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TECHNICAL NOTE

A PHYSIOLOGICAL APPROACH TO THE SIMULATION OF BONE REMODELING AS A SELF-ORGANIZATIONAL CONTROL PROCESS

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Abstract—Although the capacity of bone to adapt to functional mechanical requirements has been known for more than a century, it is still unclear how the bone adaption processes are regulated. We hypothesize that osteocytes are sensitive to mechanical loading and control the regulation of bone mass in their environment. Recently, simulation models of such a process were developed, using the finite element method. It was discovered that these models produce discontinuous structures, not unlike trabecular bone. However, it was also found that severe discontinuities violate the continuum assumption underlying the finite element method and that the solutions were element mesh dependent. We have developed a simulation model (which is physiologically and mechanically more consistent) which maintains the self-organizational characteristics but does not produce these discontinuities. This was accomplished by separating the sensor density and range of action from the mesh. The results clearly show that predicted trabecular morphology, i.e. sizes and branching of struts, depend on the actual relationship between local load, sensor density and range of influence. We believe that the model is suitable to study the relationship between trabecular morphology and load and can also explain adaptation of morphology, in the sense of 'Wolff's law'.

INTRODUCTION

It is generally accepted that bone adapts to mechanical loading. A decrease in mechanical load causes resorption of bone, whereas an increase leads to bone formation. This adaptive process is usually referred to as bone adaptive modeling or remodeling. Although this adaptive capacity of bone tissue has been known for more than a century, most of the processes involved in this behavior are still poorly understood. Specialized cells, the osteoclasts and osteoblasts, respectively, are responsible for resorption and formation, but the mechanisms involved in the regulation of these 'actor' cells are still unclear. Some way of measuring mechanical loading in bone must exist, in order for bone to adapt to the mechanical requirements. It has been hypothesized that bone contains cells which are sensitive to mechanical signals and which in turn control the actor cells. Cowin *et al.* (1991) suggested that osteocytes, because of their favorable position and architecture, may function as mechanoreceptors. It has indeed been shown that bone cells are sensitive to mechanical stimuli (Binderman *et al.*, 1984; Harrell *et al.*, 1977; Rodan *et al.*, 1975; Somjen *et al.*, 1980). More specifically, El Haj *et al.* (1990) showed that mechanical loading affects the cellular metabolism of osteocytes in cancellous bone. Recently, these studies were reviewed by Burger and Veldhuijen (1993). Osteocytes are regularly distributed throughout the bone, interconnected and connected with bone lining and actor cells at the bone surface (Menton *et al.*, 1984). This makes them very suitable candidates for the role of mechanical sensors. The hypothesis that bone contains mechanoreceptors implies that the regulation of bone mass by actor cells is governed locally by sensor cells. In other words, it is assumed that bone mass regulation occurs at a local level, which is typical for a self-organizational control process (Yates, 1987). It is noteworthy that as early as 1881 Roux suggested remodeling to be governed by such a 'quantitative self-regulating mechanism' (Roesler, 1987).

Recently, simulation models, using finite element (FE) analysis, in which bone remodeling is mathematically described to be a self-organizational biological control process (Beaupré *et al.*, 1990; Huiskes *et al.*, 1987, 1989; Weinans *et al.*, 1989, 1990, 1992) were developed. The sensor cells are assumed to 'measure' a mechanical signal and stimulate the actor cells (the osteoblasts and osteoclasts) in their vicinity to adapt bone mass accordingly. Weinans *et al.* (1990, 1992) discovered that when applied to a simple model of local trabecular bone, this process produced a discontinuous patchwork not unlike trabecular bone itself. They found that this behavior was caused by a positive feed-back loop in the regulation model. For a realistic set of parameter values the only stable solution is one in which elements are either empty or saturated to the maximal permissible density. In addition, they found that the process displayed chaotic behavior, due to its dependence on a large set of nonlinear equations (one per element). Although Weinans *et al.* (1992) emphasized the assets of the control scheme as an explanatory model for the emergence of trabecular morphology, its predictive quality was not without problems. First of all, the discontinuous element patchwork that emerges violates the continuum assumptions on which the finite element method is based. Hence, the stress calculation in the eventual mesh is highly inaccurate. Secondly, although the trends of the solution remain intact when the element mesh is refined, the solution is in fact mesh dependent.

