Modelling macrophage dynamics and their therapeutic implications in diabetic wound healing

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ECMTB08, Edinburgh, 1 July 2008

This talk can be downloaded from my web site
`www.ma.hw.ac.uk/~jas`

In collaboration with
Helen Waugh

Outline

Diabetic Wound Healing

- Wound healing in diabetics is impaired
- In some cases, wounds fail to heal over long periods (> 6 months $\leftrightarrow$ diabetic ulcer)
- Limb amputation is required in extreme cases
- Annual cost in UK is £17M

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- One component is that some aspects of repair fail to progress beyond the inflammatory phase
- In particular, macrophages persist for long times, with significant numbers present after a month (cf clearance after a few days in normal healing)
- We develop a mathematical model to investigate this persistence of macrophage numbers (and associated phenotype imbalance)

Outline

Model Ingredients

- Monocytes migrate to the wound in response to TGFβ (T)
- In the wound, monocytes differentiate into one of three macrophage phenotypes, in response to micro-environmental signals:

  Inflammatory macrophages (ϕ_I) release various cytokines that promote migration and proliferation of fibroblasts and endothelial cells

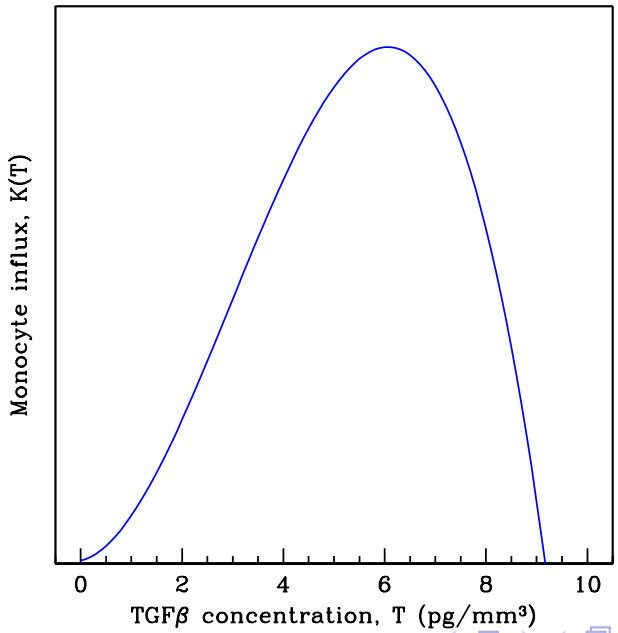
  Repair macrophages (ϕ_R) remodel the extracellular matrix

  Cytocidal macrophages remove bacteria and other debris (not included in the model)
- The balance between inflammatory and repair macrophages is different in normal and diabetic wounds

Model Equations

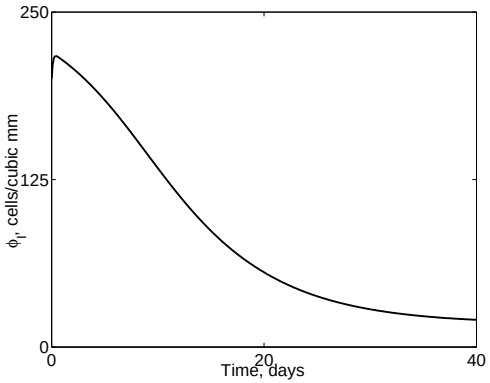
$$
\begin{aligned}
d\phi_I/dt &= \overbrace{\alpha K(T)}^{\text{influx}} + \overbrace{k_1\Phi_I(k_2-\Phi_I-\Phi_R)}^{\text{proliferation}} - \overbrace{d_1\Phi_I}^{\text{removal}} \\
d\phi_R/dt &= (1-\alpha)K(T) + k_1\Phi_R(k_2-\Phi_I-\Phi_R) - d_1\Phi_R \\
dT/dt &= \underbrace{k_3\Phi_I}_{\text{production}} - \underbrace{d_2 T}_{\text{decay}}
\end{aligned}
$$

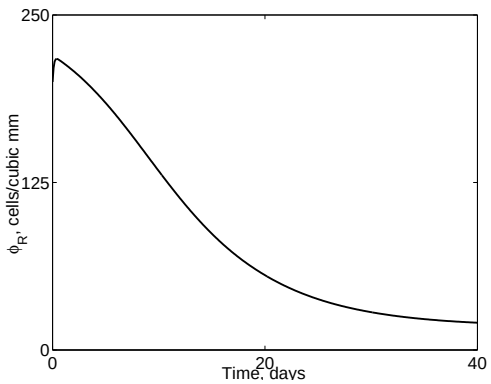
$\alpha_{\text{diabetic}} > \alpha_{\text{normal}}$

