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Effect of micro-cracks on the angiogenesis and osteophyte development in degenerative joint disease

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Osteoarthritis, one of the most common types of arthritis, is characterized by the development of osteophytes. The main cause of joint degeneration is mechanical loading, but there are also several other factors that influence the development of osteophytes. In order to formulate a mathematical model of bone spurs' development we have selected the most important factors, such as angiogenesis, micro-damage of the tissue structure and cell signaling. The proposed system of integro-differential equations describes the degenerative changes in the joint. Numerical calculations were implemented into the COMSOL Multiphysics software and the obtained results thus reflect relationships between certain parameters and variables. Additionally, the results correspond with those obtained from medical observations.

Keywords: osteoarthritis, angiogenesis, mathematical modelling, mechanical loading, micro-damage, osteophytes.

1. Introduction

Osteoarthritis (OA) is a degenerative joint disease and a very common type of joint disorder. OA develops in the articular cartilage and the heavily vascularized bone tissue in the joint. WHO reports that more than 9% of men and 18% of women over the age of sixty develop symptoms of OA. Therefore, it is obvious that the disorder in question is correlated with age and gender, while other factors contributing to the onset of osteoarthritis [12] include playing sports, being overweight and some non-physiological loadings resulting from poor posture. This degenerative joint disease results in the formation of osteophytes which make daily activities difficult and painful. However, the exact range of parameters which can activate or inhibit the disease is still not fully determined. The proposed mathematical model of osteophyte development during osteoarthritis is intended to help in identifying these parameters [18].

The mechanism of OA development is very complex and combines biological, chemical and mechanical factors. It is widely acknowledged that the process of degeneration is triggered by mechanical loading. Mechanically overloaded cartilage cells start dying. During apoptosis – the process of dying cells release biochemical factors in the form of the vascular endothelial growth factor (VEGF) [17]. This factor causes the growth of blood vessels [3].

The process of growth of blood vessels from the pre-existing vascular network is called angiogenesis [9] and plays a significant role during OA, as confirmed by a lot of experiments, for example, [6]. The network of blood vessels delivers nutrients to surrounding tissues. The blood vessels triggered by VEGF begin growing in the direction of the signal's source. In this way, the cartilage cells try to survive non-physiological loading, but the new growing blood vessels invade the cartilage domain, which accelerates the process of cell apoptosis. Usually, in order to invade the almost avascular cartilage, the blood vessels need even more boosting factors. One of them comes from the development of micro-cracks in the subchondral bone and calcified cartilage region [5, 21].

The micro-cracks are the result of mechanical loading. They develop and heal simultaneously due to the accompanying process of angiogenesis in bone tissue. As the density of the micro-cracks increases the tissue's permeability increases, further accelerating the flow of biochemical factors. The flow of different kinds of factors is a means of communication between the bone, cartilage and blood vessel cells [11, 20].

New blood vessels grow into the cartilage delivering nutrients and thus promoting favorable conditions for bone formation – the osteophytes begin to develop. Moreover, the growth of the osteophytes combined with the development of further micro-cracks accelerates concentrated stress due to the disturbance of the material properties of the cartilage tissue [10]. This causes more micro-cracks to develop, promoting further cell communication, angiogenesis and osteophytosis [4, 15]. This sequence of events is depicted in Fig. 1.

