Chapter

Multi-Scale Modeling of Mechanobiological Behavior of Bone

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Abstract

The simulation and theoretical or numerical predictive modeling of the development and growth of biological tissues mainly in the case of bone is a complicated task. As a result, many and various knowledge tools required (experimental, theoretical and numerical) are not yet mastered and even discovered. We will cite here some techniques and methods as well as results specific to the multi-scale numerical modeling methodology, and multiphysics using finite element coupling with neural network computation of biological tissues applied to the predictive behavior of cortical bone based of the microstructure of their local constituents and their reconstruction according to local mechanobiology. It follows that additional work is necessary to give more precision on the different models, the considered approaches show their potential utility to understand this behavior in terms of biological evolutions as well as the subsequent use in medical applications.

Keywords: multiscale, mechanobiology, numerical modeling, coupling, bone

1. Introduction

The human skeleton is made up of 204 articulated bones that perform several essential functions. These bones are the body's backbone, to which muscles and other structures can attach. They also provide a protective function for certain organs, such as those located in the rib cage (heart, lungs, etc.) and facilitate movement. Bones are also involved in the formation of blood cells, the metabolism of calcium and the storage of minerals. The objective of this work is to provide an overview of the bibliography relating to human bone tissue: its structure and composition, its histology and its mechanical behavior at different scales.

2. Bone structure

2.1 Functions

Bone tissue is one of the strongest tissues in the body. It is also a dynamic fabric, constantly remodeled, capable of adapting its density to the stress to minimize stress in the most stressed areas. In addition to this mechanical function of supporting the body and protecting the organs, the skeleton has two other main functions.

- A function of controlling the phosphocalcic metabolism: under the effect of mechanical pressures, the constant remodeling of bone tissue causes the release or storage of mineral salts: it thus ensures (jointly with the intestine and the kidneys) the control of the metabolism phosphocalcic.

- A hematopoietic function: the bones contain the hematopoietic marrow in their medullary spaces. At the level of this marrow are created the various blood cells.

  - Red blood cells or red blood cells are responsible for transporting oxygen from the lungs to cells throughout the body and thus allow them to function.

  - White blood cells or leucocytes are of different types (polynuclear cells, lymphocytes, plasma cells, etc.) and are responsible for the body's defense against infections.

  - Platelets are small elements that have the essential role of initiating blood clotting in the event of a wound.

2.2 Anatomical varieties

Several anatomical varieties of bones are distinguished (**Figure 1**). Each bone has a particular shape that meets a specific need.

- Long bones. This name reflects their morphology and not their size. They include a central body and two ends. The radius, the humerus, the tibia, the femur... belong to this anatomical variety.

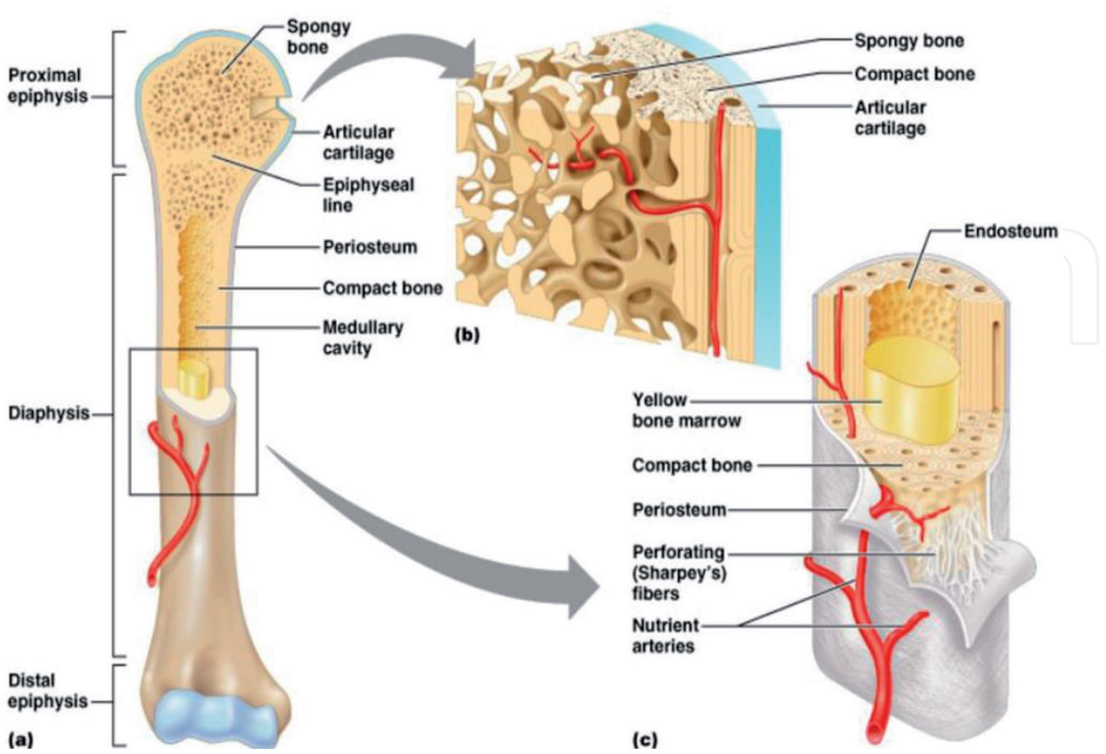


Figure 1.
Structure of a long bone [1].

- Short bones are more or less cubic and mainly contain cancellous bone, the compact bone forms only a thin layer on their surface. This is the case with the bones of the wrist, ankle, phalanges.

- Sesamoid bones are a special type of short bone embedded in a tendon, this is the peculiarity of the kneecap.

- Flat bones are thin and often slightly curved. They have two sides of compact bone more or less parallel, separated by a layer of cancellous bone. The breastbone, ribs, shoulder blades and most of the bones of the skull fall into this category.

- Irregular bones do not belong to any of the above categories. They are complex in shape and consist mostly of cancellous bone covered with thin layers of compact bone. This is the case with certain bones of the skull, vertebrae and iliac bones.

2.3 Constitution

2.3.1 Macroscopic anatomical structure of bones

2.3.1.1 The structure of long bones

Long bones all have the same structure.

- The diaphysis is the body of the bone, its longitudinal part. It's a cylinder of bone relatively thick compact that contains a central medullary canal. In adults, this duct (also called the medullary cavity) contains the yellow marrow, which is mainly from lipids.

- The epiphyses are the ends of the bone, often thicker than the diaphysis. The inside of the epiphyses is made up of cancellous bone, the outside of a thin layer of bone compact. The stressed part of the joint is covered with a thin layer joint cartilage (hyaline cartilage). This dampens the pressure on the end of the bone when moving the joint.

Apart from the articular surfaces where the articular cartilages are located, the bones are surrounded by an outer layer, the periosteum. The central cavity of the long bones is bordered by an internal layer, the endosteum.

- The periosteum is the double membrane, bright white, on the outer surface of the shaft. It mainly contains osteoblasts (cells that produce bone matter) and osteoclasts (cells that destroy bone material), cells described paragraph 1 below. The points of insertion and anchorage of tendons and ligaments are located on this periosteum. Sharpey fibers (collagen fibers which attach the periosteum to the underlying bone) are extremely dense at these points.

- The endosteum is the thin membrane of connective tissue on the internal surfaces of bone. he covers the spans of cancellous bone in the medullary cavities and lines the canals that cut through compact bone. Like the periosteum, the endosteum contains both osteoblasts and osteoclasts.

2.3.2 Cells and extracellular matrix

Bones are mainly made of bone tissue but also contain blood vessels, nerves. Bone tissue is specialized connective tissue called skeletal tissue. It is characterized by the nature of the Extra Cellular Matrix (ECM) which has the property of calcifying and solidifying.

2.3.2.1 Cells

Four types of cells make up bone tissue [1, 2]: on the one hand, bone-forming cells, which include osteoblasts, osteocytes and lining cells, and on the other, bone-resorbent cells, osteoclasts.

- Osteoblasts are bone forming cells located on the outer and inner surface of growing bone tissue. The osteoblasts develop the organic constituents of the Extra Cellular Matrix. They are transformed into osteocytes, or are put to rest in the form of bordering cells.

- Osteocytes are differentiated osteoblasts incapable of dividing and are entirely surrounded by the mineralized Extra Cellular Matrix. Osteocytes sit in cells, osteoclasts, and participate in the maintenance of the bone matrix.

- The bordering cells are osteoblasts at rest which coat the bone surfaces and are liable, if they are called upon, to become active osteoblasts again.

- Osteoclasts, very large cells 20 to 100 μm in diameter, are the seat of the bone resorption process. They are very mobile and able to move on the surface of the bone trabeculae from one resorption site to another.

Osteoclasts, osteoblasts, and bone-lining cells are found on the surface of bone tissue, while osteocytes are located inside the extracellular matrix of bone tissue.

2.3.2.2 The extra cellular matrix

The Extra Cellular Matrix of bone is calcified and has an organic part and a mineral phase.

- The organic matrix is composed of collagen microfibrils, and various elements involved in the mineralization phase of the Extra Cellular Bone Matrix.

