Modeling of Biological Systems

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CENTRO 2020
COMPETE 2020
PORTUGAL 2020
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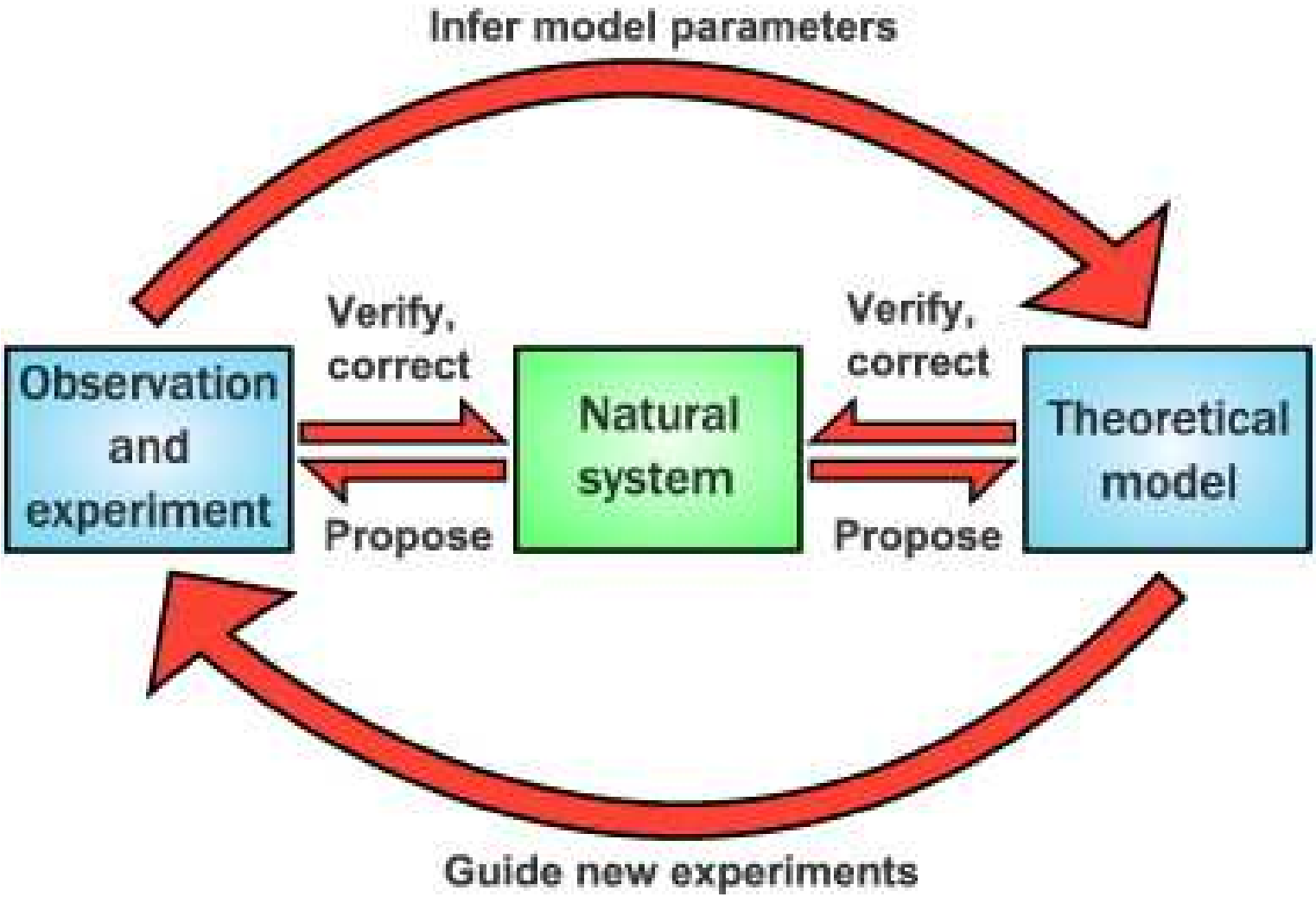

Infer model parameters
Observation and experiment
Verify, correct
Propose
Natural system
Verify, correct
Propose
Theoretical model
Guide new experiments

Models for Biology

Allow for **testing of hypothesis** [much faster and cheaper (and ethical) than *in vitro* or *in vivo*: *in silico*]

Needs **input** from experiments (**quantitative** biology) to constrain simulation parameters

Make **predictions** that can be experimentally tested (feedback)

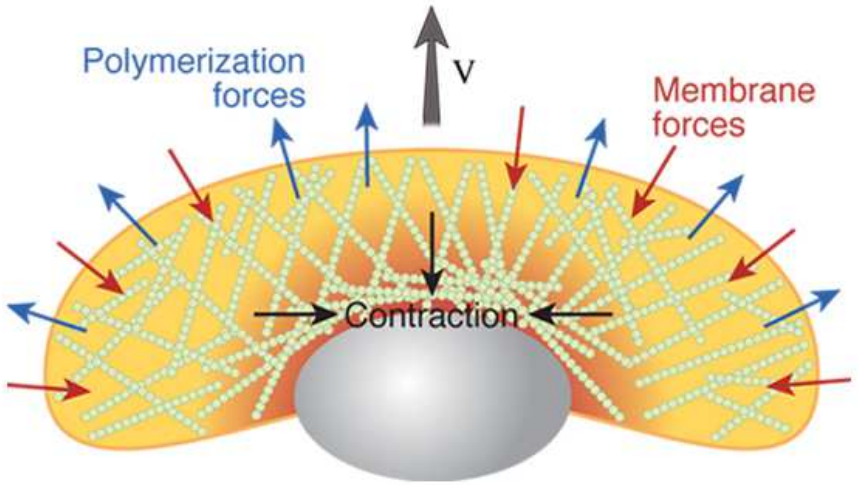
Usually a biological system is very **complex**, with many cell types and processes going on, in hugely different temporal and spatial **scales**: needs (rational) simplification to be feasible

Many different approaches available…

Biology & Physics

Often biological processes rely and/or result in **physical** or mechanical events

- Cell migration
- Shape alteration in proliferation
- Changes of Extra Cellular Matrix composition in diabetes and cancer
- Tumor growth
- Heart beat
- Embryo development
- etc.



Group Research Focus

- Cell motility
- Integrating **experimental data** into the models
- Construct **multiscale models**
- Couple intra-cellular dynamics with extra cellular behavior
- Biological modeling permits to **isolate/study** the effect of particular aspects of the system, separate causes and effects, test several **hypothesis** with larger statistics, and suggest new testable hypothesis

Discrete methods

Goal: model systems, as **biological tissues**, as a group of **cells**, with user defined **properties** and **interactions** with surrounding cells

Similar to real biological systems: **cell based** + **cell communication/interaction** with neighborhood (other cells and molecules and environment)

simple rules → complex behavior

Good to simulate the behavior of a **limited** number of cells, for extensive systems the **continuous** technique is usually a better approach

Discrete models

There are many types of discrete models (also called **agent based models**) that can be applied to describe the evolution of a **biological** system

One of them is the **Cellular Potts Model** (CPM), a lattice-based computational modeling method to simulate the collective behavior of cellular structures

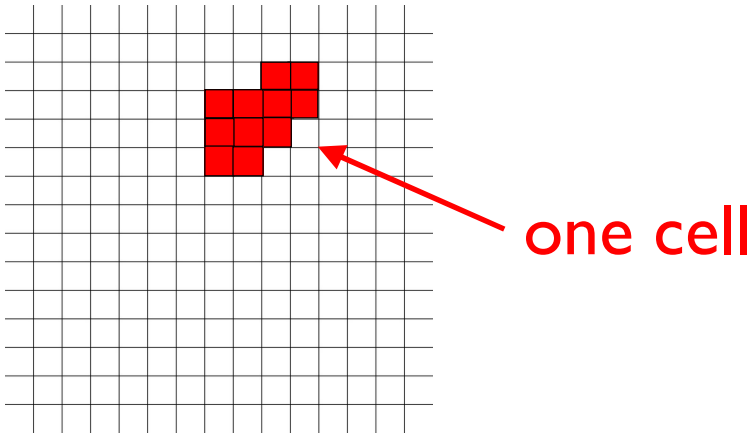
Has been used to simulate foam, biological tissues, fluid flow, reaction-advection-diffusion equations, etc.

Cellular Potts Model

Start with a regular **grid** (square in this example)

Each grid square is a **voxel** (in 2D is a pixel)

Each **cell** is made up of several voxels, and has some shape



Each cell in the system **evolves** (grows or shrinks by the copy of a voxel of a neighbor) according to a set of rules and a **Hamiltonian** (or "effective energy") function ***H***

In each attempt is tested the **change** of one voxel (in general, in each simulation step there are as many change attempts as voxels in the domain, randomly chosen)

The change on the Hamiltonian value is calculated and the system evolution goes ahead with some **probability**, which depends on ΔH

The **probability of change** is given by:

$$P(\Delta H) = \begin{cases} 1 \ , \ \Delta H < 0 \\ e^{-\Delta H / T} \ , \ \Delta H \geq 0 \end{cases}$$

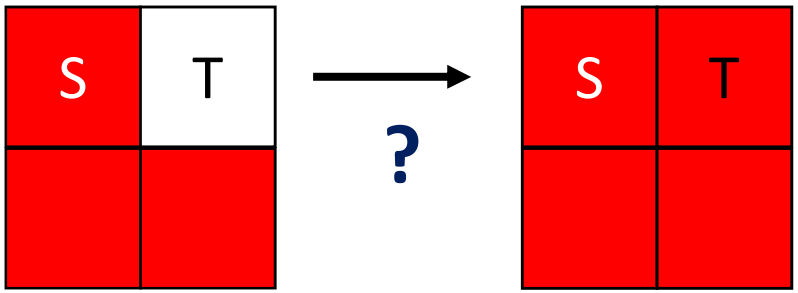
ΔH is the variation of the Hamiltonian if the attempt is successful, *T* is equivalent to Temperature in Statistical Physics, describes the level of system "agitation" (derived from the Ising model)

This introduces a **stochastic** ingredient on the system evolution

The system moves preferentially to the **state of lower energy**

Example

Attempt to copy **source** (red voxel) to **target** (white voxel)



Calculate the change on the system Hamiltonian between the final and the initial state, and accept this **copy attempt** if $\Delta H<0$, and with probability $exp(-\Delta H/T)$ if $\Delta H>0$

If successful, the red cell will have now 4 voxels, and the white cell (or ECM) lose one voxel

After this goes to another voxel copy attempt, randomly chosen

The **rules** are introduced on **Hamiltonian** definition

For example, the original CPM Hamiltonian (first developed by James Glazier and François Graner in 1992) included **adhesion energies**, and **volume** and **surface area constraints**:

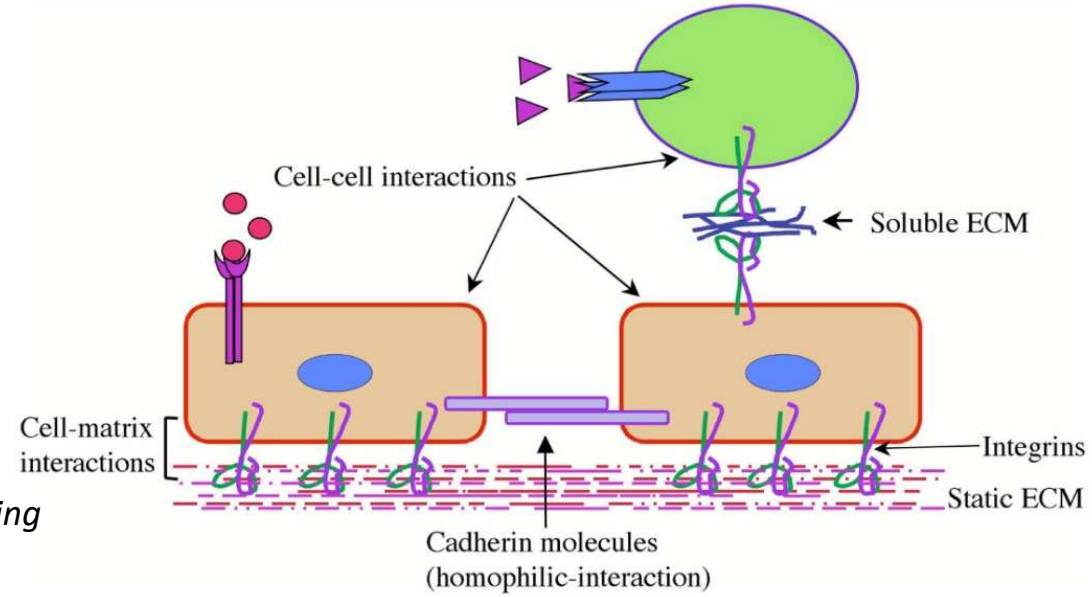
$$\Delta H = \Delta H_{\text{adhesion}} + \Delta H_{\text{volume}} + \Delta H_{\text{surface}}$$

Cell adhesion

Binding of a cell to a surface or membrane, such as extracellular matrix or another cell

Occurs from the action of proteins, called **cell adhesion molecules** (selectins, integrins and cadherins)

Essential to maintain a multicellular structure



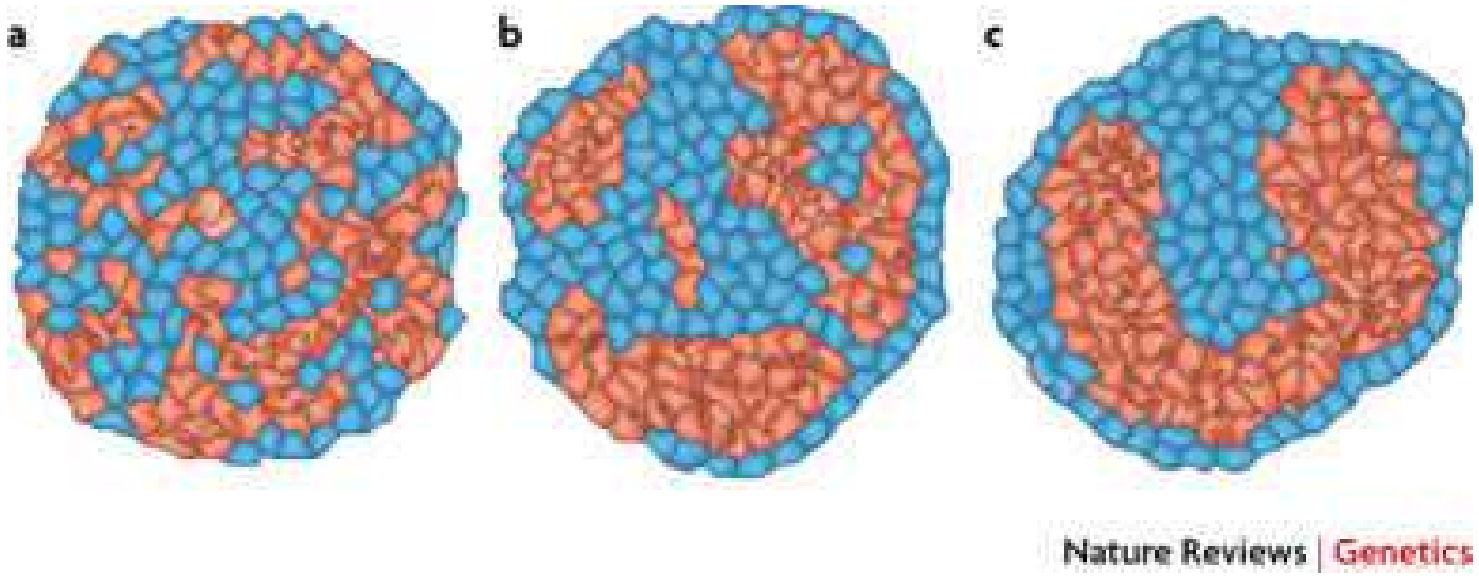
Wary *Cell Communication and Signaling* 2005 **3**:7 doi:10.1186/1478-811X-3-7

$$\sum_{i,j \text{ neighbors, } \sigma(i)\neq\sigma(j)} J\left[\tau(\sigma(i)),\tau(\sigma(j))\right]$$

The **adhesion term** says that the adhesion between two neighbor pixels *i* and *j*, from different cells ($\sigma(i)$ is the cell ID number), is given by the **adhesion energy** ***J*** between these two cells (of given types $\tau(\sigma(i))$ and $\tau(\sigma(j))$)

The different **values** of ***J*** are defined by the user (with experimental info), and the system evolution tries to minimize the (adhesion) energy

If the adhesion energy between cells of the same type is smaller than between cells of different types, cells of same type tend to stick together (**sorting**)



"Quantitative approaches in developmental biology" Andrew C. Oates, Nicole Gorfinkiel, Marcos González-Gaitán & Carl-Philipp Heisenberg, Nature Reviews Genetics 10, 517-530 (August 2009), doi:10.1038/nrg2548

$$\sum_i \lambda_{\text{volume}} \left[V(\sigma(i)) - V_{\text{target}} \right]^2 + \sum_i \lambda_{\text{surface}} \left[S(\sigma(i)) - S_{\text{target}} \right]^2$$

The **volume** and **surface area constraint** terms are positive and have a minimum (zero) when the cell volume reaches the target volume ($V=V_{target}$) and the cell area the target area ($S=S_{target}$)

λ_{volume} ($\lambda_{surface}$) is the volume (surface) **constraint amplitude**

Cells dimension aim to converge to these **target** values

Quiescent (non-proliferative) **biological** cells grow to a certain volume and shape and keep it, so have a volume and surface area **constraint** (which depends on the cell type)

The idea is to **minimize the system energy**, taking into account the different **constraints**

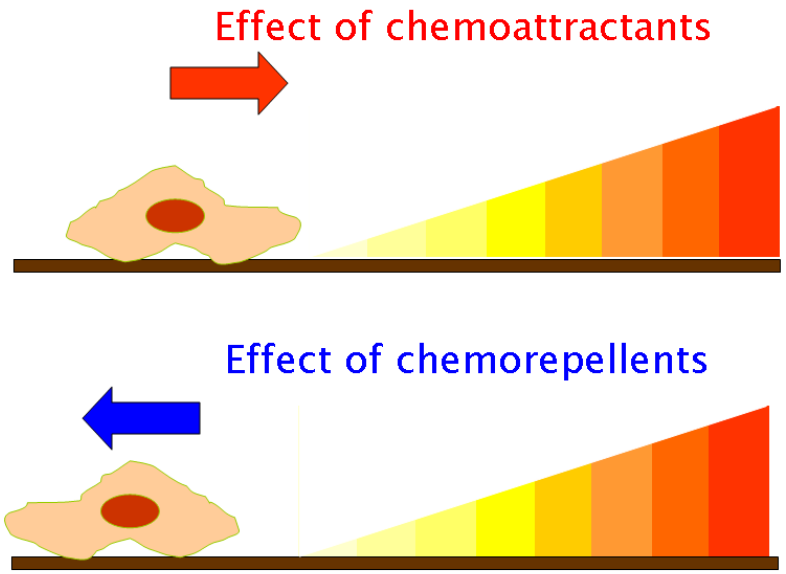
Many other **constraints** can be introduced, like on the cell length (shape), and different kinds of **directional** (preferential) movement, like **chemotaxis** (follow a chemical gradient), **durotaxis** (a rigidity gradient, as on ECM), etc.

