Advanced Course on Tissue Remodeling
ACTR'04 – (pp.143–171) – Warsaw, 2004.

Bone Remodeling in Presence of Osteoporosis

Tomasz Lekszycki

Institute of Fundamental Technological Research,
Polish Academy of Sciences,
ul. Świętokrzyska 21,
00-049 Warsaw, Poland
tlekszyc@ippt.gov.pl

Bone remodeling plays an important role in formation, maintenance and repair processes. It determines to big extent the bone internal micro-structure and influences the external shape of the bone. Therefore it has an essential impact on the bone strength necessary to ensure fundamental tasks of the skeleton which has to support mechanical loads associated with everyday activity and to protect internal organs. Osteoporosis is a disease which results in degradation of mechanical properties of a tissue and increased risk of bone fracture. It affects the remodeling activities in the bone. Despite that the real mechanisms responsible for bone tissue remodeling and development of osteoporosis are not yet completely known attempts are made to propose mathematical and computational models enabling an approximate analysis of these effects and evaluation of possible deterioration of bone strength. Such models may be useful in many situations. In the present paper a brief discussion of recent ideas proposed in the literature and concerning remodeling mechanisms, mechanosensory system and influence of osteoporosis is presented. Then a general approach is proposed enabling derivation of mathematical formulas describing tissue alterations due to functional adaptation phenomenon. This general approach, based on optimal response hypothesis, which was introduced by the author in the earlier works, enables including in the analysis different effects which are important in the control of adaptation process. For example, by this means the osteoporotic changes can be also modeled. Some of the possibilities are discussed and illustrated with the numerical example.

Key words: *functional adaptation, modeling, optimal response, osteoporosis, remodeling, tissue micro-structure*

1. Introduction

Osteoporosis is a disease when bone mineral density falls 2.5 standard deviations below the average value of a young adult. It manifests itself in degradation of mechanical properties of tissue and increased risk of bone fracture. Therefore in present-day societies with growing mean age of populations osteoporosis represents a serious social and economical problem. After the age of 30 years a negative balance in bone turnover causes progressive bone loss. In healthy cases the mechanical integrity of bone is still maintained, but in osteoporotic cases excessive bone loss can result in bone failure, see e.g. [63, 23]. Postmenopausal osteoporosis manifests itself in similar manner, that is deterioration of tissue particularly in cancellous bone where trabecular architecture plays a crucial role in structural and mechanical integrity. Thus no matter what is the real reason of osteoporosis this decease disturbs the regulation process of bone remodeling and affects associated variation of bone micro-structure, especially in cancellous regions, see [24].

Despite that the real mechanisms responsible for development of osteoporosis are not yet completely known successive attempts are made to propose mathematical and computational models enabling at least approximate investigation of its influence on bone modeling and remodeling and possible deterioration of bone strength. Such models may be useful in many situations. As an example computer-aided pre- and post-surgery planning in osteoporotic cases can be mentioned. An information concerning bone micro-structure evolution in the surrounding of the implant, deterioration of bone strength and durability of endoprosthesis-bone interface can be very useful in taking a decision before operation as well as during rehabilitation process and future life. Bone remodeling and adaptation is to a large extent dependent on mechanical state which is dramatically changed after endoprosthesis implantation and depends on implant shape and design, [36]. On the other hand it can be affected by osteoporotic changes which may significantly influence strain distribution and in turn result in directions of variation of tissue micro-structure and declination of durability of endoprosthesis. In such cases even approximate calculations and rough predictions may provide information helping in optimal choice of prosthesis.

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 accommodate the extreme loads is to big extent possible

through the bone ability to adapt to these functional demands by controlling its mass and morphology. The problem of bone adaptation attracts researchers for more than hundred years. Before the end of nineteenth century Wolff formulated statement generally known as Wolf'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 [89]. Since this time large number of theoretical and experimental works has been performed. This includes observations at different levels of magnification sometimes with use of 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 this research that living bones are in continuous alteration, an activity which manifests itself in perpetual renovation of bone "material" and possibly modification of its micro-structure and external shape. With still better experimental tools interesting results were achieved and new light was thrown into this subject. Nevertheless, in spite of all of these efforts, not everything is understood completely and sometimes our knowledge is based on hypotheses that require more investigations.

In the following sections the basic functions of cells involved in bone remodeling process are briefly discussed. The osteoporosis and its effects on bone remodeling is a subject of the subsequent section. Last section is devoted to selected problems of mathematical and computational modeling of bone remodeling. More detailed discussion is included, concerning the models derived from the hypothesis of optimal response. The numerical example illustrating application of discussed method in computer analysis of osteoporotic changes in bone is also presented.

2. Cells and their Fundamental Roles in Bone Remodeling

Bone tissue is a porous nonhomogeneous and strongly anisotropic material which undergoes continuous alteration—complex biochemical processes result, among others, in variation of bone external shape and its internal structure. 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 and play a crucial role in modeling, maintenance, repair and aging of bones. One of the important factors at macro level that contributes significantly in

local control of bone remodeling is a mechanical loading determining strain distribution in bone. The remodeling driven by variable in time mechanical state is known as functional adaptation of bone.

This is generally accepted concept that three families of cells are mainly involved in changes of bone micro-structure and evolution of bone tissue itself. These cells are osteocytes, osteoblasts and osteoclasts. This fact is already confirmed by many observations and the results of investigations. The balance between 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 taking part in bone turnover. This is more and more evident from 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, [15, 78, 8, 43, 42]. Osteoblasts are the bone-forming cells. They produce new bone matrix in the regions where bone has previously been resorbed. On the other hand osteoclasts are responsible for tissue removal. The balance between these two effects, bone formation and bone resorption, is tightly controlled by the complex and highly organized interactions between cells and extracellular matrix. Depending on the actual situation, the rate of bone formation may be in balance, may exceed or be lower than the rate of bone resorption. Faster formation results in thicker and mechanically stronger bones. This may happen, for example, in response to mechanical loading. In another case, bone resorption can be faster than bone formation, what may be associated with bone disuse or decease (osteoporosis), and 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 (probably osteocytes and bone lining cells) to effector cells (osteoblasts and osteoclasts).

In a review paper Sikavitsas et al. [81] divide the substance that affect bone development into two categories namely, attached matrix molecules and soluble factors. Among the matrix components they list those of the biggest importance. *Osteocalcin*—may be used to inhibit mineralization and could play role in bone resorption, see also [70]. *Osteonectin*—may be a nucleator for matrix mineralization, [70]. *Alkaline phosphatase*—probably promotes crystal formation in matrix vesicles, see [70, 22]. *Fibronectin*—has binding regions for collagen, fibrin and cells. Osteoblasts use fibronectin for cell attachment, while transforming growth factor-β (TGB-β) modulates its synthesis, see [70]. *Thrombospondin*—its synthesis is modulated by transforming growth factor-