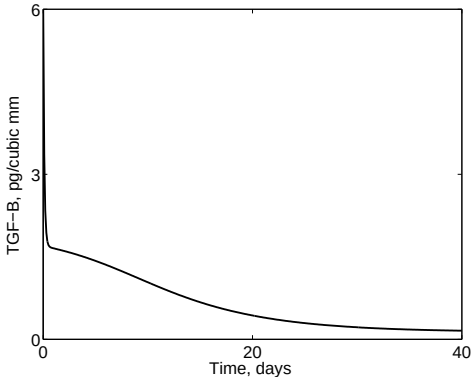


Typical Model Solution

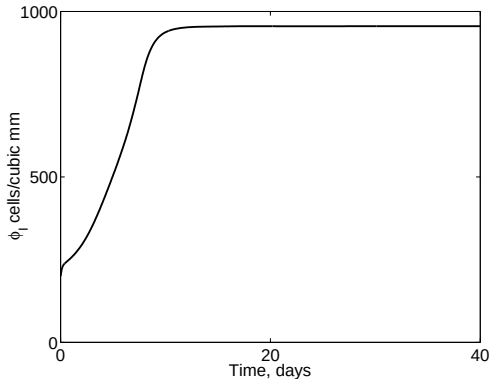
Normal wound ($\alpha = 0.5$):

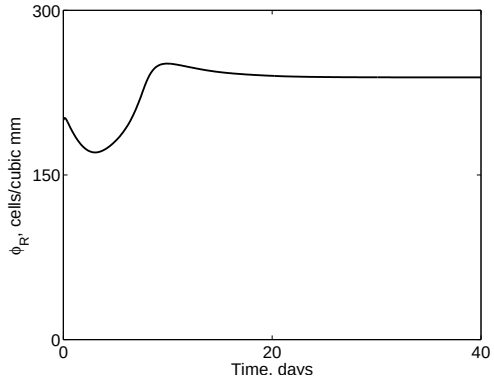


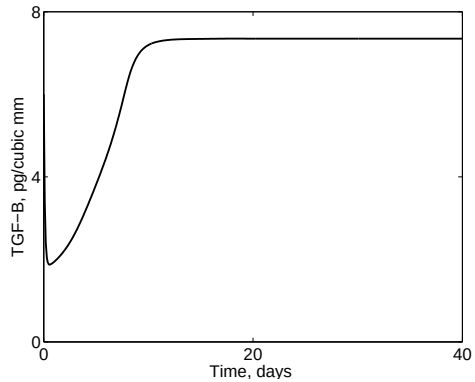




Diabetic wound ($\alpha = 0.8$):

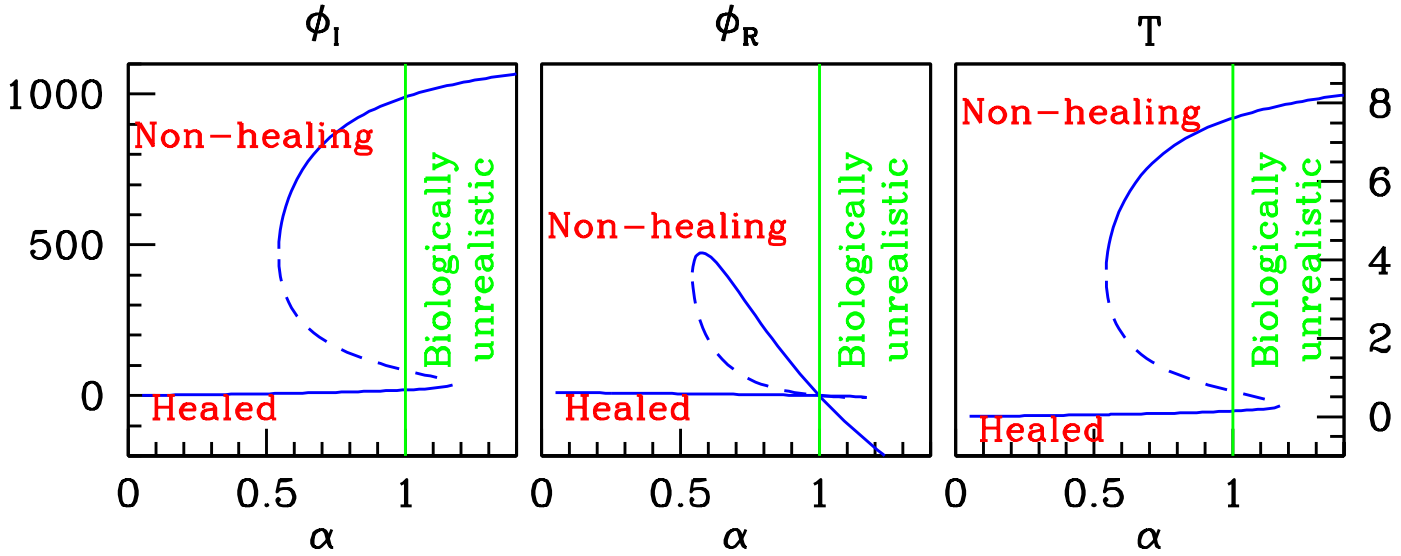






Steady States and Model Predictions

Non-negative steady states are:



