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BONE REMODELING DESCRIPTION BASED ON MICRO MECHANICAL/BIOLOGICAL EFFECTS

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Abstract. *The main idea driving this work was the need of the mathematical model of bone functional adaptation that satisfies several requirements: a) it should take into consideration basic biological effects and mechanisms responsible for bone remodeling associated with activities of osteoblasts, osteoclasts and osteocytes; b) it should relate evolution of tissue microstructure with the constitutive parameters of anisotropic bone material in macro scale; c) it should be suitable for computer calculations using reasonable in size FEM models. An approach is proposed to derive adaptation law i.e. mathematical formulas describing evolution of control parameters defining tissue micro-structure in time, which is based on the hypothesis of optimal response of bone. It follows from thermodynamical considerations that application of this hypothesis with objective functional representing the global stiffness of bone is equivalent to minimization of energy dissipation due to remodeling process what leads to interesting and physically well based interpretation of remodeling formulas.*

In order to merge the fundamental processes contributing in bone remodeling with micromechanics, so called Reference Elementary Volume (RVE) is considered where the microstructure is defined with use of a set of parameters. Adopting Galerkin method the mechanical analysis of RVE can be performed and the results are used to determine the macroscopic constitutive parameters for the point represented by considered RVE. This way no mathematical homogenization techniques are used and no assumption concerning periodicity of the micro-structure is necessary.

1 INTRODUCTION

Bone tissue is a porous non-homogeneous and strongly anisotropic material. In contrast to many other tissues the “density” of cells (number of cells in bone tissue) is significantly low compared to the amount of extracellular matrix which forms the solid part of the bone and fills the space between cells. The pores in extracellular matrix are filled basically by liquid marrow. The continuous alteration which occurs in bone tissue determines its mechanical and geometrical characteristics – complex biochemical processes result among the others in variation of bone external shape and internal micro-structure. Two simultaneous effects are responsible for bone turnover, bone formation and bone resorption implemented by specialized cells. These effects are closely coupled with each other in time and space and play a crucial role in modeling, maintenance, repair and aging of bones.

The mechanical loading determining strain distribution in bone is one of the most significant factors that contributes at the micro level in triggering remodeling phenomena. That remodeling, driven by time varying mechanical states, is generally known as functional adaptation of bones.

It is generally accepted that three families of cells are mainly involved in changes of bone micro-structure and evolution of bone tissue itself. These cells are osteocytes, osteoblasts and osteoclasts. The balance between the cells, their proliferation, differentiation and apoptosis are controlled both by local growth factors as well as by systemic hormones; all these phenomena play a crucial role in the processes taking part in bone turnover. This is more and more evident from recent investigations that osteocytes play a role – among the others – of mechanical sensor cells controlling the process of bone formation and remodeling whilst osteoblasts and osteoclasts are the “actor” cells, see e.g. [1], [2], [4], [9], [10], [13], [14]. Osteocytes are buried in the extracellular matrix and can not migrate to other positions. Osteoblasts and osteoclasts act mostly at the surface of bone – the interface between the solid extracellular matrix and the voids filled with marrow (they are also present at the external surface of bone and their activities affect bone overall shape). Osteoblasts are the bone-forming cells. They produce new bone matrix in the regions where bone tissue has previously been resorbed, and need to be re-structured, or in the regions where the new tissue should be added. On the other hand osteoclasts are responsible for tissue removal - they dissolve extracellular matrix and dig the holes at bone surface. The balance between these two effects, bone formation and bone resorption, is tightly controlled by the complex and highly organized interactions between cells and extracellular matrix. Depending on the actual mechanical and biological situation bone formation may be in balance, may exceed or be lower than the rate of bone resorption. Faster formation results in thicker and mechanically stronger bones. This may happen for example, in response to mechanical loading. In another case bone resorption can be faster than bone formation what may be associated with bone mechanical disuse or a disease as for example osteoporosis which results in loss of mass and deterioration of mechanical strength. The control of these effects is accomplished both via direct cell-to-cell signaling and via soluble molecules from the sensor cells (osteocytes and bone lining cells) to effector cells (osteoblasts and osteoclasts).

It follows from this considerations that bone remodeling is mostly associated with the activities at the surfaces of bone what results in the translation of these surfaces affecting pores sizes, distribution and orientation. Therefore mathematical models including biomechanical effects of bone remodeling and functional adaptation should be constructed with regard of the effects discussed here.

According with these remarks two basic items can be formulated: (i) constitutive parameters

of the overall bone material do not remain constant in time, because of time evolution of the microscopic architecture; (ii) micro evolution phenomena are triggered by biology, and by the coupling between the local stress/strain state and the distribution of osteoclasts and osteoblasts close to the remodeled surface.

Assuming the remodeling process to occur over a suitably low time scale, so as to admit a quasi-static analysis of the evolution process, we state that osteoclasts/osteoblasts recruitment from the marrow essentially depends on the local value of stresses when compared with a suitable stress threshold associated to steady state conditions.

We now focus our attention on cancellous bones: even if the matrix could be regarded as an isotropic continuum however the trabecular distribution is capable to induce significant anisotropic effects on the global behaviour of the bone. Moreover according with the previous remarks this anisotropy can exhibit a non trivial time evolution. Several models have been introduced in the past for describing this anisotropy induced by the local geometry of the spongy bone material, in particular those ones based on a dependence of the constitutive law on the so called fabric tensor (see e.g. [3]), or in a more general case on the orientation distribution function which is a local measure of the trabecular orientations. According with this approach the overall stress tensor is assumed to depend on strain and fabric, $\mathbf{T} = \mathbb{G}(\boldsymbol{\varepsilon}, \mathbf{H})$; which yields, because of frame indifference, at most orthotropic constitutive relations to hold true, when limiting the analysis to the linear elastic problem. However no information is available regarding the values of the orthotropic constitutive parameters.

