

# Travelling Waves in Wound Healing

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**Abstract.** We illustrate the role of travelling waves in wound healing by considering three different cases. Firstly, we review a model for surface wound healing in the cornea and focus on the speed of healing as a function of the application of growth factors. Secondly, we present a model for scar tissue formation in deep wounds and focus on the role of key chemicals in determining the quality of healing. Thirdly, we propose a model for excessive healing disorders and investigate how abnormal healing may be controlled.

## 1. Introduction

Recent advances in molecular and cellular biology have resulted in the rapid development of experimental research into the biochemical mechanisms underlying the process of wound healing. Mathematical modelling can play a crucial role by providing a theoretical framework within which these experimental results can be analysed and by suggesting novel biological mechanisms which may lead to new experimental approaches. Such models also provide experimentally testable predictions on the outcome of the healing response and how this depends on key biological parameters.

In this paper we illustrate three different ways in which the study of travelling waves contributes to understanding the biology of wound healing. In Section 2, we consider the problem of surface wound healing in the cornea. Here, wound healing occurs due to a wave of cells moving into the wounded area, in response to the secretion of chemicals known as growth factors. The model is a coupled system of nonlinear partial differential equations which describes cell motion and division in response to epidermal growth factor (EGF). We use the model to investigate two important clinical questions, namely, what is the source of EGF, and how effective will topical application of growth factors be in speeding up healing.

In Section 3 we consider the formation of scars due to wound healing. Not only are scars disfiguring, they also result in a weakness in the skin which can easily suffer more damage. In this case, then, the role of modelling is to try to understand how the quality of

healing can be enriched. One property of scar tissue is that the relative amounts of specific collagen fibres within the scar are different to that of normal tissue. We present a model which focuses on the interaction of key growth factors with the collagens in order to predict how the quality of healing changes in response to the addition of various growth factors.

In Section 4, we consider abnormal healing responses which evolve to fibrocontractive diseases, of which excessive dermal scars are inadequately-understood clinical examples. By focusing on the coupled dynamics of regulatory growth factors and fibroblastic cells, we investigate an existing model of dermal healing in order to gain insight into some invasive and regressive phenomena associated with fibrocontractive diseases. Spatio-temporal variations in key parameters may be crucial, leading to novel predictions on the development and control of these healing disorders.

## 2. Corneal Wound Healing

Cell migration and proliferation are central to the healing of wounds in the corneal epithelium (CLARK, 1989). Biological evidence suggests that both processes are regulated by epidermal growth factor (EGF), a large protein whose receptor is expressed abundantly on epithelial cells (MARTIN *et al.*, 1992). The source of EGF is an area of recent controversy. We consider the possibility that the exposed underlying tissue within the wound acts as an additional source to the overlying tear film layer, and then investigate the effects of topical application.

We propose a reaction-diffusion model to investigate the relative importance of the stimulatory affects of EGF on migration and cell division (see DALE *et al.*, 1994a for full details). We model cell movement by Fickian diffusion to capture cells moving down gradients in cell density due to contact inhibition, and we assume that the cell diffusion coefficient increases linearly with the EGF concentration. We take the EGF diffusion coefficient to be a positive constant,  $D_c$ . Following a number of previous authors, we use a logistic growth form for the cell mitotic term (SHERRATT and MURRAY, 1990, 1992) and represent the chemical control of mitosis by an increasing function  $s(c)$ , where  $c(\underline{r}, t)$  is the EGF concentration at position  $\underline{r}$  and time  $t$ . Sloughing of the outermost epidermal cells is responsible for natural cell loss, and we take this to be a first order process. Decay of active EGF is due to a combination of natural decay and cellular degradation; we assume the former to be first order in  $c$  and model the latter by a saturating term denoting the rate of internal degradation of bound EGF receptors. The production of chemical by the cells is represented by the function  $f(n)$ , where  $n(\underline{r}, t)$  is the cell density, consisting of a constant source term due to the tear film (OHASHI *et al.*, 1989) and an additional term to account for chemical released by the exposed underlying tissue within the wound, which is rapidly degraded by cells at the wound edge (BARRANDON and GREEN, 1987; DUNN and IRELAND, 1984). Hence we take  $f(n) = A + B(n)$ , where

$$B(n) = \begin{cases} \sigma & \text{if } n < 0.2 \\ \sigma(2 - 5n) & \text{if } 0.2 \leq n \leq 0.4 \\ 0 & \text{if } n > 0.4 \end{cases}$$

and  $A$  and  $\sigma$  are positive constants. The unwounded levels of cell density and EGF concentration and the time scale used in the nondimensionalization process are determined directly from experimental data (CARPENTER and COHEN, 1976; KLYCE and BEUERMAN, 1988; SHERRATT and MURRAY, 1990). The governing non-dimensional equations are:

$$\frac{\partial n}{\partial t} = \overbrace{\nabla \cdot (D_n(c) \nabla n)}^{\text{Cell Migration}} + \overbrace{s(c)n(2 - n)}^{\text{Mitotic Generation}} - \overbrace{n}^{\text{Natural Loss}} \quad (1)$$

$$\frac{\partial c}{\partial t} = \underbrace{D_c \nabla^2 c}_{\text{Diffusion}} + \underbrace{f(n)}_{\text{Production by Cells}} - \underbrace{\frac{\mu n c}{(\hat{c} + c)}}_{\text{Decay of Active EGF}} - \delta c \quad (2)$$

where  $D_n(c) = \alpha c + \beta$ , and  $D_c$ ,  $\mu$ ,  $\delta$ ,  $\alpha$ ,  $\beta$  and  $\hat{c}$  are all positive constants. These can all be estimated from experimental data (DALE *et al.*, 1994a) and throughout this section we use the biologically realistic parameter set found in this way and given in Fig. 1. We consider the problem in one space dimension (a realistic approximation for the case of surface slash wounds, where cell fronts move in from either side of the slash to close the wound) and investigate the behaviour of travelling wave solutions to these equations which move from a region where the cell density and EGF concentration are at their unwounded levels,  $n = c = 1$  (as  $x \rightarrow -\infty$ ), into a region of no cell density,  $n = 0$ , with the EGF concentration at its wounded level,  $c = f(0)/\delta$  (as  $x \rightarrow +\infty$ ).

