Coll. Antropol. **35** (2011) 2: 419–425
Original scientific paper

Multiscale Phenomena Related to Diabetic Foot

Ante Agić[1], Tatjana Nikolić[2] and Budimir Mijović[3]

[1] University of Zagreb, Faculty of Chemical Engineering and Technology, Zagreb, Croatia
[2] University of Zagreb, »Sestre Milosrdnice« University Hospital Center, Department of Rheumatology, Physical Medicine and Rehabilitation, Zagreb, Croatia
[3] University of Zagreb, Faculty of Textile Technology, Zagreb, Croatia

A B S T R A C T

Diabetes is a group of metabolic diseases causing a system disorder, i.e.; it cannot be explained or understood by phenomena on single material scale. The diabetic foot is studied as flexible multibody structure by nonlinear finite element method. The physical and geometrical multiscale heterogeneity is solved by multilevel finite element approach. The diabetic tissue is described by internal coordinate's formalism, as complex multiscale process in tissue. The accompanying problem of the axisymetric wound healing is solved numerically. Some results related to foot deformity, stress and strain concentration and wound healing are presented.

Key words: *diabetic foot, multiscale modelling, finite element method*

Introduction

Diabetes is a growing health problem round the Globe. It is a lifelong condition that seriously affects a person's quality of life. Diabetes spreading in the World (% of population) in 2005 indicates it as complex problem for every country (Figure 1)[1]. The people suffering from diabetes usually have foot ulcers, a common side effect of the disease. Peripheral neuropathy, a loss of feeling in the extremities, renders these individuals unaware of sores that develop on their feet until the wound becomes infected. Due to complications associated with diabetes, the infection often defies healing and eventually leads to amputation. Lower extremity amputation in people with diabetes continues to be a major public health problem[2]. One of the most serious complications is naturopathic foot ulceration that, untreated, can lead to lower limb amputation. The main cause of foot ulceration in the adult neuropathy diabetic is thought to be the presence of abnormally high plantar pressures secondary to neuropathy. These pressures may be present as a result of compromised foot function, such as in hind foot tendon disorders and diabetic Charcot foot. Foot deformities, such as hammer/claw toe deformity or hallux limitus, have been significantly associated with ulcer incidence in a multivariate analysis[3]. Distribution of the internal foot geometry for given population is the indicator of foot deformity, ageing, and body growth anomaly and many others. Recent literature on the diabetic foot indicates that stress concentrations in deep tissues of the plantar pad of the foot, which develop directly under bony prominences play a dominant role in the mechanism of diabetic foot injuries and may lead to foot ulceration. There are many structural and functional factors that are predictors of foot mechanics phenomena and associated pathology[4].

Diabetes is a group of metabolic diseases causing a system disorder, i.e.; it cannot be explained or understood by phenomena on single material scale[5]. It is the result of a complex interplay between a numbers of organs, metabolic sub-system, neuronal and vascular control mechanisms. A multi-scale approach, ranging from molecular to macroscopic level, is of great importance in developing reliable models for diabetes. When modelling biological systems one should be able to produce different mathematical models at different scales and provide a link between each model to get a complete description of the system. The simple task of walking may be dangerous since diabetes affect various levels of biological function from a mechanical point of view[6]. These dysfunctions result in a loss of sensation, changes in the control of movement, and the alteration of tissue and cell proper-

Received for publication December 27, 2010

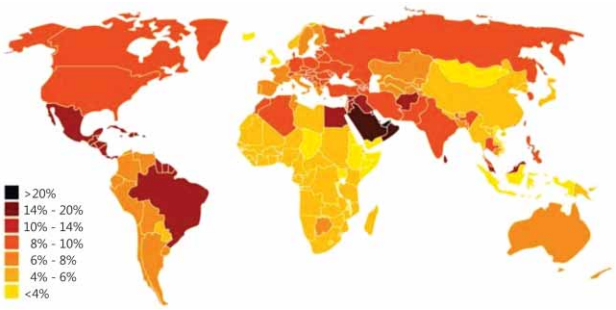


Fig. 1. Diabetes spreading in the World population.

