Models of Wound Healing

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University of Warwick, 12 July 2007

Outline

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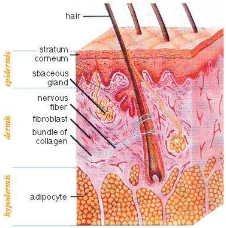
The Structure of the Skin

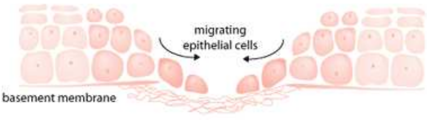
The skin consists of two layers: epidermis and dermis



The epidermis consists of closely packed cells, arranged in layers

Epidermal Wound Healing

Epidermal wounds are very shallow (no bleeding), e.g. blisters



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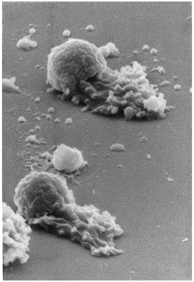

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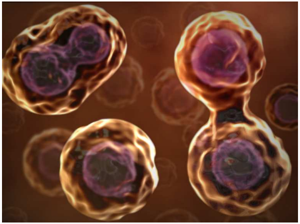

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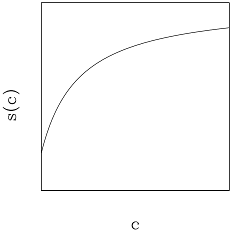

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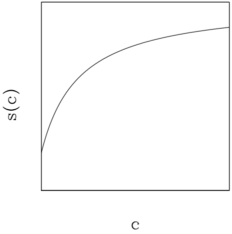

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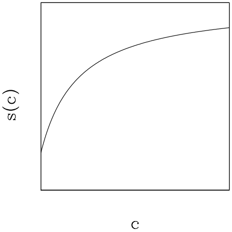

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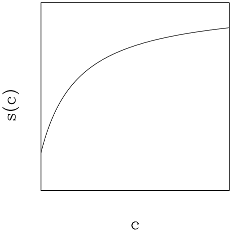

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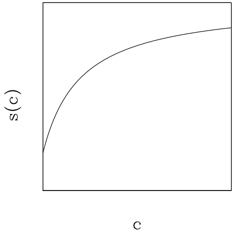

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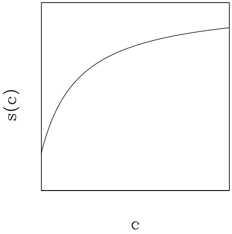

Reduction to One Equation

$$\partial n/\partial t = D\nabla^2 n + s(c)(N-n)n - \delta n$$
$$\partial c/\partial t = D_c\nabla^2 c + An/(1+\alpha n^2) - \lambda c$$

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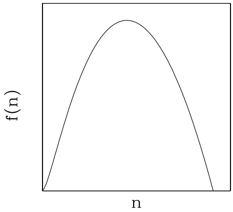
$$\Rightarrow \partial n/\partial t = D\nabla^2 n + f(n)$$

where

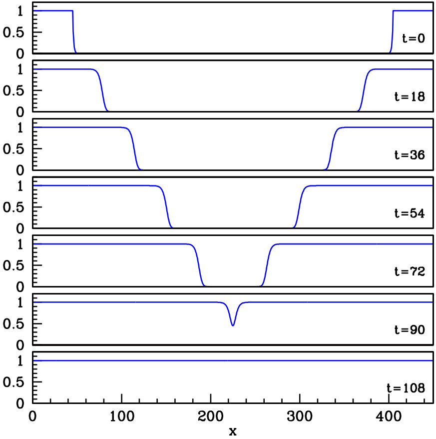
$$f(n) = s\left(\frac{An}{\lambda(1+\alpha n^2)}\right)(N-n)n - \delta n$$



Outline

1. Modelling Epidermal Wound Healing
2. Model Analysis: The Speed of Epidermal Repair
3. Modelling Scar Formation
4. Applying the Model to Anti-Scarring Therapies

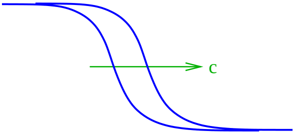
Typical Model Solution



Travelling Wave Solutions

During most of the healing, the solution moves with constant speed and shape.

