Chapter from the book *Principles of Osteoarthritis - Its Definition, Character, Derivation and Modality-Related Recognition*

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1. Introduction

In 1995 Kuttner and Goldberg defined osteoarthritis as a group of distinct simultaneous diseases, which may have different etiologies but have similar biologic, morphologic, and clinical outcomes. The disease processes does not only affect the articular cartilage, but involve the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles. Ultimately, the articular cartilage degenerates with fibrillation, fissures, ulceration, and full thickness loss of the joint surface (Kuttner & Goldberg, 1995).

Osteoarthritis (OA) is also characterised by chronic degradation of articular cartilage and hypertrophy of bone tissue in joint region. OA results from both biological and mechanical causes which lead to instability of bone degradation and remodeling processes of entire joint organ, including the chondrocytes, subchondral bone and synovium articular (Grynpas et al., 1991).

Precise classification of joint degeneration is difficult. For example, American College of Rheumatology (ACR) classifies osteoarthritis as non inflammatory condition despite the fact, that clinical observation show frequent inflammatory reaction (Pelletier et al., 1999; Wang et al., 2002; Malcolm, 2002) although the latter may actually be a manifestation of a superimposed crystalline arthritis. To evaluate degradation of joint cartilage two methods are the most frequently used: Altman scale (Altman et al., 1986) and Kellegren-Lawrence scale. First method differentiates between primary and secondary effects of degradation without taking into account etiological factors which precise identification allows to prevent development of OA. Kellegen-Lawrence defined a five level scale that is used to evaluate changes in tissue structure based on its images. Unfortunately, if computer tomography images are used then only advanced stages of OA disease can be detected.

Origins of OA are not well known but several hypothesis on its etiology were proposed. Hypothesis focus on changes in biochemical composition and physical properties of synovial fluid that debilitates cartilage nutrition, increased friction of joint surface, impaired blood supply as well as increased number of micro–cracks, especially in subchondral bone. When OA affects hip joint then those changes apply to the femoral head and acetabulum. Two, seemingly equivalent hypotheses about the origins and progress of osteoarthritis are presented in the literature (Radin, 1995). According to the first one changes in the articular cartilage cause
changes in biomechanical properties of the joint and thus in bone tissue. The second one gives the opposite statement and states that degeneration of cartilage is caused by changes in bone tissue. The common aspect of both hypotheses is a finding that degeneration of joint is related to impaired biomechanics of bone–cartilage system. Changes in mechanical properties of each element of the joint involve changes in their structure (Carter & Hayes, 1977; Rice et al., 1988) while loss of cartilage is mainly caused by reduced capability to self-repair.

2. Changes in biological structures in osteoarthritis

Literature lists loss of cartilage, loss of bone tissue and inflammatory reaction of joint capsule and surrounding soft tissue as a pathomorphologic symptoms of OA disease that soften joint surface and finally lead to collapse. Results of research conducted to investigate origins of osteoarthritis focus separately on identification of changes taking place in cartilage that lead to degradation of subchondral bone, and on modeling of processes related to mechanical friction in joint (Wierzcholski & Miszczak, 2006). Second aspect was addressed in a number of papers that focus on changes in metabolism of cartilage tissue as a function of mechanical load (Glaser & Putz, 2002; Radin et al., 1984). It was observed that loss of articular cartilage is caused by reduced capabilities of self-repairing.

Cartilage is composed of dense crossed structure of type II collagen fibers organised in arcade-like structures. Moreover, it is filled with proteoglycans, water, and chondrocytes. There is less than 10% of total volume of cartilage cells that are responsible for tissue formation and remodeling. Migration of chondrocytes is limited by a dense matrix of collagen fibers, moreover, their proliferation decreases with cell age. Therefore, even in the case of a small, superficial injury, chondrocytes located in the injury area die ensuring there is no bleeding, no infection and no proliferation of new cells. Therefore, matrix defects are not filled (Mow et al., 1994; Frost, 1994; Boyd et al., 2000; Buckwalter et al., 2006). In early osteoarthritis, swelling of the cartilage usually occurs, due to the increased synthesis of proteoglycans. This process reflects effort of chondrocytes to repair cartilage damage. As osteoarthritis progresses, the level of proteoglycans drops and becomes very low, causing the cartilage to soften and lose elasticity, thereby further compromising joint surface integrity. Erosion of the damaged cartilage in an OA joint progresses until the underlying bone is exposed. The increasing stresses exceed the biomechanical yield strength of the bone. The subchondral bone responds with vascular invasion and increased cellularity, becoming thickened and dense (eburnation process) in areas under pressure. Initiated inflammatory reaction stimulates development of subchondral cysts (pseudocysts) that accumulate synovial fluid and focus of osseous metaplasia of synovial connective tissue in subchondral bone (Lozada, 2011; Pelletier et al., 1999; Brishmar, 2003).

Modeling of synovial fluid (Wang et al., 2002; Szwajczak, 2001) as well as description of grease and wear-out of joint (Katta et al., 2008) are another issues often addressed in literature. Synovial fluid is formed through a serum ultrafiltration process by cells that form the synovial membrane (synoviocytes). Synovial cells also manufacture the major protein component of synovial fluid, hyaluronic acid (also known as hyaluronate). Synovial fluid supplies nutrients to the avascular articular cartilage. Synovial fluid is a lubricant that minimises friction and consequently wear-out of articular cartilage surfaces and provides the viscosity needed to absorb shock from slow movements, as well as the elasticity required to absorb shock from rapid movements. Loss of cartilage exposes bone tissue that release mineral content to joint capsule and change its tribological properties (e.g. friction and
lubrication) (Glimcher, 1992). Properties of synovial fluid change when lubrication mechanism is altered and simultaneously thickness of the lubrication film is reduced and even reduced in extreme cases (Radin et al., 1995). Since in vivo investigation of synovial fluid is difficult to conduct because its properties change quickly after puncture. Therefore, there is no satisfactory rheological description.