β. It may organize extracellular matrix components or act as a growth factor, [70]. *Proteoglycans* I and II (PG-I and PG-II)—they may affect collagen fiber growth and diameter of the fiber, [70]. *Osteopontin*—it is involved in cell attachment to the bone matrix, [70]. *Bone sialoprotein*—similarly as osteopontin is involved in cell attachment but for shorter periods. Among the most important soluble factors the following are listed [81]. Bone morphogenic (BMPs)—they stimulate proliferation of chondrocytes and osteoblasts, exerts increased production of matrix and induces mesenchymal stem cells to differentiate to osteoblasts, see [6, 74]. *Fibroblast growth factors* (FGFs)—they stimulate proliferation of mesenchymal stem cells, osteoblasts and chondrocytes, they may influence development through their angiogenic properties, see [74, 10]. *Insulin-like growth factors* (IGFs)—they stimulate proliferation of osteoblasts and chondrocytes and induce matrix secretion from both cell types [6, 74]. *Platelet-derived growth factor* (PDGF)—stimulates proliferation of chondrocytes and osteoblasts. However, in different concentrations, it has also been involved in bone resorption [6, 74]. *Transforming growth factor* β (TGF-β)—causes differentiation of mesenchymal stem cells to chondrocytes. It may induce chondrocyte and osteoblast proliferation. Similarly as platelet-derived growth factor it has been seen to enhance bone resorption at certain concentrations. It may play a role in coupling formation and resorption activities, see also [6, 74, 10]. *Epidermal growth factor* (EGF)—it stimulates chondrocyte proliferation while decreasing the cells' ability to synthesize matrix components [10]. *Parathyroid hormone* (PTH)—causes the release of calcium from the bone matrix and induces osteoclast differentiation from precursor cells. It probably inhibits osteoblast function [6]; *Estrogen*—a hormone that has complex functions, as a result it decreases bone resorption by osteoclasts [6]. *Dexamethasone*—involved in early stages of chondrocytes differentiation. It induces fully differentiated chondrocytes to secrete alkaline phosphatase, suggesting it may be important in cartilage calcification [6]; *Thyroxin*—it stimulates osteoclastic bone resorption [6]. *Calcitonin*—it inhibits osteoclast function [6]. *Prostaglandins*—initially inhibit osteoclasts, over extended periods encourage the proliferation and differentiation of these cells [6]. *Interleukin-1* (IL-1)—it stimulates the proliferation of osteoclast precursors what results in increasing of bone resorption [6]. *Vitamin D*—this vitamin has a complex effect on bone formation, possibly by regulating the synthesis of other molecules (e.g. osteopontin and osteonectin). It has been reported to influence both bone resorption and matrix mineralization [6, 50].

It is apparent, even from this superficial discussion, that bone tissue remodeling is a very complex process dependent on many, often associated with each other factors. Mineral homeostasis is mainly dependent on hormonal signaling. Structural integrity of bone necessary to assure mechanical functions of skeleton and required strength of bones is maintained by localized remodeling [28]. It has been shown that mechanical loads lead to increase of collagen production, osteoblast proliferation, fracture repair rate, and localized prostaglandin release [90]. On the other hand loading decreases surface area of osteoclast activities and resorptive process [12].

Osteocytes, which play the role of sensors and represent probably the key element of mechanosensory system, are the most numerous cells in mature bone. They amount about 90% of all cells in bone tissue, [64]. They do not divide and have long life time. Osteocytes are derived from osteoprogenitors. A portion of those differentiate into osteoblasts. Osteoblasts are "actor" cells which produce new bone by collagen synthesis and making it calcify. After receiving signals osteoblasts located at the internal surface of bone build osteoid composed of collagen and other organic components. They continue their activity and some of them, previously attached to bone surface, become incorporated within the newly created matrix and transform into osteocytes, [21, 2, 61]. During rapid growth of bone matrix, the proliferation of progenitor cells assures necessary number of new osteoblasts, which replace those already buried in matrix. But at the certain stage of this process proper signaling slows down the progenitor cells proliferation and remaining osteoblasts stop their production of osteoid while mineralization of matrix continues. This portion of osteoblasts, which remains on the external surface of newly created matrix, turn into the lining cells. Unlike the other cells, osteocytes (which are the former osteoblasts buried in the bone matrix) are located at fixed positions surrounded by hard matrix. This, and the fact that they do not proliferate are the reasons they are difficult to study. Only recently a unique osteocyte-like cell line MLO-Y4 was developed, that was created using SV40 large T-antigen oncogene with osteocalcin promoter, [40]. This cell line was isolated from long bones of transgenic mice and it appears to have the properties of primary osteocytes. This finding enabled further investigations of osteocytes, see e.g. [37, 34]. While osteoblast transforms into osteocyte in the space called lacunae the cellular volume decreases and the collagen synthesis decays, [59]. Simultaneously the development of long cell processes with gap junctions starts, [20]. They are placed in channels

called canaliculi. The matrix around 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 mechanosensory functions of this complex system. The osteocytes are distributed in three-dimensional space occupied by matrix and they form a complex network—they are connected with neighbors by cell processes and joined at gap junctions at their ends [20]. Some of the osteocytes remain also in direct contact with other cells—osteoblasts, with overlying lining cells, and with the internal surface of bone. The lacunocanalicular system represents a conduit for metabolic traffic and exchange, [2, 44, 43]. On the other hand this network can possibly form a system of mechanosensing and mechanotransduction in bone, [8, 42, 15, 88, 16].

The third family of cells involved in bone remodeling are osteoclasts. They are responsible for bone resorption. The relation between osteoclasts and osteoblasts activities determines the balance between bone resorption and production. Therefore this is natural to expect that these processes are not independent of each other and are somehow controlled. The 'coupling factor' discussed in [29] between osteoclast resorption and osteoblast formation has probably a mechanical nature [71]. The investigation of possible control of osteoclast activities by osteocytes was enabled after the development of MLO-Y4 osteocyte-like cell line. It was reported recently [91] that MLO-Y4 cells supported osteoclast formation and resorption via direct contact with precursor cells. It was suggested that RANKL acts as a surface molecule, and the soluble factors OPG and M-CSF play a role in controlling bone resorption.

According to one of the concepts, osteoclasts are assumed to be recruited by osteocyte apoptosis due to micro-damage or cracks [5, 60, 87]. On the other hand, the cavity called a 'notch', resulting form osteoclast resorption, produces a stress concentration close to it [56], what creates an enhanced biochemical recruitment signal for the osteoblasts from the vital osteocytes in environment [78]. Indeed, according to recent reports the life span of osteoclasts, osteoblasts, and osteocytes is an important determinant of bone mass and strength. The results of investigations of mechanisms and regulation of bone cell apoptosis, especially osteoclasts and osteoblastic cells, was reported in [51]. The relationships between osteocyte density and bone formation rate in human cancellous bone were discussed in [67]. It was assumed in [52] that osteocyte density regulates the osteon wall thickness and rela-

tive haversian canal space. The force governing the change in wall thickness and relative haversian canal space is diminishing nutrient availability sensed by osteocytes, which causes them to send an inhibitory signal to osteoblasts. The study of osteocyte density in relationship to radial location in the osteon and various remodeling parameters is presented, [45].

Bone remodeling is composed of five distinct phases, see [81]. According to [62] they can be characterized as follows. 1) *Resting state.* The surface of the bone is lined with inactive osteoblastic cells. Former osteoblasts are trapped as osteocytes within the mineralized matrix. 2) *Activation.* Hormonal or physical stimuli signal mononuclear monocytes and macrophages to migrate to the remodeling site and differentiate into osteoclasts. Sites with micro-fractures may exhibit a certain predisposition for remodeling. 3) *Resorption.* Osteoclasts begin to remove the organic and mineral components of bone and form a cavity of characteristic shape and dimensions called a Howship's lacuna in trabecular bone and a cutting cone in cortical bone. While the cavity grows and its front moves forward, the resorption ceases at the location of $60\,\mu$ from the front in trabecular bone, and about $100\,\mu$m in cortical bone. 4) *Reversal.* Osteoclasts disappear and mononuclear macrophage-like cells smooth the resorbed surface by depositing a cement-like substance that will bind new bone to old. Pre-osteoblasts begin to appear. This phase is characterized by factors that stimulate osteoblast precursors to proliferate, including IGF-2 and TGF-β. 5) *Formation.* Differentiated osteoblasts fill in the resorption cavity and begin forming new osteon in a two-stage process. First, they deposit osteoid (mostly collagen type I). The rate of matrix apposition is initially very rapid and the osteoblasts are columnar and densely packed. Mineralization of the osteoid commences when the cavity has been filled to $20\,\mu$m. With the onset of mineral apposition, the rate of mineralization exceeds the rate of matrix apposition and continues, with a substantially lower rate, even after the termination of matrix synthesis, until the bone surface returns to its original resting state.

