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A Simplified Model of Wound Healing (With Particular Reference to the Critical Size Defect)

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Abstract—This paper is an attempt to construct a simple mathematical model of wound healing/tissue regeneration which reproduces some of the known qualitative features of those phenomena. It does not address the time development of the wound in any way, but does examine conditions (e.g., wound size) under which such healing may occur. Two related one-dimensional models are examined here. The first, and simpler of the two corresponds to a "swath" of tissue (or more realistically in this case, bone) removed from an infinite plane of tissue in which only a thin band of tissue at the wound edges takes part in tissue/bone regeneration. There is no tissue or bone in the interior. The second model has a similar geometric structure, except that not all the tissue in the interior has been removed: it is a "gouge" or "graze" rather than a hole or puncture. In each model, there is a thin layer of tissue (e.g., the epidermis) or bone (depending on the context) that is responsible for increased mitotic activity at the edges of the wound by manufacturing a generic growth stimulator of concentration $C(x,t)$ small, where x is the direction of wound closure, and t is time. Using a combination of results from these two models, we have been able to predict the size of the critical size defect, which is defined as the smallest intraosseous wound that does not heal by bone formation during the lifetime of the animal being studied. We have also been able to isolate parameter ranges that will give reasonable values for both the thickness of the active region and the critical size defect, and in addition, establish that the models discussed here have the sensitivity to place reasonable bounds on such parameter values.

Keywords—Wound healing, Tissue regeneration, Critical size defect, Diffusion equation, Growth factors.

1. INTRODUCTION

The fields of bone regeneration and wound healing in general often rely on suitable animal models to test experimental bone and tissue repair materials. One accepted model for the former is the so-called Critical Size Defect (CSD), which has been defined as the smallest intraosseous wound that does not heal by bone formation during the lifetime of the animal [1]. For practical purposes, this timescale can usually be taken as one year. In [2], the definition was further extended to a defect which has less than "heal" by fibrous connective tissue formation, but since this is not

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bone, it does not have the properties (strength, etc.) that a completely healed defect would. Some typical CSDs are for rat, rabbit, dog, and monkey calvaria (skullcap), respectively: 8 mm, 15 mm, 20 mm, and 15 mm (details can be found in [1]).

Wound healing, when it occurs, does so by means of a combination of various processes. Chemotaxis (the movement of cells up a concentration gradient), neovascularization, synthesis of extracellular matrix proteins, and scar remodeling [3]. Growth factors are likely to play a very significant role in bone regeneration [4–7]. Such factors include Transforming Growth Factor β (TGF-β), Platelet-Derived Growth Factor (PDGF), Insulin-Like Growth Factor (IGF), and in the case of skin, Epidermal Growth Factor (EGF), [4,8]. Furthermore, the supply of oxygen to a wound has much influence on the quality of healing [5], and hence, angiogenesis is of vital significance in bone and tissue regeneration [9,10].

This paper is an attempt to construct a simple mathematical model of wound healing/tissue regeneration which reproduces some of the known qualitative features of those phenomena. Initially a one-dimensional model is developed, but this easily generalized to the more realistic case of a circular wound (still technically one-dimensional if the only independent variable is the radius). This will be carried out subsequently: the results will not differ in any major qualitative way from those in this paper. Obviously the results will differ somewhat in a quantitative sense, if only because of geometric factors.

This paper does not address the time development of the wound in any way; it merely examines the conditions (e.g., wound size) under which such healing may occur. The temporal development has been addressed by others in the context of rather different models; those in the present paper can be adapted somewhat to incorporate this, but the primary focus is to account for the existence of a critical size defect by means of biochemical regulation of mitosis.

Two related models are examined here. The first, and simpler of the two, corresponds to a "swath" of tissue (or more realistically in this case, bone) removed from an infinite plane of tissue (see Figure 1) in which only a thin band of tissue at the wound edges takes part in tissue/bone regeneration. There is no tissue or bone in the interior. The second model has a similar geometric structure to the first, except that not all the tissue in the interior has been removed: it is a "gouge" or "graze" rather than a hole or puncture.

