



Wiskunde en inzicht in wondgenezing

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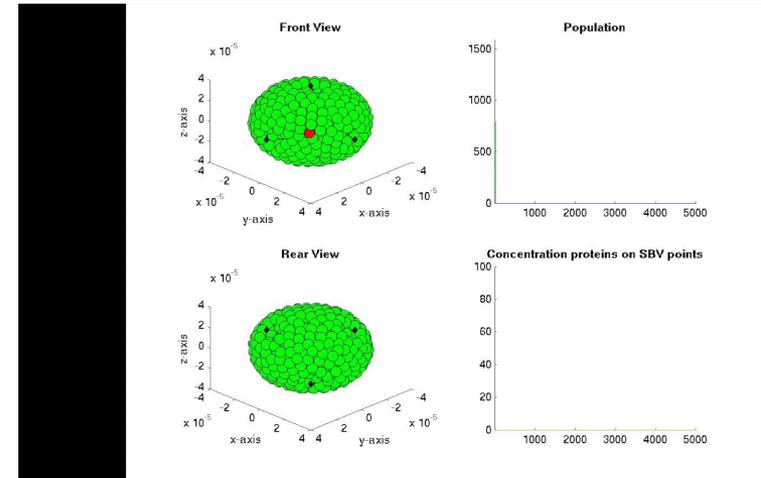
November, 2015, Wound Care Society Congress, Utrecht, The Netherlands

Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
<ul style="list-style-type: none">• Sponsoring of onderzoeksgeld• Honorarium of andere (financiële) vergoeding• Aandeelhouder• Andere relatie, namelijk ...	<ul style="list-style-type: none">• N.v.t.• N.v.t.• N.v.t.• N.v.t.

Contents

- Inleiding en probleemstelling
- Model beschrijving
- Numerieke methode
- Simulaties
- Resultaten
- Conclusies



Doel: modellering van angiogenese met een cel-gebaseerd model

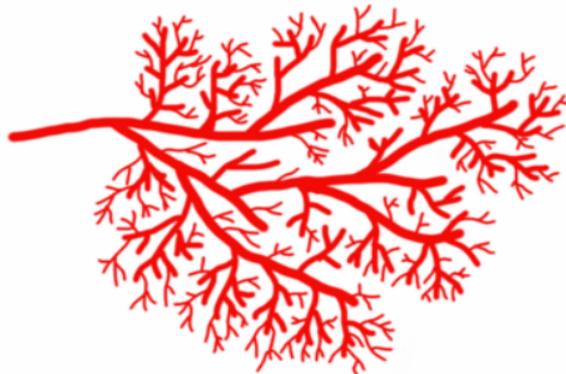
Inleiding & probleemstelling

Angiogenesis: ontspruiten van bloedvaatjes uit bestaande vaten

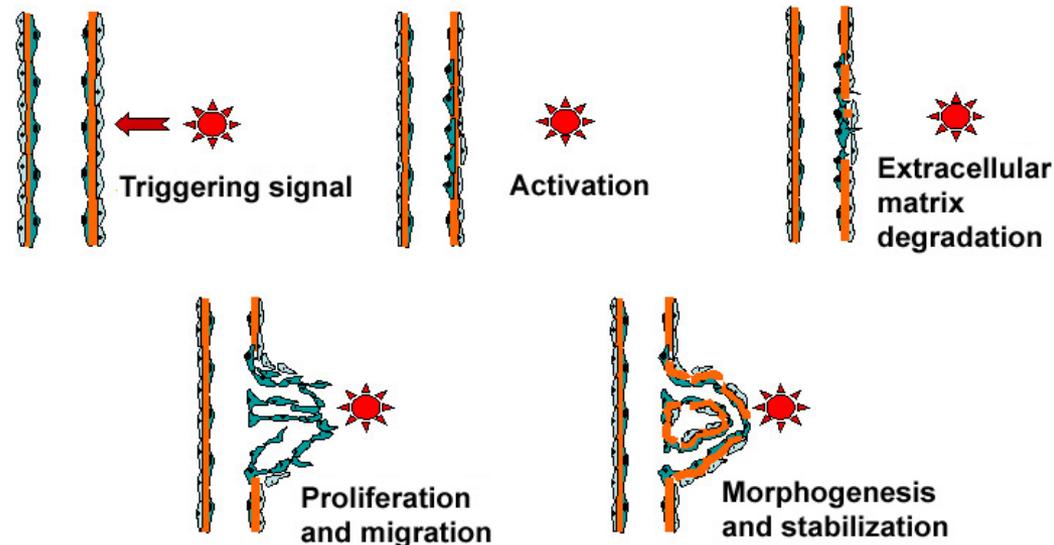
Before angiogenesis



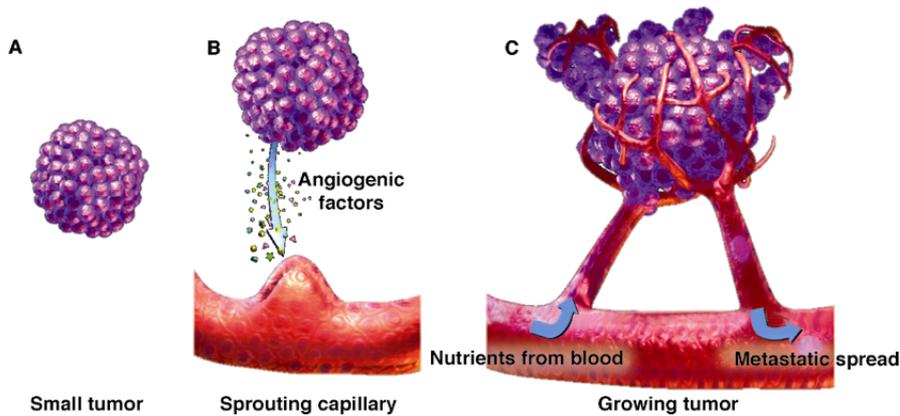
After angiogenesis



The stages of angiogenesis

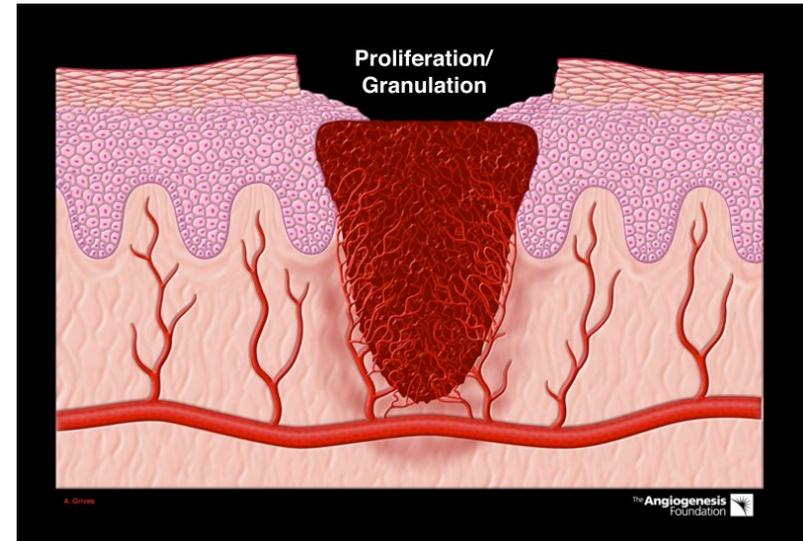


Inleiding & probleemstelling



Source: DW Siemans (2012)