In modeling of 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 mechanobiological pathways of strain induced bone metabolism are not really known. Hence, the proposed theories are partly based on assumptions, see e.g. [78]. However some of the proposed concepts win more and more prevalence in recent years and experimental data opt for their correctness. Over than ten

years ago a hypothesis was developed by Cowin and co-workers according to which in intact bone the osteocytes are mechanically activated by flow of interstitial fluid through the lacunocanalicular system [15, 88, 16]. If this assumption is correct, the main stimulus for bone adaptation is the strain-driven motion of interstitial fluid through the canaliculi, along the osteocyte processes, which is sensed and transduced by osteocytes. Osteocytes then signal the actor cells, osteoblasts and osteoclasts and control their activities. The interstitial fluid flow in canaliculi can be indeed the representative of gradients of local strain fields, since other voids as e.g. Volkman Canals and Haversian Lumens are about 1000 times larger and their pressure is more uniform and almost equal to the blood pressure [13]. It follows from some investigations, that for physiological conditions flow can reach osteocytes 4–5 concentric layers from the center of an osteon, which allows the transport of nutrients even at the outermost zone of an osteon, see [45]. This observation also indicates the importance of mechanically induced flow in osteocyte survival and activity. On the other hand a number of works have been performed to examine effect of fluid shear stress in production of different factors which might be important in control mechanisms of activities performed by osteoblasts and osteoclasts, see for example [69, 68, 38, 41, 55, 54].

3. Osteoporosis

Osteoporosis can affect bone remodeling in different ways and has negative effect on bone performance and its mechanical characteristics. Frost indicates that bone density and mass are not good parameters to adjust the severity of this disease [27]. He distinguishes at least three different cases of osteoporosis. 1) In this case people have less bone than 'normal' but no bone problems arise unless they sustain injuries. Most of their resulting fractures, usually from falls, affect extremity bones. This case can affect children, men and women. 2) The second case is associated with presence of osteopenia. In such situation voluntary physical activities (not injuries) cause spontaneous fractures and/or bone pain, mainly in the spine, more often in women than men and seldom in children (osteogenesis imperfecta excepted). 3) A third case combines features of the first two. On the other hand one may speak about osteoporotic changes associated with bone disuse, osteoporosis related to age, especially postmenopausal osteoporosis or osteoporosis associated with disturbance of metabolic processes. No matter how

it is categorized, more important than the density is a strength and immunity to mechanical impacts, what is, to a large extent, determined by bone micro-structure (porosity and its geometric characteristics) and mechanical parameters of the material (local constitutive parameters of a tissue), see e.g. [39]. For the given mass and the material but different topologies a wide range of strength can be realized. In fact, stronger effects on bone mass are not necessarily associated with better prevention of fractures [73]. For example, an inhibition of a bone resorption could lead to a preservation of bone micro-structure and mass but negatively influence material strength. On the other hand, vitamin K treatment is likely to lower fracture risk without affecting bone mass or bone resorption [80]. Human osteocalcin, a vitamin K dependent protein, contains three-carboxyglutamate (Gla) residues, and only carboxylated osteocalcin is incorporated into bone [79]. It was reported that serum osteocalcin carboxylation could be related to tibial ultrasound velocity, a possible indicator of bone material properties in healthy prepubertal children [82]. Indeed, osteocalcin is required for bone mineral maturation [4], and immature bone mineralization could induce a deterioration of bone material properties.

Since osteoporosis is often related to bone micro-structure, it is clear that the balance of proliferation, differentiation, and apoptosis of bone cells, which determines the size of osteoclast or osteoblast populations, plays an important role in development of this disease. Bone cells constantly receive signals from adjacent cells, hormones, and bone matrix that regulate their proliferation, activity, and survival. Thus, according to [51] the amount of bone and its micro architecture before and after the menopause or following therapeutic intervention with drugs, such as sex hormones, glucocorticoids, parathyroid hormone, and bisphosphonates, might be determined in part by effects of these on survival of osteoclasts, osteoblasts, and osteocytes. On the other hand it follows from [57] that significantly higher lacunae and osteocyte numbers per unit bone tissue volume is present in osteoporotic than in controls cases, while lacunar area was significantly reduced in osteoporosis. The authors mention that these findings are compatible with the hypothesis that in osteoporosis osteoblasts produce less bone per cell. The question about relationships between osteocyte density and bone formation rate in human cancellous bone is also discussed in [67]. The effect of mechanical loading in development or prevention of osteoporosis is discussed in many papers. It was reported in [76] that high frequency (10–100 Hz) and low magnitude

(<10 micro strain) stimuli were capable of augmenting bone mass and morphology, thereby benefiting both bone quantity and quality. Using animal models, it is shown that these mechanical signals can double bone-formation rates, inhibit disuse osteoporosis and increase the strength of trabecular bone by 25%.

In many works osteoporosis is discussed in context of arthroplasty. There are three factors adversely affecting maintenance of bone mass after total hip arthroplasty (THA): 1) bone loss secondary to particulate debris; 2) adaptive bone remodeling and stress shielding secondary to size, material properties and surface characteristics of prostheses; 3) bone loss as a consequence of natural aging [75]. In [1] the higher risk for failures of the implant after internal fixation of hip fractures in osteoporotic cases was reported and in [23] similar observation was made in case of total hip replacement. On the other hand, according to [31] no evidence exists that disuse osteoporosis has limited the longevity of cemented femoral stems up to 20 years. One of the important questions is if physical activities can improve bone characteristics and durability of the endoprosthesis fixation. According to [35] a lower rate of loosening of total hip replacement in patients exercising sports than in inactive people was found, but in [77], in spite of wide spectrum of physical activity, no correlation between activity and bone loss has been observed.

Regardless of sometimes contradictory clinical observations, it is a prevailing opinion that the mechanical loading influences osteoporotic changes in bone and that functional adaptation plays in this phenomenon significant role. Thus, modeling of bone adaptation with osteoporotic effects included is an important point.

4. Modeling of Bone Microstructure Evolution

Since Wolf formulated his famous statement many attempts were done to propose mathematical formulas—this "mathematical law" mentioned in his statement—according to which bones evolve. Despite intensive research on this subject, there was no unanimity for many years concerning such problems as, for instance, what effects are responsible for bone remodeling, mechanosensory mechanisms in bone including sensing of different signals and transmitting them to the effector cells, the mechanisms of bone maintenance, deposition and resorption and others, see e.g. [9, 15, 30]. 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. [84, 32, 49, 11, 18, 14, 53, 33, 65, 66]. In some of the works the osteoporosis effects can be included in an analysis, see [78, 57, 26, 46, 47].

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

The first of the mentioned groups is the largest one. In most cases the biological and medical observations and experiments are used to advance 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. Such models can be verified using numerical computations and the results of clinical and experimental investigations and have usually good theoretical basis. Some of the more recent works take into account the results discussed in the previous sections concerning the nature of mechanosensory system in bone, see e.g. [78, 58, 86, 19, 7, 48].