Our approach try to formulate a model for bone adaptation capable to account for the aforementioned microscopical phenomena, merging micro-mechanics and optimization. The behaviour of the effective bone is described by means of a coarse model which captures the main topological, mechanical and biological characteristics of the structure via a micro-mechanical analysis of the stress state in a properly defined Reference Elementary Volume (RVE) and provides a description of remodeling evolution according to some optimality conditions for properly defined control functions. Adopting a macroscopic approach bone remodeling arises from admissible variations of the constitutive parameters and is associated to a non-trivial dissipation inequality.

Our goal is to identify the basic set of control parameters, associated to cancellous bone architecture, which affect the macroscopic constitutive relations, and to describe their time evolution according to suitable control laws. The control parameters are chosen in such a way to be related to local mechanical and biological phenomena. From the point of view of micro-mechanics the idea is to describe the architecture of the bone by suitably oriented RVEs inside which inclusions aligned along the same main axes can be detected. This simplified description of bone architecture allows us to account for biology, since it seems almost well grounded that remodeling occurs on the surface of the inclusions; on the other hand no periodicity of the structure is considered, which means that no homogenization techniques are going to be developed. Every RVE is uniformly strained (or stressed) through its boundary by the corresponding macroscopic fields; this means that the characterization of the microscopic state of strain in the RVE (micro problem) provides the macroscopic constitutive law when identifying the average strain energy of the RVE with the energy associated to the average strain. Properly defined set of mechanical constraints for the fourth order elasticity tensor guarantee, via an optimization procedure, to determine the missing evolution equations for the control functions.

2 MACROSCOPIC DESCRIPTION OF BONE REMODELING

Cancelous bone is macroscopically modeled as a Cauchy continuum where the parameters which characterize constitutive relations strongly depend on the local architecture distribution of bone tissues at the scale of spongy bone characteristic inclusions. The macroscopic material particles have therefore to be regarded as non-isotropic and the overall material as non-homogeneous; moreover anisotropy and heterogeneity evolve according to remodeling phenomena occurring at the bone-marrow interphase inside the bone. As in case of (visco-)plasticity suitable internal variables can be introduced which mainly affect time evolution of stiffness (the fourth order elasticity tensor) and imply non vanishing dissipation (see e.g. [5] and [6]): apparently the corresponding evolution laws of remodeling must allow the dissipation principle to be verified.

Consider the free energy Ψ of the envisaged linear simple material; during an isothermal remodeling process its time derivative involves strain rate and stiffness rate of change according to the following formula

$$\dot{\Psi} = \int_{\mathcal{D}} \left(\mathbb{C} \nabla \mathbf{u} \cdot \nabla \dot{\mathbf{u}} + \frac{1}{2} \dot{\mathbb{C}} \cdot \nabla \mathbf{u} \otimes \nabla \mathbf{u} \right) dv, \quad (1)$$

the last term being non vanishing because of micromechanical time dependent phenomena triggered by loading conditions and chemical reactions. As for the case of plasticity we are interested in introducing special characteristic parameters capable to describe stiffness remodeling accounting in particular for evolution of local bone architecture. Let χ_j ($j = 1, \dots, N$) be these parameters regarded from now on as internal variables, they determine the behaviour of the elasticity tensor and therefore allow to give the following representation of stiffness evolution

$$\dot{\mathbb{C}} = \sum_{j=1}^N \frac{\partial \mathbb{C}}{\partial \chi_j} \dot{\chi}_j. \quad (2)$$

Using standard argument of thermodynamics and the principle of virtual power we consider the following form of the second principle

$$\mathcal{W}^{ext} - \dot{\Psi} = \Gamma \geq 0, \quad \mathcal{W}^{ext} = \mathcal{W}^{int} = \int_{\mathcal{D}} (\boldsymbol{\sigma} \cdot \nabla \dot{\mathbf{u}}) dv + \sum_{j=1}^N \int_{\mathcal{D}} (g_j \dot{\chi}_j) dv, \quad (3)$$

\mathcal{W}^{ext} and \mathcal{W}^{int} being the external and the internal power, Γ the dissipation. In eqn.(3)₂ $\boldsymbol{\sigma}$ is the Cauchy stress and g_j ($j = 1, \dots, N$) the micro balanced internal forces. Classical localization arguments, together with the hypotheses of elastic behaviour of the material, at every time step, and vanishing micro balanced forces, imply the following reduced form of Clausius-Duhem inequality

$$\gamma = \sum_{j=1}^n g_j \dot{\chi}_j - \frac{1}{2} \nabla \mathbf{u} \otimes \nabla \mathbf{u} \cdot \dot{\mathbb{C}} = \sum_{j=1}^N \left(g_j - \frac{1}{2} \nabla \mathbf{u} \otimes \nabla \mathbf{u} \cdot \frac{\partial \mathbb{C}}{\partial \chi_j} \right) \dot{\chi}_j \geq 0 \quad (4)$$

where γ is the density of dissipation per unit volume. Apparently the most simple case is that one of a dissipation prescribed by a quadratic form of the internal variables;

$$\gamma = \sum_{j,k=1}^N \frac{\partial \mathbb{C}}{\partial \chi_j} \cdot \mathcal{A}_{jk} \frac{\partial \mathbb{C}}{\partial \chi_k} \dot{\chi}_k \dot{\chi}_j. \quad (5)$$

If this was the case the evolution laws associated to the considered internal variables χ_j should be given in terms of a list of symmetric coefficients \mathcal{A}_{jk} (endomorphisms over the space of fourth order tensors), according with classical Onsanger's relations.

