A Finite Element Model for Epidermal Wound Healing

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Abstract. A finite element model for epidermal wound healing is proposed. The model takes into account the sequential steps of angiogenesis (neo-vascularization) and wound contraction (the actual healing of a wound). An innovation in the present study is the combination of both partially overlapping processes, yielding novel insights into the process of wound healing. The models consist of nonlinearly coupled diffusion-reaction equations, in which transport of oxygen, growth factors and epidermal cells and mitosis are taken into account.

Keywords: finite elements, wound contraction, neo-vascularization.

1 Introduction

Models for bone regeneration and wound healing often rely on experiments on animals. When a wound occurs, blood vessels are cut and blood enters the wound. Due to coagulation of blood inside the wound, the wound is temporarily closed and as a result the blood vessels adjacent to the wound are also closed. In due course contaminants will be removed from the wounded area and the blood vessel network will be restored, but initially due to insufficient blood supply, there will be a low concentration of nutrients which are necessary for cell division and wound healing. Wound healing, if it occurs, proceeds by a combination of several processes: chemotaxis (movement of cells induced by a concentration gradient), neo-vascularization, synthesis of extracellular matrix proteins, and scar modeling. Previous models incorporate cell mitosis, cell proliferation, cell death, capillary formation, oxygen supply and growth factor generation, including studies by Sherratt *et al.* [1], Fillion *et al.* [2], Maggelakis [3] and Gaffney *et al.* [4], to mention just a few. A recent work devoted to mathematical biology has been written by Murray [5], in which the issue of wound healing is also treated. The wound healing process can roughly be divided into the following partially overlapping consecutive stages:

1. Formation of a blood clot on the wound to prevent undesired chemicals from entering the tissue of the organism (blood clotting/inflammatory phase);

2. Formation of a network of tiny arteries (capillaries) for blood flow to supply the necessary nutrients for wound healing;
3. Division and growth of epidermal cells (mitosis), taking place during the actual healing of the wound (remodeling phase).

A good supply of nutrients and constituents is necessary for the process of cell division and cellular growth. For this purpose tiny capillaries are formed during the process of angiogenesis. Some models for capillary network formation have been proposed by Gaffney *et al.* [4] and Maggelakis [6].

Wound contraction is modeled by Sherratt & Murray [1] who consider cell division and growth factor generation simultaneously for healing of epidermal wounds. Their model consists of a system of reaction-diffusion equations. Among many others an alternative model, based on an active layer at the wound edge, for wound contraction was proposed by Adam *et al.* [7] and for more references, see [8]. Until now, the conditions for wound healing were only analyzed for geometries where only one spatial co-ordinate could be used. As far as we know, in all the mathematical studies mentioned before, either neo-vascularization or wound contraction is modeled. Hence, these processes are considered to be sequential. However, according to the medical literature [9], these sequential processes partially overlap. Therefore, this study aims at the creation of a model in which the stages of neo-vascularization and wound contraction are treated as sequential, but partially overlapping processes. Hence, the key innovations in the present study are the following: Finite Element solutions for arbitrary wound geometries; and a combination of models for angiogenesis and wound contraction as partially overlapping consecutive processes.

The present paper is organized as follows. First, an existing model for angiogenesis (neo-vascularization) with an extension is described. This is followed by a treatment of a model for wound contraction and a proposition of how to combine these models. We continue with a description of the numerical method to solve the resulting nonlinearly coupled system of partial differential equations and present some numerical experiments, followed by some concluding remarks.

2 The Mathematical Model

In this section a model for epidermal wound healing is presented. The model consists of neo-vascularization and wound contraction and the construction of the model relies on a combination of the ideas developed by Maggelakis [6], Gaffney *et al.* [4] and Sherratt and Murray [1].

2.1 Neo-vascularization

Maggelakis constructed this model on angiogenesis in 2004 [6]. It is assumed that the tips of the capillaries act as the only sources for oxygen supply. The domain of computation is assumed to be divided into the wound region Ω_w and the undamaged region Ω_u , that is $\Omega = \Omega_w \cup \Omega_u \cup (\overline{\Omega_w} \cap \overline{\Omega_u})$ and Ω_w is embedded within Ω_u . The closures of Ω_w and Ω_u respectively are denoted by $\overline{\Omega_w}$ and $\overline{\Omega_u}$.