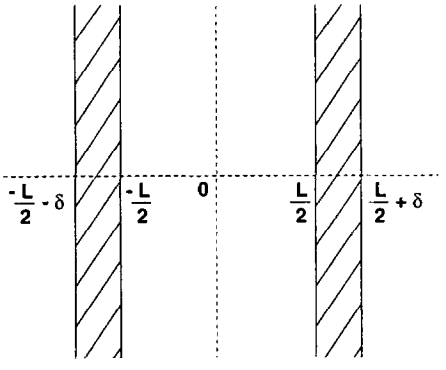

Figure 1. Schematic diagram of the wound configuration: wound width is L and active wound edge is of thickness δ.

In each model, there is a thin layer of tissue (e.g., the epidermis) or bone (depending on the context) that is responsible for increased mitotic activity at the edges of the wound by manufacturing a generic growth stimulator of concentration $C(x,t)$, where x is the direction of wound closure, and t is time, both in appropriate units discussed below.

2. BASIC CONFIGURATION: MODEL

We consider a one-dimensional "wound" of width L centered at the origin of coordinates. At

the wound "edges", $x = \pm L/2$, we suppose that a generic "Growth Factor" (GF) is produced and it is the distribution of this growth factor that determines whether or not wound healing occurs on the basis of this model. Before discussing the basic assumptions inherent in the model, we state the fundamental differential equation describing the space and time distribution of the growth factor concentration $C(x,t)$. It is given by

$$\frac{\partial C}{\partial t} - D\frac{\partial^2 C}{\partial x^2} + \lambda C = PS(x), \tag{1}$$

where D, λ, and P are, respectively, the diffusion coefficient for the GF in the tissue, the decay or depletion rate of the GF, and the production rate of GF by the enhanced mitotically active cells in the vicinity of the wound edges. These are all assumed to be constant in both models. Furthermore, $S(x)$ is the source term describing the distribution of GF production throughout the active tissue. In both models, this is assumed to be uniform; thus,

$$S(x) = 1, \qquad \frac{L}{2} \le x \le \frac{L}{2} + \delta, \tag{2}$$

where δ is the thickness of the active layer, and elsewhere

$$S(x) = 0.$$

In equation (1) above, the first term represents the time rate of change of GF concentration, the second term describes the spatial change due to diffusion of GF, and the third term is the depletion or decay rate of GF as it interacts with the system as a whole, and is changed or removed. Thus, in the absence of diffusion and production, an initial distribution of GF will decay exponentially according to this equation.

3. MAIN ASSUMPTIONS

Several assumptions have already been noted, but in this section, we identify the more important ones and their implications. The first to be noted is that of *diffusive equilibrium*: basically this means that the process of readjustment of the GF concentration as the wound heals is so fast (when compared with the typical wound-healing time) that, to a first approximation, the distribution of GF may be considered *independent* of time. This also simplifies the mathematics considerably! In order to justify this assumption, consider the diffusion timescale T as defined from equation (1):