Chemotaxis

Movement of a cell or organism in response to a **chemical stimulus**

Example: somatic cells, bacteria, and other single-cell or multicellular organisms direct their movements according to certain chemicals in their environment (glucose, etc.)

In multicellular organisms, chemotaxis is critical to early **development** (e.g., migration of neurons or lymphocytes) as well as in normal function

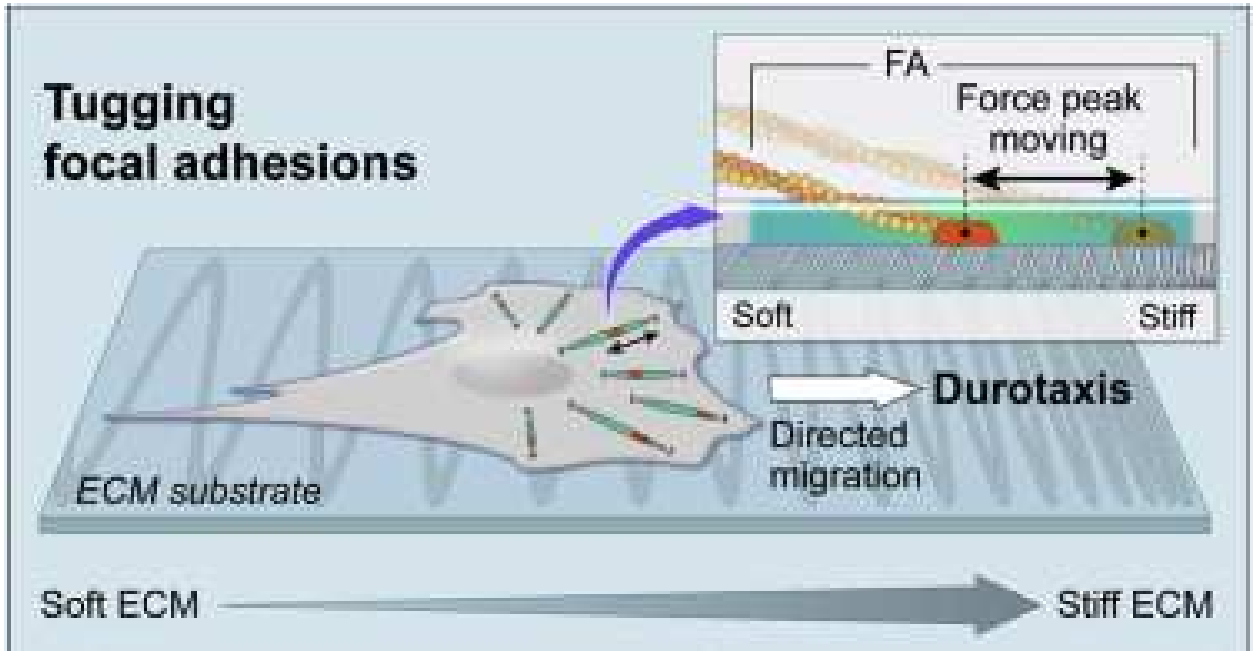


Increasing concentration of chemical specie

Kohlasz, https://en.wikipedia.org/wiki/File:Chtx-AttrRep-en.png

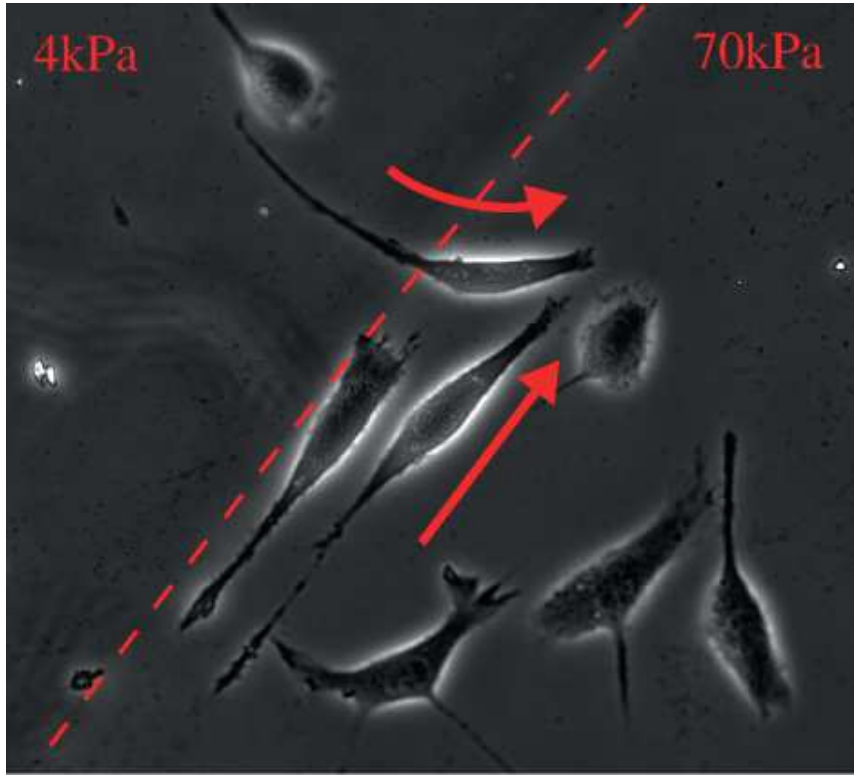
Durotaxis

Cell migration in which cells are guided by **rigidity gradients**, which arise from differential structural properties of the extracellular matrix (**ECM**)



Cell, Volume 151, Issue 7, p1513–1527, 21 Dec. 2012
DOI: http://dx.doi.org/10.1016/j.cell.2012.11.034

Most normal cells migrate up rigidity gradients (in the direction of greater **stiffness**)



"Physically based principles of cell adhesion mechanosensitivity in tissues" Benoit Ladoux and Alice Nicolas, 2012 Rep. Prog. Phys. 75 116601, doi:10.1088/0034-4885/75/11/116601

In the Hamiltonian,

$$\Delta H_{\text{chemotaxis}} = -\chi\delta\left(\sigma(i),0\right)\left[c_V\left(\sigma(i)\right)-c_V\left(\sigma(j)\right)\right]$$

c_V is the **chemical concentration** at the source (j) and at the target (i) voxel, χ is the chemotaxis amplitude

Usually in this case is required a **hybrid model**: **discrete** for cells, **continuous** for fields (diffusion of chemical species)

Concentration fields

The continuous fields, like [O_2] and [VEGF], evolve according with a transport equation (convection-diffusion-consumption equation) and with the boundary conditions

In general, the **concentration c** of a chemical specie changes with time according to a diffusion-convection-consumption equation

$$\frac{\partial c}{\partial t} = \nabla.\left(D\nabla c\right) - \nabla.\left(\vec{v}c\right) + R$$

D is the diffusion constant, *v* is the velocity) and *R* is the rate of **production** (if positive) or **consumption** (if negative)

The equation is solved by **discretization** of the concentration on grid nodes

Many other **components** can be introduced in the model in order to reproduce a living tissue properties, like chemicals production, consumption, degradation and diffusion (O_2, glucose, VEGF, signaling molecules, etc.); forces between cells and on the ECM; cells elasticity; mechanical properties of medium; …

Can be included almost any **biological phenomena**, as cells growth, proliferation and death; formation and degradation of vasculature; cell motility and invasion; etc.

And also some **new phenomena** for **hypothesis** testing

Example

A "simple" published CPM model, with only ECM and endothelial cells (EC), and a model of cell **forces** and strains on the ECM (uses a finite element method), with **cell adhesion**, **volume constraint** and **durotaxis**

Reproduces the spontaneous formation of a **vascular network** *in vitro*

OPEN ACCESS Freely available online

PLOS | COMPUTATIONAL BIOLOGY

Mechanical Cell-Matrix Feedback Explains Pairwise and Collective Endothelial Cell Behavior In Vitro

René F. M. van Oers[1,2☯¤], Elisabeth G. Rens[1,2☯], Danielle J. LaValley[3], Cynthia A. Reinhart-King[3], Roeland M. H. Merks[1,2,4*]

Published: August 14, 2014 DOI: 10.1371/journal.pcbi.1003774

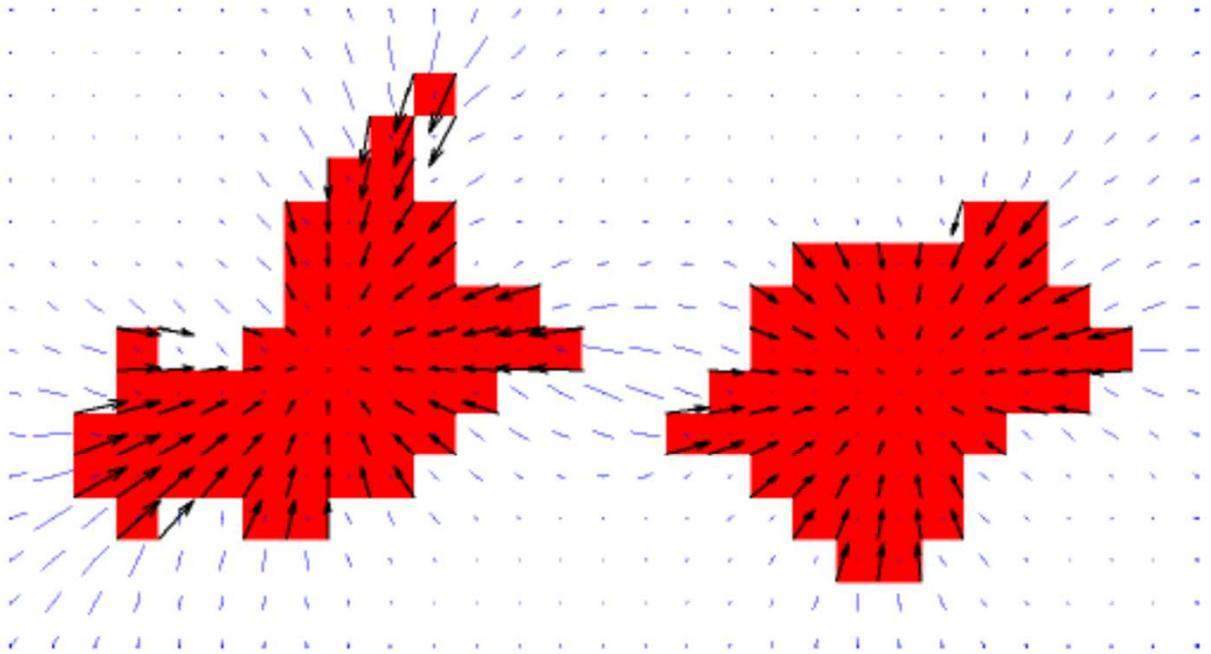
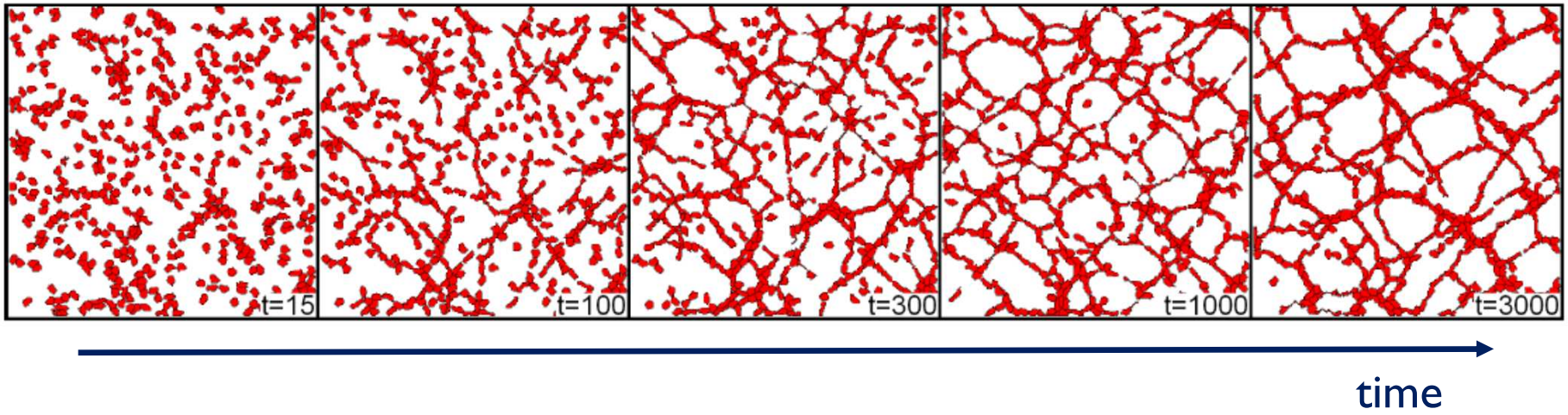


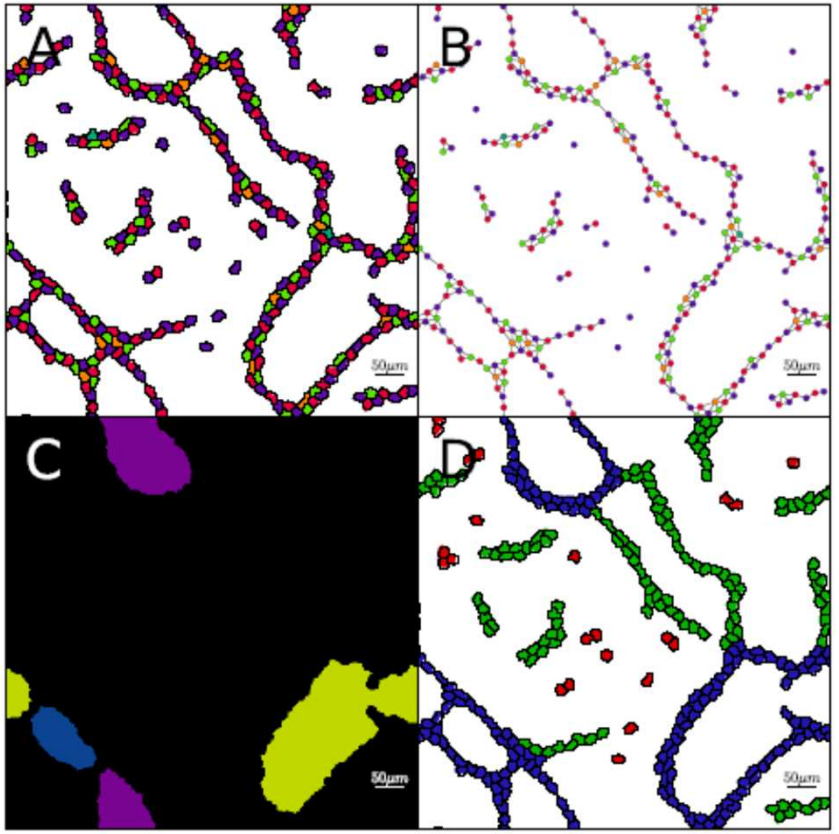
Figure 2. Visualization of simulated traction forces (*black arrows*) and resulting matrix strains (*blue line segments*) generated in the proposed hybrid cellular Potts and finite element simulation model.

doi:10.1371/journal.pcbi.1003774.g002

Time evolution of the system, from scattered endothelial cells (left) to a **network** (right, only possible for intermediate ECM **stiffness** values)