Let n and c_o respectively denote the capillary density and oxygen concentration and let them be functions of time t and space within the domain of computation Ω ; then a mass balance results into the following partial differential equation (PDE):

$$\begin{aligned} \frac{\partial c_o}{\partial t} &= D_o \operatorname{div} \operatorname{grad} c_o + \lambda_n n - \lambda_o c_o, \text{ for } \mathbf{x} \in \Omega_w, \\ \text{subject to } c_o(\mathbf{x}, t) &= c_i \text{ for } \mathbf{x} \in \overline{\Omega}_w \cap \overline{\Omega}_u. \end{aligned} \quad (1)$$

The initial oxygen concentration is assumed to be zero in Ω_w . The above equation is based on the assumption that the oxygen supply and oxygen consumption depend linearly on the capillary density and oxygen concentration respectively. When the oxygen level is low, macrophages appear at the wound site. The macrophages release MDGF's (macrophage derived growth factors) which are hormones that enhance the growth of blood vessels and collagen deposition and hence help to restore the capillaries that provide the skin with the necessary nutrients and oxygen for cell division needed for wound contraction. An assumption in the model is that macrophages are produced if the oxygen level is below a threshold value, say c_θ . The production rate, Q , is assumed to depend linearly on the lack of oxygen, that is

$$Q = Q(c_o) = \begin{cases} 1 - \frac{c_o}{c_\theta}, & \text{if } c_o < c_\theta, \\ 0, & \text{if } c_o \geq c_\theta. \end{cases} \quad (2)$$

The mass balance of MDGF's results into the following PDE's in the wound region Ω_w and out of the wound region Ω_u :

$$\begin{aligned} \frac{\partial c_m}{\partial t} &= D_m \operatorname{div} \operatorname{grad} c_m + \lambda_m Q(c_o) - \lambda_c c_m, \text{ for } \mathbf{x} \in \Omega_w, \\ \frac{\partial c_m}{\partial t} &= D_m \operatorname{div} \operatorname{grad} c_m - \lambda_c c_m, \text{ for } \mathbf{x} \in \Omega_u. \end{aligned} \quad (3)$$

The initial MDGF concentration, denoted by c_m , is assumed to be zero in the entire domain of computation Ω and a homogeneous Neumann boundary condition is used. The capillary density is assumed to grow as a result of the MDGF's in a logistic manner, that is

$$\frac{\partial n}{\partial t} = D_n \operatorname{div} \operatorname{grad} n + \mu c_m n \left(1 - \frac{n}{n_m}\right), \text{ for } \mathbf{x} \in \Omega, \quad (4)$$

where n_m denotes the maximum capillary density. The capillary density is assumed to satisfy the following initial condition

$$n(\mathbf{x}, 0) = \begin{cases} 0, & \text{for } \mathbf{x} \in \Omega_w, \\ n_m, & \text{for } \mathbf{x} \in \Omega_u. \end{cases} \quad (5)$$

A homogeneous Neumann boundary condition is used for n . We assume the capillary tips to migrate via a random walk. This random walk was not incorporated into Maggelakis' model but it was extended with a bias in Gaffney's model.

Further, Gaffney *et al.* [4] distinguish between the capillaries and the capillary tips. The bias is neglected in this paper but it will be dealt with in the future work to be presented in the talk. But it is reasonable since away from the wound the capillary network is assumed to be undamaged. Further, Maggelakis sets in a nonzero artificial starting value for the capillary density to have the capillary density to increase up to the equilibrium value. Analytic solutions are considered in [6] for the above equations under the assumptions that the diffusion of oxygen and growth factors is instantaneous and that $D_n = 0$. The induced growth of MDGF's due to a lack of oxygen can be classified as a negative feedback mechanism. In the presentation we will extend this model with model hypotheses due to Gaffney *et al.* [4] who incorporate the interaction of the capillary tip density with the endothelial cell density and use a biased random walk resulting into nonlinear cross diffusion.