- The mineral phase consists of calcium phosphate crystals (apatite) located between the collagen fibers and/or inside them, in the form of small hexagonal needles.

2.3.3 Bone tissue

Most bones are made up of an outer layer that appears smooth and dense to the naked eye, compact bone tissue, and an internal area of trabecular (or cancellous) bone tissue. Bone marrow, red or yellow, is contained in the cavities between the spans of this structure. In the case of long bones, **Figure 1**, the cancellous bone is located at the extremities (epiphyses), the central part of the bone contains the bone marrow.

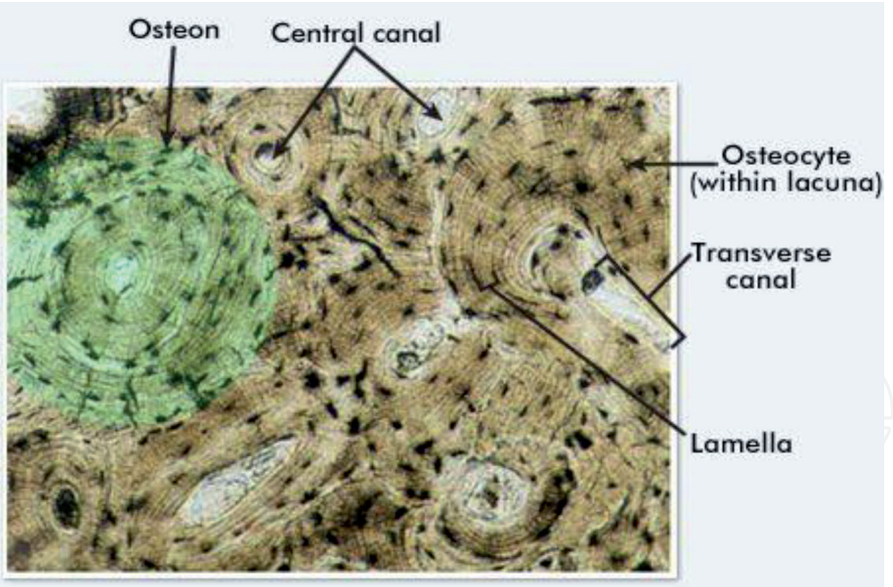


Figure 2.
Compact, cortical bone element [3].

2.3.3.1 Compact bone

The osteon, or Havers' system, is the structural unit of compact bone. Each osteon is of elongated cylindrical shape, parallel to the longitudinal axis of the bone, **Figure 2**. The osteon is made up of a set of hollow cylinders (6 to 15 per osteon) made up of bone matrix and arranged concentrically around its central canal, or Havers' canal, which contains blood capillaries and nerve fibers. These canals are interconnected with the medullary cavity and with the surface of the bone by transverse or oblique canals, the Volkmann canals. Each matrix cylinder is a lamella of the osteon: the compact bone is often called the lamellar bone. In a given lamella, the collagen fibers are all parallel but the fibers of two adjacent lamellae are always oriented in different directions. This alternation strengthens the adjacent lamellae, which provides remarkable resistance to the torsional forces to which the bones are subjected. The osteocytes are found in small empty spaces at the junction of the lamellae, called lacunae. These gaps are connected to each other and to the central osteon canal by the canaliculi, very fine canals, which allow nutrients and waste to easily pass from one osteocyte to another. Thus, the osteocytes are well nourished even though the bone matrix is hard and impermeable to nutrients. The arrangement of the osteons, with the axis oriented in the direction of the mechanical stresses, gives the compact bone maximum strength. If we consider the compressive strength in relation to the density, bone is a reference structure in the field of cellular materials [1, 3].

2.3.3.2 Cancellous bone

Spongy (trabecular) bone tissue is mainly present in short bones and flat bones (sternum, iliac wings) as well as in epiphyses of long bones. It is formed by a three-dimensional network of trabeculae (walls) of bone tissue, branched, delimiting a labyrinth of interconnected spaces reserved by the bone marrow and vessels, **Figure 3**. The shape and density of the alveolar cells depend on the intensity and direction of the stress that the bone must withstand. Cells tend to line up in the direction of greatest stress, and their density increases with the intensity of loading. Cancellous bone has no osteons, but its spans form irregular lamellae and osteocytes connected by canaliculi.

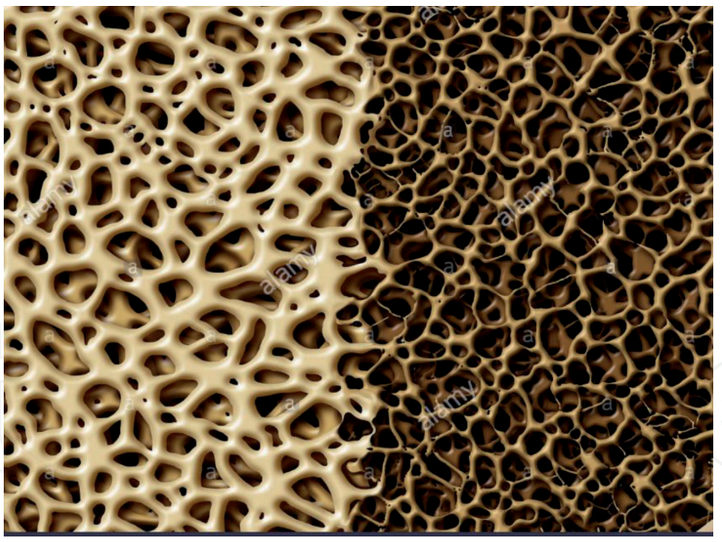


Figure 3.
spongy bone tissue. Side of the cube: 5 mm. Photo UMR 791 INSERM [3].

The nutrients leave the medullary spaces between the spans and arrive at the osteocytes of the cancellous bone by diffusion through the canaliculi.

There are three phases in the life of the bone.

- The growth phase, during which bone is synthesized. Peak bone mass is reached three years after puberty.

- Adulthood in which the phenomenon of bone remodeling maintains an approximately constant mass. Bone is a tissue that is constantly renewed during its existence. It is resorbed by osteoclasts and then reconstructed by osteoblasts. The sustainability of the bone matrix depends on the balance of this cycle. With this process, the bone can adapt to loads and rebuild itself in the event of a fracture.

- With advancing age of the individual, degradation and synthesis are unbalanced, bone mass decreases.

3. Bone development

Osteogenesis and ossification refers to the process of bone formation that leads to the formation of the bone skeleton in the embryo (**Figure 4**). Bone growth is another form of ossification that continues into adulthood as long as the subject continues to grow. In adults, ossification is mainly used for rearrangement and to bone consolidation. The embryo's skeleton is made up entirely of fibrous membranes and hyaline (joint) cartilage until the 6th week of gestation. Then most of these structures are gradually replaced by bone tissue. Two bone formation processes then exist: intramembranous ossification and endochondral ossification.

3.1 Inside the membrane ossification

Intramembranous bone is formed from a fibrous membrane. The bones produced are flat bones. The ground substance of the bone matrix is deposited between the collagen fibers, inside the fibrous membrane, to form cancellous

