Acta of Bioengineering and Biomechanics
Vol. 3, No. 1, 2001

Principles of bone remodelling – the limit cycles of bone remodelling

MIROSLAV PETRTÝL, JANA DANEŠOVÁ

Czech Technical University in Prague, Faculty of Civil Engineering,
Laboratory of Biomechanics and Biomaterial Engineering.

The bone tissue remodelling is a relatively slow process. In physiologically "normal" conditions, it tends towards the state of remodelling equilibrium. In the state of final *remodelling equilibrium*, the strain energy reaches its minimum. In the life of each human being, the bone tissue passes through the repeating *limit cycles* of its development, functioning and destruction. The paper presented is aimed at the biomechanochemical processes within one limit cycle of bone remodelling using the stoichiometric equations and kinetic equations. Each limit cycle of the bone tissue remodelling (in its assumed volume element) consists of several *stages*, in which the biochemical reactions are proceeding in a highly intensive way, and of several *periods* in which the tissue is in weakly steady states (i.e., the biochemical reactions are very slow or they almost do not take place). Generally, throughout the life of a human, a bone tissue is several times in the principal weakly steady state, i.e., in such a state in which the long-term remodelling equilibrium is reached. This period lasts for several years (roughly for 6–8 years) in the life of an adult human in his/her productive age, while in the life of a child this period is shorter. Figuratively speaking, *the stages of the bone tissue remodelling* (during one limit cycle) can be compared to the tissue "childhood and maturation" (i.e., II stage of remodelling – apposition of the tissue), and "aging–demise" (I stage of remodelling – resorption). One limit cycle of the bone tissue life (out of the series of the subsequent periodic limit cycles) that is characterized by the bone tissue development, functioning and destruction (in the unit volume element) can be synoptically, and in the real time, described by four stages. *The limit cycle is a close trajectory of solution of kinetic equations of bone remodelling.* The bone tissue (in its unit volume element) passes through the repeating harmonic limit cycles (i.e., the stable periodic processes) of its development and destruction.

Key words: bone remodelling, limit cycle/cycles, steady states, bifurcation points, kinetic equations, transport of molecular mixtures, osteoid, osteoblasts, osteoclasts

1. Introduction

This paper is aimed at the bone remodelling processes during the limit cycle in the physiologically "normal" conditions, connecting the biochemical processes with the biomechanical effects. The limit cycle is defined biochemically and biothermomechanically by both the stoichiometric and kinetic equations. Limit cycle can be also defined from the mathematical point of view like a close trajectory of solutions of

bone remodelling kinetic equations, or from the biological point of view like processes of tissue apposition and tissue resorption.

In connection with the well known data concerning of bone remodelling processes that are given by stoichiometric equations [10], it is necessary to emphasize that the figuratively expressed cycle of "childhood – maturity – demise" is assumed within the scope of the bone tissue volume element. The volume element will be defined as a bone tissue cube whose edge is approximately 0.2–0.3 mm long.

The stage of the tissue "maturity" (i.e., the long-term state of the remodelling equilibrium that normally lasts for a few years) can be shorter either as a consequence of biomechanical effects (for example, the change in the dominant directions of principal strains and principal stresses resulting from exceptional and long-term changes in the skeleton loading) or as a consequence of biochemical effects (caused by metabolic disorders). Provided that this stage is not shortened, the harmonic (periodic) genetic initiations "start" the stage of resorption in the bone tissue volume element assumed. *The genetic code initiates incidentally the resorption of the skeleton system* (in physiologically "normal" conditions). According to Parfitt [5], the resorption is initiated approximately every 10 seconds, in the incidentally distributed places, depending on an individual's age, sex, state of metabolism, bone tissue type, bone tissue character and its properties. The genetic factor *maintains* the skeleton system in its pre-determined functions. Thus, genetic factors also fulfil *the function of controlling the "longevity" of the cycle*, i.e., figuratively speaking, the function of controlling the "childhood – maturity – demise" of bone tissue.

Provided that in physiologically normal conditions the bone tissue (in its volume element) passes through several steady states (i.e., the states in which, considering the biological aspect, the tissue is relatively "calm", and the fundamental remodelling processes have been almost stopped), it is necessary to identify *the number of those states and to find out when they are either stable or unstable and when the biochemical reactions of the tissue remodelling are intensive.*

2. Steady states of the bone tissue

Within the time framework of one limit cycle, the bone tissue (in its volume element) passes through the stages of intensive biochemical reactions and through the periods of weakly steady states. The longest stable weakly steady state is the state after the osteoid mineralization. In this state, bone tissue can fulfil its basic functions, e.g. a load-bearing function of a skeleton, maintaining its geometrical stability for a long time (several years). The principal weakly steady state (PWSS) is the stable state of the bone tissue in which the long-term remodelling equilibrium is reached. Each weakly steady state is characterized by the occurrence of failures in the ideal (theoretical) steady state. The deviations from this state directly depend on the

changes in stresses (or on the changes in strains) and on the volume changes in molar mixtures in the volume element of the bone tissue assumed (see hereinafter).

The stability of each weakly steady state is, sooner or later, impaired by a considerable failure (deviation, or a series of deviations) in (from) the ideal (theoretical) steady state during which the bone tissue system is becoming unstable, and the biochemical reactions in the tissue are initiated (for example, the processes of the bone tissue resorption as expressed by the second stoichiometric equation, or the processes of the osteoid formation as expressed by the fourth stoichiometric equation, etc.). After a certain time, these biochemical reactions decelerate and, subsequently, they stop proceeding intensively. The tissue (in the volume element assumed) reaches the new weakly steady state.

Depending on biomechanical-chemical conditions, the living tissue can always reach only some of the eight steady states. Nature shows the tendency to reach such a steady state which is pre-determined by biomechanical and biochemical effects (i.e., the effects of the genetic or metabolic origin).