The biological observation of a front of cells moving into the wound at a constant speed suggests that the model solutions should have a travelling wave form. We solve the system numerically and observe fronts of cells and chemical moving into the wound domain with constant speed and shape (Fig. 1—here, by symmetry, we consider only half the wound and focus on how one cell front moves into the wound). Moreover, the speed of these travelling waves ( $\approx 64 \mu\text{m h}^{-1}$ ) compares very favourably with the healing rate of actinal corneal wounds ( $\approx 60 \mu\text{m h}^{-1}$ , see CROSSON *et al.*, 1986) for sufficiently large values of  $\sigma$  (DALE *et al.*, 1994a, b) and is robust to any small change in parameters. Qualitatively similar results are obtained when radially symmetric circular geometry is used rather than linear geometry. An important biological question is the relative importance of mitosis versus migration in the healing process. We investigate this by first reducing  $\alpha$  and  $\beta$ , which corresponds to a healing process dominated by mitosis and then reducing the mitotic generation term to consider migration dominated healing. Numerical simulations show that wounds can heal in the virtual absence of either mitosis or migration but with a much

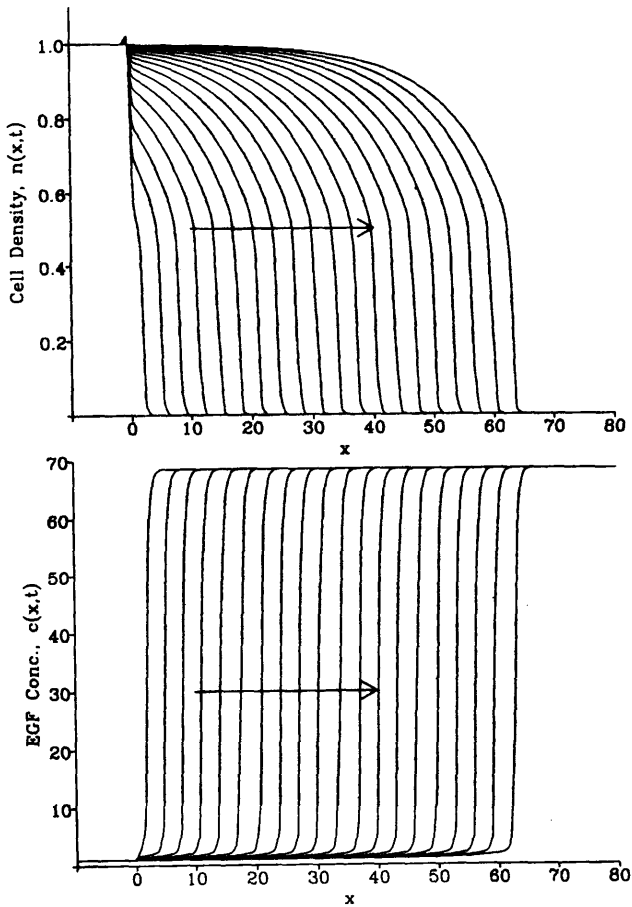


Fig. 1. Numerical solutions of the corneal model equations over an infinite domain showing cell density and EGF concentration as functions of space at equal time intervals. The parameter values are:  $\alpha = 0.01$ ,  $\beta = 0.05$ ,  $D_c = 25$ ,  $\mu = 13786$ ,  $\hat{c} = 3$ ,  $\delta = 110$ ,  $s(c) = 0.915c + 0.0851$ ,  $A = 3556$  and  $\sigma = 4000$ . The form of the solutions is a front of cells moving into the wound, with an associated wave of EGF.

slower rate of healing than is predicted experimentally. This emphasizes the importance of both processes for effective wound healing.

We investigate the dependence of the wave speed on the model parameters by introducing the coordinates,  $z = x - at$ , where  $a$  is the speed in the positive  $x$  direction and considering the eigenvalues of the fourth order system of travelling wave ordinary differential equations at the wounded and unwounded steady states. In the case of the single Fisher reaction-diffusion equation (FISHER, 1937), it is well known that the value of the parameter  $a$  at which the eigenvalues at the trivial steady state change from complex (stable spiral) to real (stable node) determines the speed of the travelling waves which

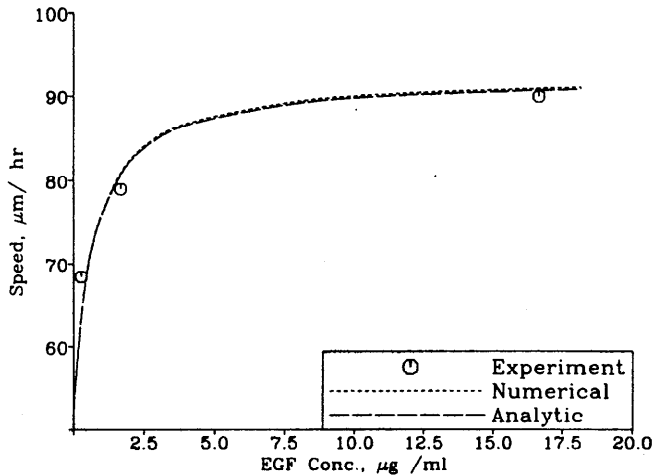


Fig. 2. The change in the rate of healing of 2 mm corneal surface wounds with topical application of EGF. The rate saturates as we increase the concentration of EGF, in agreement with experimental results. Numerically simulated and analytically derived wave speeds compare favourably. The parameter values are as in Fig. 1.

result from initial conditions with compact support. By analogy, we look for a corresponding change in character of the eigenvalues for our system. We find that the change in eigenvalues from complex to real occurs at a value of  $a$  which is very close to the wave speed observed in numerical solutions of the partial differential equation system.