Third group of investigations concerning OA focus on determination of mechanical properties of bone tissue and simulation of remodeling processes of bone, especially subchondral bone. As a result of changes that take place during osteoarthritis organism tries to do everything possible to countermeasure changes and defects of cartilage. The way to do that is to apply bone remodeling processes that lead to increased bone mass and ossify cartilaginous protrusions lead to irregular outgrowth of new bone (osteophytes) on the cartilage–bone junction (Buckwalter et al., 2006; Chen et al., 2001). Remodeling processes are local and result directly from biomechanics of the joint. Increased mass of bone tissue can be observed in areas where load–bearing conditions are changed, i.e. in subchondral bone (Grynpas et al., 2001; Glaser & Putz, 2002).

3. Load model of the hip

Osteoarthritis predominantly involves the weight-bearing joints, including the hips, knees, cervical and lumbosacral spine. Hip joint is one of the biggest and the most movable part of the human body. Its main purpose it to transfer the weight from lumbar spine to lower limbs. From the view of mechanics, hip joint is composed of two rigid elements: acetabulum and proximal femur that are interconnected with a number of ligaments and muscles. External surface of the bone is covered with compact bone and hyaline cartilage that also covers the surface of acetabulum. Cartilage is up to 3mm thick, has high resistance to load and acts as an absorber of mechanical energy while moving. Proper nutrition of cartilage depends on synovial fluid pressure that results from changing load of the hip.

Value of Neck/Shaft angle is another important parameter of the femur. Its value for healthy people equals 150 degrees for newborn babies, approximately 126-128 degrees for adults and 110 degrees for elder people. Pathology may lead to even bigger changes – even reduction up to 90 degrees was observed (Pauwels, 1976). Value of Neck/Shaft angle is crucial for load distribution, stability of the joint and also depends on load and forces that are applied by muscles (Fig.1). Consequently reduction in angle value increases probability of bone fraction.

From the mechanical point of view, hip joint is at the same time under influence of external and internal loads resulting from gravity, muscles and many others. Consequences of loading depend on load value, type of movement, joint geometry, age of the person and mechanical parameters of cartilage and bone tissue. Proximal femur is filled with trabecular bone tissues, arranged according to load directions. In 1892 Julius Wolf stated that every change in the shape and/or function of bone causes changes to bone architecture and its conformation. Investigation confirms that bones adjust its construction according to min-max rule, which states that bone minimise its mass while maximising load–bearing capabilities at the same time. According to Currey (Currey 1984), remodeling and structure of bone tissue is influenced by pressure resulting from muscle contraction. Capability to maintain upright position is a result of mutual influence of skeleton and muscles and that dynamic pressure resulting from muscle work exceeds static pressure from body mass. According to Currey, correct growth and bone structure development is a result of both
dynamic activity of muscles and strength of bone tissue. Consequently, load models of a hip joint presented by several authors (Maquet 1985, Beaupré 1990, Będziński, 1997) take into account loads that result from body mass, muscles and ligaments.

![Fig. 1. Cross-section and stress distribution of proximal femur with different Neck/Shaft (CCD) Angle: A. 128°, B. 85°, 150° (Pauwels, 1976)](image)

Capability to adapt bone’s structure to load condition may have adverse consequences and lead to pathological changes when balance between processes of bone remodeling is disturbed. Osteoarthritis is characterised with cartilage degradation, necrosis of subchondral bone that consequently lead to micro-cracks, damage of the joint and inflammation of synovial membrane. Pathological changes lead to structure alteration and result in modification of mechanical parameters.

4. Mechanical properties of cancellous bone

Numerous works (Yamada & Evans, 1970; Cowin, 2001; Huiskes, 2000; An & Draughn, 2000) that analyse mechanical properties of bone tissue showed that no simple and single relationship exist that can comprehensively describe its properties. This is due to strong anisotropy and the fact that values of mechanical parameters depend on numerous factors, among which bone structure (especially cancellous bone) is one of the most important. Cancellous bone tissue is composed of a three-dimensional network of bone trabeculae having different shapes, dimensions, and orientation. The term “cancellous bone tissue structure” means here the method of organisation of the basic tissue–forming elements. The properties of the whole examined bone tissue depend on the properties of the individual bone trabeculae as well as the way and the number of interconnections between them.
Measurements of the structural properties are based on stereological and topographical methods used to quantify bone tissue histology (Hildebrand and al., 1999). Such information concerns both parameters describing the size and the shape of tested objects, as well as parameters describing their orientation (structural anisotropy).

Mechanical properties of bone tissue depend not only on tissue density, but also on structural parameters which determine the organisation of bone tissue in the tested specimen (Tanaka et al., 2001, Nikodem et al., 2009). Description of the structural properties is based on a whole range of parameters (histomorphological properties) defining mass distribution in a bone tissue specimen Tb.Th, BV/TV, Tb.N, Tb.Sp (Parfitt et al, 1987), orientation of the structure, and its character (SMI parameter). Despite the fact that the number of new parameters that are used to describe bone properties are still growing, precise description of the bone structure and dependency between its parameters is still troublesome.

