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MATHEMATICAL MODELS FOR CELL-MATRIX INTERACTIONS DURING DERMAL WOUND HEALING

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This paper contains a review of our recent work on the mathematical modeling of cell interaction with extracellular matrix components during the process of dermal wound healing. The models are of partial differential equation type and allow us to investigate in detail how various mechanochemical effects may be responsible for certain wound healing disorders such as fibrocontractive and fibroproliferative diseases. We also present a model for wound healing angiogenesis. The latter has several features in common with angiogenesis during cancer tumour growth and spread so a deeper understanding of the phenomenon in the context of wound healing may also help in the treatment of certain cancers.

Keywords: Wound contraction; fibroproliferative disorders; angiogenesis.

1. Introduction

Recent advances in molecular and cellular biology have led to the rapid development of experimental research into the biochemical mechanisms underlying the processes of wound healing. Wound healing is an enormously complex dynamic spatiotemporal process and new insights are being gained by focussing on the interaction of specific processes involved for a particular aspect of healing. Mathematical modeling can play an important role by providing a theoretical framework within which these results can be analyzed, by exploring the potential of various proposed mechanisms to account for clinical observations, and suggesting novel biological mechanisms which may lead to new experimental approaches. Such models also provide experimentally testable predictions on the outcome of manipulating key biological parameters. In this respect, mathematical modeling may be thought of as another experimental tool.

In this paper we chose to focus on certain aspects of cell-matrix interactions during wound healing and review our recent work in this area. In Sec. 2 we consider a mechanochemical model framework for the contraction of wounds during normal healing. This is a complicated system of highly nonlinear equations and, in order to gain a greater understanding of the model, we consider caricature models within this framework that are more tractable and help us to investigate normal wound contraction (Sec. 3) and wound healing disorders, such as fibroproliferative diseases (Sec. 4). In Sec. 5 we consider the role of extracellular matrix in angiogenesis, the process by which a new vascular system is set up after wounding.

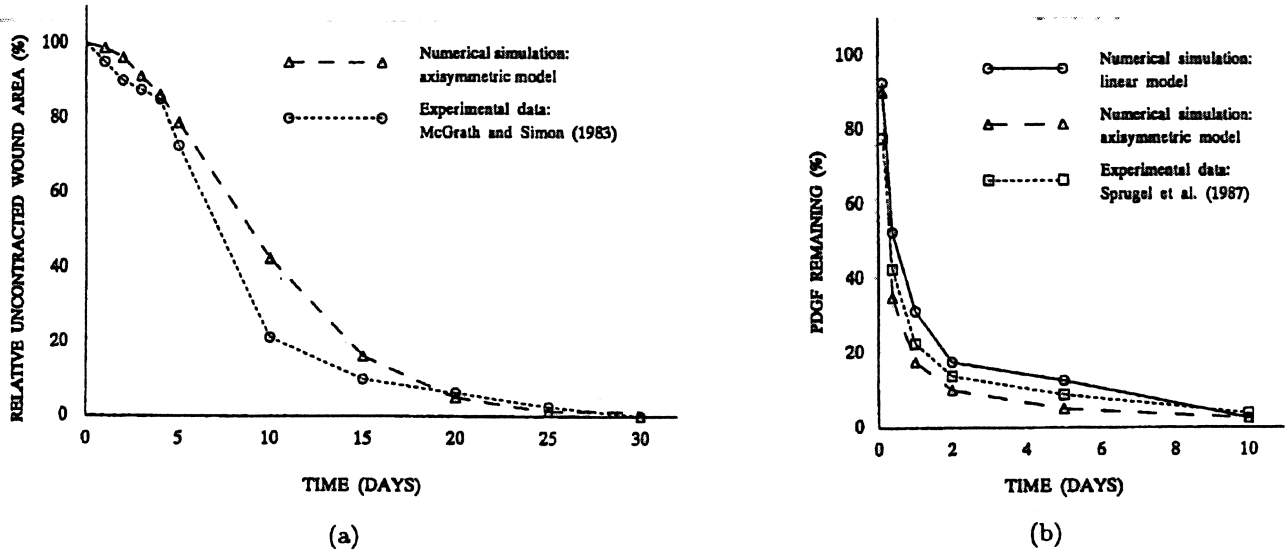

Fig. 1. Comparison of experimental data and numerical simulations of (2)–(6) for (a) wound contraction and (b) clearance of growth factor (PDGF — platelet-derived growth factor). See [Olsen *et al.*, 1995], for full details.