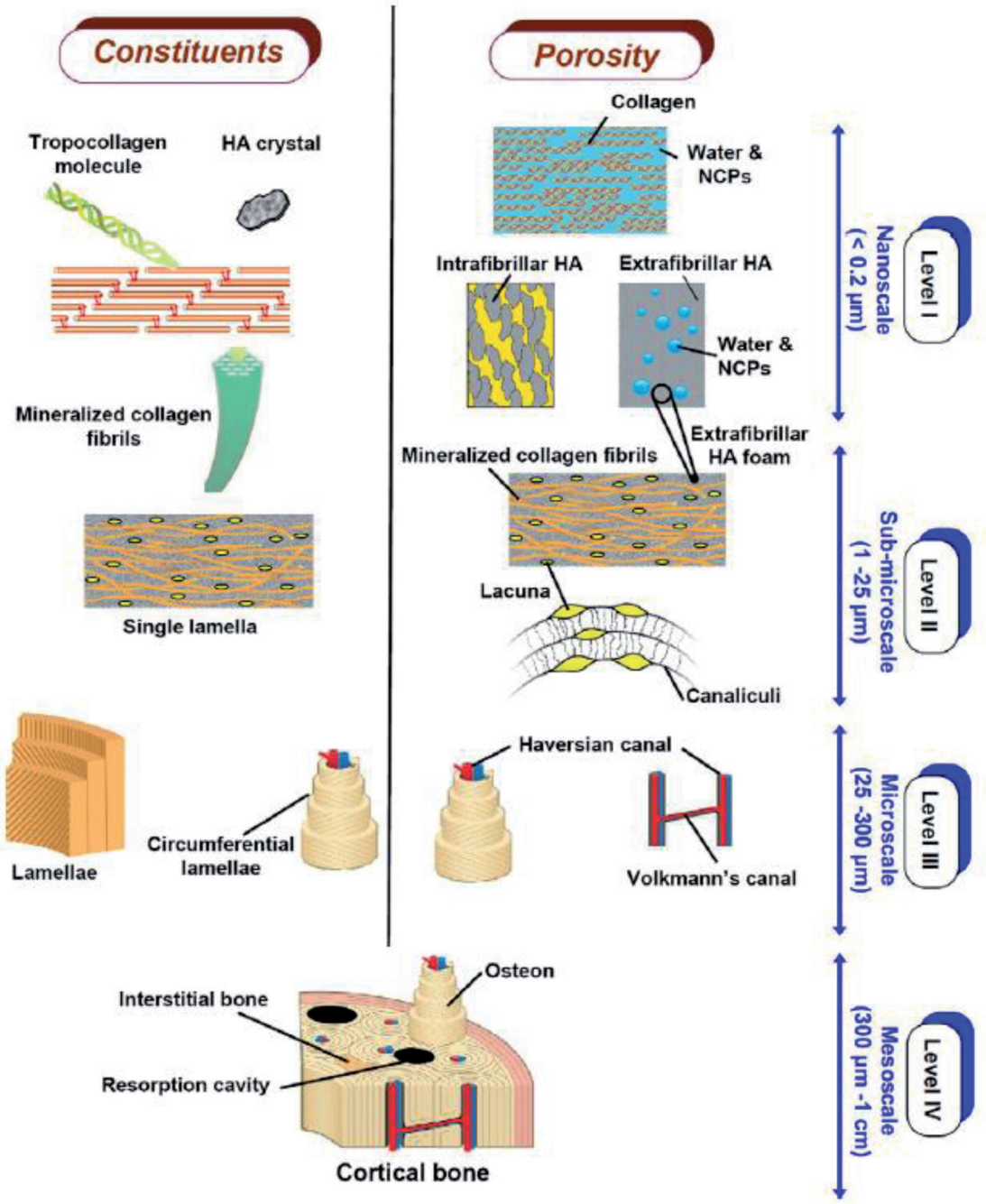


Figure 4.
Hierarchical structure of cortical bone constituents and associated porosity. HA = hydroxyapatite, NCP = non-collagenous proteins [4].

bone. Plates of compact bone eventually enclose the diploe. The successive stages of ossification are:

- the formation of an ossification point in the fibrous membrane;
- the formation of a bone matrix inside the fibrous membrane;
- the formation of fibrous bone and periosteum;
- the formation of compact bone plates and red marrow.
- Endochondral ossification.

Ossification starts from hyaline cartilage and leads to endochondral bone or cartilaginous bone. This process is more complex than the previous one because the cartilage must be disintegrated as the ossification progresses. The majority of the bones of the skeleton are formed by this ossification. The osteoblasts that lie below the periosteum secrete a bone matrix modeled on hyaline cartilage, thus forming a bone sheath. The deterioration of the cartilaginous matrix forms cavities, which allows the entry of a bud which is at the origin of the point of primary ossification: it contains an artery and a nourishing vein, lymphatic vessels, neurofibers, red marrow elements, osteoblasts and osteoclasts. Bone matrix is deposited around the remains of cartilage.

3.2 Bone growth

Bone growth takes place mainly during childhood and adolescence. Most bones stop growing in early adulthood.

3.2.1 Growth in length of bones

Long bones elongate as a result of the interstitial growth of epiphyseal cartilages and the replacement of cartilage with bone material. Growth in length is accompanied by an almost continuous rearrangement of the extremities (epiphyses), in order to maintain the correct proportions between the diaphysis and the epiphyses.

3.2.2 Growth in thickness or diameter of bones

The bones thicken with the efficient activity of the periosteum. Osteoblasts, located below the periosteum, secrete a bone matrix on the outer surface of the bone; osteoclasts, located on the endostate of the diaphysis, destroy the bone surrounding the medullary cavity. The resorption is generally less important than the formation of bone material, the bone thickens and its diameter increases.

4. Bone remodeling

In compact bone as well as in trabecular bone, bone tissue is constantly renewing [1, 4, 5]. This bone remodeling occurs by successive resorption and formation of bone tissue, a process in which osteoclasts and osteoblasts are closely associated. Bone tissue is renewed about every four months in adults. The renewal mechanism consists of several phases.

- Activation phase: under the effect of osteoresorbent factors the lining cells, which normally cover the bone surface, allow osteoclasts (bone resorption cells) to pass. At the same time, osteoblasts differentiate into osteoclasts.

- Bone tissue resorption phase: each osteoclast that becomes active binds to the Extra Cellular Matrix. The resorption phase begins with the dissolution of the mineral phase (acidification) and continues with the degradation of the organic matrix under the action of enzymes.

- Inversion phase: once the osteoclasts have created a gap in the bone tissue, they die. Macrophages then come to replace them, to smooth the bottom of the gap.

- Bone tissue formation phase: this phase, also made up of two stages, is the longest. Once the resorption is complete, the cells at the bottom of the gap

differentiate into osteoblasts which synthesize a new Extra Cellular Matrix which is progressively mineralized thereafter. In young, healthy adults, total bone mass remains constant because overall the rates of bone deposition and resorption are equal. The redesign process is not always uniform or balanced:

- bone deposition may occur in an area where the bone has sustained an injury;
- the formation of bone tissue is less rapid than the resorption as the individual advances in age, which is what leads to osteoporosis.

5. Mechanical properties of bone

5.1 Compact bone

The behavior of fresh compact bone, loaded in the longitudinal direction, is elastic up to a strain of 0.7% in tension or in compression [1, 3], failure occurs at 3% strain (**Figure 5**). In the transverse direction, in tension, the bone is less rigid and the rupture occurs at a strain of 0.6%. These values correspond to fresh bones. If they are dry, the Young's modulus increases and the tensile strength decreases. Dry bone is also more fragile. The Young's modulus of fresh compact bone is about 17 GPa longitudinally and 11.5 GPa transversely. The maximum compressive stress is 193 MPa in the longitudinal direction and 133 MPa in the transverse direction. In traction, the maximum stresses are 148 MPa in the longitudinal direction and 49 MPa in the transverse direction.

The elastic mechanical properties of bone ultrastructure scale levels depends on several geometrical and mechanical parameters such as Young's modulus bone elementary com- pounds (mineral, collagen) [6, 7], the nature of collagen (dry, wet) [6], size of the mineral crystal and the number of cross- links [8]. In order to clarify, the averaged elastic constants have been presented in **Table 1** to compare

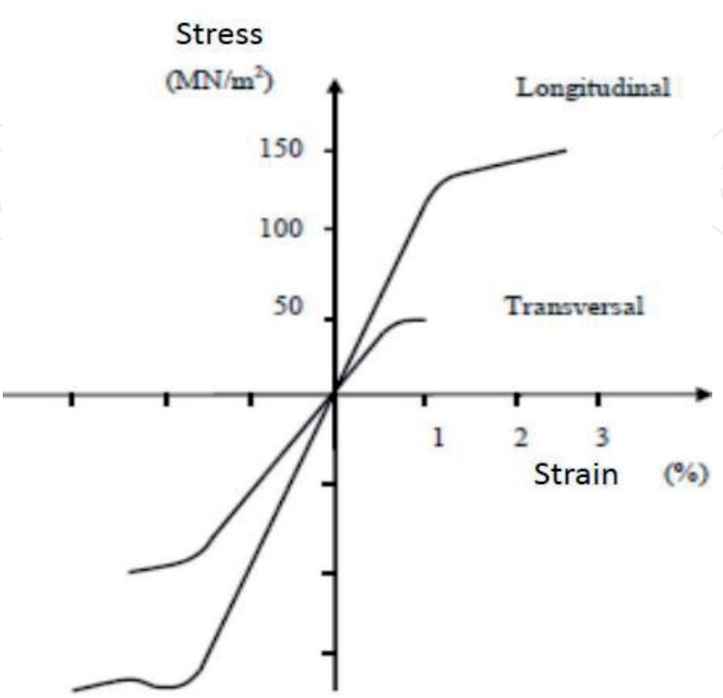


Figure 5.
Tensile-compression test of compact bone [5].

	Young's modulus (GPa)	Poisson's ratio
MCM	0.755	0.264
MCF	40.8	0.271

Table 1.
The average elestic mechanical properties of the bone ultrastructure scales [8].

our results with experi- mental and numerical results of further works performed on the same components. There are few works focused on the mechanical properties characterization of MCFR (mineralized collagen fibers (MCFRs)), for this reason, the comparison of the results is limited on MCM (Mineralized Collagen Microfibrils) and MCF (Mineralized Collagen Fibrils) scale levels.

MCFRs are formed by the assembly of MCFs surrounded by a matrix of mineral and are offset from each other with an apparent pe- riodicity noted D. Then, MCFs are made the same way by MCMs related to each other by cross-links. Finally, MCMs, a particu- lar assembly of five helical TC molecules, longitudinally offset them with the same apparent periodicity D.

5.2 Bone remodeling or renewal

Bone is constantly being renewed. It is a continuous cycle of bone formation and destruction, which is living tissue. This phenomenon is called "bone remodeling". Two types of cell are involved: osteoclasts which will first destroy the bone that has been formed in the past, and osteoblasts which will rebuild new bone.