In order to describe the bone tissue behaviour in the steady states and in their proximity, the stoichiometric equations of the bone tissue remodelling and the kinetic equations of the remodelling must be applied. The fundamental stoichiometric equations expressing the biochemical processes of the bone tissue remodelling were defined by Petrtýl and Danešová ([6], [10]). These equations can be briefly described as follows:

- the first stoichiometric equation defines the process of the osteoclast formation by merging with the mononuclear cells,
- the second stoichiometric equation indicates the osteoclast resorption activity,
- the third stoichiometric equation defines the resorption activity of the mononuclear cells and the development of substances initiating the osteoblast activity,
- the fourth stoichiometric equation defines the osteoid formation,
- the fifth stoichiometric equation describes the osteoid mineralization, i.e., formation of new bone tissue.

In the stoichiometric equations, each molar mixture is characterized by the concentration which alters in time (in the course of biochemical reactions). The biochemical reaction defined by the respective stoichiometric equation proceeds always at a certain rate. The rates of biochemical reactions and their initiation primarily depend on biomechanical effects [6], [10]. *These rates are also dependent on the concentrations of chemical substances which are responsible for the genetic control of limit cycles of the bone tissue remodelling.* The rates can be also influenced by failures in metabolic system (for example, during the initiation and the intensity of spreading osteoporosis, osteopetrosis, and other skeleton disorders).

The kinetics of the bone tissue remodelling was described in detail [10] by five above-mentioned kinetic equations (2). These kinetic equations were defined on the basis of five fundamental stoichiometric equations. The differential equations of the kinetics of the bone tissue remodelling make up the basis for determining the amount

and character of the steady states, or the weakly steady states. In spite of the fact that the steady states (considering merely the thermodynamic aspect) are characterized by the termination of chemical processes, the conditions in the living systems are different. Complete stagnation of the biochemical reactions would result in the "dying" of the tissue. The weakly steady state is characterized by deviations from the (ideal) steady state, or, in other words, by failures (fluctuations) in the steady state. Hence, in order to define the steady states and to check their number, we must set out the condition for determining the termination of chemical reactions. *The termination of biochemical reactions (in the volume element assumed) takes place under the following circumstances*:

- the temporal change in the concentration of the molar mixture of the osteoclasts is zero, i.e., $dn_3/dt = 0$,
- the temporal change in the concentration of the molar mixture of residual substrate (refuse) after the initiation of osteoclasts that have built up due to the degradation of organic and inorganic components of an "old" bone tissue is zero, i.e., $dn_6/dt = 0$,
- the temporal change in the concentration of the molar mixture of the osteoblasts (initiating the osteoid formation) is zero, i.e., $dn_7/dt = 0$,
- the temporal change in the concentration of the molar mixture of the osteoid (non-mineralized matrix of the tissue colagen) is zero, i.e., $dn_{10}/dt = 0$,
- the temporal change in the concentration of the molar mixture of the mineralized matrix (i.e., the new tissue) is zero, i.e., $dn_{14}/dt = 0$.

Provided that the above-given five conditions are fulfilled, the (theoretical) steady state is defined. If we insert the equations representing these conditions into a non-linear system of differential equations of the remodelling kinetics, we will obtain a non-linear system of *algebraic equations* for the unknown concentrations of the components investigated (molar mixtures) of the tissue remodelling. Their solution will lead to eight steady states [10] that can be characterized by the definite concentrations n_{3e}, n_{6e}, n_{7e}, n_{10e}, n_{14e}, or by the concentration vector $n_e = (n_{3e}, n_{6e}, n_{7e}, n_{10e}, n_{14e})$.

In the remodelling processes, however, each of the theoretically defined (ideal) steady states is not reached in the course of a cycle. A real number of the steady states reached is smaller and results from the qualitative analysis of the bone tissue biosystem behaviour (in the assumed volume element of the tissue) in the proximity to the steady states.

3. Behaviour of bone tissue in the proximity to the weakly steady states and the assessment of their stability

Provided that the behaviour of bone tissue biosystem in the conditions of the steady state and its proximity is to be exactly described, the general bone tissue behaviour has to be identified and exactly expressed, which means that the biomechanochemical processes proceeding in the tissue must be characterized. The description

of the general behaviour of bone tissue is based on the stoichiometric equations of its remodelling and on the kinetic equations (2).

However, the system of non-linear differential equations, which allows us to define the kinetics of the tissue remodelling, does not make it possible to find an exact analytical solution. This means that it is not possible to determine the unknown concentrations n_i (for $i = 1, ..., 14$) of molar mixtures in a given time t, for example, n_{10} (i.e., the concentration of the osteoid molar mixture in the unit volume element of the tissue), n_{14} (i.e., the concentration of the molar mixture of the mineralized – newly formed – bone tissue in the same element), etc. Approximate numerical methods of the solution of this system of differential equations (such as the Runge–Kutta method or Euler's method) do not give any opportunity to assess accurately the given issue. Therefore it is necessary to apply the qualitative solution of the system of differential equations, which means that the general behaviour of the living tissue system in the proximity to steady states is to be investigated (or, taking into consideration the mathematical aspect, *the behaviour of the general solution of the system of non-linear differential equations in the proximity to steady solutions is to be expressed*).

Each steady state is characterized by certain concentrations of the molar mixtures n_{3e}, n_{6e}, n_{7e}, n_{10e}, and n_{14e} from which the concentrations of all remaining molar mixtures, i.e., n_{1e}, n_{2e}, n_{4e}, n_{5e}, n_{8e}, n_{11e}, n_{12e}, and n_{13e}, can be derived. Considering merely the thermodynamic aspect, it is necessary to emphasize that *in the ideal steady state, all these concentrations are constant, some of them being even zero* [10]. In such a case, however, all biochemical reactions in the living biosystem would be terminated. Subsequently, an interior environment would be made perfectly inactive (figuratively speaking, the biosystem would be "dead"). In the biological system, under physiologically normal circumstances, however, *the deviations (fluctuations) from (in) the steady state arise, and the bone tissue behaviour can be characterized as an unbalanced stable system.* The fluctuations are caused by the changes in stresses (strains) of the tissue and by the changes in the concentrations of molar mixtures resulting from biochemical processes.

