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A MECHANOCHEMICAL MODEL FOR NORMAL AND ABNORMAL DERMAL WOUND REPAIR

LUKE OLSEN, † PHILIP MAINI† and JONATHAN SHERRATT‡

†Centre for Mathematical Biology, Mathematical Institute, 24-29 St Giles', Oxford, OX1 3LB, UK; and
‡Nonlinear Systems Laboratory, Mathematics Institute, University of Warwick, Coventry, CV4 7AL, UK

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1. INTRODUCTION

The healing of full-thickness excisional skin wounds in adult mammals involves a complex sequence of inter-regulatory biological processes (see [1] for review). A key process involves the movement of cells into the wound in response to mechanical and chemical cues. These cells exert traction forces which pull the wound together, leading to normal wound healing, in which the skin is in a contracted state. Abnormal regulation of this process may result in a number of healing disorders. One such disorder results in increased tissue in the wound leading to fibroproliferative diseases such as keloid scarring. In this paper we consider the general mathematical model framework for dermal wound healing proposed in [2]. We briefly describe the model in Section 2 and review its properties. In Section 3 we show, by looking at a simpler version of the model, that it can generate contracted steady states. In Section 4, we investigate another version of the model to focus on fibroproliferative diseases.

2. MECHANOCHEMICAL MODEL FRAMEWORK

Here, we briefly present a mechanochemical model for dermal wound healing based on the framework developed by Murray and coworkers (see [3] for review). For full details and experimental justification for each term, see [2]. The full model consists of five field variables and, for simplicity, we present here only the one-dimensional version of the model. The model considers two distinct cell types – fibroblasts and myofibroblasts, denoted by $n(x,t)$ and $m(x,t)$, respectively, where x is space and t is time. It is assumed that fibroblasts secrete a growth factor, $c(x,t)$, and move into the wound in response to gradients in c. The fibroblast equation takes the form:

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x}\left[\chi(c,n)\frac{\partial c}{\partial n} + n\frac{\partial u}{\partial t}\right] + R(c)n\left(1 - \frac{n}{K}\right) - \frac{k_1 cn}{C_k + c} + k_2 m - d_n n. \tag{2.1}$$

The first three terms on the right hand side model the following contributions to cell flux: cell diffusion with constant diffusion coefficient, D_n, cell chemotaxis with chemotactic sensitivity $\chi(c,n)$, and convection in response to the displacement, $u(x,t)$, of the extracellular matrix (ECM) substratum on which cells move. The next four terms describe, respectively, logistic cell growth with linear rate enhanced by growth factor, conversion to myofibroblast phenotype mediated by growth factor, conversion from myofibroblast to fibroblast cell type, and cell death.

The myofibroblasts satisfy the equation

$$\frac{\partial m}{\partial t} = \frac{\partial}{\partial x}\left[-m\frac{\partial u}{\partial t}\right] + \epsilon_r R(c)m\left(1 - \frac{m}{K}\right) + \frac{k_1 cn}{C_k + c} - k_2 m - d_m m, \tag{2.2}$$

where it is assumed that the dominant contribution to myofibroblast flux is convection, and that mitosis takes the same form as that for fibroblasts to within a scale factor ϵ_r.

The growth factor, c, diffuses, is convected by the ECM, and is secreted and degraded by both cell types. Therefore, it satisfies the equation

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + \frac{\partial}{\partial x}[-c\frac{\partial u}{\partial t}] + S(n, m, c) - d_c c. \tag{2.3}$$

The ECM, density $\rho(x,t)$, moves primarily by convection and satisfies the equation

$$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x}[-\rho\frac{\partial u}{\partial t}] + B(n, m, c, \rho), \tag{2.4}$$

where $B(n, m, c, \rho)$ represents ECM biosynthesis and degradation.

Finally, modelling the ECM as a linear, isotropic, viscoelastic material, the displacement u satisfies the force balance equation

$$\mu\frac{\partial^3 u}{\partial x^2 \partial t} + E\frac{\partial^2 u}{\partial x^2} + \frac{\partial \tau(n, m, \rho)}{\partial x} = F(\rho, u), \tag{2.5}$$

where the first two terms on the left hand side model viscous and elastic forces, respectively, and the third term models cell traction forces. These forces are balanced by the body forces $F(\rho, u)$.

Equations (2.1)–(2.5), with appropriate initial and boundary conditions (see below), constitute the mechanochemical model framework. Using biologically realistic forms for the functions $\chi(c,n), R(c), S(n,m,c), B(n,m.c,\rho), \tau(n,\rho), F(\rho,u)$, and estimates derived from experimental data for the parameters $D_n, D_c, K, k_1, k_2, C_k, d_n, d_m, d_c, \epsilon_r, \mu$ and E, it can be shown that this model exhibits solutions for the decay of growth factor and rate of wound closure that closely agree with experimental results (see [2] for full details). Using a caricature model, we now proceed to analyse the possible contracted steady states exhibited by the model.

