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The multiform bio-mechanical phenomena occurring in bones grafted with the addition of artificial materials urge for the formulation of models which are sophisticated enough to describe their complexity. In the present paper we present a continuum poro-elastic mixture model in which two apparent mass densities are introduced to describe, at a macroscopic length scale, situations in which bone tissues and artificial materials coexist and interact. We focus on the final healing stage process when the bone remodelling becomes the dominant phenomenon. Artificial materials used are obviously to be bio-compatible and must resist to externally applied mechanical loads. More recently in order to favour bone tissue re-growth in grafts, which improves the long term performances of grafted bones, it has been conceived to use substitute materials which may be, similarly to bone tissue, bio-resorbed by osteoclasts and eventually replaced by newly synthesised living tissue. To account for resorption and synthesis phenomena suitable evolution equations are introduced for Lagrangian mass densities of the mixture constituents in which an integrodifferential operator defined on deformation fields appears. This operator is chosen to model some features of the coupling between mechanical compliance and biological bone tissue activity. The obtained system of integrodifferential equations is not trivial also when one considers one dimensional cases. Treating this simplified situations will allow us to individuate more easily some important remodelling scenarios. The numerical simulations which we present here show that the introduced model is promising and deserves to be developed to give previsions in more realistic applications.

1 Introduction

In this paper we present a mathematical model aiming to describe some of the complex bio-mechanical phenomena which occur in bones tissues when they are reconstructed or reinforced by the addition of an artificial resorbable material. The mechanical behaviour of living tissues is strongly influenced by its micro-structure which may present many length scales: these phenomenological aspects can be addressed by the introduction of "composite" continuum models describing considered tissue at a macroscopic level. The modelling spirit and used methods of the present paper are similar to those presented e.g. in [18], or in [25]. Also in bones or reconstructed bones stress or deformation energy concentration may determine phenomena of crack growth and eventually material failure: see e.g. [8] where the methods used for standard engineering materials are adapted for describing bone tissue behaviour. However, a relevant difference may be recognized in living tissues: they are continuously regenerated and remodelled by means of mechanism driven by living cells. In fact, also in bones grafted with bone-substitute bio-resorbable artificial materials the living bone tissue is synthesized or resorbed and the artificial material is resorbed and possibly replaced by a living tissue: the aforementioned process of remodelling has to be suitably designed to reduce stress and deformation energy concentration and therefore crack initiation and/or propagation.

The process of remodelling in living tissues needs to be suitably described mathematically. In [26] an interesting effort is directed to get macroscopic remodelling laws by means of a micro-macro identification process. Also interesting are

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the results presented in [13] and [14] where the self-remodelling process of a living tissue under deformation is related to the local stress state. Instead, here we propose to assume as a driving signal for remodelling the density of deformation energy: this may be considered more suitable for bone tissues as the mechanism which is active in them is most likely related to the deformation of osteocytes induced by the flow of interstitial fluid. As done in all previously listed papers we adapt well-established methods from continuum mechanics by choosing to model bone remodelling as a "biologically-driven" change of mechanical constitutive equations. Indeed, the biological system which naturally has been developed by evolution is capable of an action of remodelling excited by mechanical loading which is called "functional adaptation". Our aim is to determine under which conditions the mechanisms driving the natural functional adaptation process still are able to produce their beneficial effects also in presence of grafted materials in reconstructed bones. As it is clinically observed that sometimes grafted materials may be too quickly completely resorbed thus leaving voids in reconstructed bones we want to determine in which conditions and to what extent the action of functional adaptation will lead to a replacement of bio-resorbable material with bone tissue or at least to the final constitution of a stable composite.

In the presen,t paper we show that the presented mathematical model is able to describe many important aspects of bone remodelling phenomena so that we can be confident that -once suitably developed- it may be used as a guide when formulating surgery protocols.

1.1 Framing the presented model in the context of the available literature

The model which we present here share many characteristics with some continuum models already presented in the literature. One preliminary remark is needed: as recalled in the following subsections, for what concerns the specific phenomena we want to describe here (and as described carefully e.g. in [48]), the mechanical and biological structure of bone tissue is very complicated. A complete and simultaneous description of all the phenomena occurring in its growth or resorption may lead to models too complex to be treatable. Therefore one must attempt their synthetic description by means of models reaching the suitable compromise between capability of describing the phenomena we are interested in and manageability. For instance: in the present paper we will use Cauchy continua to model the bone tissue mechanical state. However, it is well known (see e.g. [49], [42], [21]) that the mechanical micro-structure of bone tissue may oblige us, in order to suitably describe some important phenomena, to use Continua with Couple Stress since bone tissue is actually a composite material. Indeed, in the present paper we will use, for describing the process of graft resorption in reconstructed bones, a suitable mixture theory for the most complex composite constituted by the artificial material and bone tissue. Therefore, we will use some of the concept used e.g. in [35], [2], where couple stress two-phase composites continuum models are introduced. We explicitly remark here and will better explain later on that the presented mixture model only has one Lagrangian configuration for the two constituents. It means that each material particle actually represents a RVE in which two solid phases coexists. In order to get some preliminary indications about the efficiency of our model we presently refrain from introducing couple stresses, but we do retain the description of the two-phase constitution of the considered continuum. Once we have introduced a simplified description of stress state of bone tissue and artificial material mixture, we must address the problem of choosing suitable constitutive equations for stress: following some of the indication found e.g. in [37], in [22], or in [15], we introduce suitable elastic moduli for the considered mixture, refraining, at a first stage, from any multi-scale modelling. This modelling should generalize the considerations developed for a pure bone tissue e.g. in [19] or in [50] (where again the trabecular bone is regarded as a couple stress continuum). Again, for the sake of simplicity, we will consider in this first investigation the bone tissue/artificial material mixture as linear elastic: the present model needs to be improved by following the results shown e.g. in [40] where a fabric-dependent fracture criterion for bone is introduced. Furthermore, in [1] the problem of functional adaptation of bone tissues as an optimal control problem assuming strain energy density as mechanical stimulus is formulated. The optimization procedure there presented directs the control rule of mass density remodelling toward a compromise between two conflicting objectives, namely weight and stiffness; a two-dimensional sample is worked out via FEM analysis.

In growth phenomena an interface between pure bone tissue and the mixture of bone tissue and artificial material will be considered: we will be ale to describe some scale and boundary layers at this interface. The considerations developed in [52] are of relevance in this context.

We consider that the final application of our theoretical treatment is the design of suitable surgical techniques: therefore in our numerical simulations we have accepted the spirit which leads the investigation of many "bio-engineers" as those presented e.g. in [39] (where the bone-implant interaction is studied), in [47] (where a preoperative planning procedure is conceived and a post-operative estimation of the obtained results is presented), in [7] or in [36] (where concurrent engineering design of prostheses and surgical techniques which account for the bone remodelling phenomenon are developed).

Although for the moment we can present only purely qualitative results, in the following section it is proven that the model we present should be able to reduce the occurrence of artificial material inclusions in the completely healed reconstructed bones. We conclude this short review of some among the papers relevant for the results we present here by

underling how important are the phenomena of load transfer between bone tissue and artificial reinforcement materials used in bone reconstruction (see e.g. [41]): the numerical simulations we have obtained show how important are the modalities with which mechanical strain energy is differently distributed between the pure bone tissue and the bone tissue/artificial material mixture.

1.2 Medical and biological motivations

Application of bone substitute materials becomes an everyday practice in orthopaedic, jaw and skull surgery. Because of the large number of bone grafting procedures applied every year, the possibility of application of bone substitutes and determination of their optimal characteristics poses a substantial and still actual problem (see [12], [23], [32]). There are many bio-compatible materials of different chemical composition, form, macro- and micro-structure, mechanical and bio-chemical characteristics actually available in the market. Most of them can be categorized as biodegradable, bio-resorbable or a composition of these two.

Big efforts are directed to determine morphological, physiochemical and biological characteristics of bone substitute materials both at the macro-level of tissue as well as at the micro-level i.e. at the cellular one see e.g. [38], [16], [45], [3]), [24], [10].

Clearly the materials used for application in surgery should satisfy several fundamental requirements. Of course the first and absolutely necessary requirement is bio-compatibility, but there are also many others. One of them is mechanical strength: since the implanted graft serves after surgery, especially in case of big cavities in bone, as a supporting element then its mechanical characteristics should ensure this function. Mechanical strength depends to a great extent on the characteristics of the material which is used as a building material of a graft and on its macro- and micro-structure. Another important requirement is the ability of a graft to integrate and positively interact with the natural living bone tissue, and this integration and interaction process is determined both by the biochemical and bio-mechanical characteristics of used artificial material. Indeed, the mechanical characteristics and micro-structure of this material can promote or make more difficult the bio-resorption or at least the effective integration of artificial materials with bone tissue.

Concerning bio-mechanical and structural parameters several points should be mentioned. It is well-known that mechanical state in a bone plays a fundamental role in tissue formation, healing and remodelling. Appropriate porosity of the artificial material is necessary to enable cells migration and their expected activities (see e.g. [10]). The mechanical state and the material micro-structure influence greatly the differentiation process of the reconstructed tissue. The size of pores defines also condition for development of vascularization necessary for the survival of bone cells. As it follows from the above discussion, together with the pure biological and chemical factors, also the mechanical and structural parameters play an important role in good integration of bone graft and also in its durability.