At first, the osteoclasts arrive and dig real "holes" called gaps: this is the resorption phase.

Then, the osteoblasts arrive in the gaps dug previously. These cells will then fill in with bone tissue without calcium (called osteoid tissue), this is the formation phase. Finally, on this young osteoid bone tissue, the calcium will be fixed: this is the phase of the mineralization.

Bone tissue is a dynamic tissue which is constantly renewed by synthesis and resorption. This mechanism is induced by the action of hormones and local factors (parathyroid hormone, vitamin D3, prostaglandin E2) or mechanical constraints (stresses, alterations in bone tissue). Permanent remodeling makes it possible to renew bone tissue to compensate for the aging of osteocytes, to modify the architecture of bone tissue according to mechanical constraints and finally to control phosphocalcic homeostasis by recirculating calcium and phosphorus during the resorption phase.

There are 5 main phases in the bone remodeling process: the activation phase, the resorption phase, the inversion phase, the formation phase and the quiescence phase. Bone remodeling is a cellular cooperation between osteoblasts and osteoclasts. The phenomenon of bone remodeling takes place within a multicellular temporary remodeling unit called the BMU "Bone Multicellular Unit".

5.2.1 The activation phase

The activation phase is initiated by the osteocytes. These cells are anchored in the bone matrix and have numerous cytoplasmic extensions. They are able to communicate with other cell types, but also to detect mechanical signals (stresses, alterations in bone tissue such as microfractures) or hormonal signals. Faced with these signals, the osteocytes die by apoptosis and induce, through this programmed cell death, the retraction of the bordering cells to expose the bone surface which

must be remodeled. Stromal cells, mesenchymal stem cells, which are found in the environment on the surface of bone tissue, differentiate into pre-osteoblasts. These express on their surfaces RANKL, a cytokine-type ligand whose role is the recruitment of pre-osteoclastic cells, coming from the medullary environment, and the differentiation of these into mature cells by the RANK bond (expressed at the surface of pre-osteoclasts) and RANKL. Mature osteoclasts thus formed adhere to the bone surface.

5.2.2 The resorption phase

Mature osteoclasts on the surface of the bone will secrete acids which will decalcify the bone and then enzymes which will digest the collagen in the bone. In about 12 days [9], mature osteoclasts will create a resorption gap of about 40 μm [10]. By digesting bone, osteoclasts release growth factors. The osteoclasts then die by apoptosis.

5.2.3 The reversal phase

After the resorption phase, the osteoclasts are replaced by mononuclear cells of the macrophage type.

5.2.4 The training phase

Osteoblast precursors, derived from pluripotent mesenchymal stem cells in the bone marrow, are rapidly attracted to growth factors released during resorption, proliferate and differentiate into mature osteoblasts. Osteoblasts release a protein,

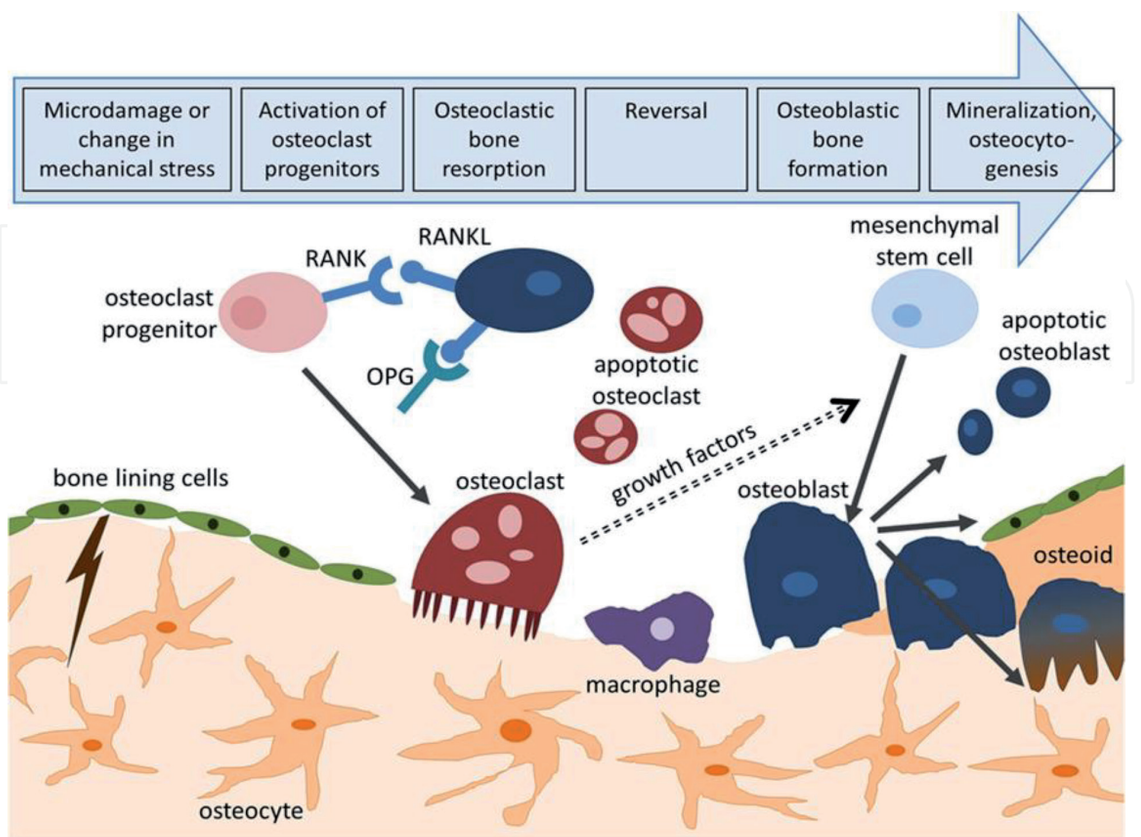


Figure 6.
Bone remodeling according to [11].

osteoprotegerin, which binds to RANKL preventing RANK-RANKL binding and therefore the activation of osteoclastic differentiation [10].

Mature osteoblasts migrate to the bottom of the resorption gap and release type I collagen microfibrils, thus creating new osteoid matrix and alkaline phosphatase, an enzyme involved in bone matrix mineralization [10]. The bone formation phase lasts about 3 months [9]. During the formation phase, certain osteoblasts (approximately 1/40) attach themselves to the bone matrix and differentiate into osteocytes.

5.2.5 The quiescence phase

The remaining osteoblast cells differentiate into bordering cells and the newly formed osteocytes rebuild their connecting network (**Figure 6**) [10].

6. Finite ellement modeling of bone mechanobiological behavior

This section presents the hybrid multiscale modeling ap-proach (Finite Element EF/Neural Network NN) of bone ultrastructure (**Figure 7**).

This approach, which is summarized in **Figure 8**, is composed of four steps: (i) development and simulation of geometric FE models for each level scale separately (microfi- bril, fibril and fiber), (ii) use of the results obtained from FE simulation in each scale level for the neural network program training phase, (iii) generalization of the results in neural network prediction phase, (iv) transition between the different scales using the same NN program.

The forth step is constituted from three NN blocks as Sembled in series (NN block for each scale level) so each NN (i + 1) Block uses as inputs the Nni block outputs (being i = 1,2). Finally, NN3 outputs allow obtaining MCFR elastic properties.

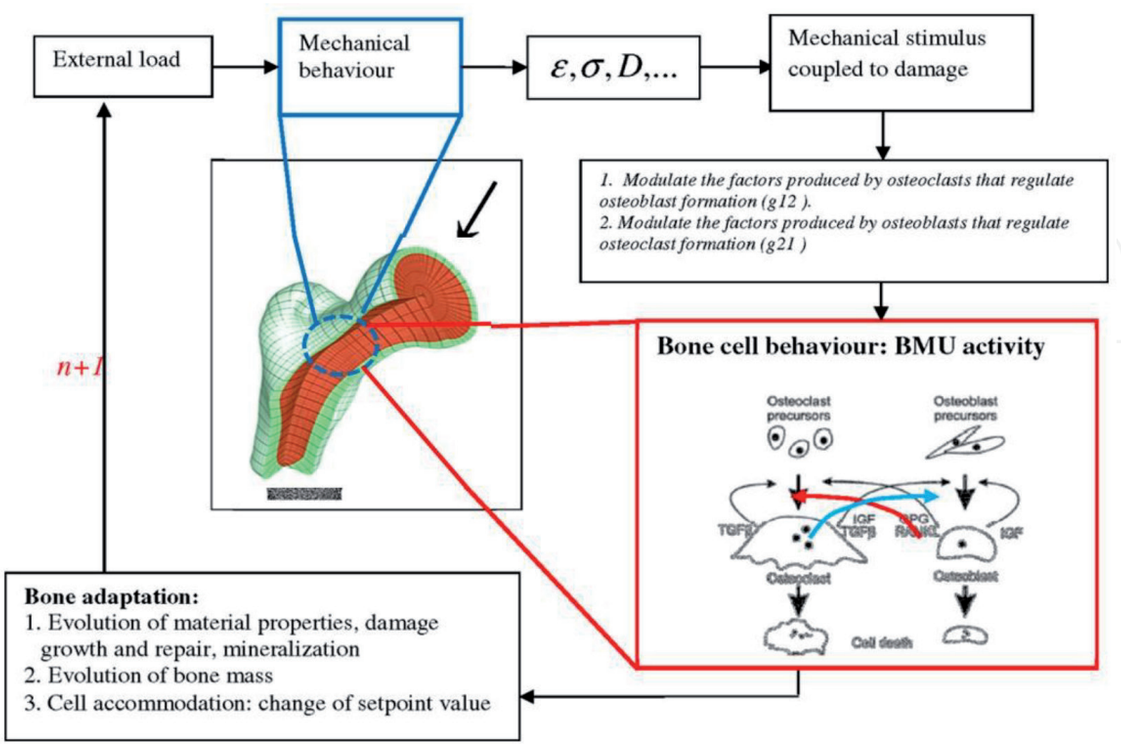


Figure 7.
Schematic representation of bone remodeling based on BMU activity coupled to mechanical stimulus: at the remodeling cycle (n), the applied load generates mechanical stress, strain, and fatigue damage states at every FE of the mesh.