Taking account of the fact that the bone tissue behaviour in the proximity to the steady state is to be investigated, the minor deviation

$$\xi(t, \lambda) = (\xi_3(t, \lambda), \xi_6(t, \lambda), \xi_7(t, \lambda), \xi_{10}(t, \lambda), \xi_{14}(t, \lambda)) \tag{1}$$

will be derived from the steady state. It is the function of the time t and the parameter $\lambda = \Delta p = (p - p_e)$. The parameter values depend on the volume change in the bone tissue, or on the changes in stresses (strains) in the volume element assumed. In the vector expression $\xi(t, \lambda)$ used for the deviation description, $\xi_3(t, \lambda)$ is the deviation of the concentration of the osteoclast molar mixture from the ideal osteoclast concentration n_{3e} in the steady state; $\xi_6(t, \lambda)$ is the deviation of the concentration of the molar mixture of the refuse substrates (resulting from the tissue resorption due to the osteoclast initiation) from n_{6e}; $\xi_7(t, \lambda)$ is the deviation of the concentration of the osteoblast molar mixture from the ideal concentration n_{7e} in the steady state; $\xi_{10}(t, \lambda)$ is the deviation of the concentration of the

osteoid molar mixtures from the ideal concentration n_{10e} in the steady state; and $\xi_{14}(t, \lambda)$ is the deviation of the concentration of the new bone tissue molar mixtures (i.e., the mineralized osteoid) in the steady state.

The deviation $\xi(t, \lambda)$ from the steady state is thus given by the following relation:

$$\xi_i = n_i - n_{ie}, \qquad \text{for} \qquad i = 3, 6, 7, 10, 14, \tag{1a}$$

i.e.,

$$n_i = n_{ie} + \xi_i\,, \tag{1b}$$

where $\mathbf{n}_e = (n_{3e}, n_{6e}, n_{7e}, n_{10e}, n_{14e})$ is the vector of molar mixture concentrations in the steady state, and n_i is the concentration of the i^{th} molar mixture (in the process of the tissue remodelling) in the weakly steady state (for example, n_3 is the concentration of the osteoclast molar mixtures, n_{14} is the concentration of the new bone tissue molar mixture, etc.).

The dependence of $\xi(t, \lambda)$ on $\lambda = \Delta p = p - p_e$, is expressed by the rate constants k_1, k_3, k_4, and k_5 (see [6], [10]) which also depend on the coefficients of volume changes in the molar mixtures D_i (for example, D_{10} in the osteoid, D_{14} in the mineralized osteoid, etc.) in the bone tissue unit volume.

The bone tissue behaviour at minor deviations ξ_i (see equations (1a) and (1b)) from the ideal steady state can be described as the behaviour of a stable system. Because the deviations ξ_i are actually the failures in the (ideal) steady state, this state will be referred to as weakly steady state (WSS). After a certain time, a *weakly steady state becomes an unstable state*. The biochemical reactions of the bone tissue remodelling as expressed by stoichiometric equations are initiated. After completion of the biochemical processes we deal with a new steady state in the tissue.

The stability of weakly steady states will be determined by means of a general method according to Lyapunov [1]–[3], [12]. If this method is applied, the system of non-linear differential equations, which express the kinetics of the bone tissue remodelling [8]–[10], will be used in the following form:

$$\begin{aligned}
\dot{n}_3 &= k_1(A_1 - n_3 - n_6)(A_2 - n_3 - n_6 - n_7 - n_{10} - n_{14}) \\
&\quad - k_2 n_3(A_4 - n_6 - n_7 - n_{10} - n_{14}), \\
\dot{n}_6 &= k_2 n_3(A_4 - n_6 - n_7 - n_{10} - n_{14})\,, \\
\dot{n}_7 &= k_3(A_2 - n_3 - n_6 - n_7 - n_{10} - n_{14}) \\
&\quad \times (A_4 - n_6 - n_7 - n_{10} - n_{14}) - k_4(A_6 - n_{10} - n_{14})n_7\,, \\
\dot{n}_{10} &= k_4(A_6 - n_{10} - n_{14})n_7 - k_5 n_{10}(A_8 - n_{14})\,, \\
\dot{n}_{14} &= k_5 n_{10}(A_8 - n_{14})\,,
\end{aligned} \tag{2}$$

where A_j (for $j = 1, ..., 9$) are constants (invariants) that equal the algebraic sum of the molar mixture concentrations n_i (for $i = 1, ..., 14$). In order to avoid rewriting the system of equations (2), we suggest to express them schematically in the following arrangement, which is convenient for further application:

$$\begin{aligned}
\frac{dn_3}{dt} &= f_3(n_3(t), n_6(t), n_7(t), n_{10}(t), n_{14}(t), \lambda), \\
\frac{dn_6}{dt} &= f_6(n_3(t), n_6(t), n_7(t), n_{10}(t), n_{14}(t), \lambda), \\
\frac{dn_7}{dt} &= f_7(n_3(t), n_6(t), n_7(t), n_{10}(t), n_{14}(t), \lambda), \\
\frac{dn_{10}}{dt} &= f_{10}(n_3(t), n_6(t), n_7(t), n_{10}(t), n_{14}(t), \lambda), \\
\frac{dn_{14}}{dt} &= f_{14}(n_3(t), n_6(t), n_7(t), n_{10}(t), n_{14}(t), \lambda).
\end{aligned} \tag{3}$$

The functions $f_3, f_6, f_7, f_{10}, f_{14}$ are non-linear, being non-linear even in the proximity to the steady state. Because this paper is aimed at examining the behaviour of the system being primarily in the above-mentioned proximity to the steady state of the bone tissue, Taylor's expansion will be applied (for these functions in the proximity to the given steady state), and merely linear terms will be considered.