Table 1 contains values of structural parameters measured for samples of normal and OA from 56 femur heads. OA femur heads were taken from patients aged 66 years on average (range 46-91 years) that were treated with alloplastic hip replacement. All cubic samples by dimension (10x10x10) mm were prepared using a rotary electric saw (Accutom-5, Struers). Samples were stored in 4% formalin solution. All samples were scanned using a microcomputed tomography system (µCT-80 Scanco Medical) providing a spatial resolution of 20 µm. Standard 3D algorithms were used to calculate volume density BV/TV, bone surface density BS/TV and Tb.Sp, Tb.Th, Tb.N (Tab. 1).

| Variable / sample (n=89) | physiology (N) | ostearthritis (OA) |
|-------------------------|----------------|--------------------|
| **Structural properties (3D µCT)** | | |
| Bone volume /total volume (BV/TV) | [%] | 25,32<sup>a</sup> 5,67 | 28,71<sup>b</sup> 6,83 |
| Bone surface/bone volume (BS/BV) | [1/mm] | 13,38 1,97 | 12,99 2,64 |
| Trabecular number (Tb.N) | [1/mm] | 1,42 0,15 | 1,47 0,21 |
| Trabecular thickness (Tb.Th) | [mm] | 0,18<sup>a</sup> 0,02 | 0,20<sup>b</sup> 0,04 |
| Trabecular spacing (Tb.Sp) | [mm] | 0,67<sup>a</sup> 0,08 | 0,64<sup>b</sup> 0,09 |
| Connectivity density (ConnD) | [1/mm3] | 6,49 2,25 | 6,08 3,28 |
| Structure model index (SMI) | [1] | 1,12<sup>a</sup> 0,08 | 1,21<sup>b</sup> 0,09 |
| Mineral density | [mgHA/cm2] | 211,99 73,43 | 207,60 75,31 |

<sup>a-b-p<0,05</sup>

Table 1. Average value of structural parameters (that can be used to quantify structural anisotropy) and mineral density for healthy and OA bone samples
Using a dedicated software (HISTOMER) and bone samples images, we have determined a fabric ellipse parameter (Fig. 2) and a mean intercept length (MIL) parameter (Whitehouse, 1974, Odgaard, 1997). Resulting MIL values can be used as a measure of structural anisotropy. Results show that as disease progresses bone tissue thickens (BV/TV increases), becomes more anisotropic and changes its structure to more plate-like (SMI increases) comparing to healthy tissue.

![Fig. 2. Structure and fabric ellipse for anatomical and osteoartrotical hip samples](image)

Literature contains a number of papers that compare bone to engineering materials, searching for similarities with properties of bone tissue. Consequently, the literature contains claims that bone can be seen as a two-phase composite material (Carter & Hayes, 1977). That material consists of a mineralised matrix made of collagen fibres characterised by a low elastic modulus and hydroxyapatite (HA) crystals with a high elastic modulus. The modulus of elasticity of two-phase materials is usually located between the values of the elastic modulus of the phases, whereas composite strength is higher than the strength of the components tested individually. Another approach is to compare bones to glass laminate, where fibreglass is the high-modulus material (similarly to the HA crystals), whereas epoxy resin is the low-modulus material (similarly to collagen) (Currey, 1984). According to Jackson, bone belongs to the group of biological ceramics which, like all ceramic materials, are brittle and rigid. Such materials cause measurement problems (samples are difficult to grasp and loading causes small displacements, which require sensitive measuring instruments). However, these approach has several unquestionable advantages, including the ability to use standard theories that assume linear flexibility and the ability to use classic methods of measurement of the mechanical properties, whose results show high repeatability.

Definition of stiffness for trabecular bone is difficult due to the fact that it is composed of 3-dimensional grid of trabeculae and empty space between them. Although, trabeculae itself can be assumed homogenous and has some stiffness (called material stiffness), it is infeasible to measure it as a single trabecula is too small. Therefore, a larger structure, that consists both of several trabeculae and space between them, is usually measured and so-called structural stiffness is determined (Turner & Burr, 1993).

Mechanical properties of the bone tissue are usually determined in strength tests conducted in in vitro condition. Strength of the tissue is a complex function of multiple parameters such as structure of the tissue, level of organic contents as well as properties of the sample (e.g. sample size and preparation procedure) and tests procedure (e.g. test condition) (Turner & Burr, 1993; Nikodem & Ścigala, 2010). As a result of strength experiments in linear region Young and Kirchoff modulus, Poisson ratio, strain and yield stress can be calculated (Fig.3).
Fig. 3. A. Stress-strain dependency and mechanical parameters such as: Young modulus, ultimate and yield stress and strain energy U, B. changes in integrity of cancellous bone sample during different phase of uniaxial compression test

Table 2 presents selected mechanical parameters (directional stiffness (E1, E2, E3), yield stress and stain energy) evaluated during uniaxial compression testing of femur heads taken from patients that were treated with allopathic hip replacement. It follows that both values of mechanical and structural parameters increase for OA samples.

| Variable / sample (n=89) | physiology (N) | osteoarthritis (OA) |
|--------------------------|----------------|---------------------|
| Mechanical properties    | Unit           | value   | SD     | value   | SD     |
| Modulus of elasticity (E1) [MPa] | 147,41     | 67,60   | 143,15 | 81,38   |
| Modulus of elasticity (E2) [MPa] | 157,36     | 118,81  | 89,32  | 47,15   |
| Modulus of elasticity (E3) [MPa] | 174,26     | 131,96  | 95,48  | 62,63   |
| Yield strength (σul) [MPa] | 11,36       | 3,96    | 12,68  | 6,97    |
| Stain energy (U) [mJ/mm²] | 30,98a      | 2,15    | 27,92b | 1,79    |

a-b-p<0.05

Table 2. Average values of mechanical parameters for samples from both normal and OA bones
Precisely, OA samples are characterised by higher BV/TV, which is caused by more complex and thickened structure (Tb.N, Tb.Th, ConnD). This bone concentration (especially in subchondral region) is relevant to gradual loss of cartilage and change in load bearing conditions. Osteoarthritis has several phases: formation of osteophytes or joint space narrowing, appearance of subchondral cysts, bone deterioration, repair and remodeling. Despite of higher bone volume, lower value of mechanical properties (30%) were observed. In this case, we didn’t notice any increase in mineral density proportional to increase in BV/TV value (the average value was even smaller than in control group). Based on measurements we can state that changes in BV/TV (especially in the second phase) are mainly correlated with deterioration of trabeculae and do not depend directly on metabolism of mineral components. Reduction in cartilage mass leads to increased friction between elements of the joint and consequently to irreversible deformation of bones and changes in parameters of bone tissue (Fig. 4).

