

A MECHANOCHEMICAL MODEL FOR ADULT DERMAL WOUND CONTRACTION

L. OLSEN¹, J. A. SHERRATT² and P. K. MAINI¹

¹*Centre for Mathematical Biology, Mathematical Institute,
24–29 St Giles', Oxford, OX1 3LB, U.K.*

²*Nonlinear Systems Laboratory, Mathematics Institute,
University of Warwick, Coventry, CV4 7AL, U.K.*

ABSTRACT

We propose a deterministic mathematical model to describe the biomechanics and cell biology of wound contraction, a ubiquitous feature in the normal healing of adult dermal excisional wounds. Our aim is to use the model to obtain a greater understanding of the mechanisms involved in wound contraction and in clinically important healing pathologies such as fibrocontractive diseases.

The model consists of two cell types — fibroblasts and myofibroblasts, a generic chemical growth factor and a viscoelastic extracellular matrix (which includes type I collagen). The essential processes of cell motility, proliferation, differentiation and mechanical interaction with the matrix are modelled from experimental data. A novel aspect of this approach is the inclusion of two cell types.

The model is shown not only to simulate normal wound contraction (in good agreement with experimental data), but also to yield valuable insight into the fundamental mechanisms involved and the pathogenesis of fibrocontractive diseases, and makes experimentally testable predictions of the effects of varying biological parameters. Two important results are that collagen remodelling is more intrinsic to scar formation than to wound contraction and that dynamic gradients in the cell and matrix densities are the driving force for wound contraction.

Keywords: Wound-contraction, mechanochemical model, cell-traction, dermal-remodelling.

1. Introduction

In the healing of full-thickness excisional wounds in adults, contraction is the phenomenon in which the size of the wound is reduced by the inward movement of the wound margins. Moreover, many clinical wounds fail to heal normally, and a broad range of associated pathologies (some of which are severe), known as fibrocontractive diseases, may arise due to apparent disorders at level of wound contraction and fibroplasia. Despite intensive research, the underlying biological mechanisms of wound contraction remain incompletely understood. The aim of this work, therefore, is to develop a mathematical model whose formulation is as simple as possible, whilst retaining the fundamental cell biology and biomechanics of dermal wound contraction.

E-mail: olsen@maths.ox.ac.uk

The continuing discussion regarding the definition of the “contracted steady state” of a wound is of vital importance. With an understanding of the physical state of the contracted wound, it may be possible not only to predict the behaviour of experimental and clinical wounds, but also to elucidate the pathogenic mechanisms of fibrocontractive diseases.