Thus, for the concentrations n_i ($i = 3, 6, 7, 10, 14$) of molar mixtures in the processes of the bone tissue remodelling (according to equations (1), (1a), according to a system of kinetic equations (3), and according to Taylor's expansion) we arrive at:

$$\frac{dn_i}{dt} = \frac{d}{dt}(n_{ie} + \xi_i) = f_i(\mathbf{n}_e + \xi) = f_i(\mathbf{n}_e) + \sum_{j=3,6,7,10,14} \frac{\partial f_i}{\partial n_j}(\mathbf{n}_e)\xi_j \tag{4}$$

for $i = 3, 6, 7, 10, 14$.

Also:

$$\begin{aligned}
\frac{d}{dt}(n_{ie} + \xi_i) &= \frac{d\xi_i}{dt}, \\
f_i(\mathbf{n}_e) &= 0.
\end{aligned} \tag{4a}$$

Relations (4a) show that temporal change in the concentrations n_i of the molar mixtures in the proximity to the steady states is given by the temporal change in deviation $\frac{d\xi_i}{dt}$ from the ideal concentration n_{ie}, for ($i = 3, 6, 7, 10, 14$) in the steady state.

If we insert relations (4) and (4a) into the system (3), the deviation $\xi(t, \lambda)$, i.e., the failure in the steady state, will be expressed by the following system of linear differential equations:

$$\frac{d\xi_3}{dt} = \left.\frac{\partial f_3}{\partial n_3}\right|_{n_e} \xi_3 + \left.\frac{\partial f_3}{\partial n_6}\right|_{n_e} \xi_6 + \left.\frac{\partial f_3}{\partial n_7}\right|_{n_e} \xi_7 + \left.\frac{\partial f_3}{\partial n_{10}}\right|_{n_e} \xi_{10} + \left.\frac{\partial f_3}{\partial n_{14}}\right|_{n_e} \xi_{14},$$

$$\frac{d\xi_6}{dt} = \left.\frac{\partial f_6}{\partial n_3}\right|_{n_e} \xi_3 + \left.\frac{\partial f_6}{\partial n_6}\right|_{n_e} \xi_6 + \left.\frac{\partial f_6}{\partial n_7}\right|_{n_e} \xi_7 + \left.\frac{\partial f_6}{\partial n_{10}}\right|_{n_e} \xi_{10} + \left.\frac{\partial f_6}{\partial n_{14}}\right|_{n_e} \xi_{14},$$

$$\frac{d\xi_7}{dt} = \left.\frac{\partial f_7}{\partial n_3}\right|_{n_e} \xi_3 + \left.\frac{\partial f_7}{\partial n_6}\right|_{n_e} \xi_6 + \left.\frac{\partial f_7}{\partial n_7}\right|_{n_e} \xi_7 + \left.\frac{\partial f_7}{\partial n_{10}}\right|_{n_e} \xi_{10} + \left.\frac{\partial f_7}{\partial n_{14}}\right|_{n_e} \xi_{14}, \tag{5}$$

$$\frac{d\xi_{10}}{dt} = \left.\frac{\partial f_{10}}{\partial n_3}\right|_{n_e} \xi_3 + \left.\frac{\partial f_{10}}{\partial n_6}\right|_{n_e} \xi_6 + \left.\frac{\partial f_{10}}{\partial n_7}\right|_{n_e} \xi_7 + \left.\frac{\partial f_{10}}{\partial n_{10}}\right|_{n_e} \xi_{10} + \left.\frac{\partial f_{10}}{\partial n_{14}}\right|_{n_e} \xi_{14},$$

$$\frac{d\xi_{14}}{dt} = \left.\frac{\partial f_{14}}{\partial n_3}\right|_{n_e} \xi_3 + \left.\frac{\partial f_{14}}{\partial n_6}\right|_{n_e} \xi_6 + \left.\frac{\partial f_{14}}{\partial n_7}\right|_{n_e} \xi_7 + \left.\frac{\partial f_{14}}{\partial n_{10}}\right|_{n_e} \xi_{10} + \left.\frac{\partial f_{14}}{\partial n_{14}}\right|_{n_e} \xi_{14}.$$

The solution of this system of linear differential equations for the deviation $\xi(t, \lambda)$ makes it possible to assess the stability of the solution in the proximity to the given steady state in the bone tissue.

Based on the theory of the solution of the system of linear differential equations, the entire task of the system (5) solution can be reduced to determining the eigenvalues ω of the system (5) matrix, i.e., to the solution of the following equation:

$$\begin{vmatrix}
\left.\frac{\partial f_3}{\partial n_3}\right|_{n_e} - \omega & \left.\frac{\partial f_3}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_3}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_3}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_3}{\partial n_{14}}\right|_{n_e} \\
\left.\frac{\partial f_6}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_6}{\partial n_6}\right|_{n_e} - \omega & \left.\frac{\partial f_6}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_6}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_6}{\partial n_{14}}\right|_{n_e} \\
\left.\frac{\partial f_7}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_7}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_7}{\partial n_7}\right|_{n_e} - \omega & \left.\frac{\partial f_7}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_7}{\partial n_{14}}\right|_{n_e} \\
\left.\frac{\partial f_{10}}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_{10}}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_{10}}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_{10}}{\partial n_{10}}\right|_{n_e} - \omega & \left.\frac{\partial f_{10}}{\partial n_{14}}\right|_{n_e} \\
\left.\frac{\partial f_{14}}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_{14}}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_{14}}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_{14}}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_{14}}{\partial n_{14}}\right|_{n_e} - \omega
\end{vmatrix} = 0. \tag{6}$$

If the system (5) matrix is indicated as **A**, then, according to (2) and (3), we have:

$$\det(\mathbf{A} - \omega\mathbf{E}) = [k_5 n_{12e} + k_5 n_{10e} + \omega][\omega + k_1 n_{2e}]$$
$$\times[-k_2 n_{5e} - \omega][k_4 n_{7e} + k_4 n_{9e} + \omega][-k_3 n_{5e} - k_3 n_{2e} - \omega] \tag{7}$$

in which ω are the eigenvalues of matrix **A** and **E** is the unit matrix.

