UDC 631.362.36:57.087.3
https://doi.org/10.47533/2020.1606-146X.98

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CONTINUUM MECHANICS: APPLICATIONS IN BONE REMODELING AND BONE RESORPTION MODELS

A brief description of continuum mechanics is given, first. Then, a general introduction on biomechanics is presented, along with some salient features of it, which should be kept in mind when one is working in this field. The manuscript will continue with an introduction on bone remodelling process, then some phenomenological models on the bone remodelling process will be introduced. A general description of bone resorption, and two mixture models, with chemical reactions, on bone resorption will make the next section. Finally, discussion and some conclusions are made on the positive, also improvable aspects of the reviewed models of bone remodelling, and bone resorption.

Keywords: *continuum mechanics; biomechanics; bone cells; remodeling; resosrption; mixture theories; chemical reactions*

Continuum mechanics. The subject of mechanics deals with the study of motion and forces in solids, liquids, and gases, and the deformation or flow of these materials. In a continuum, for analysis purposes, all quantities such as the density, displacements, velocities, stresses, and so on vary continuously, so their spatial derivatives exist and are assumed to be continuous. The continuum assumption allows us to shrink an arbitrary volume of material to a point, in much the same way as we take the limit in defining a derivative. Thus, we can define quantities of interest, such as density, stress, strain, among others, at a point. A mathematical study of mechanics of such an idealized continuum is called Continuum Mechanics. The continuum mechanics theory consider matter as indefinitely divisible. Thus, within this theory, one accepts the idea of an infinitesimal volume of materials, referred to as a particle in the continuum, and in every neighborhood of a particle, there are always neighbor particles. More than a hundred years of experience have justified such a theory in a wide variety of situations. The study of motion and deformation of a continuum can be broadly classified into four basic categories: Kinematics (strain-displacement equations); Kinetics (conservation of momenta); Thermodynamics (1st and 2nd laws of thermodynamics); and Constitutive equations (stress-strain relations). The first three ones are general principles common to all media, but the last one, i.e. constitutive equations, defines idealized materials and are material dependent, such as Hooke's law for linear elastic material. Kinematics is a study of the geometric changes or deformation in a continuum, without the consideration of forces causing the deformation. On the other hand, kinetics is the study of the static or dynamics equilibrium of forces and moments acting on a continuum, using the principles of conservation of momenta, which leads to equations of motion, also the symmetry of stress tensor in the absence of body couples. Thermodynamics principles are concerned with the conservation of energy and relations among heat, mechanical work, and thermodynamic properties of the continuum. Constitutive equations describe thermomechanical behavior of the material of the continuum and they relate the dependent variables introduced in the kinetic description to those introduced in the kinematics and thermodynamics descriptions.

Biomechanics. Biomechanics is mechanics applied to biology. In other words, biomechanics seeks to understand the mechanics of living systems. It should be noted that that biomechanics can work from the level of the whole body to organs, tissues, cells, and sub-cellular levels, such as in proteins. Mechanics helps us understand how biological tissues, such as bones and muscles, remodel, and in general how cells and tissues respond to applied loads. If we wanted to find a solution for disease, such as osteoporosis, ostepetrosis, or osteoarthritis, among others, many fields and professions must work together, such as engineers, biologists, mathematicians, biochemists, clinicians, surgeons, and material scientists, to name a few. Fortunately, this has been improved through technology in the recent years, for instance the internet helps easier international collaborations. As opposed to engineering materials, biological materials are alive and ever active, open to mass exchanges, controlled by internal and external agents, subject to chemical reactions with inside and outside sources, and are precisely structured at various hierarchical levels. Thus, it is important to identify salient features of biomechanics, which differentiate it from mechanics, such as: material constitutions; growth and remodeling; and constitutive equations, to name a few. In almost all biological materials, more than one constituent is present, so if one wanted to study their mechanics properly, existence of various constituents, as well as interaction among them should be preferably taken into account. Moreover, due to ever changing nature of biological materials, finding their constitutive equations, as well as evolution in their both geometrical and material properties can be quite challenging. In other words, one should not only take into account the effects of mechanical loading on density distribution, and thus on mechanical properties of a biological tissue, but also should consider the effects of stimuli on its cells' behavior and their reaction to the stimuli.

