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F. J. Vermolen

E. van Baaren

J. A. Adam
Old Dominion University, jadam@odu.edu

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A simplified model for growth factor induced healing of wounds

F.J. Vermolen[a,*], E. van Baaren[a], J.A. Adam[b]

[a] *Delft University of Technology, Department of Applied Mathematics, Mekelweg 4, 2628 CD Delft, The Netherlands*
[b] *Old Dominion University, Department of Mathematics and Statistics, Norfolk, VA 23529-0077, USA*

Abstract

A mathematical model is developed for the rate of healing of a circular or elliptic wound. 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 radial healing of a circular wound. The expressions for the equation of motion and the distribution of the growth factor are related in such a way that no healing occurs if the growth factor concentration at the wound edge is below a threshold 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 earlier work.

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. [1–3,5,7,6]. The model is based on the so-called Critical Size Defect (CSD), 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. [14], Fillion et al. [8], Maggelakis [11] and Gaffney et al. [9], to mention just a few. A recent work devoted to mathematical biology has been written by Murray [13], in which the issue of wound healing is also treated. The present study attempts to build a simple mathematical model for wound healing in the spirit of the work by Adam. He used the intuitively obvious notion that whereas in cancer, tumors (usually) *grow*, wound healing involves *shrinkage* of the damaged region. He and coworkers developed simple models for such shrinkage based on linear, circular and spherical geometries. This appears to be the first approach to modeling the CSD phenomenologically, given the paucity of quantitative data on this topic. In the present work these models are applied to wounds with several other geometries, since wounds are rarely if ever symmetrical.

* Corresponding author. Tel.: +31 15 278 1833; fax: +31 15 278 7209.
E-mail address: F.J.Vermolen@math.tudelft.nl (F.J. Vermolen).

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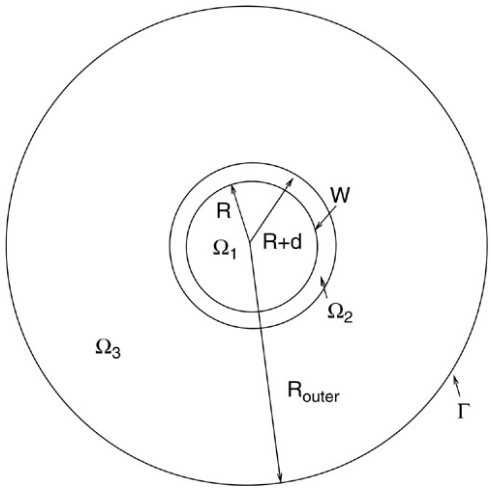

Fig. 1. The geometry of a circular wound, Ω_1, Ω_2 and Ω_3 respectively denote the wound, active layer and the outer tissue. W denotes the wound edge.

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 or elliptic. Adjacent to the wound edge, the existence of a layer of a certain thickness is assumed 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 Fig. 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. [1–3,5,7,6] 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 examined.

Prior to this, no work has been published in which both these ideas are combined. Further, the conditions for wound healing were only analyzed for geometries where only one spatial co-ordinate could be used. Hence, the key innovations in the present study are the following:

1. The combination of the two above ideas in which a wound healing rate equation is combined with a reaction-transport equation based on an active layer adjacent to the wound for the generic growth factor.
2. An extension of some results from earlier work, suitable for geometries with one spatial co-ordinate (such as circular, planar wounds) only, to general geometries with two spatial co-ordinates (such as elliptic wounds). This allows us to investigate where the wound is likely to start healing according to the model.
3. Time dependence is incorporated into the model. This allows us to analyze the incubation time before the wound actually starts healing.
4. A correction is made to the derivation of the healing rate equation in [4]. The correction is based on the introduction of a Dirac Delta function to mimic an inward wave of healing.

The present paper is organized as follows. First, the model in terms of equations for the growth factor distribution is given for general geometries. The outcome determines whether and where the wound starts healing. Secondly, the healing rate equation is derived. This is followed by a combination of the healing rate equation and growth factor distribution to actually model wound healing, for circular wounds only here. Finally, a standard Galerkin finite element method is used to solve the equations for the growth factor concentration. The solution is used to investigate the wound healing incubation time and to determine where an elliptic wound would most likely start to heal.