For biologically realistic parameter values we can derive an analytical approximation  $a_{\text{crit}}$  to the minimum wavespeed

$$a_{\text{crit}} \approx \sqrt{8\beta s \left( \frac{A + \sigma}{\delta} \right)}.$$

The analytically determined wave speed is  $63.3 \mu\text{m h}^{-1}$  which compares extremely well with the numerically evaluated wave speed  $63 \mu\text{m h}^{-1}$ . An important biological implication of this result is that the rate of healing of corneal epithelial wounds can be increased by increasing the cell diffusion coefficient or the secretion rate of EGF. However, increasing the chemical diffusion coefficient does not have a significant effect.

We can use the above model to investigate the effect of topical application of EGF to a wound. We amend our model to include an external source term and a saturating mitotic generation term. Numerical simulations again evolve to travelling waves, the speed of which increases as we increase the external source term. The analytical expression for the wave speed is modified accordingly and hence we can predict the speed of healing of corneal surface wounds with topical application of any concentration of EGF

(Fig. 2). This result could easily be tested by further experiments.

In all the above simulations, we have ignored the effect of curvature of the cornea. However, one can show that, for biologically realistic parameter values, the effect of curvature is negligible (DALE, 1995).

### 3. Scar Tissue Formation

The process of adult dermal wound healing, in contrast to foetal healing, results in scar tissue formation. This initially reddish, slightly elevated scar gradually turns pale and becomes slightly recessed. Scar tissue is less functional than the surrounding uninjured tissue due to the lack of some key components (RUDOLPH *et al.*, 1992). In response to injury, fibroblasts migrate into the wound domain and synthesize chains of amino acids called procollagens (MCDONALD, 1988), the process being activated by growth factors such as Transforming Growth Factor  $\beta$  (TGF $\beta$ ) (APPLING *et al.*, 1989). Biological experiments show that the wound site contains enzymes which activate latent growth factors and initiate the stabilization of collagen precursors (MILLER and GAY, 1992). Fibroblasts also synthesize zymogens, which when activated form collagenases. Dermal tissue contains two main types of collagen, types I and III. Type III collagen decorates the surface of the type I collagen fibril so that a higher ratio of type III to type I results in thinner fibres (WHITBY and FERGUSON, 1991). Another key difference between scar and normal tissue is collagen fibre orientation. In normal skin, the collagen fibres in the dermis exhibit a basketweave-like arrangement. In adult scar tissue, the fibres are longer and thinner than in normal tissue, due to higher levels of type III collagen (MAST *et al.*, 1992), and the fibres are orientated perpendicular to the basement membrane (i.e. in the direction of the tension) (PEACOCK, 1984). We focus on the fibre density and ratio of collagen types I to III, indicating the diameter of collagen fibres, as a measure of scar tissue.

We propose a detailed mathematical model in terms of the effect of TGF $\beta$  on fibroblast synthesis of collagens and collagenases, with all the model variables being defined at position  $\underline{r}$  and time  $t$ . Fibroblasts,  $f$ , are the main cell type in the dermis, and the cells migrate into the wound domain from the surrounding unwounded dermal tissue and from the underlying subcutaneous tissue. The exact source of fibroblasts is an area of much biological controversy. We model the movement of fibroblasts from unwounded tissue by Fickian diffusion, with constant coefficient,  $D_1$ . In the absence of TGF $\beta$ , the cell population increases exponentially at low densities but saturates for high cell densities and we thus model fibroblast proliferation by a chemically enhanced logistic growth term. We assume that normal dermal fibroblasts die at a constant rate,  $A_4$ .

$$\frac{\partial f}{\partial t} = \overbrace{D_1 \nabla^2 f}^{\text{Migration}} + \overbrace{(A_1 + A_2 \beta_1 + A_3 \beta_3) f \left(1 - \frac{f}{k_1}\right)}^{\text{Mitotic Generation}} - \overbrace{A_4 f}^{\text{Natural Loss}}.$$

In our model, we consider only two isoforms, TGF  $\beta_1$ , (representing both 1 and 2) and TGF  $\beta_3$ , with concentrations  $\beta_1$  and  $\beta_3$  respectively. It has been shown that these chemicals increase fibroblast proliferation and collagen synthesis (KRUMMEL *et al.*, 1988) and we incorporate this into the model as in the above equation. Latent TGF  $\beta_1$  and TGF  $\beta_3$ , concentrations,  $l_1$  and  $l_3$ , respectively, diffuse freely and we assume constant diffusion coefficients  $D_2$  and  $D_3$ . The fibroblasts are stimulated by the growth factors and secrete latent forms of TGF  $\beta$  (WAKEFIELD *et al.*, 1988) but the production of growth factors does not increase unboundedly, hence the saturating functional form. Latent TGF  $\beta$  also undergoes an autocrine mechanism, whereby TGF  $\beta$  induces self-secretion (ROBERTS and SPORN, 1990). Latent TGF  $\beta$  has a short half-life and we model natural decay as a first order process (WAKEFIELD *et al.*, 1990). The concentration of latent growth factor is also decreased due to activation by specific enzymes.

$$\begin{aligned}\frac{\partial l_1}{\partial t} &= \overbrace{D_2 \nabla^2 l_1}^{\text{Diffusion}} + \overbrace{\frac{A_5 f l_1}{1 + A_6 l_3 + A_7 l_1}}^{\text{Production by Fibroblasts}} - \overbrace{A_8 l_1}^{\text{Natural Decay}} - \overbrace{A_{16} e_1 l_1}^{\text{Activation}} \\ \frac{\partial l_3}{\partial t} &= D_3 \nabla^2 l_3 + \frac{A_9 f l_3}{1 + A_{10} l_3} - A_{11} l_3 - A_{17} e_1 l_3.\end{aligned}$$