![Fig. 4. Changes in stress values for human hip joint (A). and the shape of femur head and acetabulum (B), as a result of osteoarthritis (Pauwels, 1976)](image)

5. Modeling of bone tissue

Modeling of bone structures within the joint, including joints affected by osteoarthritis, is achieved by simulating formation and remodeling of bone tissue. Most often simulations of bone tissue remodeling are based on calculations using finite elements method (Będziński & Ścigala, 2011). Two approaches that differ in presentation of bone tissue are mostly used. Results are used for the same purpose – estimation of how disease influences mechanical behaviour of bone tissue. First approach assumes that bone tissue, can be treated as a continuous material. In that case it is possible to calculate remodeling stimulus as a function of stress or strain distribution in daily time period. Stress and strains can be calculated using fundamental relationships of solid mechanics. In most situations it is assumed that the value of remodeling stimulus is proportional to the density of strain energy (Carter, 1987, Carter et al., 1996; Cheal et al., 1985). Sometimes it is also assumed that this value is a function of principal stress or strain values (Cowin et al, 1985; Hernandez et al., 2001). There are also proposals to make a remodeling stimulus dependent on the signal received by a network of osteocytes deployed in mineralised bone matrix (Huiskes et al., 1987; Weinans, 1999). Simulation of bone remodeling itself is realised by changing density and mechanical properties of each finite element of the model. Value of this change is in some way proportional to the calculated previously stimulus (Carter, 1987; Lanyon, 1987). Models that
fall into this group can be described as macro-scale models and rise several objections (Będzinński & Ścigala, 2010). The most important is assumption that the tissue is a continuous material and lack of possibility to extend the model with additional parameters that are structure–related and can stimulate remodeling process. In case of compact bone, that kind of assumption is possible to made without significant restrictions. However in case for cancellous tissue, which is a high porosity material (precisely, it is a complex spatial arrangement of trabeculae), this kind of modeling represents a significant simplification. In real bone tissue control of the remodeling process is realised by a network of bone cells. In that case, osteocytes play a role of sensors, which can detect change of load distribution in whole volume of bone tissue. This signal is next transferred to the network of bone lining cells, and they differentiate in osteoclasts and osteoblasts. Those cells are responsible for change of bone mass and structure, so real remodeling process occurs only at the surface of trabeculae. The mechanical signal that stimulates cells deployed in osteocyte network of compact and cancellous bone trabecula is related to the movement of the inter-osseous fluid that fills cavities and canaliculi of the network (Bagge, 2000; Będzinński, 1997; Bartodziej & Ścigala, 2009; Będzinński & Ścigala, 2003; Jacobs et al., 1997). By default macro–scale models of bone formation and remodeling do not take these phenomena into account and for some of them, due to restrictions imposed by design, it is even impossible to extended the model. Second group of models consider actual structure of bone and include a complex system of bone trabeculae and are referred to as micro–scale models (Będzinński & Ścigala, 2010). Models from this group usually assume that the stimulus of remodeling process is a function of unequal distribution of stress in bone structure. Gradient of stress is in this case proportional to the stimulus. Stress distribution is calculated only on the surface of trabeculae and changes in bone mass is proportional to the stimulus. Formation and resorption of mass is also modelled on the surface of trabecular bone. In this respect they are more applicable to the rebuilding processes that take place in real bone. On the other hand, this group of models also does not consider influence of inter-osseous fluid flow on bone tissue remodeling processes, however it is possible to take this parameter into account in simulation because of strict definition of trabeculae in model. Formation and remodeling of bone tissue is closely related to self–repairing processes of tissue structures. Micro–cracks that appear in bone structure are repaired through resorption of bone material in the damage area and formation of new bone structure in this place. Situation changes when bone is overstrained (e.g. due to pathological strains) number of micro–cracks in bone structure may be so large that self–repairing capabilities are insufficient. In such situation micro–cracks accumulate and influence remodeling processes. Process of mechanical degradation of bone tissue should be also considered by micro–scale remodeling models through simulation of micro–cracks of bone trabeculae. For macro–scale models it can be taken into account through extended and more complex representation of remodeling stimulus (Burr, 1985; Doblare & García, 2001; Martin, 2002). Formation and remodeling of bone tissue are slow processes that are influenced by cyclic loads. Therefore, in most simulations of both processes, the models of stress and strain are evaluated for relatively long time periods. Assuming simulation is an iterative process the most frequently used time period equals 24 hours. This is due to the fact, that one day is a period of time when processes related to long–time stresses, such as creep and relaxation, occur. These processes should be taken into account when calculating stress and strain values for successive iterations of the simulation, irrespectively from the bone model used.
6. Simulation of formation and remodeling of bone structure

Micro-scale simulation procedures usually use an algorithm based on Tsubota model of remodeling processes (Ścigala et al., 2004; Będziński & Ścigala, 2011; Tsubota et al., 2002). The main factor that influences the value of remodeling stimulus in this model is uneven distribution of stress. This model assumes that value of this stimulus can be calculated as:

\[
\Gamma = \ln \left( \frac{\sigma_c}{\sigma_d} \right)
\]

where \( \sigma_c \) is a stress value in point \( C \) (that is currently analysed), and \( \sigma_d \) is a value that depends on stress in a precisely defined neighbourhood of point \( C \).