Since the mechanical and biological properties of natural tissue are better when compared to the artificial graft ones (at least when this graft uses the artificial materials which were available up to now) it can be expected that the best scenario after graft implantation is its gradual replacement by natural bone tissue. Indeed it is, presently, only a dream the possibility of using, in grafts, artificial material which are biologically active and have bio-mechanical features in all aspects improved with respect to natural bone tissue.

1.3 Some basic facts about, mechanosensation, mechanotransduction, bone tissue resorption and synthesis and artificial material resorption

In the process of replacement of artificial material with living bone tissue, different effects are present. Among them: bone tissue and graft resorption and new tissue formation. These three simultaneous processes are not independent and their individual contribution in the remodelling affects actual topology changes and resulting variations of mechanical state of the reconstructed bone. Mechanical state controls activities of cells responsible for resorption and formation of intracellular matrix what finally determines the final effect of remodelling. After implantation of graft of bio-resorbable bone-substitute material, similar effects to those present during consecutive phases of fracture healing can be observed, see. [53]. In addition the process of possible resorption of graft and its replacement by a natural bone tissue takes place.

In the present study we focus on the last phase of bone healing in presence of grafted bio-material i.e. on two simultaneous effects: i) remodelling of already formed tissue in the vicinity of wound associated with functional adaptation and, ii) possible resorption of a graft implanted during surgical treatment.

These two processes are possible because of the activities of cells specialized in mechanosensation, mechanotransduction and tissue resorption and synthesis, see e.g. [4], [46], [34], [43].

The resorption of both bone tissue and artificial material and the formation of intracellular bone matrix are guaranteed by the action of so called “actor cells”. This action is triggered by a signal determined by the mechanical state of bone tissue

and this triggering is extremely important as it is the interplay of resorption and formation processes which determines the final properties of the reconstructed bone.

To be more precise, we may distinguish between two types of cells (belonging to the introduced common class of "actor cells"), namely: the osteoblasts (specialized in new bone tissue formation) and the osteoclasts (which are able to resorb both natural bone and bio-resorbable material). These two kinds of actor cells have different roles and originate from some different precursor cells. The osteoclast is derived from cells in the mononuclear/phagocytic lineage of the hematopoietic marrow, see [4]. The osteoblasts are derived from mesenchymal progenitors. Osteoblast precursors are located near bone surfaces: the periosteum, the endosteum, and the adjacent marrow stroma (perivascular parenchymal cells). They arise from local, undifferentiated intraskeletal mesenchymal cells that are capable of mitosis, [4].

All precursor cells can freely move inside those porous materials which have a suitably large interconnected porosity. Therefore precursor cells of both types of actor cells can penetrate inside a pore and deposit at the free surfaces of both the living bone tissue and the porous artificial bio-compatible material.

In this paper we assume that everywhere in the living tissue and in the artificial material there are available precursor cells to form both osteoblasts and osteoclasts so that these transformations may occur when necessary. We assume that osteoclasts and osteoblasts will act when two simple conditions are verified: i) "effective" porosity allows for deposition of precursor cells and ii) the required stimulus is present.

Indeed, precursor cells give rise to osteoblasts or to osteoclasts following the instructions given by signals generated by a third kind of cells called osteocytes which are distributed in the intracellular matrix. They are connected with a cluster of neighbour osteocytes and form a "sensing" network. The signal emitted by osteocytes depends on mechanical state which they can "measure" at a given point (for this reason they are also called "sensor cells"). In order to accomplish their task of measuring mechanical state characteristics at a given point, the sensor cells do not move and spend all their life in that point. Sensor cells originate from osteoblasts when these latter have accomplished their task of synthesizing new bone around them: when an osteoblast is completely surrounded by new natural bone tissue it changes its nature and becomes an osteocyte, i.e. a sensor cell which starts to measure and to emit a signal proportional to the measured value of deformation energy.

Some additional remarks on the differentiation of precursor cells into an osteoclast or an osteoblast are needed at this point. When a high-level signal appears in a given position osteoblasts interprets it as an order to deposit on the available surface close to this point and to synthesize extracellular matrix. In contrast to this situation, when the signal is too small to attract osteoblasts, the osteoclasts can deposit on a free surface of bone tissue or a graft that is not occupied by osteoblasts and start their activities resorbing the material around them.

In a healing process, after the initial inflammation state and clot formation, the formation of the fibrous tissue follows, driven by many biochemical and bio-mechanical processes, in which, however, bone tissue formation is predominant. Clearly this is not the end of the biological process we want to investigate. After initial assurance of mechanical integrity and basic strength, the process of remodelling starts to enable formation of fully functional bone tissue. At this stage, depending on mechanical and topological situations, the artificial graft may be either surrounded by a new tissue or resorbed leaving a void, or resorbed and replaced by a living tissue.

Generally speaking, two basic scenarios are possible next.

In the first one, the micro-structure of the grafted material and the surrounding bone tissue does not enable migration of actor cells into the graft deep from the interface with natural tissue, or does not enable development of vascular system necessary for cells survival inside the bone tissue which is being formed in the graft. In such a situation the bone synthesis and remodelling in the graft is possible only very close to the interface with the living tissue. Therefore the majority of the graft mass remains unchanged or changes very little and represents a kind of inclusion in a natural tissue.

According to the second scenario, the actor cells can propagate into a domain occupied by a graft and can survive there. The control signals from osteocytes located in a tissue can also reach the cells in a graft so these cells can normally operate. Depending on actual activities of osteoblasts and osteoclasts the pores in a graft can be filled by a new tissue or the graft material can be resorbed and possibly replaced later by a new natural tissue. All of these complex and related-with-each-other effects are dependent on many factors. But this final process of bone remodelling in a region initially occupied by bio-resorbable material is very important and determines the final state and the final quality of reconstructed bone tissues.

In this study we focus our attention on this final stage of healing after graft implantation in bone as, together with the initial stages present after surgery and graft implantation, this process is important and determines possible success or failure of surgery on the long term.

1.4 List of the modelling assumptions which we have accepted

We start from the obvious observation that a porous graft of bio-resorbable material is located close to a porous living bone tissue. To make the formulation of the needed mathematical model more treatable we, in fact, assume that a mixture of two

porous materials – the grafted bio-material and the natural bone tissue- is present and that their apparent mass densities and resulting mixture porosity can change in time and space with respect to the mechanical state and to the associated biological activities of appropriate cells.

Let us collect below the basic assumptions made in order to formulate the mathematical description of the remodelling process in the considered mixture constituted by bone tissue/bio-resorbable material.

– osteoblasts and osteoclasts activities are proportional to the stimulus from the osteocytes, i.e. the sensor cells;

– osteocytes produce the signal proportionally to the density of strain energy in the region where they are located;

– the number of sensor cells present in a "material particle" of considered mixture continuum is proportional to the apparent density of the natural tissue and the signal originated by this material particle is proportional to the number of present sensor cells (see next subsection for a rigorous definition of these quantities);

– the signal sent from osteocytes to the actor cells decreases exponentially with the distance between them (in the sense specified in Eq. 7 later on);

– the actor cells elaborate and integrate all signals sent by surrounding sensor cells which reach them,

– the sensor cells can be located only close to real living tissue (not in artificial graft);

– the tissue can be resorbed or synthesized but the graft material can be only resorbed;

– the number of the actor cells in a given place depends on the porosity of host composite material. The minimal values are associated with great porosity (porosity = 1) and with absence porosity (porosity = 0). When the host material is too porous then the actor cells cannot deposit at the surface of the host material, simply because there is not enough matter to which they can attach to. When porosity is too low then actor cells cannot reach the considered region of host material. We therefore assume that there exists an optimal value of porosity associated with the presence of the largest number of actor cells and the highest level of their activities.

All listed features of the considered bio-mechanical systems will be incorporated into the mathematical model which we present in the following sections and finally apply to perform numerical simulations.

2 Eulerian description of a solid mixture constituted by bone-tissue and bio-resorbable material

For references concerning the basic concepts of continuum mechanics we use in these and all the subsequent sections we refer to [9], [44] and [4].

When considering a solid material constituted by a mixture of a bio-resorbable material (of the type used in bone reconstructive surgery) and living bone-tissue it is suitable to introduce the following (Eulerian!) fields, all evaluated at the position $x \in E$ (where E is the three-dimensional euclidean space) and at the time instant t:

1. the (apparent) mass density of bone-tissue $\rho_b(x,t)$;
2. the (apparent) mass density of the bio-resorbable bone-substitute material $\rho_m(x,t)$. In the sequel, when needed we will use the shorter expressions "artificial material" or "bio-material";
3. the porosity of the bone tissue/bio-material mixture $\varphi(x,t)$: i.e. the Eulerian volume fraction which is not occupied by bone tissue or bio-material;
4. the (apparent) total mass density $\rho(x,t) := \rho_b(x,t)+\rho_m(x,t)$ and the bone tissue mass fraction $\xi_b(x,t) := \rho_b(x,t)/\rho(x,t)$;
5. the (resorption-synthesis) stimulus $S(x,t)$; i.e. a scalar quantity which measures the activation signal collected at (x,t) by the actor cells, that is osteoblasts (responsible for synthesis of bone tissue) and osteoclasts (responsible for resorption of bone tissue or bio-material);
6. the volume strain-energy density $U(x,t)$; i.e. the energy needed to deform the elementary volume of the mixture bio-material/bone tissue from a "natural" configuration to the actual one;
7. the density of active sensor cells $d(x,t)$, i.e. the number of osteocytes per unit volume which are able to measure the mechanical state and send the signal which will act as stimulus for the actor cells (such sensor cells are present only in living bone-tissue). We postulate that a good indicator of mechanical state may be the strain energy density.