For  $\beta_1$  and  $\beta_3$  we again model chemical movement by simple Fickian diffusion, where  $D_4$  and  $D_5$  are constant. Experiments have shown that active TGF  $\beta$  undergoes rapid decay, which we model as a first order process for both isoforms (ROBERTS and SPORN, 1990). Biological research indicates that, during the inflammation stage, white blood cells release specific enzymes ( $e_i$ ,  $i = 1, 2, 3$ ) which activate growth factors, procollagens,  $p_1$  and  $p_3$ , and zymogens  $z_1$  and  $z_3$  (SINCLAIR and RYAN, 1994). These pools of enzyme are rapidly degraded during the healing process. We consider generic enzymes and use the law of mass action to model the activation of latent TGF  $\beta_1$  and 3 and type I and type III collagen and collagenases. The equations for  $\beta_1$  and  $\beta_3$  therefore, are,

$$\begin{aligned}\frac{\partial \beta_1}{\partial t} &= \overbrace{D_4 \nabla^2 \beta_1}^{\text{Chemical Diffusion}} + \overbrace{A_{12} e_1 l_1}^{\text{Activation}} - \overbrace{A_{13} \beta_1}^{\text{Natural Decay}} \\ \frac{\partial \beta_3}{\partial t} &= D_5 \nabla^2 \beta_3 + A_{14} e_1 l_3 - A_{15} \beta_3.\end{aligned}$$

The enzyme equations are

$$\begin{aligned}
 \frac{de_1}{dt} &= \overbrace{-e_1(A_{16}l_1 + A_{17}l_3)}^{\text{Activation of Latent Forms}} \\
 \frac{de_2}{dt} &= -e_2(A_{18}p_1 + A_{19}p_3) \\
 \frac{de_3}{dt} &= -e_3(A_{40}z_1 + A_{41}z_3).
 \end{aligned}$$

We focus on two types of procollagens, types I and III. The procollagen fibres do not diffuse within the wound milieu but are synthesized by the migrating fibroblasts (MILLER and GAY, 1992). In the absence of chemicals, we assume a constant secretion rate but experiments show upregulation of procollagen synthesis by active TGF  $\beta$  (APPLING *et al.*, 1989), hence the inclusion of a linear function of the active chemical concentrations. We assume procollagen fibres have a constant life-span and model natural decay as a first order process.

$$\begin{aligned}
 \frac{dp_1}{dt} &= \overbrace{(A_{20} + A_{21}\beta_1 + A_{22}\beta_3)f}^{\text{Secretion by Fibroblasts}} - \overbrace{A_{23}p_1}^{\text{Natural Decay}} - \overbrace{A_{18}e_2p_1}^{\text{Conversion by Enzyme}} \\
 \frac{dp_3}{dt} &= (A_{24} + A_{25}\beta_1 + A_{26}\beta_3)f - A_{27}p_3 - A_{19}e_2p_3.
 \end{aligned}$$

There is no experimental evidence for significant movement of intact collagen fibres and hence we assume no spatial dependence. We use the law of mass action to model the activation of procollagen fibres to collagen fibrils,  $c_1$  and  $c_3$ . Collagenases I and III gradually digest collagen I and III, respectively. There is little experimental evidence for the processes involved in the degradation. Therefore, for simplicity we assume a linear form.

$$\begin{aligned}
 \frac{dc_1}{dt} &= \overbrace{A_{28}p_1e_2}^{\text{Activation}} - \overbrace{A_{29}s_1c_1}^{\text{Degradation}} \\
 \frac{dc_3}{dt} &= A_{30}p_3e_2 - A_{31}s_3c_3.
 \end{aligned}$$

Zymogen I and III are not known to undergo any diffusion. The zymogens are synthesized and secreted by the migrating fibroblasts but the secretion is inhibited by the presence of active TGF  $\beta$  (JEFFREY, 1992). The natural decay of zymogens is taken to be first order.



$$\begin{aligned}\frac{dz_1}{dt} &= \frac{\overbrace{A_{32}}^{\text{Secretion by Fibroblasts}}}{1 + A_{33}\beta_1 + A_{34}\beta_3} f c_1 - \overbrace{A_{35}z_1}^{\text{Natural Decay}} - \overbrace{A_{40}e_3z_1}^{\text{Activation}} \\ \frac{dz_3}{dt} &= \frac{A_{36}}{1 + A_{37}\beta_1 + A_{38}\beta_3} f c_3 - A_{39}z_3 - A_{41}e_3z_3.\end{aligned}$$

Collagenases I and III, densities  $s_1$  and  $s_3$ , respectively, are the active forms of zymogens, which arise via enzymatic activation:

$$\begin{aligned}\frac{ds_1}{dt} &= \overbrace{A_{42}z_1e_3}^{\text{Activation of Zymogen}} - \overbrace{A_{43}s_1}^{\text{Natural Degradation}} \\ \frac{ds_3}{dt} &= A_{44}z_3e_3 - A_{45}s_3.\end{aligned}$$

The estimation of dimensional parameter values is essential for biologically realistic model predictions. The governing equations contain a large number of parameters whereas there is a limited source of experimental data. However, we know the time scale of the healing process and can hence obtain order of magnitude estimates for some of the remaining parameters.

Numerical solutions of the model equations for the foetal case, over a large spatial domain, show waves of cells and growth factors moving into the wound with constant speed and shape, with the steady states corresponding to the unwounded nondimensional level (Fig. 3). The solution profiles for collagen I and III also show fronts moving into the wound domain, evolving to new steady state levels for both collagen I and III, with a ratio of 3:1, in agreement with the unwounded dermal tissue. The collagenase equations show wave pulses moving into the wounded domain and both collagenase I and III decay to the zero dermal level. Solutions for the adult case again exhibit travelling waves, but in this case the ratio of collagen I to III is 3.57:1, which corresponds to thicker, more densely packed collagen fibres and thus scar tissue formation. We model the addition of TGF  $\beta$  by altering the initial conditions, and investigating the effect on the final level of collagen I and III. Topical application of TGF  $\beta$  increases the amount of collagen I compared to type III, thus causing thicker fibres and a reduction in scar tissue. Furthermore, numerical solutions show that early addition of growth factor is essential for effective control of scar tissue formation.