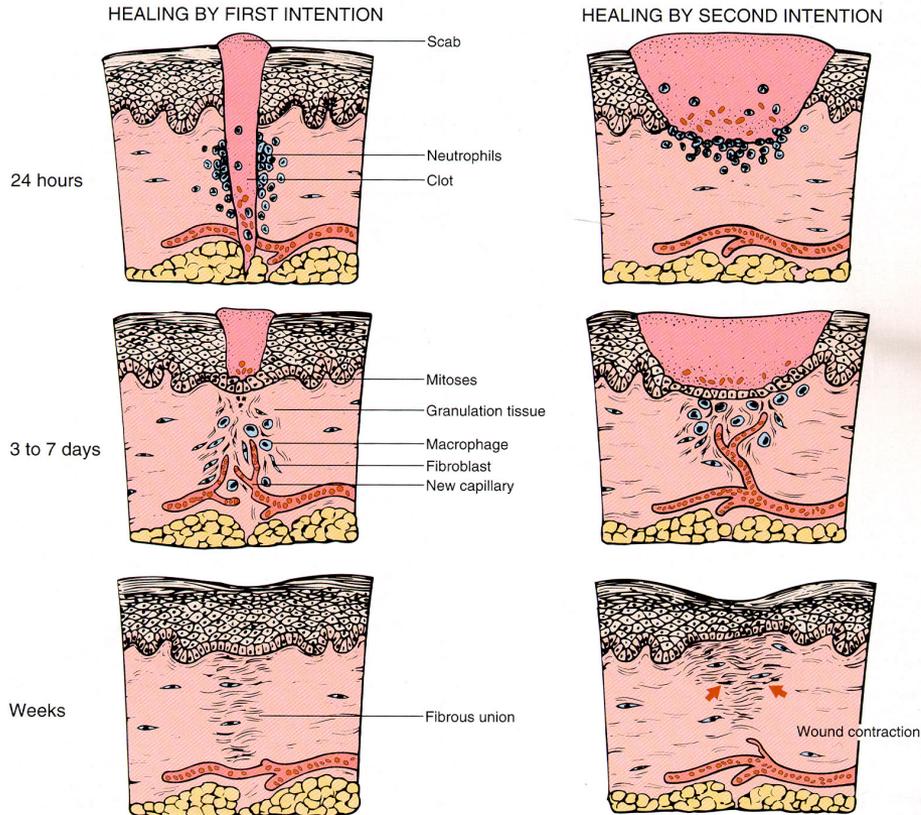
Transitie van ongevaarlijke tumor naar een kwaadaardige tumor



Source: The Angiogenesis Foundation

Aanmaak van nieuwe bloedvaatjes voor toelevering van voeding en zuurstof voor wondgenezing

Inleiding & Probleemstelling



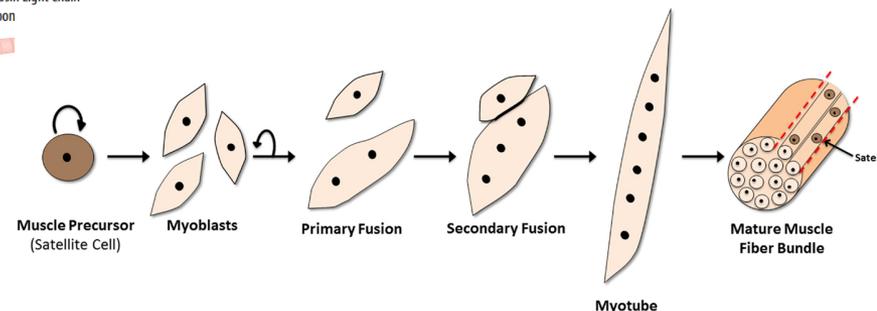
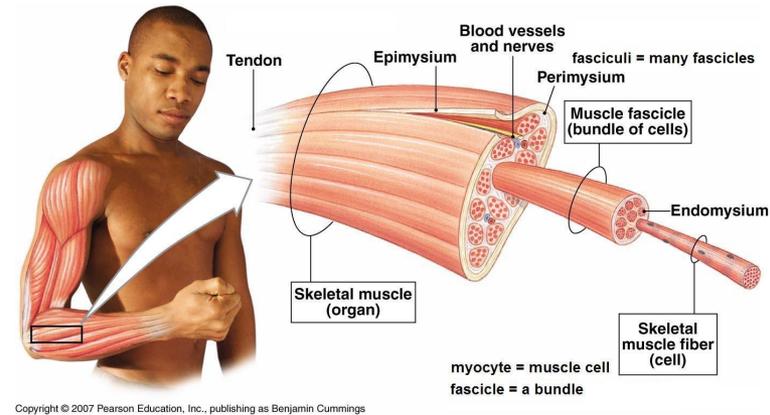
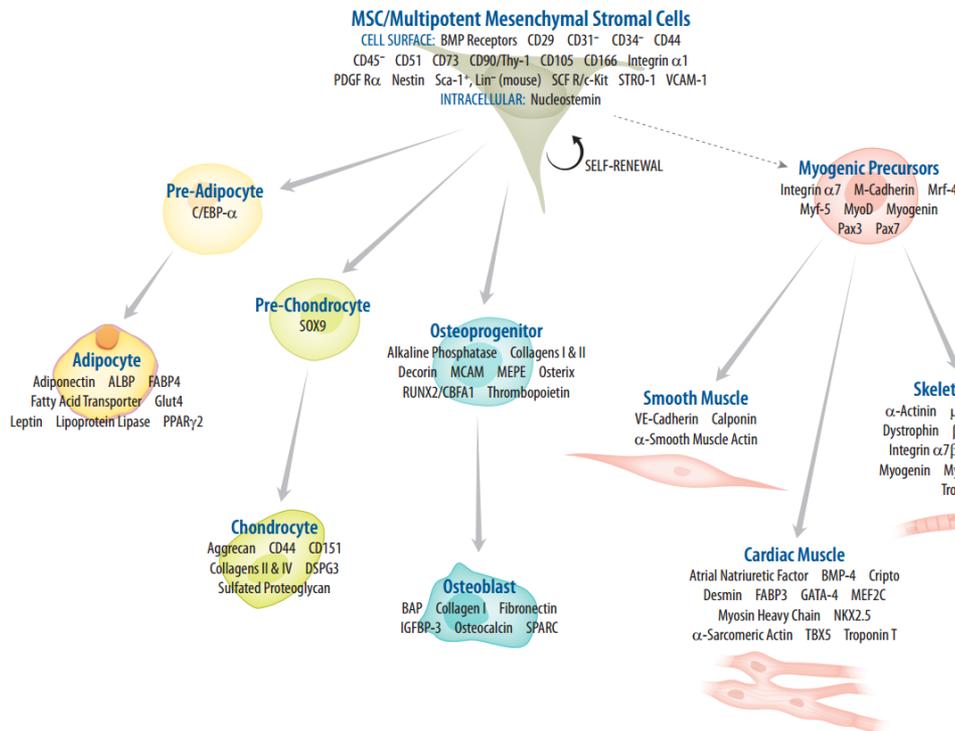
Wondcontractie: Proces tijdens wondgenezing wat leidt tot huidvernaauwing.