3. SPATIALLY VARYING CONTRACTED STEADY STATES

To consider the potential of the model framework (2.1)–(2.5) to exhibit spatially varying contracted steady states we consider a simpler version of the model of the form

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} + \frac{\partial}{\partial x}[-n\frac{\partial u}{\partial t}] + n(1-n) \tag{3.1}$$

$$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x}[-\rho\frac{\partial u}{\partial t}] \tag{3.2}$$

$$\mu\frac{\partial^3 u}{\partial x^2 \partial t} + E\frac{\partial^2 u}{\partial x^2} + \frac{\partial \tau(n, \rho)}{\partial x} = F(\rho, u). \tag{3.3}$$

Here, we have chosen to consider the purely mechanical aspects of the dynamics and have simplified the model by considering only one cell type, have non-dimensionalised the model so that the logistic growth term takes an algebraically simpler form, and assumed that there is negligible synthesis and degradation of ECM on the timescale of wound closure. This is a reasonable assumption to make in the stages prior to tissue remodelling.

By defining the initial wound space as $-1 \leq x \leq 1$ and using symmetry at $x = 0$ (the wound centre), we may restrict attention to the semi-infinite domain $0 \leq x < \infty$. The initial half-wound is set to unity by the scaling for x. The boundary conditions are thus

$$\frac{\partial n}{\partial x}(0,t) = \frac{\partial \rho}{\partial x}(0,t) = u(0,t) = 0 \quad \text{and} \quad n(\infty,t) = \rho(\infty,t) = 1, \quad u(\infty,t) = 0.$$

The initial conditions are

$$n(x,0) = H(x-1), \quad \rho(x,0) = \rho_i + (1-\rho_i)\,H(x-1), \quad u(x,0) = 0,$$

where the initial ECM density ρ_i inside the wound is due to the early, provisional wound matrix which is low in collagen and satisfies $0 < \rho_i < 1$, and $H(\cdot)$ is the Heaviside step function.

Consider now the healed steady state, $n = 1$. Linearising (3.2) about the initial profile, we have

$$\rho \approx \begin{cases} \rho_i\,(1 - \partial u/\partial x)\,, & 0 \le x < 1 \\ 1 - \partial u/\partial x, & x > 1 \end{cases} \tag{1}$$

as suggested by the small-strain restriction (since the convective flux should be small). Substituting this into the steady state equation for u, we have a second order ordinary differential equation for u, which we can write in the (rescaled) form

$$u' = v \tag{2}$$

$$v' = \begin{cases} \dfrac{s\rho_i u(1-v)}{1 - \rho_i \mathcal{T}[\rho_i(1-v)]}, & 0 \le x < 1 \\ \dfrac{su(1-v)}{1 - \mathcal{T}(1-v)}, & x > 1 \end{cases} \tag{3}$$

where $\mathcal{T}(\rho) \equiv \left.\frac{\partial \tau(n,\rho)}{\partial \rho}\right|_{n=1}$, and u satisfies the boundary conditions $u(0) = u(\infty) = 0$. He we have assumed that the body force, $F(\rho, u)$, is due to external tethering to the basement membrane and have modelled it by a linear spring, that is, $F(\rho, u) = su\rho$, where s is a constant.

Standard phase plane analysis of (3.4)–(3.5) shows that for $x > 1$, the origin is a saddle (centre) iff $\mathcal{T}(1) < 1\,(> 1)$. However, linear stability analysis of the partial differential equation system (3.1)–(3.3) shows that the healed steady state is stable iff $\mathcal{T}(1) < 1$. As this must be the case, we have that the origin of the ordinary differential equation system (3.4)–(3.5) is a saddle, and the boundary condition $u(\infty) = 0$ implies that the solution must converge towards the origin along the stable manifold as x tends to ∞. By tracing backwards in x from infinity along the stable manifold, the solution reaches a point in the (u, u')-phase plane corresponding to $x = 1$ where $u = u_1$, say. This must match the solution for $0 \le x < 1$.

Now, at the wound centre, $u(0) = 0$, but $v(0)$ is unspecified. Rather, it is determined by matching to the "outer" solution at $x = 1$. For $0 \le x < 1$, it can be shown that the origin can either be a saddle or a centre, depending on the form of the function $\tau(n, \rho)$ and the values of the parameters. If the origin is a saddle point, then the solution in $0 \le x < 1$ is expected to be either monotonic increasing with increasing gradient or monotonic decreasing with decreasing gradient. If the origin is a centre, then the solution in $0 \le x < 1$ may be oscillatory. Figure 1 illustrates the qualitative construction of such a solution and Figure 2 illustrates various theoretically-possible forms of steady state solutions. Modelling the traction term, $\tau(n, \rho)$, by $\tau(n, \rho) = \tau_0 n\rho/(T^2 + \rho^2)$, to account for the fact that traction forces depend on adhesion between cell surface receptors and binding sites on collagen fibres, but the ability of a cell to extend and retract protrusions within a collagen substrate is inhibited at relatively high collagen densities, where τ_0 and T are constant parameters, we have found, by numerical simulation, steady states for (3.1)–(3.3) of the form illustrated in Figure 2(a)–(e).

