ENGINEERING TRANSACTIONS • *Engng. Trans.* • **49**, 2–3, 155–164, 2001
Polish Academy of Sciences • Institute of Fundamental Tecyhnological Research
10.24423/engtrans.551.2001

ON A CLASS OF BONE CELL-BASED REMODELING LAWS WITH SPATIAL FADING INFLUENCE OF STIMULI

T. LEKSZYCKI

POLISH ACADEMY OF SCIENCES
INSTITUTE OF FUNDAMENTAL TECHNOLOGICAL RESEARCH
ul. Świętokrzyska 21, 00–049 Warsaw
tlekszyc@ippt.gov.pl

In the present paper the class of cell-based bone remodeling laws is considered. The fundamental assumption is that of fading in space influence on actor cells osteocytes functioning as sensors. The actor cells – osteoblasts and osteoclasts are responsible for the changes of bone micro-structure. The model proposed in the previous publications of other authors, is based on the assumption of exponential influence function and density of strain energy as the stimulus to which the osteocytes are sensitive, see [11, 12, 14]. As the result of the adaptation according to such remodeling law the porous material is created. The topology of the micro-structure of this material is dependent on the mechanical loading conditions and the characteristics of the interactions of cells. The aim of the present work was to examine if this phenomenon is characteristic only for this specific law or represents a rather general property associated with the hypothesis of fading influence of the cells. Different influence functions were examined for different functionals selected to represent the stimulus. It follows from the these considerations that the fading influence of the cells plays fundamental role for the remodeling process and the creation of trabecular structure. Such structures were obtained for several adaptation laws based on different influence functions and functionals representing the stimulus. They were compared with the results obtained for the adaptation law proposed and discussed in [11, 12, 14]. The numerical calculations suggest that the idea of spatial fading influence of the cells can be possibly combined in future with the results of the research on the biological mechanisms of the bone remodeling to propose more sophisticated models.

Key words: adaptation, bone remodeling, fading influence, osteocyte, osteoblast, osteoclast, porous material, stimulus, trabecular structure.

1. INTRODUCTION

The ability of bones to adapt to variable conditions is well-known for more than a century. In response to altered biochemical states and mechanical conditions, they change their external shapes and internal structures. The understanding of the mechanisms responsible for this process is important from both the theoretical and practical viewpoints. Despite intensive research on this subject there is no unanimity as for many related problems. For instance, the questions concerning the phenomena responsible for bone remodeling, mechanosensory mechanisms in bone including sensing of different signals and transmitting them to the effector cells, the mechanisms of bone maintenance, deposition and resorption and others, still require more investigations, see e.g. COWIN [21, 23] and BURR and MARTIN [1], HARRINGAN and HAMILTON [27]. As a result of this situation, many mathematical models of bone adaptation based on different assumptions and taking into account diverse mechanical and non-mechanical effects have been proposed, see e.g. TABBER [7], HART and DAVY [18], HART *et al.* [19], LEVENSTON and CARTER [9], CARTER and ORR [3], COWIN and co-workers [2, 4, 20, 22, 24, 25], PRENDERGAST *et al.* [17].

Different approaches are possible. In the present paper, the class of remodeling laws that are based on the assumption of influence of cells fading with the distance is considered. Although the true biological stimulus responsible for bone remodeling was much discussed in the literature, it is still not precisely known, see [21]. On the other hand, some knowledge is available concerning a connected cellular network (CCN). The fundamental bone cells that are involved in the bone maintenance and remodeling are osteocytes, osteoblasts and osteoclasts. The osteoblasts that lie on all bony surfaces can be active or inactive. Inactive osteoblasts have potentiality to be activated. In the bone extracellular matrix there are located osteocytes that have many cytoplasmic processes (approx. 80). These processes are connected with other processes from neighbor osteoclasts. The length of the processes is approximatelly 15μm. They lie inside the channels called canaliculi. This way all of the cells, except osteoclasts, are connected into the complex three-dimensional network, cf. COWIN [23]. This is a commonly accepted idea that remodeling mechanism in bone is composed of three important elements namely, i) the system that is stimulated by mechanical loading, ii) the system necessary to "translate" the information about mechanical state to a communicable signal and, iii) the system transmitting the signal to the effector cells. The cells that are responsible for bone maintenance and remodeling are osteoblasts and osteoclasts. The cells that work more or less as the sensors are osteocytes.

