A simplified model for growth factor induced healing of circular wounds

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Abstract

A mathematical model is developed for the rate of healing of a circular wound in a spherical skull. In this paper the regeneration, decay and transport of a generic 'growth factor', which induces the healing of the wound, is taken into account. Further, an equation of motion is derived for the actual healing of the wound. The expressions for the equation of motion and the distribution of the growth factor are related in a way that no healing occurs if the growth factor concentration is below a certain value. In this paper we investigate the influence of the behaviour of the thickness of the active layer, in which the growth factor is produced, on the healing process. Also a correction is made to a result in an earlier paper [4] (see also [5]).

Keywords: wound healing, healing times, radial contraction, growth factor, moving interface

1 Introduction

Models for bone regeneration and wound healing often rely on experiments on animals. Among many others a recently developed model was proposed by Adam *et al* [1, 2, 3, 5, 7, 6]. The model is based on the so-called Critical Size Defect, which is defined as the smallest wound that does not heal within the lifetime of an animal or human being. Wound healing, if it occurs, proceeds by a combination of several processes: chemotaxis (movement of cells induced by a concentration gradient), neovascularization, synthesis of extracellular matrix proteins, and scar modelling. Some models incorporate cell mitosis, cell proliferation, cell death, capillary density, oxygen supply and growth factor generation coupled to a cell density, including studies by Sherratt *et al* [12], Fillion *et al* [8], Maggelakis [10] and Gaffney *et al* [9], to mention just a few. A recently published interesting book about mathematical biology has been written by Murray [11] where the issue of wound healing is treated as well. The present study attemps to build a simple mathematical model for wound healing in the spirit of Adam's work. In the present work Adam's models are applied to wounds with several geometries.

We consider a wound that heals as a result of a generic growth factor. This growth factor is a protein that stimulates cell differentiation and growth. The wound is assumed to

be circular. Adjacent to the wound edge, there is a layer of a certain thickness in which the growth factor is produced. This layer is referred to as 'the active layer'. The growth factor diffuses within the active layer into the wound and into the skin adjacent to the active layer. The geometry is depicted in Figure 1. In the present study it is assumed that the healing process occurs at the wound edge. This healing results from bone or tissue regeneration. A further assumption is that bone or tissue can only be generated if the concentration of the growth factor exceeds a certain threshold value. In earlier papers of Adam *et al* [1, 2, 3, 5, 7, 6] either the healing process was considered in which the concentration at the wound edge was assumed to exceed the needed threshold value at all stages of the healing process, or the distribution of the growth factor near the wound edge was considered. The present paper combines both ideas of Adam [5] in which the concentration at the wound edge is monitored at all stages of the healing process. This implies that wound healing stops if the growth factor concentration at the wound edge is lower than the threshold value. We investigate the healing of a wound in which the thickness of the active layer is varied.

The paper is organized as follows. First the model for the growth factor distribution and the model for the healing rate of the wound are given. Subsequently, some numerical results from the model for the growth factor distribution are given for several geometries. We end with some conclusions and some comments.

2 The model

In this section the two models based on the ideas of Adam [5] are presented. Firstly, the model for the regeneration, decay and transport of the growth factor is given (see for instance [1]) and subsequently the healing process as a result of the presence of the growth factor is described (see Adam [4]). Finally, a description of the coupling of the two models is presented.

2.1 The growth factor distribution

We consider a wound as in Figure 1. Wound healing is caused by, among others, mitotic generation and cell migration. If healing occurs, then, it is enhanced by the presence of a growth factor that stimulates cellular growth and cell-division. We will analyze a necessary condition for wound healing. Wound healing is a complicated biological process and therefore some simplifications are needed for a feasible mathematical model within the scope of this paper. A nice model on the healing of cutaneous wounds is presented by Gaffney *et al* [9]. As their paper involves the solution of a set of partial differential equations, our study attempts to arrive at a relatively simple model for wound or bone healing.

Due to the damage of tiny blood vessels around the wound, there is an increased activity of cellular growth, cell-division and production of the growth factor that enhances wound

healing. We assume that this layer, commonly referred to as the *active layer*, has a constant thickness of d. The situation is as sketched in Figure 1.

Further, we assume that healing takes place if and only if the concentration of the growth factor at the wound edge, see Figure 1, exceeds a threshold value $\hat{c}$. In Figure 1 we use Ω_1, Ω_2 and Ω_3 to denote the wound itself, the active layer and the outer tissue respectively. Far away from the wound, i.e. at the boundary of the domain of computation Γ we assume that the concentration of the growth factor is zero. The wound edge, the interface between the wound (Ω_1) and the active layer (Ω_2), is indicated by W.