ties. It is not clear how system level mechanical loads, e.g. contact pressures at the foot, influence cellular deformations that may cause cell damage. Molecular level is the fundamental scale needed to understand or predict the property and structure of molecules (Figure 2). In order to speed-up the simulation on nanoscale a coarse-grain method is used, grouping some molecular chains in one particle unit[7]. The stochastic changes of particle numbers in the volume elements representing intracellular space illustrate molecular diffusion with chemical reactions. The cell state transitions and their consequences on micro scale are formulated in terms of finite state automata. The cellular automata treat the single »cell« as agent that carries their states with them as they move on the grid space. There are many simulation examples of multicellular systems such as the adaptive immune system, populations and migrating cells, organ level phenomena[8]. At the end of the macro scale, whole-body bio simulation explicitly accounts the systematic and multifactor character of diabetes type 2, by modelling all of the major physiological phenomena involved in human metabolism. In this work we analysed diabetic foot structure and function by multiscale modelling methodology. Diabetic foot ulceration is an example where the interaction of the tissue deformation and pharmacokinetic processes is important on micro scale, especially if we have wound healing at the same time. The foot type, foot deformities are significant risk factors for ulceration development on macro scale.

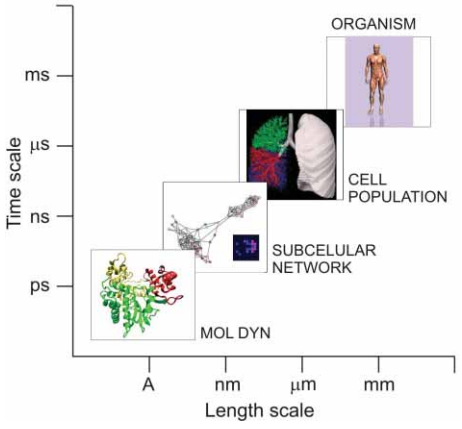


Fig. 2. Multiscale biostructural Model (r,9,ϕ).

Materials and Methods

In our previous paper[9] we studied diabetic foot as flexible multibody structure, as a part of multiscale model for human body locomotion. The computational model (finite element method) of the foot combines the geometric structure of the foot, the material properties of the foot segments and the pressure on the bottom of the foot. The foot cross-section of an adult male was scanned using magnetic resonance imaging (MRI). The foot geometry is transferred to a commercial finite element analysis program GID[10] adopted for this problem, in order to solve multibody flexible structural problems. The foot geometry is discretized into isoparametric finite element mesh representing the bones, cartilages; ligaments and soft tissue (Figure 3).

Material characterization

Material characterization of the diabetic tissues has been influenced by chemo-dynamics processes specific for diabetic body. The material model philosophy should be able to distinguish the difference between diabetic and healthy tissue. It is well-known that the material properties of each organ are different for diabetic and non-diabetic persons, as well. A multiscale material model is proposed in the work[11], based on chemo-mechanical foundations. On macro scale, the Helmholtz free-energy function is decupled in the following form[12].

$$\Psi(\bar{C}, a_1, a_2) = U(J) + \Psi_0(\bar{C}) + \sum_{i=1}^{2} \left\langle \Psi^{\mathrm{i}}_{\mathrm{fibre}}(\bar{C}, a_1, a_2) \right\rangle \qquad (1)$$

$\mathrm{J}=\det(\mathrm{F})$

Where the first term on right side U is a purely volumetric contribution, second term Ψ_0 is noncollagenous ground matrix potential and last term is transversally isotropic potentials Ψ^{i}_{fibre} embedded two families of collagen fibre. J is the determinant of the deformation gradient tensor F representing the local volume ratio. $\bar{C}$ is