We are aware of the fact that the biological phenomena occurring in a bone tissue (in presence of bio-material artificially added to it) are very complex.

The kinematical descriptors we have just introduced seems to us to supply the simplest mathematical model which is able to describe an elementary bone remodelling process in presence of added artificial material. The process which we are

considering here occurs after the end of the initial stages of healing which immediately follow surgery, as more carefully discussed in the introduction.

3 Reference configuration and Lagrangian description for bone/bio-resorbable material porous solid mixtures

A reference configuration needs to be introduced to describe deformation occurring in considered solid mixture. Indeed, it is well-known that at least the strain deformation in bone-tissue is a physical quantity of relevance in the resorption/synthesis phenomena arising in it. Similarly, it will be of relevance in the considered mixture composed by bio-material and living bone-tissue, this last being the only which is carrying the sensor cells. These last, after having measured the deformation energy, will convey a suitable stimulus to the actor cells which are assumed able to be activated whenever in the whole bone tissue/bio-material mixture the values of "effective" porosity allow the deposition of precursor cells.

We start assuming that it is possible to suitably introduce a reference "average" configuration C^* and

1. an "average" placement field

$$\chi : C^* \times \mathbb{R} \to E$$

2. together with two referential mass density fields

$$\rho_b^* : C^* \times \mathbb{R} \to \mathbb{R}^+, \qquad \rho_m^* : C^* \times \mathbb{R} \to \mathbb{R}^+.$$

We will then denote $C_t := \chi(C^*, t)$ the current configuration of the bone/bio-material solid mixture.

At this stage we refrain from any effort directed to introduce any "homogenization" procedure, producing, after suitable averages, an expression for deformation energy in terms of "microscopic" phenomena occurring at a smaller scale.

Actually, the field χ is introduced to describe the placement and deformation of the solid mixture under consideration, and is assumed to be able to "fully" determine the "biologically measurable" deformation energy and to relate (with well-known classical formulas) the introduced referential and spatial mass densities.

Once the notations ($\mathbf{F}$ is called deformation gradient, J its determinant, describing the volume variation between Lagrangian and Eulerian configuration and $\mathbf{G}$ is the Green Saint-Venant strain tensor)

$$\mathbf{F} := \nabla\chi; \qquad J := \det \mathbf{F}, \qquad 2\mathbf{G} := \mathbf{F}^T\mathbf{F} - \mathbf{I}$$

are introduced, the physical meaning of the all previously introduced fields is specified once the following assumptions are accepted:

$$J^{-1}\rho_b^* = \rho_b \circ \chi, \qquad J^{-1}\rho_m^* = \rho_m \circ \chi, \qquad J^{-1}U^* = U \circ \chi$$

As a consequence, once having introduced the notation $\rho^* := \rho_b^* + \rho_m^*$ one also has $J^{-1}\rho^* = \rho \circ \chi$.

The introduced reference configuration is the domain in which all fields describing the remodelling process under study will be defined. It is most suitable and must be preferred to any kind of Eulerian configuration, as this last is, in general, a time-varying domain.

4 Constitutive Equations

In this section we specify the interaction between sensor cells and actor cells (see [43]) as mediated by stimulus intensity. It is well-established (see e.g. [4] and [43]) that sensor cells produce a signal which is sent to actor cells surrounding them. The overall signal collected by any actor cell is the stimulus it perceives. The signal depends on the deformation energy which is "measured" by sensor cells in the portion of tissue where they are placed. This signal reaches actor cells and drives their behavior and its intensity depends on the distance between sensor cells and actor cells. All these cause/effect relationships we model by means of suitable constitutive equations. Another phenomenon to be accounted for by our model concerns the effect of biological actions on mechanical behavior of the mixture of bone tissue and bio-material: these actions affects the (apparent) densities of both materials, the mixture porosity and its elastic coefficients.

We model the listed cause/effect relationships by means of simple evolution equations, similar to those derived in [28] but extended to take into account i) the effects of "effective" porosity on cell activities, together with ii) the presence of artificial material in which the sensor cells are not present.

We explicitly remark that the postulated equations allow us to simultaneously deal with resorption of both bio-material and bone tissue or with synthesis of bone tissue. On the other hand, we introduce suitable constitutive equations to model the relationships among biological and mechanical states, signal and stimulus, or stimulus and remodelling.

4.1 Deformation energy

We will assume that it is possible to represent the Lagrangian deformation energy density as a function of the Green Saint-Venant strain tensor, the apparent volume Lagrangian mass densities and eventually on the considered material particle X^*. We explicitly remark that the assumed deformation energy does not depend explicitly on time and that, differently to what happens in standard continuum mechanics, the Lagrangian mass densities are, in general, evolving with time. However these changes are assumed to be slow enough so that no inertia effects need to be taken into account in their evolution so that the initial rate of change of mass densities and the consequent transient phenomena are not accounted for in the considered model..

In formulas, we assume the existence of a function U^*, representing the strain energy, such that

$$J^{-1}U^*(\mathbf{G}, \rho_b^*, \rho_m^*, X^*) = U \circ \chi. \tag{1}$$

In the sequel we will consider a particular case of the constitutive equation (1) for our numerical simulation, particular case which is suggested by the biological phenomena which we have in mind [1]:

$$U^*(\mathbf{G}, \rho_b^*, \rho_m^*, X^*) = \mu tr\mathbf{G}^2 + \frac{\lambda}{2}\left(tr(\mathbf{G})\right)^2 \tag{2}$$

where we assumed

$$\mu = \hat{\mu}(\rho_b^*, \rho_m^*, X^*); \qquad \lambda = \hat{\lambda}(\rho_b^*, \rho_m^*, X^*).$$

These last equations are usually taken of the form:

$$\mu = \mu_0 + \mu_{1b}\left(\rho_b^* - \rho_{0b}^*\right)^{C_b} + \mu_{1m}(\rho_m^* - \rho_{0m}^*)^{C_m}, \quad \lambda = \lambda_0 + \lambda_{1b}\left(\rho_b^* - \rho_{0b}^*\right)^{D_b} + \lambda_{1m}(\rho_m^* - \rho_{0m}^*)^{D_m}, \tag{3}$$

where all the parameters which were not introduced up to now are constant. For a discussion of this family of constitutive equations see e.g. [43], [4], Hodgskinson and Currey (1992) or Goulet *et al*. (1994).

4.2 Density of sensor cells

We assume that a material particle of the bone/bio-material solid mixture is biologically active. Indeed in living bone-tissue osteocytes are present. These are mechanosensation cells: they detect the deformation state in their neighbourhood. Osteocytes are cells which result from a biological transformation occurring in completely formed bone tissue: this tissue is built by osteoblasts, when a biological signal tells them that it is necessary to synthesize bone tissue. As soon as it is necessary to continue to build bone tissue, osteoblasts remain localized where they were deposited and go on synthesizing bone tissue. At a given moment an osteoblast is completely surrounded by bone tissue and it cannot synthesize any more. Then it becomes an osteocyte: its work will be to measure the strain-deformation energy in its neighbourhood and "to warn" all surrounding actor cells about the mechanical state of the part of bone tissue it is controlling.

Therefore to describe some of the biological mechanisms occurring in bone/bio-resorbable material solid mixture we introduce a constitutive equation relating the bone-tissue and bio-resorbable material mass densities to the density of sensor cells,

$$d = \hat{d}(\xi_b, \varphi).$$

Indeed, it is clear that the density of sensor cells are an increasing function (*ceteris paribus*) of the total mass of living tissue in the mixture bone/bio-material: therefore when introducing the parameter ξ_b also the parameter φ must appear.

In the numerical simulations which we have performed we have assumed the following constitutive assumption for the density of sensor cells:

$$d = a\rho_b, \qquad a = \eta\left(\rho_{\max}\right)^{-1}, \qquad 0 < \eta \leq 1 \tag{4}$$

where $\rho_{\max}$ is the maximum possible density of the bone tissue/bio-material mixture, i.e. the mixture apparent density corresponding to vanishing porosity.

[1] the symbol $\mathbf{a}^2$ indicates the scalar the scalar product of the tensor field $\mathbf{a}$ with itself.

4.3 Porosity

Growth and remodelling of bone tissue are made possible by the action of osteoclasts and osteoblasts. These cells are formed, by means of some complex mechanisms, when and where synthesis or resorption of bone tissue are needed. The biological process leading to the activation of osteoclasts and osteoblasts involves the diffusion of their precursor cells through the bone-tissue. Physiologically bone-tissue is porous, and a fluid is filling its pores. This fluid transports the precursor cells. In order to be assured that the activation process leading to the formation and action of osteoclasts and osteoblasts is possible (i.e. in order to be sure that the bone/bio-material solid mixture is biologically active) one needs to be sure that such a mixture is porous, and its porosity allows for both i) the needed cell diffusion phenomena and ii) the nutrition supply associated with the development of a suitable vascular network. Moreover, the actor cells need to have pore surface where to sit in order to start their action. Of course in the following considerations we will assume that the pores inside the bone tissue/bio-material mixture have a "regular" shape: this means that the pores have not any fractal nature, their shape ratio is not too big, and so on. This is needed in order to be assured that porosity is a correct measure of the available pore surface where actor cells may deposit.