Scar tissue formation following trauma or surgery is a major clinical problem, often resulting in defective growth or functional impairment. Experimental understanding of foetal wounds has increased over the past 15 years and this has led to the possibility of

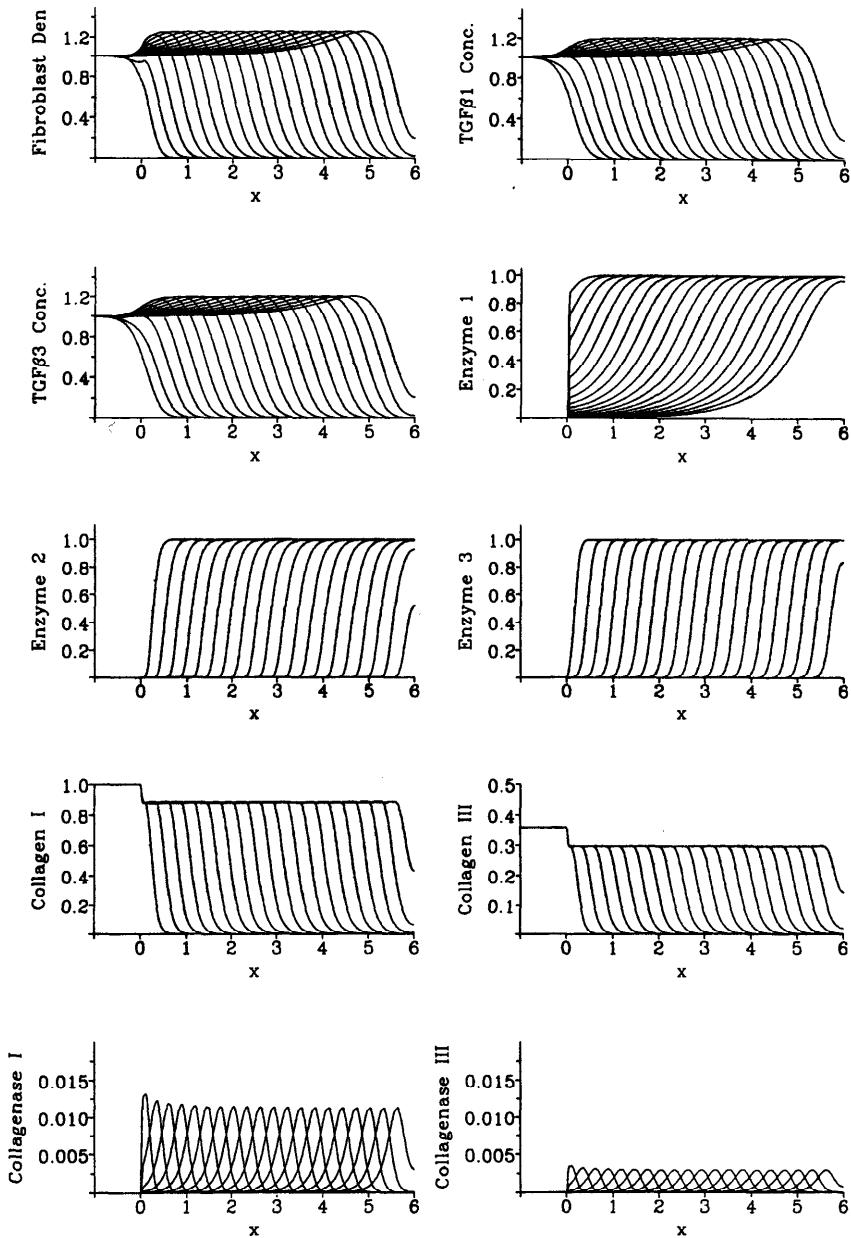


Fig. 3. Numerical solution at equal time intervals of the system of reaction diffusion equations in one dimension space, with zero flux boundary conditions. We impose step function initial conditions, with the model variables at their normal dermal level outside the wound domain. The parameters are  $D_1 = 0.015$ ,  $D_2 = 0.25$ ,  $D_3 = 0.25$ ,  $A_1 = 1.4$ ,  $A_2 = 200$ ,  $A_3 = 200$ ,  $A_4 = 0.7$ ,  $A_5 = 100$ ,  $A_6 = 5$ ,  $A_7 = 4$ ,  $A_8 = 10$ ,  $A_9 = 100$ ,  $A_{10} = 9$ ,  $A_{11} = 10$ ,  $A_{12} = 1$ ,  $A_{13} = 400$ ,  $A_{14} = 1$ ,  $A_{15} = 400$ ,  $A_{16} = 0.1$ ,  $A_{17} = 0.1$ ,  $A_{18} = 1$ ,  $A_{19} = 1$ ,  $A_{20} = 3$ ,  $A_{21} = 600$ ,  $A_{22} = 1400$ ,  $A_{23} = 1$ ,  $A_{24} = 3$ ,  $A_{25} = 600$ ,  $A_{26} = 800$ ,  $A_{27} = 1$ ,  $A_{28} = 1.8$ ,  $A_{29} = 1$ ,  $A_{30} = 0.6$ ,  $A_{31} = 1$ ,  $A_{32} = 1$ ,  $A_{33} = 400$ ,  $A_{34} = 1200$ ,  $A_{35} = 10$ ,  $A_{36} = 1$ ,  $A_{37} = 1200$ ,  $A_{38} = 400$ ,  $A_{39} = 10$ ,  $A_{40} = 50$ ,  $A_{41} = 50$ ,  $A_{42} = 1.5$ ,  $A_{43} = 1$ ,  $A_{44} = 4.5$ ,  $A_{45} = 1$ ,  $k_1 = 2$ ,  $\mu_1 = 1$ ,  $\mu_2 = 1$ ,  $\mu_3 = 1$ . The field variables move into the wound as travelling waves and the ratio of collagen types I to III is 3:1.

$$\frac{\partial n}{\partial t} = \overbrace{\frac{\partial}{\partial x} \left[ D_n \frac{\partial n}{\partial x} - \frac{\alpha}{(\beta + c)^2} n \frac{\partial c}{\partial x} \right]}^{\text{cell movement}} + \overbrace{\sigma \left( 1 + \frac{Ac}{B + c} \right) n(1 - \mu n)}^{\text{proliferation}} - \underbrace{\nu n}_{\text{death}} \equiv f(n, c) \quad (3)$$

$$\frac{\partial c}{\partial t} = \underbrace{D_c \frac{\partial^2 c}{\partial x^2}}_{\text{diffusion}} + \underbrace{\frac{\kappa n c}{\gamma + c}}_{\text{production}} - \underbrace{\delta c}_{\text{decay}} \equiv g(n, c). \quad (4)$$

