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Bone remodelling and bone adaptation

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Bone remodelling is a very complicated process that can be characterised as close relationship of biomechanical effects and biochemical reactions. It is not possible to give an exact definition of the bone remodelling if we take into consideration the aspects related merely to biomechanics or to biochemistry. Biochemical processes in a remodelled bone tissue depend on the dominant force and moment effects or on the stress and strain state of the tissue. The stress (strain) tensors initiate and govern the rate of biochemical remodelling processes.

The paper presented deals with fundamental stoichiometric equations of bone remodelling, kinetic equations of remodelling and rate constants of remodelling. The rates of bone remodelling depend on mechanical effects or on stress (strain) tensors. The spherical stress tensor controls the rate of biochemical remodelling reactions, while the deviator of a stress (strain) tensor initiates biochemical reactions. The micro-strains cause the flow of a liquid in the extra-cellular space of osteocytes and initiate the receptor activity of integrins α, β. The micro-strains of a mineralised matrix and the flow of an extra-cellular liquid result, for example, in the production of prostaglandin E_2 and in the subsequent resorption of a bone tissue.

Keywords: bone remodelling, stoichiometric equations, kinetic equations, stresss, strain, rate of remodelling, osteoclasts, osteoblasts, osteoid, osteocyte, integrin

1. Introduction

The exact expressions of biomechanical and biochemical processes of remodelling a bone tissue have not been defined satisfactorily up to now. This state of knowledge is not caused merely by the complexity of biochemical processes but also by the exacting character of the linkage between biomechanical and biochemical principles. The important tool that makes it possible to achieve the objective is biothermodynamics. Owing to the fact that biochemical reactions of creating new corticalis include the movement of masses of the individual substances (i.e. the mixture of molecules and atoms), the kinetics of the reactions can be expressed by means of differential equations. Their validity can be verified on the basis of partial cognition

of remodelling processes. Thus, the processes of bone remodelling can be precisely defined depending on mechanical loading.

Taking into consideration biochemical and biomechanical aspects of the process of corticalis remodelling, it can be divided into two fundamental stages that can be described, in the meantime, concisely and in a simplified way as follows: I. Stage of remodelling – resorption – is based on the decrease in an "old" bone tissue. II. Stage of remodelling – apposition – is based on the creation of a new non-mineralized osteoid and its subsequent mineralization. Simultaneously, osteoblasts are transformed into osteocytes located in a newly created mineralized collagenous matrix.

The observed issues are of a comprehensive character and the application of knowledge obtained in the field of biology, biomechanics, biochemistry and biothermodynamics is required. The exact expression of remodelling processes belongs to a category of extremely demanding tasks that have been solved by numerous authors since the mid seventies. The first crucial works are the publications by Cowin [1–3], who defined the theory of adaptive elasticity, particularly with regard to the stability of adaptive system. Recent works that are worth studying have been published by Currey [4], who defined the algorithm for the presentation of adaptive bone remodelling, and by Cowin [5, 6] who presented the possible variants of mechanosensors in a bone tissue and a model of its adaptation under new loading circumstances. There are also some significant works that are primarily focused on biology (on morphology of a remodelled tissue) and on biochemistry (or even on biomechanics). These include the publication by Baron [7], who takes into consideration the destructive activity of mononuclear cells in the process of completing the resorption of a given location, and publications by Rubin [8], Prigogin and Nicolis [9], Civitelli [10], Parfitt [11], and Klein-Nelund [12]. All these authors considered and proved the fact that the flow of an extra-cellular liquid is important for the irritation of osteoreceptors on the membranes of osteocytes. The publications by Landis [13], Eriksen [14], Shapiro [15], Turner [16], Wainbaum [17], and Katz [18] are also important. The research on bone metabolism was also carried out to a large extent in Czech Republic, namely by Havelka [19], Adam [21], Valenta [22] and Palička [23] and some others. In the field of biomechanics and bone remodelling, works by Petrtýl [24–27], who defined the principle of remodelling equilibrium, and works by Petrtýl and Danešová [28, 29] integrating biomechanical and biochemical processes were published. In the field of thermodynamics and biothermodynamics, there are works by Kvasnica [30] and Maršík [31], [32], who carried out the studies of a qualitative and numerical analysis related to the kinetics of remodelling the single stationary state.