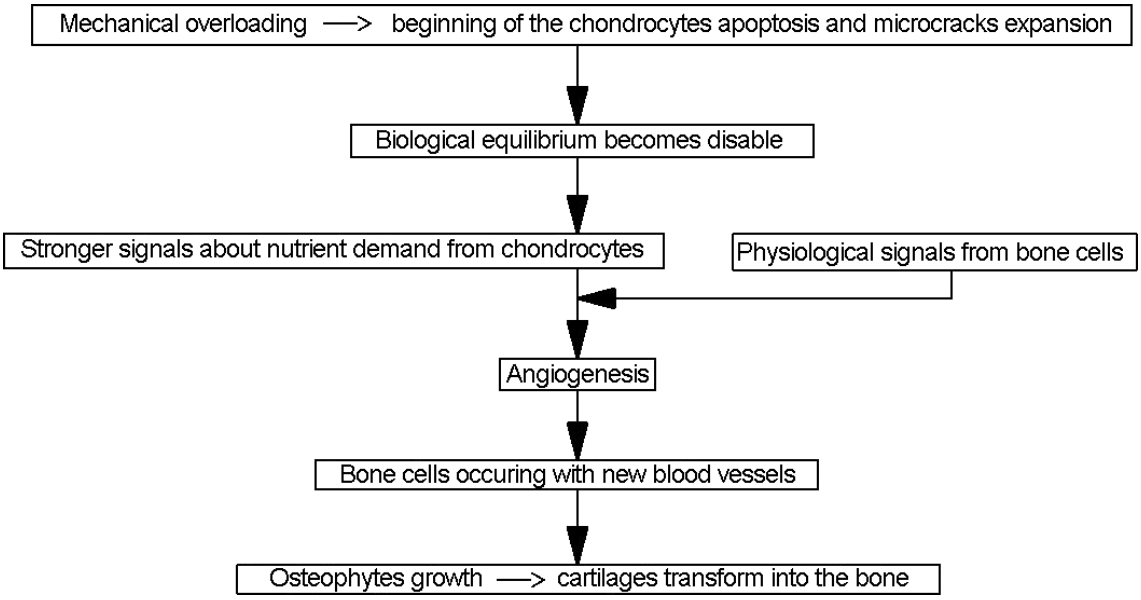

Fig. 1. Cause and effect diagram of osteophyte development.

2. Mathematical formulation of osteophyte development during osteoarthritis

The presented mathematical system of non-linear integro-differential equations describes non-local phenomena concomitant to the joint disorder. The model is intended to reflect the correlations between the densities of cells, blood vessels, nutrients and micro-cracks, as well as the extent of the deformation depending on the mechanical properties of the tissues.

In comparison to the previous model described in [1, 2] the new model was expanded to include a new formula associated with the changes in the micro-structure. The following section presents a brief overview of the whole set of equations including the new formula.

The first equation describes the evolution of bone cell density and is based on the famous mathematical formula proposed by Verhulst [19] in the XIXth century.

$$\frac{\partial \rho_B(\mathbf{x},t)}{\partial t} = \underbrace{\eta(\mathbf{x},t)\rho_B(\mathbf{x},t)}_{\text{(I)}} - \underbrace{A_1\rho_B^2(\mathbf{x},t)}_{\text{(II)}}, \tag{1}$$

where A_1 denotes a constant parameter which controls cellular overpopulation.

Two effects contribute to the evolution of $\rho_B(\mathbf{x},t)$. The first (I) is described by $\eta(\mathbf{x},t)\rho_B(\mathbf{x},t)$ and corresponds to bone cell proliferation. The negative effect of the interaction of too many cells is described in the second part (II). The variable $\eta(\mathbf{x},t)$ refers to the actual amount of nutrients consumed by a single cell in a unit of time as defined by the Monod the well-known equation proposed in 1942 [16],

$$\eta(\mathbf{x},t) = \frac{\eta_m \rho_N(\mathbf{x},t)}{K_s + \rho_N(\mathbf{x},t)}. \tag{2}$$

The η_m constant parameter in Eq. (2) refers to the maximum possible consumption of nutrients by a single bone cell. The parameter K_s is a positive constant, representing the value of nutrient density ρ_N when $\frac{\eta}{\eta_m} = 0.5$.

The second equation describes the evolution of the density of nutrients. The variation of $\rho_N(\mathbf{x},t)$ consists of two parts. The second term (III) in the following equation represents the supply of nutrients from blood vessels network,

$$\frac{\partial \rho_N(\mathbf{x},t)}{\partial t} = -A_2\eta(\mathbf{x},t)\rho_B(\mathbf{x},t) + \underbrace{A_3 \int_\Omega \rho_V(\boldsymbol{\zeta},t) e^{-\frac{R}{\alpha}} d\zeta_1 d\zeta_2 d\zeta_3}_{\text{(III)}}. \tag{3}$$

The first part of Eq. (3), preceded by a minus sign, refers to the actual consumption of nutrients by the bone cells at a given location. The term (III) mentioned before, with the integral over the tissue domain Ω, corresponds to the supply of nutrients from surrounding blood vessels to the location in question. The variable $\rho_V(\boldsymbol{\zeta},t)$ represents the density of blood vessels.

The integral enables for the summation at a certain position $\mathbf{x}$ of the nutrients delivered by blood vessels in the environment located in $\boldsymbol{\zeta}$. The nutrients delivered are sort of biochemical signals, the influence of which decreases exponentially with distance from the source following emission [7, 8, 14]. The simple scheme presented below (see Fig. 2) visualizes the variable nature of these signals.