Since porosity is considered here as a correct measure of the available pore surface where actor cells may deposit, then it is a kinematical parameter which needs to be introduced if one wants to describe remodelling phenomena in living bone-tissues and also in bone/bio-material solid mixture. In this mixture if porosity is too low (and pores have a "regular" shape!) then living cells will not be able to efficiently resorb the resorbable material neither to form new bone tissue, as the available space will not allow for the action of a suitably large number of actor cells. If porosity, on the other hand, is too large then we do not have enough matter (i.e. bone tissue or bio-material) on which actor cells may deposit. Also in this circumstance remodelling will not occur quickly enough or will not occur at all.

To describe the mechanical phenomena which influence the porosity variation in considered solid mixture we introduce a constitutive equation

$$\varphi = \hat{\varphi}(\mathbf{G}, \xi_b, \rho, X^*) \tag{5}$$

which links the "effective porosity" (effective for the deposit of actor cells) to the strain-tensor $\mathbf{G}$ and to apparent mass volume densities.

Behind the assumption (5.) there is an implicit "instantaneous local microscopic equilibrium" hypothesis. We assume that locally (i.e. inside any elementary volume of considered mixture and at a microscopic level) transient phenomena, which adjust the porosity when local deformation state and apparent mass densities vary, occur in characteristic times which are negligible with respect to the time scale at which happen the evolutionary phenomena which we want to describe. Moreover, we will assume that the final porosity in a macroscopic material particle of the considered mixture depends only on the "average" micro-elasticity moduli and on the "total" mass of bone tissue and bio-material present inside it and is nearly independent of the "micro" distribution of mass inside it. This assumption, rather standard in mixture theory seems well-grounded, even if maybe a more detailed analysis about it is required, by use of suitable and delicate homogenization arguments. This assumption allows for the formulation of a macro-theory formally self-consistent: all informations about the phenomena occurring at micro-level are assumed to be accounted for by the introduced constitutive equation.

In the numerical simulations we have performed we assumed that porosity is given to be the following constitutive equation

$$\varphi = 1 - \theta \frac{(\rho_b + \rho_m)}{\rho_{\max}}, \qquad 0 < \theta \leq 1. \tag{6}$$

This assumption is rather standard in mixture theory and its validity can be assessed in a large range of physical situations.

4.4 Stimulus

The action of osteoclasts and osteoblasts is tuned by a biological stimulus. We assume that, similarly to what occurs in physiological bone-tissue, such a stimulus is conveyed in every material particle of the bone/bio-material solid mixture by the surrounding osteocytes.

We assume that the signal stemming from a sensor cell in a given material particle of the bone/bio-material mixture is instantaneously transmitted (i.e. the transmission time scale is negligible when compared with the characteristic time of the remodelling phenomena) and that its intensity decays exponentially with the distance from it. Moreover, we assume that the signal sent by all sensor cells located in a given material particle is of the same intensity, so that the total intensity of the signal sent by considered material particle is proportional to d. Finally, we assume that all sensor cells elaborate a signal which is proportional to the deformation energy concentrated in the elementary volume in which they are located.

In conclusion we assume that

$$S(x,t) = \left(\int_{C_t} U(x_0,t) d(x_0,t) \exp(-D \left\| x - x_0 \right\|) dx_0 \right) - S_0(x,t) \tag{7}$$

where the length D^{-1} represents the range of action of sensor cells and the value S_0 is the reference value of stimulus, associated with a biological equilibrium state for which the effect of resorption and synthesis are balanced (eventually depending on the position and time). The meaning of this reference value will become clear later, when a resorption-synthesis law will be formulated. For detailed discussion of the biological evidence which is the basis of the just formulated constitutive equation we refer to [4] and [43].

5 Remodelling and Mechanical Equations:

We are now ready to formulate a well-posed evolutionary problem for the introduced kinematical fields which, in our opinion, is able to catch the most important features of the remodelling process occurring in bone tissue, after initial healing and in presence of bio-material as a bone tissue filler and support.

Again, we believe that remodelling phenomena occur without any inertial effect. Therefore the evolutionary equation for apparent densities will be simply first order ordinary differential equations with respect to time. We will also assume that no spatial gradient of apparent densities occur in the remodelling equation. Also this assumption maybe discussed: we simply assume that the process of remodelling depends on what is occurring outside the elementary volume element only by means of the stimulus and is not influenced by other non-local (e.g. purely mechanical) phenomena.

In formulas we assume that the total mass density rate depends on the local value of the stimulus

$$\frac{\partial \rho_b^*}{\partial t} = \mathcal{A}_b(\varphi, S \circ \chi) \tag{8}$$

$$\frac{\partial \rho_m^*}{\partial t} = \mathcal{A}_m(\varphi, S \circ \chi) \tag{9}$$

These equations are similar to those studied, among others, in [29], [29], [31] and [6]. However, the analysis which lead to the "bifurcation chart" in figure 4 of [29] cannot be easily repeated in the present instance. Indeed, in our problem, the aforementioned evolution equations are coupled to the stimulus ($S(x,t)$), which is itself obtained by the integral operator (7) from the solution of the PDE representing mechanical balance of force (see next subsection). The study of bifurcation in the presented instance also must account for the possible variations of resorption and synthesis parameters, which will be seen in the next sections to dramatically influence the final form and structure of reconstructed bone.

The remodelling-constitutive equations $\mathcal{A}_b$ and $\mathcal{A}_m$ account for different phenomena of biological and mechanical nature together with some geometrical circumstances: i) the surface available for resorption or synthesis "inside" the considered material particle depends, as already discussed, on the "effective" porosity field, ii) the different properties of bone tissue and bio-material determine different resorption rates, due to the different effect of actor cells on these different material, iii) the rate of synthesis of bone tissue which is consequence of a positive stimulus is different from the resorption rate determined by a negative stimulus of the same amount. The previous considerations are consequence of the biological nature of the process of synthesis and resorption: in particular osteoclasts resorb at the same time (and presumably they are not able to be completely selective!) both the bone-tissue and the resorbable material while osteoblasts produce only bone tissue.

We will assume that

$$\mathcal{A}_b(\varphi, S) = A_b(S) H(\varphi); \qquad \mathcal{A}_m(\varphi, S) = A_m(S) H(\varphi)$$

where the functions A_b and A_m are piece-wise linear functions with different slopes for negative and positive values of stimulus (remark that for the bio-material and positive values of the stimulus the coefficient A_m must vanish, as there cannot be synthesis of bio-material) and the function H has a form which qualitatively is represented by fig.1

The function H is designed in order to account for the influence of "effective" porosity on the biological activity of actor cells: when "effective" porosity is too large there is not enough material on which actor cells may deposit, when it is too small there is not enough free space in the pores to allow their mobility and deposit. We may allow for very small positive values of H for the values $\varphi = 0$ or $\varphi = 1$ if we want to account for some specific biological phenomena.

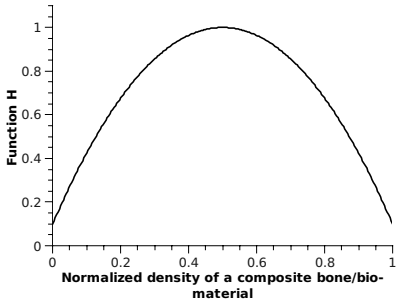


Fig. 1 Sample function H used in numerical example to account for the influence of the composite bone/bio-material density on the activities of actor cells.

The constitutive equations and evolution equations just formulated can be improved in order to take into account, in a more appropriate way, the experimental evidence: indeed it is now accepted that (see e.g. [43]) there exists so called "dead zone" for stimulus. More precisely, when the signal falls in a given range then, even in presence of a stimulus beyond the threshold, there is no activity of actor cells. In order to account for this circumstances more sophisticated models are needed, and will be object of future investigations.

Concerning the mechanical equilibrium of considered body we will assume that no inertia effects are of relevance, when considering applied load and the time scale of remodelling process.

Therefore we will assume that the loads applied to the system are varying so that a quasi-static deformation process is occurring. Therefore we can write the following formulas:

$$Div\left(\mathbf{F}\cdot\frac{\partial U^*}{\partial \mathbf{G}}\right)=-\mathbf{b}^{ext}\qquad \mathbf{F}\cdot\frac{\partial U^*}{\partial \mathbf{G}}\cdot\mathbf{N}=\mathbf{f}^{ext} \tag{10}$$

the first one being valid inside the considered body and the second on the part of its boundary (with outward unit normal $\mathbf{N}$) on which (eventually vanishing) loads are applied.

No difficulty arises when one needs to consider some "kinematical" excitation applied to the body, and we will not detail this point.

Since we are going to address a simple, linearised 1D case, we remark that if the displacement $\mathbf{u} := \chi - X^*$ has only one non-vanishing component u in the direction x_1, then the simplified form of Eqs. (10) simply reads

$$\left(\frac{(\lambda+2\mu)}{2}\,u'\right)'=-b^{ext}\quad \text{on } C^*,\qquad\qquad \frac{(\lambda+2\mu)}{2}\,u'=f^{ext}\quad \text{on } \partial C^*,$$

where the apex denote the space derivative with respect to x_1 and b^{ext} and f^{ext} are the only non vanishing components of $\mathbf{b}^{ext}$ and $\mathbf{f}^{ext}$ respectively.

6 An academic 1-D case study of remodelling in a rod-like bone/bio-material sample showing the potentialities of the presented model: numerical simulations

In order to show that the simple model presented up to now is able to describe different possible mechanisms of bone remodelling among those induced by the presence of bio-material we will study a simple 1-D problem which seems to be the simplest possible presenting some of the required complex features of formulated model.

