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ORIGINAL PAPER

On mechanically driven biological stimulus for bone remodeling as a diffusive phenomenon

Ivan Giorgio[1,2] · Francesco dell'Isola[2,3] · Ugo Andreaus[1] · Faris Alzahrani[3] · Tasawar Hayat[3,4] · Tomasz Lekszycki[5,6]

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Abstract
In the past years, many attempts have been made in order to model the process of bone remodeling. This process is complex, as it is governed by not yet completely understood biomechanical coupled phenomena. It is well known that bone tissue is able to self-adapt to different environmental demands of both mechanical and biological origin. The mechanical aspects are related to the functional purpose of the bone tissue, i.e., to provide support to the body and protection for the vitally important organs in response to the external loads. The many biological aspects include the process of oxygen and nutrients supply. To describe the biomechanical process of functional adaptation of bone tissue, the approach commonly adopted is to consider it as a 'feedback' control regulated by the bone cells, namely osteoblasts and osteoclasts. They are responsible for bone synthesis and resorption, respectively, while osteocytes are in charge of 'sensing' the mechanical *status* of the tissue. Within this framework, in Lekszycki and dell'Isola (ZAMM - Zeitschrift für Angewandte Mathematik und Mechanik 92(6):426–444, 2012), a model based on a system of integro-differential equations was introduced aiming to predict the evolution of the process of remodeling in surgically reconstructed bones. The main idea in the aforementioned model was to introduce a scalar field, describing the biological stimulus regulating the interaction among all kinds of bone cells at a macroscale. This biological field was assumed to depend locally on certain deformation measures of the (reconstructed) bone tissue. However, biological knowledge suggests that this stimulus, after having been produced, 'diffuses' in bone tissue, so controlling in a complex way its remodeling. This means that the cells which are target of the stimulus may not be located in the same place occupied by the cells producing it. In this paper, we propose a model which intends to explain the diffusive nature of the biological stimulus to encompass the time-dependent and space–time displaced effects involved in bone reconstruction process. Preliminary numerical simulations performed in typical cases are presented. These numerical case studies suggest that the 'diffusive' model of stimulus is promising: we plan to continue these kinds of studies in further investigations.

Keywords Mechanical–biological coupling · Bone functional adaptation · Growth/resorption processes · Bone remodeling

1 Introduction

One of the most challenging endeavors in contemporary applied mathematics concerns the formulation of mathematical models for the growth and possibly for the resorption of soft and hard biological tissues, in one word, for their remodeling. In this paper, we will focus on the particular case of bone tissues, even if we believe that there are many common features with other kinds of tissues. Therefore, we expect that our results may be applicable also in slightly

✉ Ivan Giorgio
ivan.giorgio@uniroma1.it

[1] Department of Structural and Geotechnical Engineering, Università di Roma La Sapienza, 18 Via Eudossiana, Rome, Italy

[2] International Research Center for the Mathematics and Mechanics of Complex Systems - MeMoCS, Università dell'Aquila, L'Aquila, Italy

[3] NAAM Research Group, Department of Mathematics, King Abdulaziz University, Jeddah 21589, Saudi Arabia

[4] Department of Mathematics, Quaid-I-Azam University, Islamabad, Pakistan

[5] Warsaw University of Technology, Warsaw, Poland

[6] Department of Experimental Physiology and Pathophysiology, Medical University of Warsaw, Warsaw, Poland

different contexts. Growth and remodeling phenomena are, indeed, very complex. They involve physical, chemical and mechanical coupled interactions and can be regarded as emerging subjects in continuum physics and biomechanics (see, e.g., Prakash et al. 2018; Ganghoffer 2012; Taber 2009; Holzapfel and Ogden 2006; Cowin 2001).

In the framework of continuous field models, various proposals were formulated to model aforementioned coupled interactions, always aiming to capture the most relevant aspects of mechanically driven living tissue growth and reconstruction. To our knowledge in the present literature, it is systematically assumed that the biological stimulus remains localized where it has been produced. In other words, if one has introduced the concept of a material particle of the continuum describing the tissue, then the biological stimulus as perceived in one material particle depends on the deformation field as measured in the same material particle. A first generalization has been proposed in Lekszycki and dell'Isola (2012), Kumar et al. (2011), Andreaus et al. (2014b), Giorgio et al. (2016): indeed, in cited papers the stimulus in a material particle depends on a space average (in the reference configuration) of the deformation in its neighborhood. This assumption seems more realistic but not completely satisfactory. Indeed, we are aware of the difficulties in understanding the true nature and relevant characteristics of biological stimulus, which although plays such a prominent role in living tissue growth. The processes of stimulus formation, propagation and reception are surely not understood in a satisfactory way yet. However, it seems to us clear that (see, for instance, Kühl et al. 2000; Pinson et al. 2000; Gong et al. 2001) a part of the biological signal is produced by means of biochemical processes and that the produced biochemical factors which are the output of said processes are diffusing in the tissue whose growth and resorption they are controlling. Mathematical physics has already, and in different contexts, produced a model for this kind of diffusive phenomena. The natural choice is, therefore, to imagine that in the growth control process one can distinguish at least two different steps. In the first, one finds the generation of the biological signal in a certain material particle subject to a specific deformation state at a given time instant. In the second step, the signal diffuses in space with a certain speed (and possibly direction), thus regulating the remodeling of different material particles in subsequent instants.

While we believe that the described approach is not present in the literature, we believe that it may contribute to the theoretical efforts needed to model growth phenomena. We are aware of the fact that simplification has to be searched, when possible, and that many interesting simpler models of continua in which growth occurs have been already proposed and carefully studied (see, e.g., George et al. 2018b; Cluzel and Allena 2018; Allena and Cluzel 2018; Goriely et al. 2008; Menzel 2005; Di Carlo and Quiligotti 2002; Epstein and Maugin 2000).

Some continuum models have been imagined which introduce generalized structured continua, as those involving the concept of mixtures (Franciosi et al. 2018; Spagnuolo et al. 2017; Ambrosi et al. 2010; Ateshian 2007), or micropolar kinematical descriptors (Goda et al. 2014; Yoo and Jasiuk 2006; Diebels and Steeb 2003; Park and Lakes 1986), see also (Eremeyev et al. 2016; Eremeyev and Pietraszkiewicz 2016; Altenbach and Eremeyev 2015; Eremeyev et al. 2013), or deformation energies depending on the second gradient of placement (Giorgio et al. 2017a; Madeo et al. 2013, 2012; Seppecher 2000, 1996). It is natural to imagine that their use may be required to capture the most complex aspects of growing tissue biomechanics. In this paper, we will limit ourselves to consider, from the mechanical point of view, the simplest possible model, by focusing on the complications involved in considering a diffusive stimulus. We are confident that by uniting our present approach with generalized continuum models an important step toward the comprehension of tissue growth may be attained.

Indeed, we are aware of the impressive progress in modeling bone mechanics occurred in the last decades. In this paper, we exploit these results and we, therefore, have accepted systematically the following concepts and paradigms:

1. mechanical phenomena play a key role in bone tissue growth (Rosa et al. 2015; Hambli 2014);
2. the growth of living bone tissues is controlled by a specific agent which has been called *biological stimulus*: the biological stimulus in bone tissues is mechanically driven, regulates and controls the action of some specialized cells which are called osteoblasts (tissue producing cells) and osteoclasts (tissue destructing cells) (Beaupre et al. 1990b; Turner 1991; Mullender et al. 1994);
3. there must be a clear distinction between the process of stimulus generation and the signal processing preceding the stimulus generation (see Lekszycki and dell'Isola 2012);
4. the driving phenomenon in signal production is deformation, which can be modeled in a more or less sophisticated way, with more or less complex continuum models (Giorgio et al. 2017a, 2016; Park and Lakes 1986; Hambli and Kourta 2015);
5. the biological stimulus results into a variation of the mechanical properties of the bone (Frost 1987);
6. the deformation state of the tissue controls its biological activity and reactivity (Huiskes et al. 1987; Lekszycki and dell'Isola 2012).

Many investigations have been dedicated to the aim of understanding all phenomena involved in stimulus generation and

stimulus activity. Its production, propagation and effects on active or capable of being activated cells which are acting in bone remodeling process (see, e.g., Komori 2013; Bonewald and Johnson 2008; van Hove et al. 2009; Hambli and Rieger 2012; Sansalone et al. 2013) have been intensively studied. At micro-level, it is possible to hypothesize that the interstitial fluid flow through the lacuno-canalicular system plays an important role in the remodeling process (You et al. 2001) as well as the number of active cells (Rieger et al. 2011). Thus, a stimulus depending on the interstitial fluid velocity can be assumed as done in Hambli and Kourta (2015). We claim that these interesting results give us an understanding of what happens at smaller scales inside a growing bone.

We must explicitly warn the reader here: we do not even try to model the enormous complexity of growth processes which is observed at said cellular or lacuno-canalicular level: the length scale which we call here 'micro-level' or 'smaller scale.' Instead, we are persuaded that at macro-level, it is acceptable and even reasonable (see Chen et al. 2005; Mlodzik 2002) to postulate that the generation of the biological stimulus and its eventual propagation are phenomena which are not directly and explicitly related to specific aspects of biological or mechanical phenomena occurring at the smaller scale. We look for a macro-model which is averaged enough to be able to capture the overall and global features of these micro-phenomena which we refrain to describe. This was the spirit which animated Lekszycki and dell'Isola (2012), Giorgio et al. (2016) where the governing equations, used to describe the mechanically driven macroscopic growth phenomena, were postulated to be an integro-differential system incorporating the information of overall stimulus generation in the neighborhood of osteoclasts and osteoblasts (active cells) which are activated by the biological stimulus.

Actually, this approach does imply the concept of immediate transmission of the biological signal as produced as a consequence of the action of sensor cells (osteocytes) to the 'active' cells.

However, the proposed macro-model can be thought of as a target model in a micro-macrohomogenization process in the same spirit of Hambli and Kourta (2015). Besides, a multi-scale modeling approach may take into account the complex and hierarchical microstructure of the bone tissues (see, e.g., Rosa et al. 2015; Hambli et al. 2011; Barkaoui et al. 2014, 2016). To our knowledge, there is some biological evidence (Arias et al. 2018; Bonewald and Johnson 2008; Kühl et al. 2000) and, we believe, there is a clear logical basis, of the fact that the biological stimulus is first produced and then diffused before reaching its target cells, i.e., the active cells governing growth and resorption. (see, e.g., George et al. 2017; Spingarn et al. 2017; Stern and Nicolella 2013; Himeno-Ando et al. 2012; Bonucci 2009). There is evidence, indeed, of the existence of mechanisms which govern the production of 'signaling chemical species,' of phenomena of diffusion of these species in the reconstructing tissue and of their adsorption to initiate the activation of osteoclasts and osteoblasts.

In this paper, we cannot describe in a careful way all these complex and somehow obscure mechanisms. Therefore, we refrain to reach a detail of description which is valid at the smaller scale and limit ourselves to formulate a model which is (1) valid at macroscale, (2) accounting for the biological stimulus diffusion during the process of tissue remodeling and growth, (3) describing the diffusive time delay and space displacement phenomena which must be expected.

The simple ansatz which we accept is the following: at macro-level the biological stimulus diffuses in space and time by following the rule given by Fourier–Fick diffusion process, in which we postulate the presence of both sink and source terms. We further postulate that these source and sink terms can be determined by means of some specific constitutive laws in which the mechanical deformation energy and the stimulus itself appear. By conjecturing the result of the previously evoked homogenization process, we assume that (1) the stimulus production (source) term depends on the local value of mechanical deformation energy, (2) the metabolic action which leads to the degradation of the stimulus intensity (sink) is governed by a simple mechanism: this mechanism leads to a decay which is proportional to the local (in space and time) stimulus concentration.

We are aware that some local aspects of the microscopic biological complexity of considered system are completely neglected but we expect that, for what concerns the considered macroscopic averaged biomechanics quantities which we have included in our model, the postulated assumptions are descriptive of real phenomena. We are confident that the obtained macro-predictions are close to describing effectively some overall biomechanics phenomena.

Referring to the wide and complex problem of the functional adaptation of bone tissue subjected to mechanical loadings, therefore, aim of this paper is proposing a phenomenological model at macroscale based on a description of bone tissue as a homogenized generalized continuum, and accounting for the evolution of the bone mass density due to the transmission of an activation signal from the sensor cells to the cells responsible of bone synthesis and resorption. In particular, the proposed model focuses on the macro-level mechanism of the transmission of the signal through a diffusive way, which averagely and macroscopically represents the diffusion phenomena of the 'signaling factors,' and which occurs at microscale, relating the signal diffusion with the macroscopic phenomenon of the remodeling process, or in other words relating biological phenomena with mechanical ones at continuum level. In addition, the proposed model has been formulated aiming at conceiving, designing and guiding feasible experimental tests able to

identify the constitutive parameters of the model, by measuring observable quantities, which pertain to the evolution of the main global quantities interesting the present study, namely the mass density of bone tissue, beyond the analysis of diffusion of single signal factors at microscale.