This is a "travelling wave solution"



$$n(x,t) = N(x - at)$$

where a is the wave speed. We will write $z = x - at$. Then $\partial n/\partial x = dN/dz$ and $\partial n/\partial t = -a\,dN/dz$

$$\Rightarrow D\frac{d^2N}{dz^2} + a\frac{dN}{dz} + f(N) = 0$$

The Speed of Travelling Waves

We know that $N \to 0$ as $z \to \infty$. Recall that

$$D\frac{d^2N}{dz^2} + a\frac{dN}{dz} + f(N) = 0$$

Therefore when N is small

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to leading order. This has solutions $N(z) = N_0 e^{\lambda z}$ with

$$\lambda^2 + a\lambda + 1 = 0 \Rightarrow \lambda = \tfrac{1}{2}\left(-a \pm \sqrt{a^2 - 4Df'(0)}\right).$$

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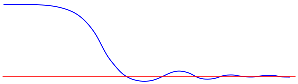
If $a < 2\sqrt{Df'(0)}$ then λ is complex $\Rightarrow$ the solutions oscillate about $N = 0$, which does not make sense biologically



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So we require $a \geq 2\sqrt{Df'(0)}$.

Applications to Wound Healing

For the wound healing model

$$f'(0) = Ns(0) - \delta$$

$$\Rightarrow \text{wave speed } a = 2\sqrt{D(Ns(0) - \delta)}$$

Therapeutic Addition of Chemical

Now consider adding extra chemical to the wound as a therapy
The equation for the chemical changes to

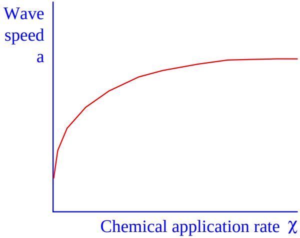
$$\partial c/\partial t = An/(1+\alpha n^2) - \lambda c + \gamma$$

$\Rightarrow$ $f(n)$ changes to

$$s\left(\frac{\gamma}{\lambda} + \frac{An}{\lambda(1+\alpha n^2)}\right)(N-n)n - \delta n$$

$\Rightarrow$ $f'(0)$ changes to $Ns(\gamma/\lambda) - \delta$

$\Rightarrow$ wave speed $a = 2\sqrt{D(Ns(\gamma/\lambda) - \delta)}$



Deducing the Chemical Profile

Since we know c as a function of n, there is also a travelling wave of chemical, whose form we can deduce. The chemical profile has a peak in the wave front.

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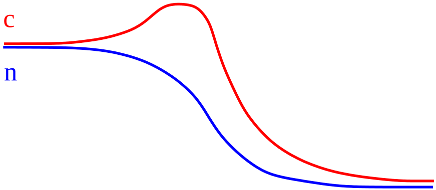

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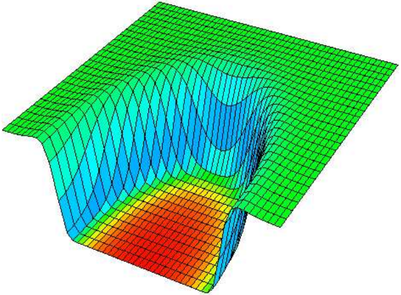

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The Structure of the Skin

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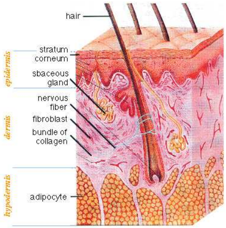
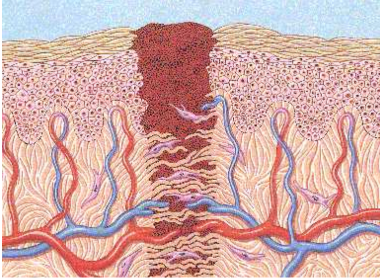


The dermis consists fi broblasts cells, collagen fi bres, blood vessels and nerve endings.

