JOURNAL OF THEORETICAL
AND APPLIED MECHANICS
43, 3, pp. 555-574, Warsaw 2005

FUNCTIONAL ADAPTATION OF BONE AS AN OPTIMAL CONTROL PROBLEM

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The functional adaptation of bone is a process of bone tissue remodeling induced by variable in time mechanical demands that the skeleton has to satisfy. It is a very complex but highly organized process composed of events at micro-level (molecular and cellular) but having effects in macro-scale (variation of bone internal structure and external shape). Mathematical models of this phenomenon proposed in the literature represent formulas postulated on the basis of the results of medical observations or laboratory investigations and describe locally the evolution of a material in space and time. In the present paper a use is made of the hypothesis of optimal response of bone, proposed earlier by the author, what enables derivation (instead of postulation) the remodeling rules from a very general and global assumption. It turns out that such a formulation has many similarities to engineering optimal control problems. The link between the postulated local adaptation rules and those derived from the global assumption is also discussed.

Key words: adaptation, bone, objective functional, optimal control, remodeling, tissue

1. Introduction

Bones are complex biological structures which have the ability to adapt their micro-structures and external shapes to variable in time conditions. There are many factors of different nature, often related to each other already identified, as these which influence the remodeling process of bone tissue and evolution of bone shape. In spite of the fact that the complete understanding of mechanisms responsible for bone remodeling is not yet possible, it is well known that mechanical state of bone is one of the major factors controlling the changes in tissue structure. Such changes governed by time-variable mechanical loads are usually called functional adaptation of bone.

Functional bone adaptation is a very complex process representing a chain of different interactions between the cells and intercellular matrix. Mathematical and computational modeling of this process is an important part of the research focused on investigation of the mechanisms responsible for tissue remodeling. It has also important practical aspects: in the future, reliable models might be used in planning the orthopedic surgery and predicting bone reactions in different situations, for instance in the context of endoprosthesis durability, rehabilitation treatment or healing processes. It follows from recent investigations that bone remodeling is a highly organized process, the mechanisms of which are controlled at different levels. Many models have been proposed with *postulated* "remodeling laws" – the mathematical relations describing evolution of bone micro-structure. On the other hand it can be expected that such an intelligent behavior of bone which is accomplished at micro-level (molecular and cellular) but has an effect at the macro-scale, should be ruled by some more general principle. Indeed, this is possible (under certain assumptions), to explain the adaptation of bone and the associated tissue remodeling as an issue that falls into a category of optimal control problems. Moreover, some of the derived necessary optimality conditions can be interpreted as remodeling law. In fact in specific cases the derived formulas are similar to the already postulated remodeling laws. The fundamental assumption that is necessary to consider bone adaptation as an optimal control problem, is a hypothesis of optimal response proposed in Lekszycki (1999, 2002). According to this hypothesis, the bone reacts to variable in time and space mechanical loads in an optimal way so that the rate of some global cost functional is extremized in order to assure the best possible improvements of bone configuration. In te following sections, the basic mechanisms responsible for bone remodeling are discussed and the "optimal control approach" is presented. To illustrate the links and differences between the "local" postulated models of bone adaptation and these following from the "global" approach presented here, a specific model is selected and briefly discussed.

2. Control of bone remodeling

The mechano-sensory system in bone represents a chain of events, cell activities and biochemical processes related to each other and controlled according to some rule. A basic understanding of the role of cells and the hypotheses concerning the mechanisms responsible for functioning of mechanosensory system in bone is necessary to propose the mathematical models of bone adaptation.

2.1. Fundamental roles of cells responsible for functional bone adaptation

One of the most important tasks of the skeleton is to support the mechanical loads associated with everyday activity and to protect internal organs. The ability to bear the extreme loads is to a large extent possible due to the bone ability to adapt to these functional demands by controlling its mass and morphology. The problem of bone adaptation has attracted researchers for more than one hundred years. Before the end of nineteenth century, Wolff formulated a statement generally known as "Wolff's law". According to it, "every change in the form and function of bones or their function alone is followed by certain definite changes in their internal architecture, and equally definite secondary alterations in their external conformation, in accordance with mathematical laws", see Wolff (1892). Since Wolff formulated this statement, a large number of theoretical and experimental works have been performed. This includes observations at different levels of magnification, sometimes employing very sophisticated methods as well as more and more advanced investigations of complex processes present in bone and responsible for its changes. Indeed, it follows from the results of the research that living bones are in continuous alteration – an activity which manifests itself in perpetual renovation of the bone "material" and possibly, in modification of its micro-structure and external shape. With improved experimental tools interesting results were achieved and new light was thrown into this subject. Nevertheless, in spite of all these efforts, not everything is understood completely and sometimes our knowledge is based on hypotheses that require more investigations. However some ideas have been already generally accepted.

Bone tissue is a porous non-homogeneous and strongly anisotropic material undergoing continuous alteration due to complex biochemical processes. It is composed of a solid matrix (build of mineral crystals and collagen fibers) and living cells – some of them buried in the matrix and others located in the pores filled with marrow. The turnover of bone is basically associated with two simultaneous effects, bone formation and bone resorption implemented by specialized cells. These effects are closely coupled with each other in time and in space. They play a crucial role in modeling, maintenance, repair and aging of bones. One of the important factors at macro-level that contributes significantly to the local control of bone remodeling is the variable in time mechanical loading determining strain distribution in bone. The process of bone remodeling is very slow compared to the mechanical loading changes. The remodeling effects can be observed at macro-level after days, weeks or even months, while for the everyday activities and the associated mechanical loads, the time scale counted in seconds can be used. Thus speaking about variable in time mechanical load we have in mind rather the mean value (or amplitudes) and not the actual instantaneous values.