Wondcontractuur: Wondvernaauwing die leidt tot functionele beperkingen

Source: www.kaomp.org

Inleiding & Probleemstelling

Nodig: Een model voor differentiatie van cellen



Source: R& D systems

Source: Enwer (2014)

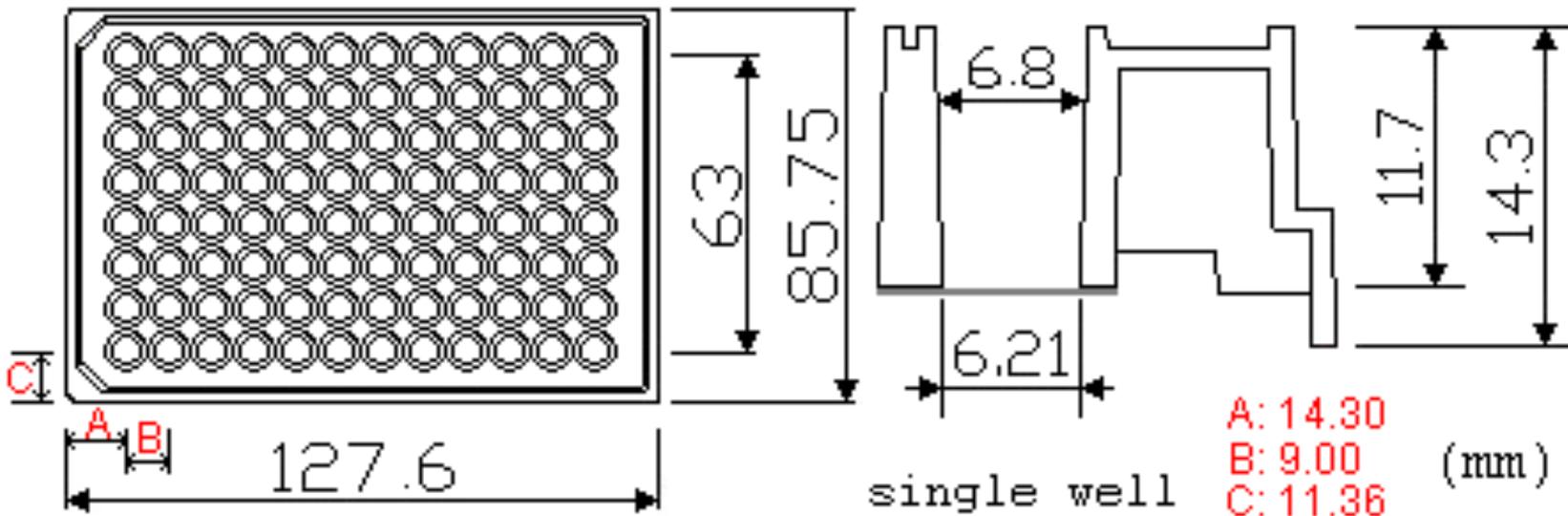
Model Beschrijving



Sue Gibbs

Experiment:

- fibrine gel + oplossing met Endotheelcellen
- Toevoeging van Tumor Necrose Factor (TNF) en VEGF om Ecs te stimuleren -> angiogenese



Model Beschrijving



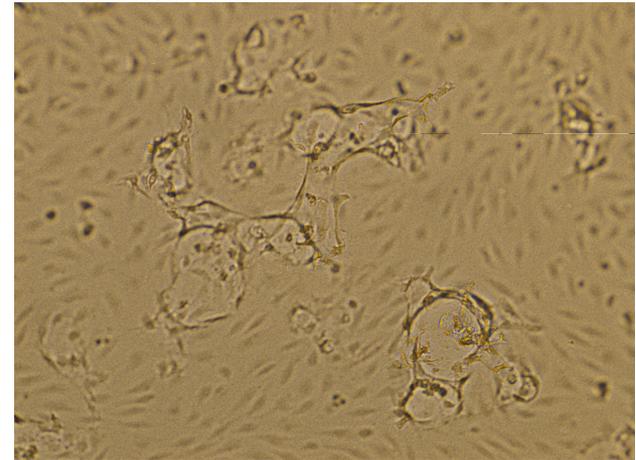
Hanneke
Monsuur

Model experiment:

- fibrine gel + solution of top containing ECs
- Toevoeging van Tumor Necrose Factor (TNF) en VEGF voor stimulatie ECs



Initial, ECs not stimulated

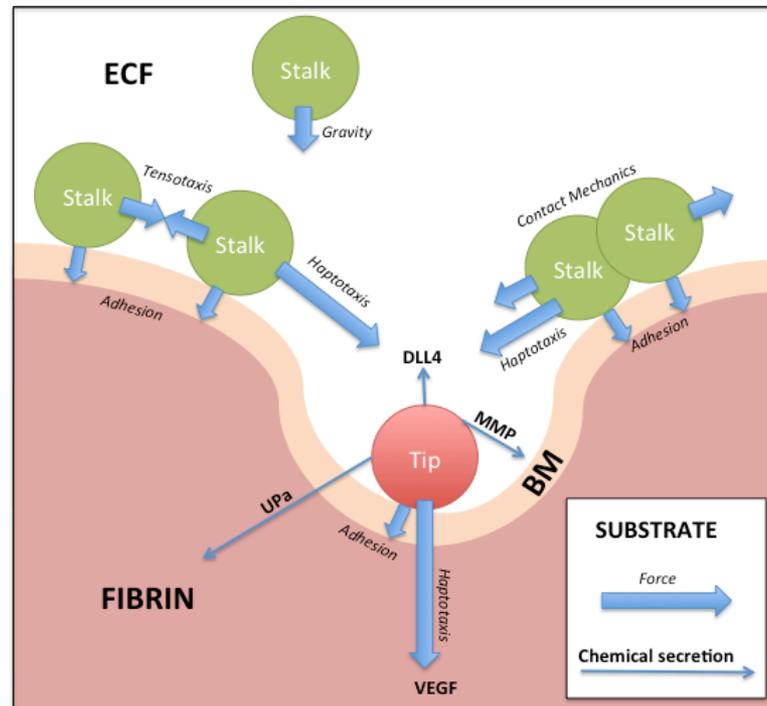


After stimulation with VEGF and TNF (magnified):
formation of cavities: sprouts

Model Beschrijving

Biologische processen in angiogenese:

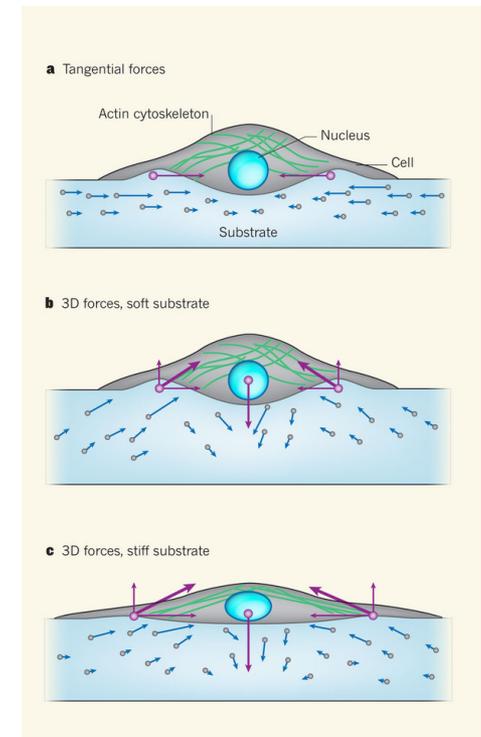
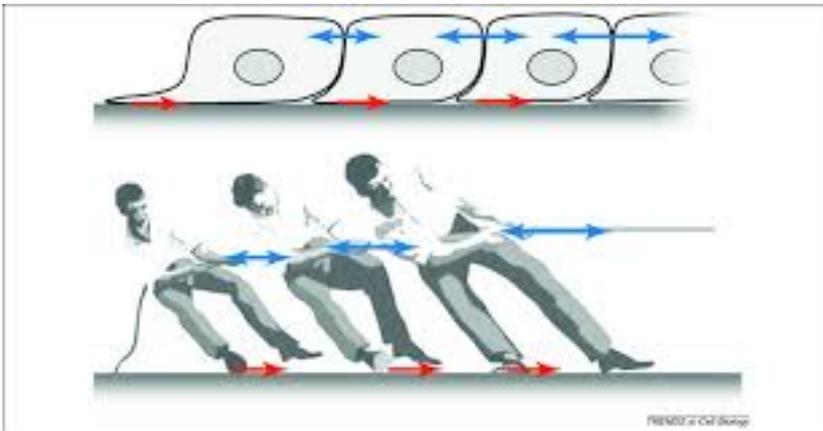
- Proliferatie (delen) van endotheelcellen;
- Cel migratie van tip en stalk cellen:
 - haptotaxis
 - durotaxis
 - random walk
- Celkrachten