This model also assumes that only stress on the surface of bone trabeculae is vital for remodeling processes. In other words, the osteocytes network, is evenly distributed in volume of trabeculae. However signal collected by those cells is proportional only to the distribution of stresses on surface of trabeculae. Assumption is justified, as cell processes (bone formation and deposition) that are elementary of remodeling of bone mineral matrix take place only on the surface of trabeculae. Additional assumptions determine the area of bone tissue that contain cells that will respond to remodeling stimulus. According to Tsubota (Tsubota et al., 2002) this area is assumed to have a circular or spherical (for 3D analysis) shape of radius \( L_L \) (Fig.5). Response of bone cells to the signal is limited in distance and radius of presented circular area. This is basically maximal distance from which bone cells can detect signal for remodeling.

![Fig. 5. Determination of local distribution of stress stimulus \( \Gamma \)](image)

As described above analysis focus only on the surface of bone trabeculae and inner area of circular/spherical shape. Value of remodeling stimulus in point \( C \) depends on stress in each point \( R \) of the analysed area. Each point \( R \) influences the value of stimulus with different coefficient that depends on the distance between points \( C \) and \( R \). Presented model determines this coefficient using a linear weight function that takes maximal value in point \( C \) and minimal value for points located on the edge of circular region:

\[
\sigma_d = \frac{\int w(L) \sigma_R dS}{\int w(L) dS}, \quad w(L) = \begin{cases} 
1 - \frac{L}{L_L} & \text{where } 0 < L < L_L \\
0 & \text{where } L > L_L 
\end{cases}
\]
where $S$ is the analysed area, $L$ is a distance between $C$ and $R$ points, $\sigma_R$ is a stress value in point $R$ and $L_L$ is a radius of the analysed area.

Initial finite element model (FEM) that is used to simulate remodeling processes is composed of a regular grid of finite elements where two groups of elements can be differentiated: bone trabeculae and space between bone trabeculae. For each type of element a different material model was defined. For elements forming trabeculae we use a linear elasticity material with properties typical for bone mineral matrix. Elements that form inter trabecular spaces are assumed to be composed of linear elasticity material, with mechanical properties of very low values (actually as low as possible without model instability). Model is constructed by ring shaped patterns randomly placed over this grid. Each ring element represents bone trabeculae, while its inner, empty area models space between trabeculae. Random and dense placement according to this pattern creates an initial model that has isotropic and homogenous pseudo–trabeculae structure (Fig.6).

![Fig. 6. Example of a initial model used in FEM modeling to simulate cancellous bone remodeling](image)

A typical simulation procedure that models remodeling processes takes an initial FEM model and calculates value of remodeling stimulus $\Gamma$ for each finite element that coincident with surface of bone trabecula. Verification is the next step of a modeling procedure. In Tsubota model, it is assumed that formation and resorption processes are initiated when the value of remodeling stimulus exceeds the threshold (Fig. 7).

![Fig. 7. Formation and resorption procedures (M) as a function of remodeling stimulus ($\Gamma$)](image)
When value of the remodeling stimulus for a finite element is greater than $\Gamma_U$, then bone formation processes are initiated and new bone material is created on the trabeculae surface. On the other hand, when remodeling stimulus is smaller than $\Gamma_L$ threshold, bone degradation processes are started and trabeculae material degrades. In FEM model both processes are implemented through changes in material of the finite element. For the first case (i.e. bone formation), material of the neighbouring elements is changed from space between trabeculae to bone trabeculae. For the second case, material of currently analysed element is changed to space between trabeculae. If remodeling stimulus is between thresholds $\Gamma_L$ and $\Gamma_U$ then no changes to the structure are made (Fig. 8).

Figure 9 presents scheme of a basic simulation procedure used to model processes that happen in cancellous bone. During each analysis of formation and remodeling of cancellous bone all the loads that characterise daily physical activity are determined but only these are taken into account that have cyclic character. Simulator takes initial bone model with isotropic and homogenous trabeculae structure and applies selected loads. It is worth to note that every cyclic load is substituted with a few static loads that are selected in order to follow changes that are specific to cyclic load simulated and model it with desired precision. In each case calculations are conducted using the FEM method and applied to finite elements selected from the model (as described above calculations only involve trabeculae from the bone surface). For each element selected, value of von Mises stress is calculated. Calculated data is stored in a table, that relates finite element with its stress value. The next step selects radius of circular (or spherical) area that is used to determine finite elements that will be taken into account when mechanical stimulus of remodeling is calculated. The selection of radius depends on the size of the FEM model. For each element in the aforementioned table parameters $c$, $\sigma$, and value of mechanical stimulus $\Gamma$ are calculated and stored.

Next step of the simulation procedure decides which finite element bone material (i.e. trabeculae or space between trabeculae) will be modified due to stimulus. Elements stored in the table are analysed once again and for each of them, it is verified whether calculated stimulus exceeds threshold values $\Gamma_L$ or $\Gamma_U$. If for a given element threshold is exceeded, element is put to the a set of elements for which bone formation or resorption processes will occur. After this procedure mechanical properties of all the selected elements and consequently, structure of the trabeculae, are modified. Modified bone model is then used as an initial model in the next iteration of the simulation procedure. Iterations are run as long as number of elements selected for bone formation or resorption process (number of elements in aforementioned set) is smaller than the threshold assumed. Threshold value depends on the complexity of the model and total number of finite elements.
Simulation procedure described above contains adaptive functions that modify distribution of mechanical stimulus on the surface of trabeculae, based on inter-osseous fluid flow. Basic parameters calculated from analysis of fluid flow include significant differences in flow pressure near the ends and middle of trabecula. According to the assumption that intensity of remodeling processes depends on stress values resulting from fluid pressure that influences bone cells in each trabecula, value of remodeling stimulus should depend on that pressure and be different for cells located in different regions of the same trabecula.