The approaches based on the assumption that bones can be considered as optimal structures fall into the second group, see e.g. [3, 25, 72, 26, 85]. This assumption is considered as controversial. Moreover, such an approach does not enable to follow the alterations in bone due to variable conditions. On the other hand it provides possible bone configuration, that is its shape and internal structure, in equilibrium state i.e. under constant in time external loading after an infinitely long time. However one should be aware of the fact that bone structure, even in equilibrium state, is not always optimal. The choice of the objective functional is an important step in this approach. This might be considered as a weak point of the procedure. Difficulties in including non-mechanical effects in the formulation determine additional drawback.

The last approach mentioned here was proposed in [46, 47] and is based on the formulated hypothesis of optimal response of a bone. It is discussed in the next section.

4.1. Hypothesis of Optimal Response and its Application in Modeling of Bone Adaptation

In many works an assumption was made that bone represents an optimal configuration. Of course if something is optimal or not is to big extent a matter of optimization criterion. According to one criterion, the object

can represent an optimal solution, according to the other it could be even the worst one. This assumption has basis in 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 overall mass, or opposite—when mass is to be minimized with the constraints for maximum level of stress or strain measures. 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 at very different levels of magnification, starting deep at molecular level with results observable at the macro-level. Moreover effects of different nature as biochemical, mechanical, electrical and others are involved in its control. 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. The other, 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 an assumption, that external and internal conditions, that stimulate changes in a bone, are constant and do no vary in time. Of course, this is not a case in a real situation. We already know that a bone is exposed to variable in time conditions both, mechanical and biological which determine 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 "optimization approach" provides only the final state under constant in time stimulation 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, [46, 47]. This approach makes possible to involve in formulation different effects as we learn more about the subject.

The starting point in this formulation is the hypothesis of optimal response. According to it the bone is not optimal but it reacts optimally to variable in time conditions. In other words bone attempts to make the changes in its configuration as much as possible within actual constraints to approach

the best solution which is never achievable since it varies due to variable in time conditions. This way, bone is still in a state of pursuit after the optimal configuration.

Let us briefly discuss the approach based on the optimal response hypothesis and illustrate its application to specific case where osteoporotic changes were taken into consideration.

The general points of the approach:

1. *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 in force. In order to describe variations of bone, the variables $\mu(\mathbf{x}, t)$ characterizing its structure should be selected. The derived remodeling law relates the velocities $\dot{\mu}(\mathbf{x}, t)$ with variable in time states of the bone.

2. *Criterion.*
   In order to compare different bone structures the comparison functional $G(\mu(\mathbf{x}, t))$ is defined. It depends on a set of time-variable parameters determining the bone configuration. Bigger (or smaller) value of this criterion means better bone structure.

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

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

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

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

Following these steps a scheme of derivation of governing formulas is presented in the next part of this section. The considerations are restricted to linear elasticity, specific comparison functional and constraints. This choice determines the resulting adaptation law.

Let us introduce the following notation: $\mathbf{C}(\mu)$—tensor of material parameters where $\mu(\mathbf{x}, t)$ is a "control function" defining the components of tensor $\mathbf{C}$ (e.g. Young modulus or density of material) and t denotes time (t is treated as a parameter—we consider only slow variations in time). As a result of this derivation appropriate formulas are obtained for time evolution of function $\mu(\mathbf{x}, t)$ following variable in time external conditions (e.g. mechanical loading or boundary conditions). Let us introduce also the following definitions,

$$a(\mathbf{u}, \mathbf{v}) = \int_\Omega \mathbf{C}\nabla\mathbf{u} \cdot \nabla\mathbf{v} d\Omega,$$

$$a'(\mathbf{u}, \mathbf{v}) = \int_\Omega \dot{\mathbf{C}}\nabla\mathbf{u} \cdot \nabla\mathbf{v} d\Omega,$$

$$l(\mathbf{v}) = \int_\Omega \mathbf{b} \cdot \mathbf{v} d\Omega + \int_{\Gamma_f} \mathbf{f} \cdot \mathbf{v} d\Gamma,$$

$$l'(\mathbf{v}) = \int_\Omega \dot{\mathbf{b}} \cdot \mathbf{v} d\Omega + \int_{\Gamma_f} \dot{\mathbf{f}} \cdot \mathbf{v} d\Gamma,$$

where

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

$$\dot{\mathbf{f}} = \frac{\partial \mathbf{f}(\mathbf{x}, t)}{\partial t}, \qquad \dot{\mu} = \frac{\partial \mu(\mathbf{x}, t)}{\partial t}.$$

Here Ω denotes a domain occupied by the body and Γ_f is a part of a boundary surface where the loading is defined.

Let $\mathcal{U}$ and $\mathcal{V}$ represent a set of kinematical admissible displacement fields and a set of kinematically admissible variations of displacement fields; $\mathbf{u}$ and

$\mathbf{v}$ are sufficiently regular functions in Ω. We can now express the potential energy as

$$\Pi(\mathbf{u}) = \frac{1}{2}\, a(\mathbf{u}, \mathbf{u}) - l(\mathbf{u}), \quad \mathbf{u} \in \mathcal{U},$$

and its time derivative as

$$\dot{\Pi}(\mathbf{u}, \dot{\mathbf{u}}) = \frac{d\Pi}{dt} = \frac{1}{2} a'(\mathbf{u}, \mathbf{u}) + a(\mathbf{u}, \dot{\mathbf{u}}) - l(\dot{\mathbf{u}}) - l'(\mathbf{u}). \tag{4.1}$$

It is easy to check that the stationarity conditions of the functional (4.1) with respect to independent variations of $\mathbf{u}$ and $\dot{\mathbf{u}}$ are satisfied,

$$\delta_{\dot{\mathbf{u}}} \dot{\Pi}(\mathbf{u}, \dot{\mathbf{u}}) = 0, \quad \delta_{\mathbf{u}} \dot{\Pi}(\mathbf{u}, \dot{\mathbf{u}}) = 0.$$

Thus the weak formulation of the analysis problem is

$$a(\mathbf{u}, \delta\dot{\mathbf{u}}) - l(\delta\dot{\mathbf{u}}) = 0 \quad \forall \delta\dot{\mathbf{u}} \in \mathcal{V},$$

$$a'(\mathbf{u}, \delta\mathbf{u}) + a(\dot{\mathbf{u}}, \delta\mathbf{u}) - l'(\delta\mathbf{u}) = 0 \quad \forall \delta\mathbf{u} \in \mathcal{V}.$$

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

$$G = \int_\Omega S(\mathbf{u}, \mu) d\Omega.$$

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

$$\Psi = \frac{dG}{dt} = \int_\Omega \dot{S} d\Omega.$$

Let us define now the optimization problem.