Model Beschrijving

Modeleeraspecten

- Celmigratie (haptotaxis, passive convection, random walk)
- Celdifferentiatie
- Celkrachten op extracellulaire matrix
- Plastische deformaties
- Apoptosis (geprogrammeerde celsterfte)
- Uitscheiding van cytokinen
- Mechanische balans



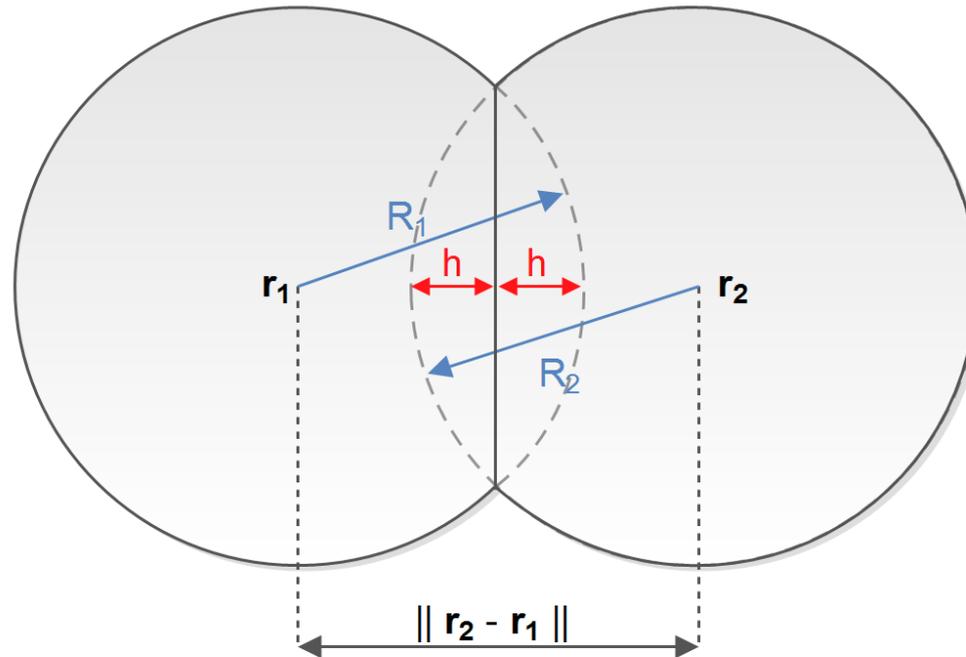
Source: www.nature.com

Source: www.cell.com

Model Beschrijving



Amit Gefen



Contact krachten dmv Hertz contactmechanica met plaatselijke celkromming

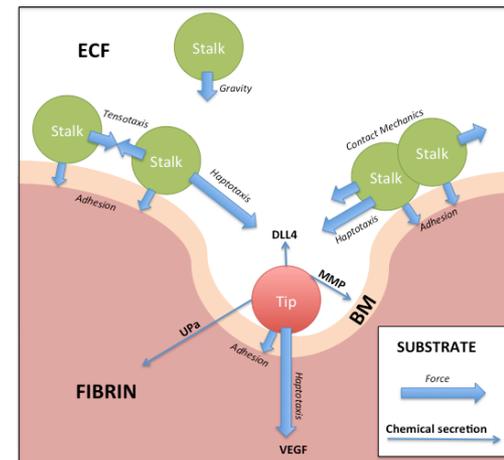
Veld rekenergie dichtheid berekend dmv FEM oplossing en gradient recovery

Vermolen & Gefen (2013)

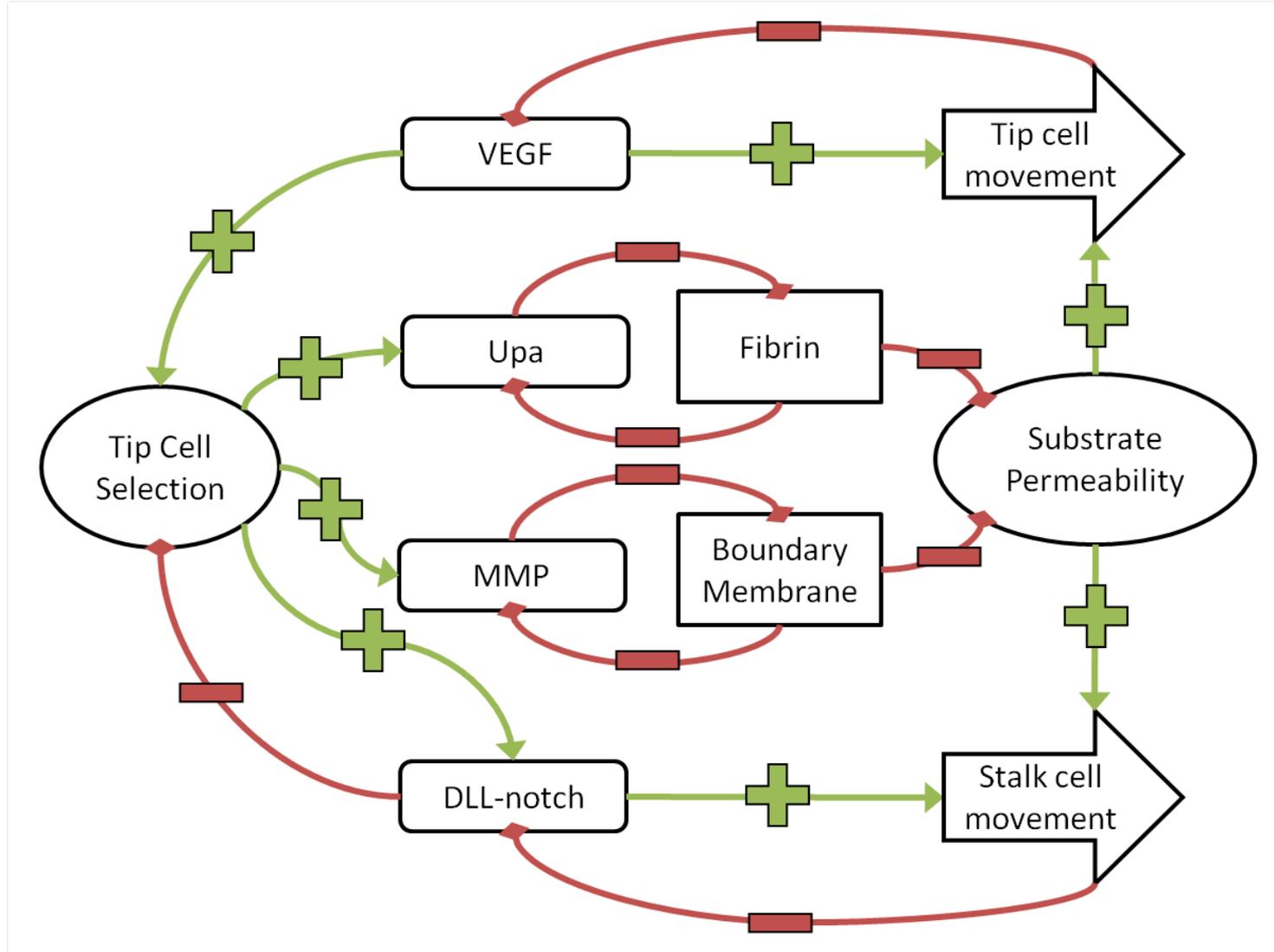
Model Beschrijving

Chemokinen:

