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The regulation of functional adaptation in trabecular bone

Citation for published version (APA):
Mullender, M. G., & Huiskes, H. W. J. (1995). The regulation of functional adaptation in trabecular bone. In *Bone structure and remodeling / Ed. A. Odgaard, H. Weinans* (pp. 181-187). (Recent advances in human biology; Vol. 2). World Scientific.

Document status and date:
Published: 01/01/1995

Document Version:
Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
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THE REGULATION OF FUNCTIONAL ADAPTATION IN TRABECULAR BONE

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ABSTRACT

The capacity of bone to adapt its structure to mechanical loads (Wolff's law) has been generally accepted. The presence of trabecular architecture in bone is commonly seen as meaningful, in the sense that loads can be resisted while little material is used. Bone turnover and adaptation is believed to be regulated locally by bone cells. We argue that insight in the manner in which these concepts fit together can be improved by mathematical modeling. A hypothetical local regulatory process was simulated using a mathematical model. The model showed that the proposed process can indeed explain the development of typical trabecular-like structures and their adaptation to changes in mechanical load. The results indicate that mechanical factors may be keys for the development and maintenance of the trabecular structure. The model also showed that the morphology depends primarily on three independent parameters. Hence, the model is useful to develop hypotheses about the importance of several factors that play a role in the bone (re)modeling process.

1. Introduction

The trabecular structure in bone is important for its mechanical function. For instance in osteoporosis, vertebral fractures and femoral fractures have been associated with a loss of integrity in trabecular architecture. It is generally assumed that the typical structure of cancellous bone is advantageous because the required strength of bone can be maintained using a minimal amount of material and hence requiring minimal bone mass. Already more than a century ago, Wolff[1] speculated that bone shape and internal structure are optimized relative to mechanical requirements. Although the adaptive capacity of bone has become known as Wolff's law, Wolff and most of his contemporaries believed that functional adaptation is an evolutionary process. In contrast, Roux[2] argued that functional adaptation is an intrinsic quality of the bone tissue itself. He suggested that the adaptive processes in bone are regulated by cells influenced by the local state of stress. It is now clear that bone is continuously turned over and that during this process bone can adapt to changing mechanical demands. Although the regulation of bone (re)modeling is still unclear, Roux's idea that structural adaptation of bone to mechanical load is the result of a locally regulated control process is now generally (often implicitly) accepted. Yet, the prediction that a local control mechanism, such as proposed by Roux, produces the typical trabecular structure which resists mechanical loads with little mass is far from trivial. Our question is: can a mathematical model be useful for our understanding of the way in which biological processes generate a specific trabecular morphology?

2. Modeling of biological processes

For centuries, models have been used to gain insight into biological mechanisms. For instance, Borelli[3] 'modeled' muscles, calculating muscle forces using an inverse dynamics approach, even before Newton's Principia were published. During the last decades, the development of computer technology has generated an exponential increase in the use of mathematical modeling and computer simulation as a research tool. Such models have also been used in the field of bone research. First, computer analysis was used to calculate the magnitude and distribution of mechanical variables within bone[4]. More recently, it was also used to predict changes in bone density and shape as a result of mechanical load[5,6,7]. In these studies a feed-back loop between the maintenance of bone mass and local mechanical variables was assumed. As these models are phenomenological, they can be used to predict global adaptations in mass distribution as a result of changed loading, but can not explain the biological mechanisms involved. As a different approach, we developed a mathematical model based on physiological parameters which, in principle, can be experimentally determined[8,9].