This work generated considerable interest from other groups working in the same area. Jacobs and Beaupre (1992)

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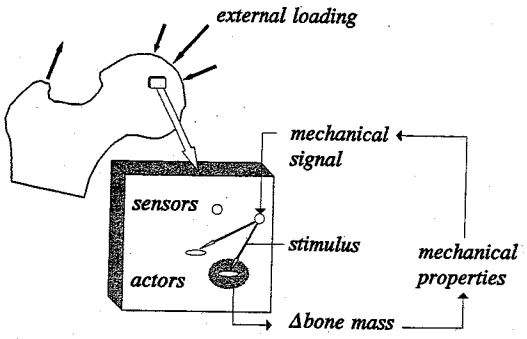

Fig. 1. The basic assumptions on the biological control mechanism of adaptive bone remodeling are shown in this scheme: a local mechanical signal is appraised by a sensor (osteocyte), which produces a stimulus for bone mass regulation to actors in its environment. Changes of bone mass are translated in changes of mechanical properties, thus also of mechanical signals.

reanalyzed the same local FE model with their bone remodeling simulation procedure (Beaupre *et al.*, 1990) and found the same effects. Harrigan and Hamilton (1992) developed analytical and numerical formulations of the problem. They confirmed the instability of the continuous solution, depending on the values of the parameters in the solution process. They stressed that the discontinuous solution, obtained for realistic parameters, was in fact impermissible. Jacobs *et al.* (1992) suggested to repair the process formulation by using quadratic instead of bilinear elements to attentuate the discontinuous behavior of the finite element model. They also suggested to average the densities calculated in the nodes over the surrounding elements, whereby the development of discontinuities is prevented.

We believe that the only problem of the self-organizational regulation models hitherto presented are the artifacts introduced inadvertently in the finite element formulation. In these models, each element is assumed to have one sensor cell which regulates bone mass in that same element. Hence, the region of sensor effect is limited by the boundaries of the elements, which are artifacts because they do not represent a physical reality. As a result, the solution is influenced by the element mesh. Or, in other words, the mesh begs the question.

In this paper an approach to the self-organizational bone regulation process which is physiologically and mechanically more consistent is presented. It is hypothesized that osteocytes act as sensors by appraising a mechanical signal (Fig. 1). Each sensor then produces a stimulus for bone mass regulation in its environment, the effect of which diminishes exponentially, away from the sensor's location. So each actor cell is stimulated by the sensor cells, depending on their remoteness from the sensor location. This approach introduces the concept of sensor (osteocyte) density, independent of the FE mesh, and of sensor influence range (Cowin *et al.*, 1991) as a model for the numerous interconnections of osteocytes and actor cells.

The purpose of this project was to investigate whether this hypothesis produces mechanically permissible solutions consistent with the trabecular morphology of bone. In addition, the effects of the parameter values in the model—sensor influence range, sensor density—the FE mesh and the external load on the predicted morphology were studied.

METHODS

The bone considered is assumed to have N sensor cells, uniformly distributed over its volume. An arbitrary sensor i measures a signal S_i, the strain energy per unit of mass, at its location calculated from (Weinans *et al.* 1989, 1992)

$$S_i = \frac{U_i}{\rho_i}, \tag{1}$$

where U_i is the strain energy density and ρ_i the density at the location of the sensor. The density $\rho(\mathbf{x},t)$ at location $\mathbf{x}$ is regulated by the stimulus value $\Phi(\mathbf{x},t)$, to which all sensor cells contribute, relative to their distance from $\mathbf{x}$. Hence,

$$\Phi(\mathbf{x},t) = \sum_{i=1}^{N} f_i(\mathbf{x})(S_i - k), \tag{2}$$

where k is a reference signal and $f_i(\mathbf{x})$ is a spatial influence function. Here, the function

$$f_i(\mathbf{x}) = e^{-[d_i(\mathbf{x})/D]} \tag{3}$$

was used, with $d_i(\mathbf{x})$ the distance between sensor i and location $\mathbf{x}$. This function is illustrated in Fig. 2; the rate of the spatial influence reduction is given by the parameter D. D represents the distance from a sensor at which location its effect has reduced to e^{-1}, i.e. 36.8 percent.