2. The model

In this section the two models based on the ideas of [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 [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 Fig. 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 detailed 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, thereby gaining more physical insight into the underlying mechanisms of healing in a simpler model.

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 Fig. 1.

Further, we assume that healing takes place if and only if the concentration of the growth factor at the wound edge, W (see Fig. 1) exceeds a threshold value $\hat{c}$. In Fig. 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, that is 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 $\Omega = \Omega_1 \cup \Omega_2 \cup \Omega_3$, then, following [1], we state the fundamental equations for the transport, production and decay of the growth factor concentration, c, which are:

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

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

$$c(x, y, 0) = 0, \quad \text{for } (x, y) \in \Omega, \tag{3}$$

$$\text{further } f(x, y) = \begin{cases} 1, & \text{for } (x, y) \in \Omega_2 \\ 0, & \text{for } (x, y) \in \Omega_1 \cup \Omega_3. \end{cases} \tag{4}$$

In the equations D, P and λ denote the constant diffusion coefficient, production rate constant and the decay coefficient of the growth factor respectively. The growth factor concentration, c, is to be determined. Further, the second and third term in Eq. (1) respectively account for growth factor transport and growth factor loss. The right-hand side of Eq. (1) accounts for the production of the growth factor. Eq. (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 wound edge W, between wound and active layer, 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

$$\begin{aligned} &v_n > 0 \text{ if and only if } c(x, y, t) \geq \hat{c} \text{ for } (x, y) \in W, \\ &\text{else } v_n = 0. \end{aligned} \tag{5}$$

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, obviously requiring the concentration equation 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], and a circular wound on a planar surface [7]. A wound with spherical symmetry is considered in terms of analytic expressions by Arnold [6]. The equations above (1)–(4) are solved numerically for elliptic wounds in the present paper. Since the finite element method is used for the growth factor concentration, the model is easily extended to any other geometry.

Far away from the wound, we assume that the growth factor concentration is zero. The results will be presented by coloured contour plots and graphs of the concentration over the wound edge in Section 3. In the following section the fundamental differential equation is discussed, based on the derivation in Appendix.

2.2. Modeling the healing process I: Continuous healing as a function of growth factor concentration

Consistent with the general discussion in Appendix, we assume that the healing rate S is a linear function of the local curvature of the wound, that is

$$S(R(t)) = \alpha + \frac{\beta}{R(t)}, \tag{6}$$

where R is the local radius of curvature and $\alpha, \beta > 0$ are considered as constants, prohibiting growth of the wound. If $S(R)$ is Lipschitz continuous in a neighbourhood of R_0, then the solution of Eq. (24), which relates the wound edge velocity to the healing rate (see Appendix), is

$$\int_{R(t)}^{R_0} \frac{\mathrm{d}s}{S(s)} = \frac{t}{2}. \tag{7}$$

For the case of Eq. (6) and a circular wound, this yields

$$t = \frac{2}{\alpha}\left\{R_0 - R - \frac{\beta}{\alpha}\ln\left(\frac{\alpha R_0 + \beta}{\alpha R + \beta}\right)\right\}, \quad \text{provided } \alpha \neq 0, \tag{8}$$

and for $\alpha = 0$, one obtains

$$t = \frac{1}{\beta}\left(R_0^2 - R^2\right). \tag{9}$$

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

$$t_h = 2\int_0^{R_0} \frac{\mathrm{d}s}{S(s)}, \tag{10}$$

provided that the above integral exists. For the case of Eq. (6), this becomes for a circular wound:

$$t_h = \frac{2}{\alpha}\left\{R_0 - \frac{\beta}{\alpha}\ln\left(\frac{\alpha R_0 + \beta}{\beta}\right)\right\}, \quad \text{provided } \alpha \neq 0, \tag{11}$$

and for $\alpha = 0$

$$t_h = \frac{R_0^2}{\beta}. \tag{12}$$

2.3. Modeling the healing process II: Threshold of healing as a function of growth factor concentration

Here we consider an extension of the above model to account for the likelihood, as in many physiological systems, of threshold behavior. Eq. (24) is solved subject to the initiation of healing once the growth factor concentration is high enough [10,12]. This is done by redefining the rate function $S(R(t))$ as

$$S(R(t)) \coloneqq S(R(t))H(c(R(t), t) - \hat{c}), \tag{13}$$

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 healing is denoted by $\hat{c}$. In the remainder of this paper the expression (6) is used for $S(R(t))$. This requires knowledge of the growth factor concentration at the wound edge

at all times in 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 Eq. (6)). This implies that once the wound edge is inwardly displaced, 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, and hence the location where the conditions for continuity of the growth factor concentration and its normal derivative are imposed, also change in time. Thus we are faced with a moving boundary problem where the velocity of the wound edge is determined by (24).