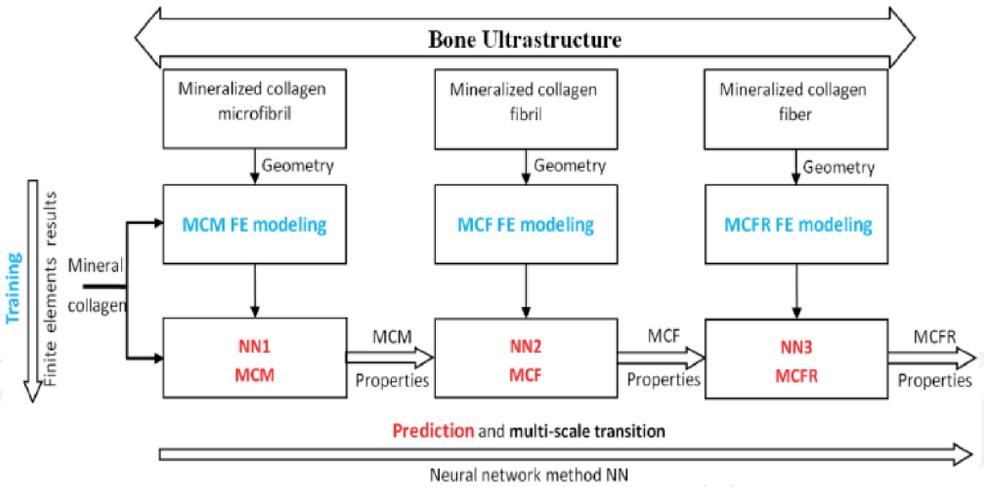


Figure 8.
Hybrid (FE/NN) multiscale modeling of bone ultrastructure [7, 12].

6.1 Results and discussions

In this study, the main results are focused on the new multi-scale hybrid modeling developed during the numerical simulation. By showing the synthetic results obtained with the NN method according to three levels of scale MCM, MCF and MCFR (**Figure 9**). By showing the variation of the generalized Young's modulus MCM as a function of the Young's modulus of the two essential bone constituents according to this scale (mineral and collagen) (**Figure 9a**). In the light of various investigations, these results found under the NN1 analysis are integrated in **Figure 9a** to construct the generalized Young's modulus MCF, obviously by integrating the elastic properties of the mineral. By analogy, the results of NN2 are likewise used to evaluate the Young MCFR's modulus (**Figure 9c**). It must be taken into account that the quantity of the mineral NN degrades in the matrix depending on the level of the scale. Our studies are flexible to have flexibility on the variation of the Young's modulus of the mineral under the effect of a significant difference between the subject amorphous structure [13]. **Figure 9a** shows that the Young's modulus of mineral has a very significant effect compared to the effect of TC modulus of Young's molecules for the MCM level scale. On the other hand, the synthesis in **Figure 9b** shows us that the elastic properties of the mineral are also slightly influential, compare to the Young's modulus of MCMs for the different scale levels of MCF. These results found, are comparable with other studies in literature [12, 14]. On the other hand, the curve of **Figure 9c** shows that the Young's modulus MCFs has a remarkable effect on the equivalent Young's modulus of the MCFR compared to the Young's modulus of the mineral.

Generally, rehological properties of the scale levels of the bone ultrastructure are related to several geometric and mechanical parameters such as the elementary bone compounds of Young's modulus (mineral, collagen), the nature of collagen (dry, wet), the size of the mineral crystal and the number of crossed links. Therefore, the estimated elastic constants have been shown in **Table 2** to compare our results with the experimental and numerical results of other studies in the literature. The literature study dealing with the characterization of the mechanical properties of MCFR are very little and even are not sufficiently developed, for this reason, the comparison of the results is limited to the MCM and MCF scale levels (see **Figures 10** and **11**, respectively).

Figure 10, configures a good correlation between predicted NN (our numerical study) and the experimental study for the small strain margin based on X-ray

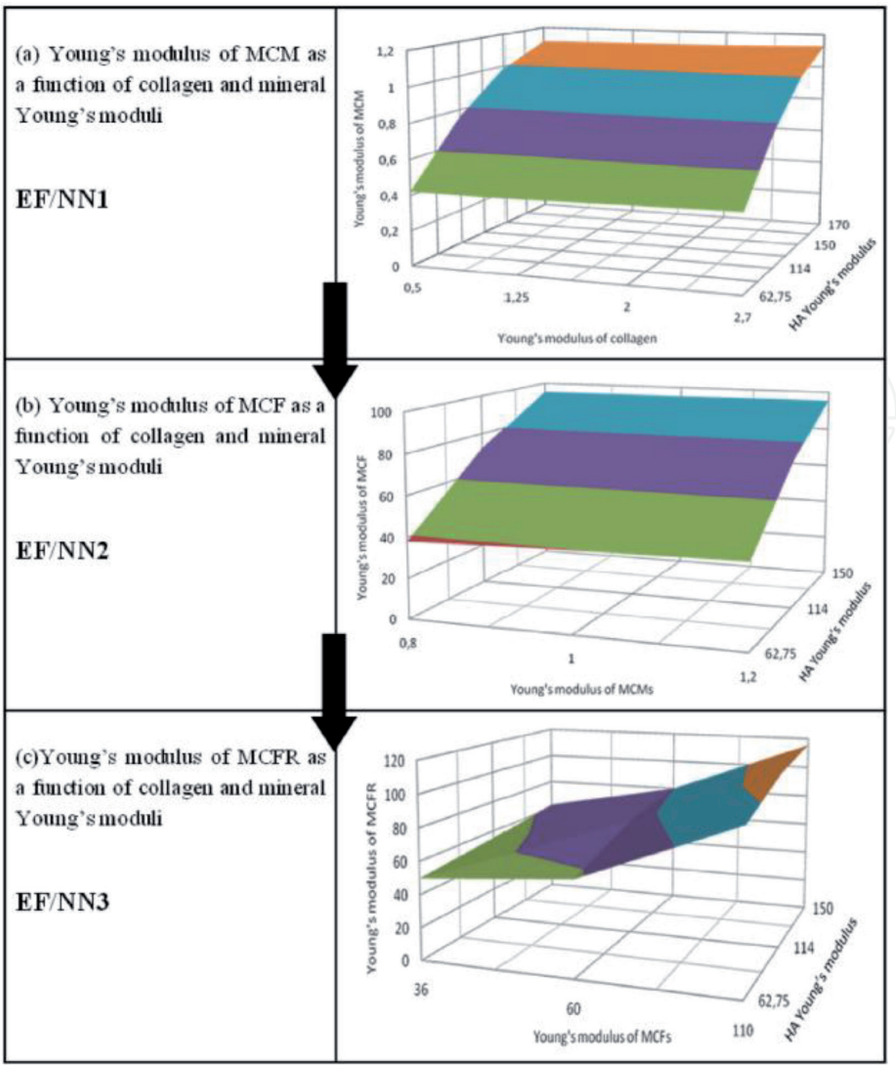


Figure 9.
Evolution of elastic moduli (GPa) of MCM and MCF as function of the mineral Young's modulus and passage between the MCM and MCF [7].

diffraction, atomic force microscopy (AFM) and the calculation of molecular dynamics. (MD).

Also, **Figure 11** records a good agreement between our study predicted NN for the MCF and the numerical and experimental results: analysis by DRX, calculation of molecular dynamics (MD) and calculation by the finite element method. However, there is a slight uncertainty which can be introduced by different sources: the different methods used, the size and nature (hydrated or dehydrated) of the MCM and MCF tested and the hypotheses considered by each. As an indication during this work, consider the mineral as a homogeneous matrix without taking into account the presence of water (PCNs are negligible). These assumptions may explain the differences mentioned above. However, due to the living nature of the materials studied (bone), the Young's modulus of MCM can be on average about 1 ± 0.2 GPa and 40 ± 2 GPa for the Young's modulus of MCF.

Moreover, the comparative study of NN predicted the average Young's modulus of MCF and also comparable to the study carried out in the literature.