The regulatory mechanism driven by the interaction between osteocytes and the actor cells was hypothesized and and discussed in many works, see e.g. WEINBAUM *et al.* [21, 26], COWIN and MOSS-SALENTJIN [23], LANYON [8], MULLENDER *et al.* [14], MULLENDER and HUISKES [11, 12, 13]. The concept of regulatory function of the system osteocytes – osteoblasts and osteoclasts was used to propose the bone remodeling law, see MULLENDER *et al.* [14]. To formulate this law, two important assumptions were postulated. The first one pertains to the stimulus to which osteocytes are sensitive. It was assumed that density of strain energy plays the role of stimulus. The second one is associated with the idea of fading influence of osteocytes onto the actor cells. The exponential influence function was used to scale the signal transmitted from the sensor cells to osteoblasts and osteoclasts depending on the distance between them. This remodeling law was examined in numerical simulations of the adaptation process. It was shown that it leads to the creation of bone trabecular structure, [11, 12, 14]. The parameters characterizing the outcoming material such as the sizes of pores, their distribution and density, the orientation, sizes and thicknesses of trabeculas are dependent on many factors: among the others, the characteristics of cell interactions, the mechanical loading and non-mechanical effects. Also density and distribution of osteocytes influence the microstructure of bone what is in agreement with the experimental observations, see e.g. [10]. An interesting question arises in connection with this adaptation model – is the creation of trabecular material microstructure associated *only* with this specific remodeling law, or is it rather characteristic for the phenomenon of the influence between the cells fading in space?

The aim of the present work is to examine if the creation of porous material is characteristic only for this specific law or represents rather a general property associated with the hypothesis of fading influence of the cells. Different influence functions were examined for different functionals selected to represent the stimulus. Selected variants of the remodeling law are shortly discussed in the next section. It follows from these considerations that the fading influence of the cells plays a fundamental role for the remodeling process and the creation of trabecular structure. Such structures were obtained in computer calculations for several adaptation laws based on different influence functions and functionals representing the stimuli. They were compared with the results obtained for the adaptation law proposed and discussed in [11, 12, 14]. In the third section, selected results of numerical calculations are presented. The discussed remodeling laws were implemented into the numerical code and illustrative examples were calculated to examine the effects of different parameters on the adaptation process. It was shown that different remodeling formulas enable the creation of quantitatively similar porous materials.

The numerical calculations suggest that the idea of spatial fading influence of the cells can be possibly combined in future with the results of the research on the biological mechanisms of the bone remodeling.

2. Remodeling law

In this section the class of cell-based remodeling laws is discussed. The general idea of the control mechanism is as follows. The osteocytes which are distributed in the bone tissue work as the sensors being capable of sensing mechanical signals dependent on the loading conditions. This signal is transformed to the signals "understandable" by the actor cells. These transformed signals are transmitted in turn to osteoblasts and osteoclasts which adapt the local mass of the bone respectively to the magnitude of the received stimulus. This is a widely used concept that the remodeling of bone results in the variation of material density. This in turn results in the variation of material parameters, as for example Young's modulus $E(\mathbf{x},t)$. Often, according to experimental data published by Currey [6], the cubic relation between the local density of the material and $E(\mathbf{x},t)$ is assumed,

$$E(\mathbf{x},t) = Cm^{\gamma}(\mathbf{x},t)\,, \tag{2.1}$$

where C and γ are constants and m denotes relative density. This formula is sometimes questionable. Thus in the present work we do not focus on the specific relation between Young's modulus and the material density. Instead, an assumption is made that osteoblasts and osteoclasts adapt the Young's modulus according to the signals received from osteocytes. The material distribution can be calculated then for the assumed specific relation between mass and mechanical characteristics. Let us assume that the material that is used to build the bone structure is isotropic. This is by no means true in reality, but in present initial study such simplification is acceptable.