$$\min_{\dot{\mu}} \Psi\,(\mathbf{u}, \dot{\mathbf{u}}, \dot{\mu})$$

with additional constraints applied,

$$a(\mathbf{u}, \delta\dot{\mathbf{u}}) - l(\delta\dot{\mathbf{u}}) = 0 \quad \forall \delta\dot{\mathbf{u}} \in \mathcal{V},$$

$$a'(\mathbf{u}, \delta\mathbf{u}) + a(\dot{\mathbf{u}}, \delta\mathbf{u}) - l'(\delta\mathbf{u}) = 0 \quad \forall \delta\mathbf{u} \in \mathcal{V},$$

$$\int_\Omega \dot{\mu}(\mathbf{x}, t) d\Omega - A_o(t) = h_1(t) = 0,$$

$$\int_\Omega \dot{\mu}^2(\mathbf{x}, t) d\Omega - B_o(t) = h_2(t) = 0,$$

$$\dot{\mu}(\mathbf{x}, t) - \dot{\mu}_{\max}(\mathbf{x}, t) = g_1(\dot{\mu}, \mathbf{x}) \leq 0,$$

$$-\dot{\mu}(\mathbf{x},t)+\dot{\mu}_{\min}(\mathbf{x},t)=g_2(\dot{\mu},\mathbf{x})\leq 0,$$

$$-\dot{\mu}(\mathbf{x},t)H(\mu_{\min}(\mathbf{x},t)+\theta-\mu(\mathbf{x},t))=g_3(\dot{\mu},\mathbf{x})\leq 0,$$

$$\dot{\mu}(\mathbf{x},t)H(\mu(\mathbf{x},t)-\mu_{\max}(\mathbf{x},t)+\theta)=g_4(\dot{\mu},\mathbf{x})\leq 0,$$

where the following notation was introduced, $\mu_{\min}$, $\mu_{\max}$, $\dot{\mu}_{\min}$, $\dot{\mu}_{\max}$—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. $H(.)$ denotes Heaviside's function. θ represents small neighbourhood of the limit values. According to the last two constraints the function μ when falls in the environment close to μ_{min} can not decrease and when falls in the environment close to $\mu_{\max}$ 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 functions α_1, α_2, β_1, β_2:

$$\begin{aligned}
&\mathcal{L}(\mathbf{u},\dot{\mathbf{u}},\mathbf{u}_1^a,\mathbf{u}_2^a,\dot{\mu},\rho_1,\rho_2,\eta_1,\eta_2,\eta_3,\eta_4,\alpha_1,\alpha_2,\beta_1,\beta_2)=\\
&\quad=\Psi(\mathbf{u},\dot{\mathbf{u}},\dot{\mu})-a(\mathbf{u},\mathbf{u}_2^a)+l(\mathbf{u}_2^a)-a'(\mathbf{u},\mathbf{u}_1^a)-a(\dot{\mathbf{u}},\mathbf{u}_1^a)+l'(\mathbf{u}_1^a)\\
&\quad+\rho_1(t)\left[\int_\Omega\dot{\mu}(\mathbf{x},t)d\Omega-A_o(t)\right]+\rho_2(t)\left[\int_\Omega\dot{\mu}^2(\mathbf{x},t)d\Omega-B_o(t)\right]\\
&\qquad+\int_\Omega\eta_1(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t)-\hat{\mu}_{\max}(\mathbf{x},t)+\alpha_1^2(\mathbf{x},t)\right]d\Omega\\
&\qquad+\int_\Omega\eta_2(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t)-\hat{\mu}_{\min}(\mathbf{x},t)-\alpha_2^2(\mathbf{x},t)\right]d\Omega\\
&\quad+\int_\Omega\eta_3(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t)H(\mu_{\min}(\mathbf{x},t)+\theta-\mu(\mathbf{x},t))-\beta_1^2(\mathbf{x},t)\right]d\Omega\\
&\qquad+\int_\Omega\eta_4(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t)H(\mu(\mathbf{x},t)-\mu_{\max}(\mathbf{x},t)+\theta)+\beta_2^2(\mathbf{x},t)\right]d\Omega,
\end{aligned}$$

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

$$\mathbf{u}_1^a=-\lambda_1\delta\mathbf{u},\quad \mathbf{u}_2^a=-\lambda_2\delta\dot{\mathbf{u}}.$$

Comment: In a general case of an arbitrary comparison functional an additional system called "adjoint system" appears. This results in necessity of

analysis of this system since adaptation relations are expressed in terms of state variables of both, primary and adjoint systems.

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

$$S = \frac{1}{2}\mathbf{C}\nabla\mathbf{u}\cdot\nabla\mathbf{u},$$

$$G = \int_\Omega S d\Omega,$$

$$\Psi = \frac{dG}{dt} = \int_\Omega \dot{S} d\Omega = \frac{1}{2}\int_\Omega \left(\dot{\mathbf{C}}\nabla\mathbf{u}\cdot\nabla\mathbf{u} + 2\mathbf{C}\nabla\dot{\mathbf{u}}\cdot\nabla\mathbf{u}\right) d\Omega$$

Then the cost functional has a form:

$$\begin{aligned}
&\mathcal{L}(\mathbf{u}, \dot{\mathbf{u}}, \mathbf{u}_1^a, \mathbf{u}_2^a, \dot{\mu}, \rho_1, \rho_2, \eta_1, \eta_2, \eta_3, \eta_4, \alpha_1, \alpha_2, \beta_1, \beta_2) \\
&= \frac{1}{2}a'(\mathbf{u},\mathbf{u}) + a(\mathbf{u},\dot{\mathbf{u}}) - a(\mathbf{u},\mathbf{u}_2^a) + l(\mathbf{u}_2^a) - a'(\mathbf{u},\mathbf{u}_1^a) - a(\dot{\mathbf{u}},\mathbf{u}_1^a) + l'(\mathbf{u}_1^a) \\
&\quad + \rho_1(t)\left[\int_\Omega \dot{\mu}(\mathbf{x},t)d\Omega - A_o(t)\right] + \rho_2(t)\left[\int_\Omega \dot{\mu}^2(\mathbf{x},t)d\Omega - B_o(t)\right] \\
&\quad + \int_\Omega \eta_1(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t) - \hat{\mu}_{\max}(\mathbf{x},t) + \alpha_1^2(\mathbf{x},t)\right] d\Omega \\
&\quad + \int_\Omega \eta_2(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t) - \hat{\mu}_{\min}(\mathbf{x},t) - \alpha_2^2(\mathbf{x},t)\right] d\Omega \\
&\quad + \int_\Omega \eta_3(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t)H(\mu_{\min}(\mathbf{x},t) + \theta - \mu(\mathbf{x},t)) - \beta_1^2(\mathbf{x},t)\right] d\Omega \\
&\quad + \int_\Omega \eta_4(\mathbf{x},t)\left[\dot{\mu}(\mathbf{x},t)H(\mu(\mathbf{x},t) - \mu_{\max}(\mathbf{x},t) + \theta) + \beta_2^2(\mathbf{x},t)\right] d\Omega.
\end{aligned}$$

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:

$$\mathbf{u}_1^a(\mathbf{x},t) = \mathbf{u}(\mathbf{x},t), \quad \mathbf{u}_2^a(\mathbf{x},t) = \dot{\mathbf{u}}(\mathbf{x},t)$$

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

$$\dot{\mu}(\mathbf{x},t) = -\frac{1}{2\rho_2(t)}\left[\frac{1}{2}\frac{\partial C_{ijkl}}{\partial \mu}e_{ij}e_{kl} + \rho_1(t)\right] - \frac{\eta_1(\mathbf{x},t)}{2\rho_2(t)} - \frac{\eta_2(\mathbf{x},t)}{2\rho_2(t)} - \frac{\eta_3(\mathbf{x},t)H_3(\mathbf{x},t)}{2\rho_2(t)} - \frac{\eta_4(\mathbf{x},t)H_4(\mathbf{x},t)}{2\rho_2(t)}.$$

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

Example—remodeling of osteoporotic bone

It follows from the presented considerations, that osteoporosis can be included in the formulation in several different ways. If the real mechanisms responsible for osteoporotic changes are known, they can be expressed in mathematical form and added to the cost functional as additional constraints. Another simpler way which do not require the detailed considerations of the processes at the molecular or cellular level can be proposed when approximate analysis is sufficient, for example when the strength of the osteoporotic bone should be evaluated. In such a case by appropriate definition of the function A_0 one can determine the rate of mass change (in the case of osteoporosis—the rate is negative). In the example presented here such analysis was performed using cell-based model which has been proposed and used in [47] to model the remodeling process of tissue micro-structure. Exemplary results of calculations are presented in Fig. 1 and Fig. 2 where white areas represent

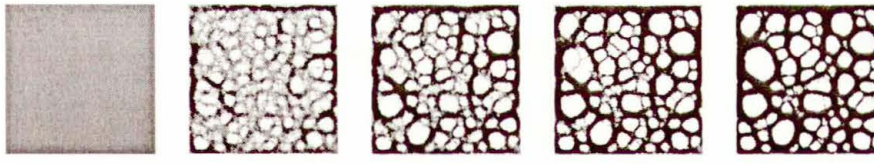

FIGURE 1. Effect of computer simulation of tissue micro-structure formation for a healthy case in a 3 mm×3 mm sample (from left to right). Cell-based model of bone adaptation was used, [47]. Initial material was homogeneous. Uniform pressure was applied in vertical and horizontal directions.

