

Modelling macrophage dynamics and their therapeutic implications in diabetic wound healing

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This talk can be downloaded from my web site

www.ma.hw.ac.uk/~jas

In collaboration with
Helen Waugh



Outline

- 1 Introduction to Diabetic Wound Healing
- 2 A Simple Mathematical Model
- 3 An Expanded Model
- 4 Using the Model to Understand the Treatments
- 5 Conclusions

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

Why is Wound Healing Impaired in Diabetics?

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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)

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Model Ingredients

- Monocytes migrate to the wound in response to $TGF\beta$ (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

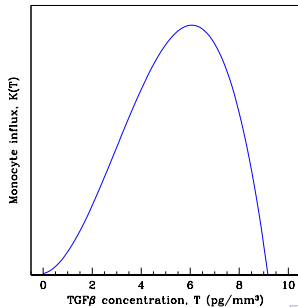
Repair macrophages (ϕ_R) remodel the extracellular matrix

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

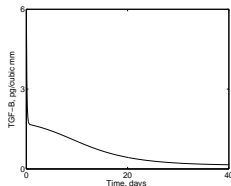
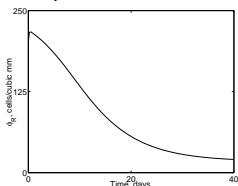
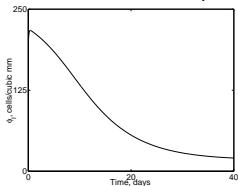
$$\begin{aligned}
 d\phi_I/dt &= \overbrace{\alpha K(T)}^{\text{influx}} + \overbrace{k_1 \phi_I (k_2 - \phi_I - \phi_R)}^{\text{proliferation}} - \overbrace{d_1 \phi_I}^{\text{removal}} \\
 d\phi_R/dt &= (1 - \alpha) K(T) + k_1 \phi_R (k_2 - \phi_I - \phi_R) - d_1 \phi_R \\
 dT/dt &= \underbrace{k_3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



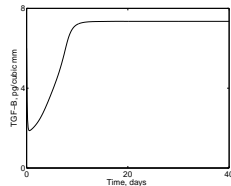
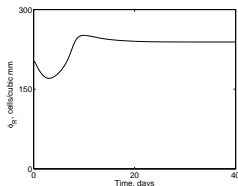
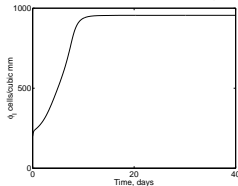
$$\alpha_{\text{diabetic}} > \alpha_{\text{normal}}$$

Typical Model Solution

Normal wound ($\alpha = 0.5$):

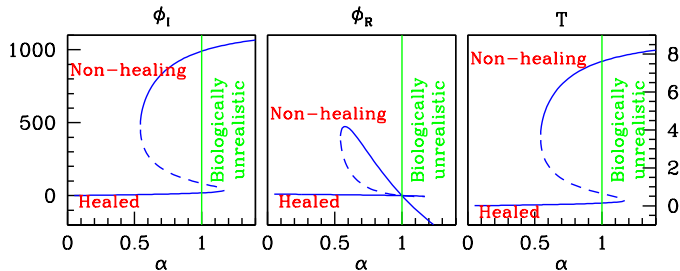


Diabetic wound ($\alpha = 0.8$):



Steady States and Model Predictions

Non-negative steady states are:



Predictions:

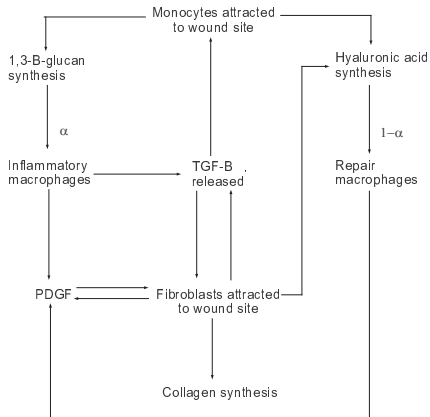
- The non-healing steady state appears abruptly, via a bifurcation, as α is increased
- The healed steady state persists and remains stable up to $\alpha = 1$, so that effective treatment is a possibility

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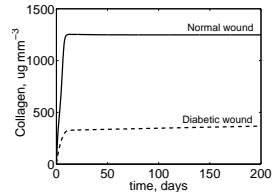
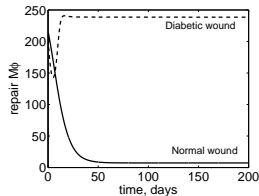
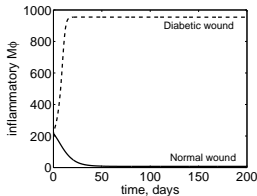
Key Interactions in the Expanded Model

To investigate possible therapies, we use an expanded model.