The density $\rho(\mathbf{x},t)$ is now governed by the rate

$$\frac{d\rho(\mathbf{x},t)}{dt} = \tau\Phi(\mathbf{x},t), \quad \text{with } 0 < \rho(\mathbf{x}) \leqslant \rho_{cb}, \tag{4}$$

were ρ_{cb} is the (maximal) density of cortical bone, and τ is a time constant regulating the rate of the process.

The elastic modulus at location $\mathbf{x}$ is calculated from the density according to (Currey, 1988, Rice *et al.* 1988)

$$E(\mathbf{x},t) = C\rho(\mathbf{x},t)^{\gamma}, \tag{5}$$

where C and γ are constants.

In the FE model used, the stress components $\boldsymbol{\sigma}$ and the strain components $\boldsymbol{\varepsilon}$ are determined at the integration points of each element, and interpolated per element to give their values in the sensor points ($\boldsymbol{\sigma}_i$ and $\boldsymbol{\varepsilon}_i$). The strain energy density is calculated from the tensor product $U_i = 1/2\boldsymbol{\sigma}_i : \boldsymbol{\varepsilon}_i$, where i refers to the sensor number. Using equation (1) the signal per sensor point S_i is then determined. The stimulus Φ_j is evaluated in the center of each element j, using equation (2); and a new density value ρ_j is calculated in element j, in accordance with equation (4), from

$$\rho_j(t+\Delta t) = \rho_j(t) + \Delta t\tau\Phi_j(t), \tag{6}$$

where Δt is the time step in the iteration process. The iteration is continued until no more significant changes in the density distribution occur.

This method was tested in a two-dimensional plate model, as applied earlier by Weinans *et al.* (1992). The plate is loaded by a compressive stress distribution, decreasing linearly over the top edge (Fig. 3). In the calculations, a uniform initial density distribution of $\rho = 0.8\ \mathrm{g\,cm^{-3}}$ was used. The bone

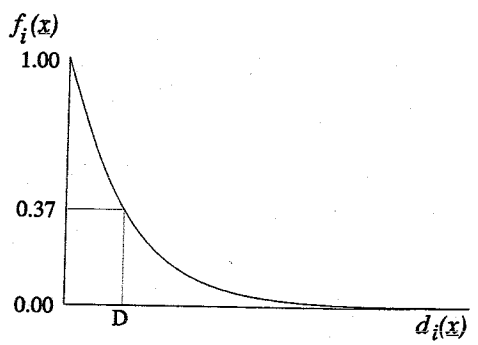

Fig. 2. The spatial influence of sensor i, expressed as $f_i(\mathbf{x})$, is a function of $d_i(\mathbf{x})$, the distance between sensor i and location $\mathbf{x}$.

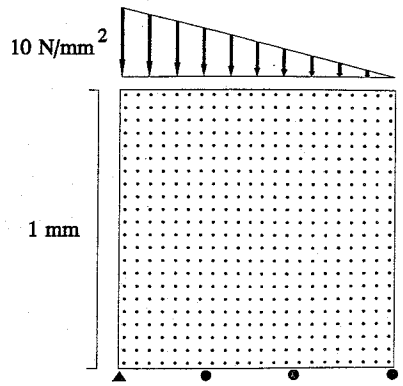

Fig. 3. Two-dimensional plate model of bone tissue with sensor cells (dots) subjected to a compressive load as indicated.