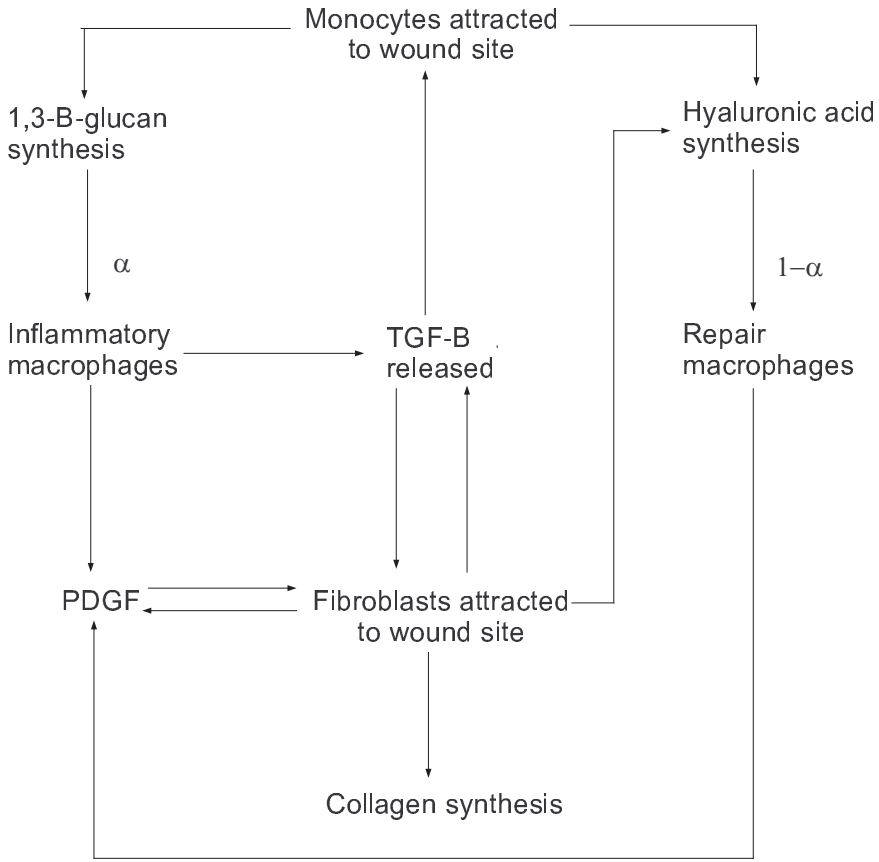
Predictions:

- The non-healing steady state appears abruptly, via a bifurcation, as α is increased
- The healed steady state persists and remains stable up to $\alpha = 1$, so that effective treatment is a possibility

Outline

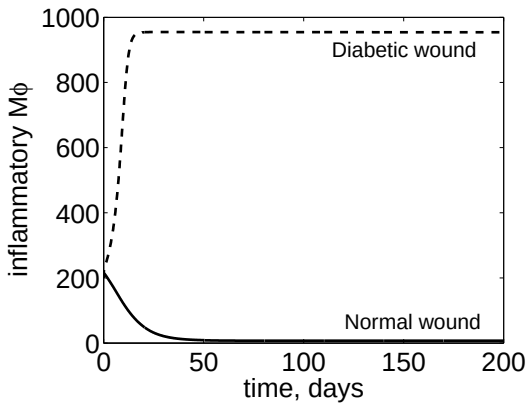
Key Interactions in the Expanded Model

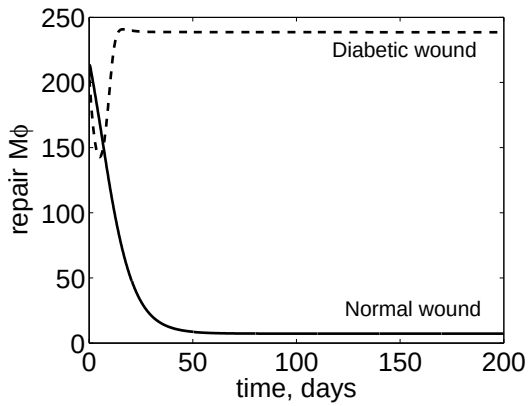
To investigate possible therapies, we use an expanded model.

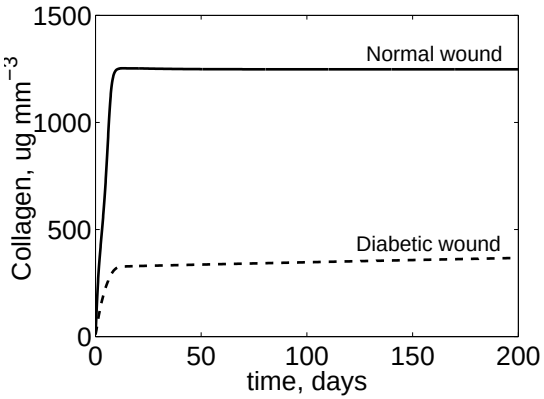


Typical Solution of the Expanded Model

Model variables: inflammatory macrophages, repair macrophages, fibroblasts, collagen, TGFβ, PDGF, hyaluronan







Apligraf Treatment

Apligraf (Organogenesis, US) is an artificial skin comprising dermal and epidermal layers in a bioabsorbable scaffold.