To make meaningful the conceptual effort presented in this work, we prepared some numerical simulations performed with COMSOL Multiphysics^. They are somehow preliminary, as they describe some meaningful, but academic, situations. They will be presented in full detail in the sequel. We believe that they prove that the model which we propose here is really promising and will deserve our future efforts to be developed and generalized.

2 Basic kinematical fields and fundamental modeling assumptions

We start this section, devoted to the specification of the set of fields which describe the kinematics in the considered model, by remarking that if one wants to describe growth and resorption in living tissues one must assume that the referential mass density of every material particle may change in time. This observation must be extended to include also at least the variability, in time, of material symmetry group for each material particle, as remodeling can change its intrinsic mechanical properties. Referential mass density and the material symmetry group are changed by biological agents as a response to mechanical deformation induced by external loads. Indeed, mechanical deformation triggers the biological actions of the designated cells which are present in the living tissue so that one can observe the establishment of a self-reorganization process (Roux 1895) in the living tissue.

It is useful to reinterpret the whole bone remodeling process as a process controlled by robust feedback and to study it with the methods of the theory of control (see Frost 1987; Turner 1991).

In the remodeling process, the mechanical properties of the living tissue are to be regarded as the controlled quantities. On the other hand, the total mass of bone and its distribution at the lower scale must be considered as the controlling quantities. In other words, we can assume that the change of total bone mass and of the macroscopic material symmetry group is changing because of the remodeling process and as a consequence of the biological action triggered by the externally applied loads.

In fact, in order to supply the mechanical strength needed to resist to externally applied loads, some active cells, which can be regarded as the process 'actuators,' can be driven to resorb or to synthesize bone tissue. The observations made during the remodeling process indicate that the whole system has efficient feedback which aims to obtain an optimized distribution of bone mass (and of its structure at the lower level) so that the most appropriate deformation pattern is maintained in the tissue. One can say that the bone microstructure and mass result from a 'functional adaptation' which is attained by a process of constrained optimization. Given the total amount of available mass, it has to be distributed in order to get the maximum of resistance with the minimum use of living tissue. Bone mass is costly and its cost has to be limited. However, too low bone mass leads to bone fragility and the consequent lack of functionality must be avoided. Together with osteoclasts and osteoblasts (the active cells adsorbing and constructing bone tissue), one finds in the living bone also another type of cells: osteocytes. They are sensors which detect the biological stimulus, i.e., the feedback signal in our scheme from the theory of control, which is a consequence of the current mechanical deformation state. This signal has to be compared with a certain threshold, i.e., a certain interval of set-point values for the stimulus. The difference (or as it is called in the theory of control: the error) between the measured stimulus and the threshold values is the biological 'command' used to initiate the action of actuator cells.

We summarize the whole previously described process in the feedback diagram presented in Fig. 1.

The analysis which we present in this paper for the bone remodeling process is based on the following limiting assumptions:

1. The model used for bone tissue is not sophisticated enough to distinguish among the different possible kinds of bone tissues: in other words, it is not distinguishing among woven, trabecular or compact bone tissue, *etc*. We are, however, aware of the fact that growth and resorption have different rates for said different kinds of bone tissues. On the other hand, we are persuaded that the described feedback control mechanism has the same fundamental features in every bone tissue (Turner 1991).
2. We choose a unique characteristic time for the complex bone remodeling process: it is fixed to have a value in the interval 120–200 days. This choice is suggested by the fact that the longest period seems to be that characteristic of trabecular bone, while it is believed that this time interval gives the average duration of a complete and single turnover cycle (Agerbaek et al. 1991; Eriksen 2010).
3. All kinds of bone tissue are assumed to be well described by the model given by a nonlinear elastic (Davy et al. 1999; Morgan et al. 2001) or viscoelastic (Gottesman and Hashin 1980) porous (Cowin 1999; Smit et al. 2002) material.
4. The material symmetry group and all other properties of these materials determined by the bone internal microstructure (Eremeyev and Pietraszkiewicz 2016)

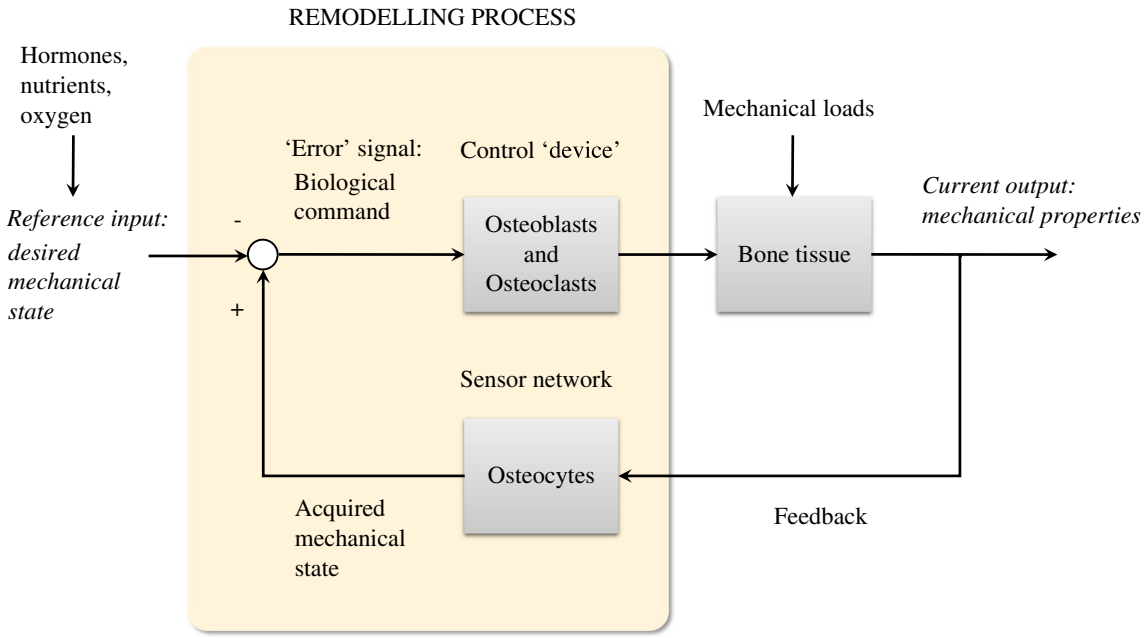

Fig. 1 A feedback control scheme to represent the biological activity involved in the remodeling process

are determined as a consequence of the action of only the three types of cells already described, that is *osteoblasts*, *osteoclasts* and *osteocytes*.

5. The *osteoblast* and *osteoclast*, i.e., the actor or actuator cells, are the living entities which are determining the synthesis or the resorption of bone tissue, respectively. Their activation is controlled by the biological stimulus. This stimulus is produced by the third kind of considered cells: the *osteocytes*, which are also called the sensor cells (Turner 1991; Katagiri and Takahashi 2002; Matsuo and Irie 2008).
6. In fact, *osteocytes* are producing the 'feedback signal,' in our control process. It is assumed to be mainly produced as a response of the density of deformation energy. This assumption has been already discussed in the introduction, and it is based on the hypothesis that deformation energy can be regarded as a good macroscopic indicator of the microscopic mechanical state, which is reliable independently of the true nature of the more fundamental mechanism determining the osteocytes response. This mechanism is being still debated and may not be unique (Aarden et al. 1994; Santos et al. 2009; Komori 2013; Graham et al. 2013). It is, however, unanimously accepted that osteocytes are organized in a network of cells interconnected each other by means of dendritic processes, namely protuberances, and they are completely surrounded by mineral bone and placed in appropriate cavities, namely lacunae and canaliculi (Burger and Klein-Nulend 1999).
7. The quantity of osteocytes which are active in a single 'material particle' of the used continuum model is related to the mass of the bone tissue present in a unit volume (Mullender et al. 1996; Baiotto and Zidi 2004). Moreover, when a certain material particle is in a certain state of deformation, the amount of signal inside the same material particle increases with the number of activated sensor cells.
8. We assume that the said increasing dependences are both linear: that is, the signal is proportional to the number of activated osteocytes and that the number of osteocytes is proportional to the bone mass density.
9. The intensity of the signal, as produced by some osteocytes, decreases with the distance between actor cells and osteocytes (Mullender et al. 1994).
10. The actuator cells receive all signals which reach them sent by surrounding sensor cells (Matsuo and Irie 2008).
11. The *reference signal* or the set point is assumed to be regulated by hormone activity or by the presence of oxygen and nutrients (Bednarczyk and Lekszycki 2016; Lu and Lekszycki 2018).
12. Living bone tissue can be resorbed or synthesized, because osteoblast and osteoclasts are always present together with osteocytes. However, the sensor cells can be located only in a real living tissue and not in artificial graft, and then in artificial grafts, the stimulus is

not produced and therefore; in the absence of stimulus diffusion, the only activated cells are osteoclasts: as a consequence, artificial grafts can be resorbed at higher rates than living tissue (Lekszycki and dell'Isola 2012).

13. The density of actuator cells available in a material particle depends on the local value of porosity of (possibly reconstructed) bone tissue. If the bone tissue has a current value of its porosity which is close to the maximum possible, then the density of active osteoclasts or osteoblast is vanishing. Indeed, these cells can act only when they are deposited on the inner surface of the internal tissue pores. If the amount of surface available to the adhesion of actor cells is too small, neither resorption nor creation of bone tissue is possible. On the other hand, actuator cells are absent when the porosity is vanishing: in fact, in this case, there is no space for the presence of active cells. As a consequence, it is possible to conjecture that there is a value for porosity which is optimal, for what concerns the largest available number of actor cells which can act (Martin 1984; Beaupre et al. 1990a).

The model which we present in this paper incorporates the aforementioned assumptions. They surely limit the range of its applicability. On the other hand, the simplifications which are made possible by their use allow for the formulation of effective numerical codes, whose predictive capacity will be discussed in what follows.

Assuming that the material body, described as a continuum, is the model of a certain class of living bone tissues, we consider the following kinematical Lagrangian fields, all to be evaluated in the position $\boldsymbol{X}$ belonging to the three-dimensional Euclidean space $\mathscr{E}$ (see Lekszycki and dell'Isola 2012 for more details):

(a) the Lagrangian bone tissue macroscopic mass density $\varrho(\boldsymbol{X}, t)$. Its value gives the mass density of the bone but referred to the whole Lagrangian volume occupied by it: this volume includes both the empty voids and the regions occupied by the bone. For this reason one can call it: 'apparent' Lagrangian bone mass density.

(b) the Lagrangian bone tissue porosity $\varphi(\boldsymbol{X}, t)$. It is the fraction of the Lagrangian volume which is actually 'empty' (at the small scale), i.e., not being occupied by bone tissue;

(c) the biological stimulus $\mathfrak{S}(\boldsymbol{X}, t)$. We assume that the results of the biological feedback of living tissue can be represented simply by a scalar field. Its value at the position $\boldsymbol{X}$ and at the instant t is an estimate of the activation signal produced by the sensor cells and then transmitted to the actor cells, that is osteoblasts, responsible for synthesis of bone tissue, and osteoclasts, responsible for resorption of bone tissue.

(d) the scalar field $\mathscr{W}(\boldsymbol{X}, t)$, which represents the volume density of strain (or deformation) elastic energy stored at the point $\boldsymbol{X}$ and at the instant t in the bone tissue. It is the energy which is used in (locally) deforming the bone tissue starting from the reference configuration—which we assume stress-free—into the configuration at the instant t;

(e) The Lagrangian density of osteocytes $d_{\mathrm{OC}}(\boldsymbol{X}, t)$. It is the number of sensing cells which are alive in the Lagrangian unit volume. These are the cells which can really 'estimate' the mechanical deformation state of bone tissue, can produce the feedback signal and effectively send it 'toward' the actuator cells.

Lagrangian fields are not sufficient to describe completely the deformation state of a body. We must, therefore, relate the just defined scalar fields

$$\varrho(\boldsymbol{X}, t), \quad \varphi(\boldsymbol{X}, t), \quad \mathfrak{S}(\boldsymbol{X}, t), \quad \mathscr{W}(\boldsymbol{X}, t), \quad d_{\mathrm{OC}}(\boldsymbol{X}, t) \tag{1}$$

to the reference configuration. It is, indeed, necessary to link them to a kinematics of bone tissue described in terms of placement from a given reference configuration. The conceptual framework in which we are operating is that which is called the finite elasticity of continua endowed with microstructure. Once specified the reference C^* and the current C_t configurations to define the 'stress-free' configuration used to label material particles and their configuration at the instant t, the placement of the body 'bone tissue' in the Eulerian $\mathscr{E}$ space of positions is given by the mapping χ, which is assumed to be a function which is continuous, differentiable and one-to-one:

$$\boldsymbol{x} = \chi(\boldsymbol{X}, t), \tag{2}$$

where with $\boldsymbol{x}$ we denote the position occupied by the material particle labeled by $\boldsymbol{X}$ belonging to the bone tissue at instant t. The following standard notation is used:

$$\boldsymbol{F} = \mathrm{Grad}\,\chi, \qquad J = \det \boldsymbol{F}, \qquad 2\boldsymbol{G} = \boldsymbol{F}^{\top}\boldsymbol{F} - \mathbf{I} \tag{3}$$

where (1) with the symbol $\boldsymbol{F}$ we denote the so-called gradient of placement or deformation gradient, (2) with J the determinant of $\boldsymbol{F}$: it describes the volume variation in the transformation from Lagrangian to Eulerian configurations, (3) with Grad$(\cdot)$ we denote the gradient operator when using the Lagrangian coordinates, (4) with $\boldsymbol{G}$ we denote the Green–Lagrange deformation (strain) tensor, and (5) with $\mathbf{I}$ the identity tensor.