Example



PHYSICAL REVIEW E **97**, 012408 (2018)

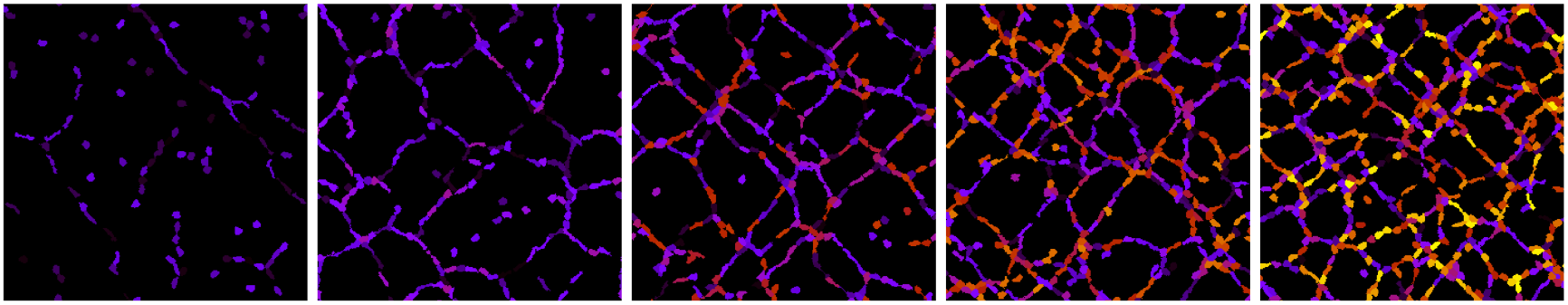
Capillary network formation from dispersed endothelial cells: Influence of cell traction, cell adhesion, and extracellular matrix rigidity

João R. D. Ramos,[1,2,*] Rui Travasso,[1,†] and João Carvalho[1,‡]

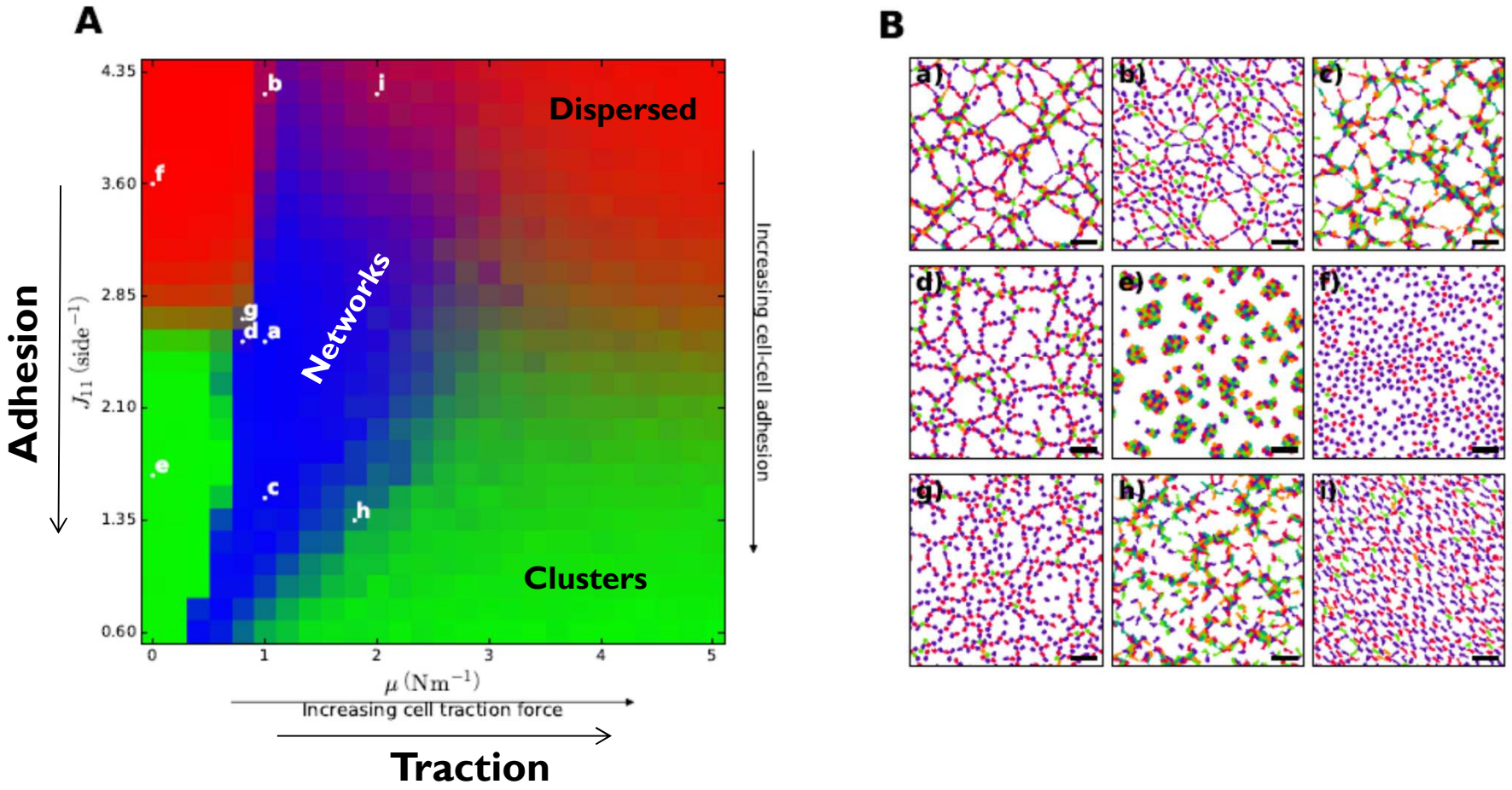
[1]*Centro de Física da Universidade de Coimbra, CFisUC, 3007-516 Coimbra, Portugal*

[2]*Max Planck Institute for Dynamics and Self-Organization, 37077 Göttingen, Germany*

Cell Based Modeling



- Model the interaction between individual cells and substrate
  - Cells on a elastic substrate
  - What is the traction force required for the cells to form a network?



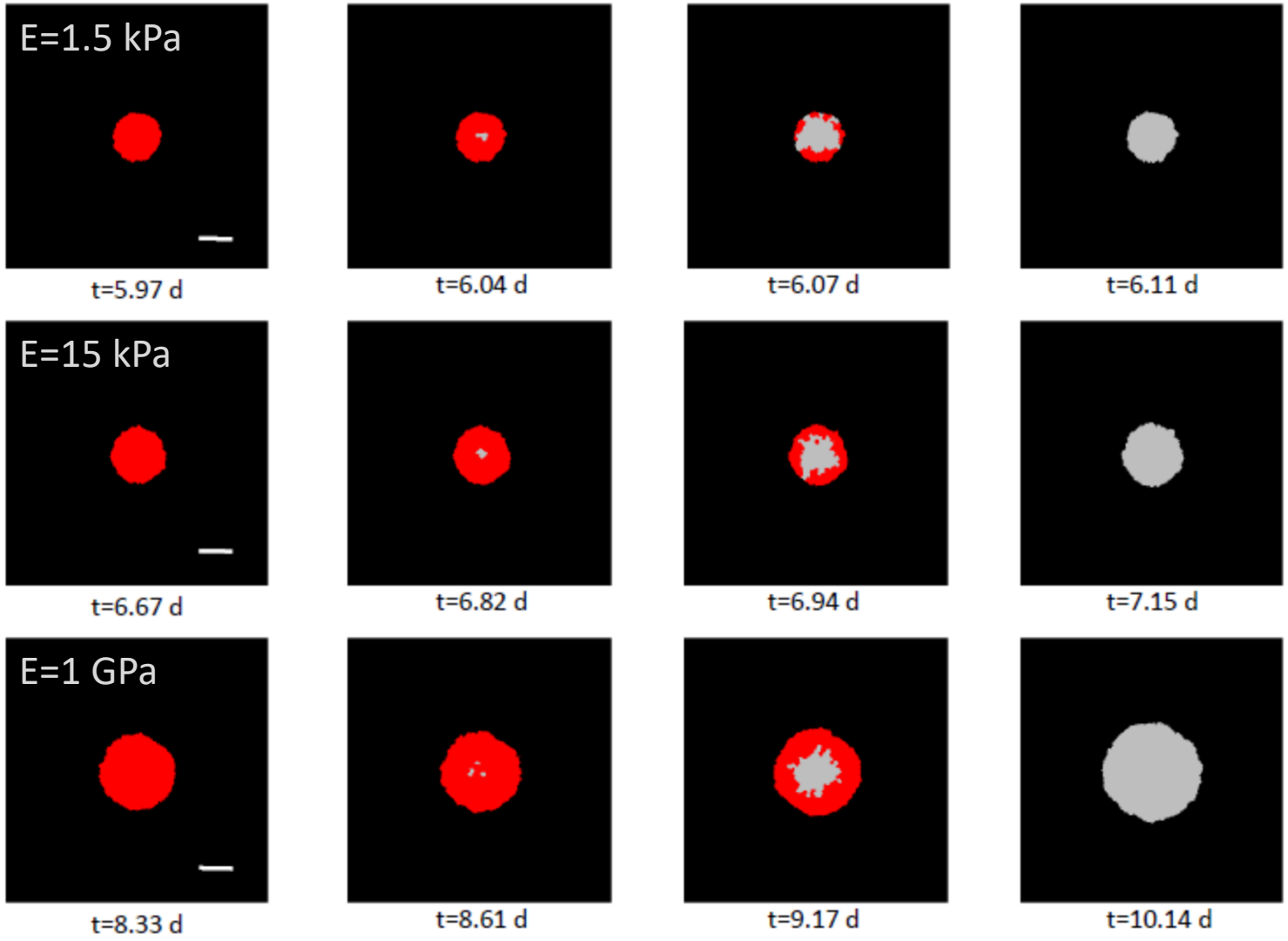
Cells can be dispersed (red), clustered (green) or in a network (blue), depending on the **parameters'** values

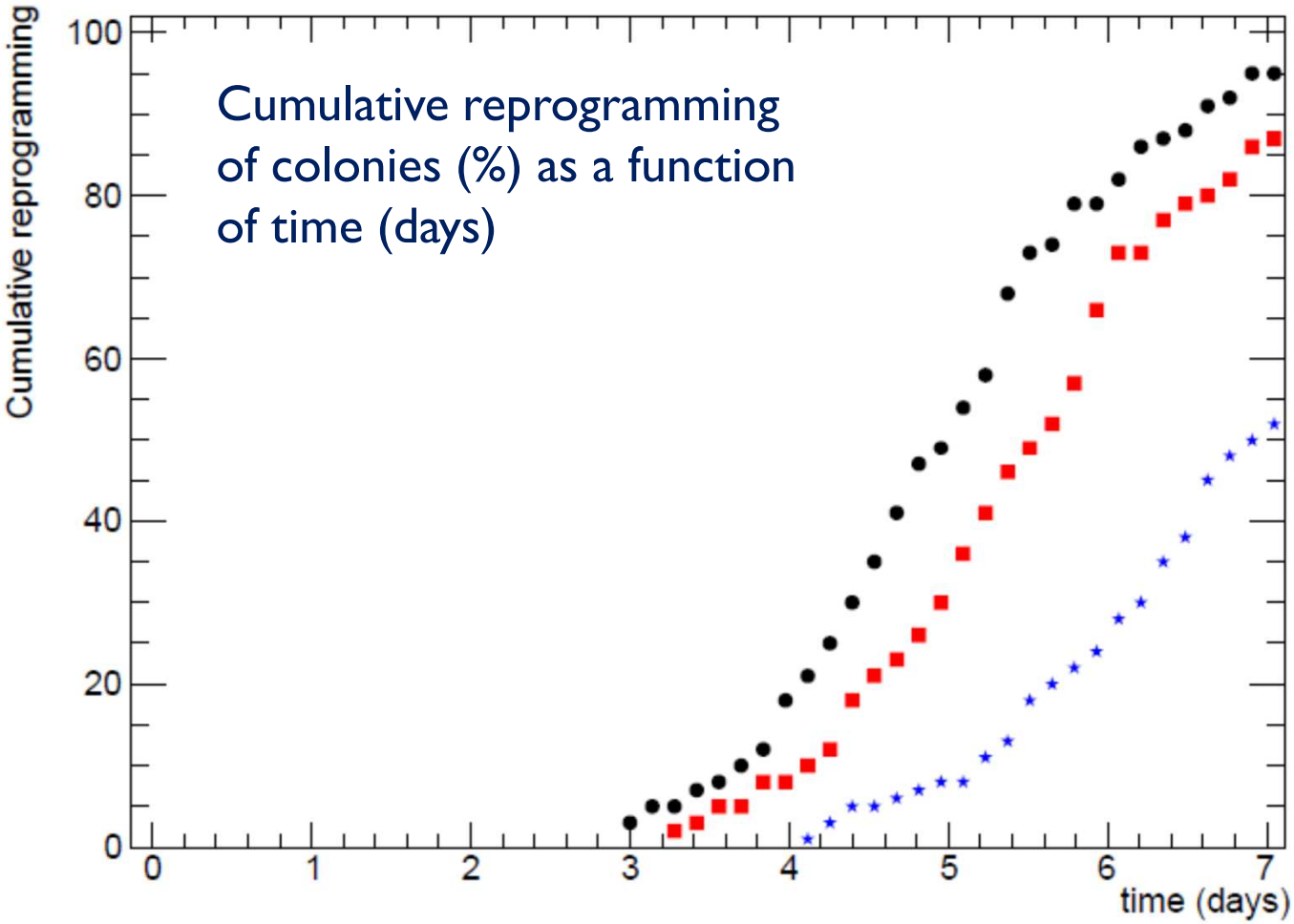
Cell reprogramming

Biology research done by Heloísa Gerardo, Ana Lima, Sofia Couceiro, Ricardo Neves & Mário Grãos at **CNC-Biotech-UC**

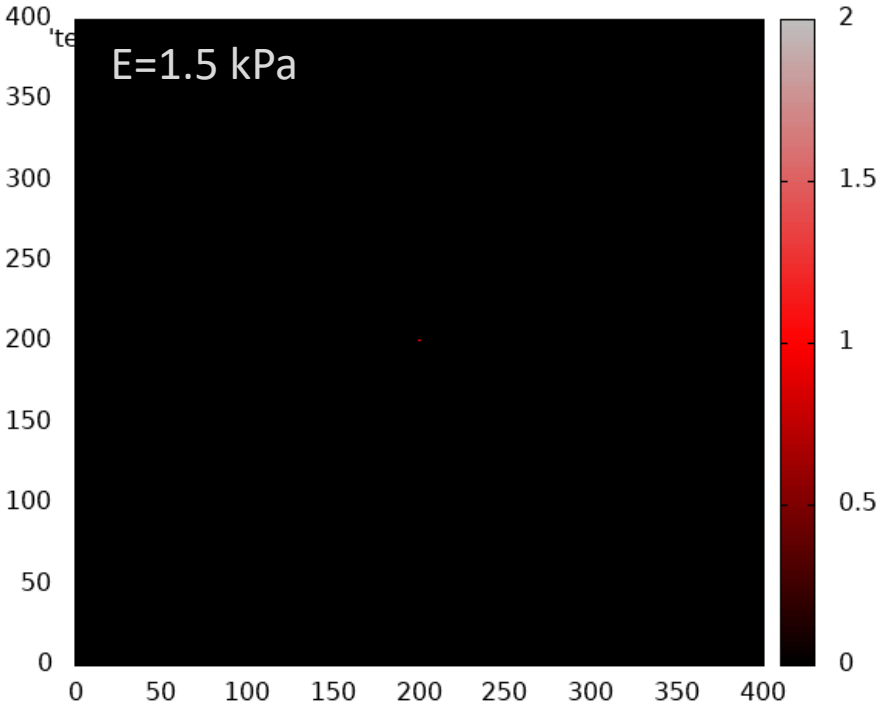
Reprogram of human mesenchymal stem/stromal cells (hMSCs) into **induced pluripotent stem** cells (iPSCs), using a lentiviral reprogramming vector, in matrices with different **rigidities**

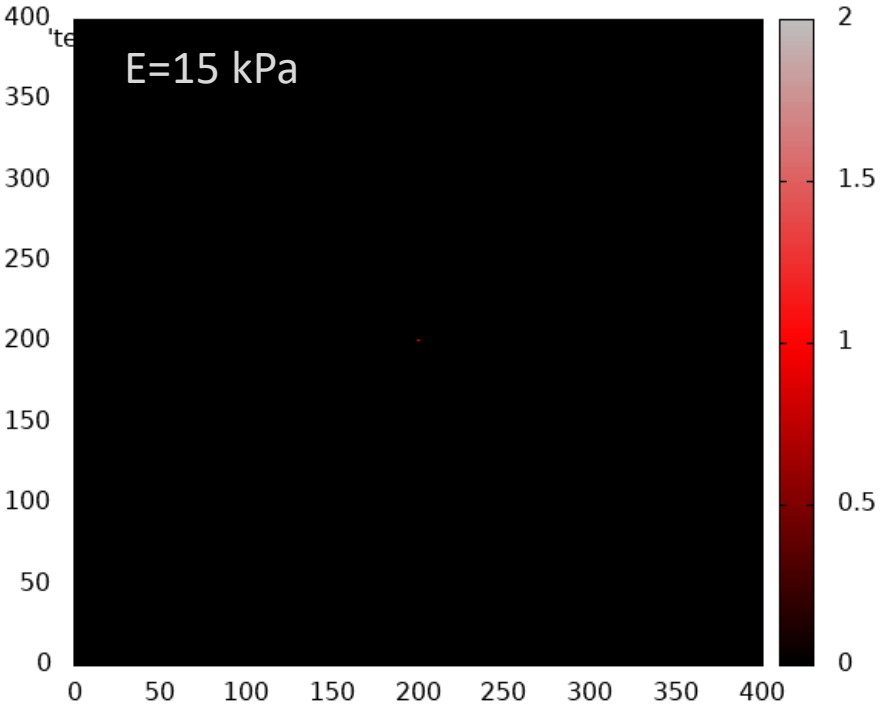
Cell reprogramming in matrices with different rigidities

