ENGINEERING TRANSACTIONS • *Engng. Trans.* • **64**, 4, 533–540, 2016
Polish Academy of Sciences • Institute of Fundamental Technological Research (IPPT PAN)
National Engineering School of Metz (ENIM) • Poznan University of Technology

Osteophyte Development During Osteoarthritis (OA) – Consideration of Angiogenesis, Mechanical Loading and Tissue Microstructure

Ewa BEDNARCZYK, Tomasz LEKSZYCKI

Warsaw University of Technology
Faculty of Production Engineering
Institute of Mechanics and Printing
Department of Construction Engineering and Biomedical Engineering
Narbutta 85, 02-524 Warsaw, Poland
e-mail: e.bednarczyk@wip.pw.edu.pl

This paper is devoted to modelling and investigation of the effects of mechanical loading, blood vessels development and tissue microstructure in osteoarthritis (OA) – a degenerative joint disease. OA is one of the most common diseases affecting the population, and therefore it is a social and medical problem of utmost importance. It predominantly affects the elderly but also sportsmen, obese people and those with curvature of the spine. Although the phenomenon of OA is not yet fully understood, it is commonly accepted that mechanical aspects are crucial in its evolution [1, 2]. Mechanical overloading leads to chondrocytes apoptosis which increases generation of vascular endothelial growth factors [3] then expansion of angiogenesis and osteophyte onset. A properly formulated mathematical model of cartilage degeneration and osteophytes development can significantly help in understanding the complexity of this process. The presented model reflects the most important aspects of the interactions between mechanical and biological factors, crucial for the phenomenon of OA.

Key words: osteoarthritis, osteophyte, angiogenesis, mechanical loading, mathematical modelling, bone, cartilage.

1. Introduction

OA – a degenerative joint disease is one of the most common types of arthritis. This very painful condition is, as of yet, not fully understood. Therefore, a new mathematical model describing the development of osteophyte during OA can contribute to determine more details related to this process. The degeneration of joints is considered to be a disease of the bone and cartilage tissues, both of which are composed of extracellular matrix with cells.

Bones are very rigid and vascularized; by contrast, articular cartilage is flexible, and with no vascular network present. Together, the rigid bones and the

glossy and slick surface of cartilage with its mechanical properties, make smooth motion possible. Unfortunately, when OA occurs, cartilage's mechanical properties deteriorate. The cartilage's surface becomes rough and brittle and the tissue layer gets thinner. At the same time, the layer of subchondral bone becomes thicker and the growth of osteophyte is observed. Consequently, the joint becomes stiff and movement becomes painful.

OA predominantly affects the elderly, women and obese people, and those with non-physiological changes in posture. Due to the aforementioned aspects, mechanical loading is known to be the most important factor in the development of OA. Mechanical loads can result in cartilage compression and abrasion as well as in the development of micro-cracks in the subchondral bone region, the calcified cartilage layer or even the cartilage itself. If the load exceeds the limit of maximal mechanical loading accepted by the cells, they start to die [4]. Overloaded cartilage cells generate a "help" signal in the form of the vascular endothelial growth factor (VEGF) [5], which is the prime stimulus for the development of new blood vessels. The released signals can reach the blood vessels residing in the subchondral bone. In response to the VEGF, blood vessels start to grow in the direction of the source of the signal. The process of angiogenesis (neovascularization) begins. If the size of the aforementioned micro-cracks is large enough for blood vessels, they can penetrate the calcified cartilage layer or even the cartilage. Concurrently with angiogenesis, the development of the osteophyte takes place. It can be said that a kind of a composite of the bone and the cartilage tissue forms.

2. Mathematical model

Because OA is a social problem, any attempt leading to a better understanding of this phenomenon is worthwhile. The proposed mathematical model reflects the relations between selected effects and parameters, which can help to understand the complexity of the process.

2.1. Assumptions, boundary and initial conditions

In order to propose an acceptable mathematical model, some essential assumptions had to be formulated:

1. The porosity of the composite of bone and cartilage depends on the contribution of cartilage. The more cartilage, the larger the porosity.
2. The signals decrease exponentially with distance from their source.
3. The mechanical overloading signal for angiogenesis is represented by a difference between the actual elastic strain energy density and the mechanical loading safety limit accepted by the cells.

4. The biological undernutrition signal is proportional to the difference between the demand for nutrients and the actual volume of nutrients.
5. The mechanical stimulus for changes in Young's modulus is proportional to the difference between the actual elastic strain energy density and the reference value of energy density associated with biological equilibrium.
6. At the beginning of the process, blood vessels and bone cells are present only in the bone domain.
7. At the beginning of the process, the Young modulus of the bone is much greater than the Young modulus of the cartilage.
8. Due to some non-physiological changes in posture or joints, a concentrated force is applied to the composite.