In the simulation procedure first module is responsible for evaluation of changes in stimulus values related to inter-osseous fluid flow. At the beginning this module carry out identification of elements at the ends of each trabecula. First each element on the surface of trabeculae is identified using previously prepared table and all surrounding elements are selected (see Fig. 10). For each element from selected group it is verified what kind of material it represents. If most of surrounding elements are defined as material of trabecula, central element is assumed to be at the end of trabecula. In other case, when surrounding elements are mostly inter-trabecular space, it is decided that the central element is located in the middle of trabecula. Number of surrounding elements investigated was estimated experimentally, by carrying numerous simulations with various trabecular structures.

The simulation procedure presented above enables to analyse formation and remodeling processes of bone trabeculae comprehensively. However, this simulation method has large computational overhead which makes this approach impractical for large bones and extended trabeculae structures.
Aforementioned approach can be simplified in several ways. The example presented here simplifies simulation procedure by modifying the way deformations and stresses in trabeculae are analysed. Initial model was created as described previously and has isotropic and homogenous structure. Next this model was used to simulate loading from the top edge while bottom edge was fixed (i.e. mounted). Measured values of force varied from high values on one side of the sample to the small on the other side (Fig. 11).

Fig. 10. Correction of value of stimulus of remodeling

As a result of analytical analysis of the model and using Huber-von Mises hypothesis, distribution of reduced stress was calculated. Values of stress was then modified in a similar way as was used for values of remodeling mechanical stimulus – i.e. to take into account distribution of inter-osseous fluid pressure.

Figure 12 presents results of these computations. Analysis of the resulting distribution lead to the observation that stress values are proportional to the remodeling stimulus calculated in the simulations. This means that it is possible to point out areas of the bone model that will be affected with bone formation and bone resorption. The area on the right side of the model is characterised with low values of von Mises stress because of low values of forces applied to the right upper corner of the sample. Values of stress increase gradually from right to left according to applied load. Looking at Fig. 12 it is obvious that element with high values of von Mises stress form structures very similar to the real trabecular structures. It is possible to observe structures similar to the thick, strong trabecular structures near to the left part of model, mostly directed vertically. In the middle part of the model, thickness of trabeculae decrease and more inter trabecular spaces can be observed. Trabeculae are not
only vertically arranged but we can also observe inclined structures and small disconnected structures near the right side of the sample.

Fig. 12. Von Mises stress distribution of analysed structure

Above analysis shows that von Mises stress value is a good parameter for description of trabecules loading. Group of elements characterised with von Mises stress value higher than minimal value estimated previously contains almost all the elements that exist in real trabecular structure. This gives an opportunity to simplify computational complexity of the simulation by using different method of calculating remodeling stimulus. This approach requires defining quantitative relation between load-bearing structure of trabecular bone determined with basic (also taking into account flow of inter-osseous fluid) and simplified procedure.

We have carried on several analyses to evaluate this relation. This was done with different bone models that were composed of a small number of elements in order to speed up computations. Basic result of this approach, for the case of a rectangular model loaded in exactly the same way as described previously, is presented in Fig. 13. Using both standard and simplified methods very similar structures of trabeculae were obtained. Both structures have two main and one additional load-bearing structure. Vertical bearing structure, composed of thick trabeculae, can be found in the area that was relatively heavily loaded (A). Second of the main bearing structures is composed of two trabeculae – diagonal (B) and vertical (C). This is a result of maximizing capacity to carry stress and reducing the mass simultaneously. Diagonal trabecula carry stress from the right side of the bone model through one single and tight structure. Additional load-bearing structure is an auxiliary structure that is composed of trabeculae of small size and mostly horizontal arrangement (D); only some trabeculae are arranged vertically and only few have diagonal orientation.

Analysis show that all the trabeculae that exist in bone structure generated with standard simulation method also appear in structure calculated using simplified simulation. Location of end points of all trabeculae from both simulation procedures differs slightly, by no more than two finite elements. Since in FEM models grid of finite elements is dense and trabeculae are relatively large comparing to a single element (A, B and C structures), it is justified to state that error of using simplified simulation method is small and negligible. For trabeculae of relatively small size (structure D) error in location of trabeculae ends is even smaller and
only in some situation exceeds size of a single finite element. Thickness of trabeculae resulting from both simulation approaches differ mainly in the basic structures with the biggest difference in B and C and small in A structure. The biggest differences concern basic structures with complex shape that carry relatively low load. For a small spread load standard definition of a mechanical stimulus allows for more precise definition of real element structures that are responsible for load-bearing. Using simplified definition it is always needed to be aware of slight overestimations of load-bearing size. In a final description of the structure those overestimates will not have significant influence on load-bearing properties – some areas of the resulting structure will be characterised with slightly smaller values of stress but will still serve mechanical function in exactly the same way as in structures resulting from standard simulation method.

Fig. 13. Comparison of structures developer form the same initial model with classic and simplified algorithm

The result depends significantly on the density of ring-shaped structures deployed in initial model and the density of finite elements grid. Density of the grid for all the models presented in this chapter was high – each pixel from the figures presenting trabecular bone structure represents a single finite element. In case of three-dimensional models density of spheres is significantly smaller, so this small density is only result of great number of element in three-dimensional models and long time of calculations. Ratio of the size of ring-shaped structure versus size of the whole model is a significant parameter that influence simulations.