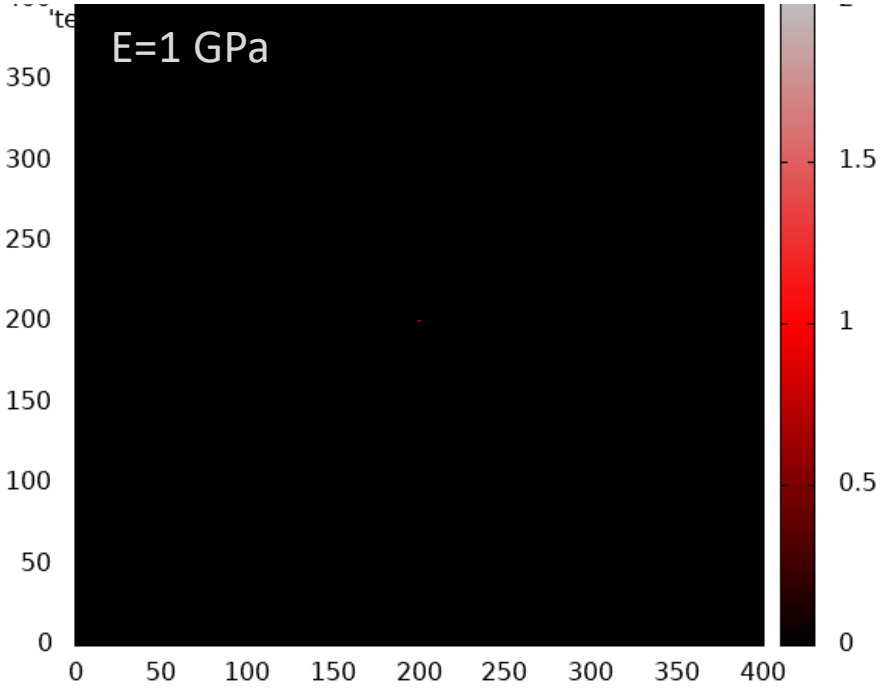




Black: E=1.5 kPa
Red: E=15 kPa
Blue: E=1 GPa





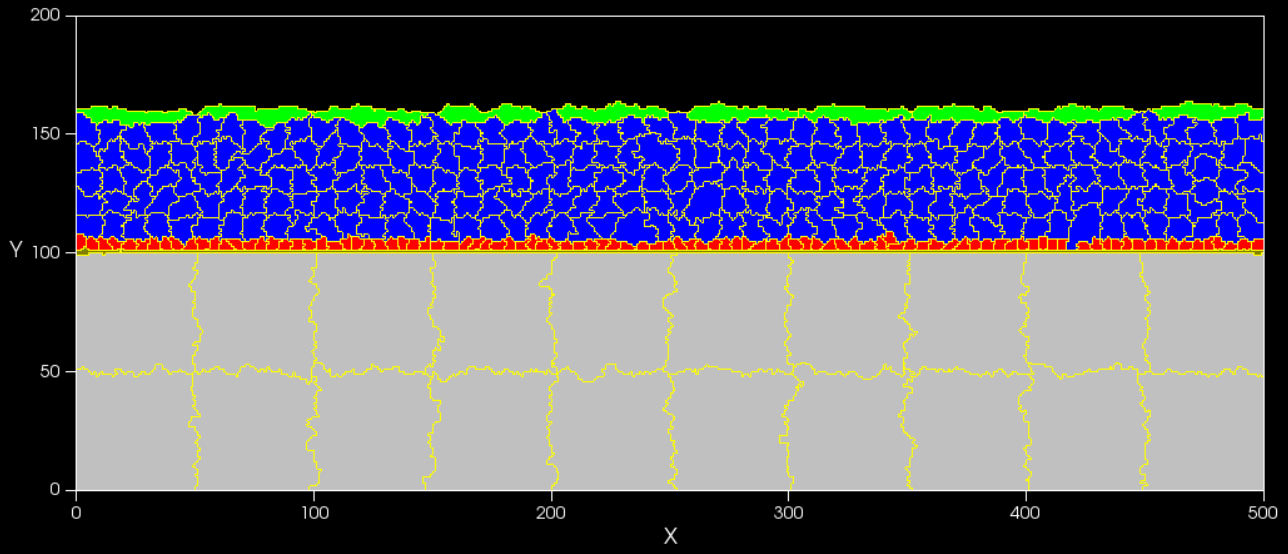


Animations with the colonies evolution and their reprogramming as a function of time, for different substrates **rigidity**

Example: urothelium model

Reproduce the different **layers**, including the basal membrane

Base from which to develop a **pathological model** (at UC, by JC, Rita Coimbra and Francisco Marques, in collaboration with the Faculty of Medicine)



Umbrella, intermediate and basal cells

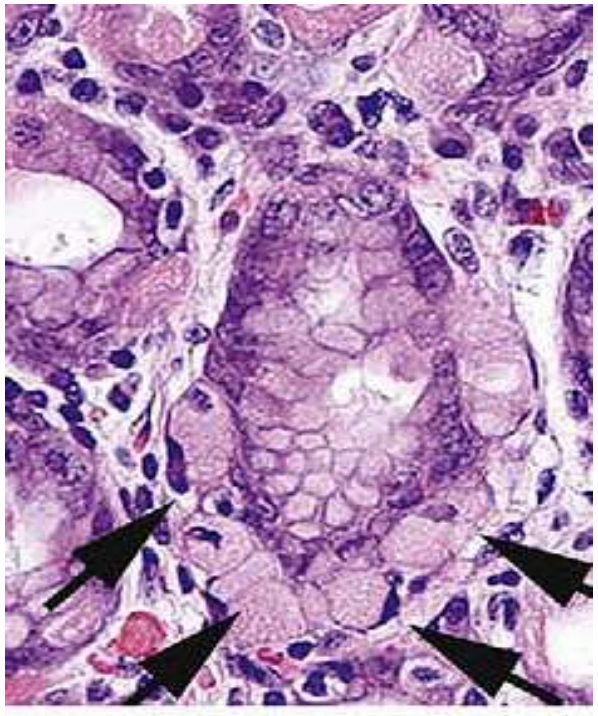
Basal membrane and stroma

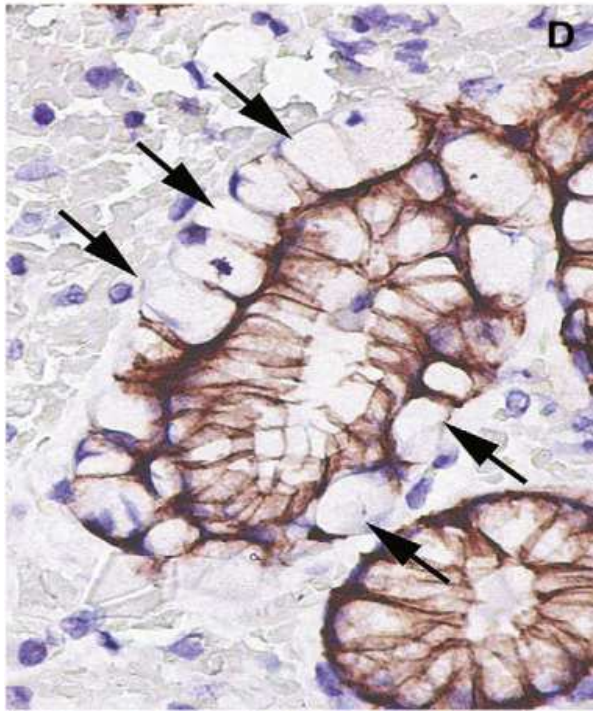
Diffuse gastric cancer

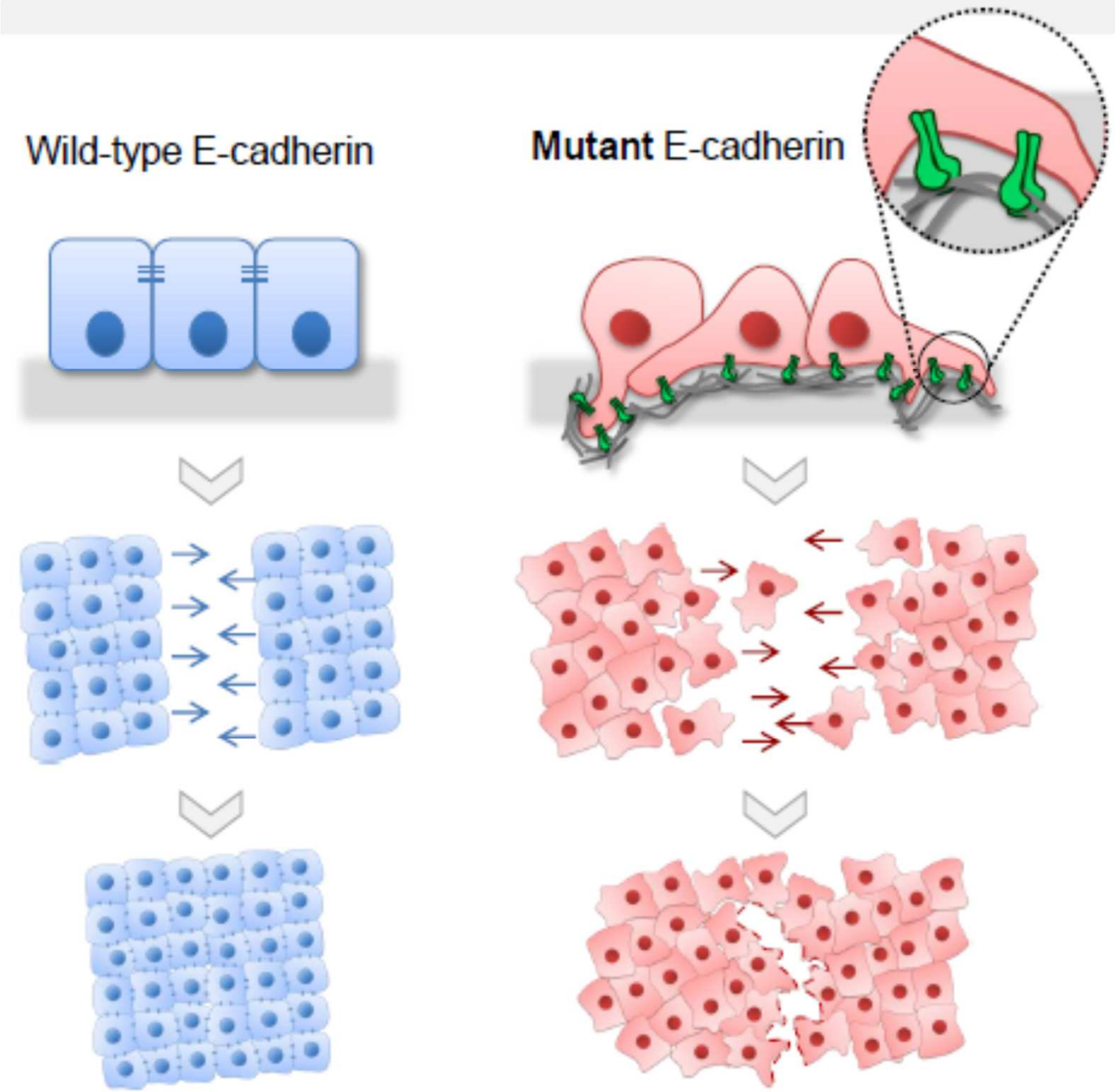
Recent collaboration with the Raquel Seruca group at **I3S in Porto**

Special (&rare) cancer, due to a mutation in the e-cadherin (cell **adhesion**)

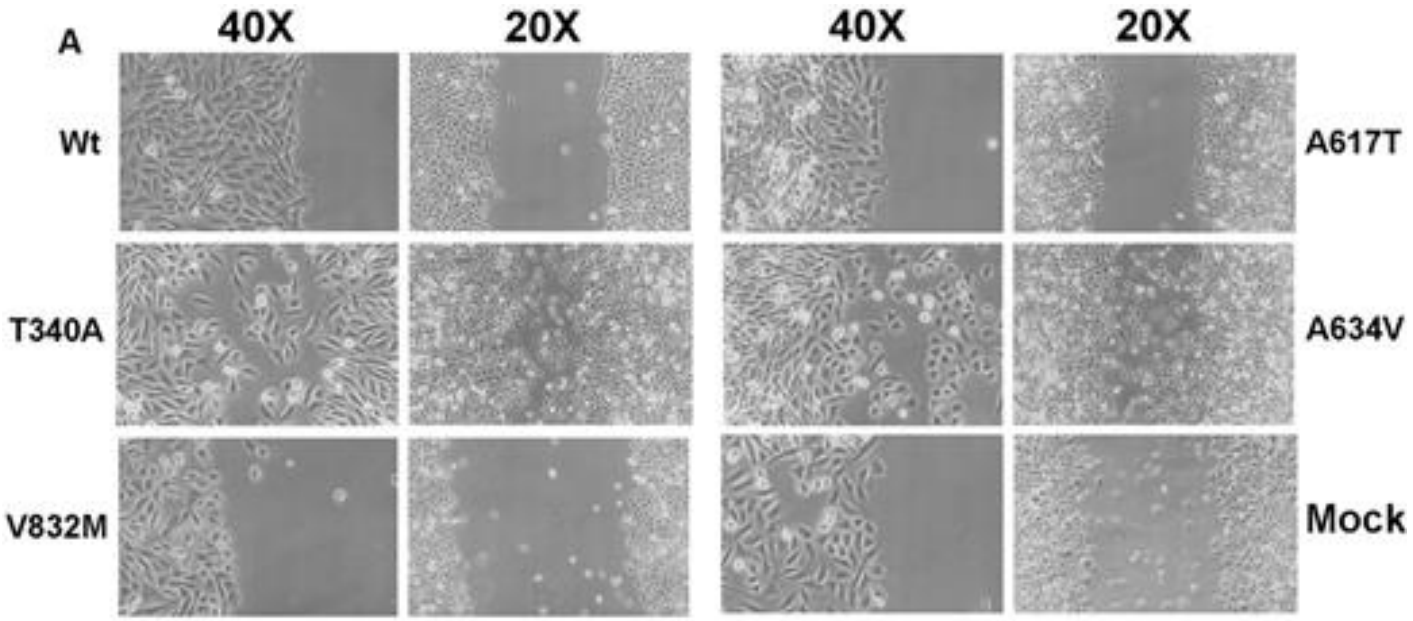
First try to **model** the *in vitro* tests