Component	100 % Density(per cubic mm)
Neonatal Fibroblasts	1550 cells
TGF-β	0.4 pg
PDGF	1 pg
Collagen	0.45 μg
Total Hyaluronan	18.0 μg
Dermal Hyaluronan	15.5 μg
Epidermal Hyaluronan	2.5 μg

Protocol: one application per week for five weeks.

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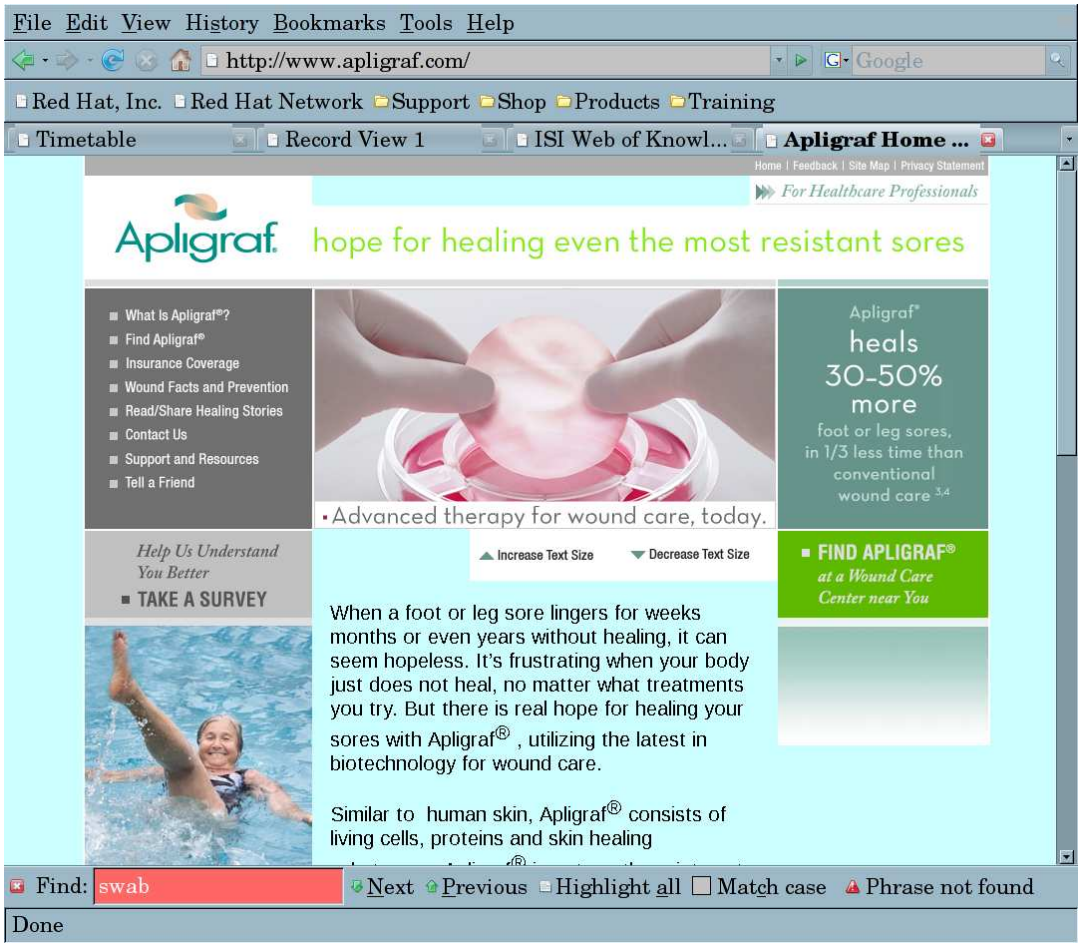
A separate modelling study suggests that the epidermal layer does not play a significant role in initiating wound repair.

The Apligraf Web Site



Dermagraft Treatment

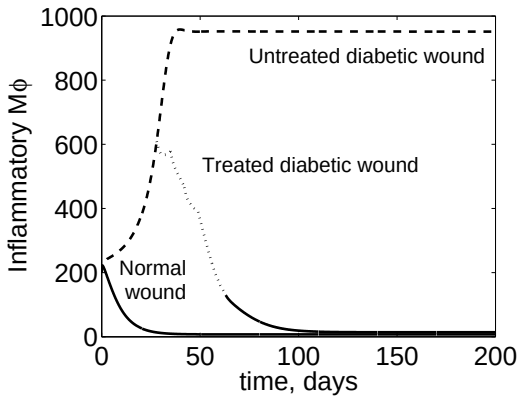
Dermagraft (Advanced Biohealing Inc, US) is an artificial dermal layer.