Remark that linearity in small strain for bone tissue is sometimes regarded as a too much simplifying assumption, since experimental evidence reported in the literature as Morgan et al. (2001), Davy et al. (1999) leaves open the possibility of considering nonlinearities. Indeed, we remark

that a nonlinear behavior has been observed even at small strain, namely below 0.4%, in a range which can be considered important from a clinical and biomedical point of view (Morgan et al. 2001). This behavior may be probably due to hierarchical and complex structure of bone as well as to the presence of micro-cracks inside the bone tissue that can trigger nonlinearities (Davy et al. 1999; Giorgio and Scerrato 2017).

The placement function specified in Eq. (2) gives the conceptual basis of the Lagrangian description of the kinematics of bone tissue.

Of course, the material frame-indifference of deformation energy is a necessary requirement. Therefore, we must assume that $\mathscr{W}$ must be a function of $\boldsymbol{\chi}(\boldsymbol{X}, t)$ via the Green–Lagrange strain tensor $\boldsymbol{G}$ only.

We recall that our description of bone tissue biomechanics is formulated at a macro-level, i.e., at a larger scale. One should need a careful homogenization procedure for deducing such a macro-model from a micro-model including all the lower scale biomechanics phenomena which may be known. We refrain from this for two reasons: (1) clearly not all relevant micro-phenomena are fully understood or known and (2) the complexity of micro-phenomena have macroscopic effects which (hopefully) can be simplified in overall average behavior. We try to describe this last simplified behavior with a direct macroscopic approach, which, however, tries to take into account the most relevant aspects of micro-phenomenology.

At higher scale level, therefore, we have introduced the porosity field, as an extra kinematical descriptor. Moreover, we will assume to be able to conjecture the results of said 'homogenization' procedure for getting an expression for deformation energy in terms of 'microscopic' phenomena occurring at a smaller scale (see Sect. 5). In order to be able to formulate such a conjecture, we will need to introduce a specific extra kinematical descriptor.

In poromechanics (see, e.g., Lurie et al. 2018; Khalili and Selvadurai 2003; Misra et al. 2015, 2013), and coherently to what done in the Biot model, we introduce the Lagrangian field $\zeta(\boldsymbol{X}, t)$ defined as the change of the effective volume of the voids per unit volume in the transformation from Lagrangian to Eulerian configuration. In formulas

$$\zeta(\boldsymbol{X}, t) = \varphi(\boldsymbol{X}, t) - \varphi^*(\boldsymbol{X}, t) \tag{4}$$

where, as already assumed before, the superscript * refers to the reference configuration. It is well known that reference configuration is to be specified clearly, as it constitutes the domain in which all kinematical fields are to be defined. The present case which deals with the process of bone remodeling does not represent an exception to such a general rule.

Moreover, we have chosen a Lagrangian (that is referential) description because it is surely the most suitable also when the problem of getting computational predictions is confronted. Lagrangian description has to be preferred to Eulerian description in general, as this last description needs time-varying domains of definition of all involved fields.

3 The evolution equations for bone mass describing in remodeling process

For the sake of simplicity, in this section, we postulate an evolution equation for bone mass density without deriving it from a variational principle. This important conceptual step will be formulated in future works. Here, we simply remark that the evolution equation which we formulate below should be deduced from a Hamilton–Rayleigh principle by using a suitable dissipation functional.

Our approach follows the now standard approach which determines the evolution of the Lagrangian bone mass density by means of a first-order ordinary differential equation (see Beaupre et al. 1990b; Mullender et al. 1994; Lekszycki and dell'Isola 2012). In this way, we believe to be able to capture the most important features of the bone adaptation process even if we are aware that it is much more complex. The postulated evolution rule for the Lagrangian apparent mass density is:

$$\frac{\partial \varrho^*}{\partial t} = \mathcal{A}(\mathfrak{S}, \varphi) \tag{5}$$

In the previous Equation (5) on the RHS a function $\mathcal{A}$ appears. It is assumed to be able to account for some phenomena which are of purely biological nature, some mechanical interactions and some interactions involving mechanical and biological couplings.

Indeed, the rate of change of the mass density is postulated to be driven by the biological stimulus, $\mathfrak{S}$. The stimulus is influenced by the osteocytes which respond to the current mechanical configuration which they sense. The osteocytes produce a source of biological stimulus which diffuses in the bone tissue. On the other hand, the cells activated by the stimulus need to deposit on the internal surface of the bone pores to start their action. It is indeed the specific available surface of bone (Martin 1984) which is the place where the resorption or the synthesis of bone tissue can occur. We assume that this specific available surface is determined as a function of the current 'effective' porosity. With effective porosity, we mean the fraction of porosity which is indeed involved in the deposit of active cells and is therefore really involved in the remodeling, growth and resorption, process.

It is clear that the effective architecture, at the lower scale, of the bone tissue, is very relevant in the determination of specific surface available to cell deposit. In the literature, it is observed that there are, in bone tissue, different kinds of porosity (Cowin 1999) and this classification is an important feature in the evolutionary phenomenon in study. It has

been, indeed, observed that, namely osteoblasts and osteoclasts, can be effectively activated only on some specific surfaces produced by the inner porosity on the bone tissue: we refer, in particular, to the inter-trabecular surface (on saucer-shaped Howship's lacunae (Clarke 2008)) when dealing with the cancellous bone, to the Haversian canals or to the endosteal or periosteal surface (inside the so-called 'cutting cones') for cortical bone (Harrison and Cooper 2015).

The most fundamental property to be accounted for is therefore exactly the bone porosity, as it is exactly the presence of porosity which permits to the bone tissue to be biologically active. Indeed, not only the presence of porosity allows for the possibility to deposit active cells, but also it allows for the diffusion of the said cells (or of their biological precursors) through the bone tissue so that they can be activated where they are needed. Finally, porosity allows to the nutrition supply to be made available where it is needed allowing for the building of the transporting vascular network. For this reason, in the macroscopic model which we propose here, a main role is attributed to the scalar field describing bone tissue porosity. The previous considerations motivate the following choice for the structure of the function $\mathcal{A}$:

$$\mathcal{A}(\mathfrak{S}, \varphi) = a(\mathfrak{S})H(\varphi), \tag{6}$$

In the previous Equation (6), the function $a(\mathfrak{S})$ is designed to calculate, when the current value of porosity allows such production, i.e., the production (or resorption) rate of the bone mass density. For clear phenomenological reasons, it is assumed to be a piece-wise linear function of the local, in space and time, value for the biological stimulus.

On the other hand, the function H triggers said production rate, by supplying a suitable weight term. Its role consists in allowing for the calculation of the specific available deposit surface. In other words, the function H supplies, at the macro-level, the needed geometric information from the microstructures architecture of the bone tissue which is being remodeled. We assume that a specific regularity in such architecture can be recognized so that the shape, and therefore the area, of internal deposit surfaces, can be uniquely determined, for physiological reasons and for each kind of bone tissue, as a function of the current porosity.

To be more precise, we will assume that the function $a(\mathfrak{S})$ is given by the formulas:

$$a(\mathfrak{S}) = \begin{cases} s_{\mathrm{b}}\left(\mathfrak{S}(\boldsymbol{X},t) - P^{\mathrm{s}}_{\mathrm{ref}}\right) & \text{for } \mathfrak{S}(\boldsymbol{X},t) > P^{\mathrm{s}}_{\mathrm{ref}} \\ 0 & \text{for } P^{\mathrm{r}}_{\mathrm{ref}} \leqslant \mathfrak{S}(\boldsymbol{X},t) \leqslant P^{\mathrm{s}}_{\mathrm{ref}} \\ r_{\mathrm{b}}\left(\mathfrak{S}(\boldsymbol{X},t) - P^{\mathrm{r}}_{\mathrm{ref}}\right) & \text{for } \mathfrak{S}(\boldsymbol{X},t) < P^{\mathrm{r}}_{\mathrm{ref}} \end{cases} \tag{7}$$

We believe that it is important, also in the simplified context of the model which we present here, to introduce the concept of 'lazy zone' (see, e.g., Beaupre et al. 1990a; Ruimerman et al. 2005; Giorgio et al. 2016) as a factor which influences the biological stimulus. Indeed, it has been observed that there is an interval in the values of biological stimulus in which the activation of osteoclasts and osteoblasts does not occur. The feedback system active in bone remodeling is, in a sense, stabilized by this lazy zone. There are situations in which the bone tissue behaves as if it were well adapted to the external loads, and therefore, it has not the tendency to change its structure.

The lazy zone is an interval characterized by two thresholds $P^{\mathrm{r}}_{\mathrm{ref}}$ and $P^{\mathrm{s}}_{\mathrm{ref}}$. The first threshold is the relative to the resorption process and the second to bone tissue synthesis. This interval characterizes the so-called homeostatic physiological equilibrium configuration for the bone tissue.

The constitutive parameters s_{b} and r_{b} can be possibly different one from the other and represent, respectively, the synthesis rate and the resorption rate for given bone tissue. It is not useless to remark that the equation governing the bone mass production or resorption has a structure similar to the equation which is governing the velocity of a phase interface in the theory of phase transition (see, e.g., Abeyaratne and Knowles 2006; Berezovski et al. 2008; Engelbrecht and Berezovski 2015; Eremeyev and Pietraszkiewicz 2009, 2011). This circumstance should not surprise too much, however, if one thinks at the deposit mechanism of active cells which has been discussed before. Bone mass is growing exactly because of an interface between calcified bone tissue and the other components of bone tissue, those which fill its porosity space. To make our analysis more specific, we estimate heuristically, the function H by calculating the available surface for a cellular square lattice, which is assumed to be able to represent faithfully enough the bone trabecular pattern. The obtained results, using different values of porosity (see for

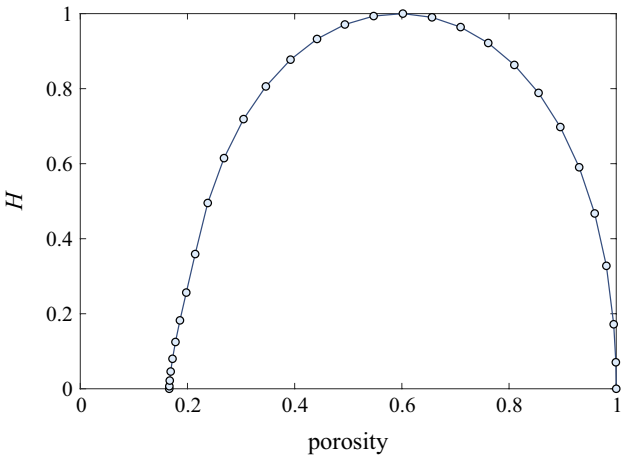

Fig. 2 The specific 'effective' surface function $H(\varphi)$

more details Giorgio et al. 2016), are depicted in Fig. 2. In conclusion, the function H must be postulated to give the specific 'effective' surface which plays a role in the remodeling process. For trabecular bone tissue, we expect that the curve depicted in Fig. 2 reflects the effective geometrical situation of bone microstructure. Remark that in the said figure there is a zone between the vanishing porosity value and the porosity value from which the plotted function has nonvanishing values. This interval of porosities refers to a bone tissue which we can call 'cortical bone.' The value of porosity for compact bone, $\varphi = 0.166$, is based on experimental data (Martin 1984). For purely computational reasons, we will consider, for the cortical type of bone tissue, a small and nonvanishing positive value for the function H. This is needed for not inhibiting completely the remodeling process when the trabecular bone becomes cortical.

3.1 A generalization of a previous model in which stimulus did not diffuse

It is clear that the most important concept in our modeling procedure regards the biological stimulus and the modalities in which it is produced starting from the mechanical configuration of the bone tissue.

We start by recalling that it is widely accepted in the literature that the osteocytes embedded in a given portion of bone tissue produce, as a response to mechanical deformation, a signal. This signal, when it is received, activates osteoblasts and osteoclasts. Of course, the signal can be received only in a neighborhood of the osteocytes' location. The questions arise: How is the signal triggered by mechanical deformation? How far is traveling the signal? In which time interval does the signal reach a certain target cell? Several possible simplifying assumptions have been proposed to give an answer to these questions. Each of these set of assumptions produced a mathematical algorithm to be used for calculating the scalar field modeling the biological stimulus. Some algorithms base their calculations on the estimate of the value of deformation energy; others start from the comparison of the current values for stress or strain with suitable effective values. In other more sophisticated models, it is introduced a measure of bone tissue damage and the signal production is related to this damage level (see for more insight on this subject Prendergast and Taylor 1994; Hambli 2014; Hambli et al. 2015 and also Placidi et al. 2018b, a; Placidi and Barchiesi 2018; Contrafatto and Cuomo 2006; Cuomo et al. 2014).