- VEGF (trekken tipcellen aan);
- MMP (breekt grensmembraam af, uitgescheiden voor tipcellen);
- uPA (breekt fibrine af, uitgescheiden door tipcellen);
- DLL4 (zorgt ervoor dat stalkcellen de tipcellen volgen);

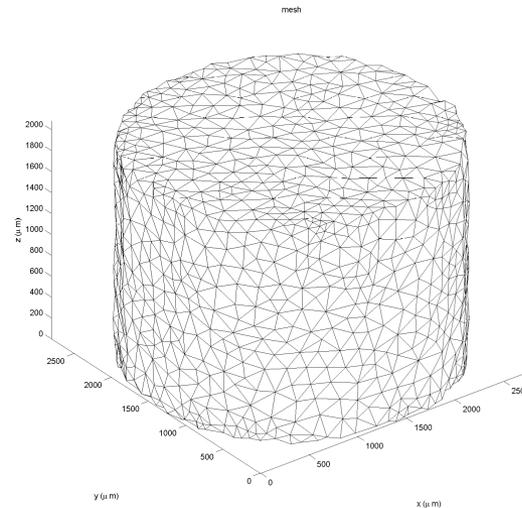


Model Beschrijving

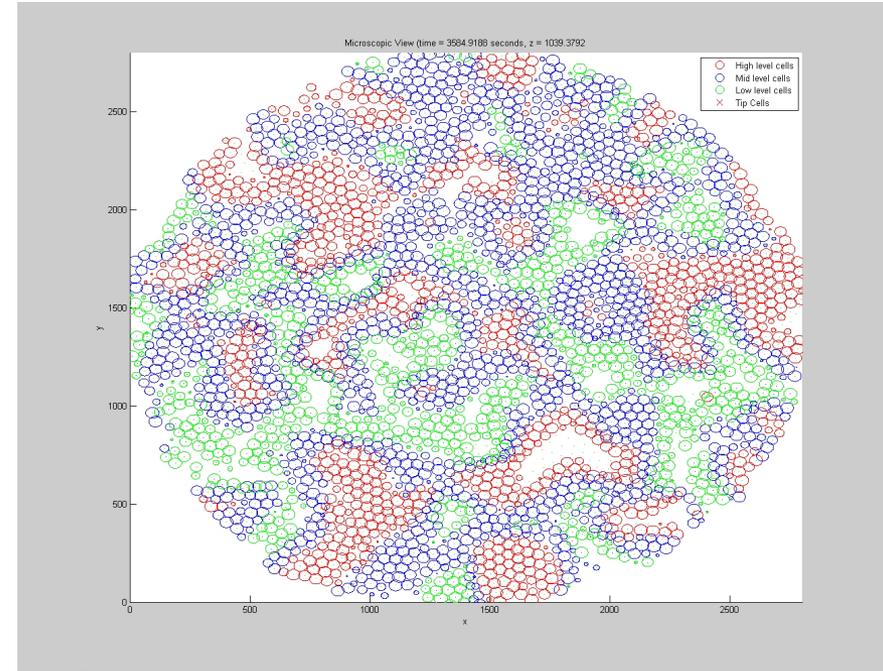
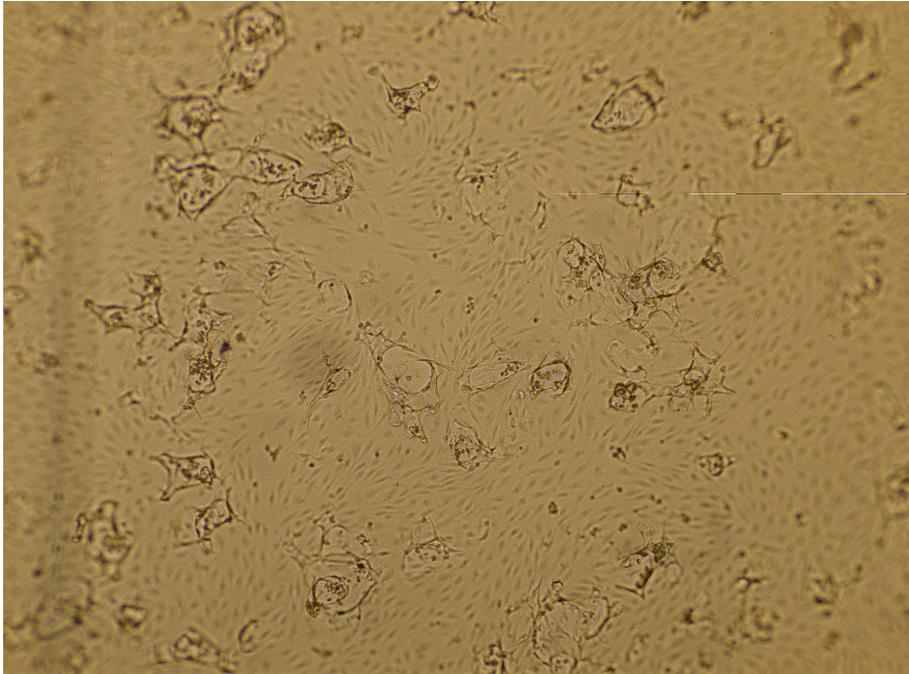


Numerieke Methode

- Finite-element methode met Euler-Backward voor PDEs
- Euler-Maruyama methode voor SDEs



Simulaties



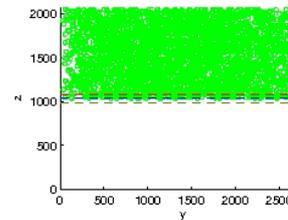
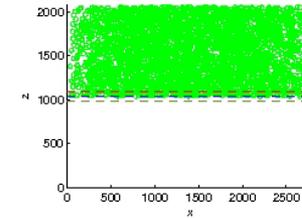
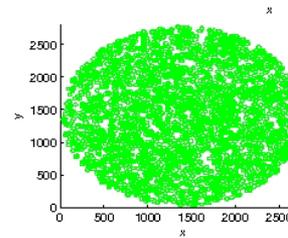
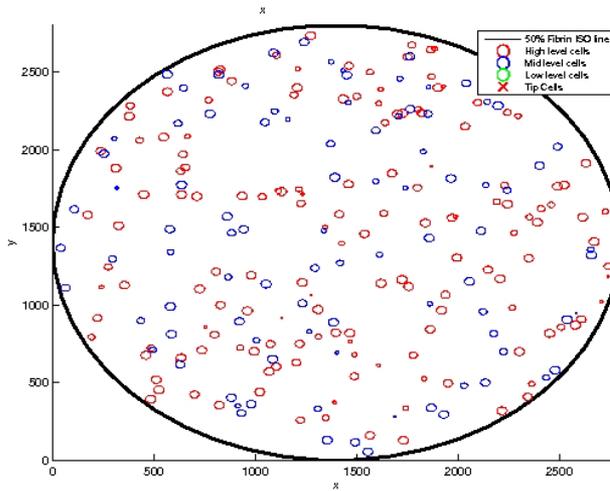
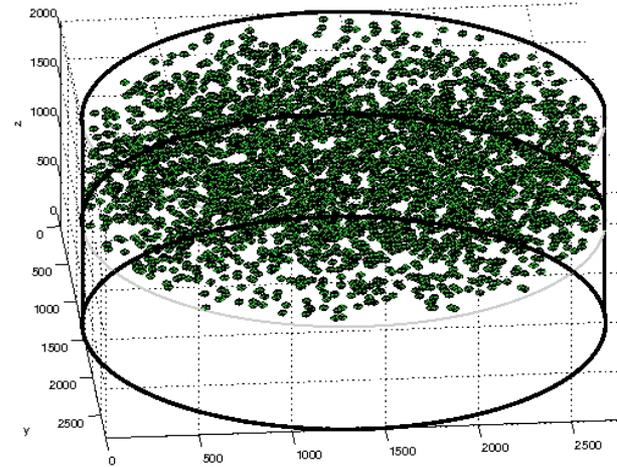
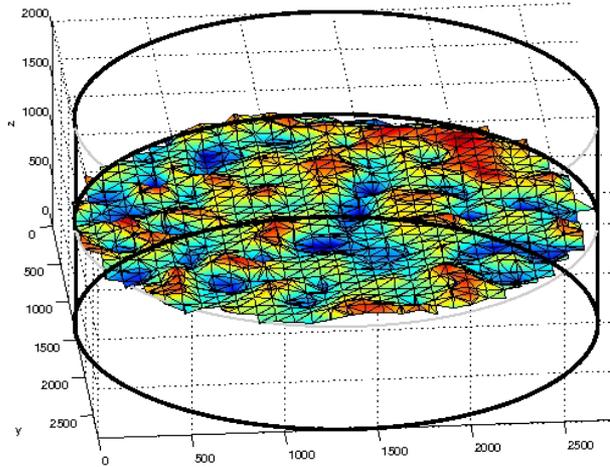
Microscopische opname met dermale ECs