Biomechanochemical processes of remodelling and the adaptation of a bone tissue can be described and defined by means of the following tools:

- stoichiometric equations that describe the kinetics of masses (molar masses) of the individual components of a bone tissue in the course of its remodelling;

- differential equations of the remodelling kinematics, i.e. the equations that show the changes in concentrations of the individual components of corticalis in the process of remodelling;
- stationary states in the process of remodelling that can be characterized as those that cause the temporary termination of chemical reactions;
- rate constants that describe the balanced stationary state of two remodelling components;
- combined remodelling functions that are the instrument which makes it possible to verify the dependence of rates of chemical reactions that are being in progress on the mechanical factor, i.e. the case in which the tissue unit volume is loaded (e.g. by compression, or by principal stress);
- constitutive biomechanical equations that describe the relation of the stress tensor components to the inner energy derivation according to the strain tensor components.

This paper is only briefly focused on the relation of the bone tissue loading (or its stress state) to biochemical processes that are being in progress during the tissue remodelling. With respect to the extensive character of investigated issues, this paper will concentrate on the fundamental stoichiometric equations related to the bone remodelling, on the kinetic equations of remodelling, and on the dependence of rates of biomechanical reactions on the stress alterations.

2. Stoichiometric equations

The remodelling of a bone tissue results from very complicated metabolic processes. On the basis of the up-to-date recognised and available knowledge of biochemical processes related to the creation of a new bone, the kinetics of chemical substances (molar mixtures) can be expressed in the following five global stoichiometric equations:

$$D_1 + D_2 \Rightarrow D_3 + D_4, \tag{1}$$

$$D_3 + D_5 \Rightarrow D_6, \tag{2}$$

$$D_2 + D_5 \Rightarrow D_7 + D_8, \tag{3}$$

$$D_9 + D_7 \Rightarrow D_{10} + D_{11}, \tag{4}$$

$$D_{12} + D_{10} \Rightarrow D_{13} + D_{14}, \tag{5}$$

in which

D_1 is a mixture of substances which initiate merging of mononuclear cells into osteoclasts,

D_2 are mononuclear cells and enzymes produced by them,

D_3 are groups of osteoclasts that are formed due to merging of mononuclear cells,

D_4 is a refuse substrate produced in biochemical reactions that are being in progress during the merging of mononuclear cells into osteoclasts,

D_5 is an "old" mineralized bone tissue, i.e. the tissue that has been formed in the previous remodelling cycle,

D_6 are residual products of the osteoclast and tissue activity that have been formed due to the degradation of an organic and inorganic components of the bone tissue,

D_7 is a molar mixture of substances initiating the activity of osteoblasts,

D_8 are residual products that have been formed due to the degradation of an organic and inorganic components of the bone tissue as a result of the activity of mononuclear cells,

D_9 is a molar mixture of the groups of osteoblasts and the enzymes produced by them as well as further synthetic components that control and allow formation of the organic (non-mineralized) matrix – the osteoid,

D_{10} is the osteoid, i.e. a high-molecular (collagenous) component of anintercellular mass that does not contain mineral components,

D_{11} is a refuse substrate that is produced in the course of biochemical oxidising processes and other reactions when superfluous (refuse) low-molecular products are formed (e.g. acid phosphatase and others),

D_{12} is a substrate that contains components initiating the subsequent osteoid mineralization,

D_{13} is a high-molecular mineralized collagen that makes up a new extra-cellular matrix,

D_{14} is a substrate, i.e. the complex of superfluous and refuse products that have been formed during the previous biochemical reactions that facilitate and control the remodelling processes.

The first stoichiometric equation describes the process of osteoclast propagation (D_3 mixture) due to merging of mononuclear cells (D_2 mixture).

The second stoichiometric equation describes biochemical processes that result in the activity of osteoclasts (D_3 mixture) after they have adhered to the surface of a bone tissue (D_5 mixture). Once the enzymatic system of the osteoclasts has been activated, the inorganic component of a bone is degraded. Equation (2) defines the process of degeneration in the bone tissue.

The third stoichiometric equation describes the production of refuse substrates (D_8) in the process of resorption of the bone tissue when the mononuclear cells are activated (D_2). The equation also describes the formation of molar substances (D_7) that subsequently participate in the activity of osteoblasts while they produce the osteoid (see the fourth stoichiometric equation).

The fourth stoichiometric equation describes the formation of the osteoid (D_{10}), i.e. the non-mineralised matrix, being accompanied by the formation of a refuse substrate (D_{11}).