Figure 14 compares results of remodeling simulations run for the same bone model but different total number of finite elements in the FEM model. In each case model was loaded with the same load but different load-bearing structure were formed. For all cases load-bearing structure was created in the part of the model that was heavy loaded. For models that used sparse grid of finite elements (A and B) this structure consist of thick, long and vertically or diagonal oriented trabeculae. For models with dense grid (C and D) structure is also composed of similar trabeculae but number of trabeculae is much larger. Diagonal trabeculae dominate in parts of the model that were less loaded with separate (unconnected) elements for the case when dense grid of finite elements was used.
Fig. 14. Comparison of structures from the same initial model with various density of finite elements mesh and initial rings (A - 50 elements along longer side of model, B – 75 element, C – 100 elements, D – 200 elements)

Use of simplified procedure for modeling formation and remodeling processes of trabecular bone is justified, possible and gives correct results. However, in order to get correct results simulation procedure has to meet several initial conditions and be constantly monitored. Precisely:

1. initial FEM model should be composed of a large number of finite elements and the ring-shaped structure with size similar to size of real tabeculae,

2. density of the initial model has to be large, which means that number of elements that represent bone trabeculae has to be much larger than the number of elements that represent space between trabeculae. Complying this requirement will allow to get load-bearing structures without the need for additional bone mass being add to the model during simulation. This is also important from the practical point of view as modification of the model extend simulation time,

3. threshold value of the stress that is used to decide which elements are kept or removed from the model should be selected on the individual basis for each model. It is recommended to run a standard simulation procedure for a few iterations and save it for comparison. Then simplified procedure should be run with different value of this parameter until the resulting structure has no significant differences from the one saved. When proper value of the parameter is found successive iterations are run,

4. simplified procedure requires use, of an additional correction module that will allow to eliminate unconnected structures from the model, as these have no influence on the load-bearing.
Fig. 15. Algorithm of bone remodeling simulation

Figure 15 presents a general structure of the simplified procedure for simulation of formation and remodeling of trabecular bone structures. Figure presents all the computational units required with correction and micro-cracks analysis modules that are
additional with respect to standard Tsubota model. Correction module is designed to take into account creep and relaxation of stress in bone structure. This is based on the analysis of number of load iterations that were already applied to the modelled structure and resulting range of deformation and stress changes. Number of load iteration is calculated assuming that each cycle of loading procedure consist of constant number of load iterations, represents full period of time and it is possible to determine number of iterations of particular type. Change in the deformation values is calculated based on the number of iterations and using Currey model for creep while change in stress results from stress relaxation model by Sasaki (Currey, 1965; Sasaki & Enyo, 1995). Second module is responsible for analysing origins and accumulation of cracks in trabecular structure and also draws from information about total number of load iterations already applied to the model.

At the beginning of each iteration the total number of cycles from the beginning of simulation is calculated and stored in a table that also contains finite element identifiers and stress value calculated for last iteration performed. This table only stores information about elements that characterize bone material. At the end of each iteration, elasticity modulus value (that is related to damage accumulation) is calculated based on stress value and number of cycles. New value of elasticity modulus is calculated for each stored in the table.

Next, examination of new elasticity modulus value allows determination of group of elements to which analysed element belongs to. This is based on threshold value of elasticity modulus that is typical for bone tissue. If actual value of elasticity modulus is lower than threshold, status of the element is changed and material properties are changed so that element will now represent inter trabecular space. In that way, micro-cracks can be introduced into the model and in further iterations damage accumulation may progress. Process of mechanical degradation can develop further in three different ways:

1. micro–crack in a bone trabeculae may lead to increased load in that trabeculae and possibly in neighbouring trabeculae. In such a case stress values increase leading to increased mechanical stimulus of bone remodeling. When value of stimulus exceeds upper threshold defined in Tsubota model, bone formation process is initiated on the trabeculae surface and usually also in the vicinity of the micro–crack. Consequently, bone repairs itself and trabeculae are reconstructed in a shape that is very similar to the original one (prior to crack). In real remodeling processes reconstructed element is a new bone material. Therefore, in simulations we erase information about number of load iterations that were applied to the finite element that contains reconstructed bone. This is a self-remodeling scenario,

2. creation of a micro–crack may not lead to significant change in stress in affected trabeculae nor in neighbouring ones. If this happens then self-remodeling processes are not initiated and no new bone material is created in the vicinity of the crack. However, stress values near the crack have increased and speed up wear–out of neighbouring bone material with consecutive load iterations. Consequently, value of elasticity modulus for elements located near the crack decrease and crack evolves. This usually leads to excessive load of neighbouring trabeculae and new micro-cracks that spread across them. As number of micro–cracks increases remodeling processes are initiated from time to time. Usually, degradation of bone structure progresses faster than remodeling leading to accumulation of micro–cracks,
3. several micro-cracks may appear simultaneously leading to significant change in elasticity modulus in several neighbouring elements. In such a case crack evolves immediately across the single of a few, neighbouring trabeculae. When trabeculae brakes, both parts are relieved and values of stress in finite elements that model them drops to minimal values. This initiates resorption processes and in successive iterations elements will represent space between bone material. Such situation also increases stress in neighbouring trabeculae that in turn initiates bone formation processes and leads to creation of new bone trabeculae. New trabeculae have different shape compared to trabeculae that broke. In some cases, when several micro-cracks appear in neighbouring trabeculae, some part of the bone mass may become disconnected from the load-bearing structure. Such structure is detected by dedicated module of the simulation procedure and removed from the model (elements that represent this mass are modified to represent space between bone mass). Relatively large cavity in the bone structure of this type, initiates formation of new bone mass in surrounding trabeculae and construction of new load-bearing structures. This scenario presents a remodeling of bone structure stimulated by mechanical degradation.

Analysis of formation and remodeling of trabecular structures was carried out using model of normal femur bone. Model of femur proximal epiphysis was created using the same algorithm as in previous case. Loading that is typical for stance phase of gait (according to Beaupré) was applied to the model.

