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# GROWTH, ADAPTATION AND AGING OF THE SKELETAL SYSTEM

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Our skeletal system requires a certain amount of maintenance in order to withstand the external loading appropriately for a long period. This maintenance is performed by specialized cells; i.e., osteoclasts and osteoblasts, which continuously resorb and rebuild the bony matrix in small packages. It is presently not known how these cells are being signalled such that they undertake appropriate actions and resorb damaged (weak) bone and replace it with a new. It is well recognized that mechanical loading has an important effect on the cellular events. Mechanical load distribution in bony structures can be calculated using the finite element method. In addition, the effects on growth, adaptation and degeneration due to this loading can be incorporated into these models as well. That gives the opportunity to study the interaction between biological and mechanical aspects in bone tissue. In this study a few examples of such an interaction are simulated numerically and their biological or clinical consequences are discussed.

*Key words:* bone adaptation, bone resorption, computer model

## 1. Bone metabolism and mechanical loading

Each year in the order of 10 to 20 percent of the entire skeleton is rebuilt (turnover), that is to say, resorbed by osteoclasts and deposited by osteoblasts. This process can be mechanically viewed as the skeletal maintenance. Turnover is required to prevent damage accumulation in the calcified matrix of the bone tissue. For instance, when the accumulation of damage is too fast for the bone to respond with its maintenance process, so-called stress fractures occur. That happens, for instance, after a relatively long period of repetitive loading without resting or repairing periods. Typical examples are marching for many

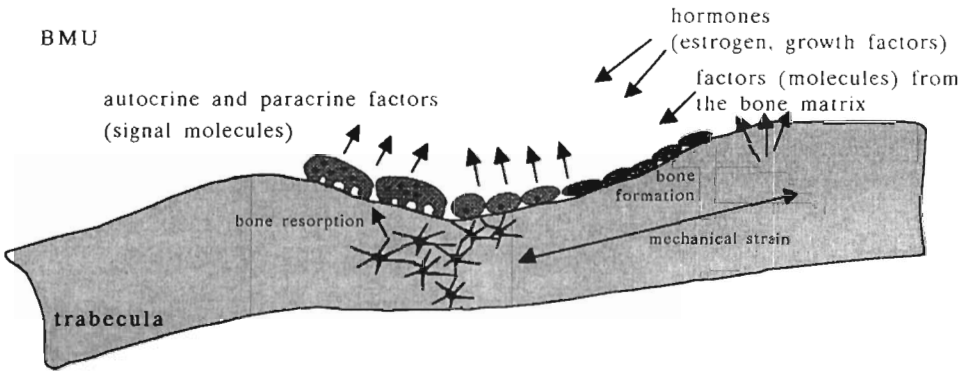


Fig. 1. Possible mediators in bone metabolism. Osteoclast are large multinuclear cells which resorb bone and make resorption pits with a depth of approximately 30 to 60 microns. Osteoblasts are smaller cells which are related to the cells inside the bone matrix (osteocytes). When an osteoblast generates bone matrix it becomes trapped in its own collagen matrix, which slowly mineralizes. The osteoblast has now become an osteocyte, a cell with many connections to its neighboring cells and the cells at the surface of the tissue. It is hypothesized that the osteocytes have a mechanosensory signal function

days with a backpack or strenuous exercise of track and field athletes. Normal turnover starts with a resorption phase where osteoclasts make small pits of about 30 to 50 microns deep (Erikson and Langdahl, 1995). Subsequently osteoblasts refill these pits with osteoid. The osteoid contains a lot of collagen tissue and is quite flexible. It slowly mineralizes until a solid calcified matrix results with the Young modulus approximately within the range of 5000 to 15 000 MPa. It is not clear what makes the osteoclasts resorb the bone matrix and what the osteoblast built it. There is some evidence that the two cellular events are coupled (Rodin, 1996) and it might actually be the osteoblast which signals the osteoclast to start its resorption phase (Duncan and Turner, 1995). It is, however, clearly shown in many experimental situations that mechanical loading can influence the cellular events. High loading stimulates osteoblast activity relative to osteoclast activity (net gain) and vice versa for unloading (net loss). It is unclear how the transduction from loading to cell activity is performed. It may be that cells inside the bony matrix (osteocytes) can sense deformation and signal the osteblasts at the surface of the bone matrix. It may also be that high mechanical loading deforms the matrix in such a way that chemical factors inside the bone matrix are released and stimulate surface cells to undertake appropriate actions. The same phenomenon may occur when the