Let us denote the stimulus sensed by the i-th osteocyte by $S_i(t)$. In the present paper this function represents the local mechanical state at $\mathbf{x} = \mathbf{x}_i$ where the i-th osteocyte is located. But in the future, also non-mechanical effects can be included in the considerations. According to Mullender *et al.* [14] and Mullender and Huiskes [11], the signal $H(\mathbf{x},t)$ received from the i-th sensor cell by the effector cell located at $\mathbf{x}$ is proportional to the difference of the stimulus $S_i(t)$ and some reference value scaled by the influence function $f(r_i(\mathbf{x}))$, where $r_i(\mathbf{x})$ denotes the distance between the i-th sensor and the effector cell:

$$H(\mathbf{x},t) = (S_i(t) - k) f(r_i(\mathbf{x}))\,. \tag{2.2}$$

The total signal Φ driving the changes of the tissue at the position $\mathbf{x}$ is the sum of the signals received from the osteocytes. The value k represents the physiological level of signal at the equilibrium state:

$$\Phi(\mathbf{x},t) = \sum_{i=1}^{N} f(r_i(\mathbf{x}))(S_i(t) - k)\,. \tag{2.3}$$

In Eq. (2.3) the total number of osteocytes was denoted by N. Now the remodeling law can be written in the form

$$\frac{dE(\mathbf{x},t)}{dt} = \alpha\Phi(\mathbf{x},t)\,, \tag{2.4}$$

where α represents the parameter used to adjust the rate of changes.

In general, the influence function depends on the phenomenon which is assumed as a driving force of remodeling and the mechanism responsible for signal transmission to the effector cells. It can be determined from the corresponding set of governing equations. The investigations of specific effects that could be possibly involved in this process do not fall within the framework of the present work. Instead, the simplified case is considered and two postulated influence functions are examined, the one proposed in [14]

$$f(r_i(\mathbf{x})) = \exp\left(-r_i(\mathbf{x})/D\right)\,, \tag{2.5}$$

and the second one in the form

$$f(r_i(\mathbf{x})) = \frac{D}{r_i(\mathbf{x})}\,. \tag{2.6}$$

In the last two equations the parameter D denotes some characteristic size. For instance, in the first case it can be the distance from osteocyte where its influence is reduced by the factor $\exp(-1)$. In the second case D can represent, for instance, the approximate size of osteocyte. It is worth to mention that in the second case an assumption has to be made that the osteocyte has some finite dimension, therefore $r_i(\mathbf{x}) \neq 0$.

In addition to different influence functions, two functions representing stimulus are considered in the present work. The first one is described by the density of the strain energy sensed by i-th osteocyte,

$$S_i(t) = \frac{1}{2}\{\epsilon(\mathbf{x}_i,t)\}^T\{\sigma(\mathbf{x}_i,t)\}\,, \tag{2.7}$$

where $\{\epsilon(\mathbf{x}_i,t)\}$ and $\{\sigma(\mathbf{x}_i,t)\}$ represent the vectors of strain and stress, respectively.

The other tested stimulus function was a function of stress only:

$$S_i(t) = \{\sigma(\mathbf{x}_i, t)\}^T \{\sigma(\mathbf{x}_i, t)\}\,. \tag{2.8}$$

In the next section it will be shown that the interactions between the osteocytes and effector cells lead to creation of porous media. The parameters characterizing the outcoming material such as the sizes of the pores, their distribution and density, the orientations, sizes and thicknesses of trabeculas are dependent on many factors. On the one hand, the characteristics of cell interactions decide about these parameters. Moreover, the mechanical loading and non-mechanical effects significantly influence the topology of the micro-structure of the bone. These complex relations are responsible for the changes of bone which are meant as the adaptation process.

3. Numerical results

The numerical calculations have been performed to examine the effect of bone tissue remodeling governed by the formulas discussed in the previous section. Two-dimensional plain stress FE model of the 2mm by 2mm square sample of