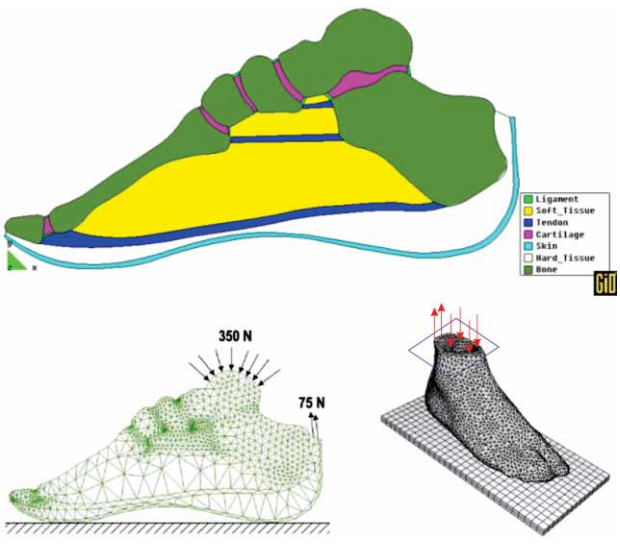


Fig. 3. Finite element model of the foot.

right Cauchy-Green deformation tensor $\bar{C} = \bar{F}^T \bar{F}$, (Where $\bar{F} = J^{-1/3} F$ is the isochoric deformation gradient tensor). Unit vectors a_1 and a_2 define fibre configuration in spherical coordinate system (r, ϑ, ϕ) (Figure 4a).The fibre strain energy can be written as average over the unit sphere

$$\left\langle \Psi^i_{fibre}(\bar{C}, a_1, a_2) \right\rangle = \frac{1}{4\pi} \int_0^{2\pi} \int_0^{\pi/2} n \cdot \Phi_i(\vartheta, \phi) \Psi^i_{\text{fibre}}(\bar{I}_1, \bar{I}_2, \bar{I}_4, \bar{I}_6) \sin\vartheta d\vartheta d\phi \quad (2)$$

i=1,2

Where $I_1 = tr\bar{C}$, $\bar{I}_2 = \lfloor tr\bar{C})^2 - tr\bar{C}^2 \rfloor$, $\bar{I}_4 = a_1 \circ \bar{C} \circ a_1$, $\bar{I}_6 = a_2 \circ \bar{C} \circ a_2$ are invariants of $\bar{C}$ and a_1 and a_2. The constant n represent isotropic network chain density, and $\Psi^i_{fibre}(\bar{I}_1, \bar{I}_2, \bar{I}_4, \bar{I}_6)$ is the microscopic strain energy. The distribution of the fibre orientations is included as the continuous average over unit's sphere. The orientation density function Φ_i has the form of 3D Normal or von Misses distribution.

Using homogenization procedure the averaging material properties on macro scale of each organ are different for diabetic and non-diabetic persons, as well. Difference in constitutive behaviour for diabetic and non-diabetics tissue comes from evolution equations on nanoscale. The collagen fibre effective properties are determined by application of bundle theory for collagen fibrils. The concept presented in the work is based on weakest-link scaling concept. The modified Weibull-Harlow-Phoenix model[13] is used to construct microscopic failure behaviour of fibril bundle. The internal variables such as; average fibril modulus, $\langle E \rangle$, collagen packing geometry, collagen fibril orientation angle, γ_0 and amplitude, A, Weibull scale x_0 and shape parameters, σ_0 respectively, provide a general description fibril structure and properties (Figure 4b and 5).

Local damage accumulation is related to two phenomenological variables, the maximum value and the arc length of the effective free energy in strain space[14] (see Figure 6).

In order to study the influence of the hyper elastic parameters on stress-strain response, we considered a transversely isotropic material with its constitutive behaviour defined by the elastic stored energy function

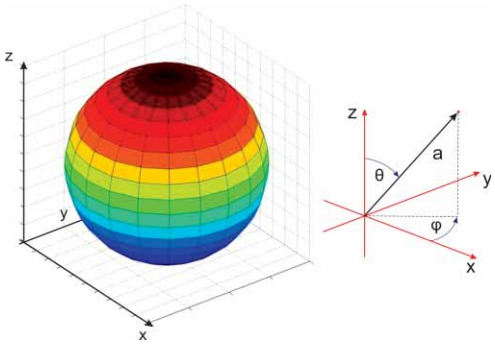
$$\Psi(\bar{C}, a) = \frac{1}{D}[\ln(J)]^2 + C_1(\bar{I}_1 - 3) + C_2(\bar{I}_1 - 3)^2 + \left\langle \Psi(\bar{I}_4) \right\rangle \quad (3)$$

Where $\left\langle \Psi_{fibre} \right\rangle$ is average strain energy collagen fibre. The sets of elastic material constants are given in Table 1.