This is a generally accepted concept that three families of cells are mainly involved in changes of bone micro-structure and evolution of the bone tissue itself. These cells are osteocytes, osteoblasts and osteoclasts. This fact has been already confirmed by many observations and the results of laboratory investigations. The balance between the cells, their proliferation, differentiation and apoptosis are controlled both by local growth factors as well as by systemic hormones and plays a crucial role in the processes contributing to bone turnover. This is more and more evident from the recent investigations that osteocytes play a role of sensor cells controlling the process of bone formation and remodeling, while osteoblasts and osteoclasts are the "actor" cells (Cowin and Moss-Salentijn, 1991; Ruimerman *et al.*, 2005; Burger and Klein-Nulend, 1999; Knothe *et al.*, 2004; Klein-Nulend *et al.*, 1995). Osteoblasts are the bone-forming cells. They produce new bone matrix in the regions where the additional material is needed to improve the bone performance. On the other hand, osteoclasts are responsible for tissue removal in the domains where material is not used. The balance between these two effects, bone formation and bone resorption, is controlled by the complex and highly organized interactions between the cells and extracellular matrix. Depending on the actual situation, the bone formation may be in balance, may exceed or be lower than the rate of bone resorption. Faster formation results in thicker and mechanically stronger bones. This may happen for example in response to increased mechanical loading. In another case, bone resorption can be faster than bone formation what may be associated with bone mechanical disuse or decease as osteoporosis and what results in loss of mass and deterioration of mechanical strength. The control of these effects is accomplished both via direct cell-to-cell signaling and via soluble molecules from the sensor cells (osteocytes) to the effector cells (osteoblasts or osteoclasts).

The most numerous cells in a mature bone are osteocytes which play the role of sensors and represent probably the key element of the mechanosensory system. They amount to about 90% of all cells in the bone tissue (Parfitt, 1977). Osteocytes have fixed positions – they are buried in the bone matrix, do not divide and have long lifetime. Osteocytes have long processes (about 80) – "fingers" which are connected with the processes of neighboring osteocytes. They form a network which is crucial in signal transmission to the actor cells. Osteoblasts are "actor" cells which produce new bone matrix by collagen synthesis and making it calcify. After receiving the signals, osteoblasts located at the internal surface of the bone, that is the surface of the pores, build osteoid composed of collagen and other organic components. Osteoid is a "brick" – an element of highly complex micro-architecture the tissue matrix is built of.

The osteoblasts continue their activity and some of them, previously attached to pore surface, become surrounded by the newly created material and transform into the osteocytes buried in a hard matrix (Dudley and Spiro, 1961; Baud, 1968; Palumbo *et al.*, 1990). During rapid growth, the proliferation of progenitor cells from the marrow present in the pores assures a necessary number of new osteoblasts which replace the ones already buried in the matrix. But at a certain stage of this process, proper signaling slows down the progenitor cells proliferation and the remaining osteoblasts stop their production of osteoid while mineralization of the matrix continues. While the osteoblast transforms into osteocyte in the space called lacunae, its cellular volume decreases and the collagen synthesis decays (Nefussi *et al.*, 1991). Simultaneously the development of long cell processes with gap junctions starts (Doty, 1981). They are placed in channels called canaliculi. The matrix around the osteocyte cells and their processes is not calcified, so mechanically it is more flexible compared to the rigid calcified regions. This is an important observation in one of the proposed concepts trying to explain the mechanosensory functions of this complex system. It was already mentioned that the osteocytes are distributed in the three-dimensional space occupied by matrix and that they form a complex network – they are connected with neighbors by cell processes and joined at gap junctions at their ends (Doty, 1981). Some of the osteocytes remain also in direct contact with other cells – osteoblasts and with the internal surface of the bone. This network can possibly form a system of mechanosensing and mechanotransduction in bone (Burger and Klein-Nulend, 1999; Klein-Nulend *et al.*, 1995; Cowin and Moss-Salentijn, 1991; Weinbaum *et al.*, 1994; Cowin *et al.*, 1995).

The third family of cells involved in bone remodeling are osteoclasts. They are responsible for bone resorption, at certain moments the signals appear in regions where the tissue should be removed and attracted osteoclasts are attached to the bone internal surface and dissolve the matrix. The relation between osteoclasts and osteoblasts activities determines the balance between the bone resorption and production. Therefore this is natural to expect that these processes are not independent of each other and are somehow controlled (among the others – by osteocytes activities). The "coupling factor" discussed in Frost (1964) between osteoclast resorption and osteoblast formation has probably a mechanical nature (Rodan, 1991).