Typical Solution of the Expanded Model

Model variables: inflammatory macrophages, repair macrophages, fibroblasts, collagen, $TGF\beta$, 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 μ g
Total Hyaluronan	18.0 μ g
Dermal Hyaluronan	15.5 μ g
Epidermal Hyaluronan	2.5 μ g

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

The screenshot shows the Apligraf website homepage in a web browser. The browser's address bar displays 'http://www.apligraf.com/'. The website features a navigation menu with links for 'Red Hat, Inc.', 'Red Hat Network', 'Support', 'Shop', 'Products', and 'Training'. The main content area includes the Apligraf logo, a headline 'hope for healing even the most resistant sores', and a central image of a hand applying a dressing to a wound. Text on the page states that Apligraf 'heals 30-50% more' foot or leg sores in 1/3 less time than conventional care. A sidebar on the left offers a 'TAKE A SURVEY' and a 'Help Us Understand You Better' section. A search bar at the bottom shows the search term 'swab'.

File Edit View History Bookmarks Tools Help

http://www.apligraf.com/

Red Hat, Inc. Red Hat Network Support Shop Products Training

Timetable Record View 1 ISI Web of Know... Apligraf Home ...

For Healthcare Professionals

Apligraf hope for healing even the most resistant sores

- What is Apligraf?
- Find Apligraf®
- Insurance Coverage
- Wound Facts and Prevention
- Read/Share Healing Stories
- Contact Us
- Support and Resources
- Tell a Friend

Advanced therapy for wound care, today.

When a foot or leg sore lingers for weeks months or even years without healing, it can seem hopeless. It's frustrating when your body just does not heal, no matter what treatments you try. But there is real hope for healing your sores with Apligraf®, utilizing the latest in biotechnology for wound care.

Similar to human skin, Apligraf® consists of living cells, proteins and skin healing

Apligraf® heals 30-50% more foot or leg sores, in 1/3 less time than conventional wound care ^{1,2,4}

FIND APLIGRAF®
at a Wound Care Center near You

Find: swab

Next Previous Highlight all Match case Phrase not found

Done

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.

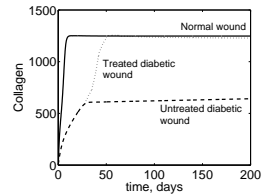
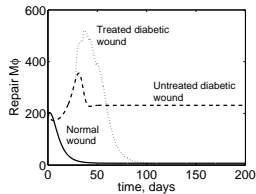
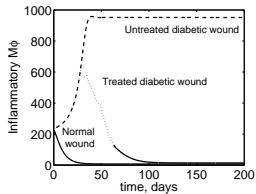
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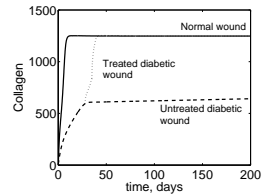
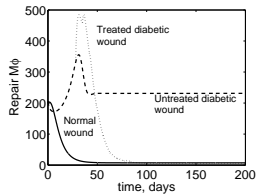
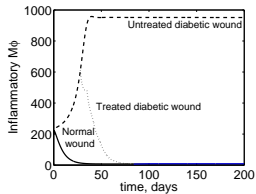
The Dermagraft Web Site

The screenshot shows the Dermagraft website homepage. At the top, there is a navigation menu with links for Home, About Dermagraft, About Diabetic Foot Ulcers, Research and Case Studies, Product Videos, and Reimbursement & Ordering Information. Below the menu is a large banner image of a smiling man and woman with the text "That's The Way to Heal". To the right of the banner is a red sidebar with "Dermagraft QUICKLINKS" and buttons for "PRODUCT MONOGRAPH", "PATIENT INFORMATION", "DIRECTIONS FOR USE", and "PRODUCT VIDEOS". Below the banner is a section for "Upcoming Events" listing "The Western Podiatric Medical Congress" in Anaheim, CA (June 19-22, 2008), "SST Woundcare" in Chicago, IL (July 17-19, 2008), and "APMA Annual Meeting". At the bottom, there is a search bar with the word "swab" entered and a search button. The footer of the page contains the text "Jonathan Sherratt www.ma.hw.ac.uk/~jas".

Simulation of Apligraf Treatment



Simulation of Dermagraft Treatment



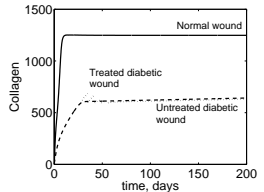
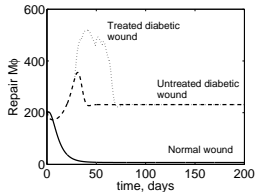
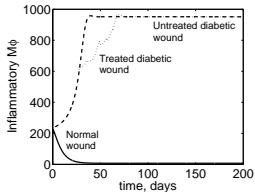
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Separating the Treatment Components

Included: TGF β , PDGF and collagen

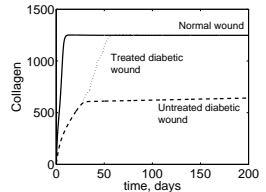
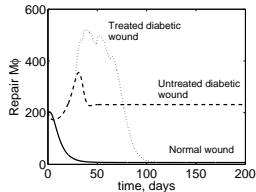
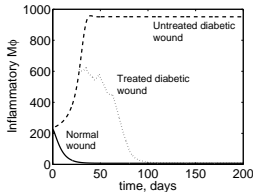
Excluded: hyaluronan, fibroblasts