2.2. Mathematical formulas

The presented system of non-linear integro-differential equations is associated with non-local effects mentioned in the previous section. The first formula, associated with the evolution of density of blood vessels $\rho_V(\mathbf{x},t)$, consists of two parts: biological (I) and mechanical (II)

$$\frac{\partial \rho_V(\mathbf{x},t)}{\partial t} = \underbrace{A_2 B_1 \int\limits_{\Omega} S_B(\boldsymbol{\zeta},t) e^{-R/\beta} d\zeta_1 d\zeta_2 d\zeta_3}_{\text{(I)}} + \underbrace{A_1 B_1 \int\limits_{\Omega} P_C(\mathbf{x},t) S_{MC}(\boldsymbol{\zeta},t) e^{-R/\zeta} d\zeta_1 d\zeta_2 d\zeta_3}_{\text{(II)}}. \tag{2.1}$$

The biological part depends on non-local biological effects associated with bone cells demand for nutrients. The undernutrition biological signal in Eq. (2.1) is proportional to the difference between the maximum consumption of nutrients and the amount of the nutrients actually transported by blood vessels

$$S_B(\mathbf{x},t) = \eta_m \rho_B(\mathbf{x},t) - n\rho_N(\mathbf{x},t). \tag{2.2}$$

The second part depends on the signals of non-local mechanical overloading for the growth of blood vessels released by overloaded, dying chondrocytes. This is assumed as a difference between the actual elastic strain energy density $U(\mathbf{x},t)$ and some reference value U_V representing the mechanical loading safety limit

$$S_{MC}(\mathbf{x},t) = U(\mathbf{x},t) - U_V. \tag{2.3}$$

$P_C(\mathbf{x},t)$ – the microstructure factor in Eq. (2.2), describes the cartilage ratio in the composite of bone and cartilage:

$$P_C(\mathbf{x},t) = \frac{E_B - E}{E_B - E_C}. \tag{2.4}$$

Both of these phenomena, associated with parts (I) and (II) of Eq. (2.1), have significant effects only in the very close vicinity of an existing vascular network. Consequently, the non-local effect of angiogenesis is expressed by factor $B_1(\mathbf{x},t)$ used to "scale" the quantity of blood vessels density:

$$B_1(\mathbf{x},t) = A_8 \int\limits_{\Omega} \rho_V(\boldsymbol{\zeta},t) e^{-R/\gamma} d\zeta_1 d\zeta_2 d\zeta_3. \tag{2.5}$$

The exponential term approximates the decreasing density of nutrients at a distance R from the source,

$$R = \sqrt{(x_1-\zeta_1)^2 (x_2-\zeta_2)^2 (x_3-\zeta_3)^2}. \tag{2.6}$$

The integrals enable the summation at a certain position $\mathbf{x}$ of the signals arriving from the surrounding domain $\boldsymbol{\zeta}$.

The next equation, Eq. (2.7), is based on the formulas defined by MONOD [6] for the excessive density of nutrients $\rho_N(\mathbf{x},t)$, and it consists of two parts. The first part (III) depends on the standard formula for nutrients consumption – Eq. (2.8) and the density of bone cells. The greater the density of bone cells the smaller the density of nutrients. The second part (IV) states that the density of nutrients increases with the supply from blood vessels:

$$\frac{\partial \rho_N(\mathbf{x},t)}{\partial t} = \underbrace{-A_5 \eta(\mathbf{x},t) \rho_B(\mathbf{x},t)}_{\text{(III)}} + \underbrace{A_6 \int\limits_{\Omega} \rho_V(\boldsymbol{\zeta},t) e^{-R/\alpha} d\zeta_1 d\zeta_2 d\zeta_3}_{\text{(IV)}}, \tag{2.7}$$

$$\eta(\mathbf{x},t) = \frac{\eta_m \rho_N(\mathbf{x},t)}{K_s + \rho_N(\mathbf{x},t)}. \tag{2.8}$$

In this formulation, we adapted the formula proposed by VERHULST [7] for the density of cells in a culture Eq. (2.9), in order to describe the density of bone cells $\rho_B(\mathbf{x},t)$. The first part (V) controls the increasing density of the bone cells by supplying nutrients to the cells, which can proliferate only from existing cells. However, it is assumed that when the density of the bone cells increases too much, the negative part of the cells' interactions (VI) predominates,

$$\frac{\partial \rho_B(\mathbf{x},t)}{\partial t} = \underbrace{\eta(\mathbf{x},t) \rho_B(\mathbf{x},t)}_{\text{(V)}} - \underbrace{A_3 \rho_B^2(\mathbf{x},t)}_{\text{(VI)}}. \tag{2.9}$$