2.2. Mechanosensory system in bones

In modeling the bone adaptation, understanding of the mechanosensory system and the mechanisms responsible for tissue variations is of crucial importance. In spite of numerous experimental data, the precise mechano-biological pathways of strain-induced bone metabolism are not really known. Hence, the proposed theories are partly based on assumptions, see e.g. Ruimerman *et al.* (2005). However, some of the concepts win more and more prevalence in recent years and experimental data confirm their correctness. Since the Wolff law was formulated, the fact that bones are dependent on mechanical state is accepted and confirmed by many research results. Later investigations have proved that osteocytes – the sensor cells – are sensitive to mechanical loading and osteoblasts build the tissue while osteoclasts remove it. What exactly the osteocytes are sensitive to and how they "fill" the mechanical situation and transform the received information into the signals directed to osteoblasts, and osteoclasts is not clear as yet. Therefore in many works an assumption is made that the stimulus which excites osteocytes is proportional to a specific measure of strain or stress fields in the bone. One of the most commonly used measures is the density of strain energy. Based on this assumption, several mathematical and computational models of bone remodeling have been proposed.

More than ten years ago, a hypothesis was presented by Cowin and coworkers according to which in intact bone the osteocytes are mechanically activated by flow of interstitial fluid through the lacunocanalicular system (Cowin and Moss-Salentijn, 1991; Weinbaum *et al.*, 1994; Cowin *et al.*, 1995). If this assumption is correct, the main stimulus for bone adaptation is the strain-driven motion of interstitial fluid through the canaliculi and along the osteocyte processes, which is somehow sensed and transduced by the osteocytes. Osteocytes then send signals to the actor cells, osteoblasts and osteoclasts and control their activities. The interstitial fluid flow in canaliculi can be indeed the representative of gradients of the local strain fields since other voids in the tissue are about 10^3 times larger and their pressure is more uniform and almost equal to the blood pressure (Cowin and Weinbaum, 1995). On the other hand, according to one of the concepts, the osteoclasts are assumed to be recruited by osteocyte apoptosis due to micro-damage or cracks that damage the canalicular system important for nutrient transportation (Bronckers *et al.*, 1996; Noble *et al.*, 1997; Verborgt *et al.*, 2000). They remove the cracked matrix while osteoblasts, due to increased level of strains associated with resorbing activity of osteoclasts, build the new one of improved mechanical characteristics. This way the tissue is renewed and changes its anisotropic characteristics according to the mechanical state.

3. Models of bone adaptation and the hypothesis of optimal response

Since Wolff had formulated his famous statement, many attempts have been done to propose mathematical formulas – this "mathematical law" mentioned in his statement – according to which the configurations of bones evolve. Despite intensive research on this subject, there was no unanimity for many years concerning such problems as, for instance, what are the most important effects responsible for bone remodeling, what are the mechanosensory mechanisms including sensing of different signals and transmitting them to the effector cells, what are the mechanisms of bone maintenance, deposition and resorption and others, see e.g. Burr and Martin (1992), Cowin and Moss-Salentijn (1991), Harringan and Hamilton (1993). Many mathematical models of bone adaptation based on different assumptions and taking into consideration diverse mechanical and non-mechanical effects have been proposed, see e.g. Carter and Orr (1992); Cowin (1995); Cowin and Hegedus (1976); Hart and Davy (1989); Hegedus and Cowin (1996); Levenston and Carter (1998); Luo *et al.* (1995); Prendergast *et al.* (1997); Prendergast and Taylor (1994); Taber (1995).

Generally speaking, the models can be classified into three groups: biomechanical models, those based on structural optimization methods, and the models derived with the use of optimal response hypothesis.

The first of the mentioned groups is the largest one. In most cases, the biological and medical observations and results of experiments are used to advance the hypothesis concerning possible causes of bone variations, the mechanisms of stimulus sensing and signal transferring to the effector cells and the essence of tissue remodeling. Based on these hypotheses and the theoretical investigations, the mathematical description of the adaptation process is postulated. Usually such models are of a local nature in the sense that, according to an information about the actual local mechanical state of a bone, the local rate of tissue remodeling is calculated at the actual time. Such models can be verified using numerical computations and the results of clinical and experimental investigations. Some of the more recent works take into account the results discussed in the previous sections concerning the nature of the mechanosensory system in bone at the cellular level, see e.g. Ruimerman *et al.* (2005), Mullender and Huiskes (1995), Tezuka *et al.* (2005), Doblaré and Garcia (2002), Burger and Klein-Nulend (2003), Lemairea *et al.* (2004).

The approaches based on the assumption that bones can be considered as optimal structures fall into the second group, see e.g. Bendsøe and Kikuchi (1988), Fernandes *et al.* (2000), Rodrigues *et al.* (1999), Folgado *et al.* (2004), Tanaka and Adachi (1999). This assumption is considered controversial. Moreover, such an approach does not enable any analysis of the alterations in bone due to conditions variable in time. On the other hand, it provides an asymptotic solution, a possible bone configuration in equilibrium state i.e. under external loading constant in time, after a sufficiently long period of time. However one should be aware of the fact that the bone structure, even in equilibrium state, is not always optimal. The choice of the objective functional is arbitrary and represents an important step in this approach. It might be considered as a weak point of the procedure. Difficulties in including non-mechanical effects in the formulation represent an additional drawback.

The last approach mentioned here was proposed by Lekszycki (1999, 2002) and is based on the formulated hypothesis of optimal response of a bone. It will be discussed in the next section.