Furthermore, the thickness of the active layer d is permitted to change with the wound radius during the healing process, according to the simple choice

$$d(R(t)) = c_1 R_0 + c_2 R(t). \tag{14}$$

This implies for the circular wound that the active layer thickness is proportional to the sum of the reciprocals of the initial curvature and the subsequent curvature at time t (see references in [1] for clinical intimations of this effect). Hence during the healing process, if $c_1 > 0$ and $c_2 > 0$, then the thickness of the active layer decreases, and the amount of growth factor that is produced in this layer decreases. Note, however, that the wound area decreases as well. So for a given β in Eq. (6) 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 prematurely (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 (this being effectively a steady-state environment) 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 Eq. (24) can be integrated up to $\hat{R}$ for which $c(\hat{R}) = \hat{c}$, hence the formal solution is given by

$$2\int_{\hat{R}(t)}^{R_0} \frac{\mathrm{d}s}{S(s)} = t, \quad \text{provided that } R(t) \geq \hat{R}. \tag{15}$$

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 Fig. 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 Fig. 2 that the growth factor concentration at the wound edge decreases during the healing process down to the threshold concentration. This is a consequence of the decrease of the thickness of the active layer, which becomes too thin to support a sufficiently high concentration at the wound edge. Then, the healing process stops and hence the final wound radius is non-zero.

3. Numerical results

The growth factor distribution in a general-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 subsection the accumulation of the growth factor is taken into account. The second subsection deals with the influence of 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 enough away such that its influence is negligible. On the outer boundary we apply the condition that the growth factor concentration is zero. The results of the finite element method have been validated by the analytical solution in [1] for a rectangular (one-dimensional) wound.

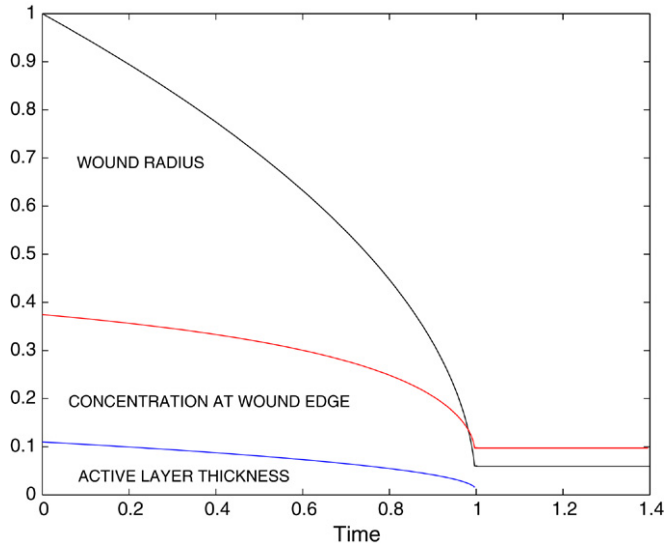

Fig. 2. The healing of a wound for $\alpha = 0$ and $\beta = 1$, $c_1 = 0.01$, $c_2 = 0.1$, $D = 1/144$ and $\hat{c} = 0.1$. Note that the units for the wound radius and active layer thickness will differ from the units of the concentration. The concentration is expressed in arbitrary units.