Simply for heuristic reasons, and being ready to generalize suitably the model, we follow the choice made in Lekszycki and dell'Isola (2012). In that paper, the stimulus has been represented, in an integral way, as a functional of the strain energy density $\mathscr{W}$. To be more precise, the signal received by each actuator cell is assumed to be the integral of all signals produced by the surrounding osteocytes. Of course, 'far' osteocytes are assumed to have a lower influence than closer osteocytes.

The functional used to calculate the perceived signal is therefore characterized by two weight functions: (1) the density of osteocytes, d_{OC} (Lekszycki and dell'Isola 2012) and (2) and a function, $K(\boldsymbol{X}, \boldsymbol{Y}, t, \tau)$, which accounts for the influence of far (in space and time) osteocytes on a given material particle of bone tissue.

The implicit assumptions accepted here are: (1) the number of present osteocytes is assumed to be proportional to their overall activity; (2) the function $K(\boldsymbol{X}, \boldsymbol{Y}, t, \tau)$ is sufficient to characterize the influence in space and time of each of the active group of osteocytes.

The functional postulated for calculating the biological stimulus which is the response to the mechanical deformation state is:

$$\mathfrak{S}(\boldsymbol{X}, t) = \int_0^t \int_{V^*} K(\boldsymbol{X}, \boldsymbol{Y}, t, \tau) \mathscr{W}(\boldsymbol{Y}, \tau) d_{\mathrm{OC}}(\boldsymbol{Y}, \tau) \, \mathrm{d}\boldsymbol{Y} \, \mathrm{d}\tau, \quad (8)$$

In this equation V^* is the volume occupied by the bone tissue in the chosen reference configuration, t is the current time instant, τ is a dummy integral variable denoting time, $\boldsymbol{Y}$ is the variable characterizing the location of considered signaling cell and $\boldsymbol{X}$ is the location where the signal may be able to active osteoblasts or osteoclasts.

Mathematically speaking, $\mathfrak{S}$ is the result of a nonlocal interaction, of the kind already studied by Piola (dell'Isola et al. 2015). This modeling procedure is somehow standard (see, Carvalho et al. (2009)), and it is used in viscoelasticity and in the so-called nonlocal elasticity. Of course, some further relations are needed to make our modeling algorithm well posed. There are some relationships among macro-fields which need to be postulated as a consequence of some features of considered systems which can be perceived only al lower scale. Refraining, once more, from any effort to introduce any homogenization procedure, we postulate some constitutive relations as follows.

The constitutive relation allowing for the calculation of the density of sensor cells is assumed to be:

$$d_{\mathrm{OC}} = \eta (1 - \varphi^*), \qquad 0 < \eta \leq 1, \quad (9)$$

In the last Equation (9), η is a further constitutive parameter. As just formulated constitutive equation assumes that the osteocytes are uniformly distributed in the bone tissue, so that their number is proportional to the volume fraction occupied by living bone tissue, the interpretation of the coefficient η is immediate. We conjecture that each kind of bone tissue will be characterized by its own value of this parameter.

If one assumes that there is an instantaneous transmission of the biological signal, its algorithmic expression can be simplified. This assumption implies that the transmission time scale can be neglected when compared with the characteristic time of the whole bone tissue growth-resorption phenomenon. In the case of instantaneous transmission, the stimulus functional assumes the form:

$$\mathfrak{S}(\boldsymbol{X},t)=\int_{V^*} k(\boldsymbol{X},\boldsymbol{Y})\mathscr{W}(\boldsymbol{Y},t)d_{\mathrm{OC}}(\boldsymbol{Y},t)\,\mathrm{d}\boldsymbol{Y}, \tag{10}$$

In the last equation, the weight function $k(\boldsymbol{X},\boldsymbol{Y})$ has not any explicit dependence on time. It has to be a decreasing function of the distance between $\boldsymbol{X}$ and $\boldsymbol{Y}$. In the literature, one finds (Mullender et al. 1994; Lekszycki and dell'Isola 2012; Andreaus et al. 2014a) at least two of such functions

$$k(\boldsymbol{X},\boldsymbol{Y})=e^{-\frac{\|\boldsymbol{X}-\boldsymbol{Y}\|}{D}} \quad \text{or} \quad k(\boldsymbol{X},\boldsymbol{Y})=e^{-\frac{\|\boldsymbol{X}-\boldsymbol{Y}\|^2}{2D^2}}. \tag{11}$$

The introduced D plays the role of a novel characteristic length scale, which controls the phenomena of signal perception.

It is now suggestive to notice that all the previously discussed influence functions have a lot of similarities with the Green function for the heat equation, both in their structure and in their properties.

4 A particular model of stimulus diffusion

The natural way for describing the process of exchange of signal from osteocytes to the actuator cells is to consider that the signal is diffusing in the bone tissue and that osteocytes excite the diffusion by means of the production of some source of signal. Mathematically speaking, this is equivalent to state that the integral functional (8) or (10) must be replaced by the operator which solves a diffusive evolution equation.

This assumption has several advantages: (1) its biomechanics and physiological interpretation is immediate and can be related to the diffusion of chemical species inside the bone tissue and (2) from the computational point of view, it allows for immediate implementation of the model.

Indeed, in many standard and commercial FEM programs, many kinds of diffusive PDEs are already implemented, while, on the contrary, very often the convolution integral formulation is avoided. Moreover, by accepting to formulate a known evolutionary equation for biological stimulus it is easier to account for possible surface effects and to implement the correct boundary conditions.

Again it is clear that we must consider the more useful Lagrangian description, so that the following parabolic evolution equation for biological stimulus $\mathfrak{S}$ is postulated

$$\frac{\partial\mathfrak{S}}{\partial t}=\mathrm{Div}(\kappa\nabla\mathfrak{S})+r+s, \tag{12}$$

In the previous Equation (12), κ is introduced as the permeability to the biological stimulus of considered bone tissue. Remark that in general, due to the microstructure of considered tissue, it is, in general, a second-order tensor field.

Most important is the source term postulated in the previous parabolic equation for the biological stimulus. We assume that there is a driving force from which the stimulus is originated. It is the source r which is assumed to depend on the current mechanical deformation. We will choose in the sequel the following expression for said source:

$$r=\varpi(\varrho^*)\mathscr{W}(\mathbf{G}), \tag{13}$$

In the previous Equation (13), we have introduced the weighting function $\varpi(\varrho^*)$. To this function, one has to attribute a role which is very similar to the role plaid by the previously introduce coefficient d_{OC}. More precisely to the function $\varpi(\varrho^*)$ must be attributed, continuing our parallel with the ideas from the theory of control, the role of 'measure of the efficiency of the sensor network.'

In the numerical simulations which we present in this paper, the particular form chosen for this efficiency function (see Fig. 3) is given by:

$$\varpi(\varrho^*)=\arctan(\xi\varrho^*)\,H_{\nu}(\varrho^*), \tag{14}$$

The coefficient ξ is a signal-saturation constitutive parameter (Giorgio et al. 2017b). The reason for which this assumption is made and the meaning of the further parameter are clear when one inspects Fig. 3. When a certain amount of sensor cells is present, that is when a certain mass density of bone tissue is reached, then the sensor network reaches its maximum efficiency. On the other hand, with fewer cells (corresponding to less dense bone tissue) the produced signal

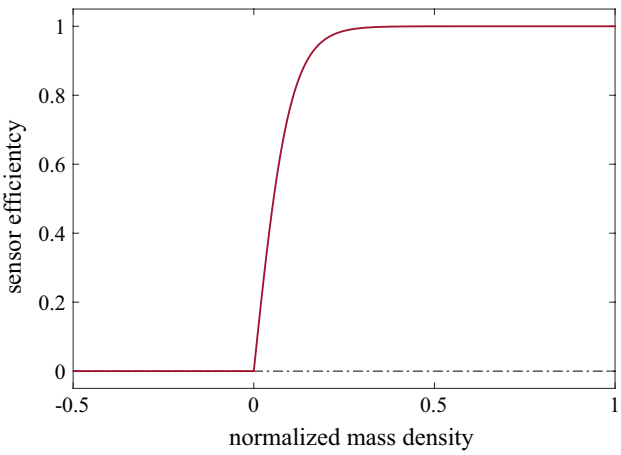

Fig. 3 Efficiency function of the sensor network $\varpi(\varrho^*)$

fades. Useless to say: there is no signal in the absence of sensing cells.

Remark also that in the previous Equation (12) a sink term appears: it is a field which models the action of metabolic tissue activity directed to resorb the stimulus. A reasonable assumption for such sink term may be

$$s = -R\,\mathfrak{S}\,H_{\nu}(\mathfrak{S}), \tag{15}$$

The constant R controls the rate of stimulus resorption, while the Heaviside function $H_{\nu}(\cdot)$ starting from zero value has been introduced. Its presence is necessary for reasons of mathematical consistency if one wants that the signal s remains always negative.

In order to describe the physical meaning of the parameters introduced in Eqs. (13) and (15), it is possible to resort to an interpretation of the biological phenomena at the cell scale, and then go back to the macroscopic level through a homogenization process of averaging. In particular, regarding the source term of the signal r in Eqs. (13)–(14), the signal formation was hypothesized to be modulated by a weight function applied to the mechanical stimulus to account for the influence of sensor cell density on signal efficiency. Specifically, it can be assumed that in a situation of scarcity of sensor cells, the signal quality is poor, while as soon as a certain critical density has more or less rapidly reached (rapidity is modulated by the parameter ξ), the signal quality stabilizes at a constant value. Regarding the sink term, s, in Eq. (15) it can be assumed that at the cellular level the osteocytes, mechanically stimulated, secrete chemical, enzymatic, hormonal and nutritive signals, the so-called 'signaling factors,' that are released and transmitted through the lacuno-canalicular system and reach the actuator cells. It can be assumed that these signaling factors remain active for a certain time interval even after the mechanical stimulus has ceased and are physiologically reabsorbed [minus sign in Eq. (15)] in a finite amount of time. With reference to Eq. (15) the parameter R, assumed to be constant for simplicity, was introduced to represent at a macroscale the phenomena described above assuming a simple proportionality between the sink and the stimulus. From the quantitative point of view, it can be thought to identify the values of the parameters introduced in Eqs. (13)–(15) (ξ and R), evaluating, e.g., with reference to Fig. 5, the rapidity of formation of the bone tissue and the value attained at equilibrium. The proposed model has been designed with a focus on the possibility of tailoring experiments in which it is possible to measure observable quantities (the apparent mass density of the bone tissue) and then to identify the above parameters from the quantitative point of view.

One can observe (observation by Cattaneo 1958) that the diffusion equation discussed up to now sees a signal which propagates with infinite speed. To obviate to this difficulty, and therefore to introduce a finite signal speed propagation, one can further modify Eq. (12). For instance, one could postulate for the evolution of signal the following PDE

$$t_{*}\frac{\partial^2 \mathfrak{S}}{\partial t^2} + \frac{\partial \mathfrak{S}}{\partial t} = \mathrm{Div}(\kappa \nabla \mathfrak{S}) + r + s, \tag{16}$$

in which the characteristic wave time t_{*} is introduced.

The proposed diffusion model can be surely improved and better adapted to try to catch the features observed in bone tissues. Besides, the intrinsic discrete nature of the sensor network system of the osteocytes present in remodeling bone may require treatment similar to the one presented in Colangeli et al. (2016), Colangeli et al. (2017) in the context of generalizing the diffusive part of presented model Allen-Cahn type equations may be of use: for the mathematical properties of this equations see De Masi et al. (1995).

5 A model for growing bone tissues using concepts from poromechanics

As already announced when introducing the Lagrangian field of variation of porosity, in the previous section, we will adapt the standard conceptual framework used in poromechanics to the present situation. As in every Lagrangian postulation of mechanics has to be done, we start by postulating an expression of Lagrangian elastic energy density. Our ansatz is the following: Lagrangian elastic energy $\mathscr{W}$ is assumed to be a function of (1) the Green–Lagrange strain tensor $\mathbf{G}$, (2) the change of porosity ζ, and (3) the considered material particle $\boldsymbol{X}$ (this assumption is needed for accounting for possible inhomogeneities. In formula

$$\mathscr{W} = \mathscr{W}(\mathbf{G}, \zeta, \boldsymbol{X}). \tag{17}$$

The reader will remark that as it is usually the case in continuum mechanics, the postulated deformation energy is not an explicit function of time. On the other hand, differently from what happens usually in standard continuum mechanics, the Lagrangian mass density does evolve with time. However, differently to what happens in the mass varying problems similar to those concerning rocket dynamics, we can assume that the mass density variations are slow enough and therefore their variations on inertial phenomena and on kinetic energy are negligible. Moreover, we do not include any 'kinetic energy' effects related to the process of mass variations, postponing to future investigations such considerations.

We will postulate and use a particular expression for the constitutive Equation (17) being guided by the results available in the literature on porous materials. Indeed, the bone, from the mechanical point of view, must be regarded as a porous medium.