Many of the proposed models fall into the category for which the adaptation law can be symbolically written in the form

$$\frac{dM}{dt} = A(S(\boldsymbol{x}, t) - S_0(\boldsymbol{x}, t)) \tag{3.1}$$

In the above relation M represents the bone mass in point $\boldsymbol{x}$ and time t, density of the material, Young's modulus or any other parameter that is responsible for local material characteristics. Of course, in the case when M represents mass, an additional relation is formulated – the relation between the local mass and the elastic characteristics of a material. $S(\boldsymbol{x}, t)$ is a stimulus – the signal that drives bone remodeling. It is often assumed that the stimulus is proportional to the density of strain energy, but also other solutions have been proposed depending of the mechanosensory effects included in the analysis. $S_0(\boldsymbol{x}, t)$ is a reference value of a stimulus, that is the value for which the bone is in a remodeling equilibrium state. This function should be assumed on the basis of other investigations (what is a week point of such an approach). In the following sections the relation (3.1) is compared with the derived adaptation law. It follows that it can be interpreted as a specific case of the relations obtained from the "optimal control" approach based on the hypothesis of optimal response of the bone.

3.1. Hypothesis of optimal response and its relation with optimal control

It follows from the considerations concerning mechanosensory functions in bone presented in the previous sections that the adaptation process of bone can be considered as a class of optimal control problem. In spite of the fact that the formulation discussed here is not a typical approach known in the optimal control theory, many similarities appear what shows that the bone adaptation process can be indeed considered as a class of optimal control problem. To formulate the problem in mathematical terms, the hypothesis of optimal response of bone, formulated by Lekszycki (1999, 2002) is used. In many works an assumption was made that the bone represents an optimal configuration. Of course, if something is optimal or not is to a large extent a matter of optimization criterion. According to one of them, the object can represent an optimal solution, according to other it could be even the worst one. This assumption is based on the observation that an internal structure of bone is similar to optimal engineering structures, especially when some measures of strains or stresses are taken as the criterion with the constraint imposed for the overall mass, or opposite – when the mass is minimized with the constraints for maximum level of stress or strain measures. Thus it is probably not baseless. However, there are two important points that should be mentioned in this context.

As it was already discussed in the previous sections, bone remodeling is an extremely complex phenomenon that depends on the processes of very different levels of size, starting deep at molecular level with the results observable at macro-level. Additional effects of different nature such as biochemical, mechanical, electrical and others are involved in its control and accomplishment. Many of these effects are closely related to each other and represent a complex control scheme, other are independent and work in parallel. Thus the ideal model should enable consideration of these effects and their possible interrelations. Another more important point is the fact that the optimal configuration – assuming that the criterion was correctly selected – represents some asymptotic, steady solution which might be achieved under the assumption that external and internal conditions that stimulate the changes in a bone are constant and do no vary in time. Of course, this is not the case in a real situation. We already know that a bone is exposed to conditions variable in time, both mechanical and biological, which determine the processes involved in control and maintenance. Therefore the optimal solution may provide some theoretical state which in fact can never be reached in practice. Nevertheless, in many cases the differences between this theoretical solution and the actual bone configuration may be small or even negligible. Unfortunately, the "optimization approach" provides only the final state under stimulation constant in time and do not enable to follow the remodeling process in time. These observations were a motivation to propose a new approach which enables derivation (instead of postulation) the remodeling formulas including time effects (Lekszycki, 1999, 2002). This approach makes it possible to include in the formulation different effects as we learn more about the subject.

The starting point in the following considerations is the hypothesis of optimal response. According to it, the bone is not optimal but it reacts optimally to conditions variable in time. In other words, the bone attempts to make the changes in its configuration within actual constraints to approach the best solution which is never achievable since it varies due to conditions variable in time. This way the bone is still in a state of pursuit of the optimal configuration. The general points of the approach are discussed below.

Basic assumptions. An assumption is made that the considered effects are slow and the inertia terms are negligible. In addition, it is assumed that the theory of small displacements and velocities is valid. In order to describe the variations of bone, the control functions characterizing its structure should be selected $\mu(\boldsymbol{x}, t)$. The derived remodeling law relates the velocities $\dot{\mu}(\boldsymbol{x}, t)$ to variable in time states of the bone.

Criterion. In order to compare different bone structures, the functional $G(\mu(\boldsymbol{x}, t))$ is defined. It depends on a set of time-variable control functions determining the bone configuration. Greater/smaller value of this criterion means a better bone structure.

The hypothesis of optimal response of a bone. According to this hypothesis, the bone reacts at each instant in an optimal way: that is, the rates $\dot{\mu}(\boldsymbol{x}, t)$ should assure the extremum of the objective functional.

The objective functional. The objective functional results from the choice of criterion and the hypothesis of optimal response of the bone. It is assumed that it is represented by the rate of the criterion G.

The global and local constraints. The constraints should be defined so as to take into account the important issues affecting the remodeling process. This is a crucial point in this formulation since different mechanical and non-mechanical effects can be included. This way, with growing knowledge concerning the mechanisms responsible for bone remodeling, an extension of actual models will be possible in future.

The adaptation law. From the stationarity condition of the objective functional, with constraints attached to it by means of Lagrange multipliers, the optimality conditions follow. Some of them can be interpreted as the remodeling law.