The evolution laws associated with the introduced internal parameters can be deduced starting from the considered zeroth order theory (see eqn.(3₂)) with vanishing microstructural bulk actions (see [8]); in other words everyone of the remodeling evolution equations can be regarded as the very basic balance law associated to the j -th kinematical state parameter:

$$g_j - \frac{1}{2} \nabla \mathbf{u} \otimes \nabla \mathbf{u} \cdot \frac{\partial \mathcal{C}}{\partial \chi_j} = \sum_{k=1}^N \mathcal{A}_{jk} \frac{\partial \mathcal{C}}{\partial \chi_j} \cdot \frac{\partial \mathcal{C}}{\partial \chi_k} \dot{\chi}_k, \quad g_j = 0 \quad \{j = 1, \dots, N\}. \quad (6)$$

The introduced symmetric coefficients \mathcal{A}_{jk} will be determined on the basis of an optimization procedure by identifying eqns.(6) with suitable control laws which describe how micro mechanical/biological phenomena take place.

According to this remark and taking into account the very basic information that remodeling occurs at the bone-marrow interface, we shall assume the internal variables to be geometrical parameters which characterize the shape and the amount of inclusions inside every RVE which can be identified in the bulk material. It is the topic of the next section to introduce the topological structure we aim to attribute to every RVE and to describe how the initial state of the cancelous bone can be characterized by setting-up suitable procedures.

3 CAPTURING THE TOPOLOGICAL STRUCTURE OF CANCELLOUS BONES

The main idea is to assume the reference initial architecture of the cancelous bone to be described by suitably oriented RVEs inside which aligned rectangular inclusions can be detected. In the following we shall refer ourselves to wideness and placement of the inclusions as the architectural properties or the characteristic parameters of the considered RVE.

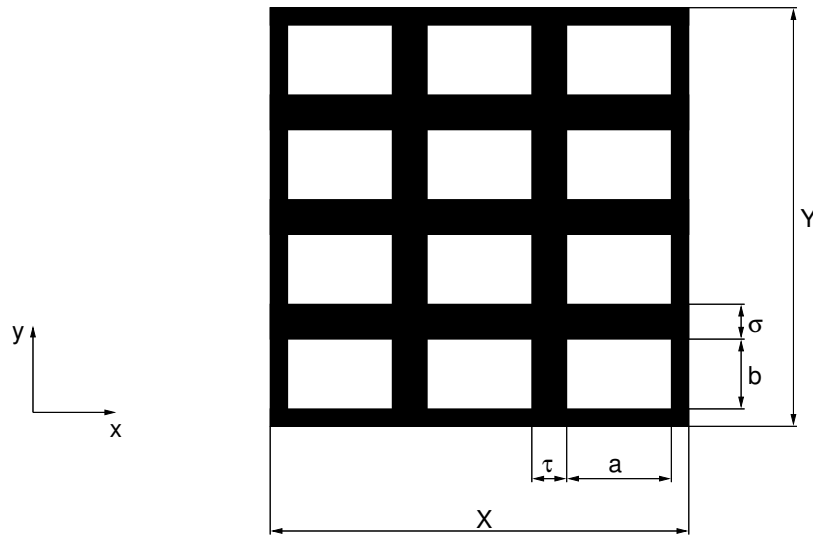


Figure 1: Representation of the rectangular prototype RVE \mathcal{Y} for a 2D problem: X and Y identify the characteristic size of the volume, n and m are the number of inclusions along the main directions (x, y) of the rectangular volume, σ and τ are the distances between two contiguous voids along the main directions and $a = X/n - \tau$, $b = Y/m - \sigma$ indicate the wideness of inclusions along x and y .

In particular we refer to a prototype reference cell \mathcal{Y} (see Figure 1) of unit volume, where wideness of the characteristic inclusions is made dimensionless with respect to the side lengths. Using tomography data for capturing this basic morphology implies a proper choice of the cell size, which we assume to be the same all over the considered bone material. The criterion of optimal size corresponds to the idea that a suitable dissimilarity measure, associated to each characteristic parameter, has to be minimum when considering two cells which have a distance between their centroids smaller than the considered characteristic size. Considering such a dissimilarity as a function of the distance h between the cells, and taking into account a properly defined norm of it, the optimal size can be determined as the solution of a suitable minimization problem for this function. It is not the purpose of the present contribution to discuss this aspect of the problem but we remind that this approach is essentially driven by the widespread idea that when considering averaging procedures, the size of the RVE has to guarantee invariance of the macroscopic material behaviour with respect to translation vectors smaller than the considered characteristic size. This is the reasoning that suggests to determine the micro-macro constitutive identification by solving a uniformly strained (stressed) boundary value problem where boundary conditions are given in terms of the macroscopic fields (see §4).

The proposed assumption about modeling bone architecture implies at least local orthotropy to be guaranteed: as a matter of fact in every RVE at least two symmetry planes and consequently two main directions can be recognized. Centroids of the inclusions are equally spaced along everyone of these directions and coincide with the cross points of a properly defined grid. It is therefore the distribution of orientation of the different RVEs which gives the spatial distribution of the grade of anisotropy for the overall material together with the shape of the inclusions.