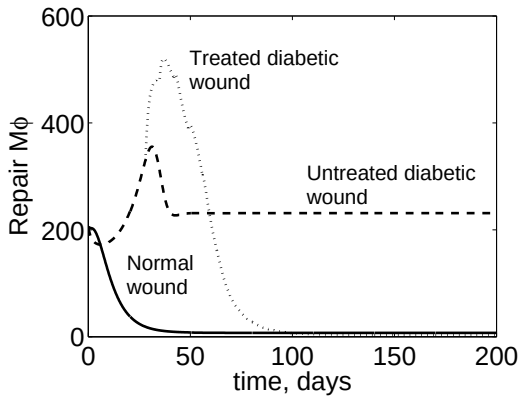
Component	100 % Density(per cubic mm)
Neonatal Fibroblasts	8000 cells
TGF-β	0.4 pg
PDGF	1 pg
Collagen	18.75 μg
Total Hyaluronan	80 μg
Dermal Hyaluronan	80 μg
Epidermal Hyaluronan	0 μg

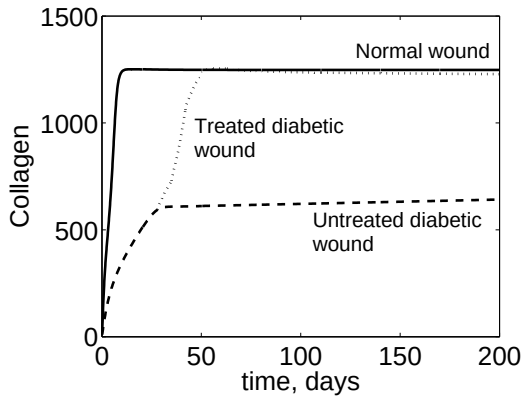
Protocol: one application per week for eight weeks.

