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Proposal for the Regulatory Mechanism of Wolff’s Law

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Summary: It is currently believed that the trabecular structure in bone is the result of a dynamic remodeling process controlled by mechanical loads. We propose a regulatory mechanism based on the hypothesis that osteocytes located within the bone sense mechanical signals and that these cells mediate osteoclasts and osteoblasts in their vicinity to adapt bone mass. A computer-simulation model based on these assumptions was used to investigate if the adaptation of bone, in the sense of Wolff’s law, and remodeling phenomena, as observed in reality, can be explained by such a local control process. The model produced structures resembling actual trabecular architectures. The architecture transformed after the external loads were changed, aligning the trabeculae with the actual principal stress orientation, in accordance with Wolff’s trajectorial hypothesis. As in reality, the relative apparent density of the structure depended on the magnitude of the applied stresses. Osteocyte density influenced the remodeling rate, which also is consistent with experimental findings. Furthermore, the results indicated that the domain of influence of the osteocytes affects the refinement of the structure as represented by separation and thickness of the struts. We concluded that the trabecular adaptation to mechanical load, as described by Wolff, can be explained by a relatively simple regulatory model. The model is useful for investigating the effects of physiological parameters on the development, maintenance, and adaptation of bone.

More than a century ago, Wolff (50) put forward his trajectorial hypothesis, which implied that the internal structure of bone is adapted to mechanical demands, such that the trabecular patterns coincide with stress trajectories. Although the hypothesis that the shape and internal structure of bone adapt to functional or mechanical requirements generally has become known as Wolff’s law, the present idea that remodeling of bone is a continuous dynamic control process originated from Roux (40). He suggested that the adaptive processes in bone are regulated by cells influenced by the local state of stress.

Only recently have scientists begun experimenting with mathematical control models of mechanical bone-mass regulation (9,16,37). The model of Cowin and Hegedus (9)—in particular, the theory of adaptive elasticity—provided the mathematical background for future developments. It assumed a continuous feedback loop between the maintenance of bone mass and local strain values in the tissues, enabling mathematical predictions of local bone regulation based on external loads. Others later proposed similar mathematical remodeling rules, albeit introducing different kinds of mechanical signals to control the feedback loop to maintenance of mass (2,7,21-23).

These authors used finite element methods to link external loads to local mechanical signals, thereby enabling computer simulations of bone-mass regulation in complex geometrical structures, such as whole bones. It was shown in validation studies that these computer simulations could accurately predict long-term formation and resorption of bone around orthopaedic implants in animals and humans (24,45,48). Nevertheless, these are empirical models, not physiological ones. They are useful to estimate the gross outcome of a remodeling process but do not explain anything about the remodeling process itself. In addition, these models regulate only bone mass and ignore the trabecular structure.

By coincidence, it was found that these kinds of computer models are likely to produce noncontinuous patchworks when used to simulate remodeling of a continuous, uniform material after application of an external load (47). It was established that this phenomenon was based on unstable behavior of the finite element solution procedure in conjunction with a positive feedback loop. Since every element in the model acts as a more or less independent strain sensor and mass regulator, it acts in competition with its neighboring elements. Each element tends to fill up to its maximum capacity or, alternatively, to fade out (47). The results of these analyses were inconsistent with their underlying theory of continuum mechanics and hence impermissible. However, they inspired us to re-examine the hypothesis of bone as a self-optimizing
structure, as proposed by Roux (40), which resulted in our proposal for a physiologically based mathematical control model of local bone-mass regulation.

We hypothesize that osteocytes act as sensors of a mechanical signal or "mechanoreceptors" (10,28,29) and regulators of bone mass by mediating the actor cells—the osteoblasts and osteoclasts (Fig. 1). The mathematical model proposed to simulate this control process uses the strain energy density as the mechanical signal that the osteocytes appraise (22). The osteocytes, distributed through the bone in a particular pattern, emit a stimulus in their environments equivalent to the difference between the local strain energy density and a constant reference value. The actor cells regulate bone density in their area between zero and maximal density, dependent on the total stimulus they receive from the osteocytes, whereby the influence of an individual osteocyte stimulus diminishes exponentially according to its distance from the actor cells concerned.

It was shown earlier that such a simulation model, when used together with the finite element method, produces trabecular patterns in an initial domain of uniform density after it is externally loaded (32). Furthermore, in contrast to other models (19,47), the solution is spatially stable and mesh-independent, provided that the mesh is adequately refined (32).