Let the total domain of computation be given by Ω, then, following Adam [1], we state the fundamental equation for the transport, production and decay of the growth factor concentration, c, which reads as:

$$\frac{\partial c}{\partial t} - D \text{ div grad } c + \lambda c = Pf(x,y), \text{ for } (x,y) \in \Omega, \tag{1}$$

$$c(x,y) = 0, \text{ for } (x,y) \in \Gamma, \tag{2}$$

$$\text{further } f(x,y) = \begin{cases} 1, \text{ for } (x,y) \in \Omega_2 \\ 0, \text{ for } (x,y) \in \Omega_1 \cup \Omega_3 \end{cases} . \tag{3}$$

In the equations D, P and λ denote the constant diffusion coefficient, production rate constant and the decay coefficient of the growth factor. The growth factor concentration, c, is to be determined. Further, the second and third term in equation (1) respectively account for growth factor transport and growth factor loss. The right-hand side of equation (1) accounts for the production of the growth factor. Equation (2) represents the boundary condition and the step-function f accounts for the growth factor production taking place in the active layer only. Adam [1] points out that for the derivation of a *critical size defect*, which is the smallest wound that does not heal, the time derivative in the diffusion reaction equation does not have to be taken into account. Healing at a certain location of the wound edge implies that the inward normal component of the velocity, v_n, of the 'interface' W is positive. In the present paper we use the assumption from [1] that the wound heals if and only if the growth factor concentration exceeds a threshold concentration $\hat{c}$, hence

$$\begin{aligned} &v_n > 0 \text{ if and only if } c(x,y,t) \geq \hat{c} \text{ for } (x,y) \in W, \\ &\text{else } v_n = 0. \end{aligned} \tag{4}$$

This implies that in order to determine whether the wound heals at a certain location at W at a certain time t, one needs to know the growth factor concentration there. This means that the concentration equation has to be solved.

Adam considers analytic expressions for the time independent case for several geometries: planar (linear) geometry [1], a circular wound on a spherical surface [2], a circular wound on a planar surface [7]. A wound in spherical symmetry is considered in terms of analytic

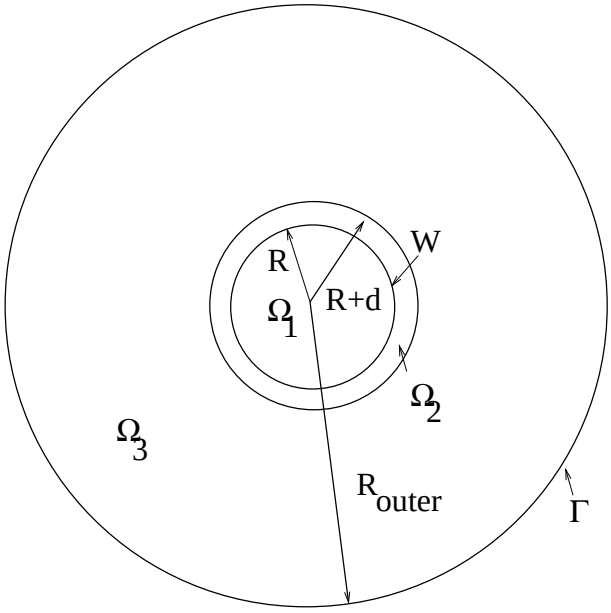

Figure 1: The geometry of a circular wound.

expressions by Arnold [6].

As an interesting case we consider the growth factor concentration in the vicinity of an elliptic wound. The results are obtained by the use of the Finite Element Method. Far away from the wound, we assume that the growth factor concentration is zero. The results are presented by coloured contour plots and a line plot of the concentration over the wound edge in Figure 5. First, however, we derive the wound healing equation.

2.2 The healing process

Following Adam [4], we consider the area of a circular wound as a hole on the 'north pole' on a spherical surface with radius a. Let R be the wound radius projected onto the Oxy-plane, then it can be seen that the area, $A(R)$, that is missing on the spherical area is given by

$$A(R) = \int_0^{2\pi} \int_0^R \frac{ar}{\sqrt{a^2 - r^2}} dr d\theta = 2\pi a \left(a - \sqrt{a^2 - R^2} \right). \tag{5}$$

Note that this reduces to the expected result $A(R) = \pi R^2$ as $\dfrac{a}{R} \to \infty$. From this expression it follows that if a circular wound shrinks from an initial radius R_0 (at $t = 0$) to $R(t)$ at time t, then, the magnitude of the change in area ΔA is

$$\Delta A = 2\pi a \left(\sqrt{a^2 - R^2(t)} - \sqrt{a^2 - R_0^2} \right). \tag{6}$$