In this model, cell movement occurs via random locomotion in addition to chemotaxis, the movement of cells up chemical gradients. The chemical mediates cell chemotaxis, proliferation and its own production by the cells (OLSEN *et al.*, 1996). The system possesses equilibria  $(n, c) = (1, 0)$  and  $(n, c) = (n_p, c_p)$  where  $n_p > 1$  and  $c_p > 0$ , corresponding to unwounded dermis and to an excessive dermal pathology, respectively. Appropriate profiles for wound initial conditions are  $n_i(x) = H(x)$  and  $c_i(x) = n_{\text{init}}(1 + x^r)$ . The boundary conditions are zero flux at the wound centre and unwounded dermal values at infinity. All model parameter values are non-negative. See OLSEN *et al.* (1995) for full details.

Existence and local stability of equilibria of this caricature model may be evaluated explicitly, with global stability obtained by  $(n, c)$ -phase space analysis, as discussed in OLSEN *et al.* (1996). The stability structure of the system

$$\frac{dn}{dt} = f(n, c), \quad \frac{dc}{dt} = g(n, c) \quad (5)$$

may thus be deduced. Figure 4 illustrates a typical bifurcation diagram in which the equilibria are plotted against  $\kappa$  (related to the maximal rate of growth factor production by fibroblastic cells), whose value in relation to  $\gamma$  and  $\delta$  (both of which we assume to be fixed) is pivotal—for example, the dermal steady state is locally stable if and only if  $\kappa < \gamma\delta$ .

With  $\kappa$  increasing from zero, two important primary bifurcations occur. First, at  $\kappa = \kappa_1$  (which may be determined analytically (OLSEN *et al.*, 1996)), where the stability of the dermal steady state,  $(1, 0)$  changes from global to local and two new equilibria,  $(n_{\pm}, c_{\pm})$ , appear—the more positive of which is locally stable and the lesser of which is unstable (Fig. 4)—whose values are explicitly available. Second, at  $\kappa = \kappa_2 = \gamma\delta$ , where  $(1, 0)$  loses stability,  $(n_-, c_-)$  ceases to exist and  $(n_+, c_+)$  becomes the globally stable equilibrium. Note that “existence” and “global” are understood in the context that attention is restricted to the subspace  $(n, c) \geq (0, 0)$  componentwise.

Thus, the qualitative dynamics of the system may be classified into three intervals (see Fig. 4):  $I_{\text{norm}} = (0, \kappa_1)$ ,  $I_{\text{bist}} = (\kappa_1, \kappa_2)$  and  $I_{\text{path}} = (\kappa_2, \infty)$ . If  $\kappa \in I_{\text{norm}}$ , then normal healing dynamics are expected. If  $\kappa \in I_{\text{path}}$ , then a transition to the pathological steady state  $(n_+, c_+)$

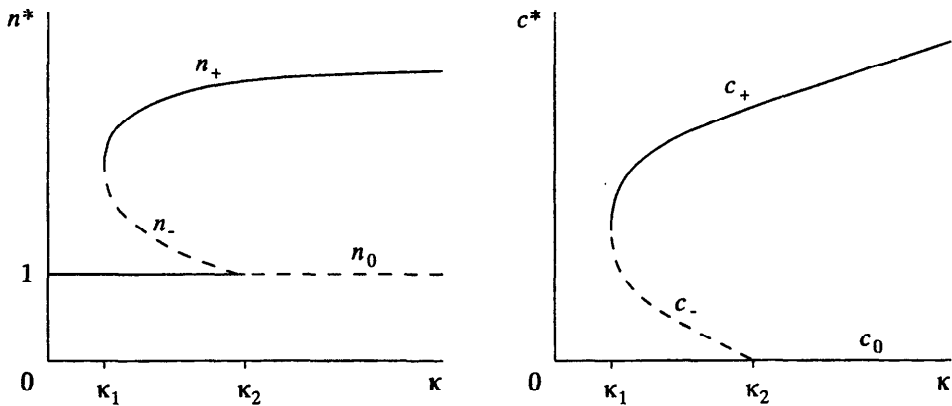


Fig. 4. Qualitative bifurcation diagrams showing the dependence of the steady states,  $(n^*, c^*)$ , of the system (5) on the parameter  $\kappa$ . Solid curves represent (locally) equilibria and broken curves represent unstable equilibria. The dermal steady state,  $(n_0, c_0)$ , and the pathological steady states,  $(n_+, c_+)$  are indicated.

occurs. For  $\kappa \in I_{\text{bist}}$ , however, the dynamics are not so straight-forward and depend on initial conditions, other parameter values, and spatial terms in the model. We investigate the consequences of this bistability and hysteresis (see OLSEN *et al.* (1996) for details) by numerical simulation. Numerical solutions of Eqs. (1) and (2) with  $\kappa \in I_{\text{bist}}$  and  $c_{\text{init}} < c_-$  yield normal spatiotemporal healing dynamics, in which cells repopulate the wound space and the active chemical profile decays back to zero (Fig. 5(a)). Pathological dynamics, however, occur when  $\kappa \in I_{\text{path}}$ , exhibiting travelling wave-like solutions (Fig. 5(b)).

From the dynamics of the ODE system, (5), we have acquired substantial information on the initiation of travelling wave solutions of (3) and (4). Wave initiation occurs in the vicinity of the wound edge, an inbound pathological wave fills the wound space and an outbound wave enables the pathology to progress into previously unaffected skin over a timescale of days (Fig. 5(b)).

Next, we analyse this behaviour by seeking travelling wave solutions of Eqs. (3) and (4) of the form  $n(x, t) = N(z)$  and  $c(x, t) = C(z)$ , where  $z = x - at$  and  $a$  is the wave velocity. This change of variables yields a fourth-order system of coupled ordinary differential equations for  $N$ ,  $C$ ,  $U = dN/dz$  and  $V = dC/dz$  in terms of the travelling wave coordinate,  $z$ .