$B(n, m.c, \rho)$, $\tau(n, \rho)$, $F(\rho, u)$, 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, ε_r, μ 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 [Olsen *et al.*, 1995], for full details and Fig. 1). Using a caricature model, we now proceed to analyze the possible contracted steady states exhibited by the model.

3. Contracted Steady States

To consider the potential of the model framework (2)–(6) to exhibit spatially-varying contracted steady states, Olsen *et al.* [1996] considered a simpler version of the model which focusses only on the mechanical aspects of the interaction. The nondimensionalized version of this caricature model takes the form

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} + \frac{\partial}{\partial x}\left[-n\frac{\partial u}{\partial t}\right] + n(1-n) \quad (7)$$

$$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x}\left[-\rho\frac{\partial u}{\partial t}\right] \quad (8)$$

$$\mu\frac{\partial^3 u}{\partial x^2 \partial t} + E\frac{\partial^2 u}{\partial x^2} + \frac{\partial \tau(n, \rho)}{\partial x} = F(\rho, u)\,. \quad (9)$$

Here we consider only the fibroblast cell type and assume a simple form for logistic growth. We also assume in this model 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 remodeling during the process of wound healing.

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

$$\frac{\partial n}{\partial x}(0, t) = \frac{\partial \rho}{\partial x}(0, t) = u(0, t) = 0$$

and

$$n(\infty, t) = \rho(\infty, t) = 1, \quad u(\infty, t) = 0\,.$$

The initial conditions are

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

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, $n = 1$. Linearizing (8) about the initial profile, we have

$$\rho \approx \begin{cases} \rho_i(1 - \partial u/\partial x)\,, & 0 \leq x < 1 \\ 1 - \partial u/\partial x\,, & x > 1 \end{cases} \quad (10)$$