The equation can be expressed in a shortened form as:

$$\det(\mathbf{A} - \omega\mathbf{E}) = 0. \tag{7a}$$

This equation is the characteristic equation of the system (5) matrix. Its roots are as follows:

$$\begin{aligned}
\omega_1(\lambda) &= -k_1 n_{2e}, \\
\omega_2(\lambda) &= -k_2 n_{5e}, \\
\omega_3(\lambda) &= -k_3 n_{5e} - k_3 n_{2e}, \\
\omega_4(\lambda) &= -k_4 n_{7e} - k_4 n_{9e}, \\
\omega_5(\lambda) &= -k_5 n_{12e} - k_5 n_{10e}.
\end{aligned} \tag{8}$$

The acquired roots (8) of the equation (7) are the eigenvalues of matrix **A** of a given system of linear differential equations (5) for the deviation $\xi(t, \lambda)$ from the steady state. It is necessary to emphasize that all acquired eigenvalues ω_1, ω_2, ω_3, ω_4, ω_5 are negative. This means that, from the mathematician's viewpoint, the deviation $\xi(t, \lambda)$ is the stable solution of the system of linear differential equations (5) assuming the initial deviation ${}^0\xi(t, \lambda) = ({}^0\xi_3, {}^0\xi_6, {}^0\xi_7, {}^0\xi_{10}, {}^0\xi_{14})$ from the steady state, according to Lyapunov [1], [12].

Taking into account the biothermodynamic aspect, the tissue system is, in such a case, in the weakly steady state [6], [10]. It is thus obvious that the stability is impaired merely due to certain "major" deviations. In other words, the bone tissue system becomes unstable only at a certain magnitude of failure. Besides, for each solution $\xi(t, \lambda)$, whose initial values are small enough (in the absolute value), we arrive at:

$$\lim_{t \to \infty} \xi_i = 0 \quad \text{for} \quad i = 3, 6, 7, 10, 14 \tag{9}$$

and thus the deviation $\xi(t, \lambda)$ is asymptotically stable.

Nevertheless, this state is merely a theory. It does not occur in a living system, otherwise the biochemical processes would be terminated and, subsequently, the system would cease to exist. Taking account of the above, it must be emphasized that each of two solutions, i.e., $\xi(t, \lambda)$ and $\xi^*(t, \lambda)$, only slightly differs from each other, provided that the initial conditions (i.e., the initial failures ${}^0\xi$ and ${}^0\xi^*$) are slightly different. It is obvious from this statement that (*at approximately identical initial failures*), considering the biological aspect, *the identical weakly steady state is always established again*, and *the cycle is proceeding approximately in the same way as the previous cycle*. It is thus the limit cycle which is characterized by the periodicity of the biomechanical-chemical processes, i.e., the trajectory of solution of kinetic equations (2) is the periodic function of time.

The deviation $\xi(t, \lambda)$ is the function of the time t and the parameter $\lambda = \Delta p$, therefore the magnitude of this deviation is directly influenced by the magnitude of the parameter λ, i.e., by the magnitude of the volume changes in the respective molar mixtures, or by the magnitude of the change in mechanical stress.

The above data prove that if the initial failures only slightly differ from each other, each of two deviations from the steady state will also show a slight difference. Biologically stable bone tissue system in a certain steady state is functioning in the proximity to this state, particularly in the modes of merely minor deviations, in other words, it is functioning in the modes of minor fluctuations. *Provided that the major changes in the magnitude of these deviations occur, the stable weakly steady state will become unstable.*

Once the eigenvalues of the matrix of the system of equations (5) were found out, we were able to determine the general solution of this system of linear differential equations for the deviations $\xi(t, \lambda)$ from the theoretical steady state.

The general solution is the linear combination of the fundamental systems of solutions. The general solution of the system (5) can be expressed in a shortened form as:

$$\xi_3(t,\lambda) = C_{1,3}e^{-k_1 n_{2e} \cdot t} + C_{2,3}e^{-k_2 n_{5e} t},$$

$$\xi_6(t,\lambda) = C_{1,6}e^{-k_1 n_{2e} t} + C_{2,6}e^{-k_2 n_{5e} t},$$

$$\xi_7(t,\lambda) = C_{1,7}e^{-k_1 n_{2e} t} + C_{2,7}e^{-k_2 n_{5e} t} + C_{3,7}e^{(-k_3 n_{5e} - k_3 n_{2e})t} + C_{4,7}e^{(-k_4 n_{7e} - k_4 n_{9e})t}, \qquad (10)$$

$$\xi_{10}(t,\lambda) = C_{1,10}e^{-k_1 n_{2e} t} + C_{2,10}e^{-k_2 \cdot n_{5e} t} + C_{3,10}e^{(-k_3 n_{5e} - k_3 n_{2e})t} + C_{4,0}e^{(-k_4 n_{7e} - k_4 n_{9e})t} + C_{5,10}e^{(-k_5 n_{10e} - k_5 n_{12e})t},$$

$$\xi_{14}(t,\lambda) = C_{1,14}e^{-k_1 n_{2e} t} + C_{2,14}e^{-k_2 n_{5e} \cdot t} + C_{3,14}e^{(-k_3 n_{5e} - k_3 n_{2e})t} + C_{4,14}e^{(-k_4 n_{7e} - k_4 n_{9e})t} + C_{5,14}e^{(-k_5 n_{10e} - k_5 n_{12e})t},$$

where the coefficients C_{ij} for $j = 1, 2, 3, 4, 5$ and $i = 3, 6, 7, 10, 14$ characterize the initial conditions ${}^0\xi(\lambda) = ({}^0\xi_3(\lambda), {}^0\xi_6(\lambda), {}^0\xi_7(\lambda), {}^0\xi_{10}(\lambda), {}^0\xi_{14}(\lambda))$ which are the initial failures (deviations) in (from) the steady state.