Bone remodeling process. Bone is continuously remodeled through a coupled process of bone resorption and formation, and this process is called bone remodeling. An early hypothesis about the relation between the structure and form of bones, and the mechanical loads they carry was proposed by Galileo in 1638 [1]. The nature of this dependence was first described in a semi-quantitative manner by Julius Wolff [2], who stated that every change in the form or function of a living bone is followed by adaptive changes in its internal architecture and also in its external shape. There are various types of bone remodeling models. Bone making cells (Osteoblasts) and resorbing cells (Osteoclasts) lie on the free surfaces of bone, thus, all bone resorption and apposition is thought to occur at these sites [3]. It is well accepted that bone remodeling is a surface phenomenon, and from a cellular point of view there is no difference between remodeling on different types of surfaces of bones [4]. The majority of bone adaptation models have been phenomenological, in which they seek to describe the stimulus and the response quantitatively [5, 6, 7], among many other papers. In the phenomenological models, the bone is being looked as a black box, assuming a special input and accordingly a special output and finally proposing an asymptotic relation between the input(s) and output(s). The remodeling process is generally viewed as a material response to functional demands that is governed by an intricate relationship between bone apposition and resorption. It is accepted that bone growth, maintenance, degeneration and remodeling are biochemically regulated processes influenced by mechanical function [8].

Some phenomenological models of bone remodeling process: free surface density and microcrack factor. Two important features of the internal structure of bone are its porosity and specific surface. Porosity is defined as the void volume per unit volume of the whole bone or the fractional part of bone occupied by soft tissues. The specific surface is defined as the internal surface area per unit volume of the whole bone. Therefore, it seems appropriate to consider the specific surface rather than volume fraction, which was used in adaptive elasticity theory (AET) [5], in the constitutive equations of bone remodeling. The 1st modification on the AET can be made by using a free surface density parameter (Free surface density is defined as the total area of interface between bone matrix (solid phase) and fluid phase per total volume of the bone), instead of volume fraction (Volume fraction is defined as volume of the bony part to the total volume of bone sample). The assumptions underlying this bone remodeling model are:

(i) when there is no free surface, there will be no bone remodeling; (ii) if the mechanical stimuli are in a neutral zone, there will be no remodeling. Using the newly developed bone remodeling equation [8], one can appreciate that a single equation can be used for surface and internal remodeling, and the effects of mechanical stimuli and bone geometry on bone remodelling [9], can be studied simultaneously. Interesting to note that geometric feedback in the bone remodeling process, as proposed by [3], can also be explored in the newly developed bone remodeling model, which was not observable in the AET. Furthermore, by considering the obvious effect of the specific surface on the bone remodeling equation, one can conclude that two people with an equal average mass density, similar shape of bones (macroscopically), similar mechanical stimuli, similar hormonal stimuli and same form of nutrition can experience different rates of osteoporosis because of the micro-structure of the bones. Thus, for evaluating risks for fracture in osteoporotic bones, besides measuring the volume fraction (solid phase volume per total volume), the microstructure of bone and the magnitude of the specific surface must be quantified. Another modification on the AET