TABLE 1
MATERIAL CONSTANTS

C_1	C_2	D
10	10	0.0035

a)



b)

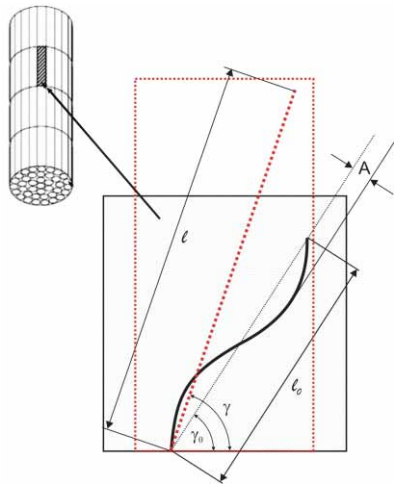


Fig. 4. a) Unit sphere for computation orientation average, b) Sinusoidal approximations of collagen fibrils.

A multilevel finite element approach

Cells are constantly subjected to mechanical stimuli, which play an important role in various cellular processes including growth, adaptation and healing. The physical and geometrical heterogeneity of the microstructure results in high, localized stress and strain levels on individual cells. To define these stresses and strains, a multilevel finite element approach was considered[15]. When an external load is applied, the stress and strain fields in the microstructure will show large gradients due to the micro structural heterogeneity. The repetive deformations justify the assumption of local periodicity around macroscopic points. The repetive micro structural deformations suggest that macroscopic stresses and strains around a certain macroscopic point can be found by averaging micro structural stresses and strains, in a small representative volume element (RVE) of the microstructure attributed to that point. At every macroscopic point, it is assumed that the local deformation gradient tensor F_{MACRO} equals the averaged deformation gradient tensor over the RVE volume $\nabla \cdot \bar{y}$

$$\mathrm{F}_{\mathrm{MACRO}} = \langle \mathrm{F}_{\mathrm{RVE}} \rangle = \frac{1}{V_0} \int_{V_0} (\nabla \cdot \bar{y}) \mathrm{dV}_0 \quad (4)$$

where $0y_1y_2y_3$ is microscale coordinate system, and V_0 is volume of the RVE in reference state. The macroscopic stress Σ_{MACRO} at a material point is assumed to be equal to the averaged microscopic $\langle \sigma_{\mathrm{RVE}} \rangle$ stress.

$$\Sigma_{\text{MACRO}} = \langle \sigma_{\text{RVE}} \rangle = \frac{1}{V_0} \int_V \sigma(\vec{y}) dV \tag{5}$$

Application of the Gauss divergence theorem, equation (5) can be rewritten in following form

$$\langle \sigma_{\text{RVE}} \rangle = \frac{1}{2V} \int_\Gamma [y(\vec{n} \cdot \sigma) + (\vec{n} \cdot \sigma) y] \sigma(\vec{y}) d\Gamma \tag{6}$$

where is Γ the RVE boundary. The effective macroscopic behaviour is is computed for each RVE. After convergence of the RVE calculation the tangential stiffness matrices are computed. This macroscopic tangent stiffness matrix provides a relationship between the incremental macro stress $\delta\Sigma_{MACRO}$ and macro strain variation $\delta\Sigma_{MACRO}$ according to the equation

$$\delta\Sigma_{\text{MACRO}} = {}^4C_{MACRO} \circ \delta \mathrm{E}_{\text{MACRO}} \tag{7}$$

The macroscopic stress Σ_{MACRO} and tangent stiffness matrices ${}^4C_{MACRO}$ are computed from microscopic model and supplied to the macroscopic integration points (Gauss points).