The elastic properties are closely linked to several material and structural parameters at the level of our study scale. This translates into a great sensitivity in terms of mechanical properties and service life. Indeed, if the boundary conditions are specified, we can assign to each scale level a unique value of the elastic properties of the bone. As a result, carrying out experimental tests or numerical

Parameters	Notation	Trabecular bone	Cortical bone
GENERAL PARAMETERS			
Initial elastic modulus	E_0 (MPa)	2000	17,000
Poisson ratio	ν	0.3	0.3
Initial density	ρ (g/cm^3)	0.764	1.4
Density coefficient	C (g/cm^3)	4000	80,003
Density exponent	P	3	3
Ash exponent	Q	2.74	2.74
DAMAGE LAW PARAMETERS			
Fatigue parameter	γ	0.2	0.2
Fatigue exponent	β	0.4	0.4
MINERALIZATION PARAMETERS			
Initial ash fraction	α_0	0.6	0.6
Maximum physiological value	α_{max}	0.7	0.7
Velocity of the mineralization	k (days^{-1})	0.0003387	0.0003387
STIMULUS PARAMETERS			
Mechanosensitivity of the osteocyte	μ_k (nmol mm J^{-1} h^{-1})	0.5	0.5
Osteocytes density	N_{oc} (mm^{-3})	10,625	10,625
Spatial influence factor	d_0 (μm)	0.1	0.1
Accommodation velocity parameter	λ (days^{-1})	0.002	0.002
Initial setpoint value	S_k^0 (J m^{-3})	0.0025	0.0025

Parameters		Notation	Trabecular bone	Cortical bone	
BMU PARAMETERS					
Osteoclasts			**Osteoblasts**		
Notation	**Trabecular**	**Cortical**	**Notation**	**Trabecular**	**Cortical**
α_1 (osteoclasts/day)	3	3	α_2 (osteoblasts/day)	4	4
β_1 (osteoclasts/day)	0.2	0.2	β_2 (osteoblasts/day)	0.0017	0.0017
k_1 (osteoclasts/day)	0.24	0.024	k_2 (osteoblasts/day)	0.02	0.002
A_1	1.6	1.6	A_1	−1.6	−1.6
B_1	−0.49	−0.49	B_2	0.6	0.6
γ_1 (g/J)	16.67	16.67	γ_2 (g/J)	33.37	33.37
x_C (t = 0) (osteoclasts)	15	15	x_B (t = 0) (osteoblasts)	1	1

Table 2.
Material properties for bone used for the remodeling simulation [15–17].

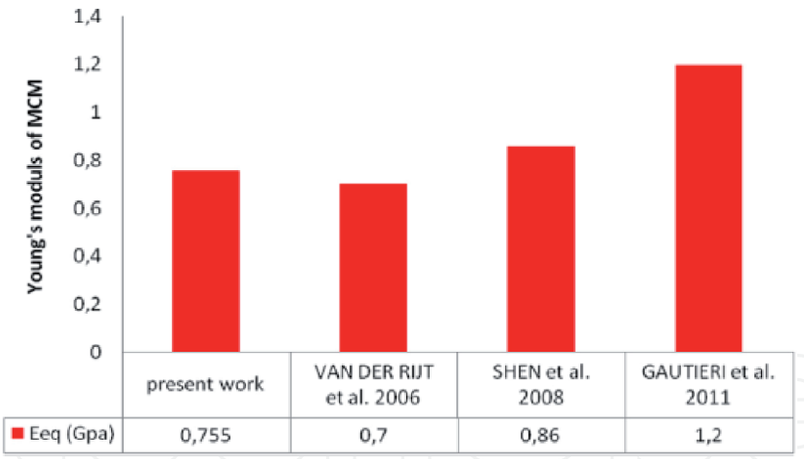


Figure 10.
Comparison between NN predicted average Young's modulus of MCM and literature results [7].

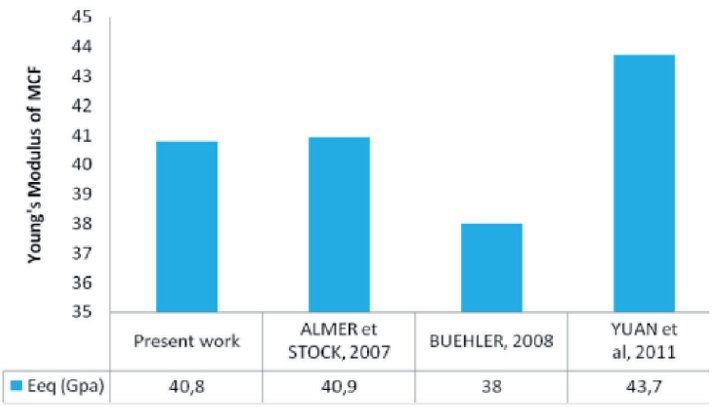


Figure 11.
Comparison between NN predicted average Young's modulus of MCF and literature results [7].

simulations on a case-by-case basis can waste time and become more expensive, hence the growing interest in the use of intelligent digital methods, such as the artificial neural networks method. This method offers a good balance between cost/quality/performance. In this study, the combinations of artificial neural network method and finite element analysis were implemented and used to determine the elastic mechanical properties at different scale levels of the bone tissue nano-structure. Second step, an approach multi-scale using neural networks has been developed. This approach uses the results of finite element analysis for the learning phase. It makes it possible to generalize the results obtained by finite elements and to make the transition between the different scale levels. The results were compared and validated by other studies in the literature and good agreement was observed. This hybrid multi-scale approach makes it possible to quickly determine (a few seconds) the equivalent mechanical properties according to the parameters entered. Here, the method was only used to determine elastic properties but can be approved to identify equivalent mechanical properties related to fracture behavior.

6.2 Relationship between the mechanics and the activities of bone cells in the process of bone remodeling

On the other hand, the complement of this work aims to develop an FE model to show the methodology of bone remodeling, by considering the activities of osteoclasts and osteoblasts (**Figure 12**). The mechanical properties of bone are demonstrated by carefully considering the accumulation and mineralization of

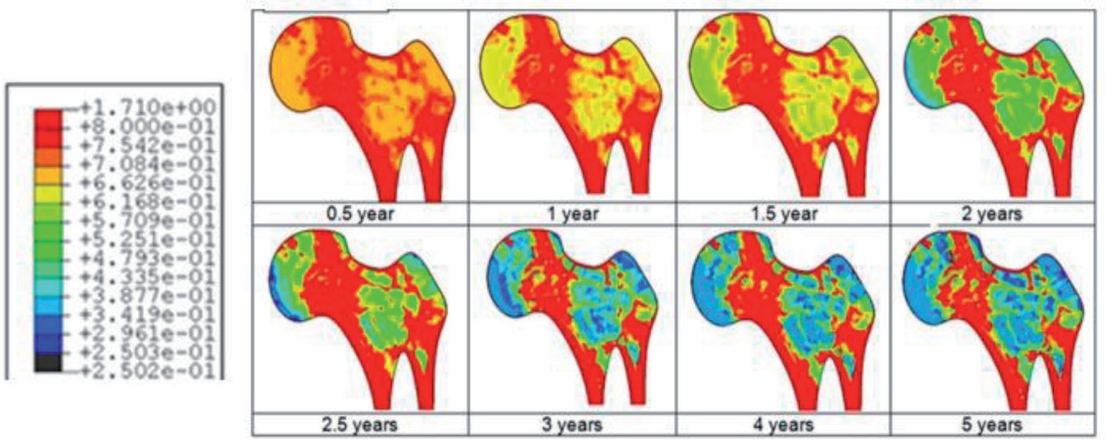


Figure 12.
Predicted bone adaptation sequences in the form of apparent bone density variation in gram per cubic centimeter [18].

failures under the effect of fatigue of the bone material. The strain-damage coupled stimulation phase is shown, which monitors the level of autocrine and paracrine factors. Cell phones and their behavior are based on the dynamic equation of, who describes autocrine and paracrine interactions between osteoblasts and osteoclasts and calculates cell population dynamics and bone mass changes at a discrete site of bone remodeling (**Figure 13**). The FE model developed was implemented in the FE Abaqus code. An example of a human proximal femur is studied using the developed model. The model was able to predict the final adaptation of the human proximal femur similar to models seen in a human proximal femur. The results obtained reveal a complex spatio-temporal bone adaptation [18]. The proposed FEM model provides insight into how bone cells adapt their architecture to the mechanical and biological environment.

The loads on the hip joint sacrificed in the current work constitute the majority of load located on the mediolateral plane of a femur and its margin is clearly greater than the other loads. Therefore, the 2D femur was a reasonable representation of the 3D remodeling behavior. Furthermore, the simulations employed the fixed model parameters given in **Table 2**. The recorded values may be subject to change due to several factors (disease, age, drugs, sex, bone sites, etc.). Finally, the analysis considers only one factor for a single parameter value of the model has been modified of all data, unlike the other parameters, which were fixed. This hypothesis showed in particular that the levels of bone cells play an important role in the process of bone adaptation, which can be modulated by specific bone drugs. Nevertheless, for a future general analysis of AS, it is necessary to consider the full variation of the factor parameters simultaneously for different geometries of femurs.