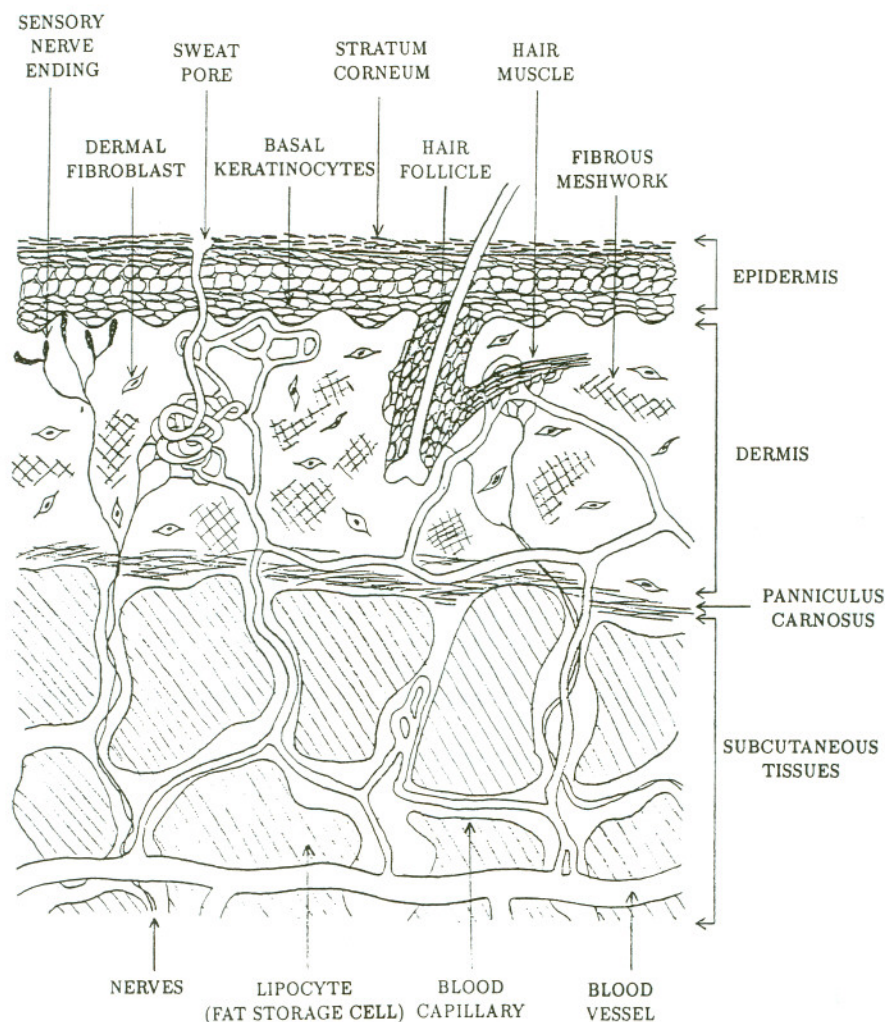


Fig. 1. A schematic representation of a section through adult mammalian skin.

2. Biological Background

Adult mammalian skin is conventionally partitioned into three layers — see Fig. 1. The outermost epidermis is composed of densely packed cells, which undergo

continual proliferation and differentiation. The underlying dermis is a thicker layer consisting of cells, extracellular matrix (ECM), blood vessels and a variety of other circulatory and structural components. Dermal fibroblasts are cells that perform several vital roles in wound healing and are inextricably involved in contraction. The ECM consists of various diffusible and structural molecules, notably proteins, such as collagen (fibrous proteins which constitute the bulk of the fat-free dry weight of the skin) and enzymes which through their degradative properties, ensure that the ECM undergoes constant turnover. Below the dermis are subcutaneous layers of fat, muscle, circulatory vessels and fibrous tissues.

We consider full-thickness dermal excisional wounds, which occur when an area of epidermal and dermal tissue is completely removed, without injury to subcutaneous tissues. Contraction is a ubiquitous feature of these wounds, and together with new ECM formation and epidermal regeneration, effects full wound closure.

The various processes involved in full-thickness dermal excisional wound healing may be crudely subdivided into three overlapping phases: inflammation, proliferation and remodelling.

In the early inflammatory phase, platelets from damaged blood vessels aggregate to form a stable clot and secrete a variety of biochemicals, including families of growth factors. These crucial healing proteins regulate many repair processes, but in particular, attract blood-borne inflammatory cells into the wound site, which in turn initiate further biochemical and enzymatic cascades, leading to fibroplasia and contraction.

In the proliferative phase (beginning several days post-wounding), the epidermal cells adjacent to the wound are stimulated to divide and migrate, thereby restoring epidermal integrity above the provisional wound matrix. New blood capillaries also begin to pervade the wound space from surrounding vessels in a process known as angiogenesis, which is essential in regulating metabolism in the wound. Importantly, growth factors recruit dermal fibroblasts from surrounding tissues by chemotaxis, which subsequently proliferate, secrete growth factors and ECM constituents (including collagen) and some cells are transformed into myofibroblasts. These modified wound fibroblasts exhibit marked intracellular actin stress fibres and other alterations suggestive of a contractile phenotype and are believed to be vital to wound contraction. One theory is that as fibroblasts move through the wound matrix, they exert traction forces on collagen fibres at the cell surfaces. The resultant tension is subsequently transduced throughout the wound space by the myofibroblast/ECM network, enabling the wound tissue to contract in response to the cell-derived traction forces.

As fibroplasia and contraction cease (these processes normally occur over about three weeks), ECM remodelling begins in earnest to form a mature scar and may continue for many months. Inflammatory cells and myofibroblasts have receded, but fibroblasts continue to regulate the ECM, especially collagen, as the tensile strength of the wound is gradually restored.

We seek to understand the processes of fibroplasia and contraction, so we focus attention onto modelling these aspects of the proliferative phase of wound healing.

3. Modelling Wound Contraction

The model is based upon conservation laws, yielding the following partial differential equation for each quantity, Q :

$$\frac{\partial Q}{\partial t} = -\nabla \cdot \mathbf{J}_Q + f_Q,$$

where \mathbf{J}_Q represents the flux and f_Q the kinetic terms. We now consider the quantities, Q , to be included.