The fifth stoichiometric equation describes the formation of a new bone tissue (D_{13}), i.e. the mineralised osteoid, being accompanied by the formation of a refuse substrate (D_{14}).

In regard to the above-described stoichiometric equations (1)–(5), it is necessary to point out that they express global metabolic processes which are initiated by mechanical loading effects as it will be described hereinafter. The biochemical reactions relating to the cortical bone remodelling and expressed by stoichiometric equations proceed at certain rates that depend on the rate constants and on the concentrations of individual substrates D_i.

Further, it is necessary to emphasise that the rate constants relating to the bone remodelling depend on the stress alterations in the bone tissue microelement. Thus, the mechanical loading effects govern the rates of biochemical reactions.

3. Differential equations of the corticalis remodelling kinetics

The differential equations of the corticalis remodelling kinetics express temporal changes in the concentrations of individual remodelling substrates. These temporal changes in concentrations depend not only on the concentrations of individual components of biochemical reactions, but also on rate constants that depend on mechanical loading or on stresses. In order to derive these equations, first of all it is necessary to determine the concentrations $n_i (i = 1, \ldots, 14)$ of individual substrates (mixtures) D_i, and then the temporal changes in concentrations of these compounds, i.e. dn_i/dt (further indicated as $\dot{n}_i$) must be determined.

The solution of the investigated issue is based on the law of atom mass conservation in the progressing chemical reactions that are, in a generalized form, described by kinetic changes of masses in the stoichiometric equations.

Temporal changes in the concentrations of compounds (i.e. their increases and decreases) are derived from the system of differential equations:

$$\dot{n}_i = \sum_{p=1}^{5} \left(\vartheta'_{pi} - \vartheta_{pi} \right) w_p , \tag{6}$$

where: $i = 1, 2, \ldots, 14$ are the indices corresponding with an appropriate molar mixture, i.e. with a chemical substance $D_1, D_2, \ldots D_{14}$; w_p is the rate of the p's chemical reaction ($p = 1, 2, 3, 4, 5$); ϑ'_{pi}, ϑ_{pi} are stoichiometric coefficients of products and reactants of the p's chemical reaction.

Subsequently, the following differential equations can be written:

$$\dot{n}_1 = -\dot{n}_3 - \dot{n}_6 , \tag{7}$$

$$\dot{n}_2 = -\dot{n}_3 - \dot{n}_6 - \dot{n}_7 - \dot{n}_{10} - \dot{n}_{14} , \tag{8}$$

$$\dot{n}_4 = \dot{n}_3 + \dot{n}_6 , \tag{9}$$

$$\dot{n}_5 = -\dot{n}_6 - \dot{n}_7 - \dot{n}_{10} - \dot{n}_{14} , \tag{10}$$

$$\dot{n}_8 = \dot{n}_7 + \dot{n}_{10} + \dot{n}_{14}, \tag{11}$$

$$\dot{n}_9 = -\dot{n}_{10} - \dot{n}_{14}, \tag{12}$$

$$\dot{n}_{11} = \dot{n}_{10} + \dot{n}_{14}, \tag{13}$$

$$\dot{n}_{12} = -\dot{n}_{14}, \tag{14}$$

$$\dot{n}_{13} = \dot{n}_{14}. \tag{15}$$

From the above relations, the following theorems, which allow us to conceive the problem of increases and decreases in molar mixtures D_i (i = 1, 2, ..., 14) – see the stoichiometric equations – in remodelling the bone tissue can be defined:

$$\dot{n}_5 = -\dot{n}_6 - \dot{n}_8 \longrightarrow -\dot{n}_5 = \dot{n}_6 + \dot{n}_8. \tag{16}$$

Relation (16) shows that the decrease in the old bone tissue D_5 in the unit volume is in proportion to the increase in the refuse substrate D_6 (in the same volume). This state is accompanied by the increase in refuse products (resorption) of the substrate D_8.

$$\dot{n}_8 = \dot{n}_7 - \dot{n}_9 \longrightarrow \dot{n}_9 = \dot{n}_7 - \dot{n}_8. \tag{17}$$

The expression given above shows that the increase in osteoblasts in the unit volume of the bone tissue is in proportion to the increase in substances that initiate their activity – the substrate D_7 (in the same volume of tissue) and to the decrease in the mixture D_8.

$$\dot{n}_9 = -\dot{n}_{11}. \tag{18}$$

From expression (18) it can be derived that the increase in osteoblasts (mixture D_9) in the unit volume of the bone tissue is in proportion to the decrease in the residual refuse D_{11}

$$\dot{n}_{11} = \dot{n}_{10} - \dot{n}_{12} \longrightarrow \dot{n}_{10} = \dot{n}_{11} + \dot{n}_{12}. \tag{19}$$

Expression (19) shows that the increase in the osteoid is in proportion to the increase in the refuse substrate D_{11} and the increase in the input substrate for mineralisation D_{12}.

