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HYPERTROPHIC SCAR FORMATION MODEL APPLIED TO BLUNT--PROSTHESIS INTERFACE: FORMING BY ACCRETION

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Abstract: *The interface blunt-prosthesis is the subject of stress and friction due to forces that act in the walking stage. The dermal wounds that can appear due to this stress and frictions can heal due to normal process of regenerative of dermal layers. In some cases, the normal process of wound healing can fail and some abnormal forms can develop: keloid and hypertrophic scars. These abnormal forms can be seen as mainly due to fibro-proliferative disorder in terms of excessive development of fibroblastic cells. In this paper we investigated the possibility to use the mathematical model for fibro-proliferative interactions to forming of scars by accretion at the interface blunt-prosthesis. The work can be used to predict the risk area of patient's stump and subsequent the use of physio kinetotherapy program to prevent this. The investigation is a theoretically one and it must be validated by medical measurements.*

Key words: *mathematical model, fibroplasia and wound contraction, hypertrophic scar, fibro-proliferative disorders, blunt-prosthesis interface, cell accretion.*

1. INTRODUCTION

The comfort and patient satisfaction is an important challenge for physicians and technicians to develop procedures that accomplish these tasks [1 and 2]. Many problems related to these objectives are analyzed and solved using biomechanical modeling of stump-socket-prosthesis ensemble. The forces and moments in the normal walking, climbing stairs, and even sportive activities are investigated in many papers.

The stress map along with statistic consideration plays an important role in discovering or maximum stress and maximum friction points (areas) [3, 4 and 5]. In [5], the authors used finite element method and MRI to investigate the internal mechanical state on surface and internal residual limb in active transaxial amputation. The knowledge of the mechanical state of the internal soft tissues give information about location of the area of risk and an estimation of the volume of muscle tissues at risk [5]. By identification of these areas and group of residual muscles, a premise to alleviate the eventually dermal wounds is created. The physicians can identify these areas and some physio-kinetotherapy procedures can be applied to solve the problem.

Tribological behavior, the rubber in prosthetic wearing skin and healthy limb skin were investigated *in vivo* in [6]. By skin, usually we understand the epidermis, dermis and subcutaneous tissue. Scars can appear after restoration caused by tissue repair in response to trauma or surgical incision but also in wearing a prosthetic limb. The subcutaneous tissue is mainly formatted by collagen. The volume of collagen gradually changes during tissue reparation. The coefficient of prosthetic skin were determined experimentally using hysteretic curves (tangential force vs. imposed displacement amplitude) in gross relative sliding, intermediate and sticking regimes.

However, an important problem still arises. The evolution of a formed scar is an open problem. Considerable attention has been devoted in the last year in terms of modeling and simulation. Researchers and clinicians become more aware of the possibilities offered by the simulation of mathematical modeling. In this way we can recognize that there is a closely related relationship between the approaches in the analytical processing of the data obtained. A continuous interchange of the biological growth and remodeling from the drawn has been received considerable attention in the last fifteen years. In [7] few preliminaries related to keloid formation and development the prosthesis usage have been discussed. Modeling and simulation of keloid scar formation can provide valuable insights in the analysis and prediction of pressures directly proportional development of scar-socket interface [8].

A complicated model is proposed in [9].The authors proposed to model one of wound healing diseases, the keloid. According to medical hypothesis, the viruses and the genetic susceptibility of patients are the main causes that can stat the formation of keloid. The mathematical model is proposed using the kinetic theory for active particles. The competition of the immune system cells with viruses, keloid fibroblast cells, and malignant cells is taken as competitors in nonlinear system interactions. The continuous model (system of five nonlinear partial

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differential equations) from [9] is discretized in [10]. The model takes into account the start of keloid disease triggered by a virus. The normal wound healing is seen as a protracting process in which the skin repairs itself. The model is based on theory of particle that is complicated. The system is decomposed in small subsystems that interact functional. The particles have local density and the local mean activity based on statistic distributions.

A six-species model has been proposed in ([11] and [12]). The authors used the species: collagen, macrophages, fibroblasts, transforming growth factor-b (TGF-b) and tissue plasminogen activator in order to develop a wound healing mathematical model. Cytokine TGF-b plays an important role in the healing cascade [11].