What is the advantage of such a model? If we consider bone tissue as a solid material filled with several cell types which interact and can also respond to local stimuli it becomes clear that this makes a very complex system. Even if the responses of each cell type to each relevant stimulus would have been established, the behavior of the total population of cells is not self-evident. The advantage of a computer model is that it can simulate the behavior of a large population of cells interacting with each other and with their environments, according to certain rules, and thereby predict the behavior of the total system. This kind of approach is not new in biology. Examples are models predicting the distributions of organisms in their particular environments[10,11,12]. In these models a typical movement response of organisms (i.e. change of speed or direction) to certain stimuli (e.g. humidity) is assumed. Further, the distributions of the stimuli concerned and the initial distribution of the organisms are given. From this, the distribution of the organisms in this particular field at a later time point can be predicted by computer simulation. In this case, the computer simulation can also be used to investigate which 'movement response' is useful for an organism to maximize its survival rate[10,11]. Analogous to this example, the model of Mullender and Huiskes[9] can be used to simulate the response of bone tissue, given a 'stimulus response scheme' at the level of the 'players' in the bone (re)modeling process (i.e. bone cells). Such a model can be used in several ways. First, given a regulatory scheme, it can predict what happens at the tissue level for several 'stimulus distributions' (that is, external loads) and initial conditions (initial bone architectures). It can also be used to investigate the effects of changes in the regulatory scheme, by changing the parameters in the physiological relationships or assuming different relationships. Finally, it can serve as a starting point for experiments, since the model produces hypotheses about which factors in the regulatory scheme are important.

3. A proposal for the regulation of bone (re)modeling

Bone is turned over by the coupled activity of both resorptive and formative cells (osteoclasts and osteoblasts[13]). These cell populations are assumed to be organized in basic multicellular units (BMU's)[14]. Our hypothesis is that osteocytes are mechano-sensory cells and that these cells regulate the activity of BMU's in their local environment (Fig. 1). Osteocytes are located inside the mineralized bone matrix, their processes are connected with those of neighboring cells and with cells at the bone surface.

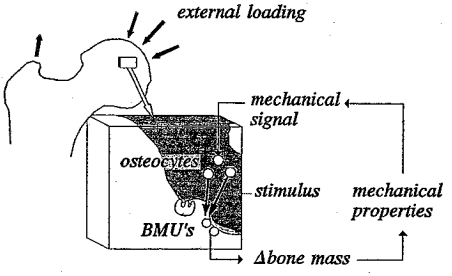

Figure 1 A schematic representation of the proposed regulatory process.

Furthermore, it has been shown that osteocytes are sensitive to mechanical stimuli[15,16,17]. Hence, these cells are suitable candidates for the role of mechano-receptors and regulators of bone mass[18,19]. The mathematical model that we proposed is based on this hypothetical local regulatory mechanism[8,9]. It considers only the responses to mechanical stimuli, ignoring possible other factors involved. It was shown that the model produced structures similar to those of trabecular bone.

In this study we have used this model to investigate what the hypothetical regulatory mechanism implies for the (re)modeling process at a trabecular level and if the model confirms the generally assumed hypothesis that the distribution of bone mass in trabecular bone is optimal. The mathematical model is described in detail by Mullender and Huiskes[9]. It assumes that the mineralized bone contains a number of osteocytes, uniformly distributed over its volume. Each osteocyte measures a mechanical signal, the strain energy density, at its location and according to the difference between the measured and a target signal (k) it stimulates the BMU's in its environment. The stimulus from each osteocyte is assumed to decrease exponentially with increasing distance to the BMU's. The osteocyte influence parameter D characterizes the decay function by which the osteocytes' influence decreases. At each location in the bone, the bone density is adapted according to the magnitude of the total stimulus received. The local elastic modulus is then calculated from the local bone density according to an empirical relationship. This again affects the mechanical signal. Finite element analyses is used to calculate the internal strains and stresses as a function of the external load.

4. Model predictions

The model was applied to a domain of 2x2mm with a thickness of 0.02 mm. The effects of initial morphology, the magnitude of the load, the target signal and the magnitude of the osteocyte influence parameter D were investigated. It was shown earlier that the density distributions as predicted by the model converged towards discrete trabecular-like patterns where the density in a location was either minimal or

maximal[8,9] (Fig 2). The morphological effects can be characterized by relative density, the orientation of the struts, strut thickness and separation, and number of struts. In all cases, the struts align with the external stress orientations. After changing the principal stress orientation the structure adapted its morphology to match the new stress orientation[9].