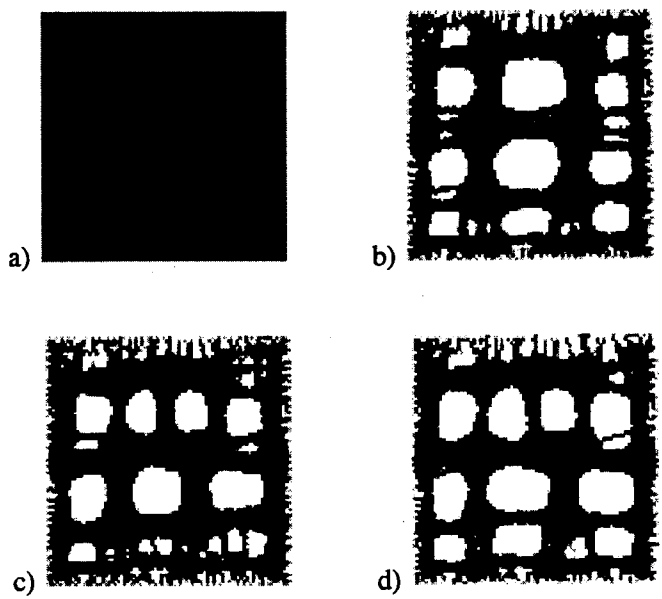

FIG. 1. Results of computer simulations. Examples of trabecular tissue configurations obtained for different adaptation laws, a) initial state, b) influence function Eq. (2.5), stimulus Eq. (2.7), c) influence function Eq. (2.5), stimulus Eq. (2.8), d) influence function Eq. (2.6), stimulus Eq. (2.7).

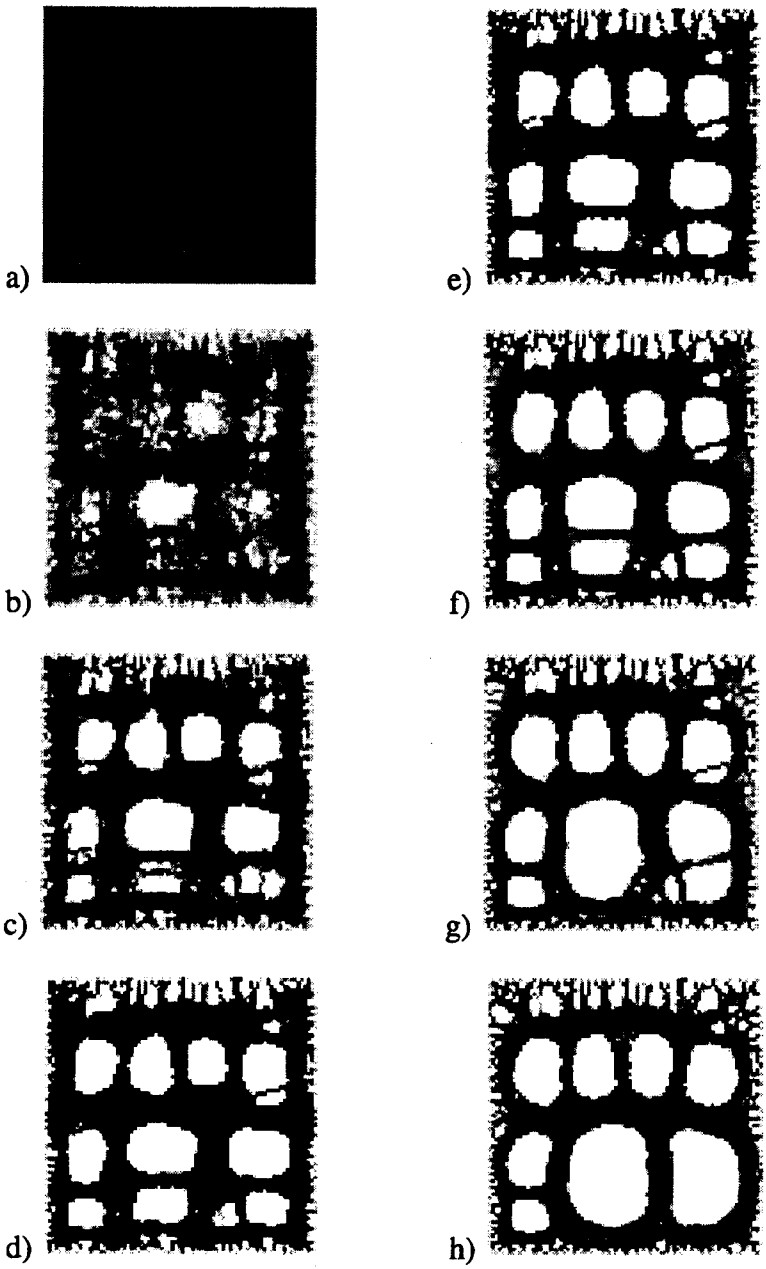

FIG. 2. Adaptation process for variable loading. a) initial state, b) – d) uniform compression in vertical and uniform tension in horizontal directions, e) – h) uniform tension in vertical and horizontal directions.

bone material was used in the analysis. The applied material was isotropic. The osteocytes were randomly distributed in the considered domain. Different values of osteocytes density and different values of influence parameter D was examined. According to MAROTTI [5], the density of osteocytes varies between $500/\text{mm}^2$ and $3000/\text{mm}^2$. In the calculations density of $1000/\text{mm}^2$ was assumed. In all of the examined cases the calculations proved similar effect to that observed by MULLENDER and HUISKES [14], who found that, increasing the values of influence parameter results in reduction of pore density and longer and stiffer struts. Another important observation, which also agrees with the results of earlier investigations, is that trabecular topology strongly depends on the loading conditions.