Assuming a constant thickness of the spherical skull of $h \ll a$, in terms of the total volume recovered by the healing process in $[0, t]$ the healed wound volume is approximated by

$$\Delta V = \Delta A h = 2\pi h \int_0^t \int_{R(\tau)}^{R_0} \frac{r\overline{S}(R(\tau), r)}{\sqrt{a^2 - r^2}} dr d\tau. \tag{7}$$

In the above equation the function $\overline{S}(R(t), r)$ represents a measure for the rate of the regeneration of bone or tissue as a function of position and the wound radius. The above equation is combined with equation (6) and subsequently the result is differentiated with respect to time, to obtain

$$\frac{dR^2}{dt} = -2\sqrt{a^2 - R^2(t)} \int_{R(t)}^{R_0} \frac{r\overline{S}(R(t), r)}{\sqrt{a^2 - r^2}} dr. \tag{8}$$

If the measure for the rate of bone -or tissue regeneration is chosen to be a Riemann integrable function, then, it can be seen that the right hand side is Lipschitz continuous with respect to R and that $R(t) = R_0$ is the only solution here (This was not noted in [4]). Therefore, in the present work we will use a Dirac Delta distribution for this function $\overline{S}$ in order to have a non-zero healing rate at the initial stage. This triggers the healing process. For this purpose we will use $\overline{S}(R(t), r) = S(R(t))\delta(r - R(t))$ in the integral formulation. Here $\delta(x)$ denotes the Dirac Delta 'function' and $S(R)$ represents a continuous rate function depending on R. For these functions, we get for $R(t) \leq R_0$ and an arbitrary function $f(r)$:

$$\lim_{\epsilon \to 0} \int_{R(t)}^{R_0} f(r)\delta_\epsilon(r - R(t)) dr = \frac{1}{2} f(R(t)). \tag{9}$$

From the general definition of the Dirac Delta distribution, it follows that the result of the above integral can range between zero and $f(R(t))$, but we chose the above value. Then, this gives the following relation:

$$\frac{dR^2}{dt} = -2\sqrt{a^2 - R^2(t)} \int_{R(t)}^{R_0} \frac{rS(R(t))\delta(r - R(t))}{\sqrt{a^2 - r^2}} dr = -R(t)S(R(t)). \tag{10}$$

From the nature of the Dirac Delta distribution, it follows that this also gives a non-zero initial healing rate. Noting that the dependence of the radius of the sphere, a, vanishes, S could be made dependent on a; alternatively the dependence of a follows from the solution of the equation for the growth factor. Using the Chain Rule for differentiation, then, gives

$$\frac{dR}{dt} = -\frac{1}{2} S(R(t)), \text{ with } R(0) = R_0. \tag{11}$$

This equation is integrated to obtain R as a function of t. Further, at a certain time the wound only heals if the growth factor concentration exceeds the threshold value. Therefore at each time during the healing process, we need to know whether the growth factor

concentration at the wound edge exceeds the threshold value.

We assume that the healing rate is proportional to the local curvature of the wound, i.e.

$$S(R(t)) = \alpha + \frac{\beta}{R(t)}, \tag{12}$$

where R is the local radius of curvature and $\alpha, \beta > 0$ are considered as non-negative constants, prohibiting growth of the wound. Now we consider the case that the growth factor concentration exceeds the threshold value at all times of the wound healing process. If $S(R)$ is Lipschitz continuous in a neighbourhood of R_0, then, the formal solution is given by

$$\int_{R(t)}^{R_0} \frac{ds}{S(s)} = 2t. \tag{13}$$

For the case of equation (12) and a circular wound, this yields

$$t = \frac{1}{2\alpha}\left\{R_0 - R - \frac{\beta}{\alpha}\ln\left(\frac{\alpha R_0 + \beta}{\alpha R + \beta}\right)\right\}, \text{ provided } \alpha \neq 0, \tag{14}$$

and for $\alpha = 0$, one obtains

$$t = \frac{1}{4\beta}\left(R_0^2 - R^2\right). \tag{15}$$

This implies that there exists a healing time, t_h, which is given by

$$t_h = \frac{1}{2}\int_0^{R_0} \frac{ds}{S(s)}, \tag{16}$$

provided that the above integral exists. For the case of equation (12), this becomes for a circular wound:

$$t_h = \frac{1}{2\alpha}\left\{R_0 - \frac{\beta}{\alpha}\ln\left(\frac{\alpha R_0 + \beta}{\beta}\right)\right\}, \text{ provided } \alpha \neq 0, \tag{17}$$