bone matrix is resorbed by osteoclasts. This results in release of factors in the matrix and may in turn affect osteoblast activity (Mundy, 1989). Figure 1 shows the factors which may play a role in mechanical signal transduction.

Up to the age of about 25 there is a net gain in bone mass and after that period there is a slow yearly loss. The bone loss clearly results in degeneration and reduced strength. However, there is more to bone strength and fracture incidence than bone mass. In a large epidemiological study, Melton et al. (1989) showed that there is a large overlap in bone density levels from subjects with and without fractures. Hence, in a general subject or patient, fracture risk can not be detected very well by measuring bone density only. From a mechanical perspective this finding is not surprising at all. The strength of a bridge can not be determined by its amount of steel, although on average there likely is a positive correlation between the amount of steel and the strength. Two remaining factors contributing to the strength are of course the architecture and the mechanical properties of the basic materials (the matrix tissue).

## 2. Assessment of mechanical loading in cancellous bone

For bone tissue both the basic material properties and the exact geometry (architecture) are difficult to quantify. For trabecular bone one would like to have the complete reconstruction of the three dimensional architecture in combination with the tissue properties of the bone matrix. Together with the external loading that would provide all information required to completely analyze the load distribution, deformation and fracture risk of the structure. Unfortunately, for many bones the loading conditions are not well defined and only known in a general sense. Tissue properties depend on location within the body and may vary among individuals as well, which is another complication. The three dimensional architecture of trabecular bone, however, can be measured quite accurately, using serial sectioning techniques (Odgaard, 1997) or micro-CT scanners (Ruegsegger et al., 1996). These computer reconstructions exist of many rectangular bricks (voxels) without any differentiation of the degree of mineralization within these bricks. Hence, the models describe geometry and not the mineral content. The usual assumption is that the mineralization levels are equal in all the voxels, however, we know from the literature that this is not entirely true (Boyde et al., 1993). Given this assumption, however, it is possible to generate a finite element model of the trabecular architecture. The number of elements usually is in the order of $10^5$ to $10^6$ elements. A special purpose finite element code was developed which could

handle such a finite element data set. By taking advantage of the fact that all elements had the same geometry the mesh could be analyzed either on a supercomputer or for smaller meshes a powerful workstation (Van Rietbergen et al., 1995; Rietbergen et al., 1998). Using these finite element computer models the entire load distribution and deformation can now be analyzed, which can be used to estimate fracture risk or to assess the local mechanical stimuli in the bone tissue. This information could be helpful to further elucidate the relation between mechanical loading and cellular activity.

## 3. Bone adaptation

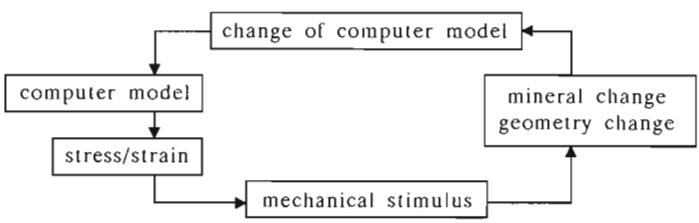


Fig. 2. Feedback loop where the finite element computer model is iteratively changed based on the mechanical stimulus calculated in the finite element model