Having applied the law of mass conservation, basic equations for the rates w_p of the progressing biochemical reactions can be derived. In regard to the fact that there are five stoichiometric equations of remodelling, five rates of biochemical reactions are taken into consideration, then, in accordance with the above-mentioned law, we can write:

$$w_1 = n_1 n_2 k_1, \tag{20}$$

$$w_2 = n_3 n_5 k_2, \tag{21}$$

$$w_3 = n_2 n_5 k_3, \tag{22}$$

$$w_4 = n_7 n_9 k_4, \tag{23}$$

$$w_5 = n_{10} n_{12} k_5, \tag{24}$$

where: n_i are the concentrations of molar mixtures D_i (see the stoichiometric equations) and k_j are the rate constants of remodelling:

$$k_5 = k_2 K_{5e} \mathrm{e}^{-\eta_5 (p - p_e)}, \tag{25}$$

$$k_4 = k_2 K_{5e} K_{4e} \mathrm{e}^{-(\eta_5 + \eta_4)(p - p_e)}, \tag{26}$$

$$k_3 = k_2 K_{5e} K_{4e} K_{3e} \mathrm{e}^{-(\eta_5 + \eta_4 + \eta_3)(p - p_e)}, \tag{27}$$

$$k_1 = k_2 K_{1e} \mathrm{e}^{-\eta_1 \cdot (p - p_e)}. \tag{28}$$

In the equations for the rate constants (functions) we have: K_{ie} (i = 1, 3, 4, 5) – combine remodelling balanced constants at stationary states; η_j (j = 1, 3, 4, 5) – volume changes of appropriate substrates (mixtures); $(p - p_e)$ – changes in stress.

The kinetic equations of the bone tissue remodelling are as follows:

$$\dot{n}_3 = k_1 n_1 n_2 - k_2 n_3 n_5, \tag{29}$$

$$\dot{n}_6 = k_2 n_3 n_5, \tag{30}$$

$$\dot{n}_7 = k_3 n_2 n_5 - k_4 n_9 n_7, \tag{31}$$

$$\dot{n}_{10} = k_4 n_9 n_7 - k_5 n_{10} n_{12}, \tag{32}$$

$$\dot{n}_{14} = k_5 n_{10} n_{12}. \tag{33}$$

The kinetic equations of remodelling show that temporal changes in the concentrations of osteoclasts (Eq. (29)), temporal changes in the concentration of a refuse substrate D_6 (Eq. (30)), temporal changes in the concentration of a molar mixture that initiate the osteoblast activity (Eq. (31)), temporal changes in the concentration of a molar mixture of the osteoid (Eq. (32)), and temporal changes in the refuse substrate during the formation of a new mineralised tissue (Eq. (33)) are dependent on the concentrations n_i and on the rate constants k_i that are stress functions. Thus, the kinetic equations (29)–(33) of the bone tissue remodelling describe the "linkage" between

temporal changes in the concentrations of the individual components of biochemical reactions and the mechanical effects (stresses).

4. Conclusions

The remodelling of a bone tissue is conceived as a functional adaptation of this tissue to new physiologically acceptable conditions. From the viewpoint of biomechanics, this adaptation can be presented as the alteration in the tissue structure and the change in its properties. The processes of remodelling result from the close relationship between biomechanical effects and biochemical processes that have been in a generalized form described herein.

Biomechanical effects (changes in a stress state and changes in strain) initiate "mutually linked" biochemical processes and govern the rate of the tissue remodelling. Each alteration to the stress state/strain in the bone tissue has an influence on the rate of chemical reactions. The dominant effects of stress state and strain, i.e. relatively the most extensive impacts that occur repeatedly for a long time, are of fundamental importance.