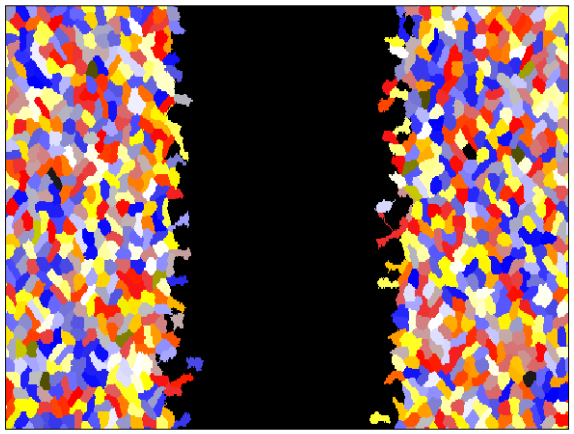



Wild-type E-cadherin
Mutant E-cadherin

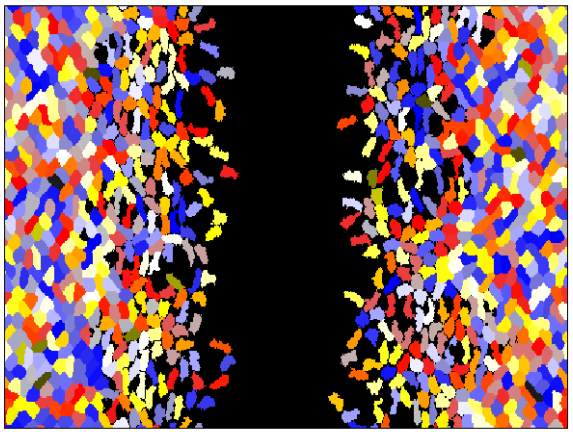
Wound healing assay



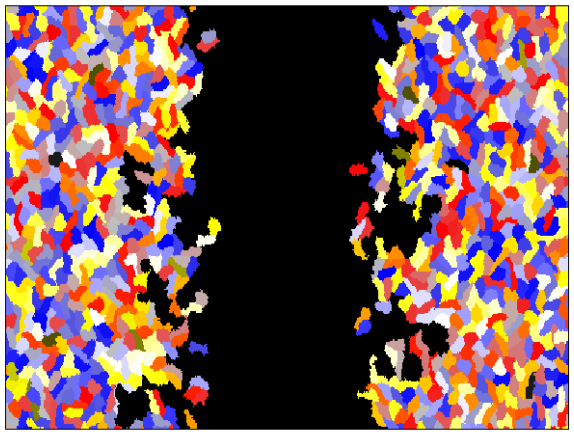
Computational model



std



J_{11}=3.5



J_{11}=1.5

Example of a more complex model

PLOS | COMPUTATIONAL BIOLOGY

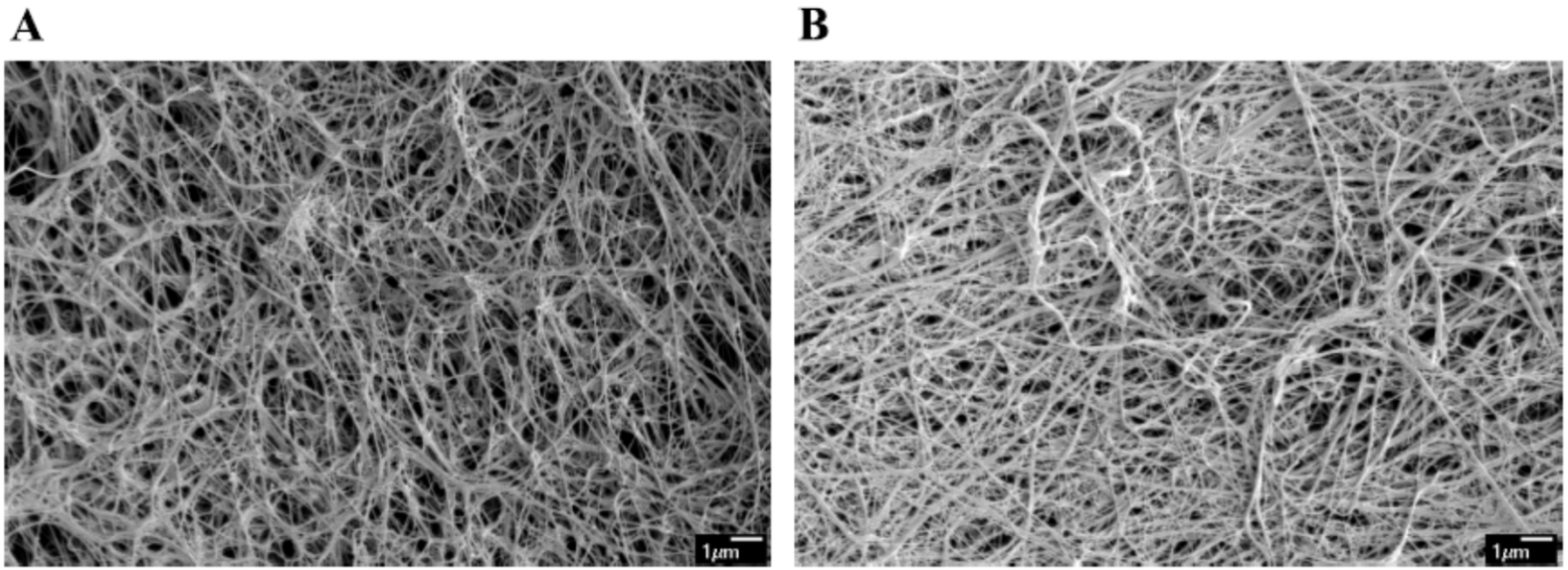
RESEARCH ARTICLE

A local uPAR-plasmin-TGFβ1 positive feedback loop in a qualitative computational model of angiogenic sprouting explains the *in vitro* effect of fibrinogen variants

Sonja E. M. Boas[1,2☯], Joao Carvalho[1,3☯], Marloes van den Broek[4], Ester M. Weijers[4], Marie-José Goumans[5], Pieter Koolwijk[4], Roeland M. H. Merks[1,2¤*]

1 Centrum Wiskunde & Informatica (CWI), Amsterdam, The Netherlands, **2** Mathematical Institute, Leiden University, Leiden, The Netherlands, **3** CFisUC, Department of Physics, University of Coimbra, Coimbra, Portugal, **4** Amsterdam Cardiovascular Sciences, VU University medical Center, Dept. of Physiology, Amsterdam, The Netherlands, **5** Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands

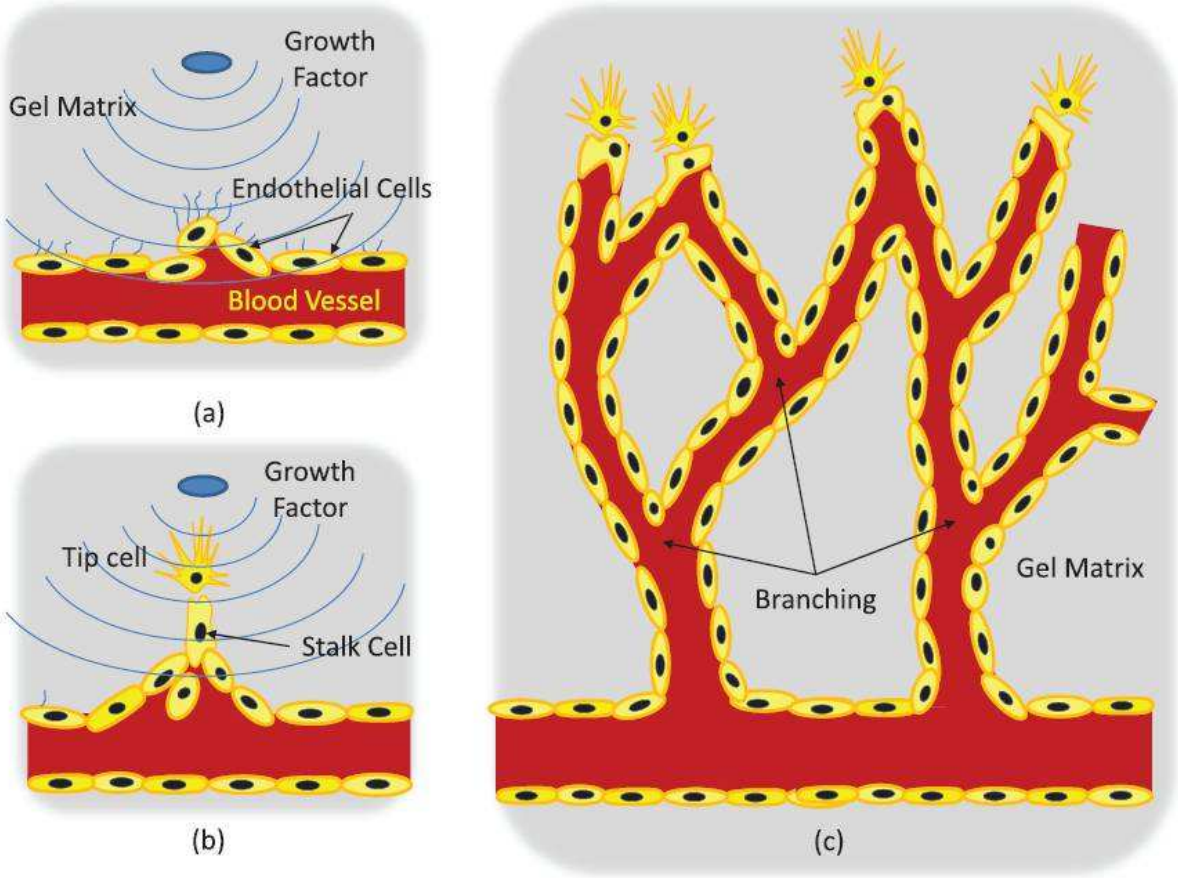
in vitro assay of **sprouting** in fibrin matrices: Weijers *et al.* showed that composition of **fibrin** changes sprouting progress; more **ingrowth** on high molecular weight (HMW) than on low molecular weight (LMW) fibrin



A: HMW fibrin, thicker fibers, more open network, than B: LMW fibrin

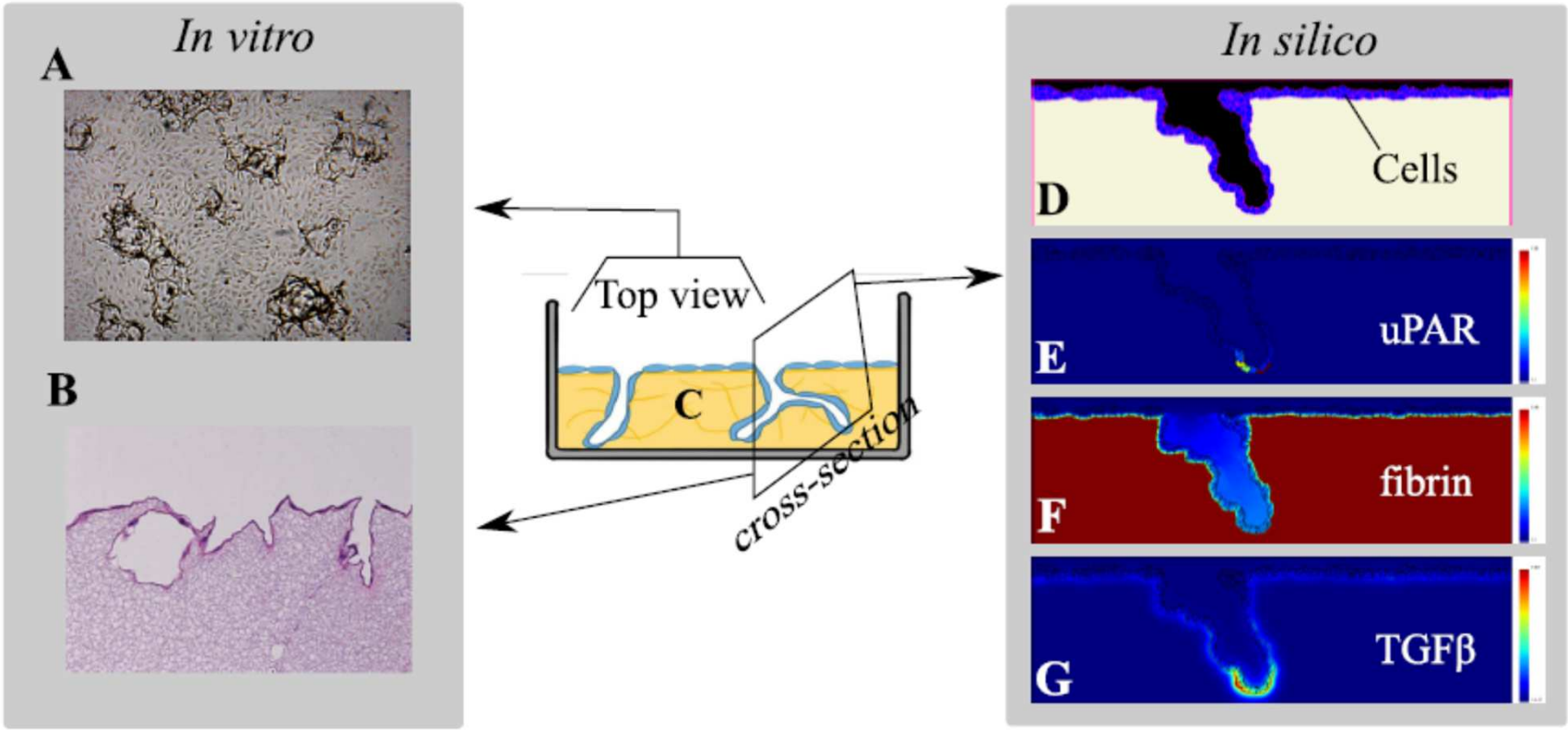
Fibrin: fibrous, non-globular protein involved in blood clotting

Sprouting angiogenesis: fundamental mechanism of **vessel growth** and branching, both in health and in disease



BioSystems and Micromechanics (BioSyM) Inter-Disciplinary Research Group, http://web.mit.edu/smart/research/biosym/BioSyM-Research-Thrust%203-Archives.html

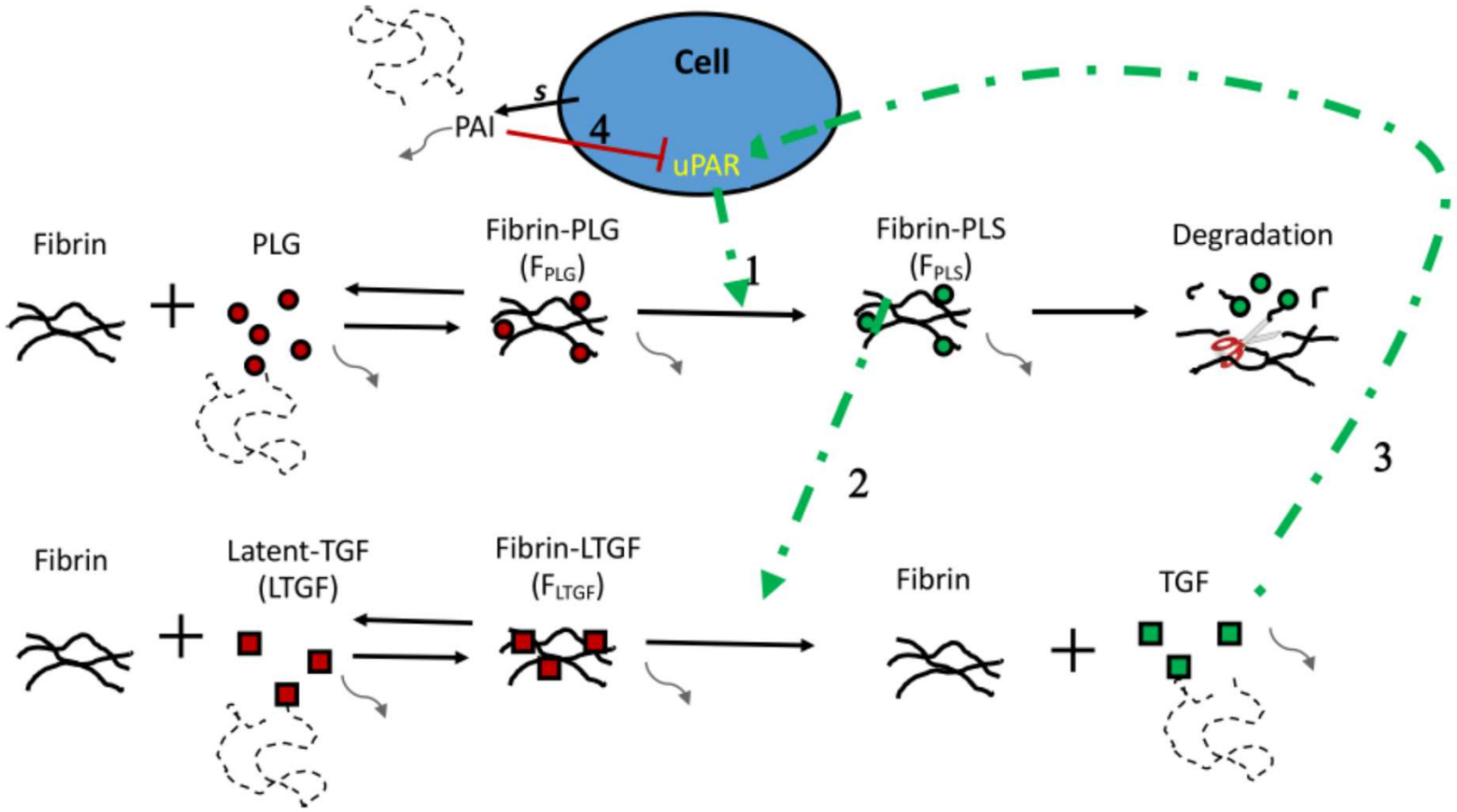
Sprouting *in vitro* and *in silico*



Ingrowth of monolayer of endothelial cells (and growth medium) on top of fibrin matrix