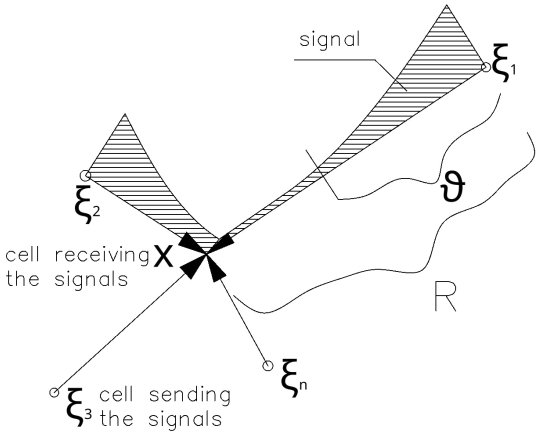

Fig. 2. The scheme of emission of signals.

The exponential term approximates the decreasing density of nutrients at a distance R from the original vascular network,

$$R = \sqrt{(x_1 - \zeta_1)^2 + (x_2 - \zeta_2)^2 + (x_3 - \zeta_3)^2}. \tag{4}$$

Coefficients A_2 and A_3 denote weight parameters.

The next equation, which presents the evolution of the density of blood vessels, was expanded to account for the influence of micro-cracks in the tissue structure. The presented formula is a consequence of the process of angiogenesis and consists of two parts related to various effects,

$$\frac{\partial \rho_V(\mathbf{x},t)}{\partial t} = \left(\underbrace{A_4 \int\limits_{\Omega} S_B(\boldsymbol{\zeta},t) e^{-\frac{R}{\beta}} d\zeta_1 d\zeta_2 d\zeta_3}_{\text{(IV)}} + \underbrace{A_1 P_C S_{MC}(\mathbf{x},t)}_{\text{(V)}} \right) \rho_D A_{17} \underbrace{\int\limits_{\Omega} \rho_V(\boldsymbol{\zeta},t) e^{-\frac{R}{\gamma}} d\zeta_1 d\zeta_2 d\zeta_3}_{\text{(VI)}}. \tag{5}$$

The first part (IV) of the Eq. (5) includes $S_B(\mathbf{x},t)$ that defines the growth of blood vessels in physiological conditions. The biological signal $S_B(\mathbf{x},t)$, defined below, describes the demand for nutrients from the bone cells. This signal diminishes with distance from its source, as described earlier

$$S_B(\mathbf{x},t) = \eta_m \rho_B(\mathbf{x},t) - n\rho_N(\mathbf{x},t), \tag{6}$$

where n is a parameter related to sensing, which we assume to be constant. The introduced signal (Eq. (6)) is proportional to the difference between the optimal nutrient consumption and the supply of nutrients actually transported by the blood vessels. The meaning of η_m is explained in the discussion of Eq. (2).

The second part (V) of Eq. (5) describes the development of blood vessels caused by mechanically overloaded dying cartilage cells. Mechanical signals $S_{MC}(\mathbf{x},t)$ for blood vessels growth are released by chondrocytes. It is assumed that the difference between the integral of actual elastic strain energy density $U(\mathbf{x},t)$ and some reference value U_V representing the maximal energy density value acceptable by living cartilage cells defined for this signal is

$$S_{MC}(\mathbf{x},t) = \int\limits_{\Omega} (U(\boldsymbol{\zeta},t) - U_V) e^{-\frac{R}{\xi}} d\zeta_1 d\zeta_2 d\zeta_3. \tag{7}$$

The nature of this signal is similar to the signals described before. Here, it needs to be noted that cartilage tissue has the ability to distribute stress. This property is compromised when micro-fractures appear or osteophytes invade and the irregularities begin to develop in the micro-structure of the cartilage. These irregularities cause changes in the distribution of the density of elastic strain energy, which regulates mechanical signals.

The mechanical effect is controlled by the micro-structure parameter described by Eq. (8) depending on the changes in Young's modulus and weight parameter A_5

$$P_C = A_5 \left(\frac{E - E_C}{E_B - E_C} \right). \tag{8}$$

Both effects, biological $S_B(\mathbf{x},t)$ and mechanical $S_{MC}(\mathbf{x},t)$, can influence the evolution of blood vessel density only in close distance, which is includes in term (VI). The integral over blood vessel density $\rho_V(\boldsymbol{\zeta},t)$ reflects the fact that angiogenesis is possible at a very close distance from already existing blood vessels. Both of the effects also depend on the spreading of micro-crack density Eq. (9).

