of the grant, the new knowledge generated will be disseminated by various media. Financial support from the SCHADOC programme will be duly acknowledged in all communications.

In order to allow further exploration of the results, the results of the proposed project will be freely accessible in scientific literature. The dissemination of research results will be ensured by the following actions:

- Publications in international peer-reviewed journals: It is planned to publish several articles in international journals such as Journal of Biomechanics, Computer Methods in Biomechanics and Biomedical Engineering, Composite Structures, Biomaterials, International Journal of Experimental and Computational Biomechanics. The papers will cover the research carried out in each work package.

- Oral presentations at international conferences and seminars where the results of the project will be discussed and disseminated directly to the research community, thus having a significant impact on the field and the public.

- Organization of scientific meetings and workshops with industrial partners involved in offshore installations in order to maximize the impact of the project results.

- Dissemination on professional social networks such as LinkedIn.

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3. IMPLEMENTATION (2 pages max)

The originality of the project stems from two key points: the consideration of interfaces in bone tissue and the consideration of multiphysical couplings (chemo-mechanics). Relevant instances of chemo-mechanical interactions include, for example, cellular migration, the rupture and restoration of the adhesive links among the cells, and the agglomeration of cellular aggregates, with characteristics depending on the environment in which the cells are cultured. These specific phenomena are manifestations of more general classes of internal transformations of biological tissues, which, in turn, comprise aging, damage, growth, and remodeling [4,19]. This should provide a more detailed understanding of the materials in comparison to what is currently available in the literature. Interfaces in bone tissue are essential because they play a key role in the mechanical and regenerative properties of bone tissue. Hence, it is important to take them into account:

1. Transmission of mechanical loads. Bone is a composite material made up of different phases (cortical bone, cancellous bone, periosteum, endosteum) and interfaces. These interfaces influence the transmission of mechanical forces, fracture resistance and the bone's adaptation to stress.

2. Regulation of bone growth and regeneration. Interfaces, such as that between bone and growth plate, are essential for bone development. Similarly, the interface between bone and periosteum plays a role in post-fracture repair.

3. Bone-implant interface in biomedicine. When an implant (prosthesis, screw, plate) is placed, the interface between the bone and the implant influences osseointegration. Good adhesion prevents loosening and guarantees the implant's durability.

4. Role in bone diseases. Pathologies such as osteoporosis and osteoarthritis modify the structure and function of bone interfaces. For example, deterioration of the bone-cartilage interface can lead to joint pain and degeneration. A more accurate multiscale model of the bone structure can help in elucidating the role of microstructural arrangement of the bone's constituents to address poorly understood experimental data related to bone stiffening in aged patients [9].

In summary, bone tissue interfaces are crucial for biomechanics, growth, regeneration and medical applications, particularly in tissue engineering and orthopaedics.

The objectives are fully achievable within the 36 months of the doctoral thesis, for a number of reasons. The main reason is the complementary nature of the partners, who provide expertise on all aspects of the subject. This expertise will mitigate possible pitfalls that could arise during the project development. For example, a very difficult point in the work consists of obtaining a complete model by addressing every hierarchical level of organization across several scales: the scale of the interface and the scale of the representative volume. This complexity can be reduced by simplifying the modeling assumptions such that phenomena happening at different scales can be decoupled.

The timetable for the thesis is shown in the GANTT diagram below. The doctoral student will spend time in the three partner universities (Aix-Marseille, Glasgow and Ferrara). The mentoring part will take place during the stays at the LMA in Marseille.

The first part of the work will be devoted to a literature review. The second part will be devoted to the development of an imperfect interface model that takes account of chemo-mechanical effects. In the third part, we will look at the homogenisation of the medium (bone tissue), taking into account the interfaces. The models will then be implemented numerically in a finite element code and validated on the basis of an in-depth literature review (clinical trials in particular). Finally, the last part will be devoted to writing the manuscript and scientific articles.