$$T \approx \frac{(l)^2}{D},$$

where l refers to a typical length scale (size) of the system, i.e., the wound. The value of D of course depends on the particular GF or enzyme in general (the higher the molecular weight, the smaller is D), and the medium in which it is diffusing. However, some indication of this can be found by considering the diffusion of oxygen and sucrose in water. At a temperature of 25° C, $D \approx 2.4 \times 10^{-5}\,\mathrm{cm^2\,sec^{-1}}$, while for sucrose at 20° C, D$\approx 4.6 \times 10^{-6}\,\mathrm{cm^2\,sec^{-1}}$ [11]. Sherratt and Murray [12,13] carried out a best fit analysis from data on epidermal wound healing (there being no direct experimental data from which D could be determined) and estimated that for epidermal GF, $D \approx 3.1 \times 10^{-7}\mathrm{cm^2\,sec^{-1}}$, considerably smaller because of the high molecular weight (about 6000, see [14]). In their papers, they also considered growth *inhibitors*, for which $D \approx 5.9 \times 10^{-6}\,\mathrm{cm^2\,sec^{-1}}$ (we will not consider such inhibitors in this paper). Thus, it seems not unreasonable to take a value of $D \approx 10^{-5}\,\mathrm{cm^2\,sec^{-1}}$ for oxygen (clearly, an important factor in wound healing) and D$\approx 5 \times 10^{-7}\,\mathrm{cm^2\,sec^{-1}}$ for GF, the quantity of primary concern here. Using this value of D for l-values of 1 μm (10^{-4} cm), 10 μm, 1 mm, and 1 cm, we find typical diffusion times of 2×10^{-2} sec, 2 sec, $\approx 5(1/2)$ hr and ≈ 23 days, respectively. The corresponding

diffusion timescales for *oxygen*, it should be noted, are 10^{-3} sec, 10^{-1} sec, ≈ 15 min and ≈ 1 day, respectively. Clearly, the approximation is less well justified for GF in wound sizes of order one centimeter if we are considering wound healing *per se*, but recall that we are here interested in a mechanism that may shed light on the existence of the *critical size defect*, i.e., that wound size above which no essential healing occurs *during the lifetime of the animal* [1]. Over such a timescale, the diffusive approximation is certainly a very good one for GF distributions. Under these circumstances, $\frac{\partial C}{\partial t} = 0$ in equation (1).

The second assumption is that the tissue growth or bone regeneration is regulated by the GF concentration $C(x)$ (recall: no time dependence for C in the light of the first assumption) via a discontinuous switch mechanism, such that increased mitotic activity, and hence, regeneration occurs at the wound edges when the GF concentration reaches or exceeds a critical or threshold value θ, i.e., when

$$C\left(\pm\frac{L}{2}\right) \geq \theta. \tag{3}$$

The third basic assumption is that there are no mechanical constraints: by this we mean that the tissue/bone is free to grow (when the above criterion is satisfied) into the wound space without any resistive pressure constraints (e.g., as would be present for an expanding benign tumor). Finally, we make explicit an already implicit assumption, namely that of the continuum approximation. This means that the dependent variable $C(x)$ is a continuous and suitably differentiable function: we do not encounter on the present scale of description the discontinuities which must inevitably be present on the molecular scale. We are now in a position to discuss Model I. Because in both models the system and solutions are symmetric about $x = 0$, we shall only address the domain $x \geq 0$. The results for $x \leq 0$ are then easily established. To obtain results valid for either sign of x, merely replace x by $|x|$ in equations (6), (7), (10), (11), and (14).

4. MODEL I: EQUATIONS AND SOLUTION

The governing differential equation may now be written in the simple form

$$\frac{d^2C}{dx^2} - \alpha^2 C = -\frac{P}{D}, \qquad \frac{L}{2} \leq x \leq \frac{L}{2} + \delta \tag{4}$$

and

$$\frac{d^2C}{dx^2} - \alpha^2 C = 0 \tag{5}$$

elsewhere (the domain of $C(x)$ is $[L/2, \infty)$). Here the constant

$$\alpha = \sqrt{\frac{\lambda}{D}}.$$

The boundary conditions to be satisfied are

(i) $C(x)$, $\frac{dC(x)}{dx}$ are both continuous at $x = L/2 + \delta$,
(ii) $\lim_{x\to\infty} C(x) = 0$,
(iii) $\frac{dC(x)}{dx} = 0$ at $x = L/2$.

The second of these conditions is necessary because there are no distant sources of GF production, and so the concentration must decrease as the distance from the wound increases. The final condition means that there is no flux of GF into the (empty) interior. This will be modified in Model II for which interior tissue will be present.