In order to fit this model with the effective bone structure we aim to develop a procedure capable to determine for every RVE in the domain: (i) the axis along which the widest openings can be detected, this information is useful to establish which is the asset of the RVE with respect to its reference shape (apparently in a 2D case only an angle is needed conversely in a 3D case three scalar parameters must be identified); (ii) the number of voids which are expected to be included in the RVE; (iii) the characteristic lengths of the side of the rectangles which represent the considered prototype inclusions inside the RVE.

To do this, starting for instance from tomography pictures, fix a set of sample RVEs, in the domain, centered over the nodes of a properly defined grid, and develop the following items for every RVE:

- Starting from the star of straight lines passing through the centroid of the RVE (∞^1 in 2D, ∞^2 in 3D) consider for every sample direction a grid of parallel lines equally spaced inside the RVE and measure the length fraction of voids (L_v/L) along the considered direction with respect to the total length of the grid lines. This will allow to establish which is the widest voids direction (wvd), i.e. the direction characterized by the maximum value of the length fraction index (ϑ_{wvd}). Measuring the amount of bone-marrow intersections (\mathcal{N}_i) along this direction provides an estimate of the corresponding mean amplitude of voids as the ratio between $L_v(\vartheta_{wvd})$ and \mathcal{N}_i when considering convex inclusions. According to the envisaged model for the prototype RVE this average length can be identified with the largest side of the prototype rectangular inclusion (a).

When considering 3D samples the same analysis can be developed along the plane orthogonal to the considered bundle; in this case we decide to identify the narrowest voids planar direction (nvpd) and consequently the corresponding mean amplitude of voids (c).

We label ϑ_{nvpd} the angle with respect to a fixed frame in the aforementioned plane which corresponds to the nvpd direction.

Finally the remaining direction orthogonal to those two previously identified provides an estimate of the intermediate side length (b) of the prototype rectangular inclusion. In the same way as before we label it intermediate voids planar direction (ivpd). Apparently when considering 2D samples the narrowest wideness is not meaningful to be considered. According to these remarks the following measuring rules can be defined

$$a = \frac{2L_v}{\mathcal{N}_i} \Big|_{\vartheta_{\text{wvd}}}, \quad b = \frac{2L_v}{\mathcal{N}_i} \Big|_{\vartheta_{\text{ivpd}}}, \quad c = \frac{2L_v}{\mathcal{N}_i} \Big|_{\vartheta_{\text{nvpd}}}. \quad (7)$$

The basic quantities which affect the size of the equivalent pores placed in the prototype RVE are therefore the number of intersections \mathcal{N}_i and the ‘‘volume length’’ parameter L_v for every admissible direction.

- Once the side lengths of the prototype inclusion have been captured, then the number of voids along the considered main directions are determined by the following conditions:

$$\mathcal{N}_{\text{wvd}} = E \left[\frac{L_v(\vartheta_{\text{wvd}})}{a} \right], \quad \mathcal{N}_{\text{ivpd}} = E \left[\frac{L_v(\vartheta_{\text{ivpd}})}{b} \right], \quad \mathcal{N}_{\text{nvpd}} = E \left[\frac{L_v(\vartheta_{\text{nvpd}})}{c} \right], \quad (8)$$

where $E[t]$ denotes the integer part of the real number t .

Apparently the overall number of voids $\mathcal{N}_v = \mathcal{N}_{\text{wvd}} \mathcal{N}_{\text{ivpd}} \mathcal{N}_{\text{nvpd}}$ is related to porosity according to the following condition

$$abc = \frac{\varphi|\mathcal{D}|}{\mathcal{N}_v}. \quad (9)$$

RVE size, number of voids and wideness of characteristic inclusions provide, according to eqns.(7)-(9), a complete characterization of the parameters introduced for describing local bone architecture (see Figure 1).

The information listed above allows us to sample the basic topological structure of the reference configuration of the bone; \mathcal{N}_{wvd} , $\mathcal{N}_{\text{ivpd}}$ and $\mathcal{N}_{\text{nvpd}}$ the number of voids in the RVE along the main directions, $\mathbf{R} \in \text{Orth}^+$ the rotation matrix describing the asset of the RVE (with respect to a fixed frame) and (a, b, c) the side lengths of the rectangular prototype inclusion represent the microstructural control parameters. It is worth to notice that the addressed choice of regarding architectural quantities as control parameters is essentially driven by the idea that bio-chemical resorption and rebuilt phenomena occur at the bone-marrow interface and therefore affect the overall constitutive behaviour because of inclusion shape change.

Starting from this sampling information we aim to use geostatistical techniques, in particular kriging (see e.g. [12] and [15]), in order construct a suitable interpolated map for every control parameter. In this framework the basic idea is that of considering the partially known fields as random functions and therefore their measured values in the considered sample points as admissible realizations of the random variables which represent the behaviour of the function in the sample points. Apparently different grades of refinement can be envisaged when dealing with these kind of approach, here we decide to embrace ordinary (co-)kriging avoiding in particular to deal with geostatistical simulations. It is not the purpose of this paper to illustrate how these techniques work, however we remind that they essentially represent a generalization of classical

linear regression applied to $n_i + 1$ values of the i -th random field ($i = 1, \dots, N$) defined over the considered domain; the random fields we aim to deal with are in this case those ones which describe the shape of the inclusions and the number of inclusions inside every RVE as well as the orientation of the RVE.