A way to study the regulation mechanism of bone metabolism and adaptation is to simulate the possible consequences of mechanical loading on the net changes of the bone matrix. This can be done by introducing a mechanical feedback into the finite element computer code (Fig.2). From the stresses and strains calculated in the elements of the computer model, a mechanical signal can be defined. The assumption is that cells (for instance the osteocytes, see Fig.1) can somehow detect this mechanical signal and thereby be stimulated in such a way that bone resorption or bone apposition results. A few assumptions have to be made in order to further specify the theory, such that it can be used in a computer code. The first specification is the mechanical signal. What is the precise mechanical signal which is detected by the cells? From the biology there is not much support for one specific mechanical signal in favor of another. Strain and stress are tensor quantities, but for practical purpose a scalar would be the first choice. Strain energy density or other related parameters were introduced (Fyhrie and Carter, 1986; Carter, 1987) and seem to work reasonable well; i.e. it gives realistic predictions of bone adaptation

in various computer models (Carter et al., 1987). Another assumption which has to be made is related to the transfer of this signal to the actors: the osteoblasts and osteoclasts. How are those actor cells stimulated dependent on the magnitude of the mechanical signal? One assumption is that the mechanical signal has a direct effect on the net gain or loss in bone mass at the location of the mechanical signal. In a finite element computer model this is the actual element where the signal is detected. For example in a finite element model of a proximal femur this gives quite rational predictions of the density distribution, see Fig.3.


Fig. 3. End configuration showing the density distribution of a finite element model of a proximal femur. The model started with a uniform density distribution and finally adapted (converged) to the density distribution which represents the actual distribution of the mid-section of a proximal femur quite well. See also Carter et al., (1989) and Weinans et al. (1994)

This method of bone remodeling computer simulation is also very useful to predict bone adaptation around orthopaedic implants (Huiskes et al., 1992). However, for detailed computer models at the level of individual trabeculae this scheme does not provide the distinct trabecular patterns of cancellous bone. When it is assumed that there exist a diffuse interaction between the signalling cells and the actor cells, the model however, predicts trabecular patterns (Mullender et al., 1994; Mullender and Huiskes, 1995). The following equations can be used to describe the rate of change in bone mineral per element at a location $j$, $(dM_j/dt)$

$$\frac{dM_j}{dt} = \tau \sum_{i=1}^{n} f_{ij}(S_i - S_0) \tag{3.1}$$

$S_i$ – deformation energy measured in an element at location $i$
$S_0$ – constant threshold value
$\tau$ – constant time step
$f_{ij}$ – spatial influence function or spread function (Mullender et al., 1994) which specifies how the signal at a location $i$ is spread in the environment and used by the actor cells a location $j$ to adjust the amount of bone tissue $dM$ per time step $dt$.

The function $f$ is defined as $f_{ij} = \exp(d_{ij}/D)$ with $d_{ij}$ the distance between the locations $i$ and $j$ and $D$ a constant representing the influence or "dispersion" parameter (Mullender et al., 1994 and Mullender and Huiskes, 1995). For small $D$, the range of the signal is only to its direct neighbors (small dispersion) whereas with large $D$ the signal is transferred over a long range (large dispersion). The result is a blurred deformation energy signal. The amount of bone mineral in one element is limited to a maximum value of $2.0\,\mathrm{gr/cm^3}$ (maximum mineralization) and a minimum value of zero (no mineral). The equation is solved using the forward Euler integration which finds after a certain number of time steps a mineral distribution representing a cancellous bone architecture. This scheme was applied to a beam in three-point bending or a bridge (Fig.4). The initial conditions assumed a uniform density distribution and Young's modulus of each element was taken as a quadratic function of the local density (amount of mineral). This quadratic function represents a more than proportional increase in stiffness with an increase in mineral content (Currey, 1988). Various end configurations can be generated using this algorithm depending on the starting configuration and the size of the time step. Normally, the simulation of the beam under three point bending ends in a symmetrical end configuration. In Fig.4 this symmetrical end configuration was slightly changed manually at one side and restarted with the

feedback algorithm, which resulted in the asymmetrical figure shown. Many different end configurations could be obtained all fulfilling Eq (3.1) and the boundary conditions. The fundamental reason that a trabecular pattern arises in the algorithm is that there is a discrete system (elements) which tend to diverge from the equilibrium condition with $S_i = S_0$ (Eq (3.1)). The diversion generates the pattern configuration, which can be understood as a far from equilibrium system with $S_i = S_0$ the equilibrium (Weinans and Prendergast, 1996; Prendergast and Weinans, 1998) The scattering of the signal ($f_{ij}$ in Eq (3.1)) makes the trabeculae of a specific thickness arise.