We remark that our aim here is to propose a model that, at macroscale, is able to describe in an average sense the mechanotransduction activity which drives the remodeling process. Therefore, for the sake of simplicity, an isotropic expression for deformation energy is assumed to be valid to avoid unneeded complexity in the mechanical formulation (Cowin 1999). Indeed, some comparative studies between isotropic and anisotropic modeling of bone show that the differences in the results are sufficiently small and, as a first approximation, an isotropic model can be adopted (Peng et al. 2006). We are aware that for a complete and exhaustive mechanical formulation an anisotropic model should be adopted but this choice introduces only more details not much relevant at this stage of model development. The strain energy density which we conjecture has the following expression:

$$\mathscr{W}(\mathbf{G},\zeta,\boldsymbol{X}) = \mu\,\mathrm{tr}\big(\mathbf{G}^2\big) + \frac{\lambda}{2}(\mathrm{tr}\,\mathbf{G})^2 + \frac{1}{2}K_{\mathrm{c}}\,\zeta^2 + \frac{1}{2}K_{\mathrm{nl}}(\nabla\zeta)^2 - K_{\mathrm{cp}}\,\zeta\,\mathrm{tr}\,\mathbf{G}, \tag{18}$$

where we introduce a dependence of the Lamé moduli on Lagrangian porosity Lekszycki and dell'Isola (2012):

$$\mu = \mu_0(1-\varphi^*)^\beta; \qquad \lambda = \lambda_0(1-\varphi^*)^\beta, \tag{19}$$

In the previous formulas μ_0, λ_0 are assumed to be, in general, functions of $\boldsymbol{X}$ in order to be able to account for nonhomogeneous material. We recall from the definition of porosity that, in the presence of only bone tissue, the volume fraction occupied by living bone tissue is

$$\frac{\varrho^*}{\varrho_{\mathrm{Max}}} = (1-\varphi^*) \tag{20}$$

The interpretation of the quantity ϱ_{Max} is easy: it represents the maximum value possible for bone density.

We have assumed (but this assumption can be easily relaxed) that the Lamé moduli produce a constant Poisson ratio, ν. As a first approximation, in what follows we set it to 0.3. On the other hand, the Young modulus is given by the expression

$$Y = Y_0(1-\varphi^*)^\beta. \tag{21}$$

Of course, the assumption of isotropic bone is not completely realistic, also at the macroscale which we have used for our modeling procedure. However, the reader will agree that it is easy to generalize the previous constitutive assumption to incorporate anisotropies. This generalization will be the subject of future investigations.

In the paper Giorgio et al. (2016), it was proven that the value $\beta = 2$ is a reasonable choice. Clearly, we will associate to Y_0 the value of the Young modulus as estimated for the compact bone. One has to remark that the power low (21) has some bases in the literature: indeed, it has been systematically used for the formulation of the models for cellular solids, for instance, see Gibson and Ashby (1997), Ashby et al. (2000).

Again basing our considerations on the results from poromechanics, it is possible to estimate the compressibility stiffness K_{c} as follows:

$$K_{\mathrm{c}} = \left(\frac{\varphi^*}{K_{\mathrm{f}}} + \frac{(\alpha_B-\varphi^*)(1-\alpha_B)}{K_{\mathrm{dr}}}\right)^{-1} \tag{22}$$

by considering the so-called drained bulk modulus of the porous bone matrix,

$$K_{\mathrm{dr}} = \frac{Y}{3(1-2\nu)}, \tag{23}$$

and the bulk modulus K_{f} of the fluid which may fill the pores, namely bone marrow or interstitial fluid. The parameter $\alpha_B \in [\varphi^*, 1]$ is what has been called Biot-Willis coefficient.

The parameter K_{nl} in Eq. (18) is a modulus related to the nonlocal interactions between neighboring pores and is assumed to be constant for the sake of simplicity. It is worth noting that the term in Eq. (18) which takes into account the gradient of the change of porosity allows us to also apply boundary conditions on the porosity which otherwise are not sustainable. Some studies have been proposed to better characterize the complex behavior of systems as bone tissue, see, e.g., Li et al. (2019), Camar-Eddine and Seppecher (2001), Lekszycki et al. (2017), Misra and Poorsolhjouy (2015), Abali et al. (2012), Chatzigeorgiou et al. (2014).

We assume that the coupling parameter K_{cp} related to the interaction between the Green–Lagrange strain measure and the Lagrangian porosity is given by the following expression

$$K_{\mathrm{cp}} = \sqrt{\hat{g}(\varphi^*)\,\lambda\,K_{\mathrm{c}}} \tag{24}$$

In it, the function $\hat{g}(\varphi^*)$ is postulated to have the form

$$\hat{g}(\varphi^*) = \frac{A_{k_3}}{\pi}\left\{\mathrm{atan}\left[s_{k_3}\left(\varphi^* - \frac{1}{2}\right)\right] + \mathrm{atan}\left(\frac{s_{k_3}}{2}\right)\right\} \tag{25}$$

where $A_{k_3} \in (0,1]$ and s_{k_3} are suitable extra material coefficients.

In order to get the parts of the governing equations which refers to specifically mechanical principles for the considered continuum model, as we have argued before, we accept that there are no inertial effects of relevance, when the loads are applied to the bone tissue with a characteristic time scale which is the same as the typical characteristic time of the remodeling process. We are therefore aware of the fact that in the present model we cannot describe the growth phenomena, induced by loads having some specific (relatively

high) frequencies, which have been observed in some clinical situations.

In order to be consistent with this assumption, we must consider applied to the bone tissue only loads which are varying very slowly, so that one can be assured that a quasi-static deformation process takes place.

By applying in the considered situation the principle of virtual work, we get that the following variational equality

$$\delta\mathfrak{W}^{\text{int}} + \delta\mathfrak{W}^{\text{ext}} = 0 \tag{26}$$

holds for any regular subbody $\mathcal{B}$ included in the considered body.

Having specified the function which assigns the density of deformation energy, the virtual work of internal interactions is given by the expression

$$\delta\mathfrak{W}^{\text{int}} = -\int_{\mathcal{B}} \delta\mathscr{W}\,\mathrm{d}\mathcal{V}, \tag{27}$$

Instead, the external virtual work, that is the work expended on virtual displacements by the external loads, is given by

$$\delta\mathfrak{W}^{\text{ext}} = \int_{\partial_\tau\mathcal{B}} \tau_{\text{i}}\delta u_{\text{i}}\,\mathrm{d}\mathcal{S} + \int_{\partial\mathcal{B}} \Xi\,\delta\zeta\,\mathrm{d}\mathcal{S}, \tag{28}$$

In the last expression (1) the symbol τ_{i}, represents the surface traction on the boundary $\partial_\tau\mathcal{B}$: it expends work on the virtual displacement having components u_{i}, (2) the symbol Ξ, represents the microstructural action which is associated with the local dilatation of matrix pores: it expends work on the virtual change of porosity ζ.

6 Forecasting capabilities of considered models: targeted numerical simulations

The aim of this section is to prove that the theoretical efforts presented in the previous sections give some promising modeling possibilities. Indeed, we have performed some numerical simulations which deal with some representative academic cases, which can be regarded as benchmarks for future investigations. We believe to have concluded that the actual forecasting capacities of the introduced model are very interesting. In particular, we deal with remodeling situations in which the mechanical stimulus guides the process in a way that the results obtained *via* the proposed diffusive model of the stimulus, Eq. (12), can be compared with the previously developed nonlocal instantaneous model, Eq. (10), from both qualitatively and quantitatively point of view.

We start by the consideration of the remodeling process occurring to a rectangular specimen of bone tissue when it is subjected to some extension tests. We treat the evolution process occurring in the presence of several different values of the externally applied loads and explore the situations in which the deformation is both uniform or nonuniform. These tests are inspired by the aim of simulating the physiological behavior of a portion of bone tissue subjected to a load continuously varying in time. Secondly, we consider a sample with a wide area characterized by the absence of osteocytes, from which area no stimulus is originated. The assumed situation could be referred to as partially necrotic tissue, and the consequent remodeling activity could be thought of as a healing process. Of course, the healing stage is a very complex process involving angiogenesis into the diseased zone of bone which is driven by a set of mechanobiological and biochemical factors. A reliable model of angiogenesis effect on healing bone tissues has been already proposed, e.g., by Lu and Lekszycki (2017); thus, we analyzed only the following stages after that this first preliminary step is completed.

As already announced before, it was possible to perform the numerical simulations by using, with few technical expedients, a commercial software: that is COMSOL Multiphysics^. As it is well known this software is based on the finite element method. There are no specific computing difficulties in treating the more general three-dimensional evolution and remodeling problem. For making a first interpretation of the novelties of the presented model, we study here a simpler two-dimensional problem. The geometry is very simple, also, and we refrained from introducing any complex geometrical or mechanical feature. We want to be sure that the first results which we obtain have a straightforward interpretation and can be understood in a univocal way.

6.1 Physiological remodeling

The simulations deal with a rectangular specimen having aspect ratio 2:1. We consider the constitutive parameters to be those of a cancellous bone. Since the remodeling process is more active in cancellous bone than in cortical bone due to wide availability of space (inter-trabecular porosity) and supply of nutrients coming from bone marrows and blood vessels, we do choose to consider as the initial state of our simulations the spongy tissue which provides a more complete and exhaustive case to be analyzed. Due to the complexity of cancellous bone structure, the proposed macro-model is quite effective (being a coarse-grained model) to predict the evolution of the bone mass density which may resolve also in a cortical bone in the presence of a sufficiently high level of deformations. The specimen has a

Table 1 Material parameters used in the numerical simulations

Y_0	ϱ_{Max}	K_{f}	K_{nl}
17 GPa	1800 kg/m^3	0.1 Y_0	1.7×10^5 N
s_{b}	r_{b}	$P_{\text{ref}}{}^{\text{s}}$	$P_{\text{ref}}{}^{\text{r}}$
4.9×10^{-15} s/m^2	6.13×10^{-15} s/m^2	3.4×10^4 kN/m^2	3.4×10^3 kN/m^2

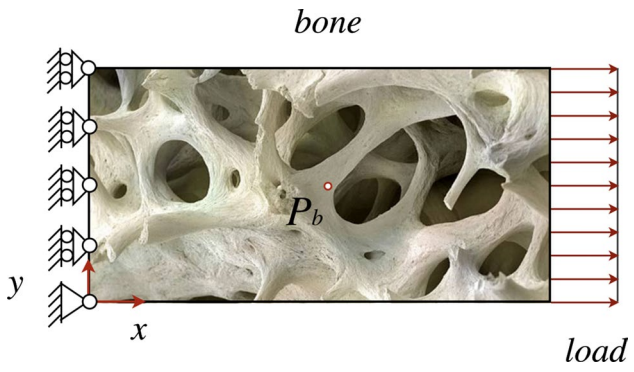

Fig. 4 Uniform extension test: a physiological case

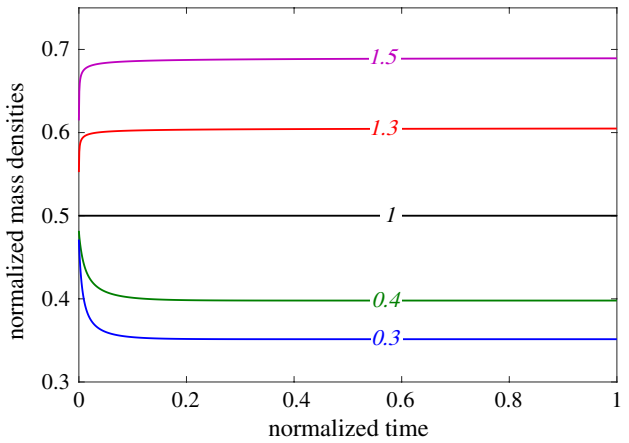

Fig. 5 Time history of the apparent bone mass density at the center of the sample with the diffusive model of the stimulus

length $L = 1$ cm, and its initial porosity is uniform and equal to 0.5. In Table 1, we give the constitutive parameters which are used in the presented simulations.

6.1.1 The remodeling resulting from a uniform loading

The first performed simulations considered those boundary conditions which are needed to produce a uniform distribution of deformation energy along the whole considered specimen. These conditions are: (1) on the left short edge (see Fig. 4) the longitudinal displacement is imposed to be zero, (2) the displacement of one point of the same side is imposed to vanish (so that rigid motions are not allowed), and (3) a spatially uniform load, which is also constant in time, is applied to the right short edge so that an extension of the specimen is determined (see Fig. 4).

We remark again here that in the present context, the fact that the load is constant in time means simply that, in the considered class of phenomena, the loads are varied 'slowly,' when compared to the remodeling characteristic time. Five different levels of externally applied loads were considered: the level of these loads have been calibrated in order to estimate when the condition of homeostatic equilibrium is already present with the initial considered bone configuration (see Fig. 5 and refer to the label '1').

Other values of externally applied loads increased by a factor of 1.3 and 1.5 (reported on the labels in Fig. 5) induce growth phenomena which increase the value of bone mass density in homeostatic equilibrium. Finally, to induce resorption at homeostatic equilibrium it was considered a decrease in the applied force, by multiplying the initially homeostatic force times a factor of 0.4 and 0.3 (values again used as labels in Fig. 5). We report that the externally applied load to assure that the initial configuration was already in a homeostatic state was $F_H = 3.1 \times 10^{-3}\, Y_0\, L$.