Using an iterative notation we also remind that the co-kriging linear estimator for the value of the random field Z_{i_0} , in x_0 in terms of the value of the fields Z_i , can be given as follows

$$Z_{i_0}^*(\mathbf{x}_0) = \sum_{i=1}^N \sum_{\alpha=1}^{n_i} w_{\alpha}^i Z_i(\mathbf{x}_{\alpha}), \quad (10)$$

where the coefficients w_{α}^i , $i = 1, \dots, N$ and $\alpha = 1, \dots, n_i$, are determined as the solution of a linear problem involving, in case of stationarity of the random functions, the so called cross-variogram (see [15]). Notice that N is the amount of control parameters and n_i the amount of sample RVEs taken into account for constructing a suitable spatial estimator of the i -th control parameter.

The obtained maps are necessary once the proper governing equations describing bone remodeling have been stated; in particular they allow to identify the initial conditions of the problem.

4 MICROMECHANICS

According to our hypotheses on bone microstructure we now address the problem of micro-macro identification assuming the introduced prototype RVE to represent the behaviour of a macroscopic material point, the constitutive characteristics of which should arise from the corresponding micro properties and micro architecture. In this section we shall provide a characterization of the fourth order macroscopic elasticity tensor introduced in §2 starting from the micro, i.e. identifying the average strain energy over the RVE, as determined by solving a properly defined boundary value problem, with the density of strain energy as stated at the macroscopic level by the inner product between macro-strain and macro-stress. We refer to the classical micromechanical approach based on Hill's Lemma – see e.g. [7] – and consider a local uniformly strained (stressed) boundary value problem; the basic idea is that of considering the RVE uniformly strained (stressed) by the macroscopic strain (stress) field and solving the relative boundary value problem so as to capture an explicit relation between the microscopic displacement field and the macroscopic strain (stress). This relation will allow us to match the two models requiring the energy identification.

Assume the aforementioned micro boundary value problem to be defined over the RVE depicted in Figure 1 and characterize the heterogeneity of the material via a mesoscale description in which the material itself is spread all over the reference domain and a non-homogeneous distribution of the elastic properties is taken into account. The RVE is replaced by a kind of grey material whose constitutive coefficients are not uniform over the domain but fit the effective spatially discontinuous distribution of the elastic moduli which characterized the RVE. Considering the constitutive law, at every time step, as the classical linear isotropic one, we assume the Young modulus to be spatially distributed over the RVE according with the Fourier series of the characteristic function $\mathcal{I}_{RVE}(\mathbf{x})$ of the spongy bone in the RVE. Moreover we regard the Poisson ratio as a spatially uniform field over the same domain. According with these assumptions

the following formula is considered for the Young modulus scalar field

$$Y(x, y) = Y_0 \sqrt{\frac{nm}{XY}} \sum_{k=-\infty}^{\infty} \sum_{j=-\infty}^{\infty} \left[c_{(k,j)} \exp \left(i \frac{2\pi nkx}{X} + i \frac{2\pi mjy}{Y} \right) \right], \quad (11)$$

where Y_0 is the Young modulus of the spongy bone material, X/n and Y/n the spatial periods along x and y and $c_{(k,j)}$ the coefficients of the Fourier expansion determined by the classical condition

$$c_{(k,j)} = \int_0^{X/n} \int_0^{Y/m} \left[\mathcal{I}_{RVE}(x, y) \exp \left(-i \frac{2\pi nkx}{X} - i \frac{2\pi mjy}{Y} \right) \right] dx dy. \quad (12)$$

Bearing in mind the characterization of the constitutive law we now state the governing equations of the envisaged uniformly strained boundary value problem. Consider in particular the following decomposition of strain and displacement

$$\boldsymbol{\varepsilon}_{tot} = \mathbf{A} + \boldsymbol{\varepsilon}_0, \quad \mathbf{u}_{tot} = \mathbf{A}\mathbf{r} + \mathbf{u}_0; \quad \mathbf{A} := \mathbf{R}^\top \bar{\boldsymbol{\varepsilon}} \mathbf{R} \quad (13)$$

where \mathbf{R} is the rotation matrix from the local RVE frame to the global frame, $\bar{\boldsymbol{\varepsilon}}$ is the value of the strain field in the macroscopic material point, which is identified with the centroid of the RVE, and \mathbf{r} the position vector inside the RVE with respect to its centroid.

According with the previous remarks the displacement field \mathbf{u}_0 is required to be homogeneous on the boundary of the RVE and therefore will be determined as the solution of the following boundary value problem:

$$\operatorname{div} [2\mu(x, y) (\mathbf{A} + \boldsymbol{\varepsilon}_0) + \lambda(x, y) \operatorname{tr}(\mathbf{A} + \boldsymbol{\varepsilon}_0) \mathbf{I}] = 0 \quad \text{in } \mathcal{D}_{RVE}, \quad (14)$$

$$\boldsymbol{\varepsilon}_0 = \frac{1}{2} (\nabla \mathbf{u}_0 + \nabla \mathbf{u}_0^\top), \quad \mathbf{u}_0 = 0 \quad \text{on } \partial \mathcal{D}_{RVE}; \quad (15)$$

where $\mu = Y\nu/2(1+\nu)$ and $\lambda = Y\nu/(1-2\nu)(1+\nu)$; consequently the micro-strain field $\boldsymbol{\varepsilon}_0$ could be represented as a strain concentration tensor $\mathbb{L}(\mathbf{x})$ times the uniform macro-strain $\bar{\boldsymbol{\varepsilon}}$.