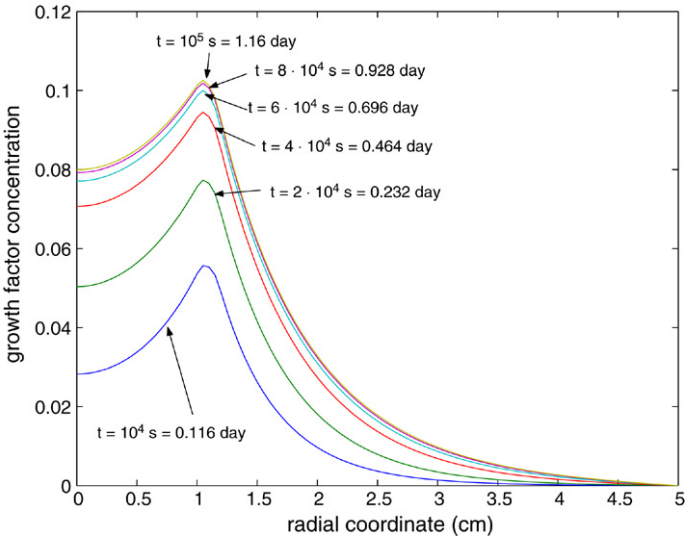

Fig. 3. The radial growth factor concentration profile at sequential instants of time for a circular wound. The concentration is expressed in arbitrary units.

3.1. The growth factor accumulation

For the sake of illustration we compute the growth factor profile for the following data following Adam [1]

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

The results are shown in Fig. 3.

In Fig. 3 the radial profile of the growth factor concentration has been plotted at consecutive times up to $t = 10^5$ s. From the calculations it can be seen that the differences between the solutions at consecutive times become smaller and smaller and hence it follows that the profile at $t = 10^5$ s does not differ much from the profile for the time-independent solution, that is as $t \to \infty$. 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. In

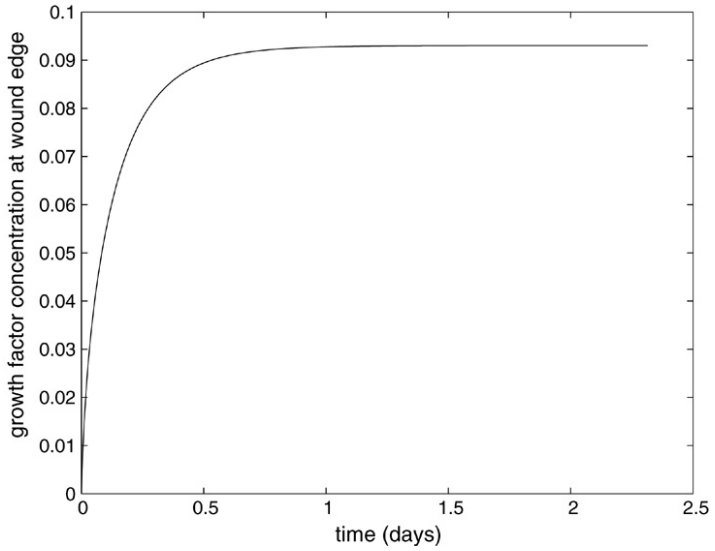

Fig. 4. The accumulation of the growth factor concentration profile at the wound edge for a circular wound. The concentration is expressed in arbitrary units.

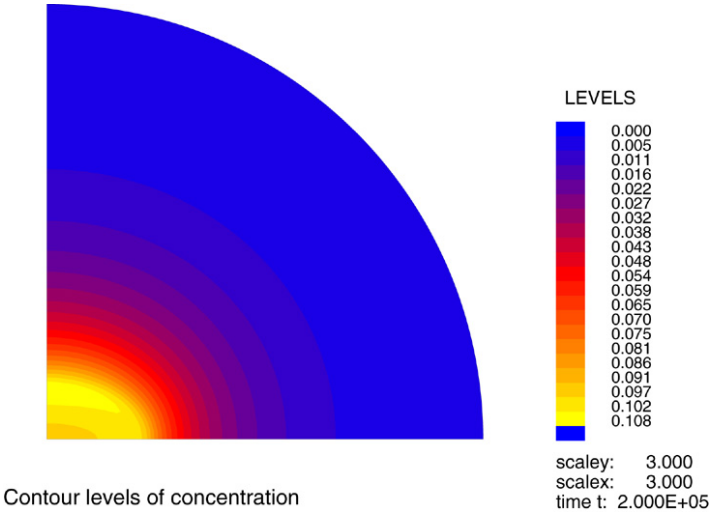

Fig. 5. Contour lines of the growth factor concentration for an elliptic wound. The concentration is expressed in arbitrary units.

Fig. 4 the growth factor concentration at the wound edge is plotted for the same circular wound as a function of time. It can be seen that after approximately a day the growth factor concentration is about to converge to its maximum. This may be seen as an incubation time before the actual healing starts.