Gesimuleerd resultaat met gelaagde ECs

Simulations

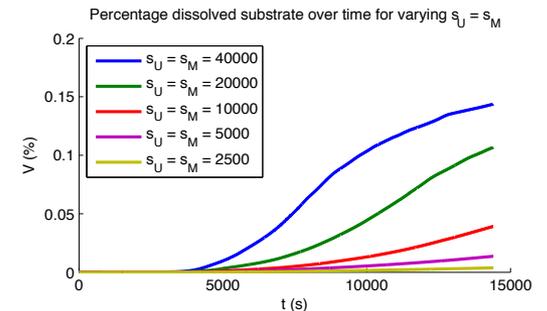
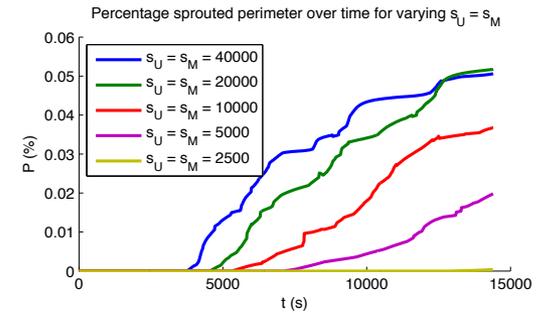
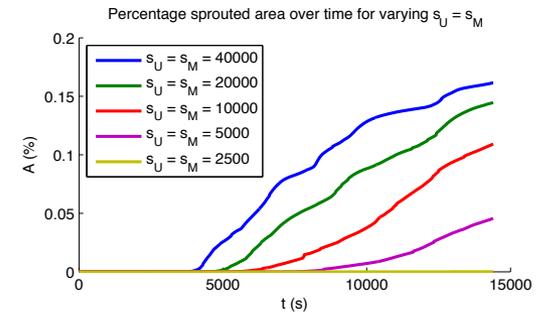
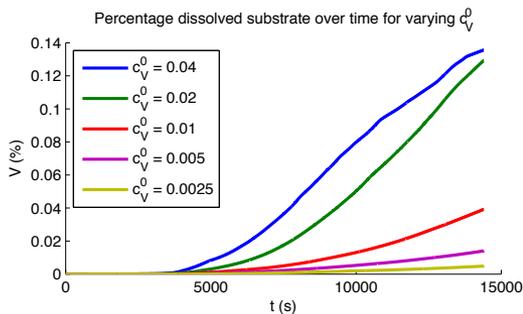
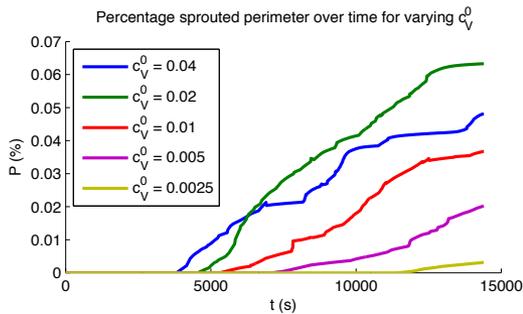
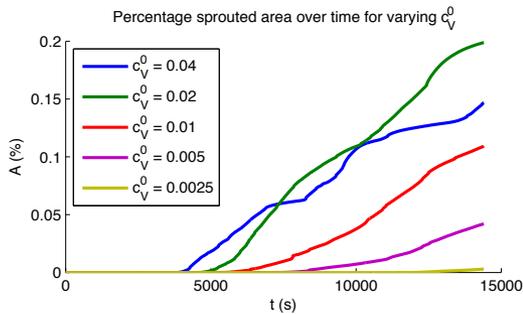