Using standard techniques to solve the above ordinary differential equations, we find after some algebraic manipulation that in the active or "epidermal layer" defined by $L/2 \leq x \leq L/2 + \delta$, the concentration of GF is given by

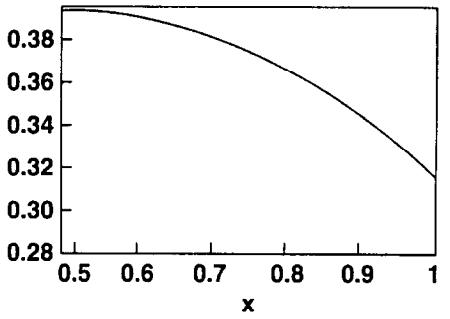

Figure 2. Growth factor profile from Model I in active layer (wound edge: $L/2 \leq x \leq L/2 + \delta$). For illustrative purposes, the following values have been chosen: $\alpha = 1, \delta = 1/2$, and $L = 1$.

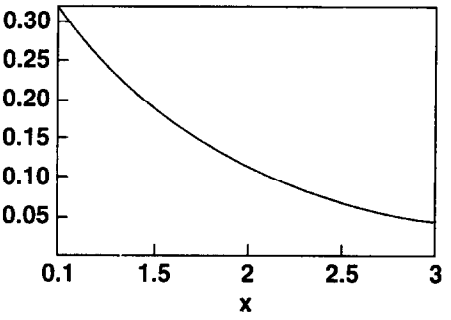

Figure 3. Growth factor profile from model I in wound exterior region ($x \geq L/2 + \delta$). For illustrative purposes, the following values have been chosen: $\alpha = 1$, $\delta = 1/2$, and $L = 1$.

$$C(x) = \frac{P}{\lambda}\left\{1 - \exp(-\alpha\delta)\left(\cosh\alpha\left(x - \frac{L}{2}\right)\right)\right\}. \tag{6}$$

The shape of the GF distribution, namely $\lambda C(x)/P$ in dimensionless form, is illustrated schematically below. In this figure, and all the graphs of $C(x)$ in Models I and II, we have chosen the values $\alpha = 1$, $\delta = 1/2$, and $L = 1$ to show the basic qualitative features of each GF profile. Obviously it is a straightforward matter to modify the graphs for more biologically realistic parameter values.

Finally, in the region exterior to the wound, $x \geq L/2 + \delta$, the corresponding solution is

$$C(x) = \frac{P}{\lambda}\sinh(\alpha\delta)\left(\exp\alpha\left(\frac{L}{2} - x\right)\right). \tag{7}$$

Note that the ratio of the GF concentration at the edge ($x = L/2$) to that at the other edge of the mitotically active region ($x = L/2 + \delta = m$) is given by

$$\frac{C(L/2)}{C(m)} = (\exp(\alpha\delta) - 1)\operatorname{csch}\alpha\delta.$$

Using equation (6), we apply the criterion that

$$C\left(\frac{L}{2}\right) \geq \theta,$$

i.e.,

$$\frac{P}{\lambda}(1 - \exp(-\alpha\delta)) \geq \theta. \tag{8}$$

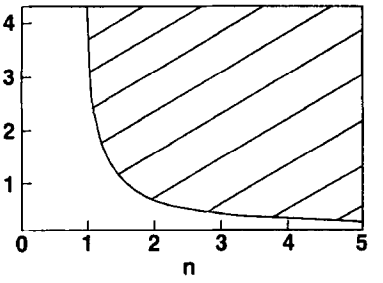

Figure 4. Graph of the dimensionnless quantity $\alpha\delta_c$ as a function of the parameter $n = P/\lambda\theta$. Note that $\alpha\delta_c$ is undefined for $0 \leq n \leq 1$. Healing occurs in the region above the curve.

After some rearrangement, this can be rewritten as

$$\delta \geq \delta_c = \alpha^{-1} \ln\left(\frac{n}{n-1}\right), \tag{9}$$

where n is a parameter defined in terms of the tissue constants P, λ, θ by

$$n = \frac{P}{\lambda\theta} \geq 0.$$

In the graph of the dimensionless quantity $\alpha\delta_c$ as a function of the j parameter $n = P/\lambda\theta$, note that $\alpha\delta_c$ is undefined for $0 \leq n \leq 1$.