[5] corresponds to the inclusion of microcracks factor. Microcracks have been observed in bone with the use of laser scanning electron confocal microscopy and transmitted light microscopy. They have been associated with causing stress fractures [10], and remodeling [11, 12], and it has been hypothesized that fatigue damage acts as a stimulus for bone maintenance [7]. It is well accepted that damage can initiate and accelerate bone remodeling process [12, 13]. When one considers microcracks factor, a modification on the definition of volume fraction, Helmholtz free energy, and constitutive equations should be made as well. When we replace volume fraction with the free surface density, and introduce microcracks factor into the constitutive equations, the resulted bone remodeling equation contains not only the effect of mechanical stimuli, but also their time history, and their time rate [14]. Some studies suggest that strain rate is a mechanical stimulus which affects bone remodeling process [15]. Furthermore, it has been shown experimentally that the history of loading is also an important factor in the rate of bone remodeling [16]. Equality of mechanical stimuli does not necessarily result in equality of microdamage depends on the history of the mechanical stimuli, the bone micro- and macrostructure, and the material properties of bone [14]. Furthermore, our model showed that the rate of remodeling is not a function of the rate of damage production, but the damage factor itself [14]. Novel to the literature is the idea that microdamage, the pattern of solid mass distribution, mechanical stimuli, rate of change

in mechanical stimuli, and history of the mechanical stimuli are coupled and influence bone remodeling process.

It is well known that bone remodeling is comprised of bone resorption followed by formation with a coupling between the two processes [17]. Optimal remodeling is responsible for bone health and strength throughout life. An imbalance in bone remodeling may cause diseases, such as osteoporosis. When bone resorption outstrips bone formation for a long period of time, osteoporosis arises. Current methods of tackling osteoporosis place the most attention on inhibiting or decreasing osteoclastic activity. The increasing rate of osteoporosis in an aging population calls for a greater understanding of the cellular mechanism of bone resorption. Bone resorption is considered as a chemical process that occurs between osteoclasts and the matrix. Osteoclasts dissolve bone mineral by acid secretion that degrades the organic matrix [18]. There are different approaches to model multi-phasic media, e.g. mixture theory, the effective medium, and homogenization approaches. Considering the time duration of the bone resorption process, and also the significant effect of resorption in osteoporotic cases, only the first phase of the remodeling process, i.e. bone resorption, was modeled using a bi-phasic mixture model first [19], then through making a tri-phasic model [20]. In the bi-phasic mixture model of bone resorption [19], bone was treated as a biphasic mixture of matrix and fluid, and modeled resorption as an exchange of mass between the solid and fluid phases. This exchange is caused by the secretion of H+ and Cl from osteoclasts, which creates an acidic environment in a sealed zone [2]. In our bi-phasic model, demineralization depends on the rate of surface processes. Mixture theory with chemical reactions will be used to derive conservation laws of mass, linear and angular momentum, energy, and the entropy inequality. In the conservation of mass equations, the rate of mass transferred to different constituents is assumed to be given by an empirical relation arising from the dissolution kinetics of the solid phase. The governing equations for bone resorption are derived using the conservation laws, as well as entropy inequality and the appropriate constitutive equations. In the constitutive equations, it is assumed that dependent variables (e.g., free energy) are functions of temperature, deformation gradient, rate of deformation gradient, and the extent of chemical reactions. Since biological, chemical, and mechanical factors have a definite effect on the rate of dissolution, we hypothesize that a biochemomechanical driving force should be considered in the dissolution relation, instead of just a chemical driving force. We used a dissipation law to find the biochemomechanical affinity. Dissipation in the system was defined as the difference between the external work rate and the rate of change in free energy, which according to the Second Law of Thermodynamics, it should be nonnegative. Our bi-phasic model showed that not only mechanical stimulus, i.e. strain energy, but also chemical and biological factors determine the rate of bone resorption, so we proposed a biochemomechanical affinity for the bone resorption process. Interesting to note that strain energy density was proposed to be a likely stimulus for bone remodeling [21], and it was used extensively in many theoretical modeling of bone adaptation, for instance in [22, 23, 24, 25, 26]. In our bi-phasic model, using 2nd law of thermodynamics, it is theoretically shown that strain energy is an effective mechanical stimulus for the bone resorption. Also, it was shown that hydrostatic pressure is another mechanical stimulus for the bone resorption, and thus should be taken into account in the bone remodeling theories, which is missed in the currently developed models in the literature. Using the bi-phasic model, it was also shown that increasing either strain energy density or hydrostatic pressure will enhance rate of bone resorption. Nowadays, the most common method in treating osteoporosis is anti-bone-resorption drugs which inhibit or reduce the bone resorbing cells (i.e. osteoclasts) activity. The reason for using this way of treatment is the lack of information about all the factors affecting osteoclasts' activity. This preliminary theoretical research shows that the activity of osteoclasts and, thus, the rate of bone resorption are not only dictated by biological factors (e.g., hormone levels), but also by engineering factors (hydrostatic pressure, strain energy density, and concentration of different ions present in the resorption process).