The already mentioned strain energy identification between the micro and the macro model allows to establish an explicit representation formula of the average stiffness \mathbb{C}^{hom} once the solution of the micro boundary value problem has been determined

$$\frac{1}{2} \bar{\boldsymbol{\varepsilon}} \cdot \mathbb{C}^{\text{hom}} \bar{\boldsymbol{\varepsilon}} = \frac{1}{2|\mathcal{D}_{RVE}|} \int_{\mathcal{D}_{RVE}} \{ [\mathbb{I} + \mathbb{L}(\mathbf{x})] \mathbf{R}^\top \bar{\boldsymbol{\varepsilon}} \mathbf{R} \cdot \mathbb{C}(\mathbf{x}) [\mathbb{I} + \mathbb{L}(\mathbf{x})] \mathbf{R}^\top \bar{\boldsymbol{\varepsilon}} \mathbf{R} \} d\nu, \quad (16)$$

where \mathbb{I} is the fourth order identity tensor.

In the following we present the procedure developed in order to solve the considered micro problem on the basis of a Galerkin based approach.

Consider the solution for \mathbf{u}_0 as a linear combination of a set of appropriate functions which represent a basis of $H_0^1(\mathcal{D}_{RVE})$ and approximate both the x and y components, say u_1 and u_2 , with a finite sum of them:

$$u_1 = \sum_{i=1}^p U_i \psi_i(x, y), \quad u_2 = \sum_{i=1}^p V_i \psi_i(x, y). \quad (17)$$

The basis functions $\{\varphi(x, y)_{(i,j)}\}$ ($i, j = 1, \dots, P$) are progressively numbered so as to be arranged in a one dimensional array $\{\psi_k\}_{k=1, \dots, p(P)}$; in the following we call shape functions the elements of this list. Introducing the shape function rectangular matrix

$$\Psi(x, y) = \begin{pmatrix} \psi_1 & \dots & \psi_p & 0 & \dots & 0 \\ 0 & \dots & 0 & \psi_1 & \dots & \psi_p \end{pmatrix} \quad (18)$$

and the coefficient vector $\mathbf{U}^\top = (U_1 \dots U_p V_1 \dots V_p)$; the solution for \mathbf{u}_0 can be represented as $\mathbf{u}_0 = \Psi(x, y) \mathbf{U}$; consequently the average stiffness, according with eqn.(16) and considering the index notation, will come from the following condition

$$\frac{1}{2} \bar{\varepsilon}_{\alpha\beta} \mathbb{C}_{\alpha\beta\sigma\tau}^{\text{hom}} \bar{\varepsilon}_{\sigma\tau} = \frac{1}{8|\mathcal{D}_{RVE}|} \int_{\mathcal{D}_{RVE}} [A_{ij} + (\Psi_{ik,j} + \Psi_{jk,i}) U_k] \mathbb{C}_{ijkl} [A_{lm} + (\Psi_{lp,m} + \Psi_{mp,l}) U_p] dv \quad (19)$$

where $U_k = \mathbb{M}_{krs} A_{rs}$ and A_{rs} are the (r, s) components of the rotated strain tensor introduced in eqn.(13). Summation over doubly repeated indices is understood. Apparently the third order tensor \mathbb{M} depends on the solution of the boundary value problem defined over the RVE and allows to determine a representation of the concentration tensor \mathbb{L} .

The solution of the boundary value problem stated by eqns.(14) is obtained considering its weak formulation and introducing suitable test functions defined in terms of the introduced shape functions:

$$\int_{\mathcal{D}_{RVE}} [2\mu \nabla \mathbf{u}_0 \cdot \nabla \mathbf{u}_{(k)} + \lambda \text{tr} \nabla \mathbf{u}_0 \text{tr} \nabla \mathbf{u}_{(k)}] dv = - \int_{\mathcal{D}_{RVE}} (2\mu \mathbf{A} \cdot \nabla \mathbf{u}_{(k)} + \lambda \text{tr} \nabla \mathbf{A} \text{tr} \nabla \mathbf{u}_{(k)}) dv, \quad (20)$$

where $(\mathbf{u}_{(k)})_i = \Psi_{ij} \mathbf{U}_j^{(k)}$ and $\mathbf{U}^{(k)} \in \mathbb{R}^{2n}$, this last is a vector of zeros except of the k -th element which is equal to one. The \mathbf{u}_0 expansion given by eqn.(17) is stated on the basis of the following representation formula for the $\varphi_{(k,j)}$ shape function

$$\varphi_{(k,j)}(x, y) = \left[1 - \cos \left(\frac{2\pi n}{X} kx \right) \right] \sin \left(\frac{2\pi m}{Y} jy \right) + \left[1 - \cos \left(\frac{2\pi m}{Y} jy \right) \right] \sin \left(\frac{2\pi n}{X} kx \right), \quad (21)$$

where, according with the nomenclature of Figure 1, X/n and Y/m represent the x and y period of the RVE.