The following new equation describes the density of micro-cracks. Changes in micro-structures have a great influence on the development of osteoarthritis [13]. Locally calculated elastic strain

energy is the direct cause of the spreading of the micro-cracks. At the same time, the density of the micro-cracks decreases by dint of the process of healing, which is reflected in the rate of multiplication of the micro-cracks themselves and in the density of the bone cells. The whole formula can be also controlled by the micro-structure parameter P_C and weight parameter A_6

$$\frac{\partial \rho_D(\mathbf{x},t)}{\partial t} = P_C A_6 (A_7 U^2 - \rho_D(\mathbf{x},t)\rho_B(\mathbf{x},t)). \tag{9}$$

Equation (10) defines the evolution of Young's modulus. The changes of stiffness depend on the changes of the density of bone cells and the changes in the mechanical signal Eq. (11),

$$\frac{\partial E(\mathbf{x},t)}{\partial t} = A_6 S_{ME} \rho_B(\mathbf{x},t). \tag{10}$$

The changes in the mechanical signal for Young's modulus refer to difference between the integral of the actual elastic strain density $U(\mathbf{x},t)$ and reference value U_E,

$$S_{ME}(\mathbf{x},t) = \int_{\Omega} U(\boldsymbol{\zeta},t) e^{-\frac{R}{\vartheta}} d\zeta_1 d\zeta_2 d\zeta_3 - U_E, \tag{11}$$

where U_E denotes the reference value associated with the bone remodeling equilibrium.

The functions appearing in all of the proposed integral operators resemble the Green function describing diffusion effects. Here, it was adapted to describe blood vessel expansion and signal propagation.

3. Simulation

3.1. Initial and boundary conditions

The aim of the proposed mathematical model of osteophyte development during osteoarthritis is to reflect the relationships between certain variables and parameters. Therefore, to verify the usefulness of this model simple examples were calculated with the use of the COMSOL Multiphysics software.

Figure 3 shows the mixture of bone and cartilage tissue. At the beginning, bone cells and blood vessels are present only in the bone domain on the left-hand side. The Young modulus of the bone tissue is much greater than the Young modulus of the cartilage. External cartilage surface was loaded by the continuous distribution of force P.

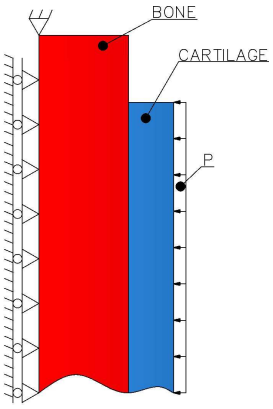

Fig. 3. Simple 2D geometrical model of computational domains.

It can be projected that after applying the force, the elastic strain energy density will be the highest near the border of tissues around the end of the cartilage domain. The designated area refers to joint margins and should be the seedbed of biomechanical changes and osteophyte onset.

3.2. Numerical results

In Fig. 4, the so-called effective stress (von Mises stress), which corresponds to the distribution of energy strain density is presented.

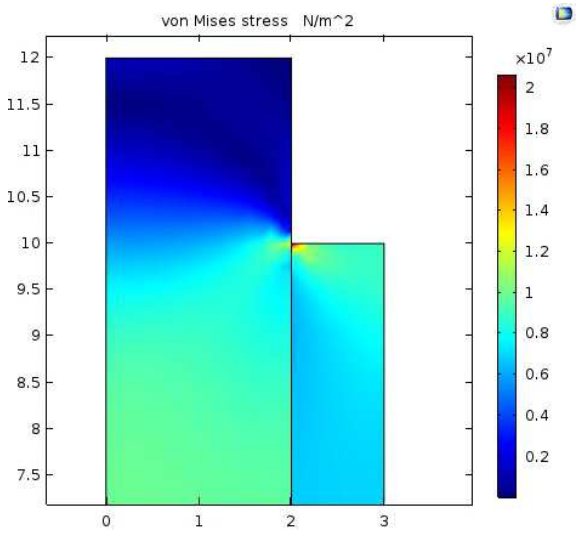

Fig. 4. The distribution of von Mises stress.

The areas with greater volume of stress represent the seedbed of micro-cracks. In area at the cartilage side the cartilage cells were mechanically overloaded. It can be predicted that in this area the process of osteophyte formation will begin.