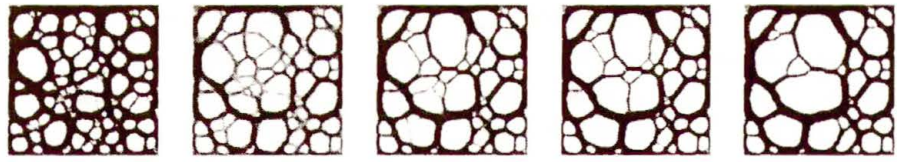

FIGURE 2. Effect of computer simulation of tissue remodeling for an osteoporotic case in a 3 mm×3 mm sample (from left to right). Cell-based model of bone adaptation was used. Uniform pressure was applied in vertical and horizontal directions.

domains of very low material density (voids). Specific values of the parameters that appear in the adaptation law should be evaluated on a basis of clinical observations and experimental works.

5. Conclusions

Several models of bone remodeling including new results concerning mechanosensory mechanisms were proposed in recent years. Since osteoporotic changes in the bone are closely associated with the bone remodeling process, they can be incorporated in some of these models. Model of bone adaptation based on the hypothesis of optimal response enables consideration of osteoporosis in different ways. The simplest one is possible because this model enables to control the total mass of bone under consideration. Another possibility is to include appropriate mathematical formulas by means of Lagrange multipliers.

In practical calculations an isotropic material was considered and the relation between the density of the material and Young modulus was assumed. Another, more advanced option is to consider the evolution of fabric tensor and this way to follow the anisotropy variations due to remodeling process. This problem will be discussed in the forthcoming paper.

For specific comparison functionals a stationarity condition of a cost functional is associated with an extremum but it is difficult to prove in a general case an extremum of an arbitrary functional and this matter should be considered in each individual case separately.

Acknowledgement

Part of this work was supported by Polish State Committee for Scientific Research, grant KBN 3T11F 007 27.

References

1. C. Barrios, L.A. Brostrom, A. Stark, and G. Walheim, *Healing complications after internal fixation of trochanteric hip fractures: the prognostic value of osteoporosis*, J. Orthopaedic Trauma, **7**(5) : 438–442, 1993.

2. C. A. Baud, *Submicroscopic structure and functional aspects of the osteocyte*, Clinical Orthopaedics and Related Research, **56** : 227–236, 1968.

3. M.P. Bendsøe and N. Kikuchi, *Generating optimal topologies in structural design using a homogenisation method*, Comput. Methods Appl. Mech. Eng., **71** : 197–224, 1988.

4. A.L. Boskey, S. Gadaleta, C. Gundberg, S.B. Doty, P. Ducy, and G. Karsenty, *Fourier transform infrared microspectroscopic analysis of bones of osteocalcin-deficient mice provides insight into the function of osteocalcin*, Bone, **23** : 187–196, 1998.

5. A.L.J.J. Bronckers, W. Goei, G. Luo, G. Karsenty, R.N. D'Souza, D.M. Lyaruu, and E.H. Burger, *DNA fragmentation during bone formation in neonatal rodents assessed by transferasemediated end labeling*, Journal of Bone and Mineral Research, **11** 1281–1291, 1996.

6. J.A. Buckwalter, M.J. Glimcher, R.R. Cooper, and R. Recker, *Bone Biology*, J. Bone Jt. Surg., **77A** : 1256–1289, 1996.

7. E.H. Burger, J. Klein-Nulend, and T.H. Smit, *Strain-derived canalicular fluid flow regulates osteoclast activity in a remodelling osteon—a proposal*, J. Biomech., **36** : 1453–1459, 2003.

8. E.H. Burger and J. Klein-Nulend, *Mechanotransduction in bone—role of the lacuno-canalicular network*, FASEB J., **13S** : S101–112, 1999.

9. D.B. Burr and R.B. Martin, *Mechanisms of bone adaptation to the mechanical environment*, Triangle, **31**(2/3) : 59–76, 1992.

10. A. Caplan and B. Boyan, *Endochondral bone formation: the lineage cascade*, [in:] B. Hall, [ed.] Bone, **8** : 1–46, CRC Press, London 1994.

11. D.R. Carter and T.E. Orr, *Skeletal development and bone functional adaptation*, J. Bone Min. Res., **7** : S389–S395, 1992.

12. J.W.M. CHOW, C.J. JAGGER, and T.J. CHAMBERS, *Characterization of osteogenic response to mechanical stimulation in cancerous bone of rat caudal vertebrae*, Am. J. Physiol. **265**(Endocrinol. Metab. 28) : E340–E347, 1993.

13. S.C. COWIN and S. WEINBAUM, *Strain amplification in the bone mechanosensory system*, Am. J. Med. Sci., **316** : 184–188, 1998.

14. S.C. COWIN and D.H. HEGEDUS, *Bone remodeling I: theory of adaptive elasticity*, J. Elasticity, **6**(3) 313–326, 1976.

15. S.C. COWIN, L. MOSS-SALENTIJN and M.L. MOSS, *Candidates for the mechanosensory system in bone*, J. Biomech. Eng., **113** : 191–197, 1991.

16. S.C. COWIN, S. WEINBAUM, and Y. ZENG, *A case for bone canaliculi as the anatomical site of strain generated potentials*, J. Biomech., **28** : 1281–1296, 1995.

17. S.C. COWIN, *The search for mechanism in bone adaptation studies*, Comp. Meth. Biomech. Biomedical Eng., **2** : 125–138, 1999.

18. S.C. COWIN, *On the minimization and maximization of the strain energy density in cortical bone tissue*, J. Biomech., **28**(4) : 445–447, 1995.

19. M. DOBLARÉ, and J.M. GARCIA, *Anisotropic bone remodeling model based on a continuum damage-repair theory*, J. Biomech., **35** : 1–17, 2002.

20. S.B. DOTY, *Morphological evidence of gap junctions between bone cells*, Calcif. Tissue Int., **33** : 509–512, 1981.

21. H.R. DUDLEY and D. SPIRO, *The fine structure of bone cells*, J. Biophys. Biochem. Cytology, **11** : 627–649, 1961.

22. E. EANES, *Dynamics of calcium phosphate precipitation*, [in:] E. Bonucci, [ed.] Calcification in biological systems, pp.2–17, CRC Press, London 1992.

23. C.A. ENGH, J.P. HOOTER JR., K.F. ZETTL-SCHAFFER, M. GHAFFARPOUR, T.F. MCGOVERN, G.E. MACALINO, and B.A. ZICAT, *Porous-coated total hip replacement*, Clinical Orthopaedics & Related Research, **298** : 89–96, 1994.