Analysis of remodeling process for model of intact femur bone shows significant deposition of trabecular structures in the proximal part of grater trochanter – region marked as A (Fig. 16). Bone reposition in this area results from simplified loading model in which muscle force (from hip abductors) was applied to the middle part of lateral surface of greater trochanter. In real hip joint there are several muscle forces. One of the muscles is attached in the upper part of this surface. Because of that in real bone that kind of low density trabecular structure are not observed.

Fig. 16. Successive iterations (from left to right) of bone formation and remodeling processes for trabecular structures in model of femur bone
Trabecular structures in femur head (marked as B on Fig. 16) changed significantly. This is clearly seen for trabeculae located close to articular surface as they become longer and diagonal arranged. In the central part of the femur head directed structures are not so well visualized. Trabecular structures in the region of lesser trochanter (marked as C in the Fig. 16) also changed significantly and two main load-bearing structures can be seen. First of them is a structure placed in the close range form layer of compact bone. It’s a dense structure with almost even distribution of trabeculae. Second structure, is characterised by highly directed trabeculae – this structure connects greater and lesser trochanter. Trabeculae can be characterised as inclined structures and, in case of supportive structure, trabeculae are directed horizontally.

In the case of pathologically deformed femur, we can observe significant differences in trabecular structures distribution in comparison to the model of intact femur bone. In first part of simulation we can observe significant deposition of trabecular structures in the distant part of the model, especially in central region (Fig. 17 A). Deposition of that kind can be observed also in the proximal part of grater trochanter, as well as in the lower part of femur head (Fig. 17 B). Trabecular structures in the femur head and most part of proximal epiphysis of femur are not modified significantly, still ring shaped structures from initial trabeculae distribution are visible (Fig. 17 C). During remodeling the trabecular structures in the femur head become more directed (Fig. 17 D). However, trabecular structures are still dense. Most of trabeculae are significantly thicker than in other areas and length of those trabeculae is small. In upper and central part of femur neck, small deposition of trabecular structures can be observed (Fig. 17 E). In the main part of inter – trochanter region it is possible to observe gradual deposition of directed structures, in form of two arches crossing each other and connecting lateral and middle part of bone (Fig. 17 F). After next step of simulation it is possible to observe clearly formed marrow cave (Fig. 17 G). Directed structures in the inter – trochanter region are also clearly formed (Fig. 17 H). Similarly, in the head of femur we can observe more and more directed trabecular structures.

Fig. 17. Successive iterations (from left to right) of bone formation and remodeling processes for trabecular structures in model of pathologically deformed femur bone
It follows that in the case of deformed femur, pathological distribution of trabecular structures can be characterised by much more directed structures than in case of intact femur. In most parts of the bone deposition of trabeculae can be observed. However cancellous tissue is still dense in the head of femur. In some parts of this area porosity, of trabecular structures is even lesser than in model of intact bone.

7. Conclusion
Presented work consists both experimental and numerical analysis. Value of each part can’t be underestimated. Experimental investigations are essential for understanding of connection between trabecular structure and mechanics. First look at any bone tissue leads to conclusion that it is really complicated result of biological processes of tissue differentiation and formation. Details of this complicated structure, which have significant influence on bone properties, can be analysed at different levels – whole bone, bone tissue, bone structure, bone trabecule, trabecula internal structure, bone cells. One way to understand and describe processes that take place in bone tissue on different levels is to introduce new parameters and relationships between them. Unfortunately, in many cases, number of measured parameters – structural and mechanical – is so large that the bone description becomes so complex that people start to wonder if it is still useful and necessary. However, the amount of data is priceless for preparation of bone models and simulation of biological processes that take place inside of bone tissue. Moreover, detailed description of structure is necessary to understand bone tissue mechanics, which is needed in case of surgical treatment, and to understand mechanics of pathology. From that point of view, we are unable to understand in details, complex behaviour of bone without experimental investigations, and we are unable to simulate trabecular structures comprehensively without data collected during experiment.

Numerical simulations give us a wider view at bone tissue as a living organ. Number of processes that we can model nowadays allow us to observe changes in structure as a result of changes in loading conditions. Simulations allow introduction of patient related disturbances to modelled process easily (e.g. deformation of bone, changes in daily physical activity, changes in mass of patient, changes related to treatment, etc.). We can predict with some precision what kind of structures will exist in bone and whether they will lead to pathology or recovery. Observation how trabecular structures form give us perspective an how our skeleton develops and how it is influenced by mechanical parameters. Finally such analysis, should develop analytical models of bone tissue. Both, experimental and numerical work, take significantly long time to prepare and to conduct. Full understanding of ongoing process will be possible at the level of generalized model.

Presented results show how different is mechanical behaviour and internal structure of pathological bone tissue in femur bone comparing to healthy. Changes are not only related to the values of parameters evaluated for both intact and pathological bone, but also bone structure is affected significantly. Clearly there is a relationship between bone structure and mechanics that can be described using the same functions for both healthy and OA bones, however parameters and constants in those functions will be different for both cases. Numerical simulations allow analysis of how distribution of mechanical parameters lead to different structure in case of intact and pathological bone. We can observe details of process of forming ‘correct’ and pathological structures. We can easily detect regions in bone where changes are significant, and the regions where changes are irrelevant. It is even possible to
analyze relationship between change in particular mechanical parameters and bone response to that changes which enables estimation of loading conditions which will result in bone structure changes that will be the most dangerous to patient.

Changes in bone structure and behaviour during development of osteoarthritis are not fully understand. Presented research is strongly focused on biomechanics of bone tissue, and in simulations mostly biomechanical parameters were taken into consideration. Relationships, between bone structure and mechanics, loading and structure formation or remodeling were described as equations or models.

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Yamada H., Evans F.G. (1970). *Strength of biological materials*, Williams & Wilkins, ISBN: 0-6830-9323-1, Baltimore MD
This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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