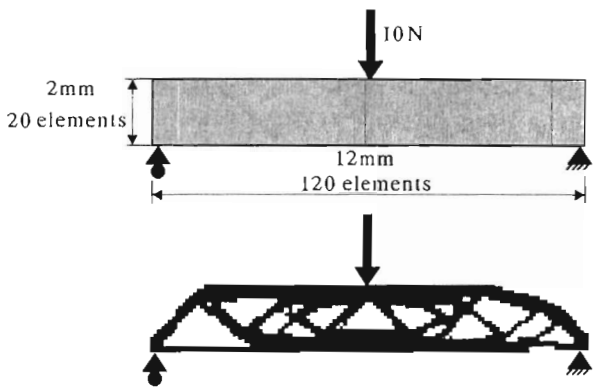


Fig. 4. Finite element computer model of a "bridge" (beam under three point bending). The model started from a uniform density distribution and using Eq (3.1) and the boundary conditions described in the text, the final distribution has no intermediate density values left. The structure in the end configuration has a trabecular-like distribution and is virtually equal to a topology optimization searching the stiffest structure with the least weight (Sigmund, 1994)

The result of this bone adaptation algorithm is strikingly similar to the results found in the topology optimization literature (e.g. Sigmund, 1993). The goal of many topology optimization algorithms is to find a geometry of maximum stiffness and minimal weight (Allaire and Kohn, 1993). This problem can be solved by finding the architecture where the strain energy taken up by the structure is minimal, with a preset value for the amount of material used. Minimization of strain energy density is in fact the same as finding the point at which the strain energy density is most uniform. This goal is not explicitly described in the bone adaptation algorithm, although it may be evident from Eq (3.1) that the strain energy density distribution which equals the preset threshold value $S_0$ fullfills the exact equilibrium conditions. In practice, however, that point is never found by the algorithm. In both bone

adaptation and topology optimization, the final end configuration is never extremely far apart from this equilibrium distribution with $S_i = S_0$. The reason for this is that the maximum values for the amount of mineralization was limited to a maximum value of 2.0 g/cc and all elements tend to hit this maximum value. Apparently bone adaptation mimicks a global optimization algorithm to a minimal mass and maximal stiffness structure quite well.

## 4. Bone resorption

As it was demonstrated in the computer simulations of trabecular bone generation or adaptation (Fig.4), the stress distribution within the trabecular structure (the end configuration of the algorithm) was reasonably close to the preset threshold value $S_0$. The discrepancy from $S_0$ represents the quality of the structure: how well is the architecture adapted to its most optimal configuration? With the recently introduced method of micro-CT the entire loading distribution in trabecular bone can be analyzed and thereby its quality can be assessed based on the criterion of how uniform the strain energy density distribution is. A well formed (optimal) bone architecture should have a more or less uniform strain energy density distribution: all bone is carrying the same amount of load. From a proximal tibia a trabecular bone specimen was three dimensionally reconstructed with a resolution of 20 microns and a finite element computer model was generated. This procedure resulted in a model with over 100 000 brick elements all of the same size and geometry. It was assumed that the Young modulus of the trabecular tissue was 5000 MPa. The model was loaded in its physiological direction resulting in an apparent stress on the specimen of 0.5 MPa. The strain distribution within the trabeculae was determined and most strains were within the range of 400 to 4000 microstrain. This is in the same range of strain values measured on cortical bone (Biewener, 1993). Hence, there seems to be no large difference in normal physiological strain levels between cortical and trabecular bone tissue. Of course the strain levels determined in the model depend linearly on the assumed Young's moduli of the tissue. From experiments (Choi et al., 1990) and comparisons between experiments and computer models Young's modulus was found to be in the range of 3000 to 10 000 MPa (van Rietbergen et al., 1995; Ladd et al., 1998). Also the mineralization levels within a trabecula may vary (Boyde et al., 1993) generating variations of Young's modulus in this range. Whatever assumption we make, with any Young's modulus in the range of 3000 MPa to 10 000 MPa instead of the value of 5000 MPa in the present analysis, the strains change