4. Application of hypothesis of optimal response in derivation of bone adaptation law

4.1. General considerations

A scheme of derivation of governing formulas is presented in this section. Let us introduce the following notation. $\mathbf{C}(\mu)$—tensor of material parameters where $\mu(\boldsymbol{x},t)$ is a *control function* defining the components of material tensor $\mathbf{C}$ (e.g. Young's modulus in case of isotropic material or density of material in a more general case) and t denotes time (t is treated as a parameter – we consider only slow variations in time and inertia effects are neglected). As a result of this derivation, appropriate formulas are obtained for evolution in time of the function $\mu(\boldsymbol{x},t)$ following external conditions variable in time (e.g. mechanical loading or boundary conditions). Let $\mathcal{U}$, $\mathcal{W}$ and $\mathcal{V}$ represent the set of kinematically admissible displacement fields, the set of kinematically admissible variations of displacement fields and the set of kinematically admissible variations of velocities of displacement fields, respectively. Let us introduce also the following definitions

$$
\begin{aligned}
a(\boldsymbol{u},\boldsymbol{v}) &= \int\limits_{\Omega} \mathbf{C}\nabla\boldsymbol{u}\cdot\nabla\boldsymbol{v}\;d\Omega \qquad & a'(\boldsymbol{u},\boldsymbol{v}) &= \int\limits_{\Omega} \dot{\mathbf{C}}\nabla\boldsymbol{u}\cdot\nabla\boldsymbol{v}\;d\Omega \\
l(\boldsymbol{v}) &= \int\limits_{\Omega} \boldsymbol{b}\cdot\boldsymbol{v}\;d\Omega + \int\limits_{\Gamma_f} \boldsymbol{f}\cdot\boldsymbol{v}\;d\Gamma \qquad & l'(\boldsymbol{v}) &= \int\limits_{\Omega} \dot{\boldsymbol{b}}\cdot\boldsymbol{v}\;d\Omega + \int\limits_{\Gamma_f} \dot{\boldsymbol{f}}\cdot\boldsymbol{v}\;d\Gamma
\end{aligned}
\tag{4.1}
$$

where

$$
\dot{\boldsymbol{C}} = \frac{d\mathbf{C}}{d\mu}\dot{\mu} \qquad \dot{\boldsymbol{b}} = \frac{\partial \boldsymbol{b}(\boldsymbol{x},t)}{\partial t} \qquad \dot{\boldsymbol{f}} = \frac{\partial \boldsymbol{f}(\boldsymbol{x},t)}{\partial t} \qquad \dot{\mu} = \frac{\partial \mu(\boldsymbol{x},t)}{\partial t}
$$

and Ω denotes a domain occupied by the body while Γ_f is a part of a boundary surface where the loading is defined. We can now express the potential energy as

$$
\Pi(\boldsymbol{u}) = \frac{1}{2}a(\boldsymbol{u},\boldsymbol{u}) - l(\boldsymbol{u}) \qquad \boldsymbol{u}\in\mathcal{U} \tag{4.2}
$$

and its time derivative as

$$
\dot{\Pi}(\boldsymbol{u},\dot{\boldsymbol{u}}) = \frac{d\Pi}{dt} = \frac{1}{2}a'(\boldsymbol{u},\boldsymbol{u}) + a(\boldsymbol{u},\dot{\boldsymbol{u}}) - l(\dot{\boldsymbol{u}}) - l'(\boldsymbol{u}) \tag{4.3}
$$

It is easy to check that the stationarity conditions of the functional (4.3) with respect to independent variations of $\boldsymbol{u}$ and $\dot{\boldsymbol{u}}$ are satisfied

$$
\delta_{\dot{\boldsymbol{u}}}\dot{\Pi}(\boldsymbol{u},\dot{\boldsymbol{u}}) = 0 \qquad \delta_{\boldsymbol{u}}\dot{\Pi}(\boldsymbol{u},\dot{\boldsymbol{u}}) = 0 \tag{4.4}
$$

Thus the weak formulation of the analysis problem is

$$\begin{aligned} &a(\boldsymbol{u},\delta\dot{\boldsymbol{u}}) - l(\delta\dot{\boldsymbol{u}}) = 0 && \forall\ \delta\dot{\boldsymbol{u}} \in \mathcal{V} \\ &a'(\boldsymbol{u},\delta\boldsymbol{u}) + a(\dot{\boldsymbol{u}},\delta\boldsymbol{u}) - l'(\delta\boldsymbol{u}) = 0 && \forall\ \delta\boldsymbol{u} \in \mathcal{W} \end{aligned} \tag{4.5}$$

Let us now define the comparison functional which represents a measure needed to compare different systems (bones)

$$G = \int\limits_{\Omega} S(\boldsymbol{u},\mu)\, d\Omega \tag{4.6}$$

According to the hypothesis of optimal response, the cost functional is defined as (we assume that the domain Ω does not evolve in time),

$$\Psi = \frac{dG}{dt} = \int\limits_{\Omega} \dot{S}\, d\Omega \tag{4.7}$$

Let us define now the optimization problem

$$\min_{\dot{\mu}} \Psi(\boldsymbol{u},\dot{\boldsymbol{u}},\dot{\mu}) \tag{4.8}$$

with additional global and local constraints applied

$$\begin{aligned} &a(\boldsymbol{u},\delta\dot{\boldsymbol{u}}) - l(\delta\dot{\boldsymbol{u}}) = 0 && \forall\ \delta\dot{\boldsymbol{u}} \in \mathcal{V} \\ &a'(\boldsymbol{u},\delta\boldsymbol{u}) + a(\dot{\boldsymbol{u}},\delta\boldsymbol{u}) - l'(\delta\boldsymbol{u}) = 0 && \forall\ \delta\boldsymbol{u} \in \mathcal{W} \\ &\int\limits_{\Omega} h_i(\dot{\mu}(\boldsymbol{x},t))\, d\Omega - A_i(t) = 0 && i = 1,\dots,N_g \\ &g_i(\dot{\mu}(\boldsymbol{x},t)) \geqslant 0 && i = 1,\dots,N_l \end{aligned} \tag{4.9}$$

where the following notation has been introduced: $g_i(\cdot)$ and $h_i(\cdot)$ – local and global constraints defined for the control function $\dot{\mu}$, A_i is a limit imposed globally on the control function, N_l and N_g denote the numbers of local and global constraints, respectively.