The Dermagraft Web Site

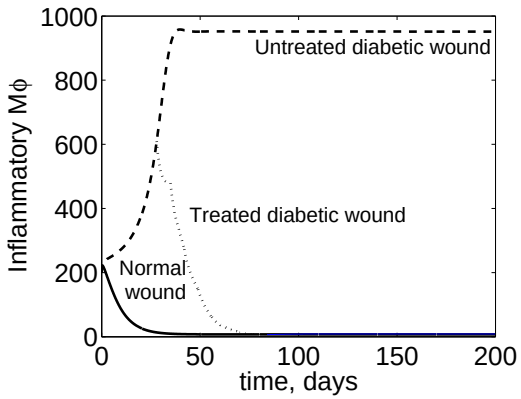
Simulation of Apilgraf Treatment

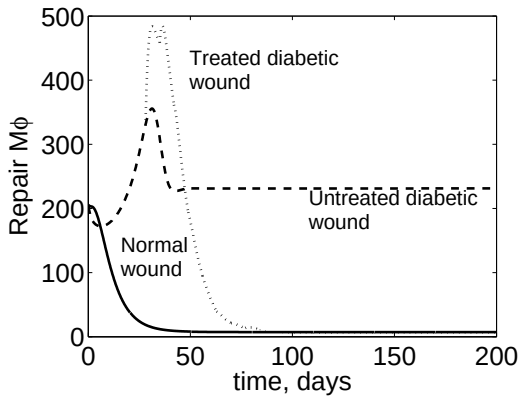


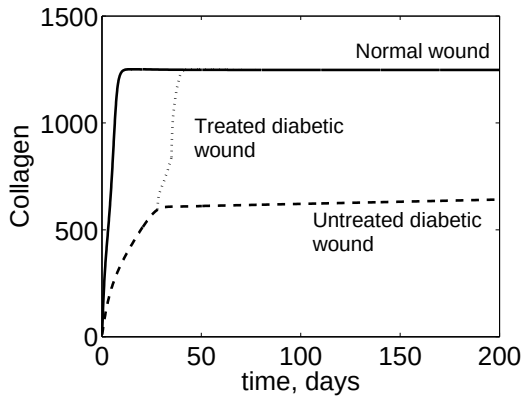




Simulation of Dermagraft Treatment





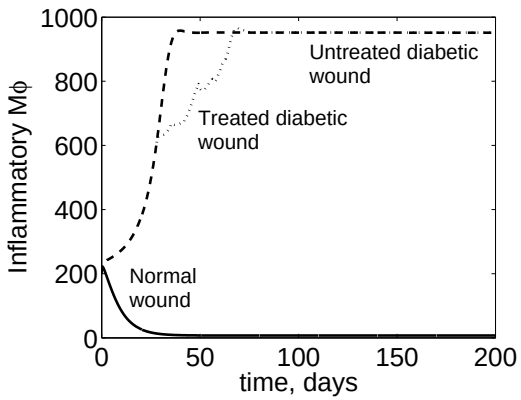


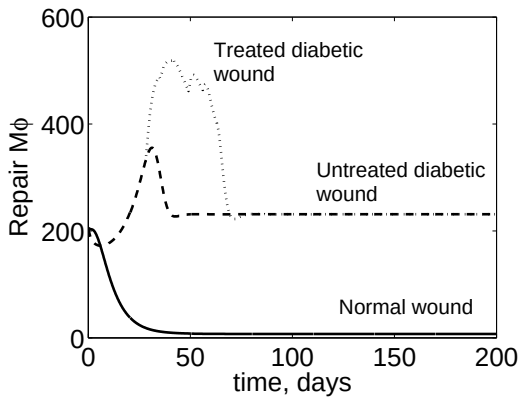
Outline

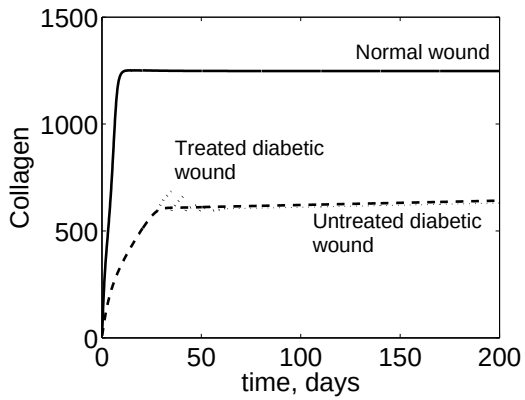
Separating the Treatment Components

Included: TGFβ, PDGF and collagen

Excluded: hyaluronan, fibroblasts







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Included: fibroblasts

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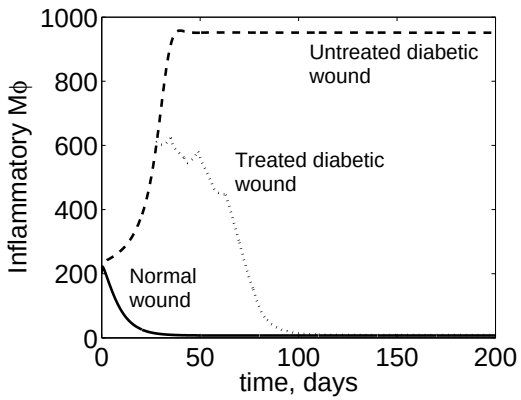

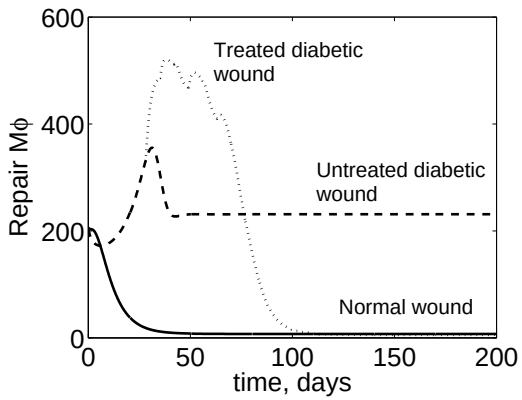

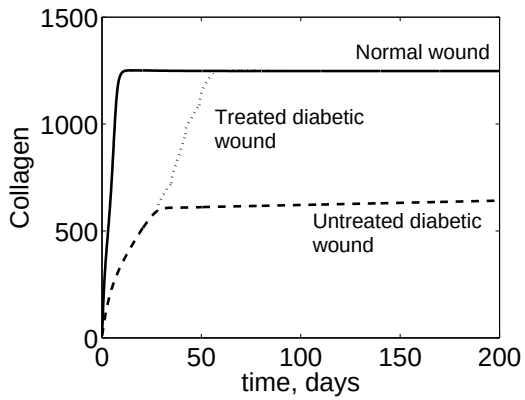

Separating Fibroblast Functions

Fibroblasts secrete a range of regulatory chemicals:

- TGFβ
- PDGF
- collagen
- collagenase
- hyaluronan

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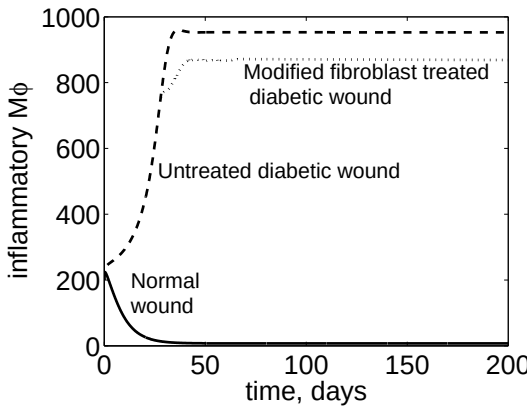
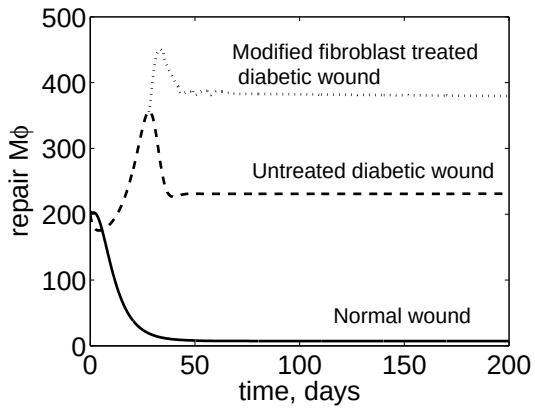
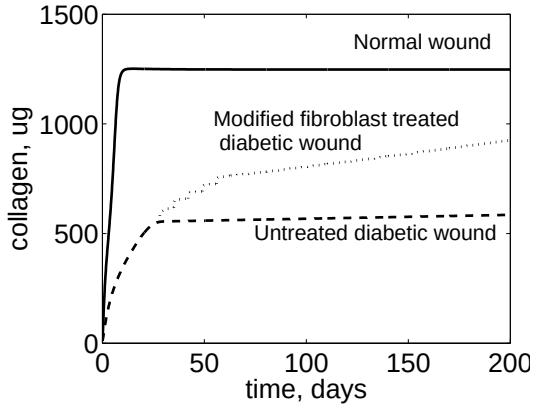
Answer: our model predicts that only hyaluronan secretion is critical