Figure 5 is introduced to show how the bone apparent mass density evolves in the bone material particle located at the geometrical center of the specimen. To get the nondimensional evolving value of the bone mass density, we have used the maximum value of bone mass density (ϱ_{Max}) as reference quantity, while to get nondimensional time scale we have considered as characteristic time the period of 200 days.

Obviously, the deformation energy density is uniform, in the considered instance. Therefore, also the biological stimulus as estimated with Equation (12) results to be uniform. In this elemental case, all the material points of the specimen experience the same time evolution.

By inspection of the results obtained, as presented in the previously mentioned plots, we can conclude that: 1) with increasing applied loads, the bone tissue mass growth increases; 2) there is at least a specific value for the externally applied load which leads to homeostatic equilibrium; 3) for values of the applied loads smaller than the homeostatic load, the resorption increases with smaller loads; 4) the time of approach toward the homeostatic equilibrium seems to be approximately the same for all growth and all resorption processes. However, the resorption process is surely slower than the growth process.

Subsequently, the same extension test for a growing bone tissue is simulated with the model in which the stimulus is given with the nonlocal instantaneous biomechanical interaction described in formula (10). In this last formula, the function k is postulated to have the structure specified in formula $(11)_2$ and the characteristic signal influence range is assumed to have the value $D = 0.1L$. In Fig. 6, one finds the obtained results for the spatial average of the apparent bone mass density in the case in which the considered extension test is performed with the same settings as in the previously presented numerical simulations which concern the stimulus diffusive model. Indeed, the distribution of the biological stimulus with the instantaneous model is not uniform for the presence of significant boundary effects despite

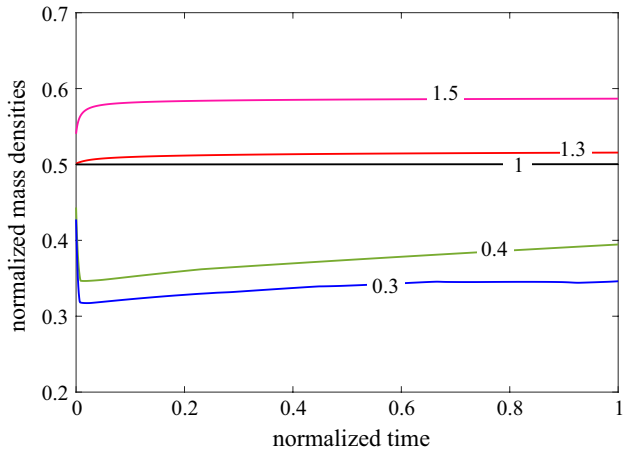

Fig. 6 Time history of the average apparent bone mass density with the nonlocal instantaneous model of stimulus under uniform tension load

the uniformity of the deformation energy density. This lack of uniformity for the stimulus entails an evolution of the bone mass density which is not uniform over the sample. Figures 7 and 8 show indeed the distribution of the bone mass density at the end of the simulation and the time history of the maximum and minimum values of it, respectively. In Fig. 7 the distribution related to the homeostatic value of the load F_H has been dropped out because the bone tissue remains in the homeostatic state without any evolution.

The reasoned comparison of Figs. 5 and 6 leads to conclude that the predicted evolutions, with the two models, are rather different and different is also the final product of the evolutionary growth/resorption processes.

Indeed, in the case of the instantaneous signal model, the final structure of remodeled bone represents a nonuniform homeostatic equilibrium condition. On the other hand in the diffusive model for stimulus propagation, we observe that different levels of porosity are finally reached when different are the values of the applied loads. This feature of diffusive stimulus model is rather promising, as it seems to be able to describe the observed experimental evidence.

In the instantaneous nonlocal stimulus model the final consequence of the difference in the values of the applied loads is a difference in the characteristic time needed for reaching homeostatic equilibrium: if the loads are more intense, this time becomes shorter, and the remodeling process is faster at least for the loads larger than the

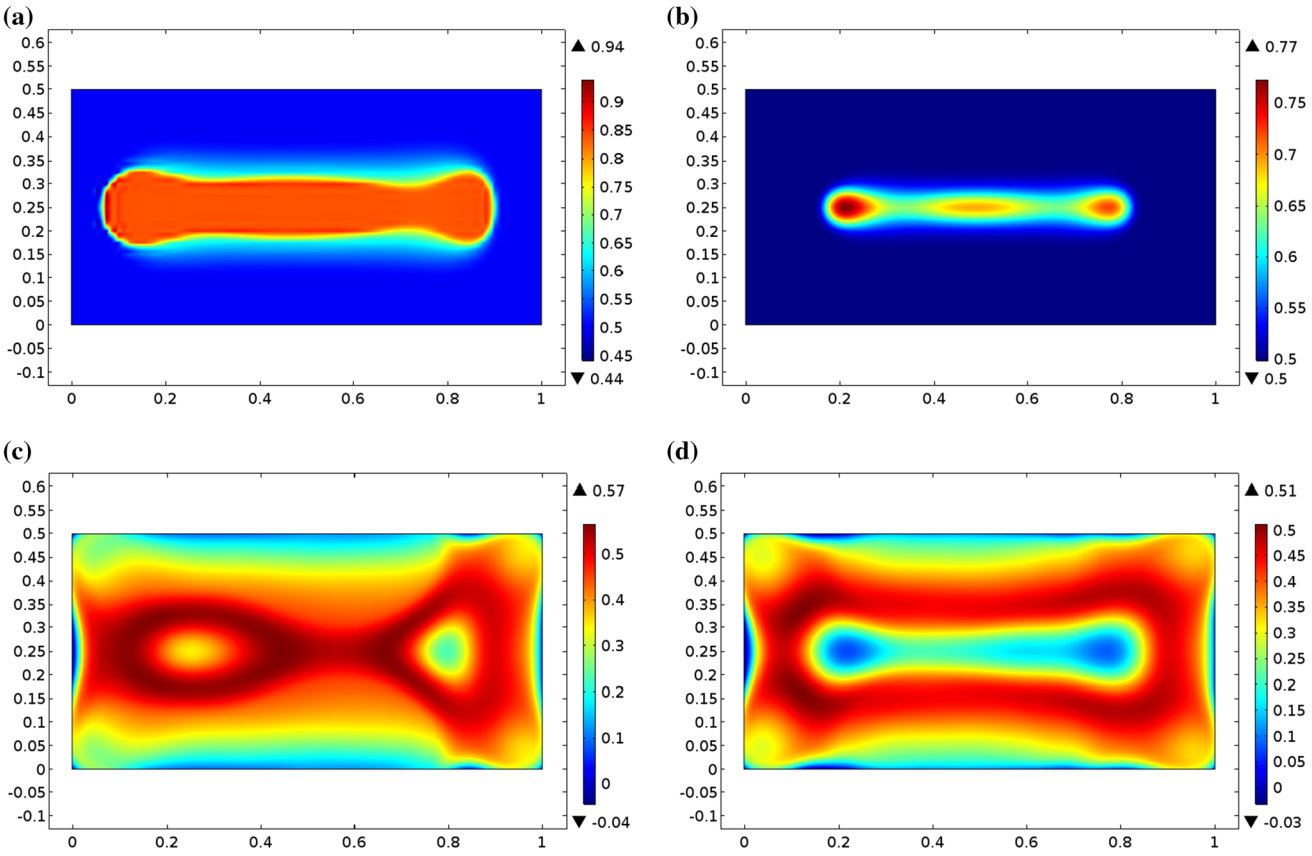

Fig. 7 Normalized mass density for the nonlocal instantaneous model of stimulus under uniform tension load at the end of simulation: **a** $1.5F_H$; **b** $1.3F_H$; **c** $0.4F_H$; **d** $0.3F_H$

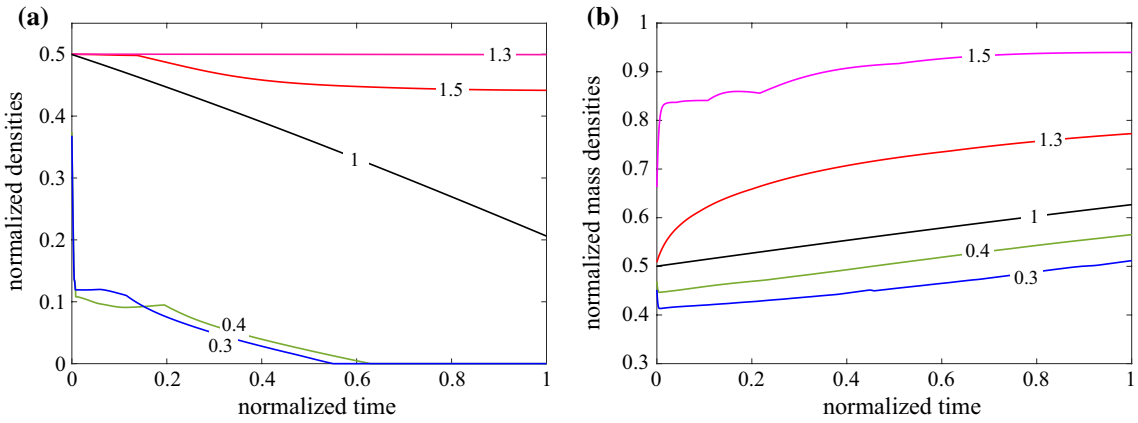

Fig. 8 Time history of the apparent bone mass density with the nonlocal instantaneous model of stimulus under uniform tension load: **a** minimum value; **b** maximum value

homeostatic value. We also note that the boundary condition iv) for the diffusive model (see before) allows for the uniformity of growth and deformation processes, while in the nonlocal instantaneous stimulus model, because of some obvious border effects (related to the nature of the integral operator used for calculating the stimulus), the calculated stimulus, and as a consequence the evolving bone mass density, elastic stiffnesses, and deformation fields, are not uniform. This circumstance does not seem to be related to any physiological situation and requires an *ad hoc* correction of the integral functional to be used close to the specimen boundaries. (For more details, the reader is referred to Giorgio et al. (2016).)

It has to be remarked, also, that the properties of remodeled bone tissues as predicted with the use of the diffusive stimulus model seem to be more consistent with the experimentally observed porosity distributions in physiological and pathological bone tissues, at least from a qualitative point of view.

In this context it is worth to recall one of the so-called rules for bone adaptation: Turner (1998): "*Bone cells accommodate to a customary mechanical loading environment, making them less responsive to routine loading signals*". The diffusive stimulus model, by including the metabolical resorption of stimulus and its removal by diffusion from the region in which it was originated, seems able to predict the aforementioned rule: indeed, as already observed before (see Fig. 5), in the diffusive model the remodeling process, in presence of a continuously applied load, tends to be less and less responsive when the application interval of time becomes greater and greater. Indeed, when the stimulus is outside the lazy zone, the diffusive model manages to predict the existence of different bone densities under different load values, always reaching a homeostatic equilibrium state. When the lazy zone reduces to a point, the diffusive stimulus model still allows for the prediction of the bone tissue tendency to homeostatic equilibrium, a tendency which is widely proven experimentally.

Instead, the instantaneous nonlocal stimulus model leads to a different prediction: when one simulates with it the remodeling tissue process in the presence of a constant load, which produces a stimulus outside the lazy zone, it seems that the final produced tissue exhibits a trend, at the local level, toward the attainment of only two values for the field of porosity (as indeed confirmed by the findings of Mullender and Huiskes (1995)): (1) that characteristic of cortical bone, (2) that for which the bone is completely resorbed (void volume fraction equal to 1). In the instantaneous nonlocal stimulus model, one can attain a homeostatic equilibrium state only with loads producing signals inside the lazy zone. Moreover, when the lazy zone reduces to a point, then the only two homeostatic equilibria predicted by the instantaneous nonlocal stimulus model are the cortical bone and the absence of bone. It seems to us that to induce homeostatic equilibrium by triggering the thresholds and the width of the lazy zone for the signal is rather artificial. We, therefore, believe that the instantaneous stimulus model shows some relevant limitations in its predictive capacities.