and for $\alpha = 0$

$$t_h = \frac{R_0^2}{4\beta}. \tag{18}$$

2.3 Combination of the two models

Here we couple the two simple models for the rate of regeneration of bone or tissue and the distribution of the growth factor. Equation (11) is solved in which the the growth factor concentration at the wound edge is monitored. This is done by redefining the rate function $S(R(t))$ by

$$S(R(t)) := S(R(t))H(c(R(t), t) - \hat{c}), \tag{19}$$

where $H(s)$ represents a heaviside function, defined as

$$H(s) = \begin{cases} 0, & s < 0, \\ 1, & s \geq 0. \end{cases}$$

The threshold concentration of the growth factor for wound- or bone healing is denoted by $\hat{c}$. In the remaining text equation (12) is used for $S(R(t))$. This implies the necessity of knowing the growth factor concentration at the wound edge at all times of the simulation of the healing process, since the wound heals further if and only if $c(R(t), t) \geq \hat{c}$, consistent with the introduction of the Heaviside function in equation (12). This implies that once the wound edge is displaced, then the equation for the growth factor concentration has to be solved. Since the position of the wound edge moves in time, the position of the interface conditions at the wound edge, i.e. continuity of the growth factor concentration and its normal derivative, changes in time. Hence we are faced with a moving boundary problem where the velocity of the wound edge is determined by (11).

Furthermore, the thickness of the active layer, d, is allowed to change with the wound radius and changes during the healing process, according to the choice

$$d(R(t)) = c_1 R_0 + c_2 R(t). \tag{20}$$

This implies for the circular wound that the thickness is proportional to the sum of the reciprocals of the initial curvature and the subsequent curvature at time t. Hence during the healing process, if $c_2 \geq 0$, then the thickness of the active layer decreases. Hence the amount of growth factor that is produced decreases. Note, however, that the wound area decreases as well. So for a given β there is a trade-off as to whether this gives rise to a decrease or an increase of the growth factor concentration at the wound edge. If the growth factor concentration at the wound edge decreases, then this may cause the healing process to cease (see also Section 2.1.).

We remark here that if the distribution of the growth factor is assumed to be instantaneous, implying that the time derivative in the growth factor equation vanishes, then, the growth factor concentration at the edge of the wound is well-defined by the solution of the growth factor equation as a function of the wound radius $R(t)$. Further, the wound radius decreases continuously and since the wound edge concentration depends on the wound radius continuously, the wound edge concentration depends on time continuously as well. This implies that equation (11) can be integrated up to $\hat{R}$ for which $c(\hat{R}) = \hat{c}$, i.e. the formal solution is given by

$$\frac{1}{2} \int_{R(\hat{t})}^{R_0} \frac{ds}{S(s)} = t, \text{ provided that } R(t) \geq \hat{R}. \tag{21}$$

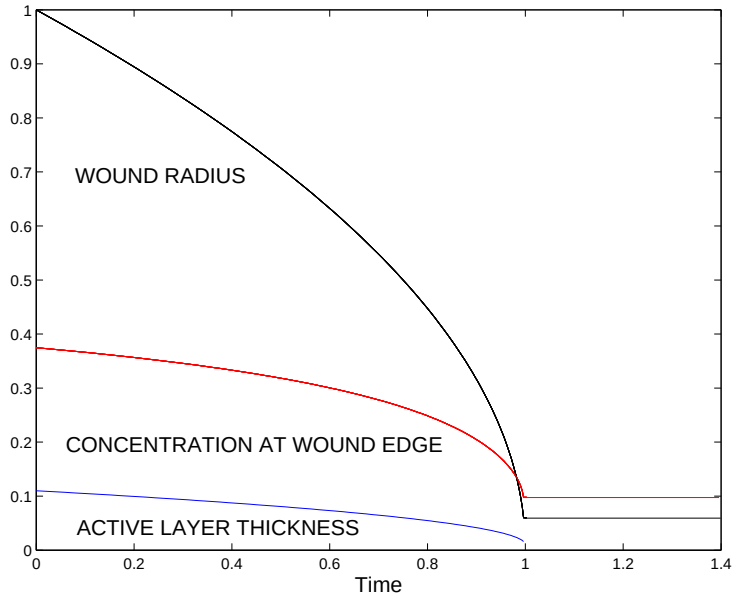

Figure 2: The healing of a wound for $\alpha = 0$ and $\beta = 1$, $c1 = 0.01$, $c_2 = 0.1$, $D = 1/144$ and $\hat{c} = 0.1$. Note that the units for the wound radius and active layer thickness differ from the unit of the concentration.