The epidermal response of wound is well documented [12]. The wound healing is composed from four overlapping phases named hemostasis, inflammation, proliferation, and remodeling. However some researches consider that the first two stages are practically combined in a single one, inflammation. There are three overlapping processes, inflammation, wound closure and matrix remodeling in epidermal tissue [13, 14 and 15]. The rate of increasing cell density depends on cell migration, mitotic generation, phenotypic conversion and natural loss of cell. The rate of increasing chemical concentration depends of diffusion process, production of cells by mitosis, phenotypic conversion and natural death of cells. Chemical concentration depends on diffusion and convection, production by cells and decay. The collagen concentration depends on convection and synthesis and degradation of cells. Finally, the tissue displacement depends on elastic stress, active cell traction stress and resistance which are usually represented by linear restoring force [14].

The excessive scar formations are *Hypertrophic scar*, *Keloid*, and *Desmoid*. In our paper we used mathematical model for hypertrophic scar proposed by [14] in order to model the forming of scars by accretion at the interface blunt-prosthesis. The proposal work is a theoretical one and the experimental results must be validated by medical investigations.

2. EPIDERMAL HYPERTROPHIC SCAR FORMED BY ACCRETION

The processes involved in normal and abnormal dermal wound healing are complex and related to cell proliferation mechanisms. Epidermal wound can happens in the first stage of patient's prosthetic wearing. This stage involves small lesion on the skin surface without affecting the internal tissues and muscles (residual muscles). Dermal wounds that can appear in depth lesion in the skin and the internal tissues can be severely affected in the case of abnormal treatment. Excessive dermal response can conducts to gross hypertrophic scar, an accretion of deposits in the area of wound which can become an elevated zone above the plane of the skin. The higher the elevated zone, the higher are the rubber between residual limb and ensemble stump-prosthesis and area becomes more sensitive to pressure during patient's normal gait cycle.

Fretting can be another source of worsening of the work conditions for ensemble residual limb-socket prosthesis. Traditional approach for fretting at the interface organ-prosthesis is taken for few millimeters only, so in our first approach the fretting is neglected.

Just before the inflammatory phase is initiated, a hemostasis take place that is a fibrin clot is forms in order to stop the blood loss.

Fibroblasts are the most common connective tissue. Fibroblasts are motile during wound healing and they are responsible to synthesize the extracellular matrix (ECM) and collagen. Fibroblasts can also degrade some ECMs components and as follows some internal tractions and stress in tissue is generated. Brownian motion and chemotactic response in the growth model are used to modeling random and migration fluxes of these types of cells. Mitosis process creates new cells. Different forms of function are used to model this process but the most common one is logistic growth. The death of cells can be also modeled by some decay function but in [14] a simple linear one is preferred. A part of fibroblasts follows a phenotypic transformation into myofibroblasts cell that are contractile now.

Myofibroblasts can move only by passive convection due to moving tissue. Myofibroblasts contribute also to degradation of ECM with the same rate or at different rate of fibroblasts. One of the main roles played by fibroblasts is transmission and tuning of traction forces that generates stress in tissues in the process of wound healing. The growth rate of myofibroblasts is usually linearly one and the death rate take place in "apoptosis".

There are many growth factors involved in wound healing: epidermal growth factor (EGF), transforming growth factor beta (TGF-b), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), granulocyte macrophage colony stimulating factor (GM-CSF), platelet derived growth factor (PDGF), connective tissue growth factor (CTGF), interleukin (IL), and tumor necrosis factor-α. Growth factors regulate fibroplasia. Among these factors two promoters are considered: platelet-derived factor and a transformation growth factor denoted by β [14].

Many components of ECMs are also involved in wound healing. The authors [14] used only one of them, the fibrillar type I collagen because this type plays an important role in fibroplasia and contraction.

The system of PDEs used in [14] has five equations and 31 parameters. It is very hard to determine experimentally the values of these parameters so we take the values known in literature.

Fibroplastia and contraction are during normally about three weeks. ECM (Extracellular matrix) modeling starts from mature scar and can continue many months. Fibroblasts adjust continually ECM and collagen and the tensile strength of wounded area come to be restored.