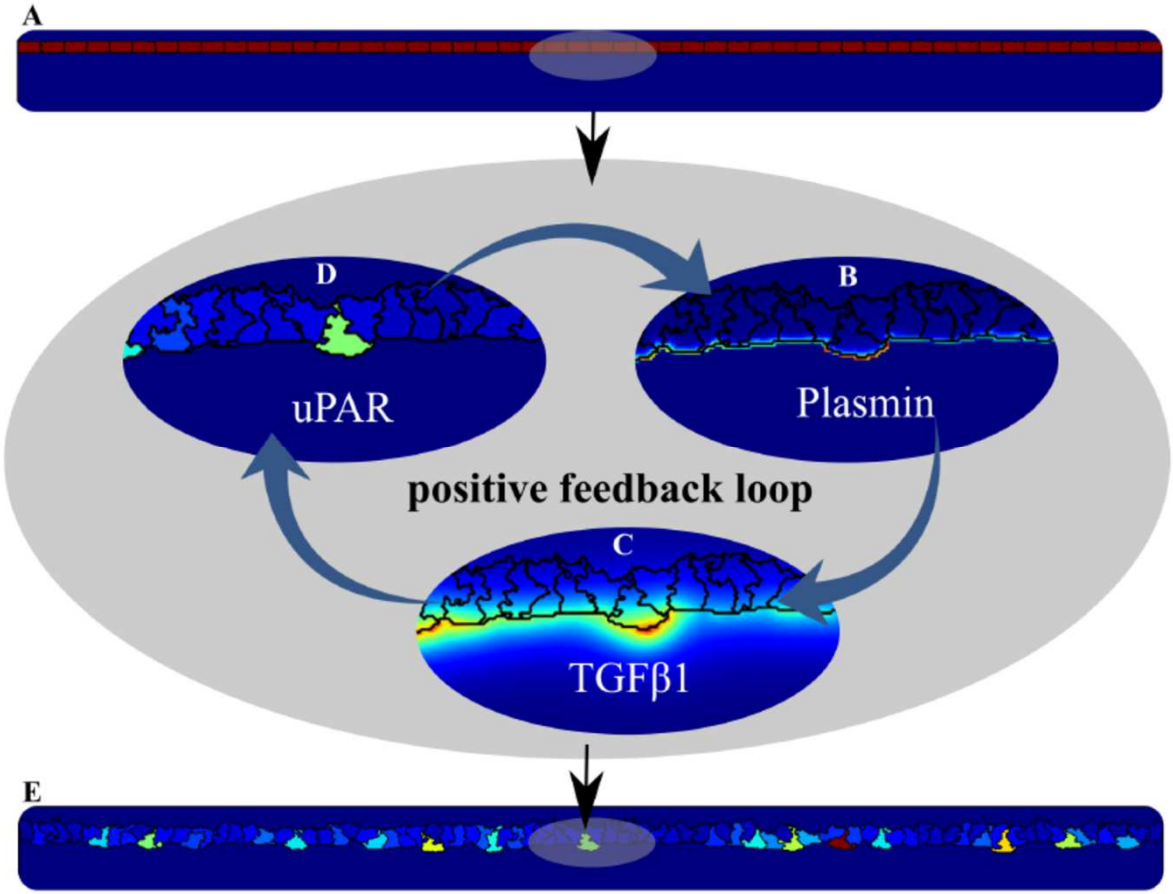
D: endothelial cells and fibrin (Cellular Potts Model), E: urokinase plasminogen activator receptor (uPAR), F: fibrin, G: Transforming Growth Factor β1 (TGFβ)

Plasmin and TGF-β1 interactions



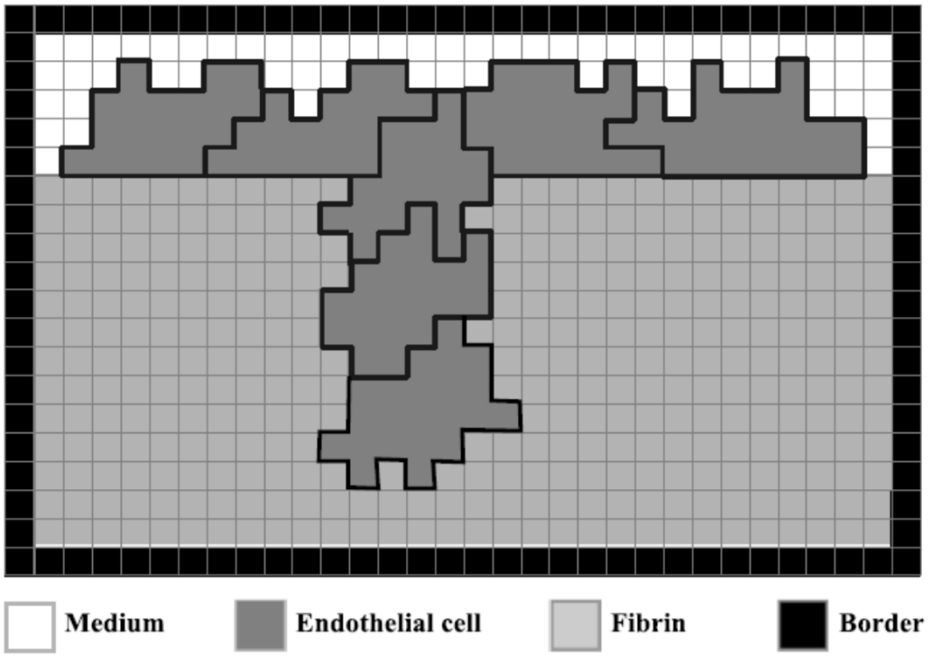
Plasminogen (PLG), fibrin-bound plasminogen (F_{PLG}), urokinase plasminogen activator receptor (uPAR), fibrin-bound plasmin (F_{PLS}) Transforming Growth Factor β1 (TGF), latent TGF-β1 (LTGF), fibrin-bound latent-TGF-β1 (F_{LTGF}), plasminogen activator inhibitor 1 (PAI)

Positive feedback loop on uPAR



Initially the same uPAR concentration, local fluctuations on the fibrin-cell contact leads to plasmin concentration increase, fibrin degradation and release of TGF-β1(stimulates uPAR and selects **uPAR rich** cells)

Model



Cellular Potts Model of HMVEC-fibrin assay (*in vitro*), implemented in CompuCell3D framework

Monolayer of endothelial cells on top of fibrin matrix (+ some medium)

Cells degrade and invade fibrin, form sprouts

Equations

$$\frac{\partial F}{\partial t} = \overbrace{-PLG * F * k_{f1} + F_{\text{PLG}} * k_{r1}}^{PLG-Fibrin\ binding\ (1A)} + \overbrace{F_{\text{LTGF}} * k_{r2} - LTGF * F * k_{f2}}^{LTGF-Fibrin\ binding\ (2A)} + \overbrace{\frac{F_{\text{LTGF}} * (F_{\text{PLS}} + F_{\text{PLS,LTGF}}) * k_{u2}}{k_{m2} + F_{\text{LTGF}}}}^{Release\ TGF\ (3A)}$$

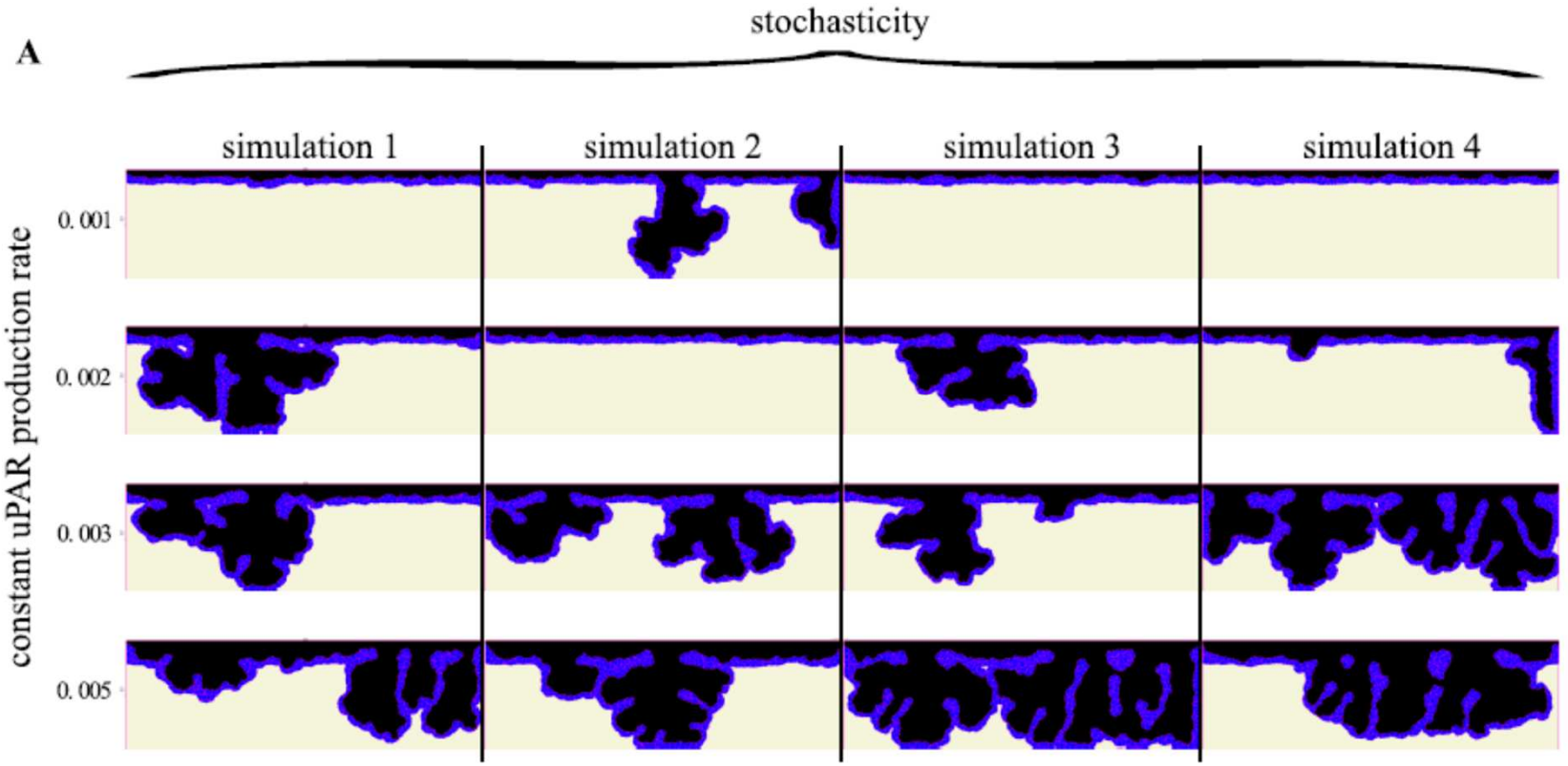
$$\frac{\partial uPAR_\sigma}{\partial t} = \overbrace{-\sum_{i \in C_\sigma} (uPAR_\sigma * PAI(i) * k_{f3})}^{Internalization} - \overbrace{\epsilon_{\text{uPAR}} uPAR_\sigma}^{Decay} + \overbrace{c}^{Constant\ production} + \overbrace{\frac{k_{u3} (\sum_{j \in P_\sigma} TGF(j))^2}{k_{m3} + (\sum_{j \in P_\sigma} TGF(j))^2}}^{TGF-induced\ uPAR\ production} \forall \sigma \in 1, .., 50$$

$$\frac{\partial PAI}{\partial t} = \overbrace{-\sum_{\sigma=1}^{n} (uPAR_\sigma * PAI * k_{f3})}^{Internalization} - \overbrace{\epsilon_{\text{PAI}} PAI}^{Decay} + \overbrace{\alpha 1_{\tau(x)=\text{cell}}}^{Secretion} + \overbrace{D_{\text{PAI}} \nabla^2 PAI}^{Diffusion}$$

$$\frac{\partial TGF}{\partial t} = \overbrace{D_{\text{TGF}} \nabla^2 TGF}^{Diffusion} - \overbrace{\epsilon_{\text{TGF}} TGF}^{Decay} + \overbrace{\frac{F_{\text{LTGF}} * (F_{\text{PLS}} + F_{\text{PLS,LTGF}}) * k_{u2}}{k_{m2} + F_{\text{LTGF}}}}^{Release\ TGF\ (3A)} + \overbrace{\frac{F_{\text{PLG,LTGF}} * (F_{\text{PLS}} + F_{\text{PLS,LTGF}}) * k_{u2}}{k_{m2} + F_{\text{PLG,LTGF}}}}^{Release\ TGF\ (3B)} + \overbrace{\frac{F_{\text{PLS,LTGF}} * (F_{\text{PLS}} + F_{\text{PLS,LTGF}}) * k_{u2}}{k_{m2} + F_{\text{PLS,LTGF}}}}^{Release\ TGF\ (3C)}$$

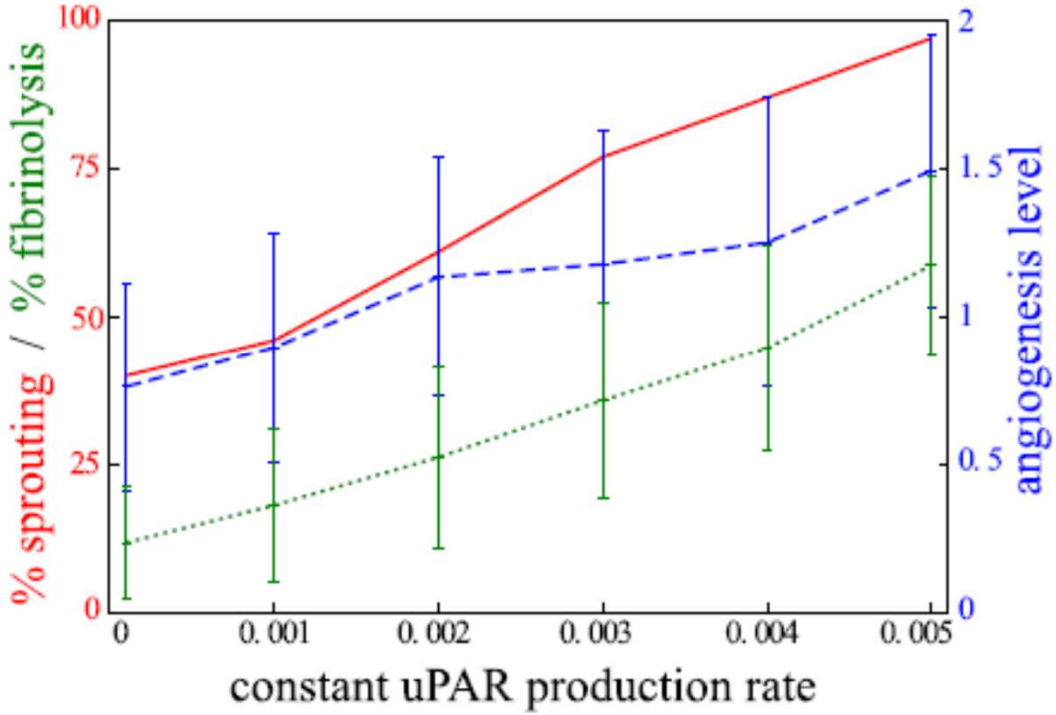
PDEs describe the **concentration** changes for each chemical specie (11 of them)

Results



Example of four runs with four different uPAR production rates (after 6000 MCS)

uPAR production rate



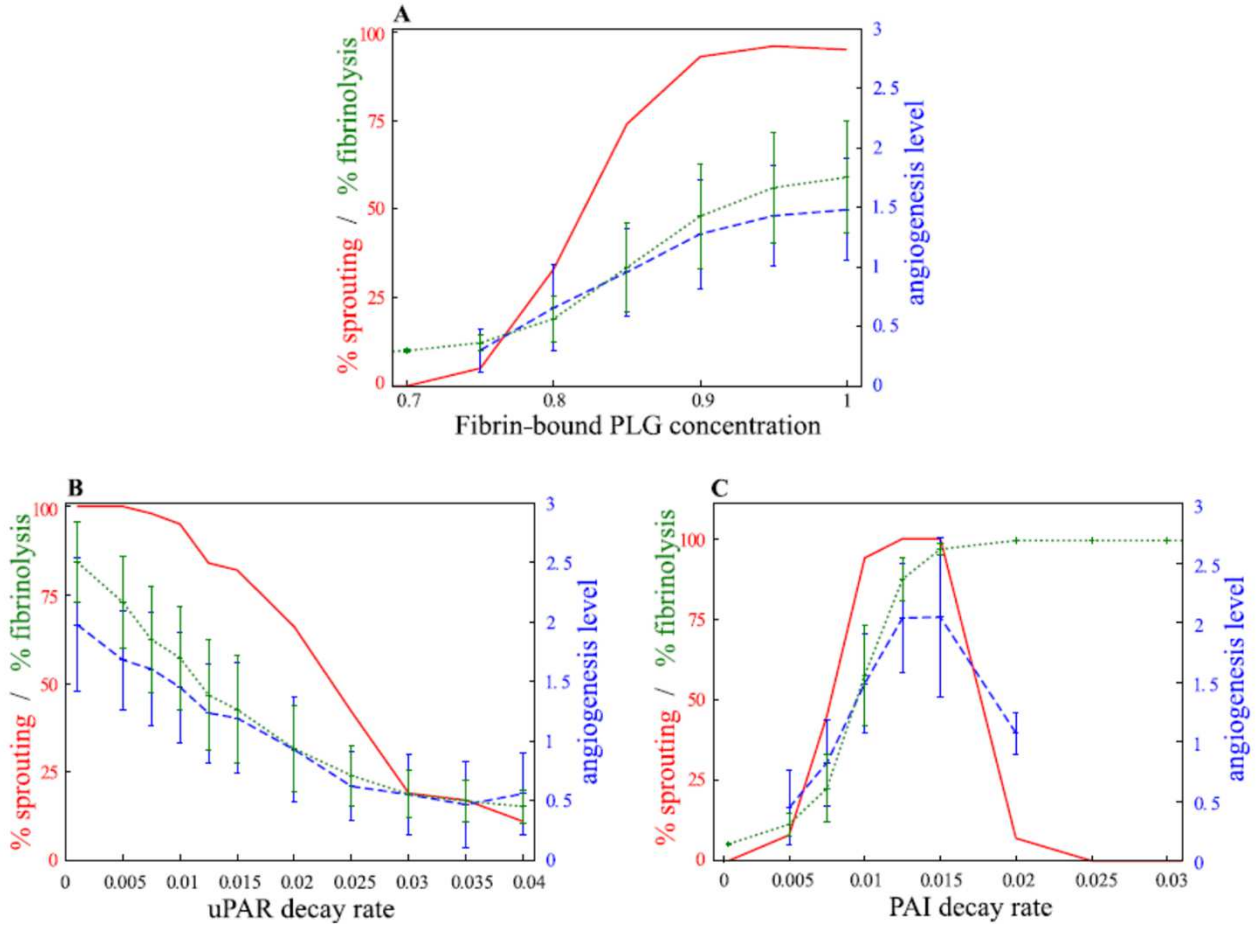
Sprouts form more **frequently** and more **extensively** at higher **uPAR** production rates (results at MCS 6000)