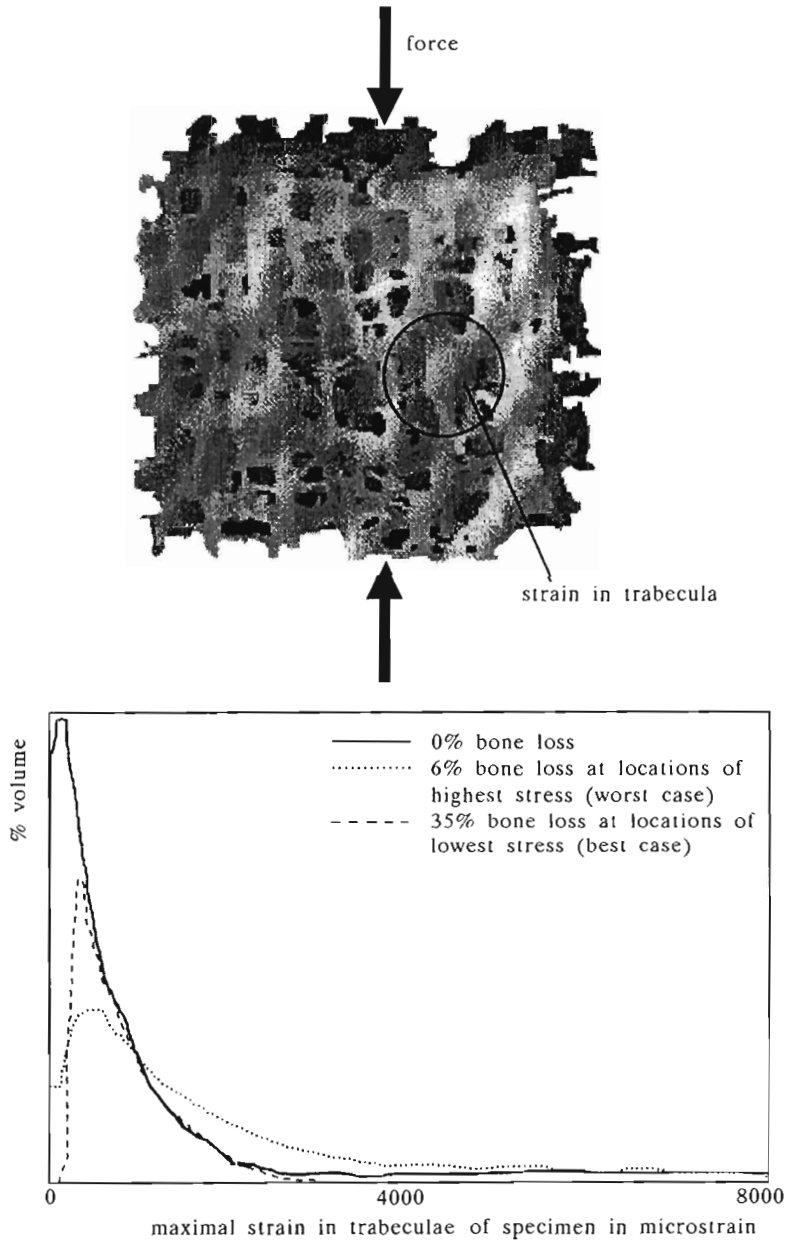


Fig. 5. Computer model of a small cube of trabecular bone scanned with a micro-CT scan. Bone loss was simulated in a worst case and best case scenario. In the computer model the stresses and strains in all elements were calculated and the highest absolute value of the principle strains was plotted in a distribution diagram. Percentage of occurrence (vertical) was plotted against the strain value (horizontal). There is an extreme difference between the two scenarios, demonstrating the relevance of how bone loss is achieved in cancellous bone

but would still lay well in the physiological range measured on cortical bone tissue (Biewener, 1993).