In order to account for the fundamental cell biology of wound contraction as outlined above, we incorporate as distinct model variables the fibroblast and myofibroblast cell densities, the collagen concentration and a "generic" growth factor concentration. Note that in reality, many inter-regulatory growth factors are involved [1], but for simplicity we consider a single chemical, acting as a promoter of healing. The platelet-derived growth factor (PDGF) exhibits much of the requisite behaviour of our generic chemical [3], and we therefore refer to experimental data for PDGF to determine the relevant parameter values.

Modelling the biomechanics of wound contraction is not a straightforward problem and is the subject of considerable research. Our approach is to follow previous mechanochemical models for morphogenesis by considering the conservation of tissue momentum [4–6]. This yields a governing equation for the tissue displacement, thus providing a useful means of quantifying wound contraction.

The five space- and time-dependent model variables for the fibroblast density, n , myofibroblast density, m , chemical concentration, c , collagen concentration, ρ , and tissue displacement, \mathbf{u} , satisfy the following equations (based upon Sec. 2 — see [9] for details):

Fibroblasts, $n(\mathbf{x}, t)$:

$$\begin{aligned} \frac{\partial n}{\partial t} = \nabla \cdot \left[D_n \nabla n - \frac{a_n}{(b_n + c)^2} n \nabla c - n \frac{\partial \mathbf{u}}{\partial t} \right] + \left(r_n + \frac{r_{n_{\max}} c}{C_{1/2} + c} \right) n \left(1 - \frac{n}{K} \right) \\ - \frac{k_{1_{\max}} c}{C_k + c} n + k_2 m - d_n n. \end{aligned}$$

The cell fluxes are due to random dispersal (assuming Fickian diffusion with a constant coefficient), growth factor-regulated chemotaxis (using a cell surface receptor mechanism to derive the chemotactic sensitivity function [12]) and passive convection by the wound tissue. For the kinetics, there is mitosis (logistic form — in excellent agreement with tissue culture data [15], with marked growth factor enhancement of the linear growth rate [11]), transformation into myofibroblasts (stimulated by growth factors [2,13]), a source term arising from the reverse transformation and natural cell death.

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Myofibroblasts, $m(\mathbf{x}, t)$:

$$\frac{\partial m}{\partial t} = \nabla \cdot \left[-m \frac{\partial \mathbf{u}}{\partial t} \right] + \epsilon_r \left(r_n + \frac{r_{n_{\max}} c}{C_{1/2} + c} \right) m \left(1 - \frac{m}{K} \right) + \frac{k_{1_{\max}} c}{C_k + c} n - k_2 m - d_m m.$$

Assuming that the myofibroblasts are not actively motile, and without evidence to the contrary, passive convection is the only flux. The kinetic terms are similar to those for fibroblasts: the mitotic rate is intrinsically slower ($\epsilon_r < 1$) [15], there is phenotypic transformation (as for fibroblasts) and the cell death rate is higher due to *programmed* cell death ($d_m > d_n$) [2].

Chemical, $c(\mathbf{x}, t)$:

$$\frac{\partial c}{\partial t} = \nabla \cdot \left[D_c \nabla c - c \frac{\partial \mathbf{u}}{\partial t} \right] + \frac{(p-1)k'_p(n + \zeta_p m)c}{\Gamma_p + c} - \frac{k'_c(n + \zeta_c m)c}{\Gamma_c + c} - d_c c.$$

The generic chemical diffuses (with a constant coefficient) throughout the tissue, and is also carried passively. For the kinetics, both fibroblasts and myofibroblasts produce and consume the chemical (a receptor density argument yields the given form for the auto-regulation of these processes [9]), and there is a natural (linear) degradation term.

Collagen, $\rho(\mathbf{x}, t)$:

$$\frac{\partial \rho}{\partial t} = \nabla \cdot \left[-\rho \frac{\partial \mathbf{u}}{\partial t} \right] + \left(r_\rho + \frac{r_{\rho_{\max}} c}{C_\rho + c} \right) \frac{n + \eta_b m}{R_\rho^2 + \rho^2} - d_\rho(n + \eta_d m)\rho.$$

Collagen forms a fibrous network in granulation tissue, and the only flux contribution is due to passive convection. The kinetics are due to biosynthesis (by complicated molecular pathways involving collagen precursors and fibre aggregation), which is upregulated by growth factors [10]) and degradation (by cell-derived enzymes), by both cell types.