For different initial conditions the equilibrium morphologies differ but all morphological parameters are similar for both initial conditions (Fig. 3). For one case (Fig. 2), the apparent elastic modulus of the predicted morphology as a whole in the directions of the applied principal stresses was calculated using the method described by Van Rietbergen et al.[20]. The apparent modulus was 1304 MPa, which is much higher than the elastic modulus calculated in a uniform mass distribution (703 MPa) with an equal relative density of 0.52.

The relative density of the structure depended primarily on the magnitude of the applied load and the target signal k[9]. Reducing the load or increasing the value of k resulted in a decrease of the relative density, due to a reduction in strut thickness (Fig. 4).

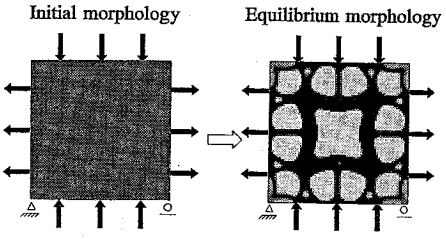

Figure 2 The model converges towards a trabecular-like density distribution.

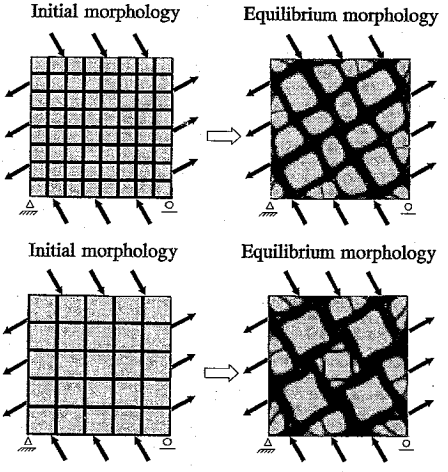

Figure 3 Two initial morphologies are compared. Although the results differ, the morphological parameters are similar.

The osteocyte influence parameter D affected the refinement of the structure as represented by strut thickness, separation and number[8,9]. Increasing the value of D resulted in increasing strut thickness and separation, and a smaller number of struts.

5. Discussion

The increasing prevalence of clinical problems such as osteoporosis, prosthetic loosening and fracture healing has caused research to focus on the processes involved in bone (re)modeling. Many biochemical factors affecting this process have been described and investigated[21,22]. Due to the difficulty of controlling mechanical factors in experimental studies, these have often been ignored. Yet, since over a century, it has been acknowledged that mechanical factors play an important role in the adapta-

tion of bone structure. We suggest that mathematical analysis is useful to investigate the effects of mechanical factors. For this purpose a mathematical model proposed earlier by Mullender and Huiskes[8,9] was used, which assumes that the local regulation of bone mass is driven by mechanical stimuli. Other factors were ignored. The underlying hypothesis is that osteocytes regulate bone mass by stimulating BMU's, based on local mechano-sensory information. The objective was to investigate if the proposed regulatory mechanism can explain the genesis and transformation of the typical trabecular structure.

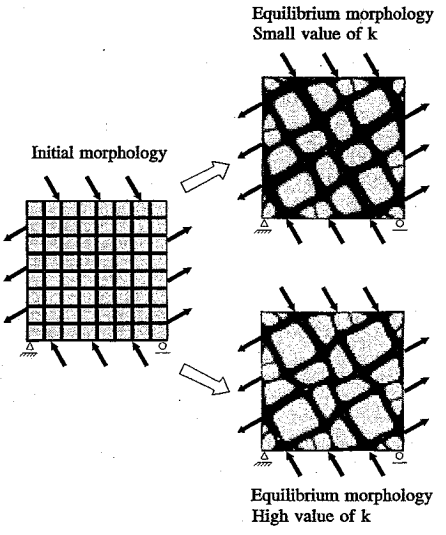

Figure 4 The target signal k affects the relative density of the structure: for a smaller value of k, the struts become thicker.