The last equation for changes of Young's modulus depends on the non-local mechanical effect – Eq. (2.11) and the density of bone cells,

$$\frac{\partial E(\mathbf{x},t)}{\partial t} = A_7 \int_{\Omega} S_{ME}(\boldsymbol{\zeta},t)\rho_B(\mathbf{x},t)e^{-R/\vartheta}d\zeta_1 d\zeta_2 d\zeta_3, \tag{2.10}$$

$$S_{ME}(\mathbf{x},t) = U(\mathbf{x},t) - U_E. \tag{2.11}$$

The Young modulus mechanical stimulus $S_{ME}(\mathbf{x},t)$ refers to a difference between the actual elastic strain density $U(\mathbf{x},t)$ and the reference value U_E representing the reference value of energy associated with the state of biological equilibrium [8].

The parameters α, β, γ, ϑ, ξ represent characteristic effective distances and A_1–A_7 are the weight parameters. The values of these parameters have been selected during the numerical experiments and systematic parametric study in order to obtain the results resembling clinical observations.

3. Results of numerical calculations

To investigate and verify the interactions between certain effects and parameters and their influence on the process of osteophyte development a numerical example was formulated (see Fig. 1) and solved (see Fig. 2). The formulas introduced earlier were implemented into the software COMSOL [9].

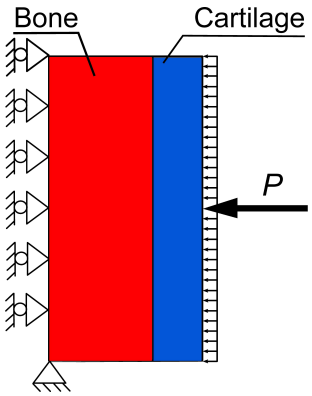

Fig. 1. Schematic geometry considered in numerical examinations.

The most important parameters, which regulate the activity and quantity of bone cells involved in the development of osteophytes, are the ones defining the consumption of nutrients by cells and the factors regulating the distribution of nutrients in the tissue. Changes of the stiffness of the bone-cartilage composite

following the development of osteophytes affect the distribution of strain energy. The stiffness of osteophytes differs significantly from the stiffness of surrounding cartilage, which results in energy concentration in the region close to the bone spurs. This effect promotes further development of osteophytes. According to the proposed model, this distribution of strain energy contributes to both a biological process, see Eq. (2.1), describing development of blood vessels and the mechanical changes, see Eq. (2.10), describing evolution of Young's modulus.

In the numerical calculations, dimensionless values were considered and only mutual relations between the densities of cells, blood vessels and mechanical loading were examined. Figure 2 illustrates changes associated with the ingrowth

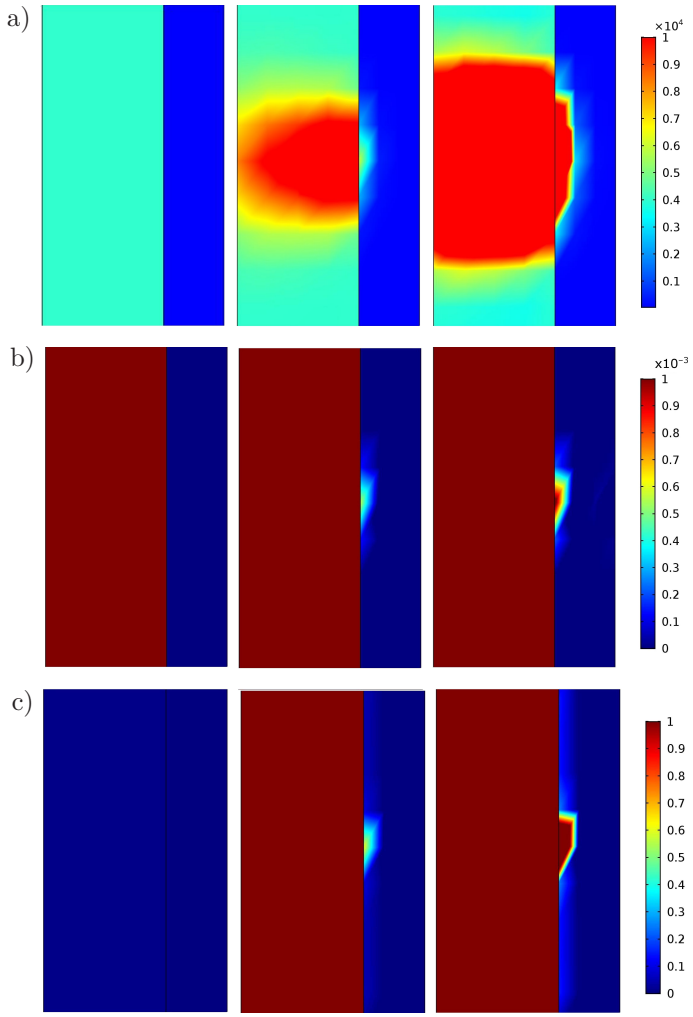

FIG. 2. Comparison of the changes in time in: a) Young's modulus, b) density of blood vessels, and c) distribution of bone cell density.