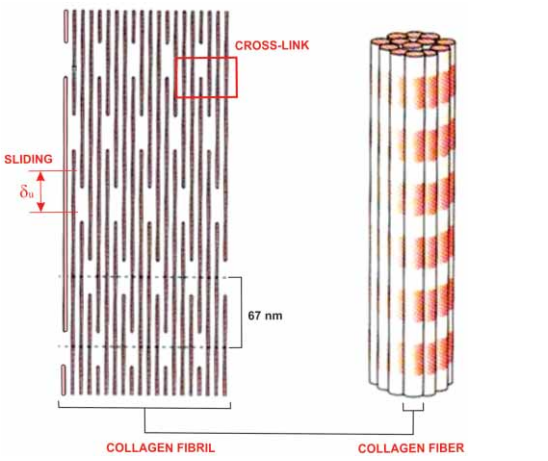


Fig. 5. Collagen fiber with fibrils.

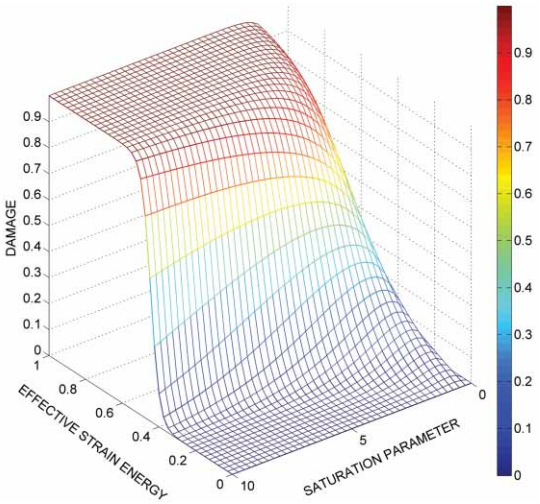


Fig. 6. Damage dependence on strain and saturation parameters.

Tissue damage and wound healing

As it has been pointed out above, the wound is closely connected with diabetic foot phenomena. In order to establish the connection between deformation and wound chemo kinetics, the wound healing problem is described in short. The wound region is assumed to be a circular plate with an axis normal to the skin and, for simplicity, we consider only the one dimensional axisymetric circular cross-section. Figure 8 depicts the circular wound, surrounded by a partially healed annulus, embedded in a healthy tissue as the boundary of the open wound. The focus will be on the first stages of wound healing after haemostasis, that is, inflammation and wound closure, but not on the remodelling of the scar. The model is based on the following variables: *w*-concentration of oxygen; *e*-concentration of vascular endothelial growth factor (VEGF); *p*-concentration of platelet derived growth factor (PDGF); *m*-density of macrophages; *f*-density of fibroblasts; *n*-density of capillary tips; *b*-density of capillary sprouts; ρ-density of extracellular matrix (ECM); and *v*-velocity of ECM[16].

We model the extracellular matrix (ECM) as a growing viscoelastic continuum; more specifically, we model it as a single-phase Maxwell fluid with pressure depending on its density ρ. The momentum equation has the following form

$$\frac{\partial(\rho v)}{\partial t} + \nabla(\rho v \otimes v) = \nabla \cdot \sigma \tag{8}$$

where σ is the stress tensor. The continuity equation for the matrix can be described by following equation

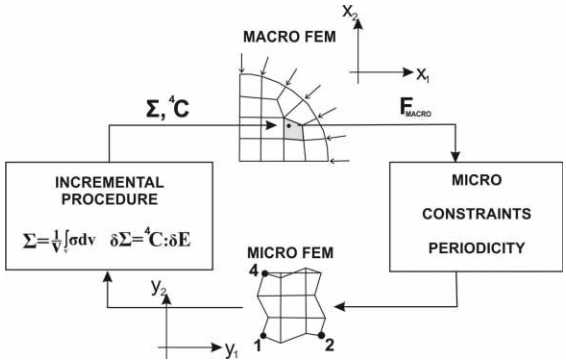


Fig. 7. A multilevel finite element approach.

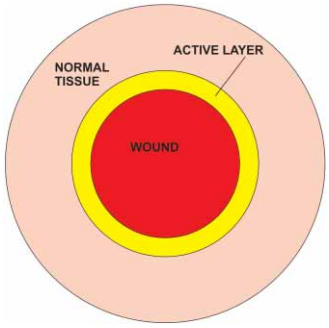


Fig. 8. The open wound geometry.