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

In this section the concentration of the growth factor is considered numerically for several wound geometries. The healing process is not modeled analytically here; subsequent work will be devoted to this. 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 Fig. 5.

For the same geometry, the growth factor concentration over the edge of the wound is shown in Fig. 6. In Fig. 6 the growth factor concentration increases from the position where the curvature of the elliptic wound is maximal up

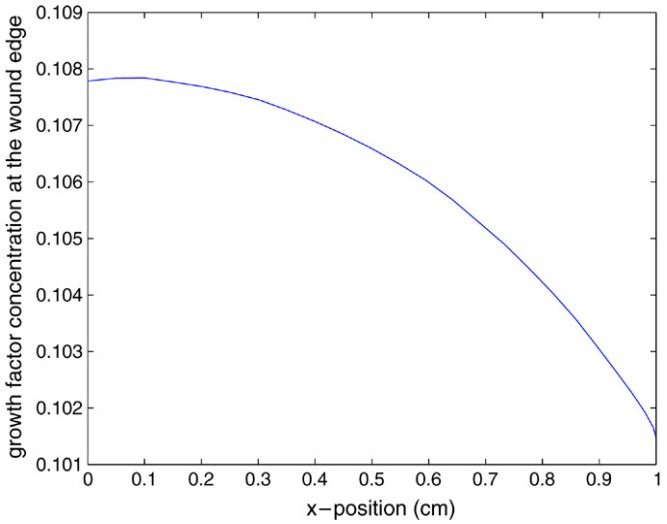

Fig. 6. Line plot of the growth factor concentration over the edge of the elliptic wound. The equation of the elliptic wound edge is given by $x^2 + 4y^2 = 1$. The concentration is expressed in arbitrary units.

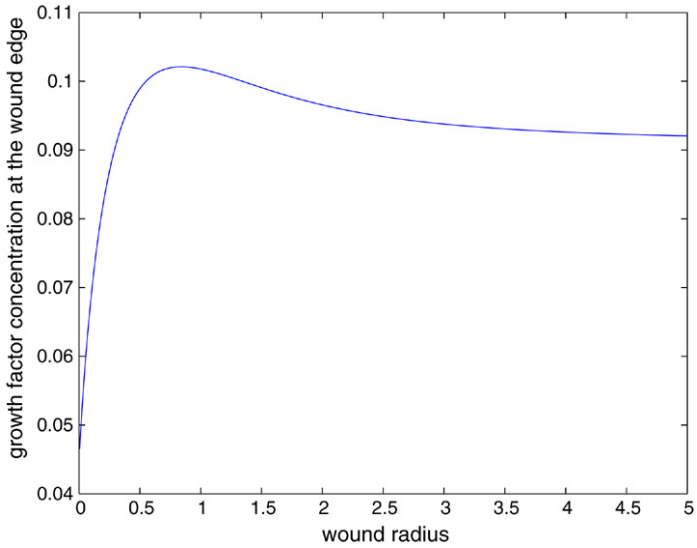

Fig. 7. The growth factor concentration at the wound edge as a function of the wound radius as computed using the analytic solution in [4]. The thickness of the active layer is fixed. The concentration is expressed in arbitrary units.

to a maximum value where the curvature of the wound is minimal. There is a small decrease of the growth factor concentration on the wound edge as $x \to 0$, that is the position with the minimum curvature. This is consistent with the results using the analytic solution in [7] plotted in Fig. 7. The analytic solution also predicts a slight decrease of the growth factor concentration as the wound radius becomes larger, that is, the wound curvature decreases. This effect takes place if the wound radius exceeds the radius for which the growth factor concentration is maximal. It can be seen in Fig. 5 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 lifetime of an animal. We remark that the results for the concentration at the wound edge from the analytical solution for a circular wound due to Adam agree perfectly with the results from the finite element method.