In general the determination of this $\hat{R}$ involves a zero-point iteration method. However, for the case that the time derivative is not dropped or that a numerical solution for the concentration is used, then there is no explicit relation between $c(R(t), t)$ and $R(t)$. Hence, the determination of $\hat{R}$ is less straightforward and a time stepping method has to be used, where at each time-step the growth factor concentration at the wound edge has to be monitored. As an example we show a computation with an active layer whose thickness varies with the wound radius in Figure 2. The concentration at the wound edge is determined by the use of the Bessel function solution of Arnold et al [7]. Then, at a certain wound radius, the healing criterion is checked and then the wound radius is displaced accordingly. It can be seen in the above that the growth factor concentration at the wound edge decreases during the healing process down to the threshold concentration. Then, the healing process stops and hence the final wound radius is non-zero.

3 Numerical results

The growth factor distribution in a generally shaped wound is computed by the use of a standard Galerkin finite element method with piecewise linear basis functions. The time-dependent problem is solved by the use of the Euler backward method.

In this section we consider the growth factor distribution obtained by the use of the Finite Element method in the vicinity of an elliptic wound. In the first section the accumulation of the growth factor is taken into account. The second section deals with the influence of

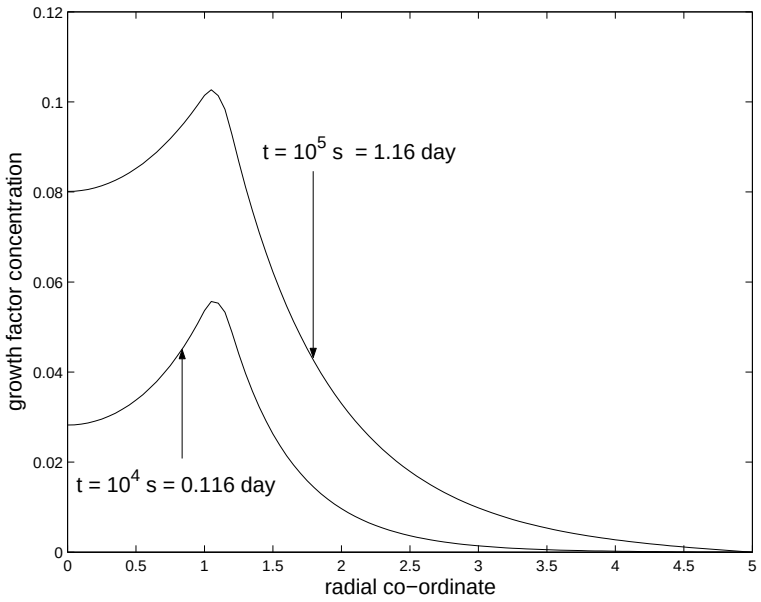

Figure 3: The radial growth factor concentration profile at two time instants.

the wound geometry on the growth factor distribution. Finally, we consider the healing rate for a circular wound in relation to the concentration profile of the growth factor. In all the calculations that are presented in this section the outer boundary is taken far away such that its influence is negligible. On the outer boundary we have the condition that the growth factor concentration is zero. The results of the Finite Element method have been validated by the analytical solution of Adam [1] for a rectangular (one-dimensional) wound.

3.1 The growth factor accumulation

For the sake of illustration we compute the growth factor profile for the following data

$$P = \lambda = 5 \cdot 10^{-5} s^{-1}, D = 5 \cdot 10^{-5} cm^2/s, R = 1cm, \delta = 0.2cm.$$

The results have been shown in Figure 3. In Figure 3 the radial profile of the growth factor concentration has been plotted at two times $t = 10^4$ s and $t = 10^5$ s. The profile at $t = 10^5$ s does not differ significantly from the profile for the time-independent solution, i.e. for $t \to \infty$. From this it can be seen that the growth factor accumulates at the wound edge up to the threshold concentration. This time is referred to as an incubation time for the healing process to start.

