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The Effect of Surface Curvature on Wound Healing in Bone

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Abstract - The time-independent nonhomogeneous diffusion equation is solved for the equilibrium distribution of wound-induced growth factor over a hemispherical surface. The growth factor is produced at the inner edge of a circular wound and stimulates healing in regions where the concentration exceeds a certain threshold value. An implicit analytic criterion is derived for complete healing of the wound. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords — Diffusion, Surface curvature, Growth factor, Wound healing.

On the surface of a sphere of radius $R$ with azimuthal symmetry, the Laplacian operator becomes the ordinary differential operator [1]

$$\nabla^2 \equiv R^{-2} \left[ \frac{d^2}{d\theta^2} + \cot \theta \frac{d}{d\theta} \right],$$

where $\theta$ is the polar angle. Hence, the governing differential equation for the diffusion of growth factor (GF) across the surface of the sphere becomes, in the usual diffusive equilibrium approximation,

$$D \nabla^2 \tilde{C} - \lambda \tilde{C} = -P, \quad 0 < \alpha_1 \leq \theta \leq \alpha_2 < \frac{\pi}{2},$$

$$= 0, \quad \theta > \alpha_2. \quad (2)$$

This describes the steady-state distribution of GF concentration $\tilde{C}(\theta)$ outside a circular wound of radius $R\alpha_1$, with production of the bone-producing GF occurring within an annular rim of width $R(\alpha_1 - \alpha_2)$, both measured across the surface of the sphere. $D$, $\lambda$, and $P$ are, respectively, the constant diffusion coefficient, decay or depletion coefficient, and production rate for the GF. The notation is the same, apart from the geometry, as that in [2,3] which dealt with one-dimensional and two-dimensional planar models, respectively. Some of the clinical literature underlying the development of these models can be found in those papers.

With the change of variable $z = \sin^2 \theta$, equation (2) becomes, after a little manipulation, the following equation, where $\tilde{C}(\theta) \equiv C(z)$:

$$z(1-z) \frac{d^2 C}{dz^2} + \left( 1 - \frac{3}{2}z \right) \frac{dC}{dz} - \frac{\lambda R^2}{4D} C = -\frac{PR^2}{4D}, \quad 0 < \alpha_1 \leq \theta \leq \alpha_2 < \frac{\pi}{2}, \quad (3)$$