Frans Bookholt



normalAdhesion
Time = 0s
Sprout Area = 0%
Sprout Perim = 0%
Tip cells = 0

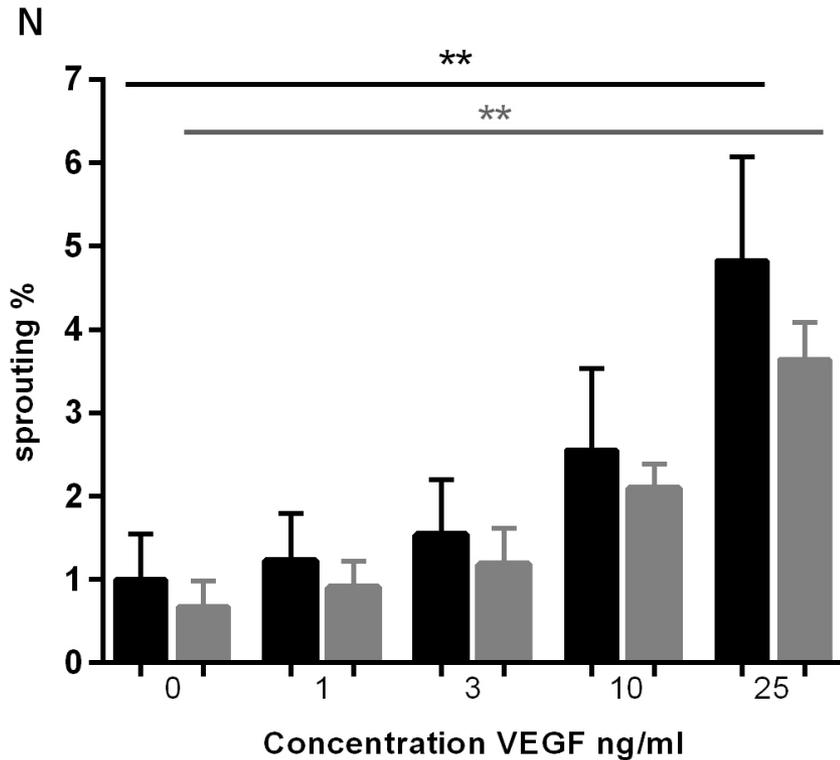
Resultaten en experimenten



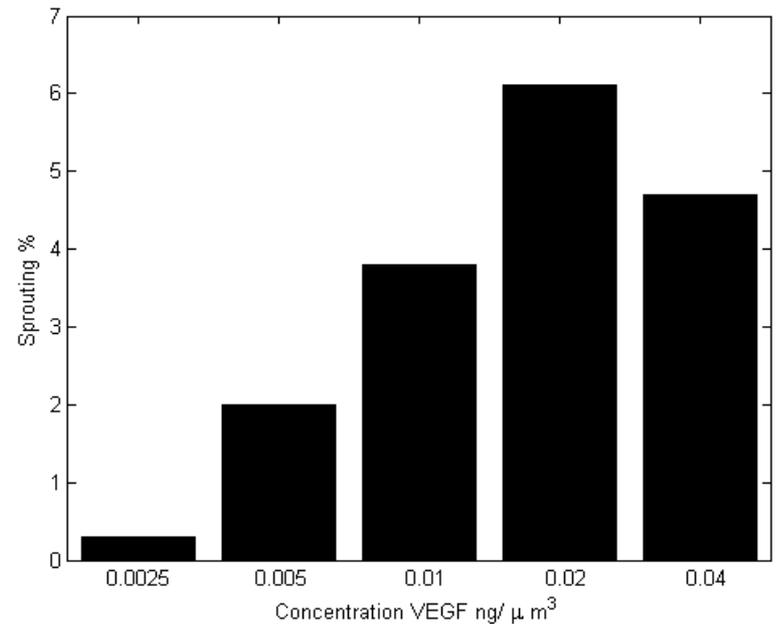
Variation of initial VEGT concentration in fibrin

Variation of production of uPA and MMP

Resultaten en experimenten



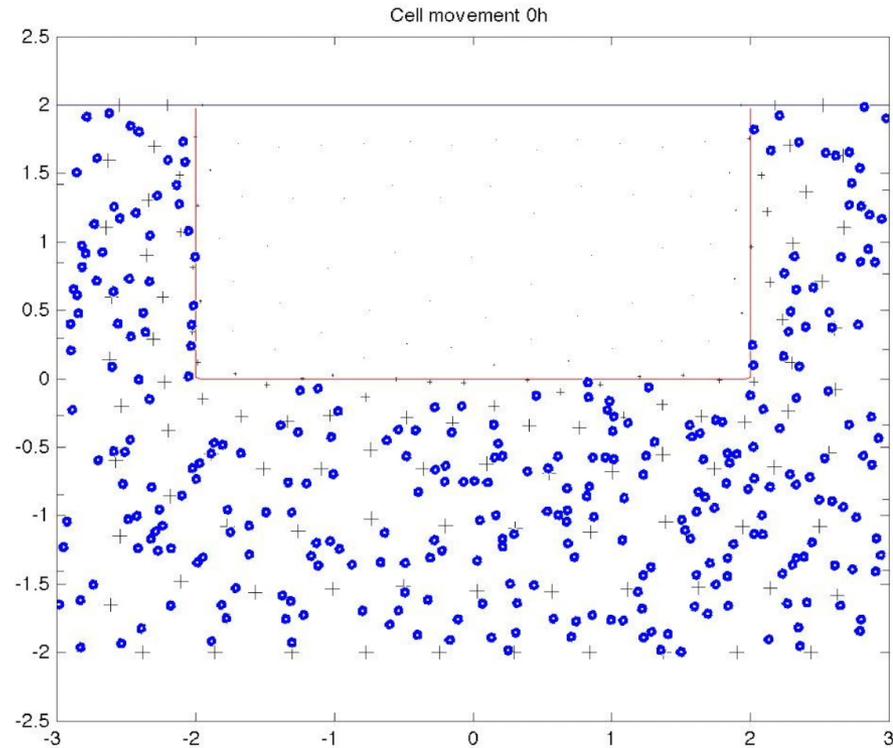
Measured, black: Dermal tissue ECs,
Grey: adipose tissue ECs



Simulated, no distinction between
ECs

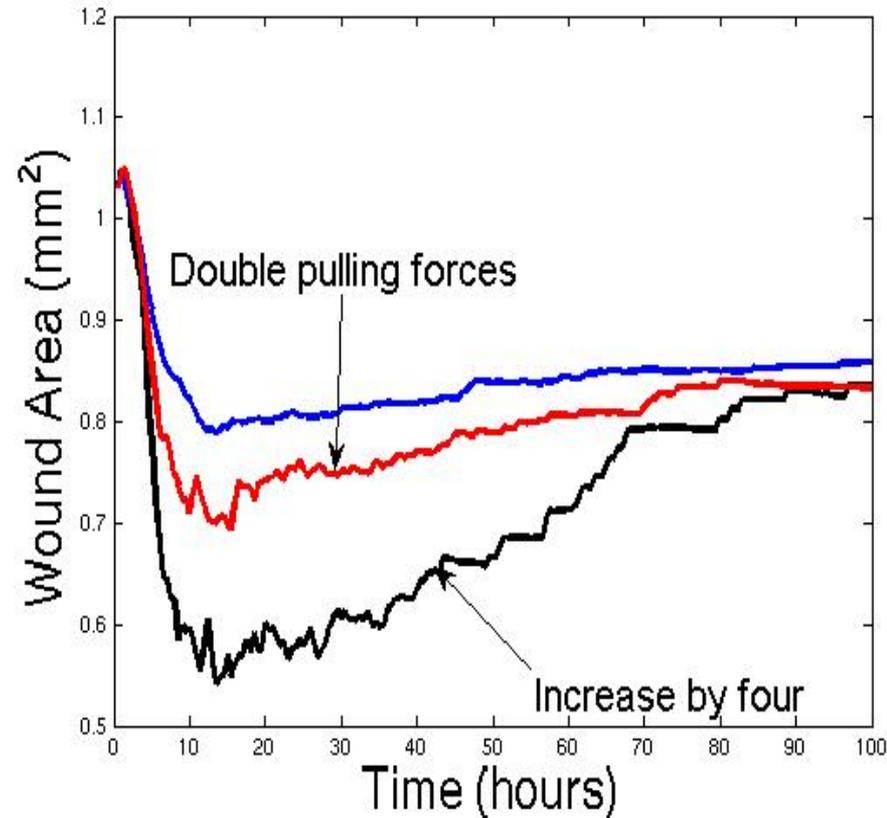
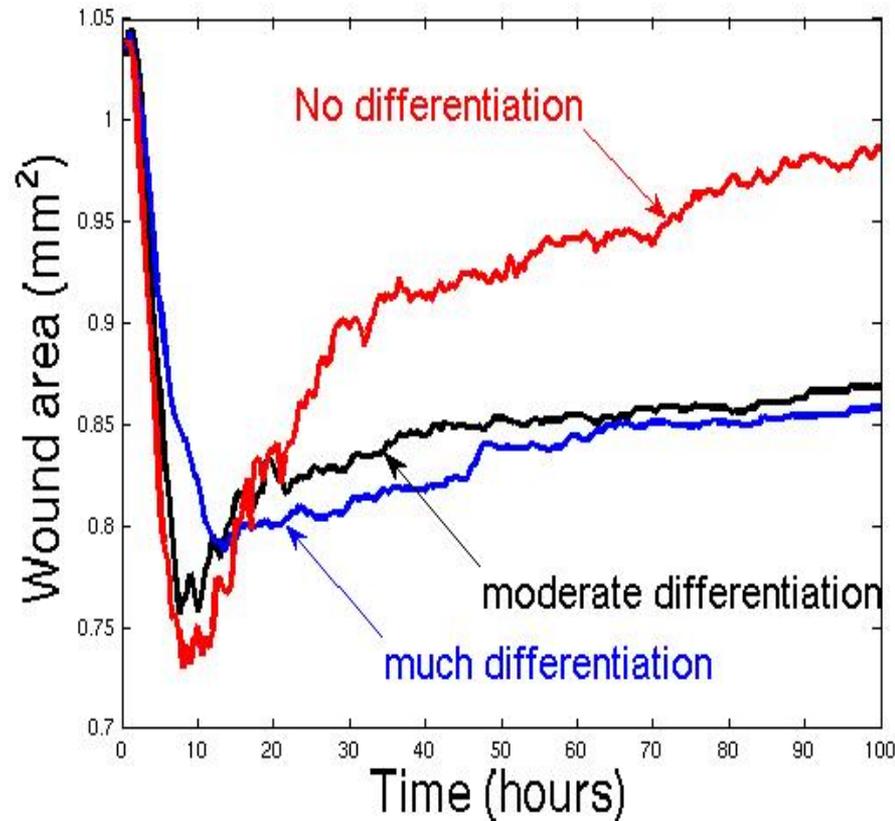
Percentage of sprouted area at top level