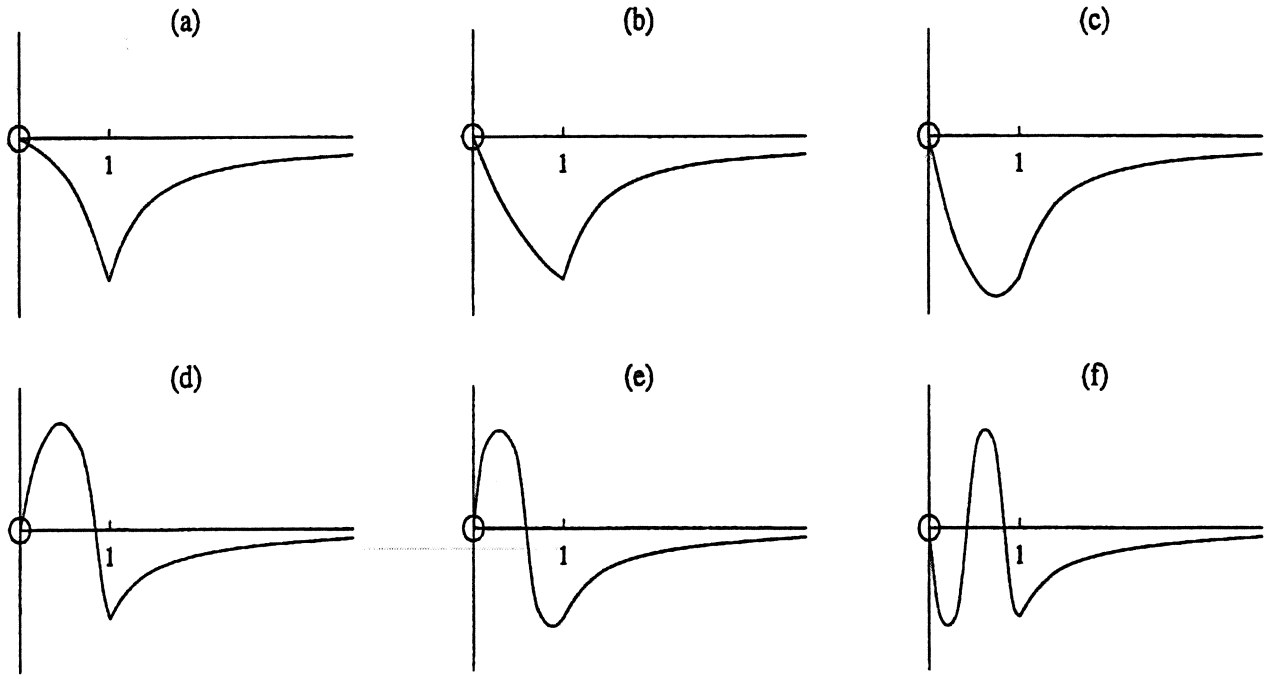

Fig. 3. Possible qualitative forms of the solution $u(x)$ to (11) and (12), representing contracted tissue displacement profiles. The point $(u, u') = (0, 0)$ must be a saddle point for $x > 1$ in the (u, u')-phase plane, with u increasing to zero and u' decreasing to zero monotonically along the stable manifold in the top-left quadrant as $x \to \infty$. For $0 \leq x < 1$, 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 center, in which case u and u' oscillate about the origin as shown in (b–f); within this region, any number of oscillations is possible — e.g. (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 (11) and (12), representing expanded tissue displacement profiles since $u(1)$ would be positive. Recall that $x = 1$ is the initial wound boundary.

Hence, this caricature model enables us to more fully understand the properties of the full model (2)–(6) and shows clearly that the model can exhibit spatially-varying contracted steady states, and is thus consistent with clinical observations on normal healing. For full details, see [Olsen *et al.*, 1998].

4. Fibroproliferative Wound Healing Disorders

We now consider the application of the framework developed in Sec. 2 to fibroproliferative wound healing disorders. These disorders are characterized by the generation of abnormally large amounts of tissue during the healing process, leading to, for example, keloid scarring. Numerical simulations of the full model (2)–(6) show that it can exhibit solutions in which an excess of cells is observed, corresponding to a pathological state. To understand this more fully, we again consider a caricature model of the full system. In this case, however, we focus purely on the chemical aspects of the mechanochemical framework (2)–(6) by considering the cell-chemical submodel

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x}\left[\chi(c, n)\frac{\partial c}{\partial n}\right] + \sigma\left[1 + \frac{Pc}{Q + c}\right] n\left(1 - \frac{n}{K}\right) - d_n n \quad (13)$$

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + \frac{\kappa_c n c}{\gamma + c} - d_c c, \quad (14)$$

where $\chi(c, n) = \alpha/(\beta + c)^2$, and α, β, P, Q, κ_c and γ are positive constants (see [Olsen *et al.*, 1996] for full details).

This caricature model has two uniform steady states, $(n, c) = (0, 0)$, $(K, 0)$ corresponding, respectively, to the trivial, or nonhealing, state, and the normal dermal state. For appropriate parameter values, two other steady states exist which have both n and c nonzero, with $n > K$. These are the pathological, or diseased, steady states. Results from bifurcation analysis of (13) and (14), in the absence of diffusion, show that for a critical value, κ_c^1,

are all non-negative. The haptotactic and haptokinetic coefficients are given, respectively, by $C(m) = C_0(K_C + m)^{-2}$ and $D(m) = D_0 m(K_D^2 + m^2)^{-1}$. The cell proliferation rate is given by $A(m) = A_0 m(K_A^2 + m^2)^{-1}$. We refer the reader to the original paper for the motivation and derivation of the above functional forms.

The model was considered on a one-dimensional domain to approximate "slash" wounds. To complete the model formulation, the following boundary and initial conditions are imposed: by symmetry, solutions need only be defined on the semi-infinite domain $x \geq 0$ subject to zero-flux at the wound centre, i.e. $C(m)n\partial m/\partial x = D(m)\partial n/\partial x$ at $x = 0$; also, the cell and ECM variables remain at their normal dermal values far away from the wound, so $n \to n_0$ and $m \to m_0$ (say) as $x \to \infty$.

Initially, there are no endothelial cells and a low level of ECM (due to the early deposition of provisional matrix) inside the wound, so $n = 0$ and $m = m_{\text{init}}$ (say) at $t = 0$ for $0 \leq x \leq L$, with the unwounded values $n = n_0$ and $m = m_0$ outside the wound ($x > L$). Note that $0 < m_{\text{init}} < m_0$.