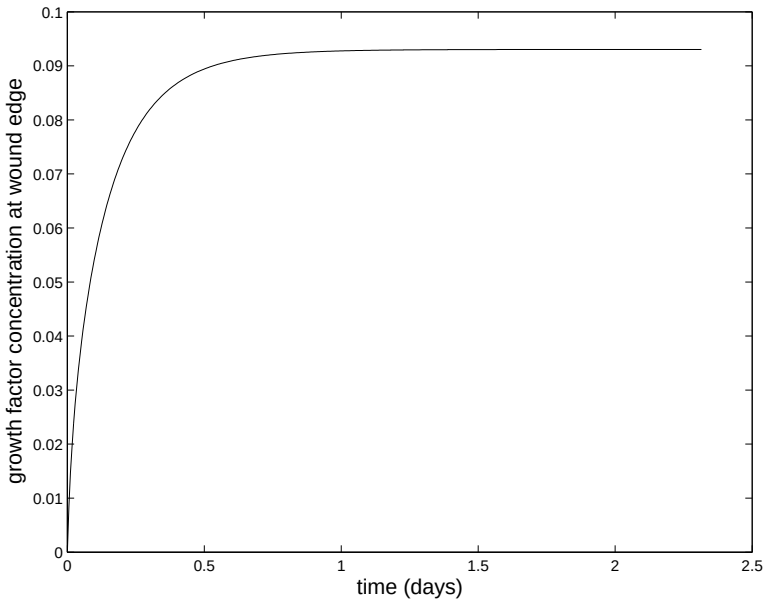

Figure 4: The accumulation of the growth factor concentration profile at the wound edge for a circular wound.

3.2 The geometrical aspects of the wound on the growth factor concentration

In this section the concentration of the growth factor is considered for several wound geometries. The healing process is not modelled here, this will be future work. The first example is for an elliptic wound whose equation is given by $x^2+4y^2 = 1$. In the simulations the thickness of the active layer is chosen constant over all positions of the wound edge. The contour lines of the growth factor concentration are shown in Figure 4. For the same geometry, the growth factor concentration over the edge of the wound is shown in Figure 5. In figure 5 the growth factor concentration increases from the position where the curvature of the elliptic wound is maximal up to a maximum value where the curvature of the wound is minimal. It can be seen that the maximum concentration is located near the wound edge and near the spot of minimum curvature of the wound edge. This is contrary to the expectations where for a spherical wound there exists a critical size under which the wound is expected to heal within the life-time of an animal. A careful analysis of the growth factor concentration at the edge of a circular wound as a function of the wound radius, as computed by the analytic solution due to Adam [4], for a constant thickness of the active layer reveals the behaviour as plotted in Figure 6. We remark that the results for the concentration at the wound edge from the analytical solution for a circular wound agree perfectly with the results from the Finite Element method. From Figure 7 it can be seen that the growth factor concentration increases as the wound radius increases up to a critical wound radius. If this critical radius is exceeded, then, the wound radius decreases. This latter decrease motivates the critical size defect as explained in Adam's

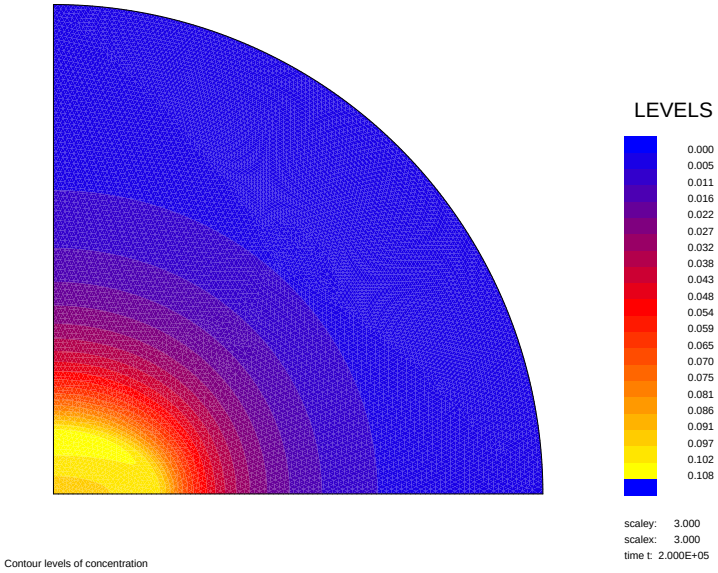

Figure 5: Contour lines of the growth factor concentration for an elliptic wound.

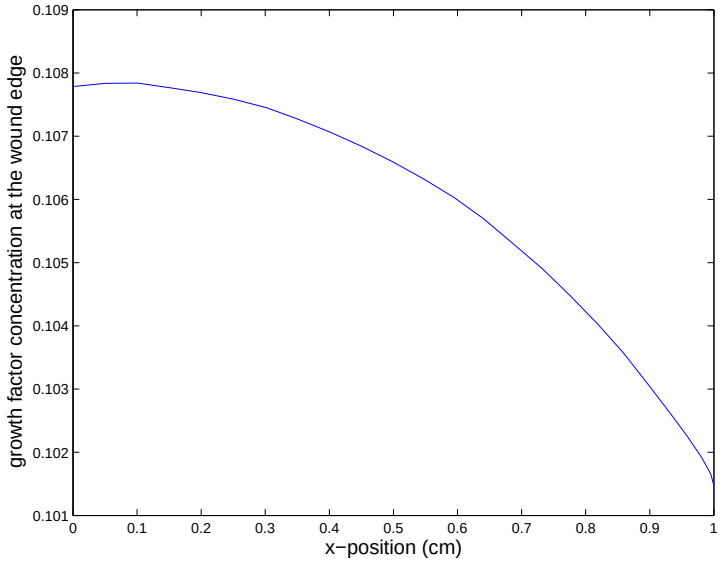

Figure 6: Line plot of the growth factor concentration over the edge of the elliptic wound. The equation of the elliptic wound edge is given by $x^2 + 4y^2 = 1$.