Momentum, $\mathbf{u}(\mathbf{x}, t)$:

$$0 = \nabla \cdot \left[\mu_1 \frac{\partial \boldsymbol{\varepsilon}}{\partial t} + \mu_2 \frac{\partial \boldsymbol{\theta}}{\partial t} \mathbf{I} + E'(\boldsymbol{\varepsilon} + \nu' \boldsymbol{\theta} \mathbf{I}) + \frac{\tau_0(1 + \xi m)n\rho}{R_\tau^2 + \rho^2} \mathbf{I} \right] - s\rho \mathbf{u}.$$

Here, we follow previous work in mechanochemical models of tissue morphogenesis by including momentum fluxes from two contributions [6,8,14]. Firstly, the traction stresses exerted by fibroblasts at their cell surfaces are modelled as the isotropic unit tensor multiplied by some traction force, which we take to be proportional to the fibroblast density and to the collagen concentration. We assume (strong) enhancement by the presence of myofibroblasts and inhibition by high collagen densities (those characteristic of normal dermis, for example). Secondly, there are intrinsic ECM stresses in response to tissue deformation. Using the simplifications of tissue isotropy, a linear (i.e. for small strains) stress-strain relationship and a

viscoelastic rheology, we derive our constitutive formula for the ECM stress tensor, as detailed elsewhere [4,5,14]. The kinetics are the body forces exerted on the tissue, which we model simply as restoring forces acting against tissue displacement (due to the fibrous attachments between the dermal tissue and subcutaneous layers), with resistance per unit of fibrous matrix assumed to be proportional to the displacement.

With these considerations, and an implicit assumption that inertial effects are negligible (since the tissue is very viscous), we obtain the so-called “force balance” equation above [6,14]. Despite its complexity, no simpler formulation for the biomechanics of the dermis (wounded or not) has been proposed, and the required detail of the constitutive relation for the dermis is a topic of continuing debate.

3.1. *The Nondimensional 1-D “Linear” Wound Model*

With the following simplifications, we may reduce the spatial dimensionality from three to only one. Firstly, we assume that the processes involved in wound contraction are independent of wound depth (this is generally accepted). Secondly, we incorporate the effects of the wound base without recourse to a special boundary condition (by modelling the dermal attachments to underlying tissues as simple, linear restoring forces on the tissue — see above). Finally, we restrict attention to geometries that require only one spatial coordinate in the plane of the skin. In particular, we consider axisymmetric and linear geometries (modelling circular and long rectangular wounds respectively): we shall note that the model predictions in the two cases are analogous and that quantitative accuracy is marginally improved in the axisymmetric formulation. This is reassuring, given that the circular wound geometry is ubiquitous in experimental studies (from which we derive parameter estimates and compare the model results [9]).

To obtain a greater understanding of the roles of the model parameters, we nondimensionalize the variables and the parameters [9], thereby yielding the five nondimensional model equations for the 1-D “linear” wound model (omitting tildes for notational simplicity):

$$\begin{aligned} \frac{\partial n}{\partial t} = \frac{\partial}{\partial x} \left[D_n \frac{\partial n}{\partial x} - \frac{\alpha}{(\beta + c)^2} n \frac{\partial c}{\partial x} - n \frac{\partial u}{\partial t} \right] + \sigma \left(1 + \frac{Ac}{B + c} \right) n(1 - \gamma n) \\ - \frac{\kappa_1 c}{C + c} n + \kappa_2 m - \delta n, \end{aligned} \quad (1)$$

$$\begin{aligned} \frac{\partial m}{\partial t} = \frac{\partial}{\partial x} \left[-m \frac{\partial u}{\partial t} \right] + \epsilon_\sigma \sigma \left(1 + \frac{Ac}{B + c} \right) m(1 - \gamma m) \\ + \frac{\kappa_1 c}{C + c} n - \kappa_2 m - \lambda \delta m, \end{aligned} \quad (2)$$