Expressions (10) show that the magnitude of the deviation $\xi_3(t, \lambda)$, i.e., the deviation from an ideal value of the concentration n_{3e} of the osteoclast molar mixture in the weakly steady state, and also the magnitude of deviation $\xi_6(t, \lambda)$, i.e., the deviation from an ideal value of the concentration n_{6e} of the molar mixture of the residual substrates of the osteoclast resorption of the old bone tissue in the weakly steady state, are influenced by the processes expressed by the first and second stoichiometric equations. Deviation $\xi_7(t, \lambda)$, i.e., the deviation from an ideal value of the osteoblast

concentration n_{7e} in the weakly steady state, is substantially dependent on the biochemical processes expressed by the first, the second, the third and the fourth stoichiometric equations.

We have investigated the solution of the system of differential equations (2) in the proximity to the steady state that is characterized by the concentration vector $\mathbf{n}_e(\lambda) = (n_{3e}(\lambda), n_{6e}(\lambda), n_{7e}(\lambda), n_{10e}(\lambda), n_{14e}(\lambda))$ of the bone tissue molar mixtures for a given parameter $\lambda = \Delta p = p - p_e$, i.e., for a given change of stress in the bone tissue volume element under investigation.

Each weakly steady state of the bone tissue system is impaired after a certain time, which means that its stability is destroyed. The initiation of biochemical processes (characterized by the respective stoichiometric equation) in the tissue is very intensive and subsequently the weakly steady state of bone tissue system changes in another weakly steady state. The conditions enabling the change in the stability of the weakly steady state have not been defined yet. That is the reason why the dependence of the steady solution $\mathbf{n}_e$ on the changes in parameter $\lambda = \Delta p = p - p_e$ must be analyzed. The changes in the parameter λ are caused by mechanical and chemical effects. *The mechanical effects include changes of stress in the bone tissue. The primary chemical effects result from the genetic control of the limit cycle of the bone tissue remodelling or are caused by metabolic disorders. The secondary chemical effects are the consequence of the primary biomechanical effects.*

4. Bifurcation points and non-stability of the weakly steady state

Up to now, we have been dealt with the weakly steady states for a given parameter λ, i. e., for a given change of stress in the bone tissue. This means that the general solution $\mathbf{n}(t, \lambda) = (n_3(t, \lambda), n_6(t, \lambda), n_7(t, \lambda), n_{10}(t, \lambda), n_{14}(t, \lambda))$ of equations (2) in the proximity to the *stationary solution* $\mathbf{n}_e(\lambda) = (n_{3e}(\lambda), n_{6e}(\lambda), n_{7e}(\lambda), n_{10e}(\lambda), n_{14e}(\lambda))$ for a given parameter λ has been investigated. Now, our attention will be focused on the behaviour of *the stationary solution* of a given system of differential equations (2), depending on the changes in the parameter λ, i.e., on the changes in stress (because $\lambda = \Delta p = p - p_e$, where p_e is the stress in the ideal (theoretical) steady state, and p is the actual stress in the volume element of the tissue under investigation, for example, in a given time during walking or during other loading of the skeleton system). The attention is to be focused on such values of parameter λ that destroy the stability of the weakly steady state. These values are called bifurcation values.

If the parameter λ is changed, i.e., if the stress in the assumed volume element of the bone tissue is changed (due to the changes in skeleton loading), the stability of the steady state can be changed for a certain value of the parameter λ (in terms of mathematics, the stability of the stationary solution can be changed). The change in the stability of the steady state occurs in *bifurcation points*. The bifurcation point is the exactly defined point in the solution diagram at which the bone tissue system becomes

unstable. In other words, the failures (that are characterized, for example, by the principal change in mechanical stress) reach, in this case, such values that the weakly steady state becomes unstable.

At the bifurcation points, in which one solution changes into another solution, the branching of the solution occurs. The solutions at these points are ambiguous. There is a change in stability of the weakly steady state at the bifurcation points. These ("dubious") points are determined by such a value of parameter λ (i.e., the bifurcation value of the parameter λ) that makes obtaining the conditions for the theorem of the implicitly defined function impossible. Taking the above into account, it is necessary to emphasize that only in the case of a certain change in the parameter λ (i.e., in reaching the bifurcation value of parameter λ), the stability of the weakly steady state of the bone tissue is changed. Within the limit cycle of bone remodelling (in physiologically *natural conditions*) the knots represent the principal types of bifurcation points ($\omega_i(\lambda) < 0$, i.e., negative).

The bifurcation condition has the following form:

$$\det J(n_e, \lambda) = 0 \tag{11}$$

or

$$\det \left\{ \frac{\partial f_i}{\partial n_j}(n_e, \lambda) \right\} = 0 \tag{11a}$$

for $i, j = 3, 6, 7, 10, 14$.

After specifying (11a), we obtain the bifurcation condition (11b) in the following form:

$$\begin{bmatrix} \left.\frac{\partial f_3(\lambda)}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_3(\lambda)}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_3(\lambda)}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_3(\lambda)}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_3(\lambda)}{\partial n_{14}}\right|_{n_e} \\ \left.\frac{\partial f_6(\lambda)}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_6(\lambda)}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_6(\lambda)}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_6(\lambda)}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_6(\lambda)}{\partial n_{14}}\right|_{n_e} \\ \left.\frac{\partial f_7(\lambda)}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_7(\lambda)}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_7(\lambda)}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_7(\lambda)}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_7(\lambda)}{\partial n_{14}}\right|_{n_e} \\ \left.\frac{\partial f_{10}(\lambda)}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_{10}(\lambda)}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_{10}(\lambda)}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_{10}(\lambda)}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_{10}(\lambda)}{\partial n_{14}}\right|_{n_e} \\ \left.\frac{\partial f_{14}(\lambda)}{\partial n_3}\right|_{n_e} & \left.\frac{\partial f_{14}(\lambda)}{\partial n_6}\right|_{n_e} & \left.\frac{\partial f_{14}(\lambda)}{\partial n_7}\right|_{n_e} & \left.\frac{\partial f_{14}(\lambda)}{\partial n_{10}}\right|_{n_e} & \left.\frac{\partial f_{14}(\lambda)}{\partial n_{14}}\right|_{n_e} \end{bmatrix} = 0. \tag{11b}$$