In Fig. 1 the results of the calculations are presented for three different remodeling laws and the same loading conditions. Uniform compression in vertical and uniform tension in horizontal directions were applied to the samples. In this example the external loading did not vary in time and the effect of remodeling of initially homogeneous and isotropic material was observed. Figure 1b corresponds to the adaptation law with density of strain energy Eq. (2.7) as stimulus and the influence function defined by Eq. (2.5). In Fig. 1c the result of calculation for influence function given by Eq. (2.5) and stress function (2.8) as the stimulus is presented. Figure 1d corresponds to the strain energy as the stimulus but the influence function is given by Eq. (2.6). We observe that the results of remodeling, according to these three different laws, are qualitatively similar to each other.

In Figs. 2 the steps of adaptation for variable loading are displayed. The calculations were performed for the strain energy as the stimulus and the influence function given by Eq. (2.6). Figures 2a – d correspond to constant uniform compression in vertical and uniform tension in horizontal directions. Then the loading was changed. Figures 2e – h correspond to uniform tension in vertical and horizontal directions. As could be expected, the structure of the material evolved a to new topology after application of a new loading.

4. CONCLUDING REMARKS

Careful study of the papers devoted to cell-based remodeling law including in the formulation fading influence of sensor cells on the actor cells suggests that the resulting trabecular structure of bone is rather an effect of fading interaction hypothesis than the characteristic phenomenon for this specific model. The present paper is a study performed to examine different adaptation laws based on the same assumption of fading influence. Different influence functions and stimulus

functions were considered. There is no quarantee that the remodeling laws discussed and examined in the previous sections are justified. However, the results of these initial investigations suggest that the obtained formulas result in adaptation effects similar to these observed in the nature. Among other important issues is the fact that the porous media are created as the effect of mechanical load and the interaction between osteocytes, osteoblasts and osteoclasts. The characteristics of such materials are time-variable and vary with respect to mechanical loading and non-mechanical effects what is understood as the adaptation process. The results show that the creation of porous material during adaptation to mechanical loading can be obtained as an effect of application of different remodeling formulas. This also suggests that the assumption of fading influence can be combined in future with the deeper investigations of remodeling mechanisms in order to propose more reliable remodeling laws. For instance, the models based on damage accumulation effect proposed in recent years, see e.g. LEVENSTON and CARTER [9], PRENDREGAST and TAYLOR [15], PRENDERGAST and HUISKES [16], are possible candidates for such extension. This subject requires however more investigations.

ACKNOWLEDGMENT

This work was supported by Polish State Committee for Scientific Research, grant No. 8T11F00517.

REFERENCES

1. D. B. BURR, R. B. MARTIN, *Mechanisms of bone adaptation to the mechanical environment*, Triangle, **31**, 2/3, 59–76, 1992.
2. D. H. HEGEDUS, S. C. COWIN, *Bone remodeling II: small strain adaptive elasticity*, J. Elasticity, **6**, 337–355, 1976.
3. D. R. CARTER, T. E. ORR, *Skeletal development and bone functional adaptation (review, 36 refs.)*, Journal of Bone & Mineral Research, **7**, S389–95, Dec. 1992.
4. G. LUO, S. C. COWIN, A. M. SADEGH, Y. P. ARRAMON, *Implementation of strain rate as a bone remodeling stimulus*, J. of Biomechanical Engineering, **117**, 3, 329–338, 1995.
5. G. MAROTTI, V. CANÉ, S. PALAZZINI, C. PALUMBO, *Structure-function relationship in the osteocyte*, Ital. J. Miner. Electrolyte Metab., **4**, 93–106, 1990.
6. J. D. CURREY, *The effect of porosity and mineral content on the Young's modulus of elasticity of compact bone*, J. of Biomech., **21**, 131–139, 1988.
7. L. A. TABER, *Biomechanics of growth, remodeling and morphogenesis*, Appl. Mech. Rev., **48**, 8, 487–545, 1995.
8. L. E. LANYON, *Osteocytes, strain detection, bone modeling and remodeling*, Calcif Tissue Int., **53**, S1, 102–106, 1993.