Demonstration that Hyaluronan Production is Critical

Using the model, we simulate treatment with fibroblasts that have been modified to not produce hyaluronan, but are otherwise normal.



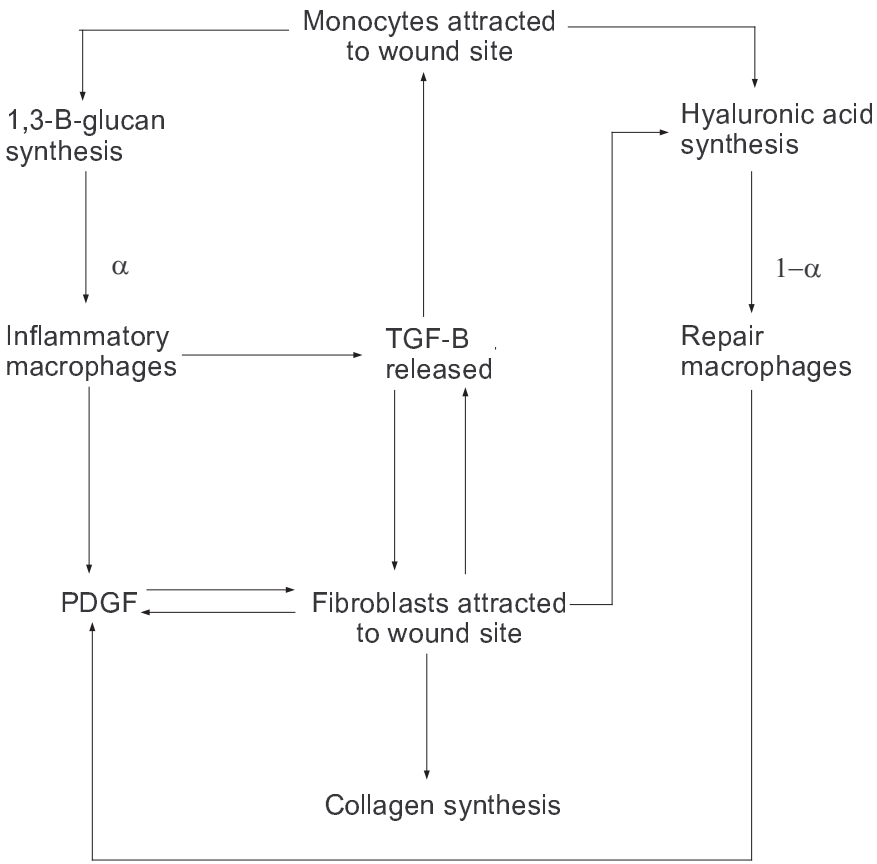




Outline

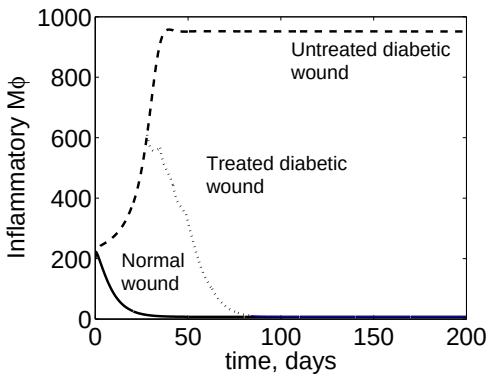
Conclusions

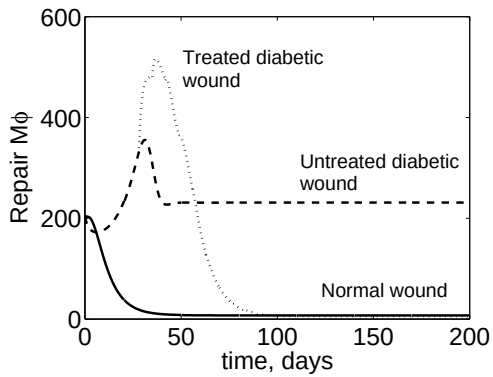
- The key component of Apligraf and Dermagraft treatments is the production of hyaluronan by the added fibroblasts
- Hyaluronan initiates healing by switching macrophages from the inflammatory to the repair phenotype