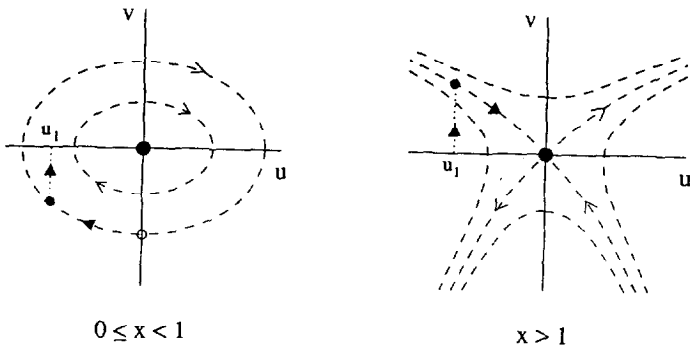

Fig. 1. Qualitative illustration of a possible solution trajectory as described in the text, showing a case in which the origin is a centre for $0 \le x < 1$ and a saddle point for $x > 1$ with $u(x) \to 0$ from below as $x \to \infty$. See also Figure 2(b) below. Dashed curves denote phase trajectories, with the contracted solution curve highlighted by solid arrows.

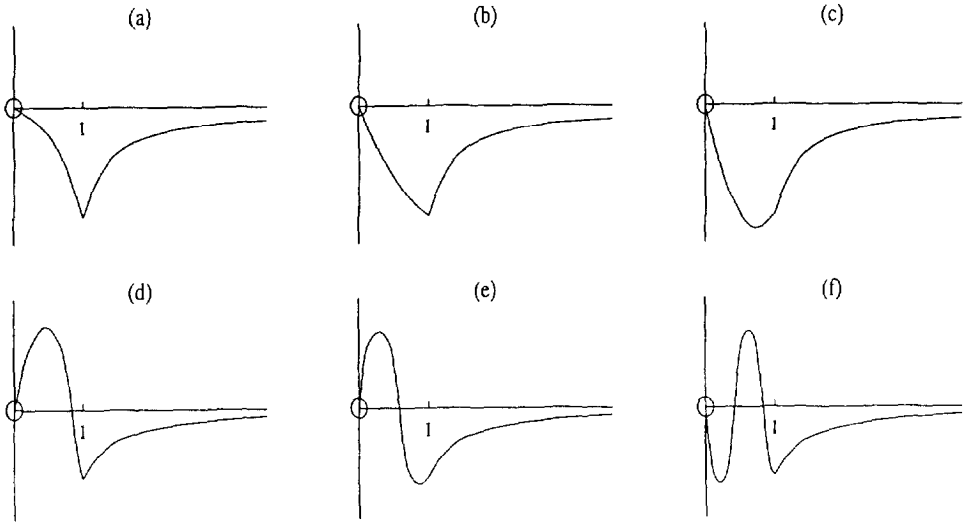

Fig. 2. Possible qualitative forms of the solution $u(x)$ of the boundary value problem (3.4)–(3.5), representing contracted tissue displacement profiles. The point $(u, u') = (0, 0)$ must be a saddle point for $x > 1$ in the (u, u')-phase plane, with u increasing to zero and u' decreasing to zero monotonically along the stable manifold in the top-left quadrant as $x \to \infty$. For $0 \le x < 1$, the origin may be either a saddle point, in which case the profiles for u and u' are monotonic decreasing as shown in (a), or a centre, in which case u and u' oscillate about the origin as shown in (b–f); within this region, any number of oscillations is possible—for example, (f) is equivalent to (b) modulo one period. Note that the above steady-state profiles but with reversed signs of u and u' are also admissible solutions of (3.4)–(3.5), representing expanded tissue displacement profiles since $u(1)$ would be positive. Recall that $x = 1$ is the initial wound boundary.