Let us build an extended cost functional by means of the Lagrange multipliers λ_1, λ_2, ρ_i, η_i, and slack variables α_i

$$\begin{aligned} &\mathcal{L}(\boldsymbol{u},\dot{\boldsymbol{u}},\boldsymbol{u}_1^a,\boldsymbol{u}_2^a,\dot{\mu},\rho_i,\eta_i,\alpha_i) = \\ &= \Psi(\boldsymbol{u},\dot{\boldsymbol{u}},\dot{\mu}) - a(\boldsymbol{u},\boldsymbol{u}_2^a) + l(\boldsymbol{u}_2^a) - a'(\boldsymbol{u},\boldsymbol{u}_1^a) - a(\dot{\boldsymbol{u}},\boldsymbol{u}_1^a) + l'(\boldsymbol{u}_1^a) + \\ &+\sum_{i=1}^{N_g} \rho_i(t)\Big[\int\limits_{\Omega} h_i(\dot{\mu}(\boldsymbol{x},t))\, d\Omega - A_i(t)\Big] + \sum_{i=1}^{N_l}\int\limits_{\Omega} \eta_i(\boldsymbol{x},t)\Big[g_i(\dot{\mu}(\boldsymbol{x},t)) - \alpha_i^2(\boldsymbol{x},t)\Big]\, d\Omega \end{aligned} \tag{4.10}$$

where additional functions $\boldsymbol{u}_1^a(\boldsymbol{x},t)$ and $\boldsymbol{u}_2^a(\boldsymbol{x},t)$ are defined using Lagrange multipliers λ_1 and λ_2. They represent state variables of the so-called adjoint system

$$u_1^a = -\lambda_1 \delta \boldsymbol{u} \qquad u_2^a = -\lambda_2 \delta \dot{\boldsymbol{u}} \tag{4.11}$$

Comment. In a general case of an arbitrary comparison functional, an additional system called "adjoint system" appears. This results in the necessity of analysis of this system since the adaptation relations are expressed in terms of state variables of both the primary and adjoint systems.

4.2. Examplary derivation of the adaptation law for a specific case

In a specific case when the comparison functional G represents the global measure of stiffness, the situation is simpler because both systems, the primary and the adjoint ones are equal to each other

$$\begin{aligned} S &= \frac{1}{2}\mathbf{C}\nabla\boldsymbol{u}\cdot\nabla\boldsymbol{u} \qquad G = \int_\Omega S\,d\Omega \\ \Psi &= \frac{1}{2}\int_\Omega (\dot{\boldsymbol{C}}\nabla\boldsymbol{u}\cdot\nabla\boldsymbol{u} + 2\mathbf{C}\nabla\dot{\boldsymbol{u}}\cdot\nabla\boldsymbol{u})\,d\Omega \end{aligned} \tag{4.12}$$

Let us apply the specific constraints to derive a sample adaptation law

$$\begin{aligned} &a(\boldsymbol{u},\delta\dot{\boldsymbol{u}}) - l(\delta\dot{\boldsymbol{u}}) = 0 && \forall\, \delta\dot{\boldsymbol{u}} \in \mathcal{V} \\ &a'(\boldsymbol{u},\delta\boldsymbol{u}) + a(\dot{\boldsymbol{u}},\delta\boldsymbol{u}) - l'(\delta\boldsymbol{u}) = 0 && \forall\, \delta\boldsymbol{u} \in \mathcal{W} \end{aligned} \tag{4.13}$$

$$\begin{aligned} &\int_\Omega \dot{\mu}(\boldsymbol{x},t)\,d\Omega - A_0(t) = h_1(\dot{\mu}) = 0 \\ &\int_\Omega \dot{\mu}^2(\boldsymbol{x},t)\,d\Omega - B_0(t) = h_2(\dot{\mu}) = 0 \end{aligned} \tag{4.14}$$

$$\begin{aligned} &\dot{\mu}(\boldsymbol{x},t) - \dot{\mu}_{max}(\boldsymbol{x},t) = g_1(\dot{\mu},\boldsymbol{x}) \leqslant 0 \\ &-\dot{\mu}(\boldsymbol{x},t) + \dot{\mu}_{min}(\boldsymbol{x},t) = g_2(\dot{\mu},\boldsymbol{x}) \leqslant 0 \\ &-\dot{\mu}(\boldsymbol{x},t)H(\mu_{min}(\boldsymbol{x},t) + \theta - \mu(\boldsymbol{x},t)) = g_3(\dot{\mu},\boldsymbol{x}) \leqslant 0 \\ &\dot{\mu}(\boldsymbol{x},t)H(\mu(\boldsymbol{x},t) - \mu_{max}(\boldsymbol{x},t) + \theta) = g_4(\dot{\mu},\boldsymbol{x}) \leqslant 0 \end{aligned} \tag{4.15}$$

where the following notation has been used, μ_{min}, μ_{max}, $\dot{\mu}_{min}$, $\dot{\mu}_{max}$ – minimal and maximal values of the function μ and its velocity, respectively, A_0, B_0 – global constraints imposed on $\dot{\mu}$. These functions should be defined on the basis of experimental results and clinical observations. $H(\cdot)$ denotes Heaviside's function. θ represents small neighbourhood of the limit values. According to the last two constraints, the function μ in the neighbourhood close to μ_{min} can not decrease and when it is close to μ_{max}, it can not grow. Let us build an extended cost functional by means of Lagrange multipliers λ_1, λ_2, ρ_1, ρ_2, η_1, η_2, η_3, η_4 and slack variables α_1, α_2, β_1, β_2.