tissue is assumed to be isotropic. The reference signal value $k=0.25\ \mathrm{J\,g^{-1}}$, the maximal density $\rho_{cb}=1.74\ \mathrm{g\,cm^{-3}}$, $\tau=1$ $(\mathrm{g\,cm^{-3}})^2/(\mathrm{MPa\ time\text{-}unit})$, $C=100\ \mathrm{MPa}/(\mathrm{g\,cm^{-3}})^2$ and γ is 2.0, as in the calculations of Weinans *et al.* (1992). The plate was meshed with 40×40 four-node elements. The sensor distribution was uniform and its density was assumed to be $1600\ \mathrm{mm^{-2}}$ ($N=1600$), associated with a sensor influence parameter of $D=0.025$ mm. The behavior of the model was studied for variations of the mesh density, the sensor density (N), the sensor range of influence D and the external load.

RESULTS

First the model was tested relative to the earlier one used by Weinans *et al.* (1992), by reproducing its conditions. For that purpose, the distance-influence parameter was diminished to $D=0.001$ mm. The results shown in Fig. 4 are very similar for both models, indicating that indeed the conditions of earlier models can be reproduced. For a larger range of

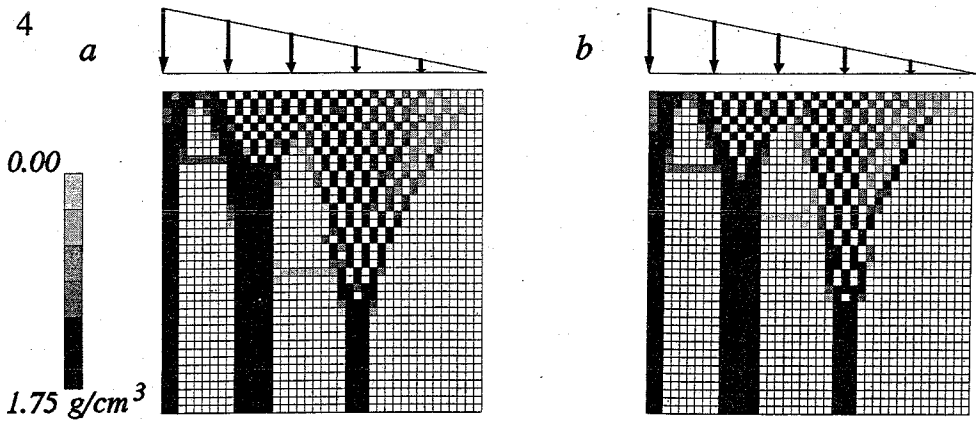

Fig. 4. Comparison of the density distributions as predicted by the earlier model (a), used by Weinans *et al.* (1992), and the model described here, where the distance-influencing parameter is diminished to $D=0.001$ mm (b). In both models the number of sensors is equal to the number of elements: $N=1600$.

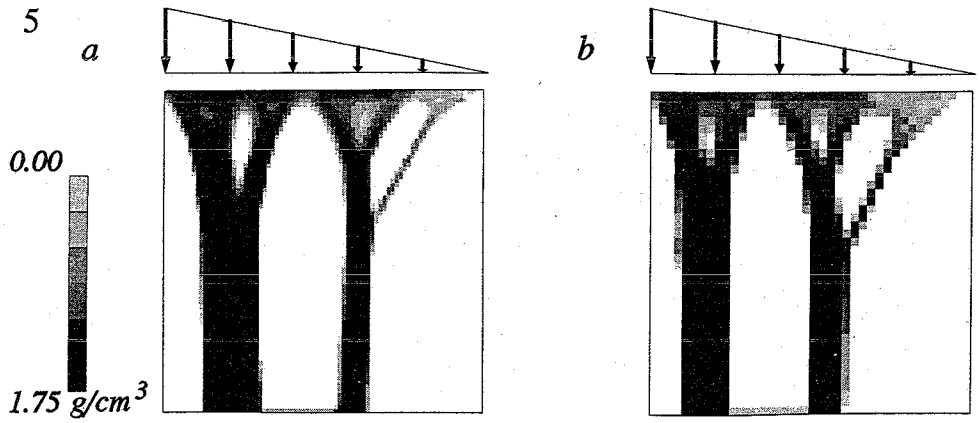

Fig. 5. Density distribution resulting from the bone remodeling simulations using a 80×80 FE mesh (a) and a 40×40 FE mesh (b). The number of sensors $N=1600$ and the influencing parameter $D=0.025$ mm.