6.1.2 The remodeling induced by a nonuniform tension test

In physiological situations, bone tissues are often subject to loads which produce nonuniform space distributions of the deformation energy density. To test the performance of the diffusive stimulus model, we have simulated the effect on the bone growth process of some applied loads whose density varies linearly as shown in Fig. 9. The maximum amplitude of the force is assumed to be $F_H = 4.51 \times 10^{-3}\, Y_0\, L$. The other features of considered specimens are exactly the same

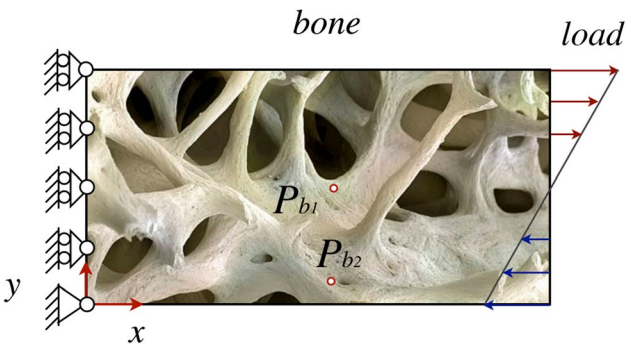

Fig. 9 Nonuniform extension test: a physiological case

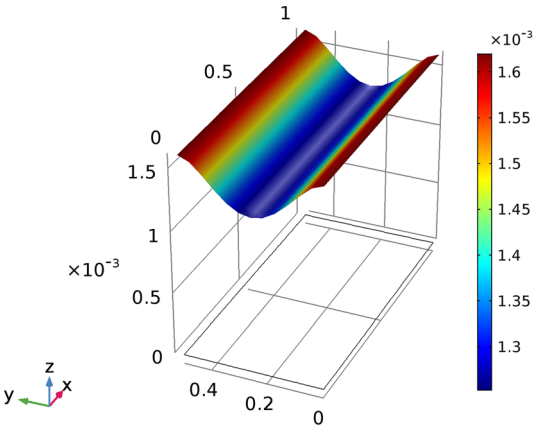

Fig. 10 Biological stimulus at the beginning of the nonuniform tension test with the diffusive model of the stimulus

as in the already treated uniform extension test. We start by showing in Fig. 10 the values for the biological stimulus when the modeling process begins. As it was expected, the stimulus values vary inside the specimen being influenced by those of the deformation energy density. This influence is mainly governed by the field of permeability coefficient κ. In fact, this is the parameter which controls the speed at which the diffusion process occurs. Of course, if the permeability is modeled with a tensor quantity, by generalizing the assumption of isotropic diffusion, then its values will determine also the directions of stimulus propagation.

To be more precise: if the value of κ is very large, then the transient regime related to the stimulus diffusion is too short and, as a consequence, the scalar field describing the biological stimulus becomes quickly uniform in space. This seems against the experimental evidence (see Cowin 2001). Therefore, the choice of the values for the permeability κ has to be performed using a careful fitting procedure. The global properties of the remodeled bone and the process of approaching the homeostatic equilibrium, as predicted by the diffusive stimulus model, depend in a very sensitive way on permeability! The performed fitting process which produced the simulations described in this section led to the identification, for the physical and biological characteristic values for the specimens used in this paper, of the following value $\kappa = 1.0 \times 10^{-4} L^2/t_{\text{ref}}$. This value has been checked to be that which allows for the description of a phenomenon often observed in real clinical cases: the nonuniform initial bone mass distribution and initial deformation energy distribution affect greatly the final homeostatic equilibrium attained and the whole time-dependent process of bone remodeling.

The just described effect is proven by our numerical simulations and in particular by Figs. 11 and 12. In them (1) two probe points in the specimen are chosen and the time history of their mass density is shown; (2) the mass density distribution in the specimen is shown in two important time instants: that is in an intermediate stage of remodeling (occurring after 2 days) and the final one (after 200 days).

Also in this case study, we perform numerical simulations with the nonlocal instantaneous model of stimulus. In this case, the maximum amplitude of the linearly varying force (see Fig. 9) is increased to $F_H = 1.64 \times 10^{-2}\, Y_0\, L$ to obtain an evolution showing a bone growth similar to the previously examined model. The previous value of the force results in a homeostatic value. Figure 13 exhibits the distribution of the biological stimulus with the nonlocal instantaneous model. It is quite different from the diffusive model for the presence of boundary effects directly related to the integral formulation of the stimulus. Hence, in this regard, similar considerations can be made like in the previous tests. Figures 14 and 15 show, respectively, the evolution of the apparent bone mass density in the two probe points P_{b1} and P_{b2} and the normalized mass density in an intermediate and the final stage of the evolution. Also, in this case, the time history is very different for the two considered models. The only qualitative

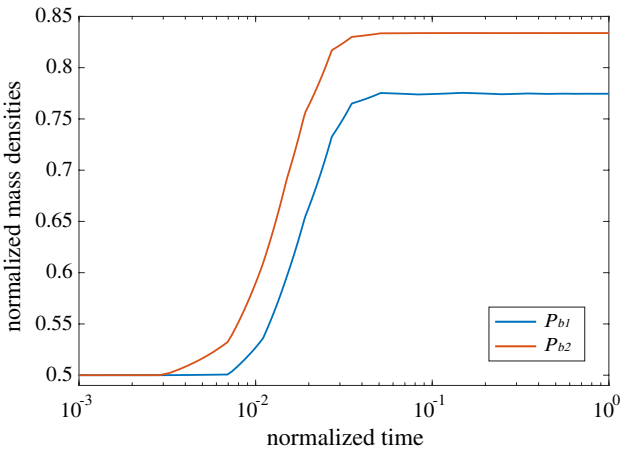

Fig. 11 Time history of the apparent bone mass density in two probe points located at the center P_{b1} and near a long side of the sample P_{b2} for the nonuniform tension test with the diffusive model of the stimulus. The normalized time is represented in logarithmic scale

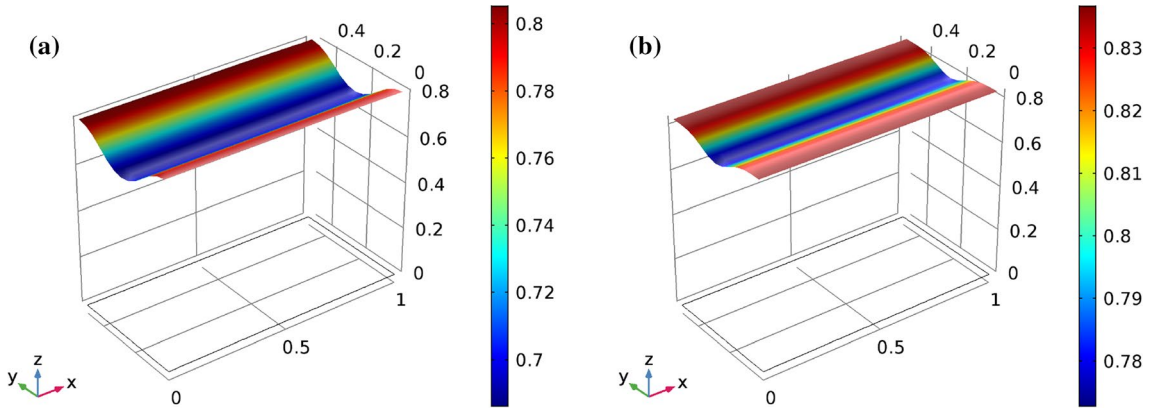

Fig. 12 Normalized mass density in nonuniform tension test with the diffusive model of the stimulus. **a** intermediate stage; **b** final stage

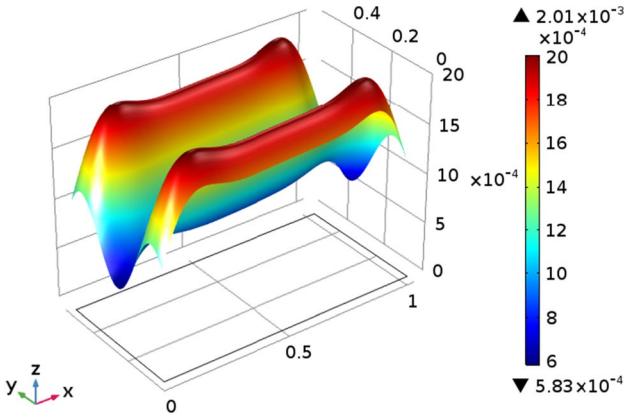

Fig. 13 Biological stimulus at the beginning of the nonuniform tension test with the nonlocal instantaneous model of stimulus

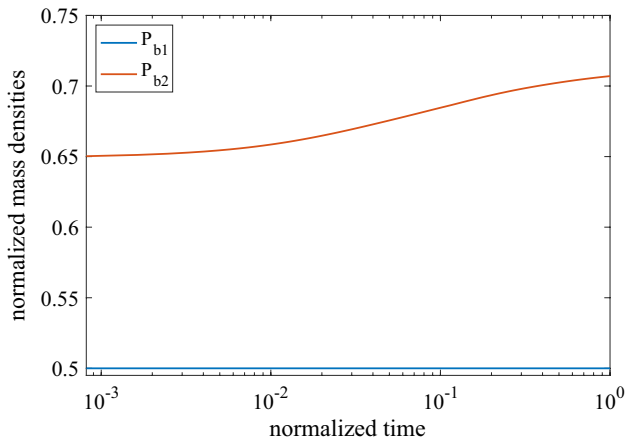

Fig. 14 Time history of the apparent bone mass density in two probe points located at the center P_{b1} and near a long side of the sample P_{b2} for the nonuniform tension test with the nonlocal instantaneous model of stimulus. The normalized time is represented in logarithmic scale

similarity with the diffusive model here is the presence of cortical bone tissue near the verges due to the distribution of the external load.

6.2 Obtained predictions in a healing process

We consider here a specimen characterized exactly by the same biomechanics parameters as done in the previous examples; thus, we assume that it is constituted, in the initial state, by cancellous bone. We assume that the externally applied loads are inducing, in the initial configuration of the bone, a uniform deformation and that the initial porosity field is constant in space and its value equals 0.5. Moreover, we assume that some injury, or a disease or some medical treatment has killed all the osteocytes in the right portion of the specimen (see Fig. 16). This is what one could call a model for a necrotized area of the cancellous bone. In our modeling process this biomechanical case is represented by assuming that the initial value of the stimulus $\mathfrak{S}$, is vanishing in the necrotized area and that, in the initial bone tissue configuration, the source of the biological signal in the right portion of the specimen has initially become zero. During the process of remodeling, the biological activity activates the remodeling evolution also in the necrotic area. This means that the function $\varpi(\varrho^*)$ which models the biological action of the osteocytes, is initially equal to zero and becomes nonvanishing only when new bone tissue is synthesized: indeed, only with the production of newly built bone tissue new active osteocytes are formed and are active. In the numerical simulations presented in this section, the intensity of the externally applied load is assumed to be equal to $5.5 \times 10^{-3}\, Y_0 L$.

The results of the simulations we have conceived for predicting the effects of the healing process subsequent to necrosis by using the diffusive stimulus model are described in Fig. 17. In it, one finds plotted the predicted distribution

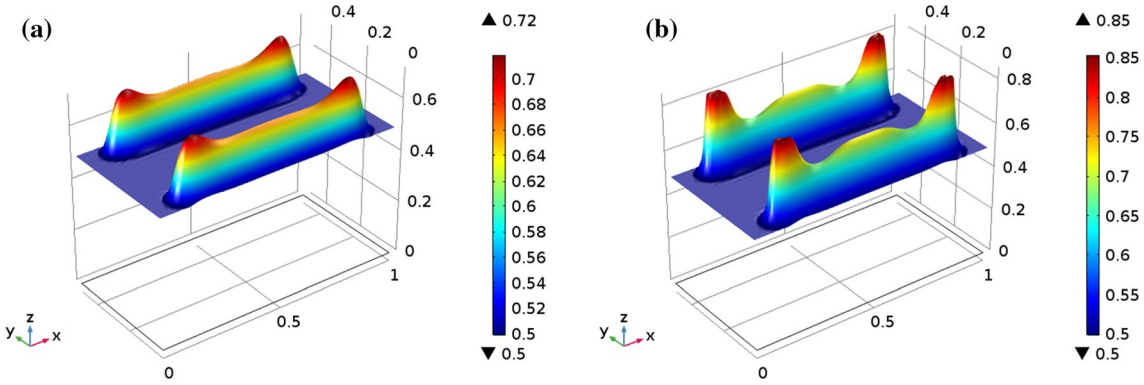

Fig. 15 Normalized mass density in nonuniform tension test with the nonlocal instantaneous model of stimulus. **a** intermediate stage; **b** final stage

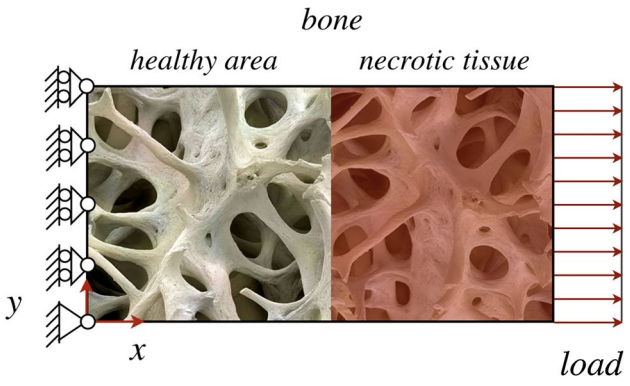

Fig. 16 Setup of the healing process under the extension test

of the apparent mass density in the bone being remodeled in four different time instants. We believe that they are representative of the main stages of the remodeling process which is being modeled here. In the initial configuration, the bone is assumed to have a uniform distribution of porosity: as already said, this constant value is assumed to be equal to 0.5. In the first stage of the evolution, the bone subject to remodeling is characterized by a biological activity starting in the healthy area in which bone tissue growth occurs. In the two subsequent stages of evolution, one can observe the synthesis of newly formed bone in the bone region where at the initial stage the necrotic area was present. The synthesis of bone tissue in the previously necrotic area is followed by the formation of osteocytes (which are a biological evolution of osteoblasts), which start to colonize it. In the last stage, one can observe a bone tissue specimen characterized by a uniform porosity field and whose physiological functionality is completely re-established.