4. FIBROPROLIFERATIVE WOUND HEALING DISORDERS

We now consider the application of the mechanochemical model framework to fibroproliferative wound healing disorders. Such disorders are characterised by abnormally large amounts of tissue. The full model can exhibit solutions in which an excess of cells is observed, corresponding to a pathological state. To understand this more fully, we focus purely on the chemical aspects of (2.1)–(2.5). Consider now the cell-growth factor sub-model of (2.1)–(2.5), namely,

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x}[\chi(c,n)\frac{\partial c}{\partial n}] + \sigma[1 + \frac{Pc}{Q+c}]n(1 - \frac{n}{K}) - d_n n. \tag{4.1}$$

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + \frac{\kappa_c n c}{\gamma + c} - d_c c, \tag{4.2}$$

where $\chi(c,n) = \alpha/(\beta + c)^2$, and $\alpha, \beta, P, Q, \kappa_c$ and γ are positive constants (see [4] for full details).

This caricature model has two uniform steady states, $(n,c) = (0,0), (K,0)$ corresponding, respectively, to the trivial, or non-healing, state, and the normal dermal state. For appropriate parameter values, two other steady states exist which have both n and c non-zero, with $n > K$. These are the pathological, or diseased, steady states. A bifurcation analysis can be carried out for (4.1)–(4.2), in the absence of diffusion, and it can be shown that for $\kappa_c = \kappa_c^1$ (calculated in terms of the other parameters) the dermal steady state remains locally stable but loses global stability as the pathological steady states appear. At $\kappa_c = \kappa_c^2$, the dermal steady state loses stability and the pathological state with higher cell density level becomes globally stable.

The spatiotemporal dynamics of the model can be analysed by travelling wave analysis, which shows that travelling wave trajectories from the dermal state to the pathological state are possible and a minimum wavespeed can be determined. Numerical simulations of the system show that such travelling waves do exist, but that reducing κ_c can cause the waves to stop and to regress (see Figure 3).

5. DISCUSSION

The mechanochemical framework presented in Section 2 has been proposed to model dermal wound healing. Numerical simulations of the full model have shown that it can capture key aspects of normal and abnormal wound healing. The complexity of the model makes it difficult to fully understand what roles the various mechanisms play during these processes. To investigate the model in more detail, we have chosen to analyse caricature models which focus on certain model mechanisms. In Section 3, we considered a purely mechanical model and showed how it could exhibit contracted steady states, characteristic in normal wound healing. In Section 4, we focussed on the chemical aspects of the full model and showed how the system could evolve to a pathological state corresponding to a fibroproliferative state. In this case, our analysis shows that reducing κ_c, the linear rate at which cells secrete growth factor, can cause the disease to regress back to the normal dermal state. More detailed analysis of this model ([4]) determines analytically how the bifurcation values of κ_c depend on the other parameters in the model. This provides a clinically-testable method to help reduce this type of fibroproliferative disorder.

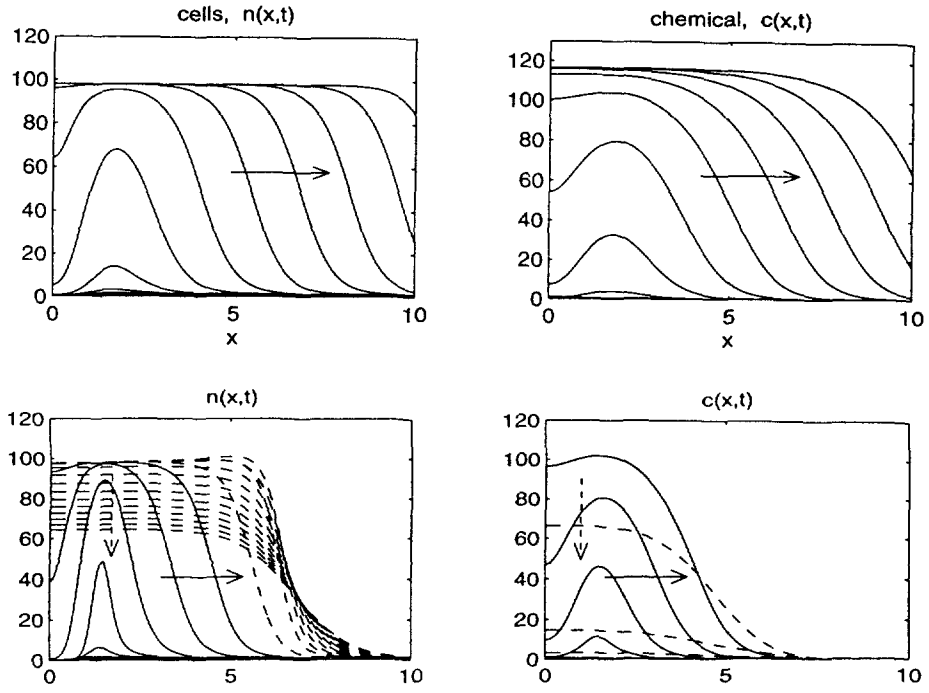

Fig. 3. Numerical simulations of (4.1)–(4.2) showing progression to pathological steady state (a), and cessation and regression for the case where κ_c in reduced to zero after a certain time (b). See [4] for parameter values.

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