In order to simplify the study of the mechanical part of the problem, we consider a sample which behaves as a rod (composed by two materials) with variable (with respect to time and space) axial rigidity and porosity. However, time variations of rigidities (which are determined by the corresponding variations of apparent mass densities (see Eq. (3)), i.e. by synthesis and resorption phenomena) and variations of loads occur in a time scale which is much bigger than the transient characteristic time leading to macroscopic mechanical equilibrium. Therefore inertia effects can be neglected in the evolutionary problems considered here. The numerical code used to calculate the sequence of configurations of the considered bar-bone includes a simple closed form expression which links external mechanical applied loads to the corresponding equilibrium deformation states, once the profile of space varying rigidity is given. It is worth to recall here that in the present treatment only mechanical boundary conditions are needed.

Therefore the evolutionary problem which we study will simply involve the equations for time variations of apparent mass densities of bone tissue and bio-material. In these equations the previously listed constitutive equations, and the parameters appearing in them, will appear, which establish the required link between mechanical and biological phenomena.

Used numerical code was written in C Language and we implemented a discrete time step increment algorithm. The flow chart of the code appears in fig. 2.

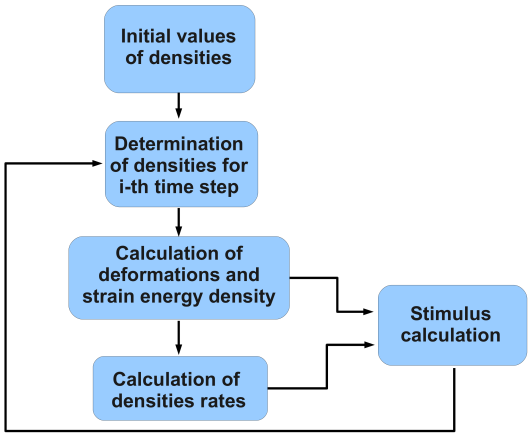


Fig. 2 A scheme of iterative numerical procedure used in an analysis of rod-bone remodeling in presence of ioresorbable bone-substitute material.

The integration scheme is based on a procedure consisting of the following steps:

1. Determination of the apparent density fields for both bone tissue and bio-material: this fields maybe those at initial time or at any subsequent time step;
2. given externally bulk applied loads, kinematical and/or load boundary conditions, using the mechanical equilibrium equations and constitutive equations for elastic moduli we determine displacement, strain and strain-energy density fields;
3. using the result of steps 1 and 2, we can determine the stimulus distribution in the body, once the constitutive equation establishing the link between mechanical deformation and biological activity is used;
4. using the remodelling evolution equation and the constitutive equation relating synthesis or resorption rate to stimulus intensity we determine the rate of the apparent mass densities and we go back to step 1.

A very delicate issue in the performed numerical simulations regards the choice of time step. Indeed the integro-differential equations we are integrating are strongly non-linear. Therefore too large time step may direct the calculated evolution towards configurations which actually are non-reachable in reality. This issue may become a serious one when dealing with coupled PDE for mechanical equilibrium and the equations for bone tissue and bio-resorbable material time evolution. In the 1-D case which we will study in the next sections, however, a careful choice of time step depending on the values of constitutive parameters used is simply resolving the problem. We explicitly remark that the numerical simulations we will present in this paper are qualitative in nature, since we do not specify here any dimensional value of the involved parameters. This will be done in further investigations in order to make easier the application of the presented results to medical practice.

6.1 The case of a sample with initially completely separated bone tissue and bio-material

We consider a sample constituted by bone tissue and bio-material which can be regarded, from a mechanical point of view, as a rod. In considered 1-D case Poisson modulus does not play any role. This is also the case section area of the rod when one considers forces per unit area as externally applied loads. Concerning characteristic length scale, as we aimed to study the behaviour of a trabecula, we have chosen its length l as the reference one, while for the parameter D^{-1} we assumed that $l/10 \leq D^{-1} \leq l$. Concerning the characteristic time we have chosen it so that in the equation for bone synthesis, for a rod bone of length l and loaded by a characteristic stress then the synthesis rate is equal to one. This characteristic stress

(i.e. externally applied force per unit area) is such that in an infinitely long pure bone tissue rod subjected to this stress state there is no bone growth or resorption.

Instead, Young modulus is relevant and it is assumed to show a dependence on apparent mass densities. The ρ_0, μ_0, λ_0 constants in equation for Lamé coefficients in formula we have chosen as vanishing, while the others produce the following Young modulus for the bone tissue/bio-material mixture

$$Y = \alpha_b \left(\frac{\rho_b}{\rho_{\max}} \right)^{\beta_b} + \alpha_m \left(\frac{\rho_m}{\rho_{\max}} \right)^{\beta_m} \tag{11}$$

where $\rho_{\max}$ was introduced in the previous formula 4, $\beta_b = 1.9$, $\beta_m = 1.9$, and the coefficients $\alpha_b,\ \alpha_m$ are fractions of compact bone Young modulus (see [4]).

We assume that one part of the rod is initially occupied by pure bone tissue and the remaining part is occupied by pure bio-material, while the rod is loaded by a static load at both ends. We are particularly interested into the phenomena occurring in the neighbourhood of the interface separating the two considered zones (it has to be remarked that most likely some interesting boundary layer phenomena may occur at this interface and that second gradient continua maybe of use in describing them, but we will postpone these considerations to further investigations, see e.g. [50] or [5] for a review of available second gradient models.

We will study the influence of the values of the parameters introduced in our model on global synthesis and resorption phenomena in space and time. The aim of the analysis is to explain and discuss the variety of phenomena which may occur depending on the different mechanical, geometrical and biological properties of used bio-materials and their placement in the grafted bone. In particular, we will consider the biological and mechanical properties of the composite material which is finally resulting, after the complete healing and reforming process, from surgical bone reconstruction.

As we were careful in relating every among aforementioned parameters to a physical or biological property of considered system, the analysis we will perform should give an indication about how the bio-material should be used in bone reconstruction.

6.1.1 The effect of applied loads on the evolutionary healing process in surgically reconstructed bones in presence bio-material graft

The following pictures illustrates two different possible scenarios depending on the level of externally applied forces. It is well known that loading dramatically affects the process of formation, healing and remodelling of bones.

We start discussing the time evolution of mass density distributions for low level of mechanical loading, which is schematically depicted in fig. 3. We can observe in this case that the insufficient loading leads to a rapid resorption of bio-material while in some regions bone tissue is resorbed and in others is formed. The formation of bone tissue is not rapid enough to fill the region of bio-material which is being resorbed too quickly (especially far from the interface with bone tissue) and, because of the absence of a sufficient number of osteoblastic cells being activated in this region, a void formation occurs. As the signal from the bone tissue towards the reconstructed region is too low, then the bio-material is finally bio-resorbed.

The second considered case, showing the time evolution of natural bone and artificial material for a higher value of external load, is illustrated in fig4. This figure shows that, for higher values of externally applied loads, a different sequence of events arises. The signal from bone tissue is much stronger and it penetrates into the region occupied by bio-material. This results into the following different steps in bone remodelling. First the bio-material far from the bone tissue starts to be resorbed, therefore porosity is available for actors cells. Simultaneously close to the interface (and in the region initially occupied by bio-material) bone formation occurs resulting into the formation of a composite. These phenomena enables the increase of stimulus also far from the interface where actor cells resorbed the bio-material. In the so formed porosity precursor cells become osteoblasts and new bone tissue appears and finally becomes dominant.

Unfortunately when this process comes to an equilibrium configuration, porosity in the central part of the bar-bone reaches the values for which no actor cells can access the composite material and any biological activity stops. This is due to the fact that no resorption of bio-material is any more possible. The presented numerical simulations show how it may happen that in a remodelling process some bio-material may be residual.

The described process has different features. The healing process is driven by large levels of externally applied loading. The resorption of bio-material far from the interface is significantly faster than close to the interface, however this phenomenon is compensated by bone tissue growth.

In fig.5 we show the final result of remodelling process with different externally applied loads. The results presented in this figure show that the externally applied load plays the role of a bifurcation parameter: under a critical value cavity formation occurs, while when applied load exceeds this critical value the reconstructed bone shows regions of bone tissues

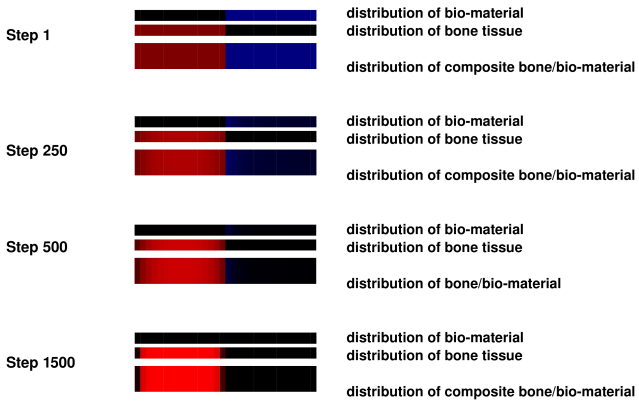


Fig. 3 Time evolution of material density distribution along the length of a rod initially composed of two rods, one made of bone tissue the other made of bio-resorbable bone-substitute material.The intensity of colours is proportional to the apparent densities of the materials. Thin bars display separately the distributions of bone tissue (red) and bone-substitute material (blue) and the thick bar reflects the sum of them the distribution of density of a composite bone tissue/bone-substitute material. The case of low level of the external load: significant resorption in a domain initially occupied by bio-material where the stimulus from the sensor cells is close to zero and formation of a very porous material can be observed.