2.2 Wound Contraction

The mechanism for wound contraction is cell division and growth (mitosis). This mechanism is triggered by a complicated system of growth factors. In the present model we use the simplification that wound contraction is influenced by one generic growth factor only. The growth factor concentration influences the production of epidermal cells. Following Sherratt and Murray [1], we assume that the main source of growth factors is the epidermal cells. Growth factors diffuse through the tissue region and the concentration decays due to reactions with other chemicals present in the tissue. Further, the epidermal cells need the supply of nutrients by the capillaries in order to be able to grow and divide. A constant blood flow through the capillaries is assumed, hence, the mitotic rate can be related to capillary density n . The mitotic rate is assumed to depend on the capillary density in a nonlinear fashion by a function $\phi_p(y)$, given by

$$\phi_p(y) = \frac{y^p}{(1-y)^p + y^p}, \quad (6)$$

where p is assumed to be positive. Herewith, the expression of Sherratt and Murray where the accumulation of the epidermal cells is determined by proliferation (diffusive transport), mitosis and cell death, is adjusted to

$$\begin{aligned} \frac{\partial m}{\partial t} &= D_1 \operatorname{div} \operatorname{grad} m + \phi_p\left(\frac{n}{n_m}\right)s(c)m\left(2 - \frac{m}{m_0}\right) - km, & \mathbf{x} \in \Omega_w, \\ \text{subject to } m(\mathbf{x}, t) &= \hat{m}, \text{ for } \mathbf{x} \in \overline{\Omega}_w \cap \overline{\Omega}_u. \end{aligned} \quad (7)$$

in order to depend on the capillary density. In the above equation $m = m(\mathbf{x}, t)$ and $c = c(\mathbf{x}, t)$ respectively denote the epidermal cell density and growth factor concentration. The function $s = s(c)$ is a nonlinear function of the growth concentration describing the mitotic rate, see [5, 1]. For the growth factor accumulation a similar relationship due to diffusive transport, production and decay is obtained with a similar adaptation for the dependence of the capillary density:

$$\begin{aligned} \frac{\partial c}{\partial t} &= D_2 \operatorname{div} \operatorname{grad} c + \phi_p\left(\frac{n}{n_m}\right)f(m) - \lambda c, & \mathbf{x} \in \Omega_w. \\ \text{subject to } c(\mathbf{x}, t) &= \hat{c}, \text{ for } \mathbf{x} \in \overline{\Omega}_w \cap \overline{\Omega}_u. \end{aligned} \quad (8)$$

As initial conditions for m and c we have $m(\mathbf{x}, 0) = 0$ and $c(\mathbf{x}, 0) = 0$. In the above equation $f(m)$ denotes a nonlinear relation for the growth factor regeneration. In the model due to Sherratt and Murray, two different types of growth factors are considered: 1. activators; and 2. inhibitors, both with their characteristic functions for s and f . We assume that within the wound initially $m = c = 0$ and at the wound edge, $m = m_0$ and $c = c_0$. Hence we want the initial state to be unstable and the boundary conditions to be stable, so that the functions m and c converge to the values of the boundary conditions m_0 and c_0 as $t \rightarrow \infty$. In other words, the unwounded state is stable with respect to small perturbations, whereas the wounded state is unstable. Note that the capillary density from the neo-vascularization model described in the previous subsection is needed. Furthermore, $\lim_{p \rightarrow \infty} \phi_p(y) = u_{1/2}(y)$, which is in the class of Heaviside functions with the jump at $y = 1/2$. The behavior is motivated by the intuitively obvious notion that the mitotic rate and production rate of the growth factors increase with the capillary density. The rest of the equations remains the same. The present coupling between the two models is an innovation and will be evaluated during the presentation. Further, the model will be extended to include the interaction of the capillary density with the endothelial cell density, which is the building block of the capillaries. A further future implementation is the feedback from the contraction model to the neo-vascularization model.

3 Numerical Method

The numerical method is explained for the wound contraction model since this model contains most of the difficulties. To solve the system of partial differential equations a finite element strategy is used. In the presentation the solution and a discussion of the entire set of model equations will be considered. In this section we present the solution method for our preliminary results consisting of the solution of the equations of Sherratt and Murray. Piecewise linear basis functions are used for the triangular elements with a Newton-Cotes integration, which makes the mass matrix diagonal. For the time integration method, we use the following IMEX method:

$$\begin{aligned} M \frac{\underline{m}^{k+1}}{\Delta t} &= M \frac{\underline{m}^k}{\Delta t} + D_1 S \underline{m}^{k+1} + M_1 (\underline{m}^k, \underline{c}^k) \underline{m}^{k+1}, \\ M \frac{\underline{c}^{k+1}}{\Delta t} &= M \frac{\underline{c}^k}{\Delta t} + D_2 S \underline{c}^{k+1} - \lambda M \underline{c}^{k+1} + \underline{b}^k. \end{aligned} \quad (9)$$