24. E.F. ERIKSEN, B. LANGDAHL, and M. KASSEM, *The cellural basis of osteoporosis*, Spine State of the Art Reviews, **8**:23–62, 1994.

25. P. FERNANDES, H.C. RODRIGUES, and C.R. JACOBS, *A model of bone adaptation using a global optimization criterion based on the trajectorial theory of Wolff*, Mechanics in Biology, ASME 2000, AMD-Vol.242/BED-Vol.46, pp.173–184, 2000.

26. J. FOLGADO, P.R. FERNANDES, J.M. GUEDES, and H.C. RODRIGUES, *Evaluation of osteoporotic bone quality by a computational model for bone remodeling*, Computers and Structures, **82**:1381–1388, 2004.

27. H.M. FROST, *Changing Views about 'Osteoporoses' (a 1998 Overview)*, Osteoporos Int., **10**:345–352, 1999.

28. H.M. FROST, *Laws of Bone Structure*, Charles C. Thomas, Springfield, IL, 1964.

29. H.M. FROST, *Dynamics of bone remodeling*, [in:] H.M. Frost [ed.], Bone Biodynamics, pp.315–333, Little, Brown, Boston, MA 1964.

30. T.P. HARRINGAN, and J.J. HAMILTON, *Bone strain sensation via transmenbrane potential changes in surface osteoblasts: loading rate and microstructural implications*, J. Biomech., **26**:183–200, 1993.

31. W.H. HARRIS, *Will stress shielding limit the longevity of cemented femoral components of total hip replacement?*, Clinical Orthopaedics&Related Research, **274**:120–123, 1992.

32. R.T. HART and D.T. DAVY, *Theories of bone modeling and remodeling*, [in:] S.C. Cowin, [ed.], Bone Mechanics, pp.253–277, CRC Press, Boca Raton, FL 1989.

33. D.H. HEGEDUS and S.C. COWIN, *Bone remodeling II: small strain adaptive elasticity*, J. Elasticity, **6**:337–355, 1996.

34. T.J. HEINO, T.A. HENTUNEN, and H.K.VÄÄNÄNEN, *Conditioned medium from osteocytes stimulates the proliferation of bone marrow mesenchymal stem cells and their differentiation into osteoblasts*, Experimental Cell Research, **294**:458–461, 2004.

35. W.R. HOFER, G. KRUGLUGER, and L. BARTALSKY, *Is there greater danger of sports injury or osteoporosis caused by inactivity in patients with hip prosthesis? Sequelae for long-term stability of prosthesis anchorage (in German)*, Zeitschrift fur Orthopadie und Ihree Grenzgebiete, **128**(2) : 139–143, 1990.

36. R. HUISKES, *Bone remodeling around implants can be explained as an effect of mechanical adaptation*, [in:] Total Hip Revision Surgery, [ed.] J.O. Galante, A.G. Rosenberg and J.J. Callaghan, Raven Press Ltd., New York 1995.

37. J.X. JIANG and B. CHENG, *Mechanical stimulation of gap junctions in bone osteocytes is mediated by prostaglandin E2*, Cell Commun. Adhes., **8** : 283–288, 2001.

38. D.L. JOHNSON, T.N. MCALLISTER, and J.A. FRANGOS, *Fluid flow stimulates rapid and continuous release of nitric oxide in osteoblasts*, Am. J. Physiol., **271** : E205–E208, 1996.

39. J.A. KANIS, E.V. MCCLOSKEY, D. DE TAKATS, and K. PANDE, *Clinical assessment of bone mass, quality and architecture*, Osteoporos. Int., **9**(Suppl 2) : S24–S28, 1999.

40. Y. KATO, J.J. WINDLE, B.A. KOOP, G.R. MUNDY, and L.F. BONEWALD, *Establishment of an osteocyte-like cell line MLO-Y4*, J. Bone Miner. Res., **12** : 2014–2023, 1997.

41. J. KLEIN-NULEND, M.H. HELFRICH, J.G.H. STERCK, H. MACPHERSON, M. JOLDERSMA, S.H. RALSTON, C.M. SEMEINS, and E.H. BURGER, *Nitric oxide response to shear stress by human bone cell cultures is endothelial nitric oxide synthase dependent*, Biochem Biophys Res Commun, **250** : 108–214, 1998.

42. J. KLEIN-NULEND, A. VAN DER PLAS, C.M. SEMEINS, N.E. AJUBI, J.A. FRANGOS, P.J. NIJWEIDE, and E.H. BURGER, *Sensitivity of osteocytes to biomechanical stress in vitro*, FASEB J., **9** : 441–445, 1995.

43. T.M.L. KNOTHE, J.R. ADAMSON, A.E. TAMI, and T.W. BAUER, *The osteocyte*, Int. J. Biochemistry&Cell Biology, **36** : 1–8, 2004.

44. T.M.L. KNOTHE, *Whither flows the fluid? An osteocyte's perspective*, J. Biomech., **36**:1409–1424, 2003.

45. R.H. KUFAHL and S. SAHA, *A theoretical model for stress-generated flow in the canaliculi-lacunae network in bone tissue*, J. Biomech., **23**:171–180, 1990.

46. T. LEKSZYCKI, *Optimality conditions in modeling of bone adaptation phenomenon*, J. Theoret. Appl. Mech., **3**(37):607–623, 1999.

47. T. LEKSZYCKI, *Modelling of Bone Adaptation Based on an Optimal Response Hypothesis*, Meccanica, **37**:343–354, 2002.

48. V. LEMAIREA, F.L. TOBINA, L.D. GRELLERA, C.R. CHOA, and L.J. SUVAB, *Modeling the interactions between osteoblast and osteoclast activities in bone remodeling*, J. Theoretical Biology, **229** 293–309, 2004.

49. M.E. LEVENSTON and D.R. CARTER, *An energy dissipation-based model for damage stimulated bone adaptation*, J. Biomech., **31**(7):579–586, 1998.

50. J.B. LIAN and G.S. STEIN, *Concepts of osteoblast growth and differentiation: basis for modulation of bone cell development and tissue formation*, Crit. Rev. Oral Biol. Med., **3**:269–305, 1992.

51. X. LIANPING and B.F. BOYCE, *Regulation of apoptosis in osteoclasts and osteoblastic cells*, Biochem. Biophys. Res. Comm., **328**:709–720, 2005.

52. L.N. METZ, R.B. MARTIN, and A.S. TURNER, *Histomorphometric analysis of the effects of osteocyte density on osteonal morphology and remodeling*, Bone, **33**:753–759, 2003.

53. G. LUO, S.C. COWIN, A.M. SADEGH, and Y.P. ARRAMON, *Implementation of strain rate as a bone remodeling stimulus*, J. Biomech. Eng., **117**(3):329–338, 1995.

54. T.N. MCALLISTER, T. DU, and J.A. FRANGOS, *Fluid Shear Stress Stimulates Prostaglandin and Nitric Oxide Release in Bone Marrow-Derived Preosteoclast-like Cells*, Biochemical and Biophysical Research Communications **270**:643–648, 2000.

55. T.N. MCALLISTER and J.A. FRANGOS, *Steady and transient fluid shear stress stimulate NO release in osteoblasts through distinct biochemical pathways*, J. Bone Mineral Res., **14**:930–936, 1999.

56. L.M. MCNAMARA, J.C. VAN DER LINDEN, H. WEINANS, and P.J. PRENDERGAST, *High stresses occur in bone trabeculae under low loads! A study using micro-serial sectioning techniques and finite element analysis*, Proc. 13th Conference of the ESB, Wrocław, Poland, 2002.