The results of calculations are presented in Fig. 5. The first row shows the densities of the variables at the initial time. The blood vessels and the bone cells are located in the bone domain

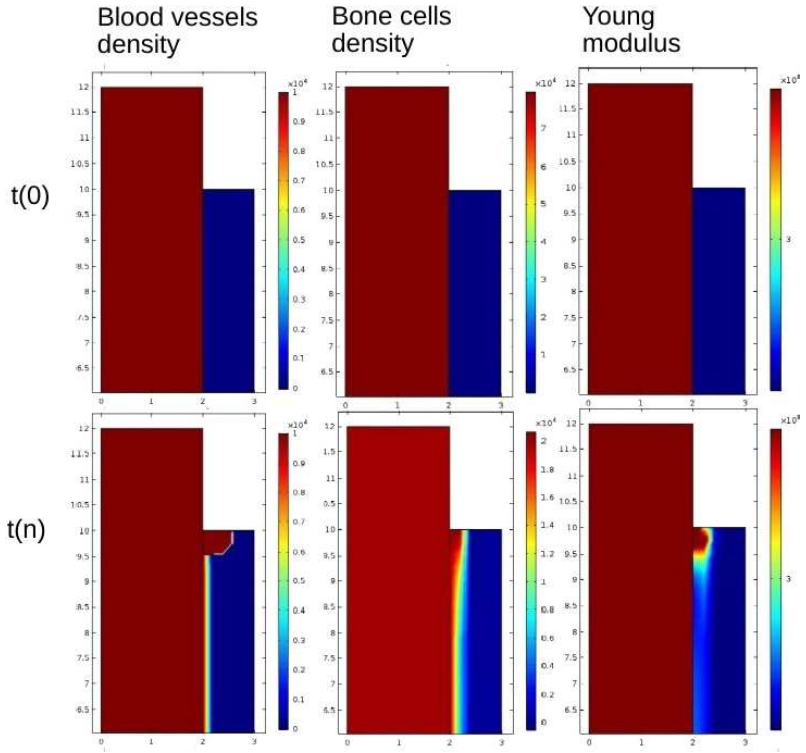

Fig. 5. Results of numerical calculations.

only. The Young modulus is much greater for the bone tissue than in the cartilage tissue. After the biological state equilibrium is disturbed, the process of degeneration begins. As time passes the density of blood vessels starts to increase and spreads in the direction of the cartilage domain from the bone region, the domain occupied by the pre-existing vascular network in the direction of dying chondrocytes. The increased density of blood vessels in the cartilage region brings about changes in bone cell density and Young's modulus. The changes after a certain time step are illustrated in the second row.

4. Conclusions and discussion

The evolution of bone cell density as described by the equation has indirect and direct influence on the rest of the equations and variables (see Fig. 6).

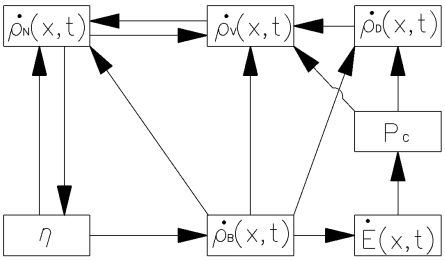

Fig. 6. A diagram of mutual relationships between the variables and their evolution.

The equation describing the evolution of blood vessel density is the most dependent on other variables and also influences the evolution of bone cell density. This is in keeping with the crucial insight concerning the role of angiogenesis in osteophyte development.

The presented system of integro-differential equations describes a very complex phenomenon. The mathematical models of bone remodeling and cell culture development were adapted to the model of osteophyte development. The new model was expanded to include further factors such as angiogenesis and micro-crack development. Simple, ordinary differential equations combine surface integrals and exponential functions. All of the equations are related to each other resulting in a complex mathematical problem.

Due to the elaborate equations and a number of parameters, the model is sensitive to small changes of these parameters and possibly prone to numerical instability. This suggests the need to conduct the sensitivity analysis of the model.

The results of numerical calculations reflect co-relationships between parameters and variables, the model is dimensionless. Regardless of the difficulties surrounding the initial choice of parameters, the numerical results reflect osteoarthritic changes observed in patients with OA (see Fig. 7).

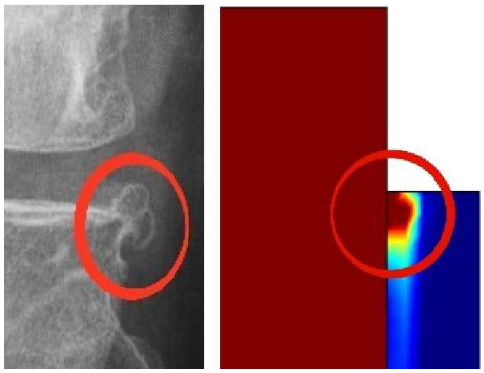

Fig. 7. X-ray image of a osteophytes and Young's modulus after calculations.

Preparation of more realistic model of a human joint will possibly enable prediction of degeneration disease. To formulate an even more precise mathematical representation of the development of osteophytes in the knee, the model should be extended to include other biochemical factors and more realistic geometry of the joint.

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