Then the cost functional has a form

$$
\begin{aligned}
&\mathcal{L}(\boldsymbol{u}, \dot{\boldsymbol{u}}, \boldsymbol{u}_1^a, \boldsymbol{u}_2^a, \dot{\mu}, \rho_1, \rho_2, \eta_1, \eta_2, \eta_3, \eta_4, \alpha_1, \alpha_2, \beta_1, \beta_2) = \\
&= \frac{1}{2} a'(\boldsymbol{u}, \boldsymbol{u}) + a(\boldsymbol{u}, \dot{\boldsymbol{u}}) - a(\boldsymbol{u}, \boldsymbol{u}_2^a) + l(\boldsymbol{u}_2^a) - a'(\boldsymbol{u}, \boldsymbol{u}_1^a) - a(\dot{\boldsymbol{u}}, \boldsymbol{u}_1^a) + l'(\boldsymbol{u}_1^a) + \\
&+ \rho_1(t)\Big[\int\limits_{\Omega} \dot{\mu}(\boldsymbol{x}, t)\; d\Omega - A_0(t)\Big] + \rho_2(t)\Big[\int\limits_{\Omega} \dot{\mu}^2(\boldsymbol{x}, t)\; d\Omega - B_0(t)\Big] + \\
&+ \int\limits_{\Omega} \eta_1(\boldsymbol{x}, t)\Big[\dot{\mu}(\boldsymbol{x}, t) - \widehat{\mu}_{max}(\boldsymbol{x}, t) + \alpha_1^2(\boldsymbol{x}, t)\Big]\; d\Omega + \\
&+ \int\limits_{\Omega} \eta_2(\boldsymbol{x}, t)\Big[\dot{\mu}(\boldsymbol{x}, t) - \widehat{\mu}_{min}(\boldsymbol{x}, t) - \alpha_2^2(\boldsymbol{x}, t)\Big]\; d\Omega + \\
&+ \int\limits_{\Omega} \eta_3(\boldsymbol{x}, t)\Big[\dot{\mu}(\boldsymbol{x}, t) H(\mu_{min}(\boldsymbol{x}, t) + \theta - \mu(\boldsymbol{x}, t)) - \beta_1^2(\boldsymbol{x}, t)\Big]\; d\Omega + \\
&\int\limits_{\Omega} \eta_4(\boldsymbol{x}, t)\Big[\dot{\mu}(\boldsymbol{x}, t) H(\mu(\boldsymbol{x}, t) - \mu_{max}(\boldsymbol{x}, t) + \theta) - \beta_2^2(\boldsymbol{x}, t)\Big]\; d\Omega
\end{aligned}
\tag{4.16}
$$

From the stationarity condition of the cost functional we obtain:

- state equations for the primary system,
- state equations for the adjoint system,
- set of applied constraints,
- set of equations for Lagrange multipliers and slack variables,
- adaptation rule.

For the specific case considered here (global compliance as a comparison functional) we have

$$
\boldsymbol{u}_1^a(\boldsymbol{x}, t) = \boldsymbol{u}(\boldsymbol{x}, t) \qquad\qquad \boldsymbol{u}_2^a(\boldsymbol{x}, t) = \dot{\boldsymbol{u}}(\boldsymbol{x}, t) \tag{4.17}
$$

and the remodeling equations, representing one of the necessary conditions for stationarity of the cost functional can be expressed as follows

$$\begin{aligned}\dot{\mu}(\boldsymbol{x},t) &= -\frac{1}{2\rho_2(t)}\Big[\frac{1}{2}\frac{\partial C_{ijkl}}{\partial\mu}e_{ij}e_{kl}+\rho_1(t)\Big]-\frac{\eta_1(\boldsymbol{x},t)}{2\rho_2(t)}-\frac{\eta_2(\boldsymbol{x},t)}{2\rho_2(t)}+\\ &-\frac{\eta_3(\boldsymbol{x},t)H(\boldsymbol{x},t)}{2\rho_2(t)}-\frac{\eta_4(\boldsymbol{x},t)H(\boldsymbol{x},t)}{2\rho_2(t)}\end{aligned} \tag{4.18}$$

Lagrange multiplier ρ_1 can be interpreted as a variable in time *reference value*, often used in the "postulated" models.

A numerical example of application of this adaptation law was calculated. In Fig. 1 the results of simulation are presented. At the initial state a homogeneous material was used. After application of mechanical load the microstructure has developed. This microstructure was rearranged due to remodeling after endoprosthesis implantation. The micro-structures presented in this figure are similar to the clinical observations of the real bones.