The purpose of this study was to investigate whether this proposed control model is indeed a viable candidate for the cell-based bone-mass regulation process suggested by Roux. For that purpose, three questions had to be answered. First, if the parameters of the model (initial pattern of bone density, external load, reference strain energy density, osteocyte density, and maximal bone elastic modulus) are given realistic values, does the model produce trabecular patterns of realistic morphology? Second, can the model confirm the trajectorial hypothesis of Wolff? And third, can the model reproduce adaptive remodeling phenomena found in reality? These questions are addressed in this paper. In addition, the effects of the physiological parameters in the model are investigated.

**METHODS**

The bone tissue is assumed to contain n osteocytes per cubic millimeter located in the mineralized matrix, with a total of N in the domain considered. Each osteocyte i measures a mechanical signal \( S_i(t) \) (MPa), the strain energy density in its location. In turn, the osteocyte stimulates actor cells (osteoclasts and osteoblasts) to adapt the bone mass depending on the difference between the measured signal, \( S_i(t) \), and a reference signal, \( k \) (Fig. 1). The influence of an osteocyte on its environment is assumed to decrease exponentially with increasing distance from the actor cells. The influence of osteocyte i on the actor cells at location \( x \) is described by the spatial influence function

\[
f_i(x) = e^{-D|d(x)|}
\]

where \( d(x) \) is the distance (mm) between osteocyte i and location x. The parameter D represents the distance (mm) from an osteocyte at which its effect has reduced to \( e^{-1} \), i.e., 6.87\*.

The relative density at location x is regulated by the stimulus value \( f(x,i) \), to which all osteocytes contribute, relative to their distance from x, hence

\[
f(x) = \sum_{i=1}^{n} f_i(x) S_i(t) + k
\]

The regulation of the relative density \( m(x,t) \) in location x is governed by the rate

\[
\frac{dm(x,t)}{dt} = \tau f(x,i) \quad \text{with} \quad 0 < m(x,t) < 1
\]

where \( \tau \) (MPa \(^{-1}\) s \(^{-1}\)) is a time constant regulating the rate of the process. It is assumed that the osteocytes disappear at locations where the density approaches zero; hence, these sensors are disconnected in the model during the process. The local elastic properties were calculated from the local relative density with use of a cubic power relationship in accordance with experimental data from Currey (11). Therefore, the elastic modulus at location (x) is calculated from

\[
E(x) = C m(x,t)^\gamma
\]

where C (MPa) and \( \gamma \) are constants.

The model was applied to a square domain of \( 2 \times 2 \) mm, with a thickness of 0.02 mm (20 pm). The domain was loaded at each face with uniform tensile or compressive and shear stress distributions, such that a particular principal state of stress was mimicked, albeit...
RESULTS

The simulations were used to explore the dynamic distributions when the reference parameter values that have been described were used. The dynamic simulations were used to explore the dynamic distributions obtained when the reference parameter values that have been described were used.

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converged to trabecular patterns of struts of maximal density surrounding empty pores after application of load. This occurred regardless of the initial distribution of density or the principal orientation of stress (Fig. 2). The morphological qualities of the resulting architectures can be characterized by three independent global parameters: the relative apparent density (or analogously, the bone area fraction), the average trabecular orientation, and the perimeter/area ratio (corresponding to the three-dimensional surface/volume ratio [36]).

The relative apparent density in the equilibrium morphology depends predominantly on the magnitude of the external load in relation to the value of the reference strain energy density $k$. For $k = 0.02$ MPa and the chosen principal stress magnitude of 4 MPa, the resulting relative apparent density was about 0.5, associated with a bone area fraction also of 0.5. The osteocyte influence parameter $D$ had an effect as well; however, twice the magnitude of $D$—from 0.050 to 0.100 mm—resulted in only a 10% increase in the relative apparent density. The effect of the initial morphology on the relative apparent density was marginal. This is remarkable, because its effect on the final architecture was considerable (Fig. 2).

Trabecular orientation always was directly related to the external principal stress orientation. This implies that when, for a particular equilibrium morphology (e.g., Fig. 2B), the principal stress orientation is rotated, the architecture "transforms" and the trabeculae are realigned to the principal stress orientation (Figs. 3 and 4). During this process, bone formation occurs at the surfaces of the trabeculae. Evidently, although the overall equilibrium orientation of the trabeculae is in accordance with the principal stress orientation, not every single trabecula is aligned similarly (Figs. 3 and 4).