In the skeleton of subjects above the age of 30 an average bone loss in the range of 0.3 to 0.5% per year is quite normal (Burger, 1995). For woman that even increases for some years in the period after menopauze. Hence, at the age of 80 many individuals have a bone mass which is 30 to 40% reduced, relative to their peak level at the age of 25 to 30. The mechanical effects of this bone loss is clearly loss of stiffness and strength. In some cases this leads to a drastic magnification of fracture risk. Skeletal deformations in the vertebra, bone pain and multiple fractures are in such a case the hallmarks of osteoporosis. However, for diagnostic purposes, the most reliable tool is a measurement of the Bone Mineral Density (BMD). When the BMD is drastically reduced, relative to the peak bone mass of an average 30 year old subject, it is concluded that the patient has osteoporosis. However, there are many subjects with a reduced BMD who never fracture a bone. It may be that stiffness and strength reduce somewhat, but not to the point leading to any clinical problems. Notwithstanding that BMD measurement is a very valuable clinical instrument, the BMD is by no means a very specific and sensitive parameter to justify clinical treatment. It is not clear why some subjects are more sensitive to fracture than others, but clearly genetic and life style factors play an important role (Burger, 1995). An aspect which is often referred to as well, besides the BMD, is cancellous architecture (Recker, 1993).

Using our computer models it is now possible to simulate bone loss and evaluate the quality of architecture by means of the strain distribution within the individual trabeculae. It seems obvious from a mechanical perspective that the precise location where the bone loss takes place is very important. In finite element computer analyses *best case* and *worst case* situations of bone loss were simulated in small steps of 1 percent bone loss. First, the bone tissue was removed from locations with the lowest strain range. Up to 30% bone loss resulted in virtually no difference in the strain levels of the individual trabeculae. Hence for this specific loading condition the bone has at least 35% more tissue as strictly needed. However, if the bone is removed from locations of highest stress one gets the worst case scenario and only 3.5% bone loss results in elements with high strain levels (4000 microstrain and higher). With 6% bone loss the strain levels become completely a-physiological and the structure is mechanically declined. It may be clear from these findings that the location of bone loss or the location of the resorption pits can dramatically alter the risk of fracture. Whether this aspect plays a role in osteoporosis needs to be experimentally investigated.

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## Wzrost, przystosowanie i starzenie się układu kostnego

Streszczenie

Nasz układ kostny, aby dobrze znosić przez pewien czas obciążenia zewnętrzne, wymaga pewnej dozy podtrzymywania. Podtrzymywanie to przeprowadzane jest przez pewne wyspecjalizowane komórki, tzn. komórki kościogubne (osteoklasty) i komórki kościotwórcze (osteoblasty). Komórki te w małych porcjach ciągle wchłaniają i przebudowują substancję międzykomórkową. Aktualnie nie wiadomo jak te komórki otrzymują sygnały nakazujące podjęcie odpowiednich działań, wchłaniania uszkodzonej (słabej) kości i zastępowania jej nową tkanką kostną. Uważa się, że obciążenie mechaniczne odgrywa ważną rolę w zdarzeniach komórkowych. Rozkład obciążeń mechanicznych w strukturach kostnych można wyznaczyć przy zastosowaniu metody elementów skończonych. W tych modelach może być ponadto uwzględniony wpływ na wzrost, przystosowanie i degenerację wywołaną obciążeniem. Daje to możliwość badania interakcji pomiędzy aspektami biologicznymi i mechanicznymi w tkance kostnej. W niniejszej pracy podano kilka przykładów symulacji numerycznej takiej interakcji oraz przedyskutowano konsekwencje biologiczne czyli kliniczne.

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