The modeling of wound contraction applies to each of regulatory equations [14]:

$$\frac{\partial V}{\partial t} = -\nabla \cdot J_V + f_V \,. \tag{1}$$

V represents the quantity of variable, J_V represents the flux and f_V represents the kinetic term. The equation apply to five variables: n (fibroblast density), m (myofibroblast density), c (chemical concentration), ρ

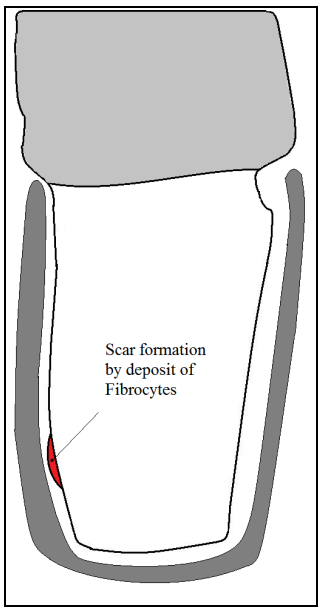

Fig. 1. Scar formation by accretion (deposit) of fibrocytes.

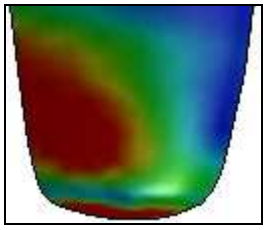

Fig. 2. The region of risk susceptible to scar formation by accretion.

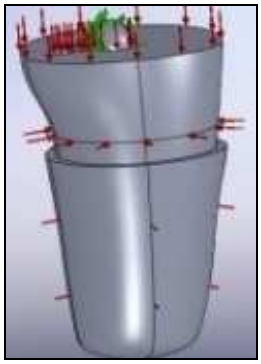

Fig. 3. Application of forces (red arrows) and constraints (indicated by green arrows).

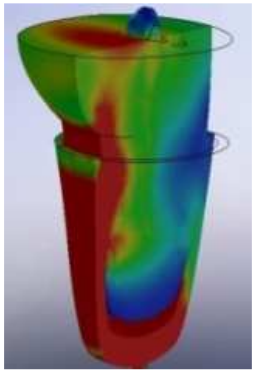

Fig. 4. The influence of bone tissue (red is maximum stress force).

(collagen concentration) and *u* (tissue displacement). The cell fluxes are modeled by Fickian diffusion with constant coefficient meanwhile for kinetics, mitosis with logistic form transform the cell into myofibroblast using a stimulation growth factor.

The development of equation (1) conduct to a complicated form in 3-D space (e.g. fibroblasts) [13]:

$$\frac{\partial n}{\partial t} = \nabla \cdot \left[D_n \nabla n - \frac{a_n}{(b_n + c_n)^2} n \nabla c - n \frac{\partial u}{\partial t} \right] + \\ + \left(r_n + \frac{r_{n,\max} c}{C_{0.5} + c} \right) \cdot n(1 - n/k) - \frac{k_{1,\max} c}{c_k + c} + \\ + k_2 m - d_n n. \tag{2}$$

The equations are transformed in a non-dimensional model by division of each variable to *V* to a V_o value resulting a new non-dimensional variable $V^* = V / V_0$. Five non-dimensional equations are obtained for 1-D nonlinear model [13, 14 and 15].

The regions with high pressure and rubber are considered (Figs. 1 and 2). The pressure is due to load forces that act over residual limb tissues on three directions: X, Y and Z (Fig. 3). The effect of forces can be seen deeply inside the tissue and residual limb. Residual bone plays also a resistance role in ensemble prosthesis-socket-tissue-residual limb (Fig. 4).

For simplicity, we considered the wounded area as a circular plate in a single spatial coordinate, *x* (*x* is the spatial vector) and *t* denotes time.

$$\begin{cases} \mu \cdot x_{xxt} = g_5 \\ n_t = g_1 - n_x u_t - n \cdot u_{xt} \\ m_t = g_2 - m_x u_t - m \cdot u_{xt}, \\ c_t = g_3 - c \cdot u_{xt} \\ \rho_t = g_4 - \rho \cdot u_{xt} \end{cases} \tag{3}$$

where

$$g_1 = D_n \cdot u_{xx} + \frac{2}{(\beta + c)^2} (c_x)^2 + \frac{\alpha}{(\beta + c)^2} \cdot n_x \cdot c_x + \\ + \frac{\alpha}{(\beta + c)^2} \cdot c_{xx} + f_{m1} + f_{fc} + f_d; \tag{4}$$