The perimeter/area ratio depended mostly on the range of the osteocyte regional influence, as represented by the influence parameter $D$ (Fig. 5). For a smaller $D$, the architecture became more refined, with more and smaller pores and thinner trabeculae. For

**FIG. 3.** One particular equilibrium configuration (Fig. 2B) was used as the initial morphology. After the orientation of the applied stresses was changed from $\varphi = 30^\circ$ to $\varphi = 0^\circ$, the architecture adapted to align with the new stress orientation. The trabeculae that were unloaded gradually disappeared, while other, overloaded trabeculae adapted by realigning and thickening. The parameter values $D = 0.050$ mm and $k = 0.02$ MPa.

**FIG. 4.** With use of the same initial morphology as in Fig. 3, the principal stresses were rotated by $15^\circ$, from $\varphi = 30^\circ$ to $\varphi = 15^\circ$. In this case, all existing trabeculae remained but they adapted to the new loading situation. All trabeculae realigned, some trabeculae thickened and other trabeculae became thinner. The parameter value $D = 0.050$ mm and $k = 0.02$ MPa.
The process also depends on the external load in its context and location, where three theoretical effects can be considered. The internal deformation, which is based on the initial configuration, is dependent on the magnitude of the external load, which is affected by the thickness of the sample. The internal deformation is dependent on the thickness of the sample and the magnitude of the external load, which is affected by the thickness of the sample and the rate of the process. The internal deformation is dependent on the thickness of the sample and the magnitude of the external load, which is affected by the thickness of the sample and the rate of the process. The internal deformation is dependent on the thickness of the sample and the magnitude of the external load, which is affected by the thickness of the sample and the rate of the process.
relation to the initial configuration. When the principal stress orientation was rotated slightly relative to the directions of the trabeculae, the trabeculae realigned (Fig. 4). However, when the principal stress orientation was rotated considerably relative to the directions of the trabeculae, some trabeculae became totally unloaded and disappeared, while other trabeculae, which were overloaded, realigned and thickened at the same time (Fig. 3). The effect of overloading and unloading on trabecular adaptation also is demonstrated in Fig. 6, where a trabecula was artificially disconnected while the same externally applied load was maintained. The disconnected and therefore unloaded trabecula disappeared, while the neighboring, overloaded trabeculae thickened.

The rate of remodeling was affected by both the parameter D and the osteocyte density, as both parameters influence the magnitude of the stimulus received in the bone tissue. The remodeling rate increased for larger values of D and higher osteocyte densities (Fig. 7).

The mechanical quality of the equilibrium architectures can be characterized by their principal strain, principal stress, and strain energy-density distributions. These distributions were determined primarily by the value of the reference signal k, but the influence parameter D also had a small effect. When D = 0.050 mm, the principal strain in the structure averaged 4,200 μstrain, with principal strain values of 1,000-7,000 μstrain in more than 90% of the bone tissue. The principal stress averaged 7.7 MPa, with a variation of 0-20 MPa in more than 90% of the area of bone. The strain energy density, measured in the locations of the osteocytes, averaged 0.02 MPa, which equals the reference value k, and ranged from 0 to 0.045 MPa. High stress or strain values were found at the boundary of the plate and can be considered as boundary artifacts.

**DISCUSSION**

Presently, no consensus exists about the mechanisms controlling functional adaptation of bone. It was suggested that osteocytes are primary candidates for the role of mechanical sensors because of their favorable architecture and distribution (10,28). It frequently has been demonstrated that the precursors of the osteocytes, the osteoblasts, are sensitive to mechanical stimuli (see Burger and Veldhuijzen [5] for a recent review), but knowledge about the response of osteocytes to mechanical stimuli is scarce. Skerry et al. (44) and Dodds et al. (12) found that osteocytes responded rapidly to dynamic loading of bone. Recently, Klein-Nulend et al. (27) found that isolated osteocytes were more sensitive to fluid shear stress than osteoblasts. Marotti et al. (29) suggested that osteocyte death precludes bone turnover. These findings support the assumption that osteocytes are sensors of the

![Figure 7](image-url)

**FIG. 7.** The relative apparent density of the structure as a function of remodeling time, for three different osteocyte densities (n = 2,500/mm², n = 1,600/mm², and n = 500/mm²). A clear influence of osteocyte density on the remodeling rate can be seen. For higher osteocyte densities, the remodeling rate increases. The relative apparent density in the end-configuration is independent of osteocyte density.
local mechanical load. The results of Dunstan et al. (14), who found that patients with hip fracture who had extensive osteocyte death in the femoral head had little microfracture callus compared with patients with osteoporosis who had prominently viable bone, also indicate that bone remodeling and microfracture repair are related to the presence of sufficient viable osteocytes in bone.