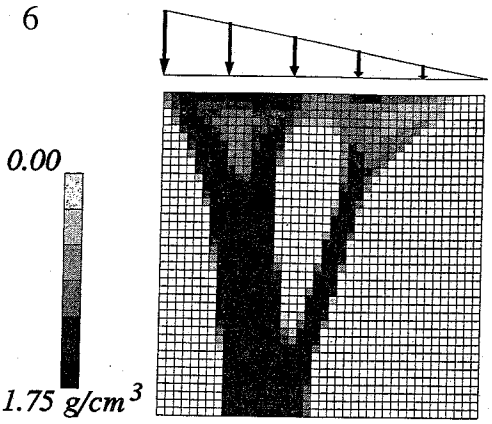

Fig. 6. Density distribution as predicted by the bone remodeling simulation, where the influencing parameter D is increased to 0.05 mm ($N=1600$).

influence of the sensors, (such that the stimuli generated by the sensors overlap), the model behaved as expected, producing trabecular-like structures without the checker board patterns seen as a result of earlier models (Fig. 5; $D=0.025$ mm).The solution has been shown to be independent of mesh refinement, as shown in Fig. 5(a) and (b), where the results for 80×80 and 40×40 meshes are compared. Although the morphology is not equal in both cases due to the differences in the density-pattern representations, the solutions are structurally similar.

As the sensor grid was separated from the FE mesh, the number of sensors could be varied independently. A saturation effect occurred when the number of sensors was increased: increasing the sensor density beyond a particular value (N about 1000) did not further influence the results. The value of this 'cut-off' density number also depended on the influence parameter D; for a larger value of D, saturation occurred at a lower sensor density.

Changing the range of action of the sensors D, for a constant sensor density, has a distinct influence on the morphology (Fig. 6). If D is small relative to the plate size,