5 CHARACTERIZATION OF THE CONTROL LAW

This section is devoted to determine the evolution laws for the introduced control parameters, according with a suitable hypothesis of optimal response, see e.g.[11]. The adaptation laws for the whole set of control variables are therefore determined requiring a suitable control functional to be extremum with respect to variations of their time derivatives. In particular we assume the control functional to be the rate of strain energy and require stationarity conditions under a suitable set of constraints involving displacement \mathbf{u} , rate of change of displacement $\dot{\mathbf{u}}$ as well as rate of change of the control parameters $(\dot{a}, \dot{b}, \dot{\mathcal{N}}_x, \dot{\mathcal{N}}_y, \dot{\vartheta})$. Apparently this is the case of a 2D problem where ϑ is the angle which characterizes the rotation tensor \mathbf{R} , moreover \mathcal{N}_x and \mathcal{N}_y indicate the amount of voids along the main directions of the considered RVE respectively. We consider $(\mathbf{u}, \dot{\mathbf{u}})$ to be just constrained by the equilibrium equations and their time derivatives

$$\begin{aligned} \text{div}(\mathbb{C} \nabla \mathbf{u}) &= 0, & \text{div}(\dot{\mathbb{C}} \nabla \mathbf{u} + \mathbb{C} \nabla \dot{\mathbf{u}}) &= 0, & \text{in } \mathcal{D} \\ (\mathbb{C} \nabla \mathbf{u}) \mathbf{n} &= \mathbf{t}, & (\dot{\mathbb{C}} \nabla \mathbf{u} + \mathbb{C} \nabla \dot{\mathbf{u}}) \mathbf{n} &= \dot{\mathbf{t}}, & \text{on } \partial \mathcal{D} \end{aligned} \quad (22)$$

whilst the rate of change of the control parameters by suitable topological conditions prescribing for instance the total amount of volume change of the voids involved in the remodeling process.

In order to give a quite general formulation of the adaptation laws let us try to consider the following form for the additional local constraints, involving only the rate of change of the

control parameters χ_j ($j = 1, \dots, N$) (see §2)

$$f_k(\dot{\chi}_1, \dots, \dot{\chi}_N) = 0, \quad k = 1, \dots, \kappa. \quad (23)$$

According with eqn.(1) and eqns.(22) the functional required to be stationary is given by

$$\mathfrak{F} = \dot{\Psi} + \int_{\mathcal{D}} \left[\lambda_{\mathbf{u}} \cdot \operatorname{div}(\mathbb{C}\nabla\mathbf{u}) + \lambda_{\dot{\mathbf{u}}} \cdot \operatorname{div}(\mathbb{C}\nabla\dot{\mathbf{u}} + \dot{\mathbb{C}}\nabla\mathbf{u}) \right] + \sum_{k=1}^{\kappa} \int_{\mathcal{D}} \lambda_k f_k(\dot{\chi}_1, \dots, \dot{\chi}_N) dv, \quad (24)$$

where $\lambda_{\mathbf{u}}$ and $\lambda_{\dot{\mathbf{u}}}$ are the Lagrange multipliers associated with the equilibrium equations and their derivatives, whilst λ_k ($k = 1, \dots, \kappa$) are those ones associated with the topological constraints of eqn.(23).

Consider the variation of \mathfrak{F} with respect to $(\mathbf{u}, \dot{\mathbf{u}}, \dot{\chi}_1, \dots, \dot{\chi}_N)$ as well as with respect to the introduced Lagrange multipliers; moreover assume boundary conditions (22)₂ to be verified by the optimal fields \mathbf{u} and $\dot{\mathbf{u}}$. Apparently equilibrium equations and topological constraints are going to be recovered from stationarity conditions together with the adaptation laws of the control parameters. Since we decided to adopt a very special control functional, say the rate of strain energy, it is possible to prove that $\lambda_{\mathbf{u}}$ and $\lambda_{\dot{\mathbf{u}}}$ coincide with $\dot{\mathbf{u}}$ and \mathbf{u} respectively.

Variation of \mathfrak{F} is given by

$$\begin{aligned} \delta\mathfrak{F} = \int_{\mathcal{D}} \left[\left(\dot{\mathbb{C}}\nabla\mathbf{u} + \mathbb{C}\nabla\dot{\mathbf{u}} \right) \cdot \nabla\delta\mathbf{u} + \mathbb{C}\nabla\mathbf{u} \cdot \nabla\delta\dot{\mathbf{u}} + \lambda_{\mathbf{u}} \cdot \operatorname{div}(\mathbb{C}\nabla\delta\mathbf{u}) + \right. \\ \left. + \lambda_{\dot{\mathbf{u}}} \cdot \operatorname{div}(\mathbb{C}\nabla\delta\dot{\mathbf{u}} + \dot{\mathbb{C}}\nabla\delta\mathbf{u}) + \lambda_k \sum_{k=1}^{\kappa} \sum_{j=1}^N \frac{\partial f_k}{\partial \dot{\chi}_j} \delta\dot{\chi}_j \right] dv = 0, \end{aligned} \quad (25)$$

where $\dot{\mathbb{C}}$ is known in terms of the derivatives of the control parameters according with eqn.(2). Assuming natural boundary conditions – eqns.(22)₂ – implies variations of traction and variation of traction time derivative to be vanishing. Thus bearing in mind equilibrium equations we finally get boundary value problems for $\lambda_{\dot{\mathbf{u}}}$ and $\lambda_{\mathbf{u}}$ which coincide with those ones stated for \mathbf{u} and $\dot{\mathbf{u}}$ in eqns.(22), respectively. This therefore implies that $\lambda_{\dot{\mathbf{u}}} = \mathbf{u}$ and $\lambda_{\mathbf{u}} = \dot{\mathbf{u}}$.