Denoting the dermal equilibrium in  $(N, C, U, V)$ -space by  $\mathbf{Q}_0 = (1, 0, 0, 0)$  and the pathological equilibrium by  $\mathbf{Q}_+ = (n_+, c_+, 0, 0)$ , a necessary condition for travelling wave transitions from  $\mathbf{Q}_0$  to  $\mathbf{Q}_+$  is the existence of a heteroclinic trajectory from  $\mathbf{Q}_+$  to  $\mathbf{Q}_0$  in  $(N, C, U, V)$ -space. Linear stability analysis of this system reveals the existence of a stable local manifold at  $\mathbf{Q}_0$  and an unstable local manifold at  $\mathbf{Q}_+$  for  $\kappa \in I_{\text{bist}} \cup I_{\text{path}}$ . Therefore, with the (necessary) conjecture that such a heteroclinic trajectory exists, travelling wave solutions are possible. A further constraint is that this trajectory lies entirely within the subspace  $(N, C) \geq (0, 0)$ . This is satisfied when  $\kappa \in I_{\text{bist}}$ , but if  $\kappa \in I_{\text{path}}$ , then this condition

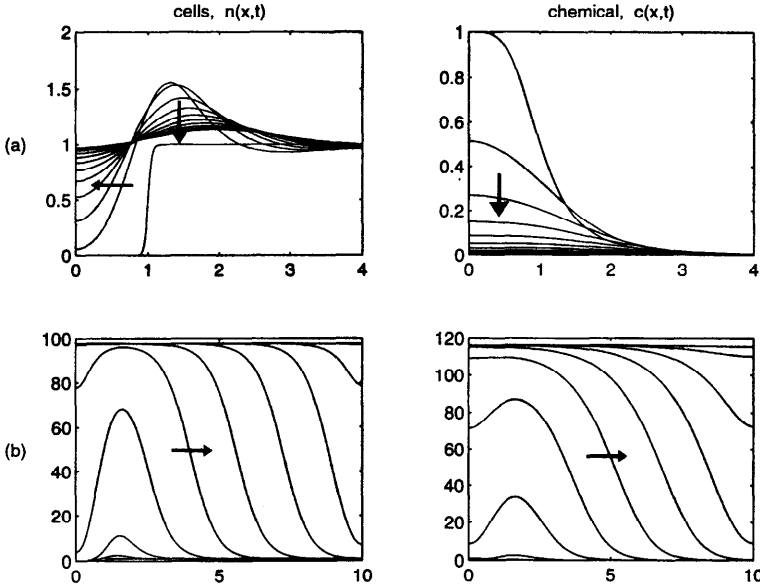


Fig. 5. Numerical solution of the caricature model given by Eqs. (3) and (4) with boundary and initial conditions as in the text. (a) Normal healing: profiles of cell density and chemical concentration are plotted against distance,  $x$ , from the wound centre at time  $t = 0$  and at ten successive time intervals of 4 days (cells) and 1 day (chemical). Parameter values are:  $D_n = 0.02$ ,  $\alpha = 0.05$ ,  $\beta = 0.2$ ,  $\sigma = 0.02$ ,  $A = 44.5$ ,  $B = 1$ ,  $\mu = 0.01$ ,  $\nu = 0.0198$ ,  $D_c = 0.2$ ,  $\kappa = 0.1$ ,  $\gamma = 1$ ,  $\delta = 0.5$ ,  $c_{\text{init}} = 1$  and  $r = 4$ . Thus,  $n_0 = 1$  and  $\kappa_2 = 0.5$ . (b) Pathological response (characterised by grossly excessive cellular and chemical levels which propagate from near the original wound margin): as in (a) but with successive time intervals of 4 days for both the cell and chemical profiles, and  $\kappa = 0.6 > \kappa_2$ . (c) Cessation (note that the spatial extent of the pathology extends beyond the value  $x_b = 4$ ; see text): as in (b) but  $\kappa(x) = 0.6$  if,  $0 \leq x \leq 4$  and  $\kappa(x) = 0$  if,  $x > 4$ . (d) Regression (the solid arrows indicate wave progression and empty arrows mark the subsequent regression): as in (b) but  $\kappa(t) = 0.6$  if  $0 \leq t \leq 20$  and  $\kappa(t) = 0$  if  $t > 20$ .

imposes a lower bound on the wave speed, namely  $a \geq a_{\min} = 2\sqrt{D_c(\kappa\gamma^{-1} - \delta)}$ .

Analogous results are obtained if one of the cell fluxes is neglected (by setting  $D_n$  or  $\alpha$  to zero). If the chemical diffusion coefficient,  $D_c$ , is zero then the inferences differ only in that no minimum wave speed is stipulated for  $\kappa \in I_{\text{path}}$ .

Having explored aspects of the initiation and progression of pathological states as a result of abnormal healing, we turn to the issue of how these diseases become spatially limited. Hypertrophic scars rarely exceed the original lateral wound confines, and keloids, whilst invasive, do not advance indefinitely (MURRAY and PINNELL, 1992; EHRLICH *et al.*, 1994).

Within the context of our mathematical model, stable cessation of the disease corresponds to a stable, inhomogeneous steady state solution of Eqs. (3) and (4) in which the dermal equilibrium is unstable in some neighbourhood of  $x = 0$  and locally stable