In another effort, we developed a tri-phasic model of bone resorption with the scope of deriving and introducing the governing equations resulting from conservation laws (conservation of mass, momentum, and energy), the second law of thermodynamics, constitutive equations, and consistency requirements of mixture theory [20]. In the tri-phasic model, bone was treated as a tri-phasic mixture of matrix, fluid, and cells. It is assumed that the solid phase obeys small deformation theory and is isotropic and linearly elastic. The velocity of the matrix and cells is assumed to be zero. The fluid phase is assumed to be viscous, and inertial effects are neglected because of the slow velocities that are at play. A non- rotational fluid is assumed for deriving the final form of the entropy inequality for the mixture as a whole. A non- polar mixture assumption is also made; thus the stress tensors and the inner part of the stress tensor are symmetric. In the constitutive equations, it is assumed that the free energy, enthalpy, specific entropy, heat flux, and stress tensor are functions of temperature, deformation gradient, and the extent of the chemical reactions. Bone resorption was considered as an isothermal and a quasi- static process. The last assumption is well justified because the characteristic time of bone resorption is much longer than the characteristic time for inertial effects. Using these assumptions, the governing equations for bone resorption were derived using the conservation laws (mass, momentum, andenergy), as well as entropy inequality and the appropriate constitutive equations. Using a relation between the momentum supplied to the solid and fluid phases, it was shown that the rate of bone resorption is inversely proportional to the bone fluid velocity. Also, our tri-phasic model showed that in a high-porosity spongy bone, by increasing the porosity, the rate of resorption will decrease, and vice versa. This result encourages one to look at normal bone resorption as a control system with a negative feedback. Based on our results, it can be speculated that bone resorption in cortical and cancellous bones should be affected by a control system, which results from a relation between the specific surface of bone and its apparent density. Using the proposed model, one can find a theoretical explanation for some clinically observed behavior of bone, for instance for the greater rate of bone resorption in cortical than cancellous bone, using the conservation equations and/or consistency requirements of continuum mixture theory. It should be noted that, considering the fact that both mixture theory with chemical reactions and the bone resorption process from the mechanistic point of view are in their infancy, our mixture models were not able to offer verifiable predictions. This point can be seen as a drawback, but on the other hand can be deemed as a positive point to encourage others to get involved in this, almost virgin, field of research to shed more light and make novel contributions.