Investigation of the spatially uniform equilibria of this system reveals a continuum of unstable "acellular" states, in which $n = 0$ and m is unspecified, and a globally stable state, in which $n = A(m)/B$ and $m = P/Q$. These values are positive, and must be equal to n_0 and m_0, respectively, so this "dermal" steady state represents normal, unwounded tissue. Numerical simulations of the full system indicate that the cell and ECM profiles appear to evolve with approximately constant speed and form, after an initial transient and before the

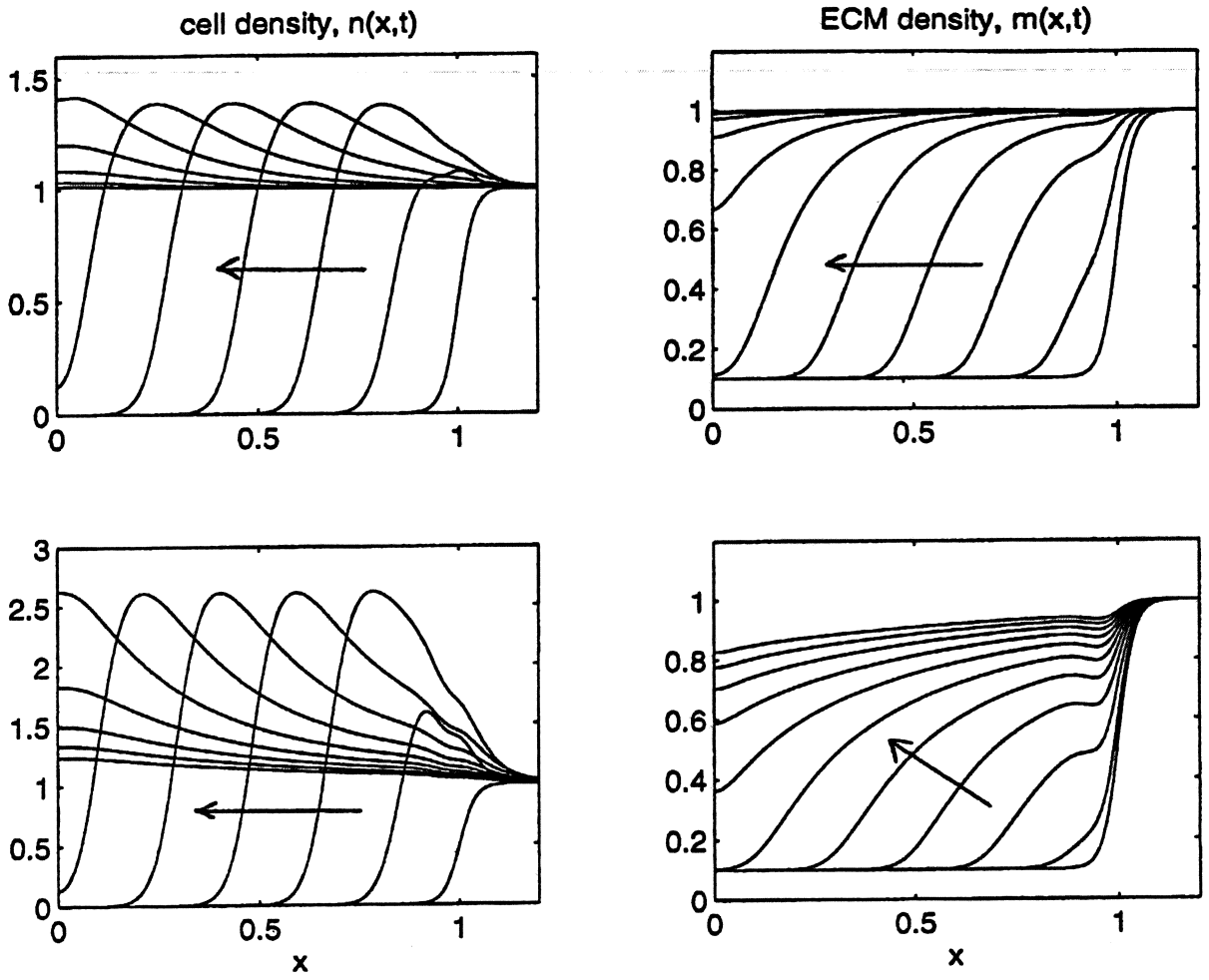

Fig. 5. Numerical solution of Eqs. (15) and (16) for different values of ε. Density profiles for cells (n) and ECM (m) are shown at time $t = 0$ and at ten successive unit intervals. End-conditions as in the text. (Top row) parameter values are $D_0 = 0.005$, $\kappa_D = 0.5$, $\chi_0 = 0.001$, $\kappa_\chi = 0.5$, $\alpha_0 = 1.01$, $\kappa_\alpha = 0.1$, $\beta = 1$, $\varepsilon = 1$ and $m_{\text{init}} = 0.1$. (Bottom row) same, except $\varepsilon = 0.2$, representing slower ECM kinetics.

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