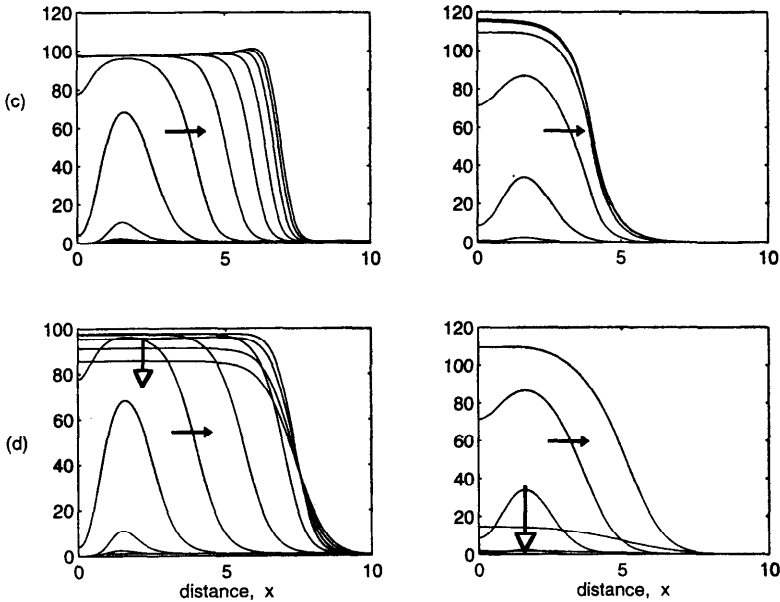


Fig. 5. (continued).

outside this region. Such solutions may exist if some parameters are spatially inhomogeneous, and as above, we focus on  $\kappa$  here. In fact, the requirement is that there exists some  $x_b$ , say, such that  $\kappa(x) \in I_{\text{norm}}$  for all  $x > x_b$ . Note that although the dermal equilibrium is locally stable for  $\kappa \in I_{\text{bist}}$ , the advancing wave in the region  $x < x_b$  ensures that a sufficient perturbation occurs to shift the dynamics into the basin of attraction of  $(n_+, c_+)$ , and the only effect is movement along this stable pathological branch (see Fig. 4), with corresponding changes in the wave profile and speed.

Simulations illustrate that the advancing wave is interrupted in the vicinity of the point  $x_b$  where  $\kappa$  decreases through the bifurcation value  $\kappa_1$  (Fig. 5(c)). Significantly, wave “overshoot” occurs due to the diffusive chemical flux which is responsible for the smooth rather than abrupt decrease in the steady state value of  $c$  at  $x_b$ .

Whilst fibrocontractive diseases always become spatially bounded, they rarely stabilize completely as suggested by the spatially varying steady state discussed above (Fig. 5(c)), and are often (albeit unpredictably) observed to slowly regress over a time scale of months or years towards a normally-healed scar (MURRAY and PINNELL, 1992; ASMUSSEN and SÖLLNER, 1993).

Here, we consider temporal parametric heterogeneity to suggest new approaches towards understanding disease regression. By similar arguments to those above, we expect disease not only to cease, but to regress back towards the dermal state if  $\kappa$  assumes a form such that  $\kappa(t) \in I_{\text{norm}}$  for all  $t > t_r$ , say, since the dermal state becomes the globally stable equilibrium. These predictions are confirmed numerically (Fig. 5(d)), again demonstrating spatial overshoot of the wave beyond the critical point at which  $t = t_r$ . Note

that regression towards the normal dermal state is monotonic, and rapid for the active chemical profile but considerably slower for the cellular response, consistent with clinical observations.

As for cessation, a decrease in the value of  $\kappa$  within the interval  $I_{\text{bist}}$  is insufficient to cause disease regression and merely effects a shift in the dynamics to a modulated pathological state. Also, wave overshoot does not occur if  $D_c = 0$ .

This work demonstrates how spatiotemporal parameter variations in the chemical dynamics may be crucial to the outcome of the healing process. By focussing on  $\kappa$ , the parameter related to the maximal rate of active growth factor production by fibroblastic cells, we have shown that imbalances in the chemical dynamics may trigger a healing pathology, and that a redress of this imbalance is required for the disease to regress. This is a new concept—extensive research has been directed towards cell phenotypes, the roles of tissue metabolites (such as oxygen) and extracellular matrix molecules (such as collagen) in fibrocontractive diseases (SKALLI *et al.*, 1989; MURRAY and PINNELL, 1992; EHRLICH *et al.*, 1994), but our propositions on the roles of growth factor dynamics are novel.

We hypothesize that in normal adult human dermis, the effective  $\kappa$  lies in the interval  $I_{\text{norm}}$ . A consequence of wounding may be to enhance  $\kappa$  in some neighbourhood of the wound centre over the time course of healing. This could be due to other wound substances which increase the rate at which cells produce growth factors or decrease the rate of their removal by the tissue (see OLSEN *et al.* (1996) for a more detailed discussion). If  $\kappa$  is enhanced sufficiently, then a pathological response may be triggered, which is likely to stabilize and/or regress with time. An alternative scenario, in which an increase in  $\kappa$  into  $I_{\text{bist}}$  alone is insufficient to initiate pathological healing, could involve an excessive initial supply of active growth factors. This possibility may be relevant to burn wounds, in which the initial inflammatory response is very acute and hypertrophic scars are more prevalent (BOYKIN and MOLNAR, 1992; EHRLICH *et al.*, 1994). Our model also suggests how relatively minor injuries can trigger fibrocontractive diseases.

This work also indicates how spatiotemporal parameter variations can modify the pathological wave behaviour, potentially leading to new therapeutic strategies. Anti-pathogenic measures could aim to reduce the value of  $\kappa$  (or equivalently, raise  $\gamma$  or  $\delta$ ) in order to halt the advance of, and possibly induce regression of the disease. Specifically, such treatments might involve biochemical inhibition of fibroblastic cells from producing active growth factors in tightly-controlled spatial regions at appropriate times (see OLSEN *et al.* (1996) for further details).

Finally, we comment that all of the fundamental results and conclusions of the caricature model can also be inferred in the full model, which also predicts the mechanical consequences of these excessive healing disorders (OLSEN *et al.*, 1996).

## 5. Discussion

In this paper we have shown how travelling waves play a vital role in the process of wound healing. We have considered three different problems and have shown how the

models proposed suggest clinical treatments. In Section 2, we quantified how the speed of corneal wound healing increases with the application of epidermal growth factor, and in Section 3, we investigated the effect of TGF  $\beta$  on the relative amounts of collagen I and III, thus determining the amount of scarring in foetal and adult wounds. In Section 4, we analysed a model for dermal healing to elucidate the underlying dynamics of excessive healing and to suggest new strategies for the clinical treatment of these diseases.

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