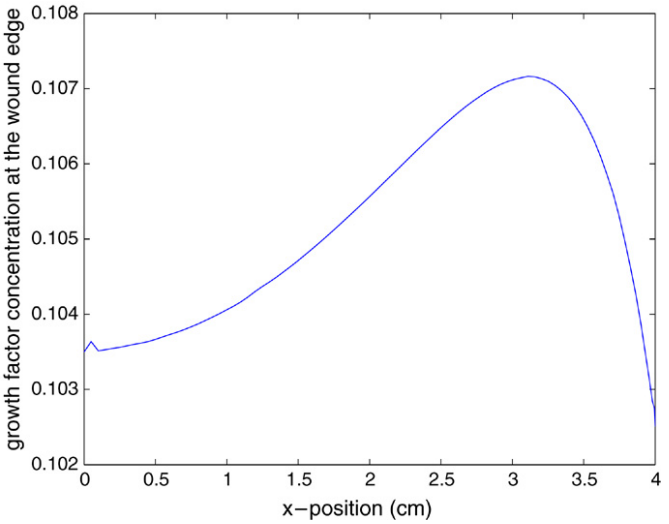

Fig. 8. Line plot of the growth factor concentration over the edge of the elliptic wound. The equation of the elliptic wound edge is given by $\frac{x^2}{16} + y^2 = 1$. The concentration is expressed in arbitrary units.

In Fig. 7 the growth factor concentration at the edge of a circular wound has been computed using the analytic solution due to Adam [4] as a function of the wound radius for a fixed thickness of active layer. From Fig. 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 due to healing. This latter decrease motivates the critical size defect as explained in Adam's 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 Fig. 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 Fig. 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. This is in line with the results from the analytic solution due to Arnold and Adam [7].

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 modeled by rotational symmetry and hence only two spatial co-ordinates are needed. The contour lines of the growth factor concentration are shown in Fig. 9 and a graph of growth factor concentration over the wound edge is displayed in Fig. 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.

4. Conclusions

Using the finite element method, some insight into the healing or non-healing of a wound is obtained based on a previous model. Along the perimeter of non-circular wounds there are regions where the growth factor concentration may exceed or be less than the threshold concentration for wound healing. This implies that the model predicts the existence of regions along a wound where healing either occurs or does not take place partially or at all and hence that the wound shape will become somewhat irregular over time. Further, due to the time dependence of the diffusion equation the model predicts a (short) incubation time before the wound starts healing. The next stage of this research will be to introduce a model in which other biological processes such as mitosis and cell death are taken into account using finite element techniques and further mathematical analysis.

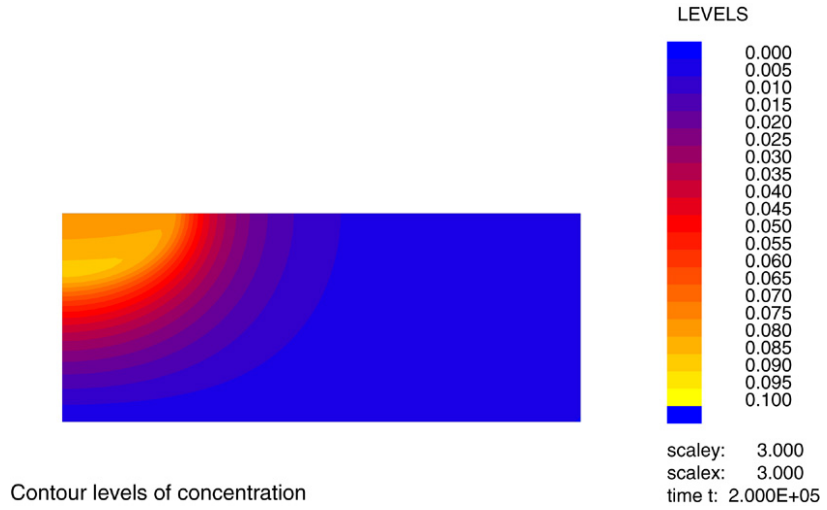

Fig. 9. Contour lines of the growth factor concentration for an elliptic wound in three dimensions with rotational symmetry. The concentration is expressed in arbitrary units.