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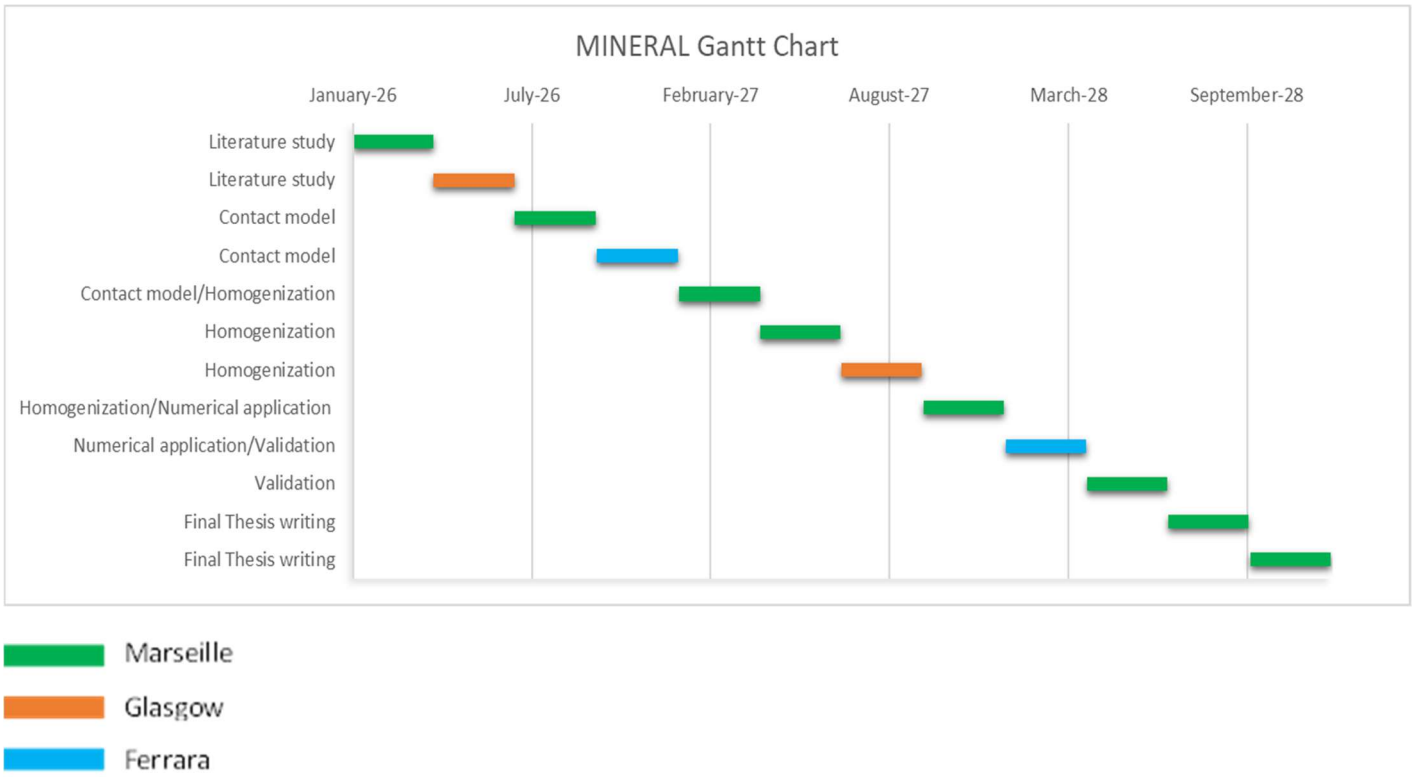

4. ETHICS SELF-ASSESSMENT

The project members commit to

- scientific integrity: avoid fraud (falsification, fabrication or plagiarism of data); respect methodological rigour and objectivity; declare conflicts of interest.

- Transparency and reproducibility: Publish results honestly, even in the event of failure; Describe methods in detail to enable replication; Share data where possible.

- Acknowledgement of contributions: Cite sources correctly and acknowledge the contributions of colleagues; Respect intellectual property rights; Encourage open and fair collaboration.

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