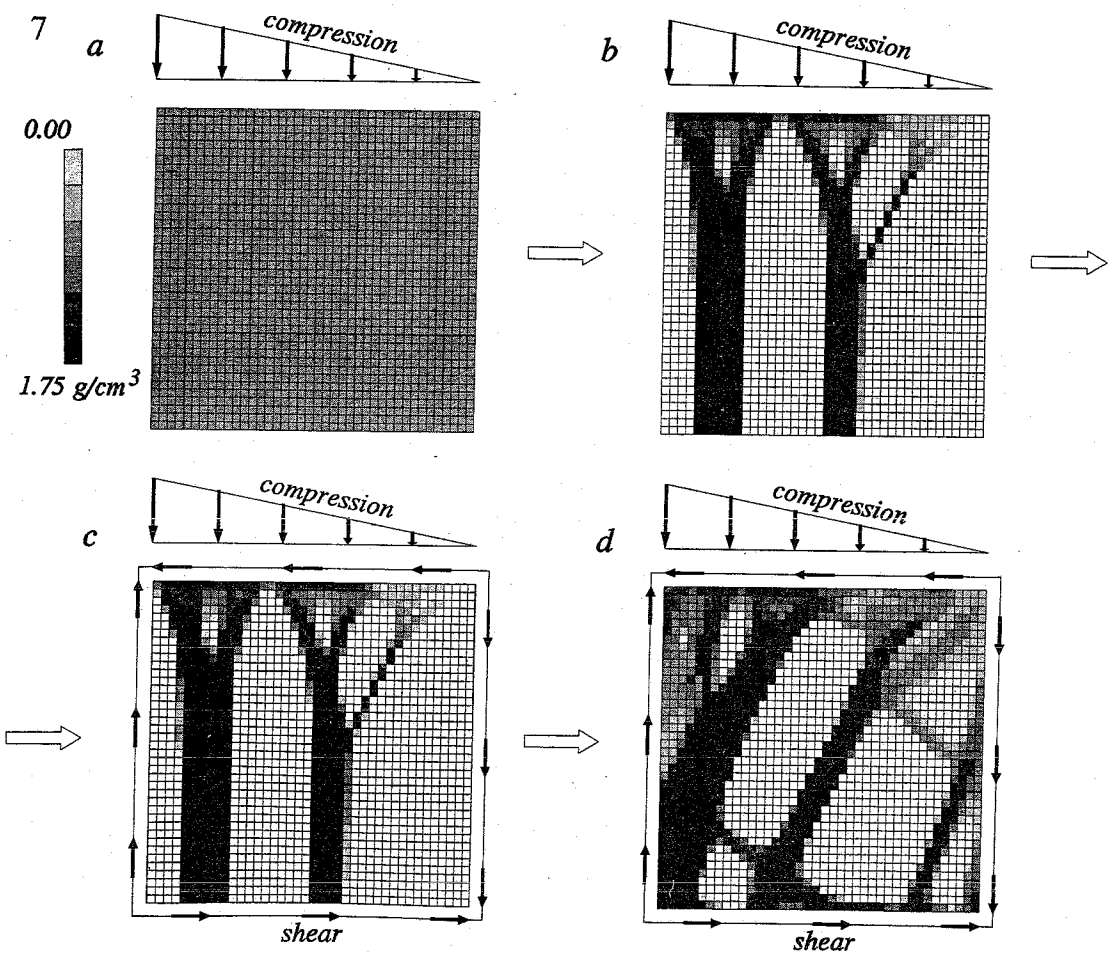

Fig. 7. Bone remodeling is simulated starting with a uniform density distribution and using a compressive ramp load (a). After remodeling, a trabecular morphology has emerged (b). When equilibrium is reached an additional shear load (3.5 N mm^{-2}) is applied (c). The simulation predicts that the morphology adapts to the new loading requirements and a new equilibrium is reached (d).

finer struts are formed and more branching than for a larger D can be seen. A form of 'self-similarity' is evident when comparing Figs 5 and 6. Similar results were obtained when the 'scale' of the problem was varied, i.e. by enlarging the plate dimensions and range of influence D by the same ratio.

Solutions hitherto produced were based on a uniform density as the initial condition. That the model can also explain transformations of morphology, in the sense of 'Wolff's law', is demonstrated in Fig. 7. The morphology that emerged from the uniform distribution as stimulated by the compressive ramp load [Fig. 7(b)] is provided with additional boundary shear stresses. As a result, the morphology transforms to a new equilibrium [Fig. 7(d)].

DISCUSSION

We have developed a simulation model of the self-organizational biological control process of bone remodeling, suitable to study the relationship between trabecular morphology and load and the hypotheses comprised in Wolff's law. It should be clear that for the purpose of studying trabecular morphology, the element mesh should be fine enough to describe the trabeculae adequately. In order to compare the results with the results from previous models some simplifications have been made in this study. We used a two-dimensional square plate and a uniform initial density distribution to investigate the model behavior. This is not a realistic assumption for bone remodeling, but as shown, the model also performs well from a non-uniform starting configuration. Further, a uniform sensor distribution was assumed, but this is no principle limitation of the model.

In this model, the sensor points are defined independently of the FE mesh. In other words, the sensor cells are modeled separately from the actors which are represented by the elements in the model, enabling us to vary sensor density and sensor influence. The model results reported by Weinans *et al.* (1992) can be reproduced if the number of sensors is equal to the number of elements and the influence domain of the sensors is smaller than the element size. The difference between the figures shown here and the figures from Weinans *et al.* (1992) are due to a difference in the time increments used. Weinans *et al.* (1992) used larger time steps which resulted in a different remodeling pathway and slightly different results. The behavior of the model confirmed our assumption that the checkerboard-type density patterns found in earlier models were caused by a discontinuous stimulus distribution due to the artificial limitation of sensor action to the bounded regions of one element.