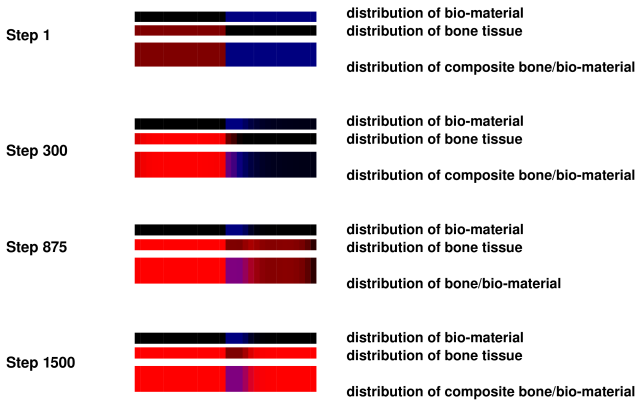
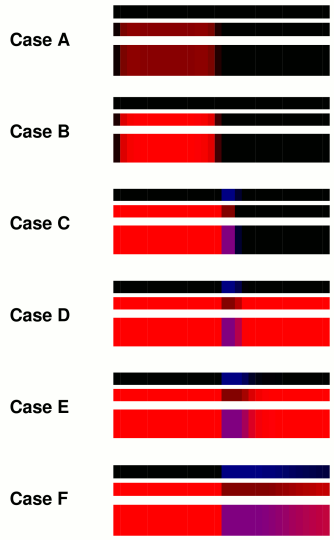


Fig. 4 Time evolution of material density distribution along the length of a rod initially composed of two rods, one made of bone tissue the other made of bio-resorbable bone-substitute material. The result of an analysis similar to the one displayed in Fig. 3 but for the case of relatively high level of the external load: a resorption in a domain initially occupied by bio-material is slower due to stronger stimulus from the sensor cells and formation of a new bone tissue in the pores present in bio-material can be observed. This process results in a partial replacement of bio-material by a natural tissue in some sub-domains and in formation of a composite bone/bio-material in others.

mixed with residual non-resorbed bio-material. We stress that this is a result we obtained by means of a series of numerical simulations: we are confident that refining the techniques presented in [29,33] [29], [31] and [6] such a result can be proven by using a perturbation analysis.

This last figure shows that a threshold value for the external mechanical load exists such that the artificial bio-material is finally resorbed or synthesized.



Case	Dimensionless force
A	0.75
B	1.00
C	1.56
D	1.57
E	1.70
F	2.50

Fig. 5 The final configurations of a rod initially composed of two sub-domain occupied by bone tissue and by bio-material for different levels of mechanical external loading. The values of dimensionless load levels for the cases A-F are collected in a table at the right hand side of a figure.

These results, although only qualitative in nature, for the moment, may result into an interesting indication for practical surgery: the reconstructed bone must be loaded, but the load cannot be too large, as otherwise the residual amount of bio-material maybe too large, while in presence of too low loads large void formation occurs in the regions initially occupied by bio-material.

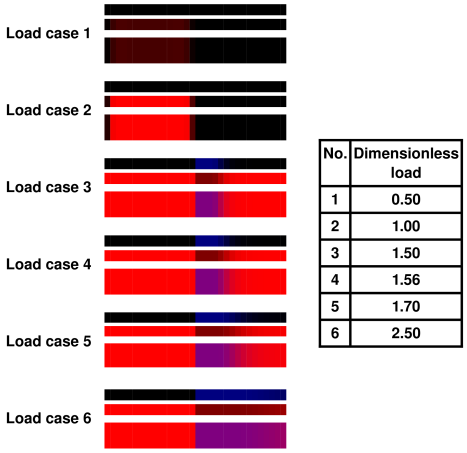
6.1.2 The effect of the value of the parameter D on remodelling.

One of the most important features of the model which we have introduced here is the formal introduction of the concept of sensor cells signals originating in given locations in the reconstructed bone and transmitted to the actor cells located in proximity of the source of the signal. We have assumed that the signal is decreasing exponentially in space (see e.g. [4] and [43]) and that the parameter D measures the range of influence of sensor cells. The numerical simulations which we have performed have shown that the effect of externally applied load on the final structure of the healed bone is remarkably influenced by this range of action. We recall here that already the results obtained in [27] and [28] show the importance of the parameter D in reforming phenomena.

In figures 6 and 7 the reforming of surgically reconstructed bone is shown for considered bar-bones in exactly the same conditions as in the previous section, however with two different values for the range of sensor cells signal. When the parameter D is increasing then the range of action of sensor cells decreases what results in low level signals in the region occupied by bio-material especially far from the interface. This consequently results in faster resorption of bio-material and slower propagation of bone tissue as the domain of synthesis results to be smaller.

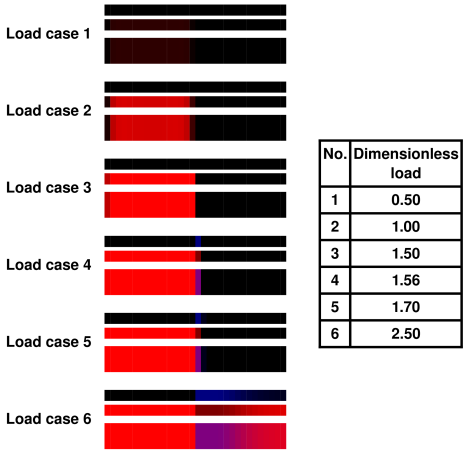
Another important consequence of the increase of the parameter D concerns the level of applied external forces which are needed to assure an efficient synthesis of bone tissue in the region initially occupied by the bio-material. We observe that with increasing values of D (and then reduced range of action of the signal emitted by sensor cells) the load necessary to assure a sufficient replacement of bio-material with natural tissue must be larger. This observation can lead to an indirect method for measuring the very important parameter D, which is related to the biological properties of the whole bone tissue. Indeed, given the applied load and known the final percentage of replacement of the artificial material, an indirect estimation of the parameter D could be performed. Of course a more detailed set of numerical simulations will need to be performed to get a careful evaluation for D.

We also remark that with exceedingly large externally applied loads the resorption process becomes again less efficient which results only in a partial replacement of bio-material so that the final configuration consists of a composite of bone tissue and bio-material in the region initially occupied by bio-material only. This can be explained with the fact that if the



No.	Dimensionless load
1	0.50
2	1.00
3	1.50
4	1.56
5	1.70
6	2.50

Fig. 6 Investigation of the influence of a value of parameter D introduced to account for the range of impact of osteocytes on the actor cells. The case of small value of D: the final configurations of a rod initially composed of two sub-domain occupied by bone tissue and by bio-material for different levels of mechanical external loading.



No.	Dimensionless load
1	0.50
2	1.00
3	1.50
4	1.56
5	1.70
6	2.50

Fig. 7 Investigation of the influence of a value of parameter D introduced to account for the range of impact of osteocytes on the actor cells. The case of big value of D - the final configurations of a rod initially composed of two sub-domain occupied by bone tissue and by bio-material for different levels of mechanical external loading. It can be observed that for big values of D associated with a small domain of impact of osteocytes for most loading cases a void or very porous material appears in a domain initially occupied by the bone-substitute bio-resorbable material..

load is too high this can result in a reduction of porosity which consequently inhibits the free circulation and activity of cells thus resulting in smaller percentages of replacements of bio-material with natural bone tissue.

6.1.3 The effects of different rates of bone tissue synthesis and resorption and bio-material resorption on final properties of reconstructed rod bones

The numerical simulations we have performed show that

1. When the rate of bio-material resorption is relatively large compared to synthesis rate (i.e. the ability of actor cells to synthesize bone tissue) and if the initial bio-material density is not too large then the synthesis of bone tissue will lead finally to bone tissue propagation into the region initially occupied by the bio-material and to the formation of a stable composite constituted by a mixture of natural tissue and bio-material. We can observe larger contribution of bone tissue far from the interface between the two initial regions, exactly where the bio-material was resorbed because

of the absence of signal from sensors. These considerations are illustrated by the right column (lowest picture) of the Fig. 8.

2. When externally applied loads are extremely low and the resorption rate is large enough (left column, lowest picture of Fig. 8) then quick resorption will start in the bio-material region and subsequently void formation will occur. When instead small resorption rate is assumed then a similar scenario appears but we observe some minor propagation of bone tissue close to the interface (left column, upper picture of Fig. 8)

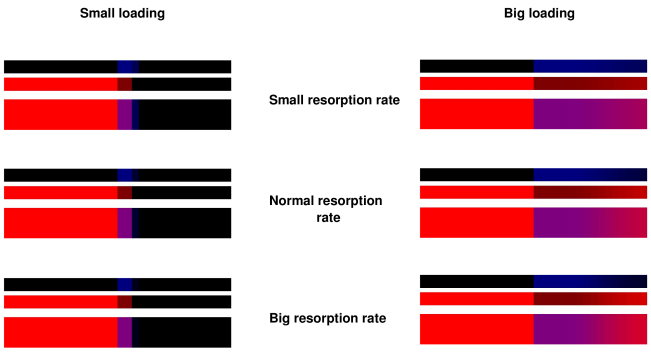


Fig. 8 Investigation of the effect of different resorption rates of bio-material. Comparison for three levels of mechanical loading (small, normal and big).

The fig.8 illustrates the previous considerations.