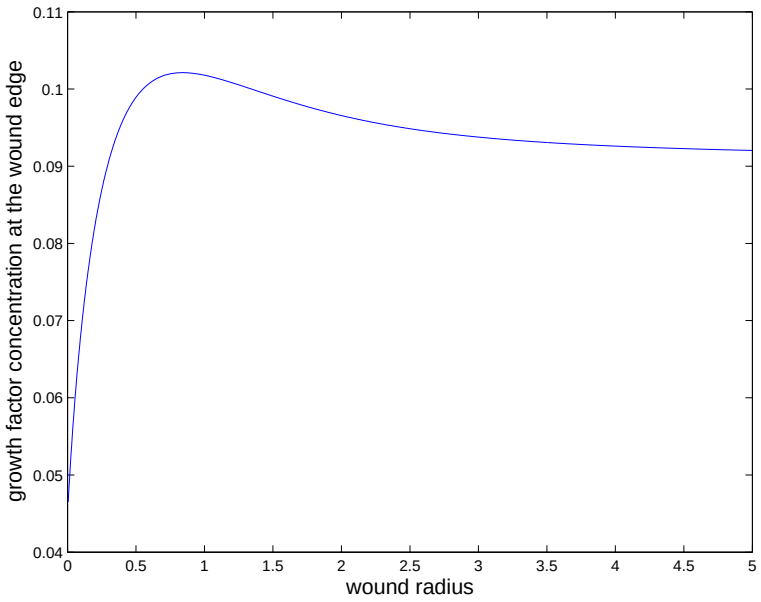

Figure 7: The growth factor concentration at the wound edge as a function of the wound radius as computed by the analytic solution due to Adam [4]. The thickness of the active layer is fixed.

work. For the case of contour lines around the elliptic wound, the maximum curvature is such that the radius of curvature is smaller than the critical radius in Figure 6. For a more elongated elliptic wound, $\frac{x^2}{16} + y^2 = 1$, the concentration of the growth factor along the wound edge differs significantly. A line plot is shown in Figure 8. It can be seen that the maximum concentration of the growth factor is obtained at neither of the locations of extremal curvature of the wound edge. At the location at the wound edge where the growth factor concentration is maximal, the wound is most likely to heal if the wound edge concentrations are almost critical.

3.3 Incorporation of the wound depth

In this application we consider a circular wound with a depth and an active layer. This configuration is modelled by rotational symmetry and hence only two spatial co-ordinates are needed. The contourlines of the growth factor concentration are shown in Figure 9 and a lineplot over the wound edge is displayed in Figure 10. It can be seen that the concentration of the growth factor is maximal at the symmetry axis. This implies that at this position the concentration is more likely to satisfy the healing condition than at the other spots if the wound edge concentrations are almost critical. Furthermore, due to accumulation of the growth factor concentration at the wound edge during the transient part, the healing process will start a little earlier there than at any other location at the wound edge.

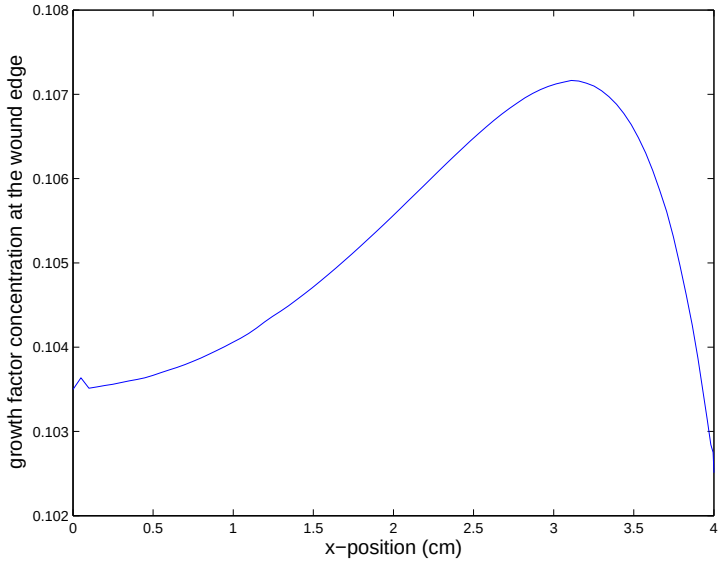

Figure 8: Line plot of the growth factor concentration over the edge of the elliptic wound. The equation of the elliptic wound edge is given by $\frac{x^2}{16} + y^2 = 1$.