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho v) = H(f, w, \rho) \tag{9}$$

where is ρ density, is the growth and decay term due to collagen secretion by fibroblasts and degradation by matrix metalloproteinase's. The chemicals and cells move inside the ECM, and we can write their constitutive equations in the following form

$$\frac{\partial u}{\partial t} + \nabla \cdot J = G \tag{10}$$

where u can be replaced by any cell density or chemical concentration, and G is a combination of generation and degradation term, and J is the flux therm. Degradation is assumed to be in Michalis-Menten form [16]. Under the radial symmetry assumption, 2D differential operator in the constitutive equation is replaced by

$$\frac{\partial *}{\partial t} + \nabla \cdot (* v) \rightarrow \frac{\partial *}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(r * v) \tag{11}$$

Results

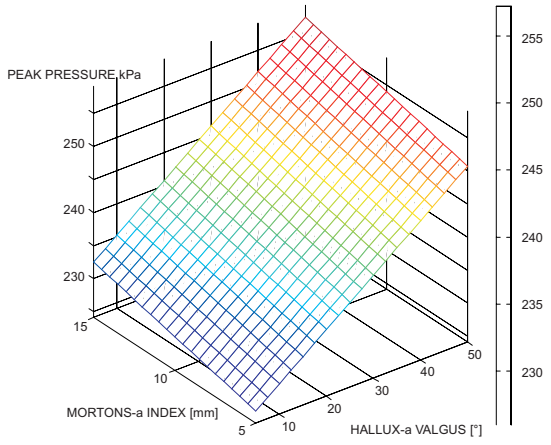
The foot deformity increases stress concentration in certain regions of the foot, and peak pressure causes ulceration in those areas. The relationship between foot deformity, plantar pressure and ulcer location are more complicated under complex foot structure. The finite element model of the foot with Hallux valgus and Morton's index were established together with plantar pressures. A mean value of peak plantar pressures was taken from great toe location. These variables were chosen because Cavanaugh suggested they are dominant parameters for predicting peak plantar pressures on healthy feet[17,18]. Linear dependence peak pressure on Hallux valgus and Morton's index are established using Surface Response Methodology[19] that is graphically illustrated by Figure 9. In research study[20] it is found that there is a strong relationship between foot deformity and ulceration, but there is no correlation between the plantar pressure and the area where ulcerations is present.

The foot cross-section of an adult male was scanned using magnetic resonance imaging (MRI). The foot geometry is transferred to a commercial finite element analysis program GID[10] adopted for this problem, in order to solve multibody flexible structural problems. The contour plot of the von Misses stress distribution in

TABLE 2
MATERIAL PROPERTIES

Component	Young's Modulus [MPa]	Poisson Ratio
Ligaments	200	–
Soft Tissue	hyperelastic	0.5
Tendon	150	0.35
Cartilage	10	0.4
Skin	hyperelastic	0.5
Fascia	350	–
Bone	7300	0.3

a)



b)

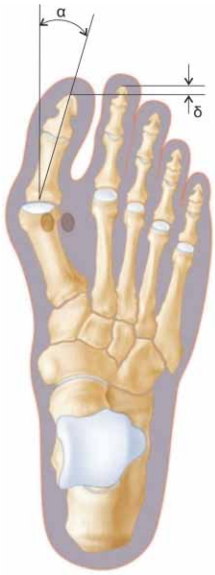


Fig. 9. a) Peak Plantar pressure dependence on Hallux valgus and Morton's index, b) Hallux valgus α and Morton's index δ.

cross-section of the foot is shown on Figure 10. The bone is removed in order to show stress distribution in tissue. Internal stress concentration near bone soft-tissue interface is visible. Therefore, it can bee hypothesized that diabetic foot ulceration might be internally initiated. The

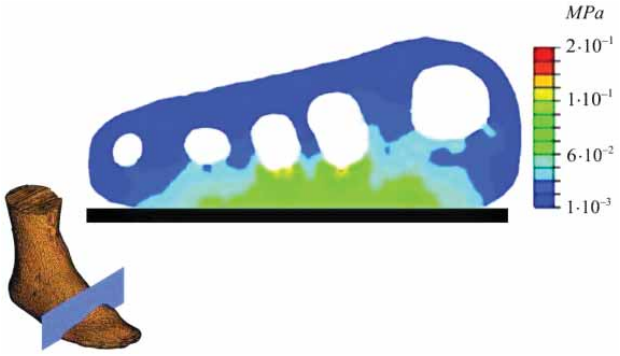


Fig. 10. Von Misses stress distribution in foot cross-section.