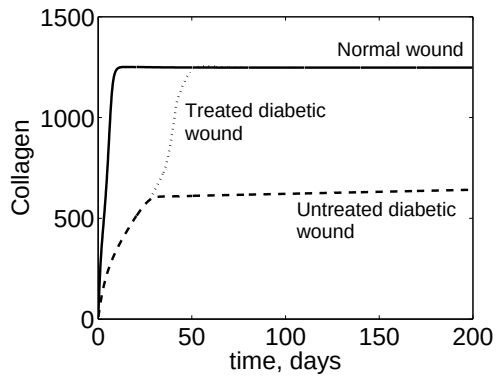


Predictions

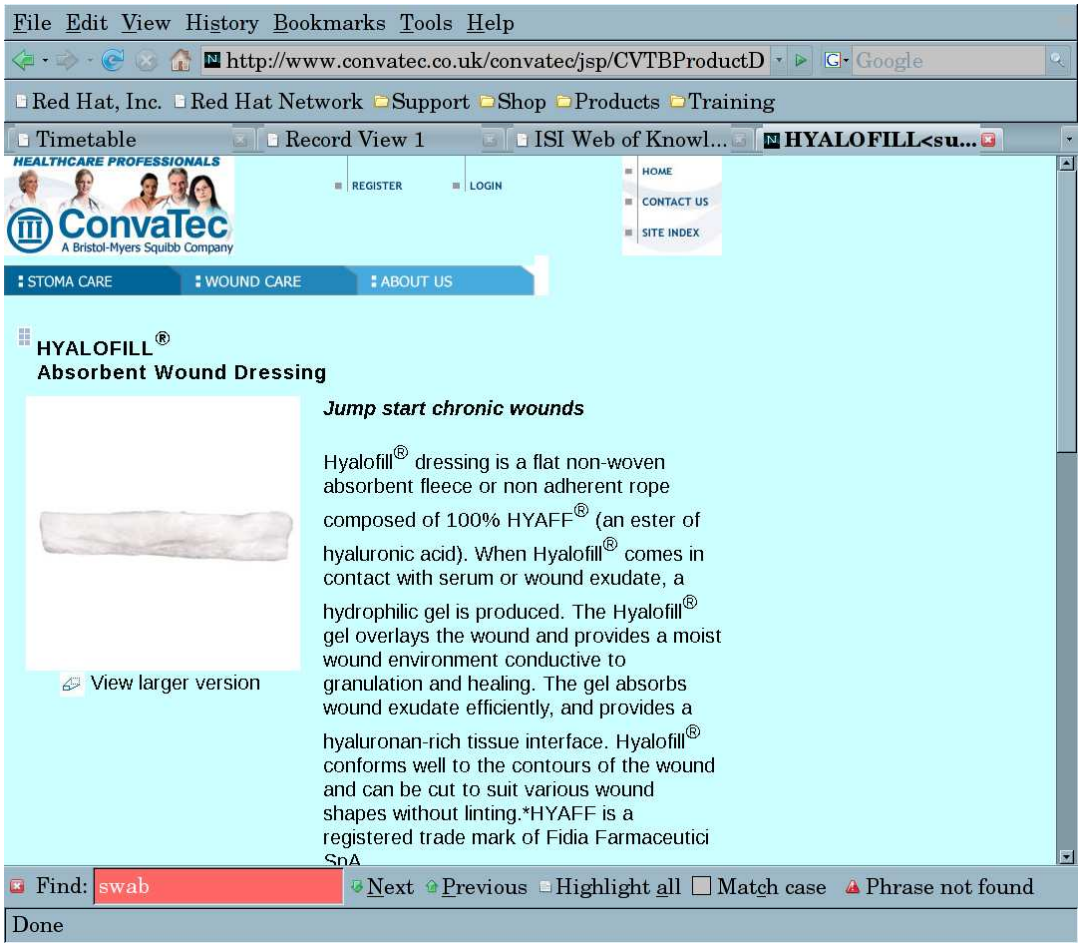
1. For both therapies, the current protocols could be improved
2. Diabetic wound healing can be initiated simply by the addition of hyaluronan







The Hyalofill Web Site



References

H.V. Waugh, J.A. Sherratt.
Macrophage dynamics in diabetic wound healing.
Bulletin of Mathematical Biology 68, 197-207 (2006)

H.V. Waugh, J.A. Sherratt.
Modelling the effects of treating diabetic wounds with engineered skin substitutes.
Wound Repair and Regeneration 15, 556-565 (2007)

These papers are available from my web site:
`www.ma.hw.ac.uk/~jas`

Both the basic and extended models have been translated into CellML by the University of Auckland; see `www.cellml.org`

List of Frames