Dermal Wound Healing



The first response to injury is the formation of a blood clot, composed of fibrin. Fibroblasts then migrate into the wound from surrounding dermis, replacing the fibrin with collagen-based scar tissue.

Scar vs Normal Dermis

Differences between scar tissue and normal dermis include

- Higher collagen density
- Thicker collagen fi bres
- Lower tensile strength
- Different pattern of collagen alignment

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- Higher collagen density
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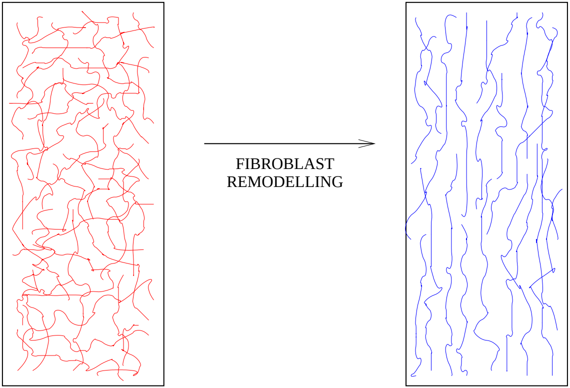
- Lower tensile strength
- Different pattern of collagen alignment: normal tissue has randomly aligned fi bres; scar tissue has fi bres primarily perpendicular to the basement membrane

Basic Process of Scar Formation



Key Ingredients of a Model

- Fibroblasts tend to move along extracellular matrix fi bres ("contact guidance")
- New collagen fi bres are produced in the direction of cell movement
- Existing collagen fi bres are reoriented towards cell movement

Model Formulation

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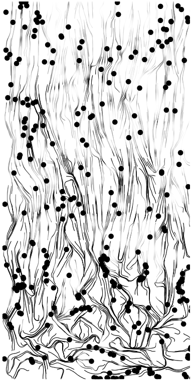
Extracellular matrix: Two types: collagen and fibrin.
Mathematically they are represented as vectors with magnitude $\leftrightarrow$ collagen/fibrin density, and direction $\leftrightarrow$ collagen/fibrin orientation.

Simulation of Scar Formation



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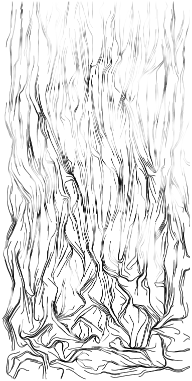

Movies of Wound Healing Simulation

Click here to play
the first movie

Click here to play
the second movie

Outline

TGF-β1 and Scar Formation

Experimental work on rats shows that TGF-β1 promotes scar formation and that competitive inhibition of TGF-β1 using mannose-6-phosphate reduces scarring.

(First report: Shah et al, Lancet 339, 213-4 1992).

This is the basis for the drug Judivex (Renovo PLC): phase II clinical trials are in progress. The related drug Juvista (also Renovo PLC) has a similar biochemical basis, and phase II clinical trials have been successful.
(See `www.renovo.co.uk`).

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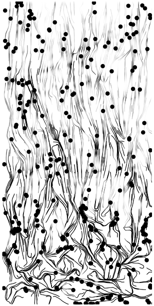
Question: what is the mechanism of TGF-β1's effect on scarring?

The Effects of TGF-β1 in Dermal Wound Healing

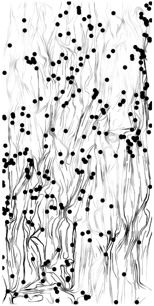
Standard literature indicates that TGF-β1 controls four important aspects of fi broblast behaviour during dermal wound healing:

- Proliferation
- Cell motility
- Collagen production
- Frequency of cell reorientation

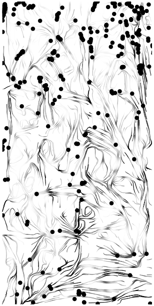
Unravelling TGF-β1's Role in Scarring



Normal healing



Removing TGF-β1's effect on proliferation, motility & collagen prod



More frequent cell reorientation

Conclusion

TGF-β1 regulates the degree of scarring via its effects on the frequency of fi broblast reorientation.

List of Frames