6.3 Examples of multiscale and multiphysics numerical modeling of biological tissues

The theoretical-numerical simulation and predictive modeling of the behavior and growth of biological tissues is a strange and new technique. As a result, different and multiple knowledge.

tools necessary, it is an overlap between experimentation, digital and also the theoretical, which are not yet well studied or even understood. George D. et al. [19] presented some specific multiscale multiphysics techniques and analyzes for biological tissues applied to the predictive behavior of cortical veins as a function of microstrural properties, taking into account bone remodeling and growth as a

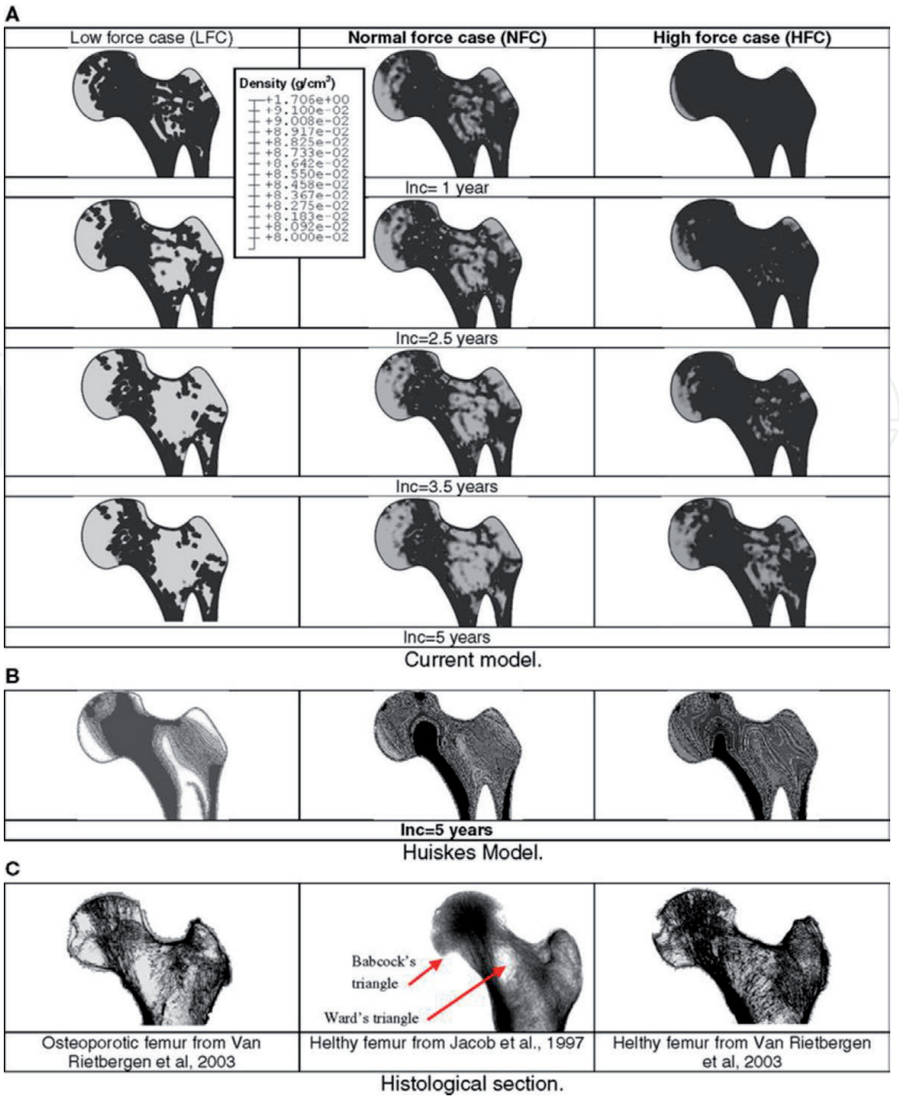


Figure 13.
Sequences of predicted density distributions (gray level) for three different remodeling load levels [18].

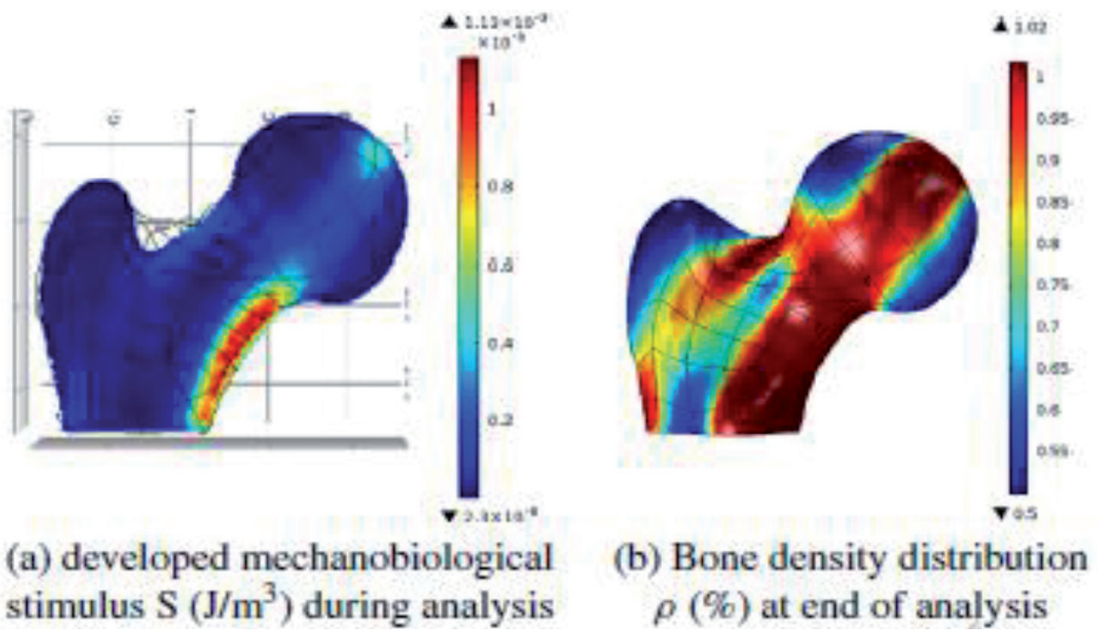


Figure 14.
Macroscopic evolution from applied external mechanical boundary conditions [19].

function of local mechanobiology (**Figure 14**). The hypotheses and the approaches used are well mastered to discover and understand the mechanical-biological phenomena, as well as a clear vision for different life periods of biological changes and their use for industrial applications.

Comparable studies, taking into account local mechanics to biology, have been developed by Ruimermann [20] to develop specific techniques of bone remodeling of patients for 3D micro-architectures but no study has shown a real link with medical applications. Real. The model of this study will allow coupling between these different scales to be able to obtain a macroscopic mechanobiological model predictive of bone changes as a function of local biological constituents.

Figure 15 shows a complementary analysis, which was carried out based on different boundary conditions. Through a triangular compressive load applied to

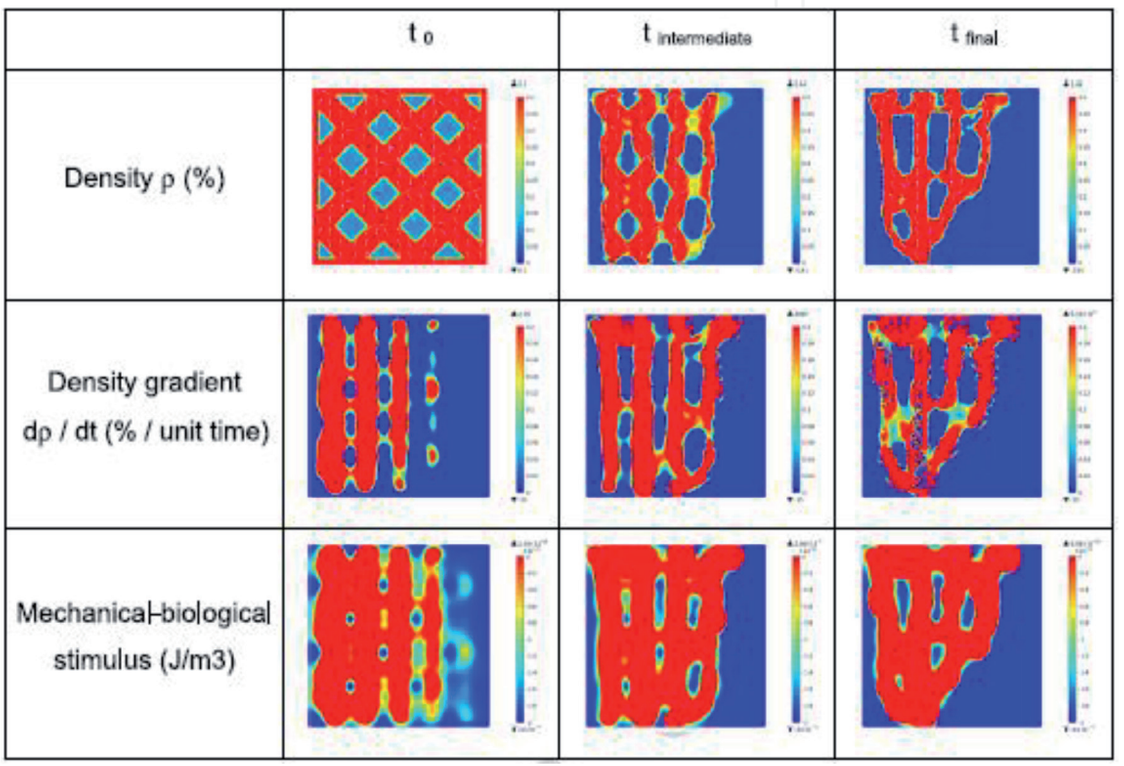
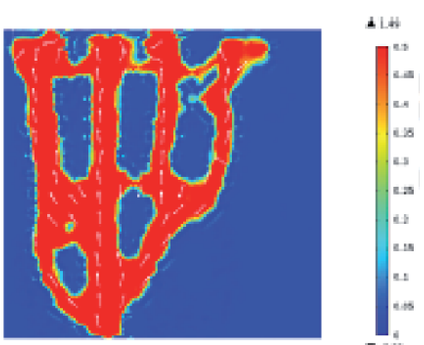