Conclusion. From the 1st modification on the adaptive elasticity theory [5, 6], i.e., by considering free surface density instead of commonly used volume fraction, and developing a new series of governing equations, some of the previous models can be extracted from this model [8]. It is also concluded that in the surface remodelling equation, one should consider the cross- sectional geometry in agreement with the experimental evidence. Moreover, on the basis of importance of the free surface in the remodelling process, it is concluded that in order to evaluate the risk of osteoporosis in high risk bones, beside of measuring bone density, the microstructural pattern of the bone should be inspected as well. From the 2nd modification on the adaptive elasticity theory, i.e. by considering free surface density and microcracks factor in the bone remodelling equation, it is concluded that mechanical stimuli, their time derivatives, and their integration over time period of remodelling are all at play in the remodelling processes. Also, it is shown that rate of remodelling is a function of microcracks factor, but not its time derivative. It also concluded that by considering a microcrack factor in the remodelling equation, one will find a very complex form of the remodelling equation even for a very simple geometry of bone. Due to multiphasic and complex substructure of bone, as well as existence of chemical reactions between bone actor cells, i.e. osteoclasts and osteoblasts, with the bone matrix, in order to be able to properly model either bone resorption or bone formation, it is better to use mixture theories with chemical reactions, instead of single phase continuum mechanics approach. Furthermore, to gain deeper insights into osteoporosis, it is better to model resorption and apposition separately, thus one should model bone resorption and then bone formation, and finally evaluate the net rate of bone remodeling. From the mixture models of bone resorption [19, 20], it can be concluded that mechanical, and chemical factors, both are at play, and can change the rate of resorption process. A bio-chemo mechanical affinity contains mechanical, chemical, and biological effects is used instead of commonly used Gibbs free energy, which contains only chemical factors (ions concentration). Ions concentration, from chemical side, and strain energy density and hydrostatic pressure, from mechanical side, and biologically generated potential, from biological side, are shown to be chemical, mechanical, and biological factors affecting resorption process. It is also shown that creating damage in bone can accelerate resorption process, because of increasing the strain energy density and, thus bio-chemo-mechanical affinity. Due to lack of experimental data on the remodeling rate coefficients, both in the adaptive elasticity theory [5, 6] and its modifications [7, 8], one of the most important step is to measure these constants using experimental techniques. In the bone resorption model, both experimental and numerical research are needed. In the experimental phase, it is needed to make a set up to measure the concentration of different ions in the microclimate between the osteoclasts and the matrix. Also, it is interesting to see the fluid phase velocity on the rate of resorption, and also on the concentration of ions in the microclimate and the bone fluid phase [27]. The effects of mechanical vibration on the rate of resorption can also be studied by employing the mixture models of bone resorption [19, 20], also through making experimental research.

Acknowledgments. Special thanks go to Amirkabir University of Technology, Iran.

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НЕПРЕРЫВНАЯ МЕХАНИКА: ПРИМЕНЕНИЕ В МОДЕЛЯХ РЕМОДЕЛИРОВАНИЯ И РЕЗОРПЦИИ КОСТИ

В статье дается краткое описание механики сплошной среды. Представлено общее введение в биомеханику, а также некоторые ее характерные особенности, которые следует иметь в виду, работая в этой области. Статья содержит введение в процесс ремоделирования кости, также представлены некоторые феноменологические модели процесса ремоделирования кости. Также в статье представлено общее описание резорбции кости и две модели смеси с химическими реакциями резорбции кости. Наконец, обсуждение и некоторые выводы сделаны по положительным, а также поддающимся улучшению аспектам рассмотренных моделей ремоделирования и резорбции кости.

***Ключевые слова**: непрерывная механика; биомеханика; костные клетки; ремоделирование; рассасывание; теории смешения; химические реакции.*

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ҮЗДІКСІЗ МЕХАНИКА: СҮЙЕКТІ РЕМОДУЛДАУ ЖӘНЕ РЕЗОРПЦИЯЛЫҚ МОДЕЛДЕРІН ҚОЛДАНУ

Алдымен континуумдық механиканың қысқаша сипаттамасы берілген. Биомеханикаға жалпы кіріспе, оның осы салада жұмыс жасағанда есте ұстау қажет кейбір ерекшеліктері берілген. Мақала сүйекті қалпына келтіру процесінің кіріспесімен жалғасады, содан кейін сүйекті қалпына *келтіру процесінің кейбір феноменологиялық модельдерін енгізу көрсетілген. Сүйек резорбциясының және сүйек резорбциясы бойынша химиялық реакциялары бар екі қоспаның моделінің жалпы сипаттамасы жазылған. Ақырында, сүйектерді қайта өңдеу мен сүйек резорбциясының қарастырылған модельдерінің оң және оңтайлы аспектілері бойынша пікірталастар мен кейбір тұжырымдар жасалды.*

***Түйін сөздер**: үздіксіз механика; биомеханика; сүйек жасушалары; қайта құру; тарау; қоспалар теориясы; химиялық реакциялар.*