$$f_{m1} = \sigma \left(1 + \frac{Ac}{B + c} \right) n(1 - \gamma n); \tag{5}$$

$$f_{fc} = -\frac{k_1 c}{C + c} n + k_2 m; \tag{6}$$

$$f_d = -\delta n. \tag{7}$$

$$g_2 = \varepsilon_\sigma \sigma \left(1 + \frac{Ac}{B + c} \right) m(1 - \gamma m) + \frac{k_1 c}{C + c} n - \\ - k_2 m - \lambda \delta m; \tag{8}$$

$$g_3 = \frac{k_c (n + \xi m) c}{\gamma_C + c} - \delta_c c; \tag{9}$$

$$g_4 = \left[\omega \left(1 + \frac{Pc}{Qc} \right) \frac{1}{\phi^2 + \rho^2} - \delta_\rho \rho \right]; \tag{10}$$

$$g_5 = -\frac{\upsilon}{\psi^2+\rho^2}[\xi(mn\rho_x + n\rho n_x + n\rho m_x) - 2((1-\xi m)n\xi)\rho\rho_x]. \quad (11)$$

The boundaries conditions for x are taken as in [14], $x = 0$ and $x = 1$. These values are the initial wound margins. The entire process is non-dimensional so initial conditions are: $n_0 = 1$, $\rho_0 = 1$, $c_0 = c_i \cdot exp(-x^2)$, $m_0 = 0$, $u_0 = 0$).

In comparison with healthy skin, the scar skin has a roughness of surface very high. In is normally to suppose that the friction force and coefficient of friction is higher than in normally skin [16, 17 and 18]. Human skin has viscoelastic properties that are somewhat similar to a soft elastomer [17]. A simple formula applied to dry conditions suppose that we have two contributors to coefficient of friction (two-term model of friction [17]), adhesion present in the interface skin-socket and deformation of the skin:

$$\mu = \mu_{adhesion} + \mu_{deformation}. \quad (12)$$

In this stage we consider the friction of skin as a function of adhesion meanwhile the deformation is related only as effect of equations (3)−(10). We neglect the hysteresis effect due to viscoelastic skin deformation to friction. It is expected that the scar skin to have a very little viscoelastic property.

From contact theory and Wolfram's development [20], the adhesion component of friction is given by:

$$\mu_{adhesion} = k_a \cdot F_N^{-1/3} \cdot E^{-2/3}. \quad (13)$$

The contribution of viscoelastic model for skin deformation due to friction is given by:

$$\mu_{deformation} == k_d \cdot F_N^{+1/3} \cdot E^{-1/3}. \quad (14)$$

In the equations above, F_t is normal load and E is the elastic modulus of skin. A common approach to estimate friction force is an empirical one, $F = k \cdot N^n$, where N is the normal load.

We propose to use an empirical formula to estimate the displacement x that increase due to additional friction at the interface skin-socket.

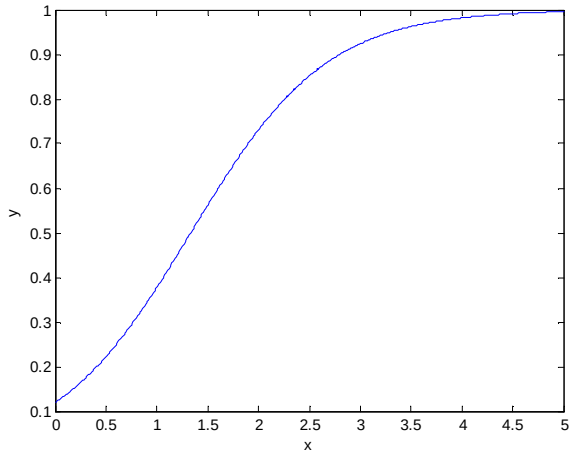

Fig. 5. Sigmoidal function.

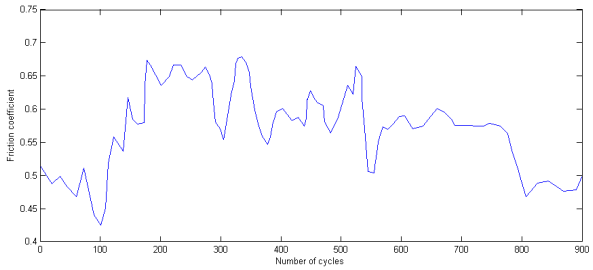

Fig. 6. Variation of friction coefficients for scar skin during 600 cycles (1 cycle ≈ 6 s).

$$w = k\frac{1}{1+e^{-at+b}}. \quad (15)$$

This function is appended to linear restoring force with minus sign (the tissue resistance, g_5) in order to model the accretion influence in development of hypertrophic scar.