Figure 15.
Mesoscopic (trabecular size) evolution for the triangular load condition [20]. (a) Trabecular bone density obtained with current 3D model and cell activation. (b) Schematic of trabecular bone density obtained froma 2D phenomenological model with same loading conditions from Weinans [21].



(a) Trabecular bone density obtained with current 3D model and cell activation

(b) Schematic of trabecular bone density obtained froma 2D phenomenological model with same loading conditions from Weinans [21]

Figure 16.
Comparison of bone density distribution between current mechanobiological model and phenomenological model after applying triangular compressive mechanical load.

the entire basic bone microstructure. As a result, the trabeculae are mostly directed along the main load directions with an increasingly smaller size and less intense loads. The localization of cell activation is linked to the calculated mechanobiological stimulus and its quantification is done in the same way.

The results obtained are compared with data extracted from a phenomenological model developed in the literature [21]. Here, comparable results are observed at the level of bone density distribution (**Figure 16**). As a result, the model developed has a good estimate of biological activations and a consistency more adaptable to the patient. The microstructural properties of the bone obtained is strongly related to mechanical and quantifiable biological parameters. Mechanical stability is obtained by provocation and localization of biological cells, and can be physically close to real cases.

7. Conclusion

In this study, three 3D FE model for each nano-scopic struc- ture of bone ultrastructure (MCM, MCF and MCFR) were proposed. Different numerical simulations were performed to identify the apparent behavior for each structure (global homogenized) and to identify the corresponding apparent mechanical properties. The proposed 3D geometric models were used to perform para- metric studies to see the influence of geometrical and mechanical properties of the elementary constituents (HA crystals, TC molecules and cross-links) on the equivalent properties. In a second step, a multiscale approach using neural networks was developed. This approach uses the results of the finite element analysis for the training phase. It allows us to generalize the results obtained by finite element and do the transition between the different scale levels. The results were compared and vali- dated by other studies from the literature and a good agreement was observed. This hybrid multiscale approach allows deter- mining quickly (a few seconds) the mechanical equivalent properties as a function of the entered parameters. Here the method was only used to determine the elastic properties but can be approved to identify mechanical equivalent properties related to fracture behavior.

Otherwise, the proposed bone remodeling model can be enriched by the integration of transduction processes in addition to cellular activities and the explicit integration of the effects of RANKL/RANK/OPG regulation. It would also be useful to study the behavior of the bone remodeling model on heterogeneous 2D and 3D femurs. The scenarios (age, sex, physical activities, etc.) illustrated in this study are not exhaustive and others (medication, calcium content, etc.) can be incorporated.

Nomenclature

MCMs	the mineralized collagen microfibrils
MCFs	the mineralized collagen fibrils
MCFRs	the mineralized collagen fibers

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References

[1] TOPPETS V, PASTORET V, De BEHRV, ANTOINE N, DESSY C, Morphologie GABRIELA. croissance et remaniement du tissu osseux. Ann. Méd. Vét. 2004;**148**:1-13

[2] WOLFF J.L. The law of bone remodeling (traducted by Marquet P., Furlong R.) Springer, Berlin; 1986.

[3] FROST H.M. Skeletal structural adaptations to mechanical usage: 2. Redefining Wolff's law: the remodeling problem. Anat. Rec. 1990; 226: 414-22.

[4] E. Hamed, E. Novitskaya, J. Li, P.-Y. Chen, I. Jasiuk, J. McKittrick. Elastic moduli of untreated, demineralized and deproteinized cortical bone: Validation of a theoretical model of bone as an interpenetrating composite material. Acta Biomaterialia 8 (2012) 1080-1092.

[5] COURET I. Biologie du remodelage osseux. Médécine Nucléaire - Imagérie Fonctionnelle et Métabolique. vol. 28-n° 2, 2004.

[6] A. Madeo, D. George and Y. Rémond, Second gradient models for some effects of micro-structure on reconstructed bone remodeling, Computer Methods in Biomechanics and Biomedical Engineering 16 (2013), S260–S261. doi:10.1080/ 10255842.2013.815856.

[7] Y. Lu and T. Lekszycki, A novel coupled system of non-local integro-differential equations modelling Young's modulus evolution, nutrients' supply and consumption during bone fracture healing, Zeitschrift fur Angewandte Mathematik und Physik 67 (2016), 111. doi: 10.1007/s00033-016-0708-1

[8] D. George, C. Spingarn, A. Madeo and Y. Rémond, in: Effects of Mechanical Loading Conditions on 3D Bone Reconstruction: A Theoretical Numerical Study for Application to Maxillo-Facial Surgery, 9th European Solid Mechanics Conference, Madrid, Spain, 2015.

[9] Dessouter, J. Le remodelage osseux normal et pathologique. Revue francophone des laboratoires. 2012. vol. 2012, no 446, p. 33-42.

[10] Servier TechBlog. L'os un tissu vivant - Le remodelage osseux : du normal au pathologique. [Vidéo en ligne]. 2013. Cité le 12 nov. 2017.

[11] Charbonnier, B. Développement de procédés de mise en forme et de caractérisation pour l'élaboration de biocéramiques en apatites phosphocalciques carbonatées. [Thèse de doctorat]. Lyon. France. ED SIS Saint-Étienne. 2016.

[12] A. Barkaoui, R. Hambli, Nanomechanical properties of mineralised collagen microfibrils based on finite elements method: biomechanical role of cross-links, Comput. Methods Biomech. Biomed. Engin. 17-14 (2014) 1590-1601.

[13] F. Yuan, S.R. Stock, D.R. Haeffner, J.D. Almer, D.C. Dunand, L. Catherine Brinson, A new model to simulate the elastic properties of mineralized collagen fibril, Biomech. Model. Mechanobiol. 10 (2011) 147-160.

[14] M. Nierenberger, G. Fargier, S. Ahzi and Y. Rémond, Evolution of the three-dimensional collagen structure in vascular walls during deformation: An in situ mechanical testing under multiphoton microscopy observation, Biomechanics and modeling in mechanobiology 14 (2015), 693-702. doi:10.1007/s10237-014-0630-4.

[15] Jason Coquim, Joseph Clemenzi, Mohsen Salahi. Biomechanical Analysis Using FEA and Experiments of Metal Plate and Bone Strut Repair of a Femur Midshaft Segmental Defect. BioMed

Research International, Volume 2018, 11 pages.

[16] T. Lekszycki, Modeling of bone adaptation based on an optimal response hypothesis, Meccanica 37 (2002), 343-354. doi:10.1023/A:1020831519496.

[17] M. Nierenberger, Y. Rémond and S. Ahzi, A new multiscale model for the mechanical behavior of vein walls, Journal of the mechanical behavior of biomedical materials 23 (2013), 32-43. doi:10.1016/j.jmbbm.2013.04.001.

[18] S. Jaramillo-Isaza, P.E. Mazeran, K. El-Kirat and M.C. Ho Ba Tho, Effects of bone density in the time-dependent mechanical properties of human cortical bone by nanoindentation, Computer Methods in Biomechanics and Biomedical Engineering 17 (2014), 34-35. doi:10.1080/10255842.2014.931090.

[19] George, Daniel et al. 'Examples of Multiscale and Multiphysics Numerical Modeling of Biological Tissues'. Bio-Medical Materials and Engineering 28 (2017) S15-S27 S15. DOI 10.3233/BME-171621.

[20] R. Ruimerman, P. Hilbers, B. van Rietbergen and R. Huiskes, A theoretical framework for strain-related trabecular bone maintenance and adaptation, Journal of Biomechanics 38 (2005), 931-941. doi:10.1016/j.jbiomech.2004.03.037.

[21] H. Weinans, R. Huiskes and H.J. Grootenboer, The behavior of adaptative bone remodeling simulation models, Journal of Biomechanics 25 (1992), 1425-1441. doi:10.1016/0021-9290 (92) 90056 -7.