In future investigations it will be necessary to establish some optimization problems with constraints: we want to see when the finally reconstructed bone will have a topology and mechanical properties suitable for sustaining applied loads. These optimization problems are expected to be extremely difficult, as the final reconstructed bone is the result of a process in time and in every time instant of this process mechanical equilibrium and fracture criteria must be verified.

Indeed, it has to be explicitly remarked that the presence of a very small bio-material apparent mass density is not forbidden when only "biological" processes are considered. Indeed when a small mass density for bio-material is present, the bone tissue from the interface may always penetrate into the region occupied by bio-material eventually reconstructing partially the rod bone. The problems related to void formations in presence of small density of bio-material are of mechanical nature: a weak bio-material graft is not able to sustain the applied mechanical loads! Therefore a warning should be formulated : in our model it is not included the description of mechanical damage and crack formation. From a mechanical point of view and in a time scale small compared with the scale characteristic of the remodelling process, the material is always assumed to be "elastic" and in the performed simulations even linear elastic. Further planned investigation will include the inclusion of damage description and evolution in our model.

6.2 Effect of the initial density of artificial material on the final percentage of replacement

In this subsection we observe that

- contrarily to what one could expect large initial density of bio-material may lead to void formation, both during the reconstruction process and/or in the final equilibrium state for reconstructed bone;
- in contrast to this situation it appears that very low density (i.e. very large porosity) in the bio-material region promotes very fast and efficient formation of bone tissue in this region.

This two points are illustrated by the following pictures (fig. 9) and are relative to the case of uniformly distributed bio-materials. In both described cases we observe that during the process there are some locations in the bar-bone where at some instants the total mixture mass density is close to vanish.

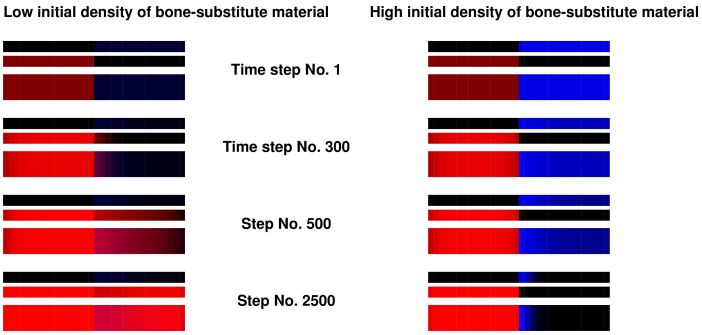


Fig. 9 The effect on remodelling of initial mass density of bio-material; the case of space-uniform mass density in the graft. On the left column it is assumed that this initial density is the minimal one for resisting to externally applied load, while on the right column this density is assumed to be close to the one of the compact bone. Contrary to what one expect high density figures void formation. However also in the case of low density during the remodelling process in some locations very low densities of bio-material is present.

Therefore it is natural to try to avoid this drawback by modifying the initial profile of bio-material mass density. Several tests have been performed, without, however, being guided by an explicit optimization algorithm. We have found an initial mass density profile which assures the following features to the resorption-synthesis process: (see fig. 10)

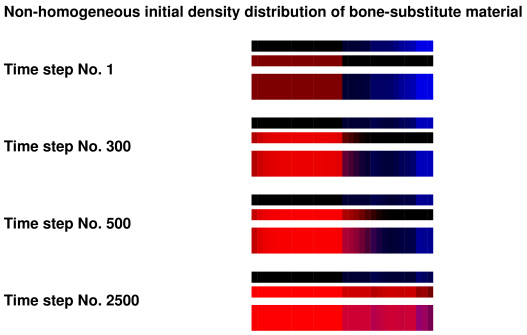


Fig. 10 The effect on remodelling of initial mass density distribution of bio-material; the case of non- uniform mass density in the graft. We assumed an initial mass density distribution with very low values close to the interface. Far from the interface these values increase to reach nearly density of compact bone. All considered mass density values are large enough to resist to the external load. In the process of remodelling it is never observed, in any location and time instant, a value lower than the threshold of mechanical resistance.

- the total mass density of bone tissue/bio-material mixture is never lower that 20% of the density of compact bone
- the final reconstructed bone is mainly constituted by living tissue
- the final mass distribution is rather uniform.

Once more we can conclude that the proposed model seems suitable to describe some clinically observed facts and promising as a guide for finding improved surgical protocols.

7 Conclusions

In this paper we aimed i) to formulate a mathematical model for describing bone tissue synthesis and resorption in presence of a bio-resorbable material of the kind used in bone reconstruction ii) to use the formulated model to get numerical simulations able to give some initial indications about the final properties of bones surgically reconstructed with the addition of artificial material grafts.

In the formulated model the “effective” porosity of bone tissue and bio-material mixture is accounted for, as it plays a relevant role in the biological activity of actor cells, activity which leads to the resorption of both bone tissue and bio-material and to bone tissue formation.

We talk about “effective” porosity because the actual geometrical quantity we intend to model is -in fact- related to the amount of pore internal surfaces accessible for the deposit of actor cells. Our modelling assumption in this respect can be formulated as follows: it is possible to measure with a single scalar field this degree of accessibility.

In the model presented different resorption and synthesis rates of living tissue and different resorption rates for the bio-material are considered possible together with different biological signal propagation distances and stimulus excitation.

In order to investigate and try to explain some of the possible mechanisms of interaction of bone tissue and bio-material a simple one-dimensional case has been formulated and studied. The interesting results which we have obtained motivate the efforts which will be dedicated to further investigations, aimed to improve the general mathematical model, to make it closer to reality, and ameliorate the numerical simulations, to make the predictions of greater value in directing experiments and surgical practise.

To see how the different external loads influence the process of interaction between bio-material and bone tissue we considered, in some numerical examples, these loads as applied to bar-type bones, the dimensions of which are few millimeters. We expect that the performed numerical tests are of relevance in describing more general features of proposed model.

The studied one-dimensional problem of bone remodelling -in presence of the bio-resorbable material used in bone reconstruction- shows all potentialities of introduced model, which will be, therefore, used to formulate two and three dimensional problems.

In particular it is shown that, in the framework of the presented model, one can forecast in which ranges of applied external loads, characteristic signal distance, synthesis and resorption rates and other bio-mechanical parameters, void formation occurs in the bone tissue/bio-material composite remodelling.

We explicitly warn the reader: in the presented model there is no attempt to describe damage and fracture phenomena. The bone tissue and the bio-material are modelled as linear elastic material with elasticity moduli depending on Lagrangian apparent mass density. Therefore voids which are forecast by our numerical simulations are caused solely by “biological” actions: i.e. quick resorption and slow synthesis of bone tissue/bio-material mixture. Further investigations will introduce the needed modelling of mechanical initiation of voids in reconstructed bones.

Another interesting results of presented numerical simulations concerns the capability of formulated model to forecast the formation of stable inclusions of bio-material in living tissue at the end of reforming process after surgery. Indeed it is seen in which ranges of the introduced bio-mechanical parameters residual regions of bio-materials remain in remodelled bone and when one can hope to get a final reconstructed bone constituted by pure bone tissue, i.e. when all bio-material is completely replaced by bone tissue.

Many important problems are left open for further investigations in the theoretical development of the model, which seems promising for future researches. One of the most intriguing from the mathematical point of view concerns the description of bone tissue and bio-material microstructure at different length scales by means of the introduction of higher gradient continuum models. Indeed (see e.g. [4] bone tissue presents a variety of microstructures at very different length scales, which is the essential feature required to a body to show the behaviour of a higher gradient or microstructured continuum. (See e.g. [51]).

However the most urgent next investigations should concern i) the effects of the interplay of the different introduced parameters when their values are changed and the determination of all the different bio-mechanical phenomena which the model may describe and their description ii) the possibility of extending the proposed model by including the fluid flow phenomena occurring in the interconnected pores present in both bone tissue and bio-material.

The introduction of a second or third dimension in the numerical examples may lead to new interesting observations as more complicated geometry will surely include more complex bio-mechanical synthesis and resorption mechanisms and scenarios.

References

[1] Andreaus, U., Colloca, M., Iacoviello, D., Pignataro, M., 2010. Optimal-tuning PID control of adaptive materials for structural efficiency. Structural and Multidisciplinary Optimization, doi: 10.1007/s00158-010-0531-9, published on-line: 16 July 2010.

[2] Bouyge, F., Jasiuk, I., Boccara, S., Ostoja-Starzewski, M.A., 2002. Micromechanically Based Couple-Stress Model of an Elastic Orthotropic Two-phase Composite. European J. Mechanics/A: Solids, 21(3), 465-481.

[3] Burchardt, H., 1983. The biology of bone graft repair, Clin. Orthop. 174:28-42.

[4] Cowin, S.C., 2001. Bone mechanics handbook, CRC Press.

[5] dell’Isola, F. and Seppecher, P., 2010. http://hal.archives-ouvertes.fr/docs/00/49/58/00/PDF/CommentaryDell_IsolaSeppecher.pdf HalArchives

[6] Di Egidio, A. Luongo, A., Paolone, A., 2007. Linear and non-linear interactions between static and dynamic bifurcations of damped planar beams. International Journal of Non-Linear Mechanics, 42, 8898.