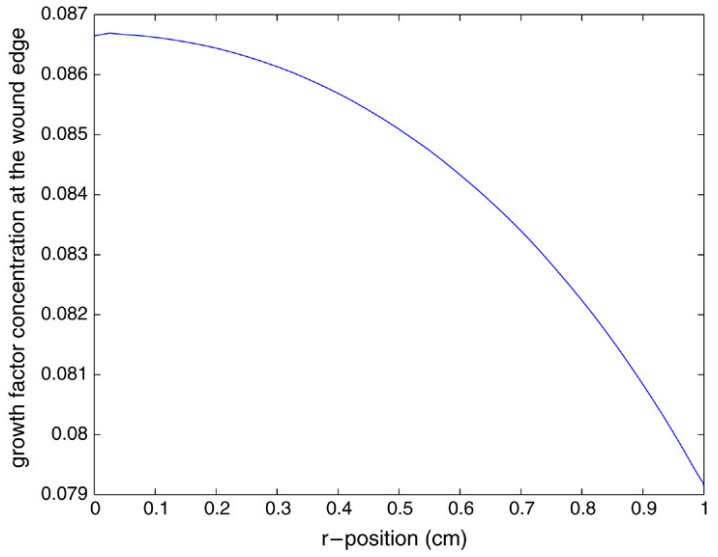

Fig. 10. Line plot of the growth factor concentration over the edge of the elliptic wound with rotational symmetry. The equation of the wound edge in polar co-ordinates is given by $r^2 + 4(z-2)^2 = 1$. Here r denotes the radial co-ordinate. The concentration is expressed in arbitrary units.

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Appendix. Derivation of the wound healing rate equation

It is known from basic multivariable calculus that the area of the surface $z = f(x, y)$ over a closed region D in the x–y plane is given by

$$A = \int_D \mathrm{d}S = \int_D \sqrt{1 + f_x^2(x, y) + f_y^2(x, y)}\mathrm{d}x\mathrm{d}y, \tag{16}$$

provided that f and its first order partial derivatives are continuous on D. For a spherical surface of radius a, we have $f(x, y) = \sqrt{a^2 - x^2 - y^2}$, so

$$\mathrm{d}A = \frac{a}{\sqrt{a^2 - x^2 - y^2}}\mathrm{d}x\mathrm{d}y = \frac{ar}{\sqrt{a^2 - r^2}}\mathrm{d}r\mathrm{d}\theta, \tag{17}$$

when expressed in polar co-ordinates (r, θ). Hence for the region $D = \{r \leq R\}$, we have

$$A(R) = \int_0^{2\pi}\int_0^R \frac{ar}{\sqrt{a^2 - r^2}}\mathrm{d}r\mathrm{d}\theta = 2\pi a\left(a - \sqrt{a^2 - R^2}\right). \tag{18}$$

Note that this reduces to the expected result $A(R) = \pi R^2$ as $\frac{a}{R} \to \infty$. 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

$$\Delta A = 2\pi a\left(\sqrt{a^2 - R^2(t)} - \sqrt{a^2 - R_0^2}\right). \tag{19}$$

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

$$\Delta V = \Delta A h = 2\pi h\int_0^t \int_{R(\tau)}^{R_0} \frac{r\overline{S}(R(\tau), r)}{\sqrt{a^2 - r^2}}\mathrm{d}r\mathrm{d}\tau. \tag{20}$$

In the above equation the function $\overline{S}(R(t), r)$ represents a measure of the volume rate of the regeneration of bone or tissue per unit area as a function of position and the wound radius. The right-hand side of Eq. (20) (when multiplied by the factor $2\pi h$) represents the time-accumulated volume of bone accrued at the (locally) instantaneous rate per unit surface area $\overline{S}(R(t), r)$. Thus Eq. (20) is essentially a statement of volume conservation: as the wound heals in a symmetrical manner (in this model) the total volume that has been 'healed' (replaced by new bone) as the radius decreases from $R(0)$ to $R(t)$ in time $t \geq 0$ is approximately $h\Delta A$. This will be inaccurate if the condition $h \ll a$ is not satisfied, but an appropriate geometrical adjustment can be made in this case. For the animal models initiating this paper it is not a concern.

The choice of the new bone growth rate per unit area $\overline{S}(R(t), r)$ should be a reasonable description of the nature of the healing in such wounds. Unfortunately, as far as we know, there appears to be no useful clinical data available in the current literature (despite an extensive search). Thus, it is necessary to choose a phenomenologically plausible functional form for $\overline{S}$; something that is a fairly sharp maximum at the wound edge, and that therefore falls sharply away from the wound edge. The reason for this is based on the fundamental notion that limited wound damage induces increased cell proliferation in the vicinity of the wound edges, and this rate of proliferation *per unit area* accelerates as the wound heals. After total healing has occurred the tissue returns to its normal state.