The parameters k, a, b are determined theoretical by curve fitting from experimental data.

3. RESULT OF SIMULATIONS

We choose the axisymmetric linear model of wound (Fig. 7) [13] with uniform grid for discretization (Fig. 8).

The system is solved using finite difference method. We denotes by Δt and Δx the time steps and space intervals respectively. We used forward difference for time and central differencing for space. We consider also mixed derivatives (finite difference in two variables):

$$\frac{\partial u}{\partial t} = \frac{u^{j+1} - u^j}{\Delta t}; \quad (16)$$

$$\frac{\partial u}{\partial x} = \frac{u_{i+1} - u_{i-1}}{\Delta x}; \quad (17)$$

$$\frac{\partial^2 u}{\partial x^2} = \frac{u_{i+1} - 2u_i + u_{i-1}}{(\Delta x)^2}; \quad (18)$$

$$\frac{\partial^3 u}{\partial x^3} = \frac{u_{i+2} - 2u_{i+1} + 2u_{i-1} - u_{i-2}}{2(\Delta x)^3}; \quad (19)$$

$$\frac{\partial^2 u}{\partial x \partial y} = \frac{u_{i+1,k+1} - u_{i+1,k-1} - u_{i-1,k+1} + u_{i-1,k-1}}{4\Delta x \Delta y}. \quad (20)$$

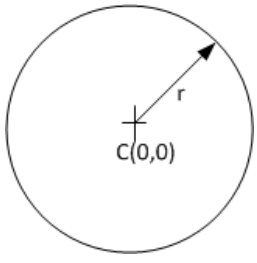

Fig. 7. Diagram for axisymmetric linear model of wound (C(0,0) is the center of circle). The radius r correspond to x variable.

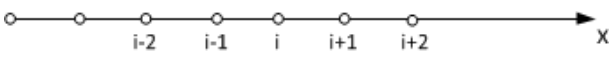

Fig. 8. Uniform grid for t and x discretization.

The finite difference scheme is accurate up to $O((\Delta x)^2)$. A uniform grid is used for t and x.

Mixed derivatives are computed using second order difference approximation:

$$\frac{\partial^3 u}{\partial x^2 \partial t} = \frac{\partial}{\partial t}\left(\frac{\partial^2 u}{\partial x^2}\right). \quad (21)$$

We denote $u_{xx} = v$ and we can solve the system using this additional variable, having new notation:

$$\begin{aligned} u_{xx} &= v; \\ v_t &= \frac{\partial v}{\partial t}. \end{aligned} \quad (22)$$

The finite difference scheme becomes:

$$u_{xxt} = \frac{u_{xx}^{j+1} - u_{xx}^{j}}{\Delta t}. \quad (23)$$

The experiments used the values given in literature [14] with small variation in order to test the local sensitivity for possible different patients. The start points for constants is that from [14]: $D_n = 0.02$, $\alpha = 0.1$, $\beta = 0.2$, $\sigma = 0.02$, $A = 44.0$, $B = 1$, $C = 1$, $\gamma = 0.01$, $k_1 = 10$, $k_2=1$, $k_c = 0.4...0.6$, $\varepsilon_\sigma = 0.5$, $\delta = 0.0198$, $\lambda = 10$, $D_c = 0.2$, $\zeta = 1.0$, $\gamma_c = 1.0$, $\delta_c = 0.5$, $\omega = 0.08$, $P = 10$, $Q = 0.1$, $\phi = 3$, $\delta_\rho = 0.0008$, $\eta = 2$, $\mu = 20$, $\nu = 0.03$, $\xi = 5$, $\psi = 0.05$, $s = 1$, $c_i = 1$ and $\rho_I = 1$.

We start with $n_0 = 1$ (initial condition) in order to evaluate the evolution of number of fibroblasts in time and space. Fig. 9 shows the evolution of number of fibroblasts in time distribute on distance as in Fig. 7. In Fig. 10, we showed the tissue displacement in time, practically the function $u(t)$.

We can remark small displacements in tissue on the x lines (Fig. 10).