This clearly places, for given n, a lower bound (δ_c) on the thickness of the active layer necessary for the wound to heal. The region *above* the curve corresponds to thicknesses δ for which healing/regeneration occurs; below the curve no such event takes place—the active region is too thin to sustain the required level of GF production and retention.

5. MODEL II: EQUATIONS AND SOLUTION

In this model, as indicated above, there is still some tissue in the wound interior, i.e., for $-L/2 \leq x \leq L/2$. However, it is considered to be dormant in that it does not contribute to the healing process, as before, the wound edges of thickness δ are the domains of GF production. As in Model I, we will invoke spatial symmetry (i.e., $C(x) = C(-x)$) to allow the mathematical convenience of working with $x \geq 0$ only. The boundary conditions now are slightly different: we demand that $C(x)$,and $C'(x)$ are both continuous at $x = L/2$ and $x = L/2 + \delta$, $C'(0) = 0$ and as before

$$\lim_{x\to\infty} C(x) = 0.$$

There are now three regions to consider for $x \geq 0$. The governing differential equation is unchanged except that the homogeneous form now applies in both the wound interior $0 \leq x \leq L/2$, and the exterior $x \geq L/2 + \delta$. In $0 \leq x \leq L/2$, the solution is

$$C(x) = \frac{P}{\lambda}\left\{\exp\left(-\alpha\frac{L}{2}\right)\right\}\{1 - \exp(-\alpha\delta)\}\cosh\alpha x. \tag{10}$$

(Again, in the graphs below we use $\alpha = 1$, $\delta = 1/2$, and $L = 1$. They represent the dimensionless quantity $\lambda C(x)/P$ as a function of distance from the center of the wound.)

In the active region of GF production, $L/2 \leq x \leq L/2 + \delta = m$,

$$C(x) = \frac{P}{\lambda}\{1 + A\cosh\alpha x + B\sinh\alpha x\}, \tag{11}$$

where

$$A = \left\{\cosh\alpha\frac{L}{2} - \exp(-\alpha m) - \exp\left(\alpha\frac{L}{2}\right)\right\} = -\left\{\sinh\frac{\alpha L}{2} + \exp(-\alpha m)\right\} \tag{12}$$

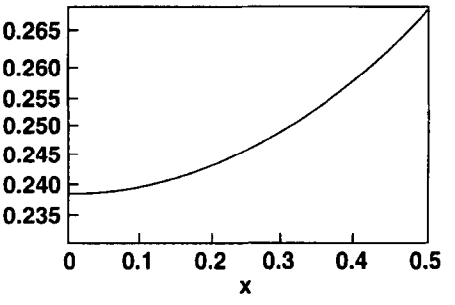

Figure 5. Growth factor profile from Model II in wound interior region ($0 \leq x \leq L/2$). For illustrative purposes, as in previous figures, the following values have been chosen: $\alpha = 1$, $\delta = 1/2$, and $L = 1$.

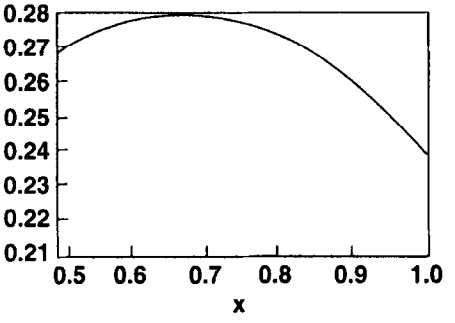

Figure 6. Growth factor profile from Model II in active layer (wound edge: $L/2 \leq x \leq L/2 + \delta$). For illustrative purposes, as in Figure 5, the following values have been chosen: $\alpha = 1$, $\delta = 1/2$, and $L = 1$.