9. M. E. LEVENSTON, D. R. CARTER, *An energy dissipation-based model for damage stimulated bone adaptation*, J. of Biomechanics, **31**, 7, 579–586, 1998.
10. M. G. MULLENDER, D. D. van der MEER, R. HUISKES, P. LIPS, *Osteocyte density changes in aging and osteoporosis*, Bone, **18**, 2, 109–113, 1996.
11. M. G. MULLENDER, R. HUISKES, *Proposal for the regulatory mechanism of Wolff's law*, J. of Orthopaedic Research, **13**, 4, 503-5-12, 1995.
12. M. G. MULLENDER, R. HUISKES, *The regulation of functional adaptation in trabecular bone*, [In:] *Bone Structure and Remodeling*, A. ODGAARD and H. WEINANS [Eds.], Recent Advances in Human Biology – Volume 2, World Scientific, 181–187, 1996.
13. M. G. MULLENDER, R. HUISKES, *Osteocytes and bone lining cells: which are the best candidates for mechano-sensors in cancellous bone?*, Bone, **20**, 6, 527–532, 1997.
14. M. G. MULLENDER, R. HUISKES, H. WEINANS, *A physiological approach to the simulation of bone remodeling as a self-organizational control process*, J. of Biomechanics, **27**, 11, 1389–1394, 1994.
15. P. J. PRENDERGAST, D. TAYLOR, *Prediction of bone adaptation using damage accumulation*, J. Biomech., **27**, 1067–1076, 1994.
16. P. J. PRENDERGAST, R. HUISKES, *Microdamage and osteocyte-lacuna strain in bone: a microstructural finite element analysis*, J. of Biomechanical Engineering, **118**, 2, 240–246, 1996.
17. P. J. PRENDERGAST, R. HUISKES, K. SOBALLE, *ESB Research Award 1996. Biophysical stimuli on cells during tissue differentiation at implant interfaces*, J. of Biomechanics, **30**, 6, 539–548, 1997.
18. R. T. HART, D. T. DAVY, *Theories of bone modeling and remodeling*, Bone Mechanics, S. C. COWIN [Ed.], CRC Press, Boca Raton, FL, 253–277, 1989.
19. R. T. HART, D. T. DAVY, K. G. HEIPLE, *A computational method for stress analysis of adaptive elastic materials with a view toward application in strain-induced bone remodeling*, J. Biomech. Engng., **106**, 342–350, 1984.
20. S. C. COWIN, *On the minimization and maximization of the strain energy density in cortical bone tissue*, J. of Biomechanics, **28**, 4, 445–447, 1995.
21. S. C. COWIN, *The search for mechanism in bone adaptation studies*, Mechanics in Biology, ASME 2000, AMD-Vol. 242/BED-Vol. **46**, 173–184, 2000.
22. S. C. COWIN, D. H. HEGEDUS, *Bone remodeling I: theory of adaptative elasticity*, J. Elasticity, **6**, 3, 313–326, 1976.
23. S. C. COWIN, L. MOSS-SALENTIJN, M. L. MOSS, *Candidates for the machanosensory system in bone*, J. Biomech. Engng., **113**, 191–197, 1991.
24. S. C. COWIN, S. WEINBAUM, *Strain amplification in the bone mechanosensory system (review, 30 refs.)*, American Journal of the Medical Sciences, **316**, 3, 184–188, 1998.
25. S. C. COWIN, R. R. NACHLINGER, *Bone remodeling III: uniqueness and stability in adaptive elasticity theory*, J. Elasticity, **8**, 3, 285–295, 1978.
26. S. WEINBAUM, S. C. COWIN, Y. ZENG, *A model for the excitation of osteocytes by mechanical loading-induced bone fluid shear stresses*, J. of Biomechanics, **27**, 3, 339–360, 1994.
27. T. P. HARRINGAN, J. J. HAMILTON, *Bone strain sensation via transmenbrane potential changes in surface osteoblasts: loading rate and microstructural implications*, J. of Biomechanics, **26**, 183–200, 1993.

Received May 15, 2001.