The impact of mechanical effects on biochemical processes can formally and practically be presented by means of stress tensors. Each stress (or strain) tensor can be expressed as a sum of the spherical stress (or strain) tensor and the deviator of stress (or strain). In general, for the stress tensor this formula can be written:

$$\sigma_{ij} = \sigma_s + D_\sigma, \tag{34}$$

in which σ_s is a spherical stress tensor, and D_σ is a deviator of stress.

The spherical stress tensor is given in the relation:

$$\sigma_s = \begin{bmatrix} \sigma_s & 0 & 0 \\ 0 & \sigma_s & 0 \\ 0 & 0 & \sigma_s \end{bmatrix}, \tag{35}$$

where $\sigma_s = p$ is a uniform stress.

The diagonal components of the spherical stress tensor $\sigma_s = p$ govern the rates of chemical reactions. They are expressed in the exponent of Eqs. (25)–(28) for rate constants (or rate functions). Thus, it is obvious that the rates of biochemical reactions that depend on rate constants and on concentrations of individual substances (components of biochemical reactions, see Eqs. (20)–(24)) are dependent, through remodelling functions, on the changes in stress. The deviator of the stress D_σ participates (through the deviator of the strain D_ε) in the initiation of chemical reactions in the osteoreceptor of corticalis. Shear components of the stress tensor cause the angular strains of the bone tissue microelement. The components of the angular strains occur in the deviator of a stress tensor. The angular strains (the "obliquity" of the bone tis-

sue microelements) have a considerable impact on the osteoreceptors. The osteoreceptor is made up of osteocytes in the mineralized osteoid. The glykoproteins – integrins α and β, whose principal function is to respond to mechanical irritation that results from the flow of an extracellular liquid in the lacunae of osteocytes (in a tangential direction) [17], are located in the membranes of osteocytes.

The mechanical irritation of the osteocyte receptors initiates chemical processes of the tissue remodelling. Klein-Nulend and Burge [12] proved in laboratory tests the initiation of prostaglandin E_2 that causes the osteoclast activity during the resorption of an "old" bone tissue.

In the process of remodelling, corticalis is gradually transformed into a new structure obtaining new properties. After reaching the stationary state of remodelling equilibrium, chemical reactions are temporarily terminated. There is the state of biochemical equilibrium, and the new principal directions of osteons are identical with the directions of the first dominant principal stress and the first principal dominant direction of strain. These directions are also identical with the first principal direction of anisotropy [24].

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References

[1] COWIN S.C., HEGADUS D.H., *Bone remodelling* I: *Theory of adaptive elasticity*, J. Elasticity, 1976, Vol. 6. No. 3, pp. 313–326.

[2] COWIN S.C., NACHLINGER R.R., *Bone remodelling* III: *Uniqueness and stability elasticity theory*, J. Elasticity, 1979, Vol. 8, No. 3, pp. 285–295.

[3] COWIN S.C. et al., *Bone remodelling of diaphyseal surfaces by torsional loads*, Journal of Biomechanical, 1987, 20, pp. 1111–112.

[4] CURREY J.D., *Can strain give adequate information for adaptive bone remodelling*, Calc. Tiss. Int., 1984, 35, pp. 118–122.

[5] COWIN S.C., *Bone-stress adaptation models*, [in:] Transaction of the ASME, Journal of Biomechanical Engineering, November 1993, Vol. 115, pp. 528–534.

[6] COWIN S.C, MOSS-SALENTIJN L., MOSS M.L., *Candidates for the mechanosensory system in bone*, Journal of Biomechanical Engineering, May 1991, Vol. 113, pp. 191–196.

[7] BARON R. et al., *The significance of lacunar erosion without osteoclasts*, [in:] W.S.S. Jee and A.M. Parfitt, *Bone Histomorphometry*, Armour Montagu, Levallois, 1981, pp. 35–40.

[8] RUBIN C.T., *Osteoregulatory nature of mechanical stimuli, function as a determinant for adaptive bone remodelling*, J. of Ortopaed. Res., 1987, 5, pp. 300–331.

[9] NICOLIS, PRIGOGIN, *Self-organization in nonequilibrium systems*, 1977, Wiley, New York.

[10] CIVITELLI R., *Cell–cell communication in bone*, Calcified Tissue International, 56, Suppl. 1, S29–31, 1995.

[11] PARFITT A.M., *The physiology and clinical significance of bone histomorphometric data*, [in:] R.R. Recker (Ed.), *Bone Histomorphometry*, CRC Press Inc. Boca Raton, 1983, pp. 143–224.