Separating the Treatment Components

Included: fibroblasts

Excluded: $TGF\beta$, PDGF, collagen and hyaluronan



Separating Fibroblast Functions

Fibroblasts secrete a range of regulatory chemicals:

- TGF β
- PDGF
- collagen
- collagenase
- hyaluronan

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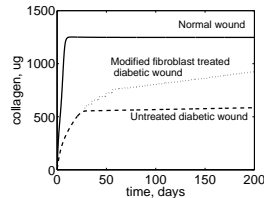
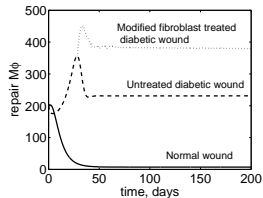
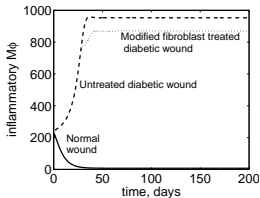
- TGF β
- PDGF
- collagen
- collagenase
- hyaluronan

Question: which of these are critical to treatment success?

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.

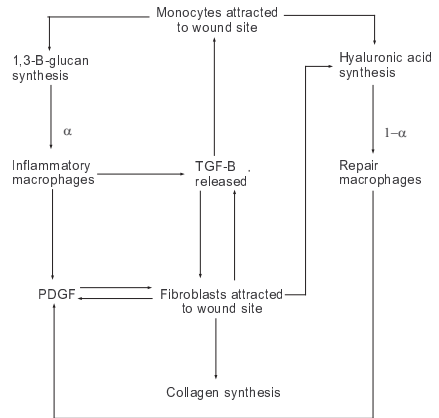


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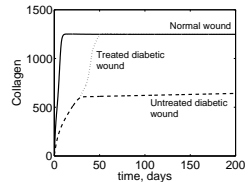
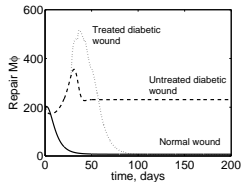
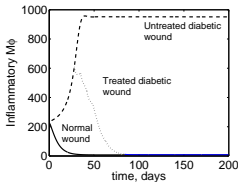
Conclusions

- 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

The screenshot shows a web browser window displaying the Hyalofill website. The browser's address bar shows the URL <http://www.convatec.co.uk/convatec/jsp/CVTBProductD>. The website header includes the Convatec logo and navigation links for HOME, CONTACT US, and SITE INDEX. Below the header, there are tabs for STOMA CARE, WOUND CARE, and ABOUT US. The main content area is titled "HYALOFILL® Absorbent Wound Dressing" and features a photograph of the product. To the right of the image is a detailed description of the dressing's composition and function. At the bottom of the page, there is a search bar with the text "Find: swab" and navigation controls for "Next", "Previous", "Highlight all", "Match case", and "Phrase not found".

File Edit View History Bookmarks Tools Help

http://www.convatec.co.uk/convatec/jsp/CVTBProductD

Red Hat, Inc. Red Hat Network Support Shop Products Training

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HEALTHCARE PROFESSIONALS
REGISTER LOGIN

HOME
CONTACT US
SITE INDEX

STOMA CARE WOUND CARE ABOUT US

HYALOFILL®
Absorbent Wound Dressing

Jump start chronic wounds

Hyalofill® dressing is a flat non-woven absorbent fleece or non adherent rope composed of 100% HYAFF® (an ester of hyaluronic acid). When Hyalofill® comes in contact with serum or wound exudate, a hydrophilic gel is produced. The Hyalofill® gel overlays the wound and provides a moist wound environment conducive to granulation and healing. The gel absorbs wound exudate efficiently, and provides a hyaluronan-rich tissue interface. Hyalofill® conforms well to the contours of the wound and can be cut to suit various wound shapes without linting.*HYAFF is a registered trade mark of Fidia Farmaceutici SpA

View larger version

Find: swab Next Previous Highlight all Match case Phrase not found

Done

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

- 1 Introduction to Diabetic Wound Healing
- Diabetic Wound Healing
 - Why is Wound Healing Impaired in Diabetics?

- 2 A Simple Mathematical Model
- Model Ingredients
 - Model Equations
 - Typical Model Solution
 - Steady States and Model Predictions

- 3 An Expanded Model
- Key Interactions in the Expanded Model
 - Typical Solution of the Expanded Model
 - Apligraf and Dermagraft Treatments
 - Simulation of Apligraf Treatment
 - Simulation of Dermagraft Treatment

- 4 Using the Model to Understand the Treatments
- Separating the Treatment Components
 - Separating Fibroblast Functions
 - Demonstration that Hyaluronan Production is Critical
- 5 Conclusions
- Conclusions
 - Predictions
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