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left[D_c \frac{\partial c}{\partial x} - c \frac{\partial u}{\partial t} \right] + \frac{\kappa_c(n + \zeta m)c}{\gamma_c + c} - \delta_c c, \quad (3)$$

$$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x} \left[-\rho \frac{\partial u}{\partial t} \right] + \left[\omega \left(1 + \frac{Pc}{Q+c} \right) \frac{1}{\phi^2 + \rho^2} - \delta_\rho \rho \right] (n + \eta m), \quad (4)$$

$$0 = \mu \frac{\partial^3 u}{\partial x^2 \partial t} + \frac{\partial^2 u}{\partial x^2} + \nu \frac{\partial}{\partial x} \left[\frac{(1 + \xi m)n\rho}{\psi^2 + \rho^2} \right] - s\rho u. \quad (5)$$

We solve the system in the symmetric 1-D linear domain, $x > 0$, impose zero species gradients at $x = 0$, and define the wound space as $0 \leq x \leq 1$. The wound is assumed to be sufficiently isolated that the model variables remain constant at infinity. However, we use a finite domain approximation ($x_\infty = 10$) for the numerical solutions and therefore impose zero flux boundary conditions instead.

The initial conditions ($t = 0$) are given at the onset of contraction. There are no cells inside the wound space and the dermal level of fibroblasts, $n = 1$, outside. There are no myofibroblasts anywhere initially. The chemical profile, c_{init} , arises due to the initial supply of growth factors in the inflammatory phase and takes a form that decreases smoothly towards zero around the wound margins (owing to diffusion). We choose the function $1/(1 + x^4)$. The collagen concentration is at some small value, $\rho_{\text{init}} \ll 1$, inside the wound and the dermal value, $\rho = 1$, outside. Finally, the displacement is zero everywhere.

4. Predictions of the Model

In determining the steady states, we immediately observe that the collagen concentration (ρ) and the tissue displacement (u) decouple from the cell and chemical equations (1–3). Nevertheless, the problem of general, spatially inhomogeneous steady states is analytically intractable, and we therefore first consider the spatially uniform case, given by the system of algebraic equations obtained by setting the derivatives to zero in (1–5).

By (5), either $\rho = 0$ or $u = 0$. If $\rho = 0$, we deduce from (4) that n and m are also both zero, as is c , by virtue of (3). This is therefore the ‘trivial’ solution of the system, which is expected intuitively, but of little biological interest, for it is relevant to neither the unwounded nor the contracted steady states. In the case $u = 0$, we obtain a fundamental result: *the tissue displacement is identically zero when the species variables are in a non-trivial spatially uniform steady state.*

A requirement of the model is that a stable, spatially uniform steady state exists, corresponding to normal dermis, of which the initial wound state is a large perturbation. The above observation that $u = 0$ is consistent with this demand. Further, the human dermis is believed to produce active growth factors in significant concentrations only in response to specific stimuli (such as tissue injury), so we first investigate steady states for which $c = 0$. This simplifies the uniform steady state equations so that analytical expressions may be calculated, with the following results (the deductions of linear stability are derived from explicit inequalities, with parameter values obtained from our estimates [9], as used in the numerical simulations in this paper):

	$[n, m, c, \rho, u]_{\text{steady state}}$	interpretation	linear stability
(i)	$[0, 0, 0, \rho, 0]$	"trivial"	unstable
(ii)	$[1, 0, 0, 1, 0]$	"normal dermis"	locally stable
(iii)	$[n^*, m^*, 0, 1, 0]$	"pathological"	unstable

The chosen scalings set the fibroblast density, n , and the collagen concentration, ρ , to unity at the unwounded steady state, (ii). In (iii), n^* and m^* are easily calculated from (1) and (2), and we find that $n^* > 1$ and $m^* > 0$, suggestive of an excessive cellular response characteristic of many healing pathologies [13].

4.1. The Problem of the Permanence of Wound Contraction

To investigate the phenomenon of contraction, we assume that the species variables (n , m , c and ρ) are at spatially uniform steady states, and deduce from (5) that the steady state displacement, $u(x)$, must satisfy the simple, linear boundary value problem:

$$\frac{d^2 u}{dx^2} - s\rho u = 0, \quad u(0) = 0, \quad \frac{du}{dx}(\infty) = 0 \quad (6)$$

The solution to (6) is $u \equiv 0$, implying that no non-zero displacement profile is possible when the species variables are spatially uniform, with a corresponding result for the axisymmetric formulation. We return to this problem shortly.