Here M and S respectively denote the mass and stiffness matrices. By the use of the Newton-Cotes integration rule, the element mass matrix for M_1 becomes for an element Ω_ε surrounded by nodes i, j and p :

$$M_1^{\Omega_\varepsilon} = \frac{|\Delta|}{6} \text{diag}(s(c_\alpha^k)(2 - n_\alpha^k)), \text{ for } \alpha \in \{i, j, p\}, \quad (10)$$

where $\frac{|\Delta|}{2}$ represents the area of the triangular element. The α -th component of the element vector for $\underline{b}$ becomes

$$b_{\alpha}^{\Omega_{\varepsilon}} = \frac{|\Delta|}{6}(f(n_{\alpha}^k)), \text{ for } \alpha \in \{i, j, p\}. \quad (11)$$

These functions have been implemented within the package SEPRAN.

4 Preliminary Results

Since the thickness of human skin is in the order of a millimeter, the model can be considered as two-dimensional. First, we show some finite element results for a circular wound with radius 1 of the neo-vascularization model. Our simulations indicate that the oxygen and growth factor concentrations reach the steady-state solution rapidly. This confirms the assumption under which Maggelakis found the analytic solutions. The capillary tip density exhibits a transient behavior. Due to diffusion, the tip density decreases for a while outside the wound region, whereas it increases at all stages within the wound region. As time proceeds, it converges towards its equilibrium value. The results are not shown in the present paper.

Subsequently, we consider the actual wound contraction time, where we assume the neo-vascularization process to have taken place entirely, as a function of the aspect ratio of rectangular and elliptic wounds. The aspect ratio is defined by the ratio of the length and the width for a rectangular wound and by the ratio of the longer and shorter axis for elliptic wounds. Following Sherratt & Murray [1] the wound edge is identified by the level curve $n = 0.8$. In Figure 1 we show the healing time as a function of the aspect ratio for ellipsoidal and circular wounds. It can be seen that the width of the wound is the most important factor to determine the healing time. However, the relation is not linear, the decrease of the healing time as a function of the aspect ratio is much less than for the linear case.

Subsequently, when the models are combined, the full system of PDE's is solved, and the influence of the oxygen production on the healing rate is shown in Figure 2. For larger values of λ_o wound healing slows down. This is caused by the decrease of the MDGF growth factor concentration as more oxygen is supplied. The decrease of MDGF growth factors, decreases the speed of capillary formation and hence the supply of nutrients needed for cell division in the wound contraction process deteriorates. This results into a delay of mitosis, and hence the wound contraction slows down. Finally, the influence of the capillary density on the healing time is investigated. The influence is quantified by the power p in the function $\phi_p(y)$. For $0 < p < 1$ the influence is large for $n/n_m < 0.5$ and small elsewhere. For $p > 1$, the behavior is opposite. The calculations, not shown here, result into a strange behavior for $0 < p \leq 1$ that the wound heals from the edge at the early stages and starts healing from the wound center at the later stages. This behavior is not realistic. Note that $p = 1$ corresponds to a linear coupling. For $p > 1$ the wound only heals from the edge, which is more realistic

Fig. 1. Healing times as a function of the aspect ratio of rectangular and ellipsoidal wounds with the same area

Fig. 2. Circular wound: Left: The influence of oxygen production on the healing time ($p = 5$); Right: The influence of the power p in ϕ on the healing time ($\lambda_o = 0.1$)

from an intuitive point of view. Therefore, the expectation is that $p > 1$ reflects the right behavior. For the input values we used the same values as Sherratt and Murray [1] and Maggelakis [6].

5 Conclusions

Some preliminary results for a wound healing model have been presented. An innovation in this paper is the assumption to allow overlapping between the processes of neo-vascularization and wound contraction. During the presentation further extensions to the neo-vascularization model will be discussed and the

coupling between the two models will be analyzed in more detail. In this paper the nonlinear impact of the aspect ratio of the wound on the healing time is also demonstrated. In future work (to be presented in the talk) the model will be extended with tip-sprout interaction (anastomosis) and a biased random walk, resulting into cross diffusion.

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