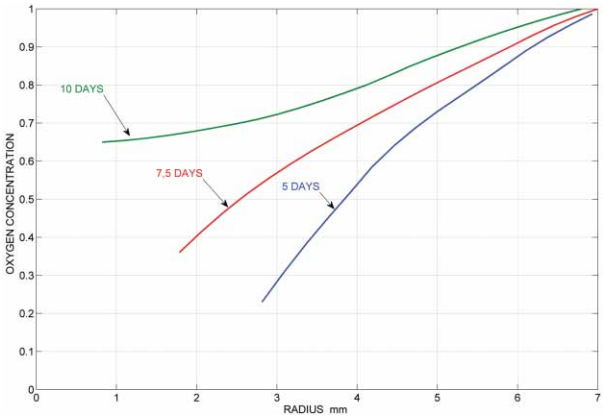


Fig. 11. Oxygen distribution round wound.

stress and strain distribution under foot structure may be a helpful toll in early prediction of the damage of the tissue. The tissue damage is complex process and depends on pharmacodynamic phenomena and today known damage models are simplified. One of the damage criteria is pressure level in capillaries.

The footwear design intervention should be made in order to protect the foot at sites that are at risk for plantar ulceration or re-ulceration by reducing pressure to a level below some threshold value. A variety insole design principles are frequently used to relieve peak plantar pressures.

For the axisymetric wound region, mathematical model in the form of partial differential equations are solved by finite element method. The data from the reference[16] and geometry of the wound (Figure 8) show oxygen concentration distribution in Figure 11.

We calculated the radius of the wound closure for different values of parameter $\gamma \in [0,1]$. The parameter $\gamma=0$ corresponds to healthy tissue and γ near 1 corresponds to extreme ischemia. From the Figure 12 it is evident; the wound closes more slowly for γ close to 1. The wound radius stops decreasing after a certain time.

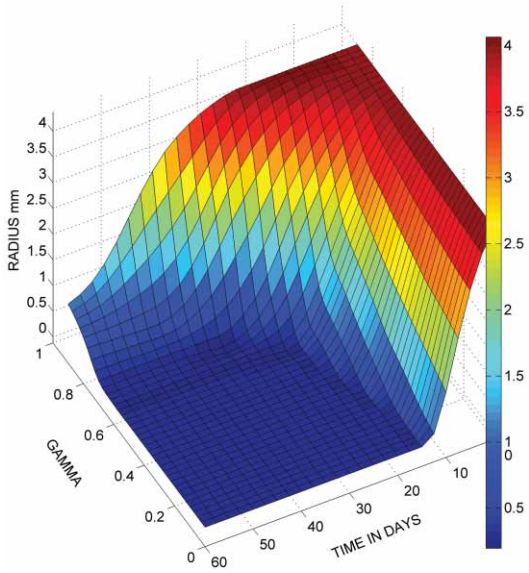


Fig. 12. Wound size dependence on time and parameter γ.

Discussion

We are currently studying more realistic multiscale diabetic related phenomena. The complex mechanical behaviours of the diabetic tissue are characterised by introducing internal coordinate concept on microscale. Stronger local variation material properties are solved by multilevel finite element method. The pressure ulceration may be internal process which can be prevented by adequate load redistribution. The biomechanical model related to diabetes needs to be extended by wound model. Due to the high number of parameters to be determined, the solutions should be reduced to only a few parameters, which is quite a daunting task. Obviously, such models will reflect the understanding of diabetic phenomena behaviour much more realistically. And it will allow us to understand the phenomena resulting from stresses applied to cell tissue as well as the role played by multifactor character of diabetes type 2. A direct connection between the pharmaco/dynamic processes and epidermal mechanics in diabetes has not been elucidated, but methods mentioned above give a new highlight on problem.