5. Numerical Simulations

The above analysis predicts that the system should evolve towards the "dermal" steady state. We confirm this numerically (Fig. 2), observing the following: (a) the fibroblast density, n , gradually reattains its dermal value; (b) myofibroblasts, m , appear transiently, most markedly around the wound margin, with peak density levels occurring early in the process; (c) the chemical concentration profile, c , decays rapidly to zero, with considerable diffusion away from the wound; (d) the collagen concentration, ρ , only deviates slightly from its initial profile within the 30-day time course of these simulations, but does attain its dermal value after several years; (e,f) the displacement profile, u , becomes negative (at a roughly uniform rate), most notably around the wound margin, consistent with experimental data.

Over a much longer time scale (several years), the simulations confirm that the displacement relaxes back towards zero. Whilst contradicting the biology of wound contraction, this does not invalidate the model, because contraction occurs when the wound is in a transient state, and it is this dynamic process, rather than the longer ("pseudo-steady state") time scale to which the model is applicable.

5.1. The Problem of the Permanence of Wound Contraction:

An Explanation

To examine this problem, we consider the role of the collagen kinetics. At the unwounded steady state, the kinetic terms in (4) fix the collagen concentration, ρ

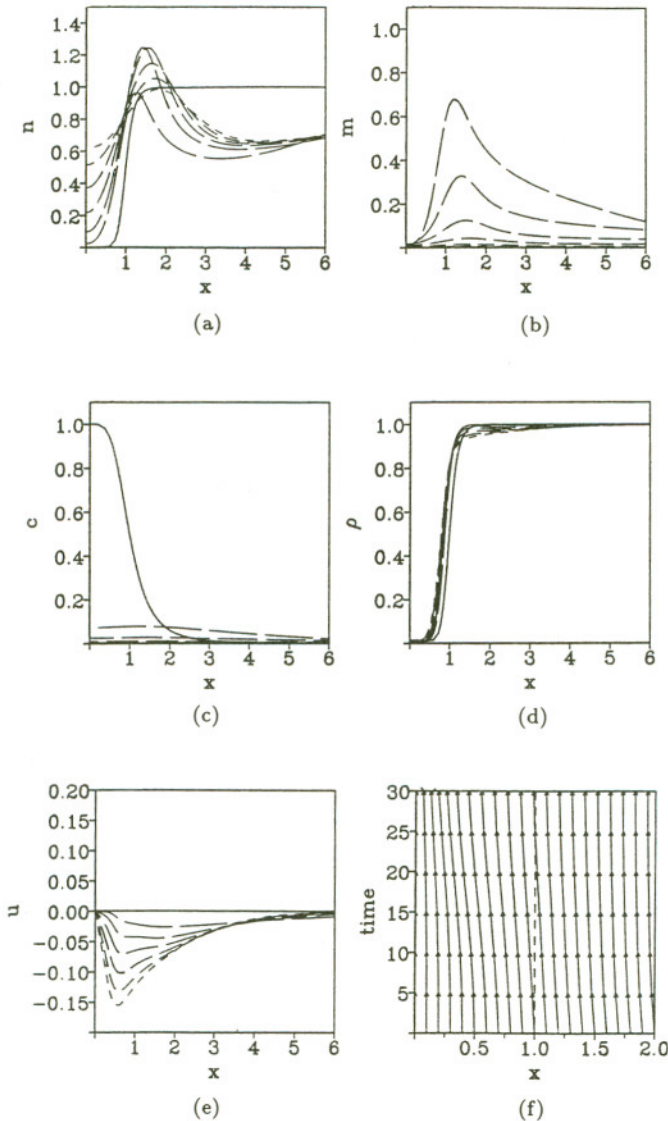


Fig. 2. Numerical simulations of the full model, using the NAG Routine D03PGF, showing the evolution of (a) fibroblast cell density, (b) myofibroblast cell density, (c) chemical concentration, (d) collagen concentration, and (e) tissue displacement profiles, plotted against the distance from the wound centre at successive time intervals of 5 days. In (f), the simulated movement of tattoo marks located across the wound and adjacent dermis is shown. Parameter values are $D_n = 0.02$, $\alpha = 0.5$, $\beta = 0.2$, $\sigma = 0.02$, $A = 44.5$, $B = 1$, $\gamma = 0.01$, $\kappa_1 = 10$, $C = 1$, $\kappa_2 = 1$, $\delta = 0.0198$, $\epsilon_\sigma = 0.5$, $\lambda = 10$, $D_c = 1.2$, $\kappa_c = 0.4$, $\gamma_c = 1$, $\delta_c = 0.5$, $\zeta = 1$, $\omega = 0.008$, $P = 10.0$, $Q = 0.1$, $\phi = 3.0$, $\delta_\rho = 0.0008$, $\eta = 2.0$, $\mu = 20.0$, $\nu = 0.02$, $\xi = 10.0$, $\psi = 0.005$, $s = 1.0$, $\rho_{init} = 0.01$.