Resultaten en experimenten



Wond contractie (brandwonden)

Wound Contraction in Burns versus differentiation rate & traction

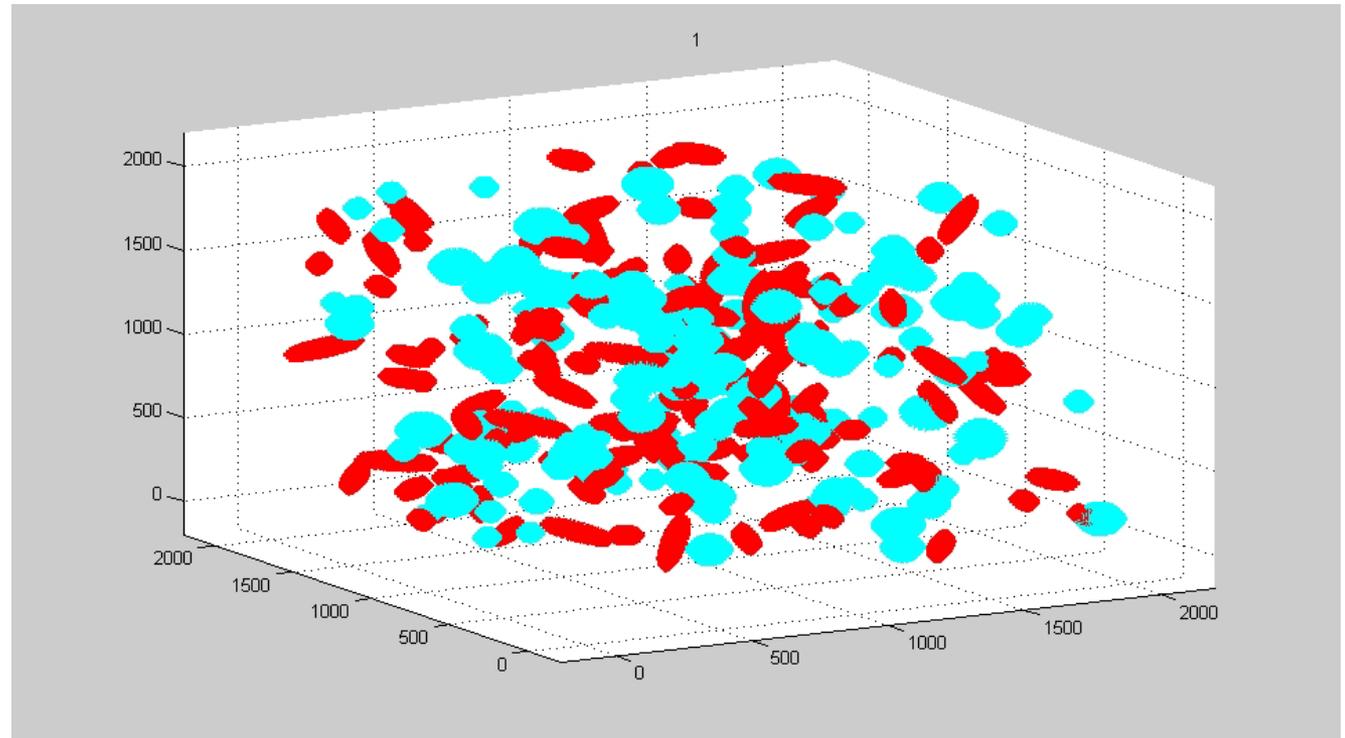


Minimize differentiation to myo-fibroblasts, by inhibiting initial wound expansion.

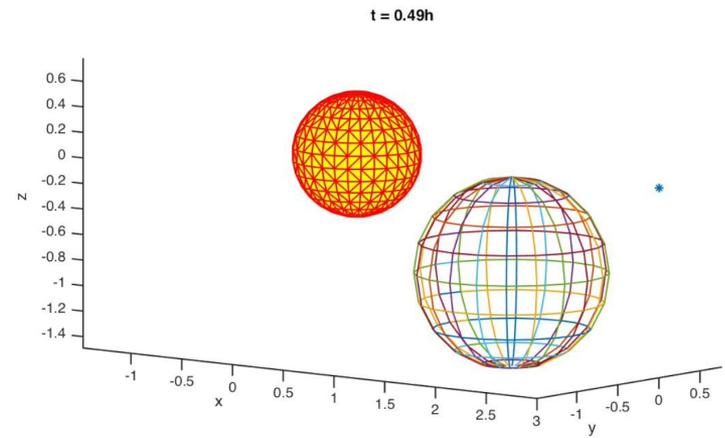
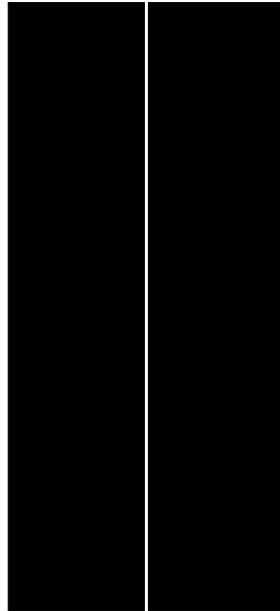
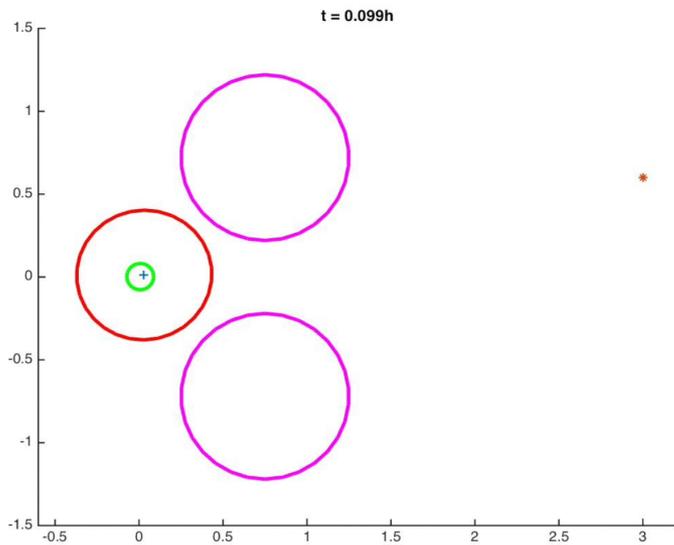
Celdifferentiatie als een continu proces: vetvorming vs spierontwikkeling



Source: Clip Art Hut



Nieuwe resultaten op celnivo: migratie en deformatie



Conclusies

- Cell-based semi continu model voor angiogenese
- Kwalitatieve, morphologische overeenkomst van model met experiments
- Kwantitatieve overeenkomst moet nog verbeterd worden

Bedankt



- U / Jij
- Mensen waarmee ik samenwerk: Frans Bookholt, Hanneke Monsuur, Sue Gibbs, Wietse Boon, Seb Harreveld, Daniel Koppenol, Amit Gefen
- De Nederlandse Brandwondenstichting voor financiële ondersteuning (project 12.103 / 13.101)