The adaptation law for the j -th control parameter ($j = 1, \dots, N$) are finally given in the following form:

$$\left(\frac{1}{2} \nabla\mathbf{u} \otimes \nabla\mathbf{u} - \nabla\mathbf{u} \otimes \nabla\lambda_{\dot{\mathbf{u}}} \right) \cdot \frac{\partial \mathbb{C}}{\partial \chi_j} + \sum_{k=1}^{\kappa} \frac{\partial f_k}{\partial \dot{\chi}_j} = 0 \Rightarrow -\frac{1}{2} \nabla\mathbf{u} \otimes \nabla\mathbf{u} \cdot \frac{\partial \mathbb{C}}{\partial \chi_j} + \sum_{k=1}^{\kappa} \frac{\partial f_k}{\partial \dot{\chi}_j} = 0, \quad (26)$$

where $\partial f_k / \partial \dot{\chi}_j$ should be at least linear with respect to $\dot{\chi}_j$.

It is worth to notice that the first term of eqn.(26) coincides with the first one of eqn.(6), i.e. with the derivative of the dissipation functional with respect to the rate of change of the j -th control parameter, when considering $g_j = 0$. This means that optimization with respect to the rate of change of χ_j implies stationarity of dissipation; thus adaptation laws can be interpreted as the stationarity conditions for the dissipation Γ under the considered topological constraints. In other words we claim that the evolution equations for the control state parameters can be straightly deduced from dissipation inequality as the stationarity conditions of dissipation when limiting the space of available control parameters by a suitable set of constraints. The governing equations of the problem, which include the adaptation laws, are finally given by the equilibrium

equations from one hand and the stationarity conditions for the dissipation functional from the other one; accordingly eqns.(26) can be stated in the following form:

$$\delta_{\dot{\chi}_j} \left(\Gamma + \sum_{k=1}^{\kappa} \int_{\mathcal{D}} \lambda_k f_k (\dot{\chi}_1, \dots, \dot{\chi}_N) dv \right) = 0, \quad j = 1, \dots, N. \quad (27)$$

We underline that identifying the obtained adaptation laws with eqns.(6) allows to determine proper constitutive assumptions on Onsanger's coefficients \mathcal{A}_{jk} , when assuming the topological constraints to be quadratic forms of $\dot{\chi}_j$.

Using notation introduced in §3 we exhibit now a specific example for the topological constraints, specifying in particular how the total amount of volume change, related to the inclusions, evolves because of the remodeling process.

$$\int_{\mathcal{D}} \left[\frac{d}{dt} (ab\mathcal{N}_x\mathcal{N}_y) \right]^2 dv = \mathbb{V}(t). \quad (28)$$

Here $\mathbb{V}(t)$ is a scalar function which describes from the outside the effect of biological phenomena on volume changes. Additional constraints could be taken into account in order to preserve the topological structure of the RVE; in particular the following conditions should be required

$$\frac{L}{\mathcal{N}_x} - a > 0, \quad \frac{L}{\mathcal{N}_y} - b > 0, \quad (29)$$

where L indicates the characteristic length of the RVE. Apparently these last can be transformed into equality constraints introducing suitable slack variables which coincide with the geometrical quantities τ and σ (see Figure 1). Both eqns.(29) imply the summation of the total voids length and intra voids length to not exceed the side length of the RVE along x and y . It is worth to notice that a proper differential of these constraints can be considered.

Notice that at least one additional constraint has to be incorporated into the model in order to account for time evolution of the RVE orientation.

6 CONCLUSIONS

The approach leading to a model of functional adaptation suitable for effective numerical simulations is presented in this paper. This model is capable to describe the evolution of an anisotropic material of bone in macro scale but taking into account the effects of cell activities resulting in alteration of tissue micro-structure. There is already a class of works where bone microstructure is considered as a result of a solution of an optimization problem and mathematical homogenization is used to express the properties of a macroscopic material point in terms of parameters characterizing local micro-structure of bone tissue. Such an approach enables determination of distribution of anisotropic characteristics of a material point in bone being in remodeling equilibrium state and treated as an engineering structure.

However living bone undergoes continuous alterations caused by cell activities due to variable mechanical and biological conditions. In the present work an approach has been proposed enabling derivation of remodeling law i.e. mathematical formulas defining time evolution of bone microstructure taking into account basic biomechanisms associated with cell activities. Because bone remodeling occurs at surfaces – the interfaces between bone tissue and marrow – the choice of the parameters used to characterize topology of tissue architecture plays a crucial role in this formulation.

In determination of macroscopic material characteristics no mathematical homogenization techniques have been used in order to avoid any assumption about periodicity of microstructure. Instead, the micro problem defined for RVE was solved using Galerkin approach; moreover, identifying the average strain energy of the RVE with the strain energy of the point represented by this RVE at the macro level, the macroscopic constitutive law can be determined.

To derive adaptation law the hypothesis of optimal response of bone has been adopted. It follows from thermodynamical considerations that application of this hypothesis is equivalent to minimization of energy dissipation due to remodeling process what leads to interesting and physically well based interpretation of remodeling formulas.

One of the motivations of the present work was the need to have at hand the model which enables numerical calculations using reasonable in size FEM models (no millions of 3D elements for simulation of bone remodeling process are acceptable). It seems that proposed approach suits this requirement.

Additional work is necessary to identify appropriate constraints for control parameters to account for different biochemical effects. For example - osteoporosis can be modeled by introducing additional constraints and merging them with the global one associated with time-evolution of the amount of the bone material (or volume of voids in cancellous bone).

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