The model predictions showed that the regulatory process produced structures resembling the structure of trabecular bone. The process always converged towards a discrete structure where the relative density in a location was either maximal or minimal. Weinans et al.[23] used a finite element model, based on a phenomenological approach. In their model each element regulates its own mass according to the magnitude of a mechanical signal measured in that same element. They explained that this 'discrete patterning' behavior is due to the regulatory feed-back loop being positive. This causes more dens areas to attract more load and hence attract more mass, while less dens areas are shielded from loading and here mass decreases.

In contrast with the model presented earlier by Weinans et al.[23], the present model produces trabecular-like structures whereas, the earlier model produced discontinuous patches. The difference in the behavior between the two models is caused by the introduction of an environmental effect of the osteocyte regulatory influence. The assumption of this distance effect is realistic, because osteocytes are located within the mineralized bone matrix whereas BMU's are located at the bone surface. Hence, in order to reach these 'actor' cells, osteocytes must signal these cells across a certain distance. It has been shown by Jeansonne et al.[24] that interconnected osteoblasts can communicate over a distance of about ten cells. The effect of the osteocyte influence domain is that areas which either attract mass or where mass disappears become larger with an increasing size of the osteocyte influence domain, represented by an increase of the osteocyte influence parameter D. Thus, while the regulatory feed-back loop causes spacial discontinuity, the influencing distance of the osteocytes determines the refinement of the trabecular pattern. As the influencing

distance in the model of Weinans et al.[23] is limited to the element size, it follows that the refinement of the structure that is obtained is prescribed by the element size used, which explains the dependency on FE-mesh refinement in their results.

It was shown here that the morphology predicted with the present model is not unique for a given applied load, but depended on the initial morphology. Transformation of a trabecular morphology occurred by shifting, thickening, thinning or resorption of individual trabeculae. Hence, the new morphology is based on the previously existing morphology. The remodeling process is irreversible, as each step in the remodeling process is a new 'initial morphology'. This suggests that the equilibrium morphology is not 'the optimal solution' but one of many adequate solutions. Still, the predicted mass distribution is almost two times stiffer in the loading direction than a homogeneous mass distribution with the same total mass. Hence, the distribution is advantageous for resisting the applied load.

As predicted by Wolff's law, the directions of the struts aligned with the principal stress orientations. Despite large variations in morphology, due to variations of the initial morphology or to variations of the influence parameter D, the relative density of the equilibrium morphology only varies within a small range for a given external load. The relative density of the structure is primarily determined by the magnitude of the external load relative to the target signal k. Either reducing the magnitude of the load or increasing k results in a lower relative density. The same effects of load magnitude on bone mass has been shown in several experimental studies[25]. Our results indicate that a change of bone mass may also be the result of a changed target signal or 'set-point'. Hence, a change in the sensitivity of osteocytes may also cause a change in bone mass.

Although only mechanical factors were taken into account, the genesis of a trabecular morphology and the adaptation of a trabecular morphology to a changed load could be explained. These results indicate that mechanical factors may be the key for the development and maintenance of the trabecular structure. The model also showed that the morphology depends primarily on three independent parameters: first the initial morphology, secondly the influence domain of the osteocytes and thirdly the magnitude of the load relative to the reference signal. These findings may give clues for finding causes for abnormal trabecular morphologies, for instance in osteoporosis.

In conclusion, a regulatory process based on the hypothesis that osteocytes are mechano-sensors and regulators of bone mass is compatible with the existence of a trabecular morphology and its capacity to adapt to mechanical loads. The proposed process produces structures with the qualities of high stiffness using a low (but not necessarily minimal) mass. The model is useful for the investigation of the (re)modeling processes.

6. Acknowledgement

This project was partly sponsored by a Grant from the Netherlands Foundation for Research, division of Medical Sciences (NWO/MW).

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