$$= 0, \quad \theta > \alpha_2.$$
The homogeneous equation is in the canonical form of the hypergeometric equation
\[ z(1-z)\frac{d^2C}{dz^2} + (c-(1+a+b)z)\frac{dC}{dz} + abC = 0, \]
from which it follows that \( c = 1, a = (1/4)[1 + \sqrt{1 - 4\lambda R^2/D}], \) and \( b = (1/4)[1 - \sqrt{1 - 4\lambda R^2/D}] \). Because of the fact that \( c = 1 \), one of the solutions is logarithmically singular at \( z = 0 \) [4]; thus, the general solution to the homogeneous problem is a linear combination of the fundamental solutions
\[ C_1(z) = \sum_{n=1}^{\infty} c_n z^n, \]
where the coefficients \( c_n \) involve combinations of the digamma function
\[ \psi(z) = \frac{\Gamma'(z)}{\Gamma(z)}. \]
Specifically, in terms of the Pochhammer symbols
\[ (a)_n = \frac{\Gamma(a+n)}{\Gamma(a)}, \quad n = 1, 2, \ldots, \]
\[ c_n = \frac{(a)_n(b)_n}{(n!)^2} [\psi(a+n) - \psi(a) + \psi(b+n) - \psi(b) + 2\psi(1) - 2\psi(n+1)], \]
where \(-\psi(1) = 0.57721566\ldots\) is the Euler-Mascheroni constant. In (6), the series
\[ \sum_{n=1}^{\infty} c_n z^n \]
converges provided that \(|z| < 1\) [4]; clearly this is satisfied for all real values of \(|\theta| \in [0, \pi/2)\). The general solution to the homogeneous problem \((z > z_2)\) is
\[ C(z) = A_2 F_1(a, b; c; z) + B \left\{ 2 F_1(a, b; c; z) \ln z + \sum_{n=1}^{\infty} c_n z^n \right\}, \]
where \(A\) and \(B\) (and also \(E, G\) below) are, at this stage, arbitrary constants. Likewise, the general solution to the nonhomogeneous problem, valid for \(z \in [z_1, z_2] \subset [\sin^2 \alpha_1, \sin^2 \alpha_2]\), is
\[ C(z) = E_2 F_1(a, b; c; z) + G \left\{ 2 F_1(a, b; c; z) \ln z + \sum_{n=1}^{\infty} c_n z^n \right\} + \frac{P}{\lambda}. \]
In keeping with the reasoning described in earlier papers [2,3], the following boundary conditions are imposed:
(i) \( C'(z_1 = \sin^2 \alpha_1) = 0 \) (i.e., \( \tilde{C}(|\theta_1|) = 0 \));
(ii) \( C(z = \sin^2 \theta) \) and \( C'(z = \sin^2 \theta) \) are continuous at \( z_2 = \sin^2 \alpha_2 \) (i.e., \( \tilde{C}(\theta) \) and \( \tilde{C}'(\theta) \) are continuous at \(|\theta| = \alpha_2\)); and
(iii) \( C(0) < \infty \) (i.e., \( \tilde{C}(\pi) < \infty \)).
This last condition, obvious in one sense, requires some elaboration. It assures us that the singularity at \( z = 0 \) (i.e., \( \theta = 0, \pi \)) is absent; although \( \theta = 0 \) is outside the domain of \( \tilde{C}'(\theta) \), the nonmonotonicity of \( \sin \theta \) in \( (0, \pi) \) ensures that imposing a condition at \( \theta = \pi \) is equivalent to imposing the same condition at \( \theta = 0 \). In practical terms, only wounds confined to the (upper) hemisphere are defined, so the nonmonotonicity does not present any problems in this domain. Note that the diffusion coefficient \( D \) is assumed constant in \([a_1, \pi] \).

In imposing the boundary conditions, use will be made of the result that

\[
\frac{d}{dz} \, 2F_1(a, b; c; z) \equiv F'(z) = \frac{ab}{c} \, 2F_1(a+1, b+1; c+1; z).
\]

Note first that \( C(0) < \infty \) implies that \( B = 0 \) in equation (9). The following notational simplifications will be used:

\[
\zeta_1(z) = \sum_{n=1}^{\infty} c_n z^n
\]

and

\[
\zeta_2(z) = \sum_{n=1}^{\infty} n c_n z^{n-1}.
\]

Imposing the condition \( C'(z_1) = 0 \) yields, from equation (10), the result

\[
E = -\frac{G}{F'(z_1)} \left\{ \frac{F(z_1)}{z_1} + \zeta_0(z_1) + F'(z_1) \ln z_1 \right\},
\]

where as implied above, \( F \) represents the basic hypergeometric function \( 2F_1(a, b; c; z) \). The continuity of \( C \) at \( z = z_2 \) yields

\[
AF(z_2) = E(G)F(z_2) + G \left\{ F(z_2) \ln z_2 + \zeta_1(z_2) \right\} + \frac{P}{\lambda},
\]

while continuity of \( C' \) there ensures that

\[
AF'(z_2) = E(G)F'(z_2) + G \left\{ F'(z_2) \ln z_2 + \frac{F(z_2)}{z_2} + \zeta_2(z_2) \right\}.
\]