Simultaneously

$$\det \mathbf{J}(\mathbf{n}_e, \lambda) = k_1 n_{2e} k_2 n_{5e} k_3 (n_{5e} + n_{2e}) k_4 k_5 (n_{9e} + n_{7e})(-n_{12e} - n_{10e}). \tag{12}$$

Accordingly, the equation for determining the bifurcation values of the parameter λ takes the form:

$$k_1k_2k_3k_4k_5n_{2e}n_{5e}\left(n_{5e}+n_{2e}\right)\left(n_{9e}+n_{7e}\right)\left(-n_{12e}-n_{10e}\right)=0, \tag{13}$$

where

$$\begin{aligned} k_1 &= k_2K_{1e}e^{-\eta_1(p-p_e)}, \\ k_3 &= k_2K_{5e}K_{4e}K_{3e}e^{-(\eta_5+\eta_4+\eta_3)(p-p_e)}, \\ k_4 &= k_2K_{5e}.K_{4e}e^{-(\eta_5+\eta_4)(p-p_e)}, \\ k_5 &= k_2K_{5e}e^{-\eta_5(p-p_e)}. \end{aligned} \tag{14}$$

In the system of equations (14) k_i (for i = 1, 2, 3, 4, 5) are the rate constants of the bone tissue remodelling, η_j (for j = 1, 3, 4, 5) are the volume changes of the respective molar mixtures, K_{me} (for m = 1, 3, 4, 5) are the remodelling functions in the steady state (see [10]).

The parameter $\lambda = \Delta p = p - p_e$ in the above equations (14) occurs in the exponents. The values of the bifurcation parameter λ influence the reaching of the bifurcation point and, subsequently, they also influence the state of non-stability during which one of the fundamental biochemical reactions is proceeding (being characterized by one of the five stoichiometric equations, see [10]).

Once the bifurcation values of the parameter λ have been determined, the exponential functions on the left-hand side of equation (13) will be *expanded in the Taylor series*. The attention is to be focused merely on linear terms.

Then, linear approximation of equation (13) in the proximity to the steady state has the following form:

$$\begin{aligned} &k_2^5K_{1e}K_{3e}K_{4e}^2K_{5e}^3\left(1-\eta_1\lambda\right)\left[1-\left(\eta_5+\eta_4+\eta_3\right)\lambda\right]\left[1-\left(\eta_5+\eta_4\right)\lambda\right] \\ &\times\left[1-\eta_5\lambda\right]n_{2e}n_{5e}\left(n_{5e}+n_{2e}\right)\left(n_{9e}+n_{7e}\right)\left(-n_{12e}-n_{10e}\right)=0. \end{aligned} \tag{15}$$

Equation (15) will be fulfilled by the parameter values:

$$\lambda_3=\frac{1}{\eta_1}, \qquad \lambda_4=\frac{1}{\eta_5+\eta_4+\eta_3}, \qquad \lambda_1=\frac{1}{\eta_5+\eta_4}, \qquad \lambda_2=\frac{1}{\eta_5}, \tag{16}$$

where:

η_1 – the coefficient of the osteoclast volume change (in a given volume element of the bone tissue),

η_3 – the coefficient of the osteoblast volume change (in a given volume element of the bone tissue),

η_4 – the coefficient of the osteoid volume change (in a given volume element of the bone tissue),

η_5 – the coefficient of the volume change in a new mineralized bone tissue (in a given volume element of bone).

These values are the bifurcation values of the parameter λ. They can be reached in the weakly steady state:

a) by primary chemical effects resulting from *a genetic control* of the limit cycles,

b) by primary chemical effects resulting from *the failures in the biosystem metabolism,*

c) by primary mechanical (biomechanical) effects such as *the change in stress /strain* in the investigated location of the bone tissue that impairs the state of remodelling equilibrium.

5. Conclusions

On the basis of the above fundamental principles of bone remodelling, the most significant conclusions can be summarized as follows:

1. Generally, the bone tissue that *is formed* within a certain limit cycle (in the unit volume element) and *ceased to exist* in the same cycle (in the same unit volume element) passes through four weakly steady states:

- The first weakly steady state (I WSS) is reached after *the formation of the osteoid*, i.e., after completion of biochemical reaction represented by the fourth stoichiometric equation. This period of the osteoid formation and the first weakly steady state can be figuratively called the *childhood* of bone tissue.

- The second weakly steady state (II WSS). We deal with this state after the *osteoid mineralization* (figuratively speaking, after the period of the tissue "maturation"). This steady state is called the principal weakly steady state, i.e., the state of remodelling equilibrium (figuratively, the state of *maturity*).

- The third weakly steady state (III WSS) is reached when the osteoclasts have been produced in the process of merging with mononuclear cells and as a result of *the osteoclast resorption activity*, i.e., after completion of biochemical processes represented by the first and the second stoichiometric equations (this period can be figuratively called *aging* of the bone tissue).

- The fourth weakly steady state (IV WSS) arises after the *resorption activity of mononuclear cells* represented by the third stoichiometric equation. The period of the bone tissue resorption by mononuclear cells can be figuratively called the tissue *demise.* The fourth weakly steady state is the period of transition to a new (subsequent) limit cycle.

2. The bone tissue for most of its life is in the *principal weakly steady state* (PWSS). Taking into consideration the biomechanical and biochemical aspects, in this

period the bone tissue is in the state of remodelling equilibrium. The periods of other weakly steady states are shorter.

3. The remodelling processes (as defined by stoichiometric equations and kinetic equations) *proceed in an intensive way between the weakly steady states.* In the second weakly steady state (PWSS), the longest one, the principle of the bone remodelling equilibrium is applied. *The coincidence of the dominant direction of the structure of osteons (their longitudinal axes) with the direction of the first principal axis of anisotropy and with the directions of the dominant principal stress (or dominant principal strain)* occurs in the bone tissue [11]. The *dominant principal stress* is relatively the greatest stress that occurs in the bone tissue during *long-term* dominant loading.