Eq. (20) is combined with Eq. (19) and subsequently the result is differentiated with respect to time, to obtain

$$\frac{\mathrm{d}R^2}{\mathrm{d}t} = -2\sqrt{a^2 - R^2(t)}\int_{R(t)}^{R_0} \frac{r\overline{S}(R(t), r)}{\sqrt{a^2 - r^2}}\mathrm{d}r. \tag{21}$$

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, to remedy this error 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. Mathematically, this corresponds to the initiation of 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. This is a correction to the earlier work [4]. Here $\delta(x)$ denotes the Dirac Delta 'function' and $S(R)$ represents a continuous rate function depending on R. This form for $\overline{S}$ then represents an inward moving 'wave of healing' as the wound shrinks. For these functions, note that $R(t) \leq R_0$ and for any arbitrary function $f(r)$:

$$\lim_{\epsilon\to 0}\int_{R(t)}^{R_0} f(r)\delta_\epsilon(r - R(t))\mathrm{d}r = \frac{1}{2}f(R(t)). \tag{22}$$

Then, this gives the following relation:

$$\frac{\mathrm{d}R^2}{\mathrm{d}t} = -2\sqrt{a^2 - R^2(t)} \int_{R(t)}^{R_0} \frac{rS(R(t))\delta(r - R(t))}{\sqrt{a^2 - r^2}} \mathrm{d}r = -R(t)S(R(t)). \tag{23}$$

From the nature of the Dirac Delta distribution, it follows that this choice predicts 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. Simplifying Eq. (23) yields

$$\frac{\mathrm{d}R}{\mathrm{d}t} = -\frac{1}{2}S(R(t)), \quad \text{with } R(0) = R_0. \tag{24}$$

This equation is integrated to obtain R as a function of t. A second assumption that can be introduced is that the wound only heals if the growth factor concentration exceeds this threshold value. Therefore at each time during the healing process, it is necessary to know whether the growth factor concentration at the wound edge exceeds the threshold value.

References

[1] J.A. Adam, A simplified model of wound healing (with particular reference to the critical size defect), Mathematical and Computer Modelling 30 (1999) 23–32.
[2] J.A. Adam, The effect of surface curvature on wound healing in bone, Applied Mathematics Letters 15 (2002) 59–62.
[3] J.A. Adam, The effect of surface curvature on wound healing in bone: II. The critical size defect, Mathematical and Computer Modelling 35 (2002) 1085–1094.
[4] J.A. Adam, Healing times for circular wounds on plane and spherical bone surfaces, Applied Mathematics Letters 15 (2002) 55–58.
[5] J.A. Adam, Inside mathematical modelling: building models in the context of wound healing in bone, Discrete and Continuous Dynamical Systems. Series B 4 (1) (2004) 1–24.
[6] J.S. Arnold, A simplified model of wound healing III: The critical size defect in three dimensions, Mathematical and Computer Modelling 34 (2001) 385–392.
[7] J.S. Arnold, J.A. Adam, A simplified model of wound healing II: The critical size defect in two dimensions, Mathematical and Computer Modelling 30 (1999) 47–60.
[8] J. Filion, A.P. Popel, A reaction diffusion model of basic fibroblast growth factor interactions with cell surface receptors, Annals of Biomedical Engineering 32 (5) (2004) 645–663.
[9] E.A. Gaffney, K. Pugh, P.K. Maini, Investigating a simple model for cutaneous wound healing angiogenesis, Journal of Mathematical Biology 45 (4) (2002) 337–374.
[10] H.P. Greenspan, Models for the growth of a solid tumor by diffusion, Studies in Applied Mathematics 52 (1972) 317–340.
[11] S.A. Maggelakis, A mathematical model for tissue replacement during epidermal wound healing, Applied Mathematical Modelling 27 (3) (2003) 189–196.
[12] S.A. Maggelakis, J.A. Adam, Diffusion regulated growth characteristics of a prevascular carcinoma, Bulletin of Mathematical Biology 52 (1990) 549–582.
[13] J.D. Murray, Mathematical Biology II: Spatial Models and Biomedical Applications, Springer-Verlag, New York, 2004.
[14] J.A. Sherratt, J.D. Murray, Mathematical analysis of a basic model for epidermal wound healing, Journal of Mathematical Biology 29 (1991) 389–404.