57. G.M. MULLENDER, D.D. VAN DER MEER, R. HUISKES, and P. LIPS, *Osteocyte Density changes in Aging and Osteoporosis*, Bone, **18**(3):109–113, 1996.

58. M.G. MULLENDER and R. HUISKES, *A proposal for the regulatory mechanism of Wolff's law*, J. Orthopaedic Research, **13**:503–512, 1995.

59. J.R. NEFUSSI, J.M. SAUTIER, V. NICOLAS, and N. FOREST, *How osteoblasts become osteocytes: a decreasing matrix forming process*, J. Biol. Buccale, **19**:75–82, 1991.

60. B.S. NOBLE, H. STEVENS, N. LOVERIDGE, and J. REEVE, *Identification of apoptotic changes in osteocytes in normal and pathological human bone*, Bone, **20**:182–273, 1997.

61. C. PALUMBO, S. PALAZZINI, D. ZAFFE, and G. MAROTTI, *Osteocyte differentiation in the tibia of newborn rabbit: an ultrastructural study of the formation of cytoplasmic processes*, Acta Anat. (Basel), **137**:350–358, 1990.

62. A.M. PARFITT, *The cellular basis of bone remodeling: the quantum concept reexamined in light of recent advances in the cell biology of bone*, Calcif. Tissue Int., **36**:S37–S45, 1984.

63. A.M. PARFITT, C.H.E. MATHEWS, A.R. VILLANUEVA, and N. KLEEREKOPER, *Relationship between surface, volume and thickness of iliac trabecular bone in ageing and osteoporosis*, J. Clin. Invest., **72**:1396–1409, 1983.

64. A.M. PARFITT, *The cellular basis of bone turnover and bone loss: a rebuttal of the osteocytic resorption—Bone flow theory*, Clin. Orthop., 236–247, 1977.

65. P.J. PRENDERGAST, R. HUISKES, and K. SØBALLE, *ESB Research Award 1996. Biophysical stimuli on cells during tissue differentiation at implant interfaces*, J. Biomechanics, **30**(6) : 539–548, 1997.

66. P.J. PRENDERGAST and D. TAYLOR, *Prediction of bone adaptation using damage accumulation*, J. Biomech., **27** : 1067–1076, 1994.

67. S. QIU, D.S. RAO, S. PALNITKAR, and A.M. PARFITT, *Relationships Between Osteocyte Density and Bone Formation Rate in Human Cancellous Bone*, **Bone**, **31** : 709–711, 2002.

68. K.M. REICH and J.A. FRANGOS, *Effect of flow on prostaglandin E and inositol trisphosphate levels in osteoblasts*, Am. J. Physiol., **261** : C429–C432, 1991.

69. K.M. REICH, C.V. GAY, and J.A. FRANGOS, *Fluid shear stress as a mediator of osteoblast cyclic adenosine monophosphate production*, J. Cell Physiol., **143** : 100–104, 1990.

70. P.G. ROBEY, *The biochemistry of bone*, Endocrinol. Metab. Clin. North America, **18** : 859–902, 1989.

71. G.A. RODAN, *Mechanical loading, estrogen deficiency, and coupling of bone formation to bone resorption*, J. Bone and Mineral Research, **6** : 527–530, 1991.

72. H.C. RODRIGUES, C.R. JACOBS, J.M. GUEDES, and M.P. BENDSØE, *Global and local material optimization models applied to anisotropic bone adaptation*, [in:] P. Pedersen and M.P. Bendsøe, [eds.], Synthesis in Bio Solid Mechanics, pp.209–220, Kluwer Academic Publishers, 1999.

73. C.J. ROSEN *Pre-emptive bone strikes in prevention of osteoporosis*, Lancet, **351** : 927–928, 1998.

74. V. ROSEN and R.S. THIES, *Adult skeletal repair*, [in:] The cellular and molecular basis of bone formation and repair, p.97–142, Springer, New York 1995.

75. H.E. RUBASH, R.K. SINHA, A.S. SHANBHAG, and S.Y. KIM, *Pathogenesis of bone loss after total hip arthroplasty*, Orthopedic Clinics of North America, **29**(2) : 173–186 1998.

76. C.T. RUBIN, D.W. SOMMERFELDT, S. JUDEX, and YI-XIAN QIN, *Inhibition of osteopenia by low magnitude, high-frequency mechanical stimuli*, DDT **6**(16), 2001.

77. P. RUEGSEGGER, P. SERTZ, N. GSCHWEND, and L. DUBS, *Disuse osteoporosis in pationts with total hip prostheses*, Archives of Orthopaedic&Traumatic Surgery, **105**(5) : 268–273, 1986.

78. R. RUIMERMAN, P. HILBERS, B. VAN RIETBERGEN, and R. HUISKES, *A theoretical framework for strain-related trabecular bone maintenance and adaptation*, J. Biomech., **38** : 931–941, 2005.

79. M.J. SHEARER, *Vitamin K*, Lancet, **345** : 229–234, 1995.

80. M. SHIRAKI, Y. SHIRAKI, C. AOKI, and M. MIURA, *Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis*, J. Bone Miner. Res., **15** : 515–521, 2000.

81. V.T. SIKAVITSAS, J.S. TEMENOFF, and A.G. MIKOS, *Biomaterials and bone mechanotransduction*, Biomaterials, **22** : 2581–2593, 2001.

82. T. SUGIYAMA and S. KAWAI, *Carboxylation of osteocalcin may be related to bone quality: a possible mechanism of bone fracture prevention by vitamin K*, J. Bone Miner. Metab., **19** : 146–149, 2001.

83. T. SUGIYAMA, A. YAMAGUCHI and S. KAWAI, *Effects of skeletal loading on bone mass and compensation mechanism in bone: a new insight into the "mechanostat" theory*, J. Bone Miner. Metab., **20** : 196–200, 2002.

84. L.A. TABER, *Biomechanics of growth, remodeling , and morphogenesis*, Appl. Mech. Rev., **48**(8) : 487–545, 1995.

85. N. TANAKA and T. ADACHI, *Lattice continuum model for bone remodeling considering microstructural optimality of trabecular architecture*, [in:] P. Pedersen and M.P. Bendsøe, [eds.], Synthesis in Bio Solid Mechanics, 43–54, Kluwer Academic Publishers, 1999.

86. K. TEZUKA, Y. WADA, A. TAKAHASHI, and M. KIKUCHI, *Computer-simulated bone architecture in a simple bone-remodeling model based on a reaction-diffusion system*, J. Bone Miner. Metab., **23** : 1–7, 2005.

87. O. VERBORGT, G.J. GIBSON, and M.B. SCHAFFLER, *Loss of osteocyte integrity in association with microdamage and bone remodeling after fatigue in vivo*, J. Bone and Mineral Research, **15**:60–67, 2000.

88. S. WEINBAUM, S.C. COWIN, and Y. ZENG, *A model for the excitation of osteocytes by mechanical loading-induced bone fluid shear stresses*, J. Biomech., **27**:339–360, 1994.

89. J. WOLFF, *Das Gesetz der Transformation der Knochen* A. Hirchwild, Berlin, 1892 (Translated by Maquet P., Furlong R., The Law of Bone Remodeling. Springer, Berlin, 1986).

90. G. ZAMAN, S. DALLAS, and L. LANYON, *Cultured embryonic bone shafts show osteogenic responses to mechanical loading*, Calcif. Tissue Int., **51**:132–136, 1992.

91. S. ZHAO, Y.K. ZHANG, S. HARRIS, S.S. AHUJA, and L.F. BONEWALD, *MLO-Y4 osteocyte-like cells support osteoclast formation and activation*, J. Bone Miner. Res., **17**:2068–2079, 2002.