After the appropriate algebraic manipulations, the following expressions are obtained:

\[
G = P \left\{ \lambda F(z_2) \left[ \frac{\zeta_2(z_2)}{F'(z_2)} - \frac{\zeta_1(z_2)}{F(z_2)} + \frac{F(z_2)}{F'(z_2)} \right] \right\}^{-1},
\]

\[
E = -\frac{P\{(F(z_1))/z_1 + \zeta_2(z_1) + F'(z_1) \ln z_1\}}{F'(z_1)\{\lambda F(z_2)[(\zeta_2(z_2))/(F'(z_2)) - (\zeta_1(z_2))/(F(z_2)) + (F(z_2))/(F'(z_2))]\}},
\]

and

\[
A = E + G \left\{ \ln z_2 + \frac{F(z_2)}{z_2 F'(z_2)} + \frac{\zeta_2(z_2)}{F'(z_2)} \right\}.
\]

**FURTHER MATHEMATICAL COMMENTS**

The parameters \( a \) and \( b \) in the hypergeometric functions will be real if

\[
R \leq \frac{1}{2} \sqrt{\frac{D}{\lambda}} = R_c
\]

and will be complex conjugates otherwise. The question may be reasonably asked: are there any *physical* differences associated with these two cases? Obviously, the demarcation occurs when the
radius of the sphere is equal to a characteristic length \( R_c \) defined above by the relative effects of GF diffusion and depletion. It is readily verified that the hypergeometric function \( _2F_1(a, b; c; z) \) is real even when \( a \) and \( b \) are complex conjugates, so the differences between the two cases may be subtle. It is of interest to note that a similar situation occurs in a completely unrelated context: that of wave propagation in a “magnetoatmosphere”, i.e., a compressible magnetofluid in an external gravitational field [5]. There it was found that when \( a \) and \( b \) are real, the resulting wave motion is nonpropagating (or evanescent) in the vertical direction; waves propagating with a component of oscillation in the vertical direction correspond to complex conjugate values for \( a \) and \( b \). This may well imply that the solutions for the present problem have a different convexity structure depending on the nature of these two parameters, possibly because the counterpart of “evanescent modes” in this context is the exponentially decaying concentration of GF away (i.e., as \( \theta \) increases) from the source region in the wound. This is certainly to be expected in view of the numerical results found in [2,3]. Obviously, curvature effects are expected to be more significant when \( R < R_c \) which indicates that \( a \) and \( b \) are real quantities. Another approach is to consider \( R_c = R_c(D, \lambda) \). Suppose that we imagine a sequence of models in which initially \( R > R_c \), but in which \( D \) is slowly increased (or \( \lambda \) is decreased) from model to model. Eventually, \( R_c \) will exceed \( R \) and the curvature effects may become relatively significant. It is clearly of interest to determine more detailed criteria in which the wound size relative to \( R \) is present, explicitly or implicitly. Subsequent numerical work may reveal such dependence.

HEALING CRITERION

The criterion for healing to occur at the wound edge is that \( C(z_1) \geq \eta \), where \( \eta \) is a threshold concentration of GF, below which healing of the wound (i.e., bone regeneration) will not occur, according to the assumptions of the model. Thus, using equation (10), this condition may be written as

\[
\frac{(F(z_1))/z_1 + \zeta_2(z_1) + F'(z_1) \ln z_1}{F'(z_1)} \leq 1 - \frac{1}{n} \quad (18)
\]

or

\[
\frac{(F(z_1))/z_1 + \zeta_2(z_1) + F'(z_1) \ln z_1}{F'(z_1)} \leq 1 - \frac{1}{n}, \quad (19)
\]

where

\[
n = \frac{P}{\lambda \eta} \quad (20)
\]

is a measure of the effectiveness of the healing process at the wound edge. As noted above, it is desirable to obtain conditions for wound healing which can be understood as a function of the wound radius (across the surface of the bone) as a function of the size of the spherical bone. While this was possible in a one-dimensional planar model (and to a certain extent in a planar two-dimensional model also), the sheer complexity of the above analysis indicates that further numerical work is necessary to elucidate this dependence [6].

REFERENCES