and

$$B = -[A + \exp(-\alpha m)] = \sinh \frac{\alpha L}{2}. \tag{13}$$

Note that the maximum value of GF concentration occurs in the active region, as would be expected. This maximum occurs at $x = x_m$, where

$$x_m = \alpha^{-1} \operatorname{arctanh} \left\{ 1 + \exp(-\alpha m) \operatorname{csch} \frac{\alpha L}{2} \right\}^{-1}.$$

Note also that

$$C(x_m) = \frac{P}{\lambda}(1 + A \operatorname{sech} \alpha x_m).$$

Finally, in the exterior $x \geq m$, the solution is

$$C(x) = \frac{PF}{\lambda} \exp(-\alpha x), \tag{14}$$

where

$$F = -[\exp(\alpha m)] \{A \sinh \alpha m + B \cosh \alpha m\}. \tag{15}$$

Of particular interest once again is the condition for healing at the wound edge, namely

$$C\left(\frac{L}{2}\right) \geq \theta.$$

From equation (10), this can be rearranged to yield the expression

$$1 + [\exp(-\alpha L)] \geq \frac{2}{n[1 - \exp(-\alpha \delta)]} = \frac{2}{N}, \tag{16}$$

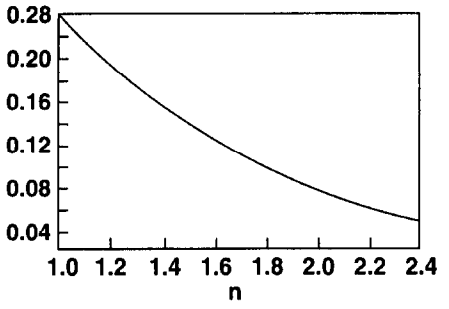

Figure 7. Growth factor profile from Model II in wound exterior region ($x \geq L/2+\delta$). Again, for illustrative purposes, the following values have been chosen: ($\alpha = 1, \delta = 1/2S$ and $L = 1$.

where $n = P/\lambda\theta$ as before and

$$\begin{aligned} N &= n[1 - \exp(-\alpha\delta)] \\ &\approx n\alpha\delta, \qquad \text{if } \alpha\delta \gg 1, \end{aligned} \tag{17}$$

so N is clearly, dependent on the active region thickness δ. Further rearrangement enables the above inequality to be written in terms of the width of the wound L that is necessary for healing to occur, namely

$$L \leq L_c = \alpha^{-1} 1n \left\{ \frac{N(\delta)}{2 - N(\delta)} \right\}. \tag{18}$$

Thus, if L is below the critical width L_c defined by this expression, then healing/regeneration occurs, and above this critical width it does not. The dimensionless quantity αL_c is illustrated in the figure below. The physical restrictions on N are $1 < N(\delta) < 2$.

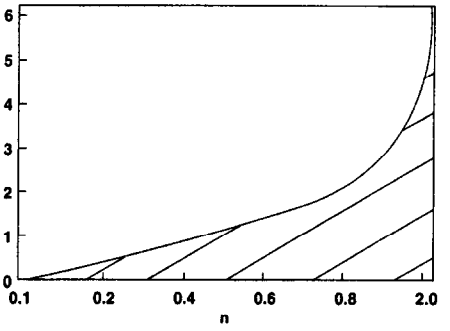

Figure 8. Graph of the dimensionless quantity $\alpha\delta_c$ as a function of the modified parameter $N = n[1 - \exp(-\alpha\delta)]/\lambda\theta$. Healing occurs in the region below the curve.

Note that $0 < N < n$, these extremes being determined by the (unphysical) values of active region thickness δ being zero and infinite, respectively.