Blue: mean angiogenesis level (sprout count and sprout depth)

Red: percentage of simulations that formed sprouts

Green: fibrinolysis (percentage of the initial fibrin invaded)

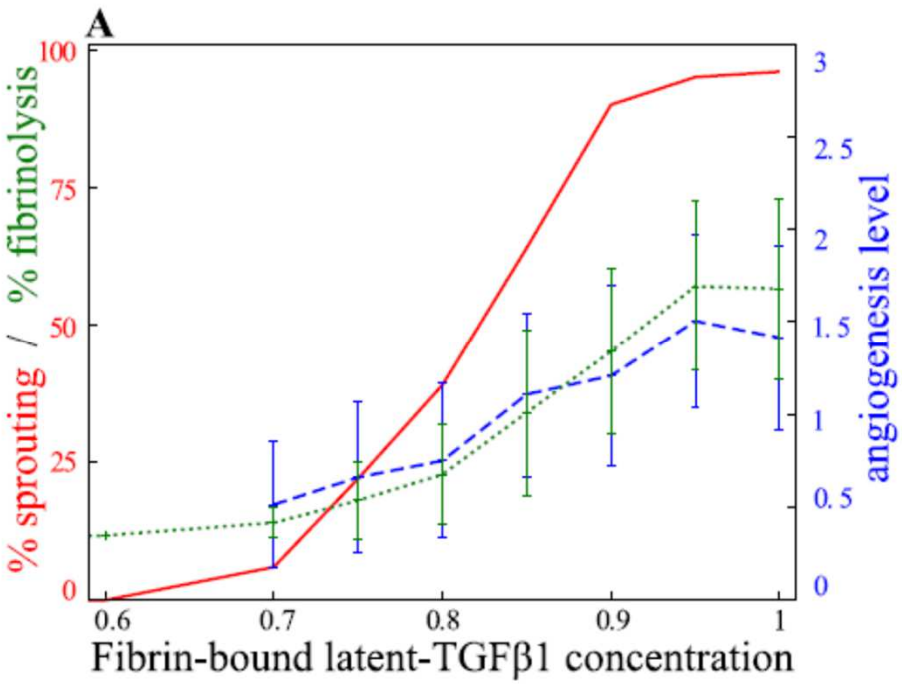
(Some) validation experiments

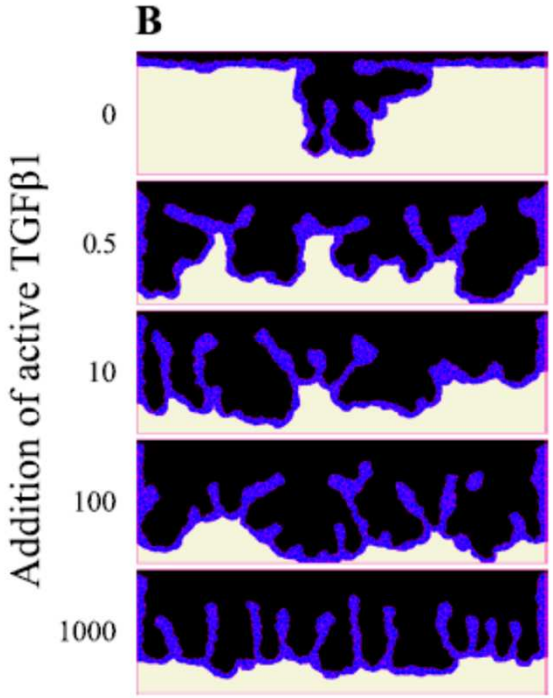


A: initial concentration of fibrin-bound plasminogen

B: decay rate of uPAR

C: decay rate of PAI-1





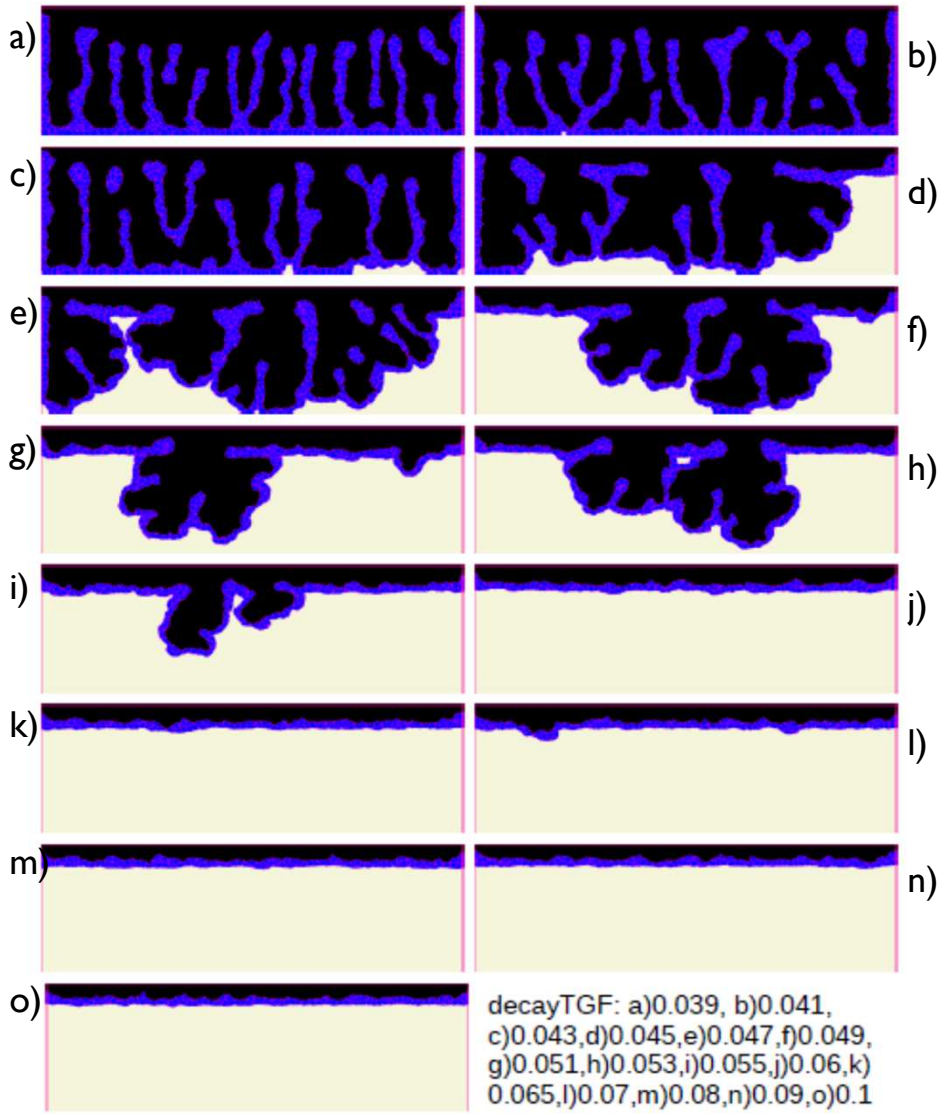
A: Initial concentration of **fibrin-bound latent-TGF-β1** (experimentally observed reduced level of TGF-β1 **bound** to **LMW** compared to **HMW**)

B: Active TGF-β1 has a **biphasic effect** on sprout formation: increases for low doses, but global degradation prevents sprout formation at high doses

With low decay rate of TGF-β1 there is too much TGF-β1 available and then **too much** fibrinolysis

When is too high there is not enough TGF-β1 and there is **no fibrinolysis**

Small interval of TGF-β1 decay rate for **good sprouting**



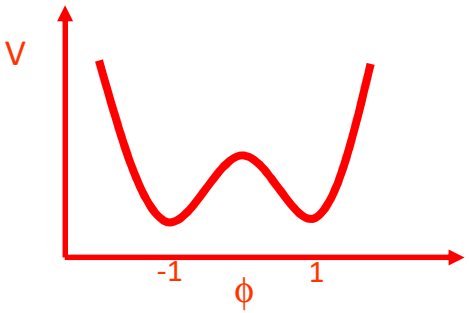
Model interprets well the experimental results: describes a **reduced level of sprouting** on LMW compared to HMW, when the uPAR-plasmin-TGF-β1 **positive feedback loop** cannot be sufficiently activated

Predicts some other results that can be **tested** *in vitro* (waiting for new experiments)

Continuous Model

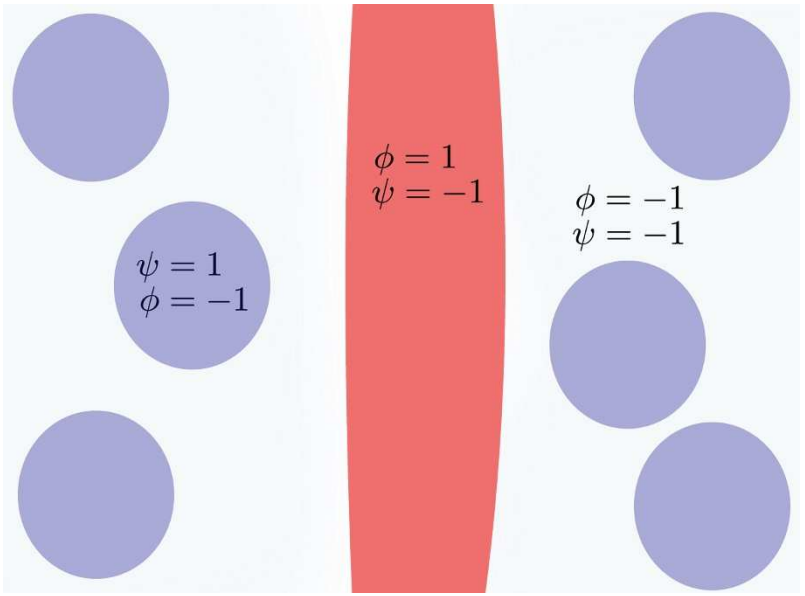
- Continuous Component
  - Diffusion: concentration of VEGF, (*T*)
  - **Phase-Field: order parameter dynamics**

$$F[\phi,\psi]=\int\left[\frac{\varepsilon^2}{2}(\nabla\phi)^2+\frac{\varepsilon_{\mathrm{h}}^2}{2}(\nabla\psi)^2+V(\phi,\psi)\right]\mathrm{d}^d\mathbf{r}$$



$$\partial_t\phi=\nabla^2\frac{\delta F}{\delta\phi}+\alpha_\phi T\phi\Theta(\phi)$$

$\phi = 1$, $\psi = -1$ inside capillary
$\phi = -1$, $\psi = 1$ inside hypoxic cells
$\phi = -1$, $\psi = -1$ outside capillary



- The **Angiogenic** Factor

$$\frac{\partial T}{\partial t} = D_T \nabla^2 T - \alpha_T T \phi \Theta(\phi)$$

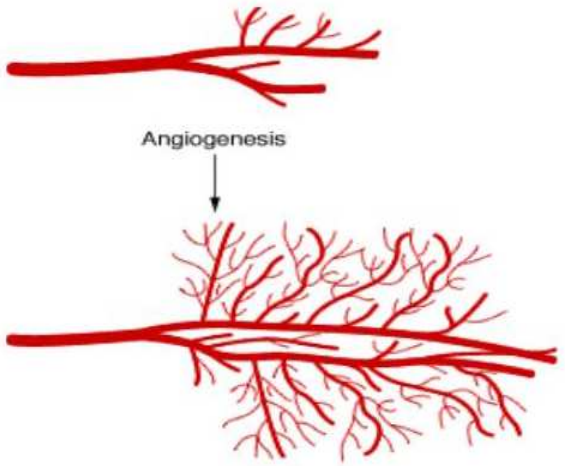
- The evolution of the capillary (continuous component)

$$\frac{\partial \phi}{\partial t} = M \nabla^2 \frac{\delta F}{\delta \phi} = M \nabla^2 \left[\phi^3 - \phi - \varepsilon^2 \nabla^2 \phi + \gamma (\phi^2 - 1)(\psi - 2)(\psi + 1)^2 \right]$$

- Tip cell (agent based component)
  - Characteristic radius R_c

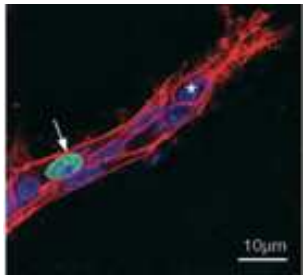
Tissue Based Modeling: Angiogenesis

- Angiogenesis is strongly correlated with solid tumor malignity
- Relevant in varied situations in health and **disease**
  - Morphogenesis
  - Inflammation
  - Wound healing
  - Diabetic Retinopathy
  - Over 50 other pathologies
  - Essential to characterize vessel growth and tissue irrigation to predict and control these pathologies



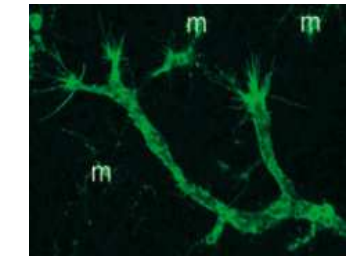
Sprouting Angiogenesis in a Nutshell

- Capillaries are constituted by
  - Endothelial cells
  - Pericytes, muscle cells



Gerhardt et al, J Cell Biol (2003)

+ VEGF (hypoxic cells) weakens capillary wall
  - Endothelial cells may divide

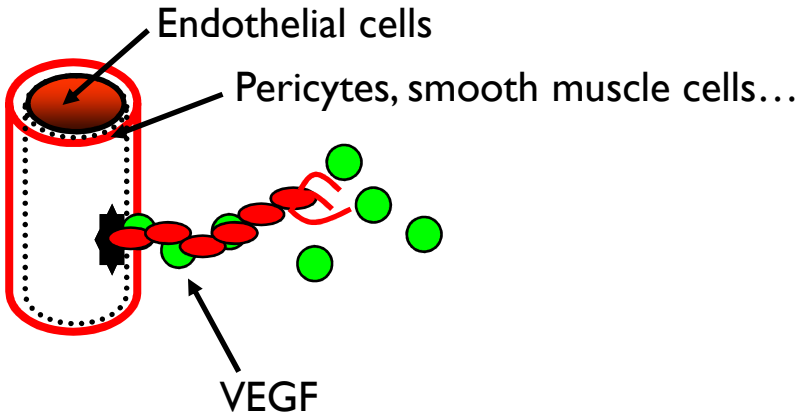


Gerhardt et al, J Cell Biol (2003)

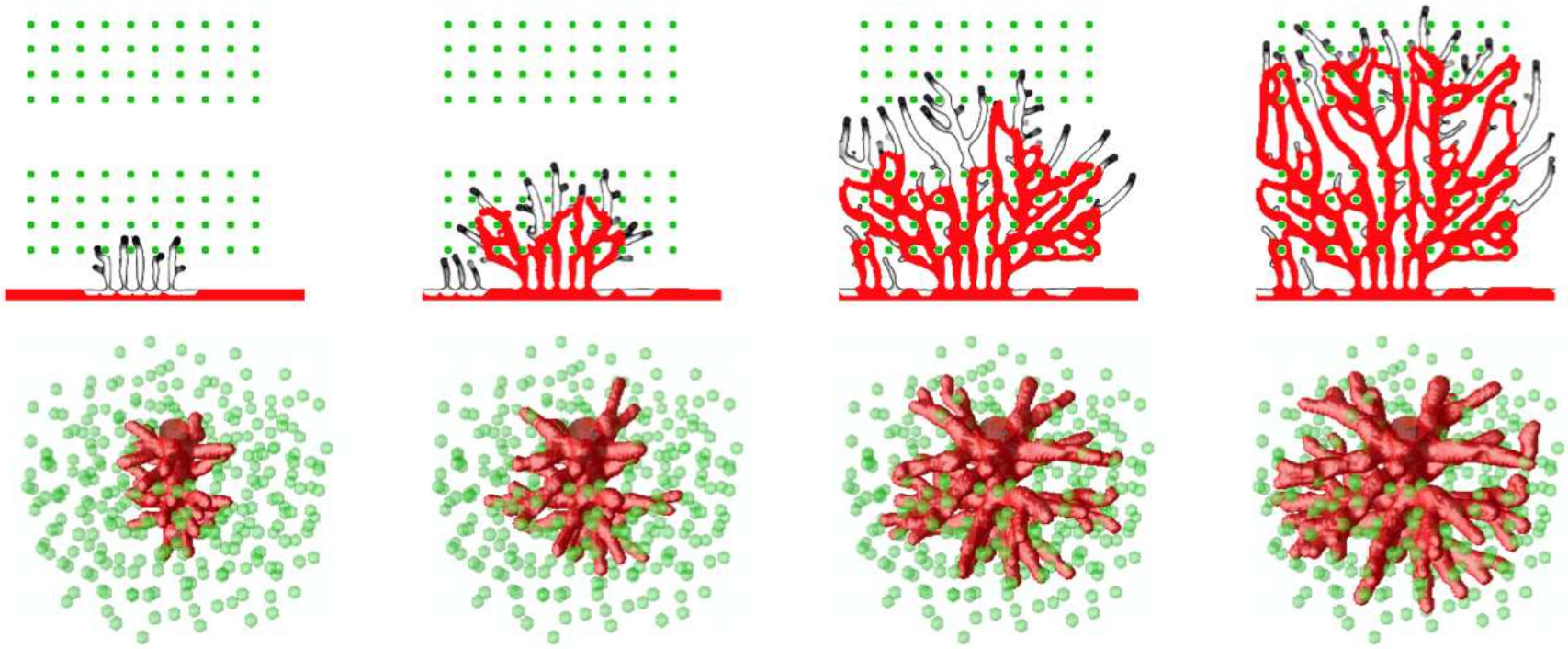
+ Cells follow VEGF gradient
  - The first cell is activated and opens way in ECM