[7] Dietrich, M., Kedzior, K., Skalski, K., Zagrejek, T., Krzesinski, G., Skoworodko, J., Borkowski, P., Wymyslowski, P., 2003. On concurrent engineering and design of an intervertebral disc of lumbar spine Computer-Aided Production Engineering: Editor: McGeough J.A. , 209-219.
[8] Gasser T.C., Holzapfel G.A. 2007. A numerical framework to model 3-D fracture in bone tissue with application to failure of the proximal femur in IUTAM SYMPOSIUM ON DISCRETIZATION METHODS FOR EVOLVING DISCONTINUITIES Combescure A; DeBorst R; Belytschko T (Eds) Vol. 5 pp. 199-211.
[9] Germain, P., 1973. Cours de Mécanique des Milieux Continus, Masson Paris.
[10] Goto, T., Kojima, T., Iijima, T., Yokokura, S., Kawano, H., Yamamoto, A., Matsuda, K., 2001. Resorption of synthetic porous hydroxyapatite and replacement by newly formed bone. J. Orthop. Sci., 6: 444-447
[11] Goulet, R.W., Goldstein, S.A., Ciarell,i M.J., Kuhn, J.L., Brown, M.B., Feldkamp, L.A., 1994. The relationship between the structural and orthogonal compressive properties of trabecular bone. J. Biomech. 27, 375.
[12] Greenwald, A.S., Boden, S.D., Goldberg, V.M., Yusuf, K., Laurencin, C.T., Rosier, R.N., 2001. Bone graft substitutes: facts, fictions & applications, 68th Annual Meeting American Academy of Orthopaedic Surgeons, February 28 - March 4, San Francisco, California.
[13] Hariton I., Debotton G., Gasser T.C., Holzapfel G.A. 2007. Stress-driven collagen fiber remodeling in arterial walls BIOMECHANICS AND MODELING IN MECHANOBIOLOGY, 6 (3): 163-175.
[14] Hariton I., Debotton G., Gasser T.C., Holzapfel G.A. 2007. Stress-modulated collagen fiber remodeling in a human carotid bifurcationJOURNAL OF THEORETICAL BIOLOGY Vol. 248,3 pp. 460-470.
[15] Hamed, E., Lee, Y., Jasiuk, I., 2010. Multiscale modeling of elastic properties of cortical bone. Acta Mechanica, 213 (1-2), 131-154.
[16] Hing, K.A., 2005. Bioceramic Bone Graft Substitutes: Influence of Porosity and Chemistry. Int. J. Appl. Ceram. Technol., 2 (3), 184-199.
[17] Hodgskinson, R. and Currey, J.D., 1992. Young's modulus, density and material properties in cancellous bone over a large density range J. Mater. Sci. Mater. Med., 3, 337.
[18] Holzapfel G.A. Ogden R.W. 2010. Constitutive modelling of arteries PROCEEDINGS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES, 466 (2118): 1551-1596.
[19] Inglis, D., Pietruszczak, S., 2003. Characterization of anisotropy in porous media by means of linear intercept measurements. Int. J. Solids Struct., 40 (5), 1243-1264.
[20] Jarcho, M., 1981. Calcium phosphate ceramics as hard tissue prosthetics. Clin. Orthop., 157, 259-278.
[21] Jasiuk, I., Ostoja-Starzewski, M., 2004. Modeling of Bone at a Single Lamella Level. Biomechanics and Modeling in Mechanobiology, 3, 67-74.
[22] Jasiuk, I., 2003. Modeling of trabecular bone as a hierarchical material. Computational Fluid Solid Mech., 1 and 2, Proceedings: 1727-1728 .
[23] Kraus, R., Stahl, J.-P., Schnettler, R., 2007. Treatment Strategies in Thoracolumbar Vertebral Fractures: Are there Indications for Biomaterials? European J. Trauma, pp.253-257.
[24] Kim H.-M., 2003. Ceramic bioactivity and related biomimetic strategy, Current Opinion in Solid State and Materials Science, 7, 289-299.
[25] Kroon M. Holzapfel G.A. 2008. A new constitutive model for multi-layered collagenous tissues JOURNAL OF BIOMECHANICS, 41 (12): 2766-2771.
[26] Kuhl E. and Holzapfel G. A. 2007. A continuum model for remodeling in living structuresJOURNAL OF MATERIALS SCIENCE, 42 (21): 8811-8823.
[27] Lekszycki, T., 2001. On a class of bone cell-based remodeling laws with spatial fading influence of stimuli. Eng. Trans., 2-3, 155-164.
[28] Lekszycki, T., 2002. Modelling of bone adaptation based on an optimal response hypothesis. Meccanica, 37, 343-354.
[29] Luongo, A., Paolone, A., 1997. Perturbation Methods for Bifurcation Analysis from Multiple Nonresonant Complex Eigenvalues. Nonlinear Dynamics, 14, 193210.
[30] Luongo, A., Paolone, A., 1998. Multiple Scale Analysis for Divergence-Hopf Bifurcation of Imperfect Symmetric Systems. Journal of Sound and Vibration, 218 (3), 527539.
[31] Luongo, A., Paolone, A., Di Egidio, A., 2003. Multiple Timescales Analysis for 1:2 and 1:3 Resonant Hopf Bifurcations. Nonlinear Dynamics 34, 269291.
[32] Mano, J.F., Sousa, R.A., Boesel, L.F., Neves Rui, N.M., Reis, L., 2004. Bioinert, biodegradable and injectable polymeric matrix composites for hard tissue replacement: state of the art and recent developments. Composites Science and Technology, 64, 789-817.
[33] Middleton, J., Jones, M.L., Pande, G.N., 1997. 3rd International Symposium on Computer Methods in Biomechanics and Biomedical Engineering MAY, 1997 BARCELONA, SPAIN.
[34] Nomura, S., and Takano-Yamamoto, T., 2000. Molecular events caused by mechanical stress in bone. Matrix Biology, 19, 91-96.
[35] Ostoja-Starzewski, M., Boccara, S.D., Jasiuk, I., 1999. Couple-stress moduli and characteristic length of a two-phase composite. Mech. Research Communications, 26 (4), 387-396.
[36] Pawlikowski, M., Skalski, K., Haraburda, M., 2003. Process of hip joint prosthesis design including bone remodeling phenomenon. Computers & Structures, 81 (8-11), 887-893
[37] Pawlikowski, M., Klasztorny, M., Skalski, K., 2008. Studies on constitutive equation that models bone tissue. Acta of Bioengineering and Biomechanics, 10 (4), 39-47.
[38] Park, J.-C. Wook, D., Suh, H., 2000. A Bone Replaceable Artificial Bone Substitute: Morphological and Physiochemical Characterizations. Yonsei Medical Journal, 41 (4), 468-476.

[39] Pietruszczak, S., Inglis, D., Pande, G.N., 1998. Modelling of bone-implant interaction. Computer Methods in Biomechanics & Biomedical Engineering, 2, 289-298.
[40] Pietruszczak, S., Inglis, D., Pande, G.N., 1999. A fabric-dependent fracture criterion for bone. J. Biomechanics, 32 (10), 1071-1079.
[41] Piszczatowski, S., Skalski, K., Swieszkowski, W., 1998. Load transfer between elastic hip implant and viscoelastic bone. Computer Methods in Biomechanic & Biomedical Engineering, 2, 123-130.
[42] Rubin, M., Jasiuk, I., 2005. The TEM Characterization of the Lamellar Structure of Osteoporotic Human Trabecular Bone. Micron, 36, 653-664.
[43] Ruimerman, R. , Hilbers, P., van Rietbergen, B., Huiskes, R., 2005. A theoretical framework for strain-related trabecular bone maintenance and adaptation. J. Biomechanics, 38, 931-941
[44] Salençon, J. 1988. Mécanique des milieux continus, tome II, Ellipse.
[45] Schilling, A.F., Linhart, W., Filke, S., Gebauer, M., Schinke, T., Rueger, J.M., Amling, M., 2004. Resorbability of bone substitute biomaterials by human osteoclasts. Biomaterials, 25, 3963-3972
[46] Sikavitsas, V.I., Temenoff, J.S., Mikos, A.G., 2001. Review: Biomaterials and bone mechanotrasduction. Biomaterials 22, 2581-2593.
[47] Skoworodko, J., Skalski, K., Cejmer, W., Kwiatkowski, K., 2008. Preoperative planning and post-operative estimation of vertebroplasty using CT/CAD/CAE systems. Acta of Bioengineering and Biomechanics, 10 (2), 15-22.
[48] Turner, C.H., Warden, S.J., Jasiuk, I., Bellido, T., Plotkin, L.I., Kumar, N., Danzig, J., Robling, A.G., 2009. Mechanobiology of the Skeleton. Science Signaling, 2 (68). Keystone Symposium Mechanotransduction in Physiology and Disease
[49] Yoo, A., Jasiuk, I., 2006. Couple-Stress Moduli of a Trabecular Bone Idealized as a 3D Periodic Cellular Network. J. of Biomechanics, 39, 2241-2252.
[50] Yoo, A., Jasiuk, I., 2003. Modeling of trabecular bone as a couple stress continuum. Advances in Bioengineering, 41-42, ASME International Mechanical Engineering Congress NOV 15-21, 2003 Washington, DC.
[51] Vernerey, F., Liu, W. K., Morana, B., 2007. Multi-scale micromorphic theory for hierarchical materials. J. Mech. Physics Solids, 55, 2603–2651
[52] Wang, C.Y., Feng, L., Jasiuk, I., 2009. Scale and Boundary Conditions Effects on the Apparent Elastic Moduli of Trabecular Bone Modeled as a Periodic Cellular Solid. J. Biochemical Engineering-Transactions of the ASME, 131 (12), DEC 2009.
[53] Webb J.C.J., Tricker J., 2000. A review of fracture healing. Current Orthopaedics, 14, 457-463.