The initial assumption for hypertrophic scar development is that no action takes place over the affected area. That is, the evolution of scar is due to only equations (3)-(11). Our approach takes into account a very simplified model when pressure due to normal load in prosthesis conducts to worsening the wounded area. However our model is a preliminary one, due to variation of load on residual and subsequent an average gait cycle should be taken into account (Fig. 11, Fig. 12).

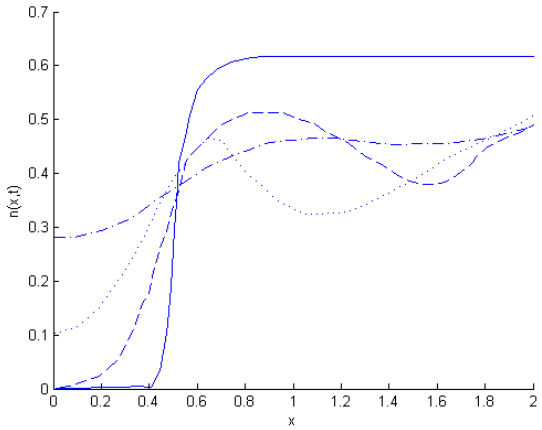

Fig. 9. Number of fibroblasts vs. distance from center of wound ($x = 0.4$ is the border of wound).

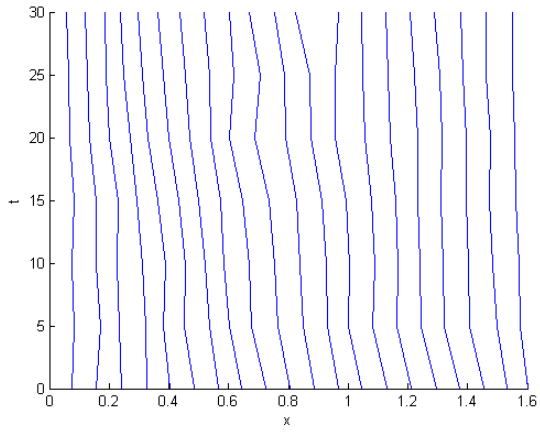

Fig. 10. Tissue displacement in time.

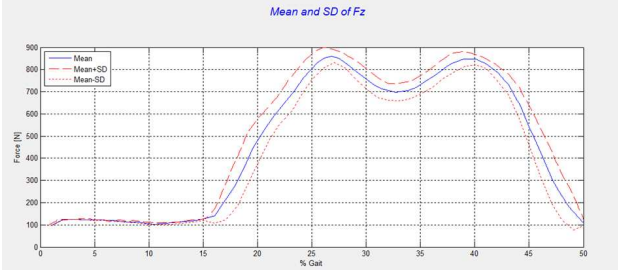

Fig. 11. Force in direction Z.

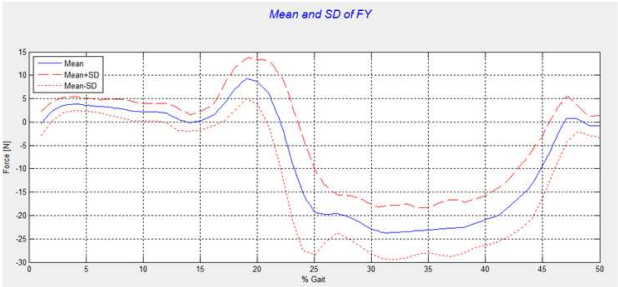

Fig. 12. Force in direction *Y* (lateral).

The friction varies in large limits during a gait cycle so an exact evaluation of the coefficient of friction in a mathematical formula for this case seems to be very difficult. There are some experimental hysteresis form that showed a large variation in the case of normal skin and scar hypertrophic skin [16].

In the future research we will develop an approximated model that could give a satisfactory solution.

4. CONCLUSIONS

A mixed system for modeling forming of scars by accretion at the interface blunt-prosthesis using wound healing equations and coefficient of friction has been proposed. The simulations showed that displacement of tissues can be realistic.

The results must be validated by medical assessments and experimental investigations.

Other aspects will be taken into further research. Hysteresis present in the friction of scar skin has not modeled in equation. Also, even the hysteresis has a variable shape for the same person during different loads and

shape. This suggests that a stochastic approach could be the answer a model that takes into account the abnormal wound healing and tissue displacement (growth) by accretion.

The stochastic approach imposes to consider a system of stochastic equation, which could be a very complicated system.

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