4. All weakly steady states (WSS and PWSS) in bone tissue can be characterized by the deviations $\xi_i(t, \lambda)$ from the (ideal) steady state. The deviations ξ_i are dependent on the time t and on the parameter λ which is given both by the mechanical changes of stress/strain and by the volume changes η_j (in the volume element of the tissue). *The oscillations of failures in the ideal steady state have merely a low amplitude. They are extremely important for keeping the bone tissue alive.* Provided that the changes in the stress (i.e., $\Delta p = \lambda = \text{const}$) in the bone tissue did not occur, all biochemical processes would be terminated.

5. All weakly steady states (WSS) in the physiologically sound bone tissue are stable for a certain period of time only. The magnitudes of the deviations ξ show an enormous dependence on the changes in mechanical stress, or on the changes in the concentrations of molar mixtures. *At a certain bifurcation value of the parameter $\lambda = \Delta p$ the stability of the steady state is destroyed* (in terms of mathematics, the *stationary solution* is impaired), in other words, the branching of the solution occurs. Subsequently, *the biochemical reactions of the bone tissue remodelling are initiated in an intensive way, and the tissue system is becoming unstable for a certain period of time.*

6. The unstable system of the bone tissue, in which biochemical reactions expressed by the stoichiometric equations are proceeding, is subsequently stabilized (after completion of the biochemical reactions) as a new weakly steady state (WSS).

7. The stability of the I WSS is destroyed at the bifurcation value of the parameter λ_1 which is determined by the volume changes in osteoid η_4 and by the volume changes in mineralized osteoid η_5:

$$\lambda_1 = \frac{1}{\eta_5 + \eta_4}.$$

Then, biochemical reactions expressed by the fifth stoichiometric equation and those defining formation of the mineralized tissue are initiated in an intensive way. After the total mineralization of the bone tissue volume element, this tissue will be in the principal weakly steady state (PWSS). This state persists for the longest time. The stability of the PWSS is destroyed by reaching the value of the bifurcation parameter λ_2:

$$\lambda_2 = \frac{1}{\eta_5},$$

where η_5 represents the volume changes in the new mineralized bone tissue.

At the bifurcation value of the parameter λ_2, the system of the bone tissue (in its assumed volume element), which has been stable for several years, becomes unstable. The period of the non-stability follows. It is described by biochemical processes of the osteoclast formation (by merging with the mononuclear cells, see the first stoichiometric equation) and of the osteoclast resorption activity (see the second stoichiometric equation). Afterwards, the third stable weakly steady state (III WSS) follows which is impaired by reaching the value of the bifurcation parameter λ_3:

$$\lambda_3 = \frac{1}{\eta_1},$$

where η_1 represents the volume changes in the osteoclasts as expressed by the first stoichiometric equation.

At the bifurcation value of the parameter λ_3, the third weakly steady state becomes unstable. During the period of non-stability biochemical reactions expressed by the third stoichiometric equation (that defines the resorption of the residues of the "old" mineralized tissue by mononuclear cells) are proceeding. Then, the fourth stable weakly steady state (IV WSS) follows which is impaired in a short, transitive period, becomes unstable, being unstable at the value of the bifurcation parameter:

$$\lambda_4 = \frac{1}{\eta_5 + \eta_4 + \eta_3},$$

where η_3 is the coefficient of the osteoblast volume change in the bone tissue unit volume element, η_4 is for the coefficients of the osteoid volume change, and η_5 is for coefficients of the volume change in the mineralized bone tissue being formed (even though the coefficients η_4 and η_5 are minor or even negligible).

8. The initiation of individual stages is determined by the values of the bifurcation parameter λ_i when the stability of the respective weakly steady state (WSS or PWSS) is destroyed. At that particular time, the biochemical reactions start to proceed intensively.

9. During each limit cycle, in the bone tissue volume element being investigated, the old (mineralized in the previous limit cycle) bone tissue is totally substituted for a new one, i.e., for a mineralized bone tissue (in the subsequent cycle). *The substitution of the old bone tissue (produced in a previous cycle) for a new one is genetically and incidentally initiated approximately every 8–12 seconds* in some parts of the skeleton.

Acknowledgement: This research was carried out due to financial support given by the Grant Agency of the Czech Republic, Project No. 106/99/0419 and Project No. 106/00/1464.

References

[1] HOLODNIOK M., *Metody analýzy nelineárních dynamických modelů* (in Czech) (*Analyses of non-linear dynamic models*), Academia, Prague, 1986.

[2] KVASNICA J., *Termodynamika* (in Czech) (*Thermodynamics*), SNTL, Praha, 1965.

[3] MARŠÍK F., Biotermodynamika (in Czech), monografie, Academia, Praha, 1998.

[4] NAGG J., *Stabilita řešení obyčejných diferenciálních rovnic* (in Czech), sešit XVII, SNTL, Praha, 1983.

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

[6] PETRTÝL M., DANEŠOVÁ J., *Weakly stationary states during the bone remodelling*, Proceedings of 12th Conference of the European Society of Biomechanics, Trinity College, Dublin, 28–30 August, 2000, p. 342.

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

[8] PETRTÝL M., DANEŠOVÁ J., *Biomechanical and biochemical mechanisms of stress/strain adaptive bone remodelling*, Proc. from 5th Conference of the European Society for Engineering and Medicine, ESSEM99, Barcelona 1999, pp. 67–68.

[9] PETRTÝL M. *Stav dynamického remodelačního ekvilibria v kortikální kosti* (in Czech), Pohybové ústrojí, 1995, 2, 3, pp. 112–123.

[10] PETRTÝL M., DANEŠOVÁ J., *Bone remodelling and bone adaptation*, Acta of Bioengineering and Biomechanics, 1999, Vol. 1, No. 1, pp. 107–116.

[11] PETRTÝL M., *Křivočaré anisotropní vlastnosti kompakty femuru* (in Czech) (*Curvilinear anisotropic properties of femoral cortical bone*), Biomechanics of man '88, AV ČR, pp. 123–126 .

[12] REKTORYS K., *Přehled užité matematiky* (in Czech) (*Applied Mathematics*), SNTL, Prague, 1988.