[12] KLEIN-NULEND J., VAN DER PLAS A.., SEMEINS C. M., BURGER E.H., *Sensitivity of osteocytes to biomechanical stress in vitro*, The FASEB Journal, Vol. 9, March 1995, pp. 441–445.

[13] LANDIS W. et al., *Structural relations between collagen and mineral in bone as determined by high voltage electron microscopie tomography*, M. Res. Tech., 1996, Feb., 33 (2), 192–202.

[14] ERIKSEN E.F., MELSEN F., MOSEKILDE L., *Reconstruction of the resorptive site in Iliac trabecular bone. A kinetic model for bone resorption.*, Met. Bone Dis. Rel. Res., 1984, Vol. 5, pp. 235–242.

[15] SHAPIRO F., *Cortical bone repair. The relationship of the lacunar-canalicular system and intercellular gab junction to the repair process*, Journal of Bone Joint Surg. Am., 1988, Aug. 70 (7), 1067–1081.

[16] TURNER C. et al., *The anisotropy of osteonal bone and ultrastructural implications*, Bone, 1995, Jul. 17(1), 85–89.

[17] WEINBAUM S., COWIN S.C., YENG Z., *A model for the excitacion of osteocytes by mechanical loading induced bone fluid shear stresses*, Journal of Biomechanics, 1994, Vol. 27, No. 3 pp. 339–360.

[18] KATZ, E. P., WACHTEL, E., *The structure of mineralized collagen fibrils*, Connect. Tissue Res., 1989, 21 (1–4), 129–154.

[19] HAVELKA S., *Základní údaje o skeletu a jeho metabolismu*, Praktický lékař, roč. 89, Vol. 69, str. 441–446.

[20] HAVELKA S., *Období růstu a osteoporoza, monografie, Revmatologie v teorii a v praxi* – IV. díl, J. Rovenský a kolektiv, 1996, vydavatel, OSVETA, str. 476–486.

[21] ADAM M., *Klinika a diagnosa osteoporosy, Compendium osteoporozy – chirurgie osteoporotické kosti, soubor přednášek, Společnost pro výzkum a využití pojivových tkání*, Praha, 1997, str. 9–14.

[22] VALENTA J.a kol., *Biomechanika*, monografie, ACADEMIA, 1985.

[23] PALIČKA, V., *Patobiochemie kostního metabolismu, Compendium osteoporozy – chirurgie osteoporotické kosti, soubor přednášek, Společnost pro výzkum a využití pojivových tkání*, Praha, 1997, str. 41–44.

[24] PETRTÝL M., *Křivočaré anizotropní vlastnosti kompakty femuru*, [in:] *Sborník ze 2. Celostátní konference biomechaniky člověka*, 1988, str. 123–126.

[25] PETRTÝL M., *Stav dynamického remodelačního ekvilibria v kortikální kosti*, Pohybové ústrojí, roč. 2., č. 3, 1995, str. 112–123.

[26] PETRTÝL, M., *Odezva zdravé a osteoporotické kostní tkáně na mechanické zatížení, Compedium osteoporozy – chirurgie osteoporotické kosti, soubor přednášek, Společnost pro výzkum a využití pojivových tkání*, Praha, 1997, 17–39.

[27] PETRTÝL M., *Remodelling of femoral cortical bone due to the dominant principal stresses*, [in:] *Biomechanical Modelling and Numerical Simulation*, Institute of Termomechanics, Prague, AV ČR, 1997, pp. 74–84.

[28] PETRTÝL M., Danešová J., *Biomechanical and biochemical mechanisns of stress/strain adaptive bone remodelling*, [in:] Proc. from 5th Conference of the European Society for Engineering and Medicine, ESSEM'99, Barcelona, 1999, pp. 67–68.

[29] PETRTÝL M., DANEŠOVÁ J., *Remodelling of femoral bone due to the dominant principal stresses*, [in:] Proc. from WORKSHOP'97 – *Biomechanical Modelling and Numerical Simulation*, Institute of Thermomechanics, Academy of Sciencec, Prague, pp. 78–84.

[30] KVASNICA J., *Termodynamika*, SNTL, Praha, *1965*.

[31] MARŠÍK F., *Účinky chemických reakcí na remodelaci kortikalis při mechanickém zatěžování, Úvodní studie* (interní zpráva), 1997.

[32] MARŠÍK F., *Biotermodynamika*, monografie, Academia, Praha, 1998.