REFERENCES

1. TRIEF PM, WADE MJ, PINE D, WEINSTOCK RS, Age Ageing, 32 (2003) 613. — 2. HANCEVIC J, Diabetic Foot, In: HANCEVIĆ J, COCE F, BOŽIKOV V (Eds) Diabetic Foot (Med. Naklada, Zagreb, 2002). — 3. NIKOLIĆ V, RADIĆ R, SELTHOFER R, MIŠEVIĆ T, DMITROVIĆ B, ŠNAJDER D, ŠIŠLJAGIĆ V, BELOVARI T, SUČIĆ Z, Coll Antropol 34 Suppl. 1 (2010) 77. — 4. MIŠIGOJ-DURAKOVIĆ M, DURAKOVIĆ Z, Coll Antropol, 33 (2009) 759. — 5. QUTUB AA, GABHANN FM, KARAGIANNIS ED, VEMPATI P, POPEL AS, Journal IEEE Eng. in Med. and Biology Magazine, 3 (2009) 14. — 6. ZHOU H, ISAMAN DJ, MESSINGER S, BROWN MB, Diabetes Care, 28 (2005) 2856. — 7. TAWHAI M, BISCHOFF J, EINSTEIN D, ERDEMIR A, GUESS T, REINBOLT J, Journal IEEE Engineering in Med. and Biology Magazine, 6 (2009) 41. — 8. HOEHME S, DRASDO D, Bioinformatics, 26 (2010) 2641. — 9. AGIĆ A, NIKOLIĆ V, MIJOVIĆ B, REISCH U, Coll Antropol, 32 (2008) 881. — 10. GiD The personal pre/postprocessor: User Manual, accessed 12.04.2006. Available from: URL: http://www.gid.cimne.upc.es — 11. AGIC A, TRNSKY D, DeSYO D, 3rd. Int. Ergonomics Conference (Mijovic Eds, Zagreb, 2007). — 12. GASSER TC, OGDEN RW, HOLZAPFEL GA, J of the Royal Society Interface, 3 (2006) 15. — 13. LAYTON BE, SASTRY AM, Acta Biomaterialia, 2 (2006) 595. — 14. PENA A, PENA JA, DOBLARE M, Int J of Solids and Structures, 46 (2009) 1727. — 15. BREULS RG, SENGERS BG, OOMENS CW, BOULEN CV, BAAIJENS FP, Journal of Biomechanical Engineering, 124 (2002) 198. — 16. XUE C, FRIEDMAN A, SEN CK, Proc Natl Acad Sci USA, 106 (2009) 16782. — 17. CAVANAGH PR, MORAG E, BOULTON AJ, YOUNG MJ, DEFFNER KT, PAMMER SE, J. of Biomechanics, 30 (1997) 243. — 18. SFERRA J, DONLEY B, CAVANAGH PR, Journal of Biomechanical Engineering, 29 (2007) 750. — 19. H. MYERS RH, MONTGOMERY DC, Response Surface Methodology (Wiley, New York 2002). — 20. MEROLLI A, UCCIOLI L, Journal of Appl. Biomaterials & Biomechanics, 3 (2005) 61.

A. Agić

University of Zagreb, Faculty of Chemical Engineering and Technology, Savska cesta 16, 10000 Zagreb, Croatia
e-mail: aagic@fkit.hr

VIŠESKALNI FENOMENI POVEZANI S DIJABETIČKIM STOPALOM

S A Ž E T A K

Fenomen dijabetesa nije moguće razumjeti niti objasniti na jednoj materijalnoj skali. Dijabetičko stopalo analizirano je kao fleksibilna višekomponentno građena struktura koristeći metodu konačnih elemenata. Materijalna i geometrijska heterogenost na višestrukoj skali riješena je primjenom višerazinske metode konačnih elemenata. Ponašanje dijabetičkog tkiva opisano je formalizmom unutrašnjih koordinata na višestrukoj materijalnoj skali. Dijabetesu pridruženi problem zacjeljivanja rana riješen je numerički. Neki rezultati vezani uz deformitet stopala, koncentraciju naprezanja te zacjeljivanje rane su kratko opisani.