The mechanism by which the osteocyte within the bone may sense a mechanical signal still is subject to speculation. It is believed that osteocytes are stimulated by the interstitial fluid flow caused by mechanical loading, either indirectly by the detection of streaming potentials (20) or directly by detection of shear stresses at the cell surface (49). In addition, very little is known about the pathway by which the local mechanical stimuli are transduced into the activation of osteoblasts and osteoclasts. A coupling between the activity of these cell types has been established (34), and units of combined resorptive and formative cell populations are referred to as basic multicellular units (16). Nevertheless, the regulation of these units still is obscure. It has been hypothesized that the osteocytes communicate directly with adjacent cells through the osteocytic processes and that a signal propagates by way of the osteocytic network toward the osteoblasts and bone-lining cells at the bone surface (20,29,49).

Support for this assumption has been supplied by Jeansonne et al. (25), who demonstrated electrical coupling and molecular transport between osteoblasts, and Doty (13) and Palumbo et al. (33), who showed that gap junctions between osteocytes and osteoblasts exist. The lining cells and osteoblasts, in turn, are thought to influence the proliferation and activity of osteoclasts (15,30). Furthermore, bone cells are involved in paracrine and possibly autocrine effects (39). It has been shown that osteoblastic cells do produce local factors, and the sensitivity of osteoclasts and osteoblasts to several mediators also has been established (4,15).

In this study, we used a mathematical model to investigate if a local control mechanism, based on the hypothesis that osteocytes are mechanoreceptors and regulators of bone mass, actually can predict remodeling of trabecular bone as we would expect according to Wolff's law. In the model, we used quite simple relationships for (a) the signal-sensing function of the osteocytes, (b) the influence of the osteocytes on the acter cells, and (c) the relationship between the stimulus received and the change in local bone density. We assumed that the actual signal measured by the osteocytes is related to stress and strain at its location. The strain energy density was used as the mechanical signal, and only the amplitudes of the strain energy density were taken into account; hence, the influence of strain rate was neglected. Only net changes in bone mass were modeled, and only the net effects of the basic multicellular units were considered. Thus, the model cannot be used to investigate changes in osteoclast or osteoblast activity. Implicitly, the material of a trabecula is modeled as being homogeneous and isotropic. This also is a simplification of reality. Finite element analysis was used to calculate the mechanical variables inside the bone specimen. The solution process was introduced earlier by Mullender et al. (32), who showed that the results were independent of the finite element-mesh, as long as the elements were smaller than the influencing parameter D and small enough to adequately describe the resulting trabecular structure from a continuum mechanics point of view.

The location of the sensors within the mineralized matrix has consequences for the remodeling behavior. The stimulus for remodeling always originates from within the mineralized matrix. Due to the decay of the stimulus with increasing distance, the model predicts that new bone is formed at the boundaries of existing trabeculae, as it is in reality. However, resorption of bone is not restricted to the boundaries of trabeculae.

In the model, in contrast to reality, it can take place at locations inside the bone matrix as well. Although this happened only if the loading configuration was changed drastically, this behavior is not physiological.

The most striking behavior of the proposed control mechanism is the formation of trabecular-like patterns. Weinans et al. (47) showed that positive feedback loops in the regulating process cause spatial discontinuity. As long ago as 1881, Roux described the regulation of bone remodeling as a positive feedback loop, when he stated that parts of the bone that are stressed more than other parts will increase their strength, thereby unloading the other parts, which then will eventually disappear, until a structure has developed where bone is present only at the locations where the highest stresses occur (40). This phenomenon also can be observed in the model and results in the formation of a trabecular structure whereby the regional influence of the osteocytes prevents spatial instability. The development of the structure is such that the load is resisted by as few struts as possible, but the number and thickness of the struts are controlled by the parameter values in the model, particularly the region of influence of the osteocyte, the reference strain energy, and the magnitude of the applied external load. The outcome of the regulatory process depends principally on the applied loads. It is noteworthy that the signal controlling the process—the strain energy density—is a scalar and independent of stress orientation. Still, the results showed that the trabecular architecture is formed in accordance with the magnitude and the directions of the external principal stresses. Hence, the osteocytes would not need...
information about the local strain orientation in order to form, in concert, an anisotropic structure.