(to unity). But if the kinetics for ρ are neglected — an approximation validated by the relevant parameter values [9], and borne out in the numerical simulations (Fig. 2(d)), then at a steady state, ρ is not explicitly specified by (4). In particular, at the dermal steady state, ρ may evolve towards a spatially inhomogeneous profile when the collagen kinetics are neglected. From (5), the steady state force balance equation thus becomes

$$\frac{d^2u}{dx^2} + \nu \frac{d}{dx} \left(\frac{\rho}{\psi^2 + \rho^2} \right) - s\rho u = 0, \quad u(0) = 0, \quad \frac{du}{dx}(\infty) = 0 \quad (7)$$

which in contrast to (6), includes a steady traction stress term, and yields a fundamental result: *a non-zero steady state displacement profile is possible when the collagen kinetics are neglected*. In this case, the behaviour of the system is very similar to the results shown in Fig. 2, except that the collagen concentration, ρ , remains close to its initial data permanently, and the displacement, u , does not relax to zero — see Fig. 3. An analogous result is again obtained for the axisymmetric wound geometry.

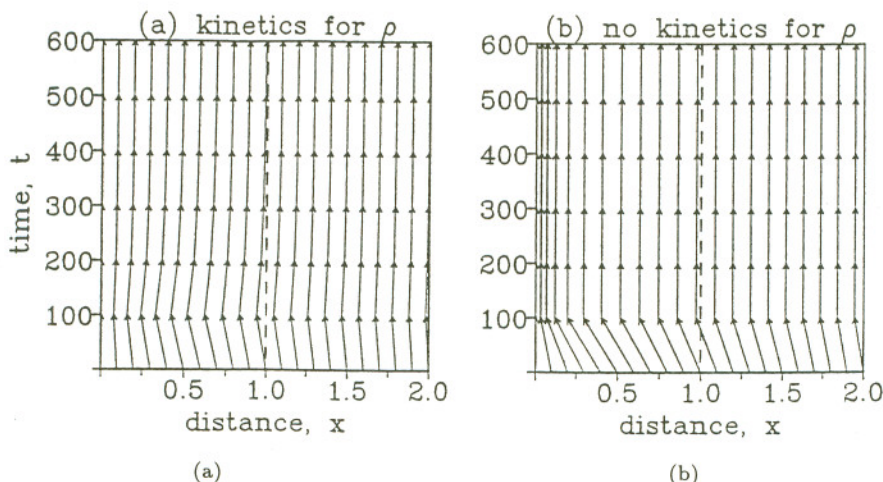


Fig. 3. Numerical simulations of the full model, using the NAG Routine D03PGF, showing the movement of tattoo marks to indicate tissue displacement, (a) as in Fig. 2(f), and (b) with no kinetics terms for $\rho(x, t)$. Parameters are as in Fig. 2. Note that the maximum time shown, $t = 600$, corresponds to a dimensional time of about 1.6 years.

6. Summary of Results and Conclusions

The model presented in this work has been shown to possess a biologically realistic spectrum of steady states, explicit descriptions of which may be readily obtained in terms of the model parameters. Furthermore, the predictions and numerical results of the model are qualitatively consistent with current biological knowledge.

All of the results for the linear (1-D) wound geometry were tested using the axisymmetric formulation, with full correspondence, notably in the roles of the

parameters and in the effects of collagen kinetics in the model. Quantitatively, some results compared well with experimental data, with improved accuracy in the axisymmetric case. This is not unexpected, given the widespread experimental research using these wounds (as opposed to the linear geometry).

An important conclusion from our model is that wound contraction is evidently driven by dynamic gradients in the species variables (fibroblasts and collagen are especially significant). In addition, fibroplasia is fundamental to the process of wound contraction, whereas collagen remodelling is more intrinsic to later stages in healing, such as scar formation.

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