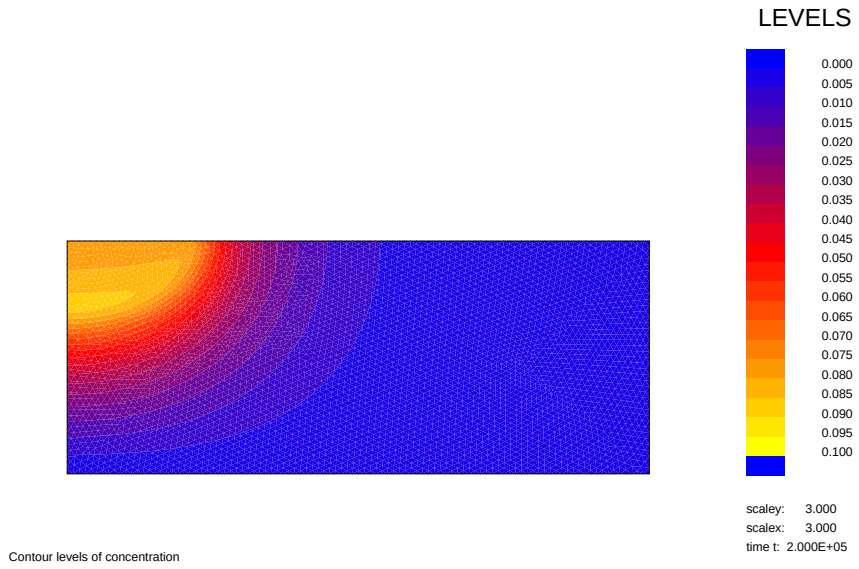

Figure 9: Contour lines of the growth factor concentration for an elliptic wound in three dimensions with rotational symmetry.

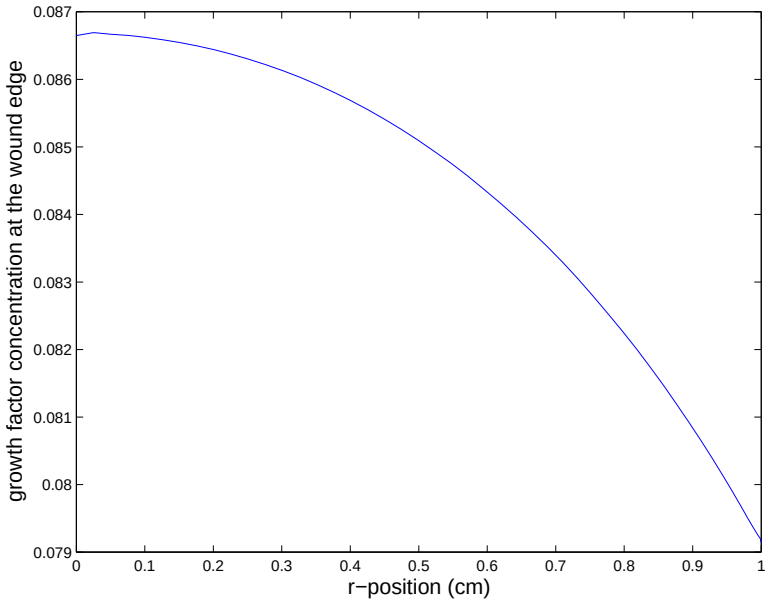

Figure 10: Line plot of the growth factor concentration over the edge of the elliptic wound with rotational symmetry. The equation of the wound edge in polar co-ordinates is given by $r^2 + 4(z-2)^2 = 1$. Here r denotes the radial co-ordinate.

4 Conclusions

Using the Finite Element method, some insight into the healing or non-healing of a wound is obtained based on a model of Adam. Along non-circular wounds there are areas where the growth factor concentration may exceed or be below the threshold concentration for wound healing. This implies that the model predicts the existence of areas along a wound where healing either occurs or does not take place partially or at all. Further, due to the time dependence of the diffusion equation the model predicts a (short) accumulation time before the wound starts healing. In a future study the model will be compared to a model where more biological processes like mitosis and cell death are taken into account using Finite Element techniques and mathematical analysis.

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