Being completely aware of the fact that the considered evolution is simply exemplary of the potential performance of the introduced model, we can, however, conclude that the presented results show without any doubt that it is able to model the observed nonlocalized effects of the biological stimulus on bone reconstruction. This point must be stressed: many simplified models presented in the literature are not capable to describe the onset of new bone tissue in a necrotized area, which, however, is observed experimentally. In said simplified models, which have indeed many merits, necrotic areas are predicted to remain in their state, as the stimulus is assumed to remain where it was produced. On the contrary, when using the models presented in this paper, while at the initial stage of the remodeling process the necrotic area cannot evolve toward any other biomechanical configuration, in the subsequent evolutionary stages the biological signal which is produced by the osteocytes present in the living tissues does diffuse in the initially necrotic area. The presence of this signal in a tissue having the appropriate porosity (i.e., the porosity which allows for the penetration of the precursor cells which can evolve into osteoblasts and osteoclasts and which allows for their deposit in the internal bone tissue surfaces) will start the biological activity needed to regenerate necrotic bone tissue. This regeneration will be operated by osteoclasts, with their action of necrotized bone tissue removal, and by osteoblasts, whose action rebuilt healthy bone tissue. Of course, in this preliminary stage, in our model we assume that there is the possibility to transport nutrients in the necrotized area: we are aware of the fact that a theoretical effort is needed to describe also this aspect of considered phenomena. Indeed, in the present model, we neglect effects related to a transient phase, considering a constant and continuous supply of nutrients and that the process of cells migration has been already completed. However, a possible generalization of the biological aspects may include the effects of nutrient concentration, e.g., oxygen, and glucose (as the most important factors for cell survival) and the migration of actor cells, as described in George et al. (2018a).

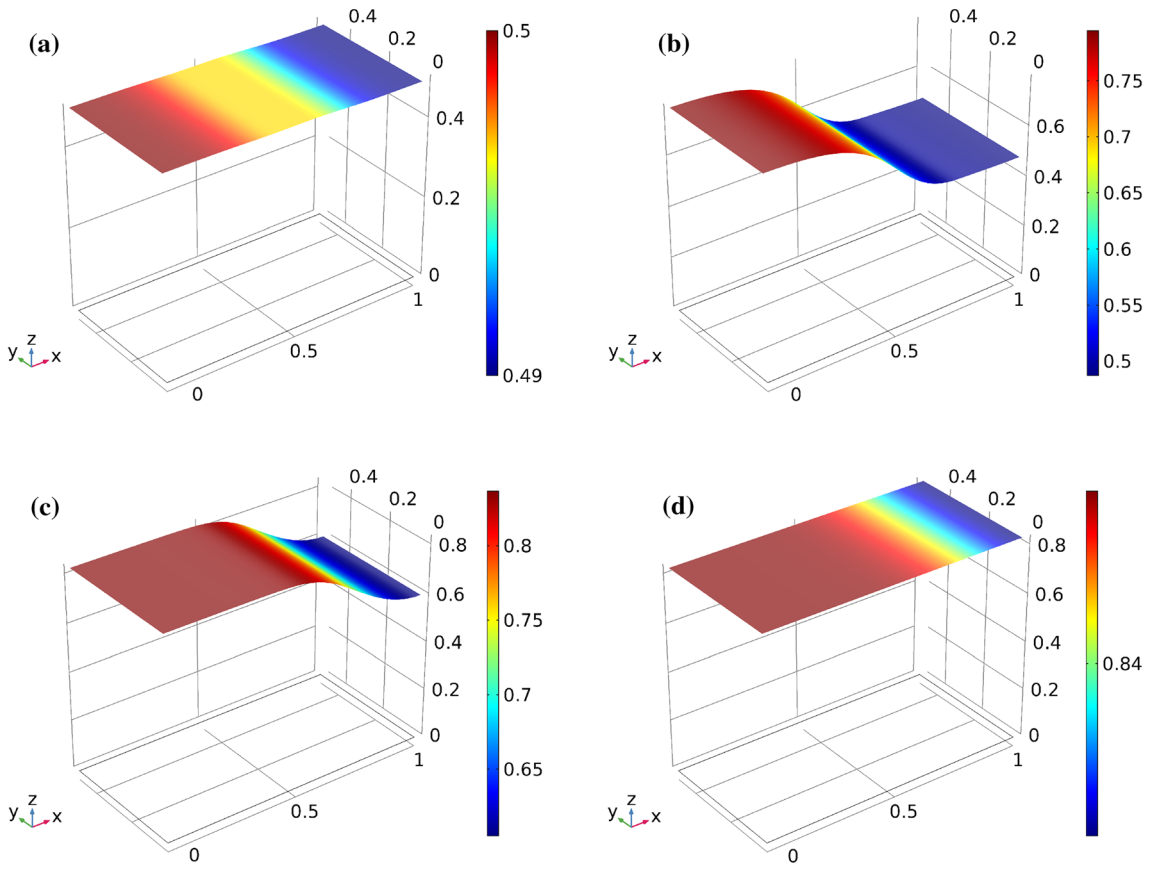

Fig. 17 Normalized mass density. **a** initial stage; **b** bone growth in the healthy zone; **c** growth of new bone in the necrotic zone; **d** final stage

7 Conclusions and perspectives

This paper is dedicated to the preliminary study of the potential descriptive capacities of a novel diffusive stimulus model aimed to describe the remodeling process in bone tissues. We have compared this novel model with a previously introduced one (see Lekszycki and dell'Isola 2012), in which the biological stimulus, which already had a nonlocal nature, is instantaneously perceived in the neighborhood of the site of its production. The biological stimulus, indeed, plays a relevant role in the feedback control process governing bone remodeling and the problem of modeling its generation, its transmission, and its effects is of great relevance.

We are aware of the complex nature of all phenomena occurring in the bone remodeling process. There are, most likely, many different concurring biomechanical processes which occur at different length scales and which determine the macroscopic behavior of bone tissues. We are not surprised by observing this complexity: indeed, vertebrates were evolved about 525 million years ago. The synthesis of bone tissue caused, most likely, the Cambrian species explosion, which consists, in practice, in the enormous organism diversity which is observed nowadays on Earth. The subphylum Vertebrata consists of at least 69,276 species (those which are presently described). In 525 million years evolution could try several methods for controlling bone growth and, most likely, many of these mechanisms currently coexist in living bone tissues. Again one should not be surprised if (1) many different microscale feedback growth control systems are being described in the literature and (2) a macroscopic simplified description of all of them is possible. Together with Darwin we share the belief that evolution may produce the coexistence of different organs and biological mechanisms collaborating synergistically for a common aim.

In the described spirit we discuss in this paper to model, at a suitably large scale, the transmission of biological stimulus in bone tissue as a phenomenon occurring in space–time. For the sake of simplicity, we use the standard diffusion equation, i.e., the equation which is sometimes called Fourier's equation for the heat or Fick's equation for the concentration of chemical species in a fluid. We are aware of the debate concerning the physical plausibility of this equation: we will explore in the future if the correction proposed by Cattaneo to Fourier equation can have a biological application in the present context.

Here, we remark that, obviously, the integral formulation introduced in the previous papers (see Lekszycki and dell'Isola 2012; Giorgio et al. 2016) can be easily generalized to include the case treated here: it is sufficient to introduce there a suitable time-dependent Green's function. Another important step in our modeling procedure was to assume that (1) the generation of stimulus is controlled (we repeat once more: at macroscopic level!) by the deformation energy density, (2) the stimulus resorption is determined by a standard decay process. The most important feature of the novel model introduced consists in the introduction of a 'characteristic time' which governs the time needed to the stimulus to travel inside the bone tissue before being resorbed. Both the present model and that used in Lekszycki and dell'Isola (2012), Giorgio et al. (2016) are nonlocal: however, the model introduced in the just cited papers neglects the (obviously important) time delay occurring between the signal (stimulus generation) and the action which is determined by it. Obviously, also the range of validity of the novel proposed model is limited. This range is defined by the assumed hypotheses which can be summarized as follows. From a purely mechanical point of view, bone tissue is represented as a microstructured medium whose behavior is assumed to be isotropic, nonlinear elastic and viscous. In the framework of poroelastic materials, the additional kinematical descriptor of the microstructure is the change of the effective volume of the fluid content per unit volume. From a biological point of view, the stimulus is evaluated at a macroscale without formulating explicitly its dependence on the signaling factors which act at a microlevel. As a result, the stimulus is assumed to be depended on a scalar quantity as the strain energy density which averagely represents the effects of phenomena (e.g., velocity of fluid flow at the lacuno-canalicular system, damage due to fatigue and micro-cracks onset *etc.*) at small scales. Moreover, the spatial density of sensor cells is assumed to be proportional to the apparent mass density of bone tissue; the spatial density of actor cells depends on the porosity of bone tissue according to the parabola-like law (see Fig. 2). Finally, biological migration is neglected during mass density evolution of bone.

In this article, the most relevant point of novelty consists in describing the transmission of the stimulus in a nonlocal time-delayed way by a diffusion model in which the stimulus evolves according to a differential equation conceived to match its behavior as observed at a macroscale. Then, this new model is compared with a previously developed nonlocal model of the stimulus. In this former description, the stimulus is defined through a convolution integral extended to the whole domain and it is assumed to be instantaneously transmitted. In the new formulation, instead, the diffusion differential equation allows taking into account the time delay due to the diffusion of the stimulus. A further point of novelty of this work lies in the development of a model that is also able to take into account the permanence of the signal even after the cessation of the stimulus for a limited period of time (Sims and Martin 2014; Crane and Cao 2014) due to the presence of the sink term (reabsorption of the signal) in the diffusion Eq. (12) according to the definition of Eq. (15).

To make our modeling analysis more explicit and in order to show the performance of the introduced model, we considered some specific study cases. 1) A remodeling process in a *physiological situation*: in this process, a specimen of bone tissue is subject to different external loads determining its extension. 2) A *healing process*, in which a specimen of bone tissue partially necrotic in a large area is loaded with a mechanical load. In the introduced model the necrosis is described by assuming that the generation of stimulus is blocked. Mathematically, this is implemented by assuming that in the source term of the postulated diffusion equation for biological stimulus a coefficient depending on osteocyte concentration appears. This coefficient is assumed to vanish when osteocytes are absent. In a healthy bone a mechanically active material particle is also biologically active because of its 'equipment' of osteocytes: in this situation, it can produce a source of stimulus. We assume that this source of stimulus is proportional to the local density of deformation energy measured. In this first stage of our investigations, we wanted to avoid the introduction of complicated further evolution equations. We expect that such a more sophisticated model may be needed to describe carefully enough clinical cases. However, we want to build our model step by step by checking its performance and by initiating a scientific debate. Therefore, presently and for the presented numerical simulations we conjecture that the density of osteocytes can be assumed to be proportional to the bone density, in the physiological case. Necrosis, in this context, has to be described by a total absence of biological stimulus source.

A necessary condition for having postulated a model whose true applicability can be assessed consists in its capacity to describe: (1) physiological remodeling processes, including the attainment of homeostatic equilibrium; (2) regeneration of necrotic tissues, which are in contact with living bone tissues.

To verify such necessary condition we have considered, at first, a bone sample in the physiological case and in a uniform tension test: different values of the load are applied and different evolutions of the bone mass density field are simulated. The obtained numerical results demonstrate that for uniform tension tests: (1) in a suitable range of values of the external loads, they produce a physiological homeostatic equilibrium for bone tissues having a certain porosity, (2) for external loads having greater values than those in the previously determined range one can observe the growth of cancellous bone, (3) for lower load values one observes resorption. As a second test, we have considered

a nonuniform load: more specifically we have considered a linear distribution of the externally applied mechanical load. We have observed a consequent nonuniform evolution of the bone mass density: it is dictated by and parallels the calculated field of the deformation energy density in all the subsequent equilibrium configurations calculated in the evolutionary process. Finally, we have simulated the healing process after necrosis. The results which we have obtained in these simulations are very promising and indicate, in our opinion, that the proposed model deserves to be further developed. Indeed, the numerical results provide a prediction for the bone mass density evolution which is qualitatively very close to what has been experimentally observed. In our numerical simulations we have clearly distinguished three characteristic growth and remodeling stages: (1) initially, the bone tissue is remodeled in the healthy zone only and a biological stimulus is produced there; (2) subsequently, a new bone tissue starts to be synthesized in the necrotic zone (where the osteocytes are supposed to be initially not active, i.e., either absent or died and where the present not living part of the bone tissue supplies, however, the mechanical support to remodeling process); (3) finally, the whole specimen of bone tissue acquires again its full functionality: indeed, after the formation of new bone tissue, new osteocytes colonize anew what had been a necrotic tissue.

We can, therefore, conclude that the behavior of the proposed model does mimic indeed, from a qualitative point of view, the actual remodeling process which can be observed in living bone tissue. Moreover, the introduced model does explain the coexistence of different levels of bone porosity with different externally applied load. In the immediate future, we plan to try to get a deeper insight in the bone remodeling process by studying the most efficient tuning of the introduced physiological parameters to get some quantitative coincidence with experimental evidence. Indeed, while the selected results are fully demonstrating the potentiality of the proposed diffusive model, it is clear that its further validation is necessary.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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