of bone tissue into a cartilage domain close to the concentrated mechanical loading. Left-hand side of the area occupied by the bone cells represents a healthy bone tissue. The right-hand side is poorly populated by the bone cells and blood vessels, and represents the cartilage tissue. In the domain occupied by cartilage, cartilage tissue degeneration can be observed. Some osteophytes are growing after the expansion of blood vessels caused by the angiogenic signals sent by mechanically loaded chondrocytes. Furthermore, a density of bone cells, in the bone domain, is also increasing at mechanical overload state – biological equilibrium is not maintained. The process of bone remodeling is present in this situation. Thereafter, the growth of bone tissue is accompanied by the development of capillaries and evolving nutrient concentration takes place.

4. Conclusions

The model of bone remodeling [8] and the models of the development of cell culture [6, 7] have been expanded and adapted to describe the growth of osteophytes during OA, including the process of angiogenesis, mechanical loading and tissue microstructure. The proposed model takes into consideration nonlocal and non-linear mechano-biological effects.

The complicated nature of equations and the large number of parameters results in big sensitivity of the results with respect to small variations of the parameters and possible numerical instability. Despite this, the results of numerical calculations confirm the inseparability of neovascularization and bone growth as well as the significance of tissue microstructure in this process. It was also observed that the mechanical and biological effects considered in the formulation significantly affect the process of cartilage degeneration.

The presented results are consistent with clinical observations and experimental data of the development of osteophytes during OA. These results are strongly correlated with the observations on animal models carried out by the research group of S. Hashimoto [10] as well as a team of S. Kamekura [11]. Due to strong correlation between the results and clinical observations, future efforts will focus on extension of the present model to include a wider spectrum of microstructural and mechano-biological factors.

References

1. Felson D.T., *Osteoarthritis as disease of mechanics*, Osteoarthritis and Cartilage, **21**(1): 10–15, 2013, doi: 10.1016/j.joca.2012.09.012.

2. Wang T.-M. *et al.*, *Loading rates during walking in adolescents with Type II osteonecrosis secondary to pelvic osteotomy*, Journal of Orthopedic Research, 2016, doi: 10.1002/jor.23239.

3. D'Lima D.D. *et al.*, *Human chondrocyte apoptosis in response to mechanical injury*, Osteoarthritis and Cartilage, **9**(8): 712–719, 2001, doi: 10.1053/joca.2001.0468.

4. Pfander D. *et al.*, *Vascular endothelial growth factor in articular cartilage of healthy and osteoarthritic human knee joints*, Annals of Rheumatic Diseases, **60**(11): 1070–1073, 2001, doi: 10.1136/ard.60.11.1070.

5. Pufe T. *et al.*, *Mechanical overload induces VEGF in cartilage discs via hypoxia-inducible factor*, The American Journal of Pathology, **164**(1): 185–192, 2004, doi: 10.1016/S0002-9440(10)63109-4.

6. Monod J., *The growth of bacterial cultures*, Annual Review of Microbiology, **3**: 371–394, 1949, doi: 10.1146/annurev.mi.03.100149.002103.

7. Verhulst P.F., *Deuxième memoire sur la loi ďaccrossement de la population*, Mémoires de l'Académie Royale des Sciences, Des Lettres et des Beaux-Arts de Belgique, **20**: 1–32, 1847, http://eudml.org/doc/178976.

8. Lekszycki T., dell'Isola F., *A mixture model with evolving mass densities for describing synthesis and resorption phenomena in bones reconstructed with bio-resorbable materials*, ZAMM (Journal of Applied Mathematics and Mechanics/Zeitschrift für Angewandte Mathematik und Mechanik), **92**(6): 426–444, 2012, doi: 10.1002/zamm.201100082.

9. *COMSOL Multiphysics*® v. 5.2, COMSOL AB, Stockholm, Sweden. www.comsol.com.

10. Hashimot S. *et al.*, *Development and regulation of osteophyte formation during experimental osteoarthritis*, Osteoarthritis and Cartilage, **10**(3): 180–187, 2002, doi: 10.1053/joca.2001.0505.

11. Kamekura S. *et al.*, *Osteoarthritis development in novel experimental mouse models induced by knee joint instability*, Osteoarthritis and Cartilage, **13**(7): 632–641, 2005, doi: 10.1016/j.joca.2005.03.004.

Received October 6, 2016; accepted version November 9, 2016.