4.3. Postulated and derived models

In the previous section, a simple adaptation model was mentioned (3.1). This formula has a similar form to the derived one (4.18). It can be noticed that remodeling according to (4.18) is also proportional to the difference between some stimulus and its reference value, similarly as it was assumed in (3.1). But in the present case the reference value is not assumed and is not constant. It follows from the analysis and is dependent on the Lagrange multipliers that have to be determined during the analysis. Therefore such a model is more realistic. On the other hand, the "optimal control" approach enables the control of the total amount of material via global and local constraints, what can be useful in many situations as, for example, in cases of osteoporosis or bone growth. The postulated model enables also the control of the material but indirectly – by modification of the reference value of the stimulus. In practical considerations it is very difficult since the reference value is not known.

5. Conclusions

In the present paper the idea has been presented that the functional adaptation of bone can be considered as a modified optimal control problem. Such a formulation is associated with significant advantages. However, the

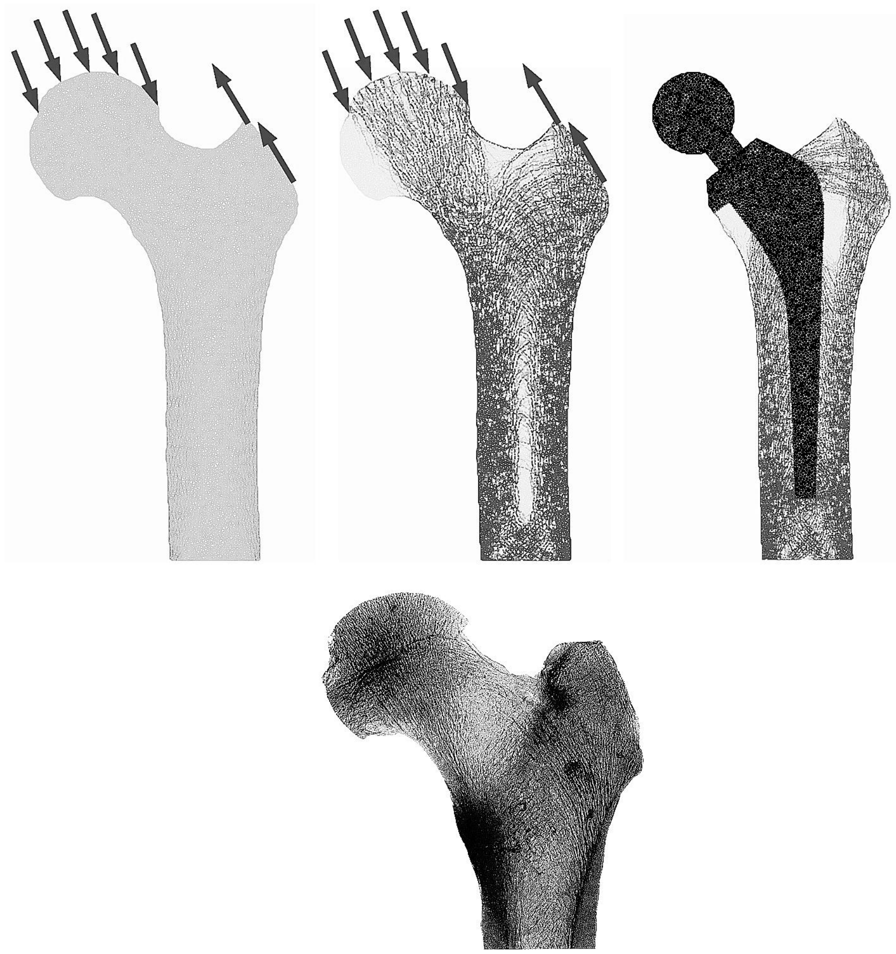

Fig. 1. The effect of a numerical simulation of bone adaptation before and after endoprosthesis implantation (from the left to right: initial state, adapted configuration after application of the mechanical load, remodeled configuration after endoprosthesis implantation). The structure of a real bone is presented below

formulation should be very carefully proposed to enable consideration of important biological effects that are involved in the control process. Among the others, the interactions between different families of cells should be included. An attempt to do so was already made by Lekszycki (2002), but an improved formulation is still necessary.

Acknowledgement

This work was supported by the Polish State Committee for Scientific Research, grant KBN 3T11F 007 27.

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Funkcjonalna adaptacja kości jako zagadnienie optymalnego sterowania

Streszczenie

Funkcjonalna adaptacja kości jest procesem polegającym na przebudowie tkanki kostnej wywołanej zmieniającymi się w czasie wymaganiami mechanicznymi, jakie musi spełniać szkielet kostny. Proces ten jest niezwykle złożony, ale doskonale zorganizowany i składa się z szeregu zjawisk zachodzących na poziomie mikro (molekularnym i komórkowym) lecz mających efek na poziomie makro (zmiana zewnętrznego kształtu kości oraz jej struktury wewnętrznej). Matematyczne modele tego zjawiska, postulowane w oparciu o obserwacje medyczne i badania laboratoryjne, opisują lokalną ewolucję materiału w czasie i przestrzeni. W tej pracy zastosowano hipotezę optymalnej odpowiedzi kości zaproponowaną wcześniej przez autora w celu wyprowadzenia (zamiast postulowania) związków rządzących przebudową kości w oparciu o bardzo ogólne założenia. Okazuje się, że takie sformułowanie ma wiele wspólnego z zagadnieniami optymalnego sterowania. W pracy zaprezntowano przykład zastosowania omawianego podejścia oraz przeprowadzono krótką dyskusję na temat związków między postulowanymi modelami i wyprowadzonymi w oparciu o przyjętą hipotezę.

Manuscript received May 16, 2005; accepted for print June 1, 2005