The sensors are considered to control the remodeling process by comparing the mechanical signal with a reference signal. Further, we presumed that their influence decreases exponentially with increasing distance. Obviously, as it is still unknown if the remodeling process is controlled by the sensor cells, as opposed to the actor cells for instance, and how sensor cells influence actor cells, no evidence exists to support these assumptions. But, if we assume that the osteocytes, located in the bone matrix, are sensitive to mechanical stimuli as was shown by El Haj *et al.* (1990) and that they activate the actor cells by using chemical pathways (Binderman *et al.*, 1984; Rodan *et al.*, 1975), these propositions are quite realistic. The distance over which the sensor cell can influence actor cells is also speculative. The existence of a connective network of osteocytes is widely accepted, and osteoblasts and bone lining cells are also believed to take part in this network (Cowin *et al.*, 1991; Menton *et al.*, 1984). Thus, it seems reasonable to assume that the area which is influenced by a sensor is limited, yet, that this area is large enough, such that the actor cells at the trabecular surfaces can be reached. Therefore, we assumed that the influence domain of the osteocytes has a magnitude in the order of the trabecular thickness (about 0.15 mm). Using this more realistic environmental-sensor-influence model, trabecular-like structures are formed, without the formation of alternating density patterns near the load application surface. Hence, the problem of checkerboard-type density patterns can be solved by using a more realistic model without the addition of the averaging procedures proposed by Jacobs *et al.* (1992), provided that the element size is small enough in proportion to the sensor influence range (i.e. the element size should be in the range of the influence parameter D or smaller).

Due to the separation of FE mesh and sensor grid, the FE mesh can be refined without changing the essential model characteristics. The similarity between the solutions for different mesh refinements confirm that the solution is no longer FE mesh dependent.

The model can be used to study the relationship between sensor distribution (e.g. osteocyte density) and trabecular morphology. The results obtained suggest that the effects of sensor cell density are subject to a saturation criterion. It appears that the solution is independent of the number of sensors, provided that the stimulus from the sensors is 'adequately' distributed over the structure. A reduced number of sensors relative to the 'saturation' amount results in a coarser structure. Note that reducing the number of sensors while maintaining a constant range of influence will ultimately lead to a discontinuous stimulus distribution and hence an alternating density pattern. Accordingly, the sensor influence parameter D affects the minimum number of sensors necessary to obtain a continuous stimulus distribution. For a larger D the critical number of sensors is smaller. The critical sensor density was about $1000\ \mathrm{mm}^{-2}$ where D is 0.025 mm. This value lies in the same order of magnitude as the values of osteocyte lacunae numbers found in spongy bone of several different species, which ranged between 1000 and $3000\ \mathrm{mm}^{-2}$ (Marotti *et al.*, 1990). However, these figures should be considered carefully. Marotti *et al.* (1990) only measured the number of osteocyte lacunae per area of bone tissue. The number of osteocytes per volume of bone is still unclear. In order to make a valid comparison between experimental data and the model results, it is necessary to establish the number of osteocytes per volume of bone tissue.

It was also shown that D has a distinct effect on the eventual morphology of the structure. The results indicate that the formation of trabecular-like structures is characteristic of the model behavior, as has been suggested earlier by Weinans *et al.* (1992) and Harrigan and Hamilton (1992), but the thickness of the struts and the degree of branching is determined by the range of action of the sensors, whereby a smaller range results in finer struts and more branching. This effect may be explained by a less homogeneous stimulus distribution, i.e. larger stimulus gradients, in the case of a smaller range of action of the sensors. It was found that the thickness of the trabeculae produced by the model was similar to the magnitude of the sensor influence domain. This was in agreement with our assumption stated earlier.

The results presented here clearly show that predicted trabecular morphology, i.e. sizes and branching of struts, is dependent on the actual relationship between local load, sensor density and range of influence. Our hypothesis is that differences in trabecular morphology in various species can be explained by variations in these parameters. We believe that trabecular morphology can be explained as a result of a load-dependent local self-organizational biological control process. We conclude that the method described here is suitable to study the effect of the various parameters presumably controlling this process and may be used to estimated physiological parameters.

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