6. ESTIMATES OF PARAMETER VALUES

We have already noted some possible values for the diffusion coefficient D, but other quantities are still harder to pin down for a conceptual model of this type. Based on studies of DNA synthesis suppression by repeated injection of epidermal extract, Sherratt and Murray [3,4] estimated the half-life of chemical decay as 12 hours, so for pure exponential decay this corresponds to $\lambda = \ln 2/12\,\text{hr}^{-1}$ or approximately $1.6 \times 10^{-5}\,\text{sec}^{-1}$. For $D \approx 5 \times 10^{-7}\,\text{cm}^2\text{sec}^{-1}$ this gives $\alpha \approx 6\,\text{cm}^{-1}$. The most difficult of our parameters to assess is the ratio P/θ, though at least this does not require us to know each quantity independently. The reciprocal of this ratio is a measure of how long it would take the active region to "pump out" enough GF to initiate the healing process (by reaching the threshold concentration θ) *in the absence of GF decay and*

diffusion. With these processes included of course this takes considerably longer. It seems entirely reasonable to expect that $P \ll \theta$ and so noting from Model I the requirement that $n > 1$, we must have $P/\theta > 1.6 \times 10^{-5}\,\mathrm{sec}^{-1}$. This means that even in the absence of the depletion effects mentioned above, the required time from wounding to the start of the healing process (*not* the time to heal, note) is *at most* about 17 hours. This will be increased of course by the presence of depletion. We are now in a position to estimate the critical thickness of the active region δ by using equation (9). We write this now as

$$\delta \geq \delta_c \approx \frac{1}{6} ln \left(\frac{n}{n-1} \right). \tag{19}$$

Consider the following examples: for

$$\begin{aligned} n &= 1.2, \quad \delta_c \approx 0.30\mathrm{cm}, \\ n &= 1.4, \quad \delta_c \approx 0.21\mathrm{cm}, \\ n &= 1.7, \quad \delta_c \approx 0.15\mathrm{cm}, \\ n &= 2.0, \quad \delta_c \approx 0.12\mathrm{cm}, \\ n &= 3.0, \quad \delta_c \approx 0.07\mathrm{cm}. \end{aligned}$$

Choosing a representative value of $\delta \approx 0.18\,\mathrm{cm}$, and $n = 3$, we find from (17), using $\alpha = 6$ that $N \approx 1.98$, whence from (18), $L_c \approx 0.75\,\mathrm{cm}$, that is, *the critical size defect is about 0.75 cm for this choice of parameters*. A reasonable question may be asked at this stage. Why do we choose a value for δ of $0.18\,\mathrm{cm}$, rather than $\delta_c = 0.07$ as indicated for this choice of n? The answer is that the model indicates that δ is *at least* δ_c and so we are free to choose a larger value consistent with biological considerations. A further point to be noted is that Models I and II are related in formulation, but are independent, so we use only general information on δ as provided by Model I to ascertain general features from Model II, such as the size of L_c. It is also clear that some, indeed many, choices of parameter values will give very small (and hence, unrealistic) values of the critical size defect. In our present state of knowledge about, for example, values of D, λ, P/θ, and hence, n, δ, and N, what we *have* been able to accomplish is to isolate parameter ranges that *will* give reasonable values for both the thickness of the active region and the critical size defect, and also to establish that the models discussed here have the sensitivity to place reasonable bounds on such parameter values.

7. FURTHER COMMENTS

It is of course highly desirable to carry out the above analyses in circular geometry. This will be more complicated mathematically because the solutions and inferences therefrom will involve modified Bessel functions ($I_0(\alpha r)$ and $K_0(\alpha r)$) rather than hyperbolic functions which possess relatively simple properties. Nonetheless, the major qualitative features of the present models will still apply, but there may well be some subtle, and perhaps unexpected quantitative changes which could raise the models to a higher level of biological relevance. This work is currently in progress (Adam and Arnold, to appear). The present model predicts critical size defects which are somewhat on the low side when compared with the observational data, yet certainly of the right order of magnitude. It is clear that when circular geometry is employed, the wound will "feel" its other side (via the wound curvature) and this may well affect the numerical value of the critical size defect. The planar model has no such capability and as such serves as a useful comparison for the more realistic model.

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