The adaptive behavior of the model was investigated by change of the orientation or the magnitude of the principal stresses and by artificial disconnection of one strut in an equilibrium architecture. In all three cases, the behavior of the model showed similarities with actual remodeling behavior observed in cancellous bone. After the orientation of the principal stress was changed, the architecture transformed to resist the new pattern of stress. In the newly formed structure, the orientations of the trabeculae approximate the new principal stress orientation. These predictions are consistent with Wolff's traumatic hypothesis. When the level of load is changed, the model predicted that the architecture adapts by changing the thickness of the struts while maintaining the same number of struts. This is consistent with the results from 26, who found that, in the overloaded limb of a rat, the trabecular number and separation remained unchanged whereas the trabecular thickness increased significantly. Mosekilde 31 showed that, once disconnected, trabeculae are removed by resorption and suggested this was due to mechanical adaptation. This behavior also was reproduced by the model. An important observation is that, again, the regional influence of the osteocyte is essential to the remodeling behavior of the model. In order to form new bone, the osteocytes' stimulus must reach outside the area of mineralized bone.

The model is particularly suited for investigation of the dependence of the remodeling behavior on the physiological parameters in the remodeling process. Variation of the osteocyte density within a certain range influenced only the remodeling rate in the model. This result is in agreement with the finding that osteocyte lacunae are larger and more numerous in regions of bone with a higher bone turnover than in regions with a lower turnover 6. However, lack of experimental data prevents further verification of this finding. For extremely low osteocyte densities, remodeling rates depend predominantly on the distance from the osteocytes, whereas resorption especially occurs most rapidly at the location of the osteocyte itself. The result is that in some areas the osteocytes disappear, while the surrounding bone remains, in the end leaving very few osteocytes. Although this behavior of the model is not compatible with reality, it implies that a certain minimal number of osteocytes is necessary for adequate functional adaptation.

The function I(x) with the influencing parameter D represents the relationship between distance and the osteocyte's influence on its environment, where an increase of D results in a larger influencing domain of the osteocyte. If it is assumed that osteocytes communicate through the osteocytic network and by way of the release of local mediators, the relationship depends on the extent of the network, its connectivity, and the diffusion rate of the local mediators. Actual information about these factors is far from complete. It was shown here that the effect of distance not only is essential to the formation of trabecular patterns and to the adaptive capacity of the model but that it also has important effects on the structure formed. The parameter D affects the refinement of the architecture as represented by the perimeter-to-area ratio, dependent on trabecular separation and thickness. Trabecular thickness is about twice the magnitude of the parameter D. This indicates that the domain of influence of an osteocyte indeed has the same range as the extent of the connected osteocytic network. Smaller values of D also resulted in a slightly lower total mass, which caused higher resultant strains and stresses in the trabeculae. This implies that the existence of a network in the bone, by which a local mechanical stimulus can affect the local area within a certain distance, is useful for the regulation of the maximal local load.

If, for instance, we compare the results from the model with the experimental finding that the trabecular thickness of the iliac cancellous bone in normal humans is 100-200 μm and the trabecular plate separation, 400-600 μm (35), we can estimate that the influence parameter D should be 50-100 μm. Nevertheless, although the predicted morphologies show a general resemblance to actual trabecular morphologies, the trabecular structure essentially is a three-dimensional structure, and a three-dimensional model is needed in order to compare the predicted morphology with actual trabecular bone.

The distribution of mechanical variables, principal stress, principal strain, and strain energy density was nonuniform, 17,18 and van Riethergen et al. 46 showed that values for stress, strain, and strain energy density varied widely in a piece of trabecular bone loaded by uniaxial displacement. Although these authors did not use physiological loads, it seems likely that there are always parts in the bone that are stressed more than other parts. This assumption is consistent with our results.

In conclusion, it was demonstrated that the genesis of trabecular morphology, its transformation induced by changes in the loading pattern and the alignment of trabeculae with the principal orientations of the stress patterns—in accordance with Wolff's hypothesis—can be explained as the result of a local biological control process. It was shown that many features of bone remodeling can be explained by assuming a relatively simple mechanical regulatory process. The behavior of the model corresponds very well with actual remodeling behavior observed in trabecular bone. This mathematical model can be useful for the investigation of the effects of physiological parameters.
such as density of osteocytes, domain of their influence, degree of mineralization, and distribution of stress. Further validation of the hypothetical regulatory mechanism currently is ongoing.

Our results do not prove that the regulation model proposed is correct. They do prove, however, that Roux’s hypothesis was realistic: morphogenesis, maintenance, and adaptation of bone can be explained by a (surprisingly simple) local, cell-based control process.

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