+ Cells organize to form lumen

+ Blood flows when capillaries form loops (anastomosis)
  - Blood reorganizes network



Characterization of the Networks



- Tissue irrigation, vessel density, vessel diameter as a function of
  - EC proliferation rate
  - VEGF levels
  - VEGF bioavailability

+ EC migration velocity

+ Distribution of hypoxic cells

+ 2D vs 3D

SCIENTIFIC REPORTS

OPEN

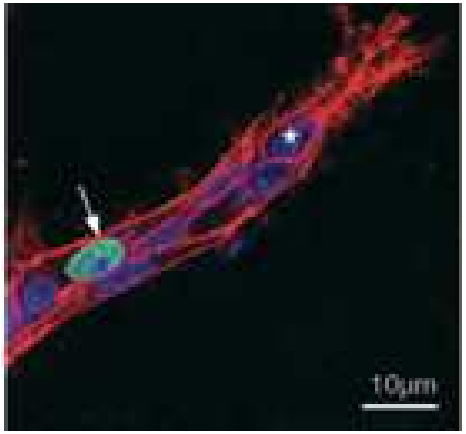
Angiogenic Factors produced by Hypoxic Cells are a leading driver of Anastomoses in Sprouting Angiogenesis–a computational study

Received: 16 May 2017
Accepted: 29 May 2018
Published online: 07 June 2018

Maurício Moreira-Soares[1], Rita Coimbra[2], Luís Rebelo[3], João Carvalho[1] & Rui D. M. Travasso[1]

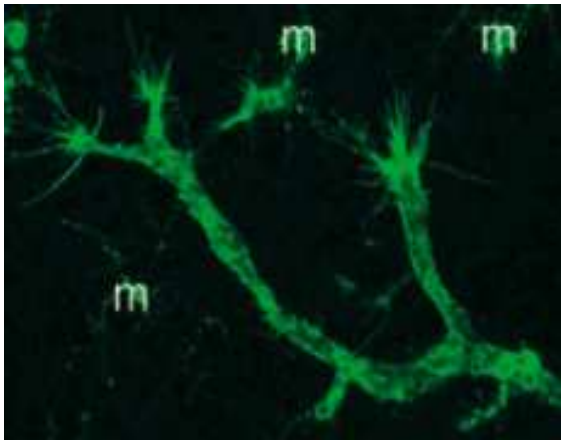
Simulating Angiogenesis: Two types of cells

- **Tip cells** are special (agent based)
  - Have filopodia
  - Follow gradients of VEGF
  - Produce MMPs which degrade ECM
  - Construct path
  - Do not proliferate



Gerhardt et al, Cell (2003)

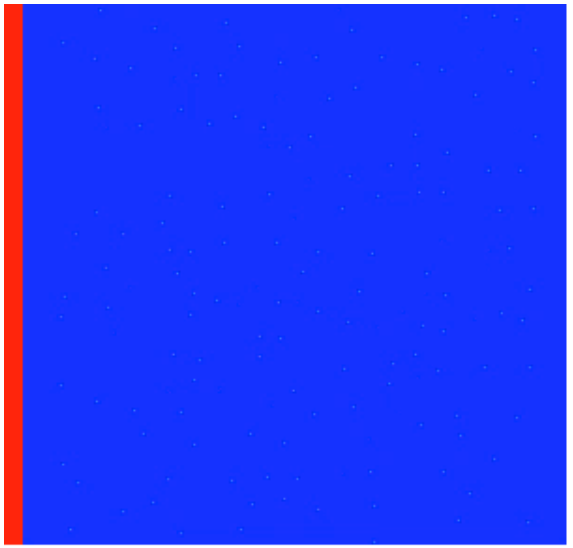
- **Stalk cells** (continuous)
  - Proliferation regulated by VEGF
  - Not diggers
    - Follow tip cell created pathway

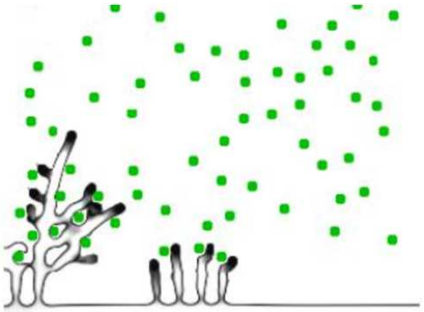


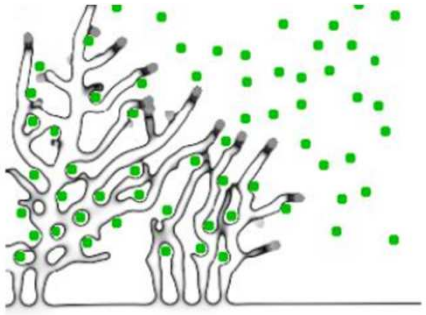
Gerhardt et al, Cell (2003)

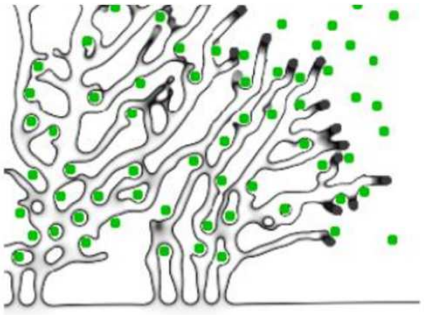
Vessel Growth in Hypoxic Tissue

- Starting configuration
  - Capillary close to tissue in hypoxia
  - Concentration of VEGF at hypoxic cells constant
  - Vessels are able to surround cells in hypoxia

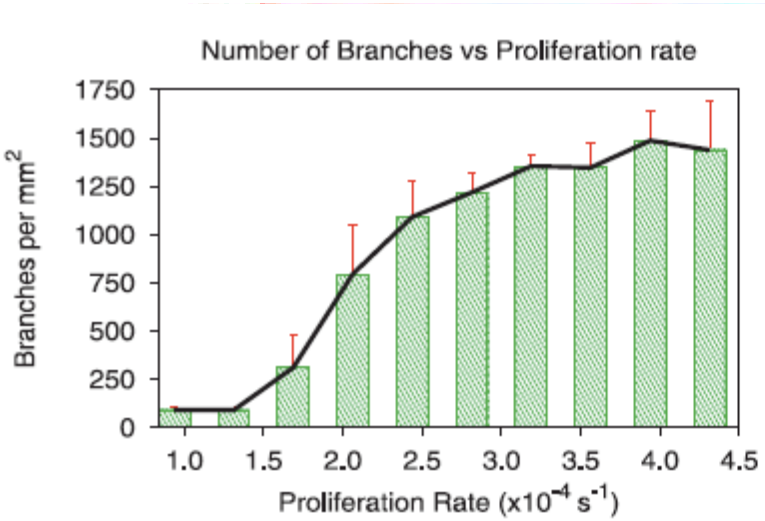


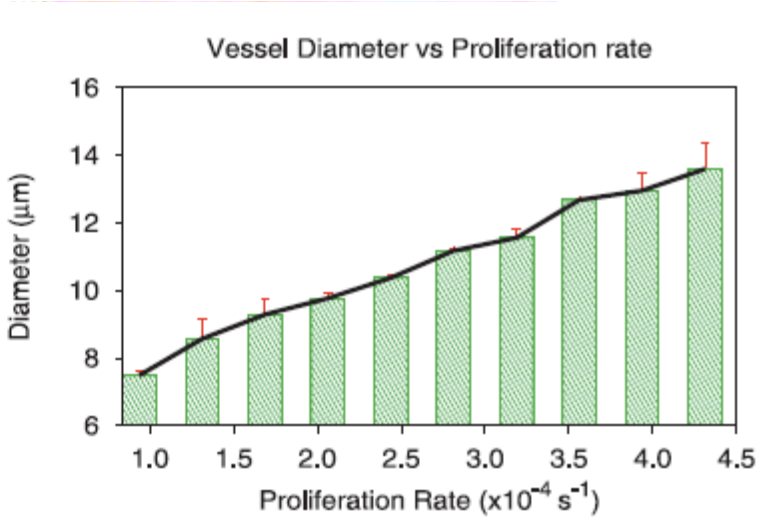






Network Morphology - Proliferation



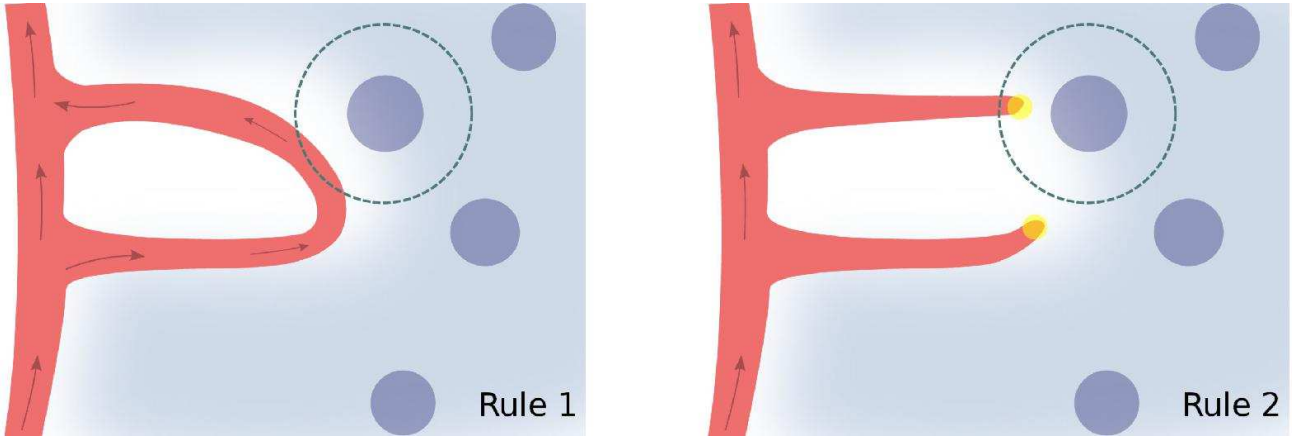


Low Proliferation **High Proliferation**

- High proliferation rate leads to many thicker vessels

VEGF guided Vessel Anastomosis

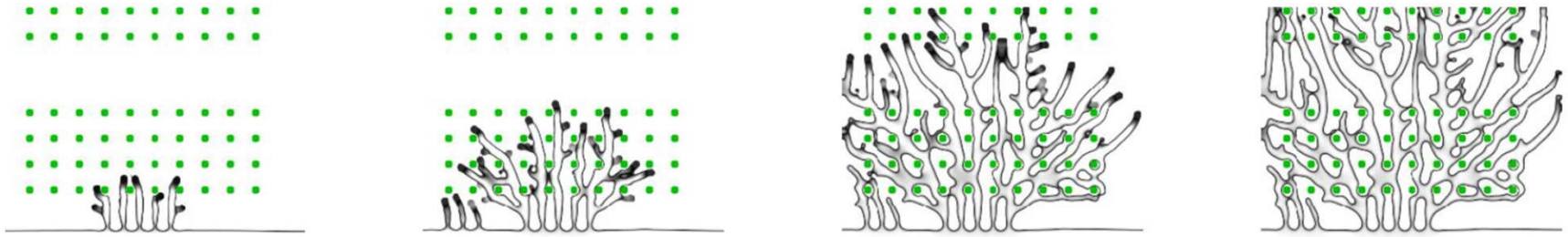
- Role of VEGF production in triggering **anastomosis**
  - Two rules for tip cell deactivation

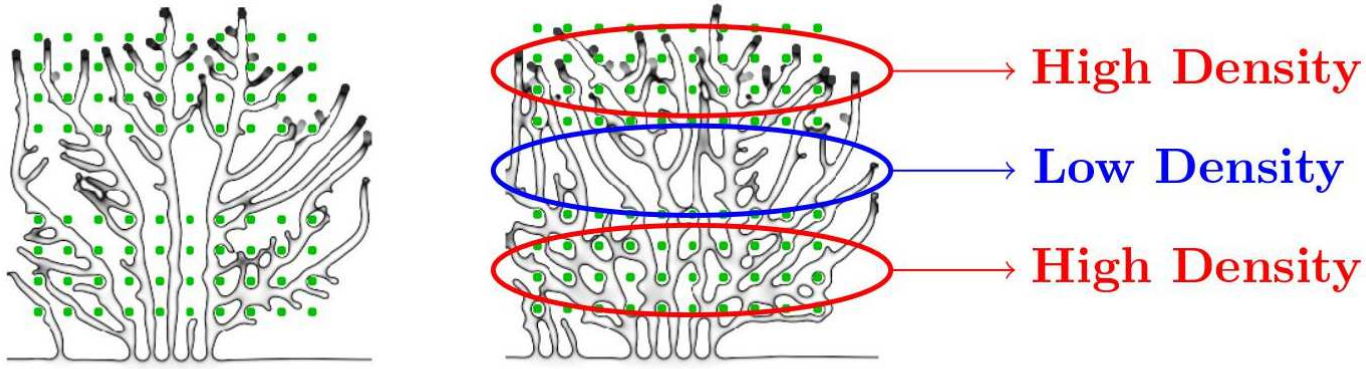


- **Rule 1**: A cell produces angiogenic factor in the model if it is located at a distance larger than the average oxygen diffusion length (25 μm) from all vessels with blood flow rate different from zero
- **Rule 2**: A cell produces angiogenic factor in the model if it is located at a distance larger than the average oxygen diffusion length (25 μm) from all vessels

Hypoxic Cells Determine Vascular Network

- Growth of vessels through a gap



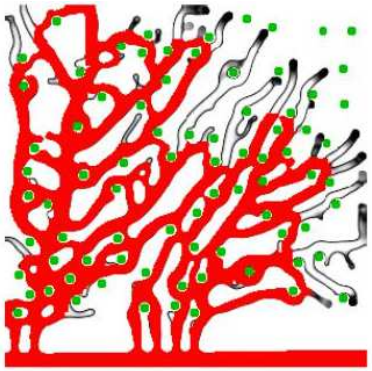


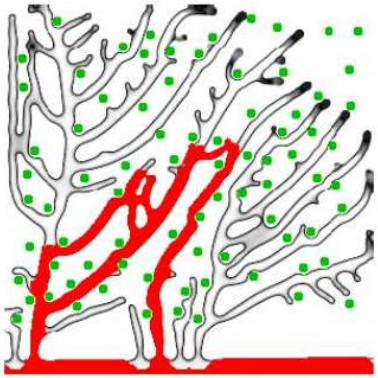
Rule 2 Rule 1

- The density of hypoxic cells determine the density of vessels

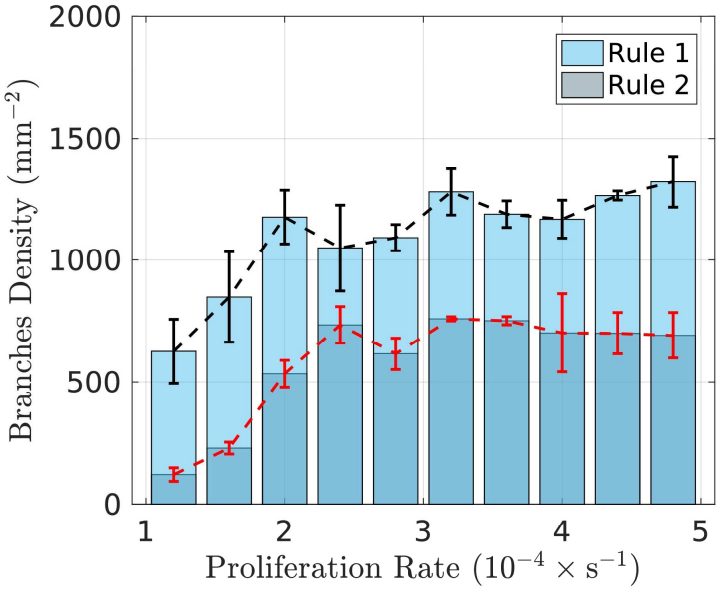
Vessel Network as Function of Proliferation

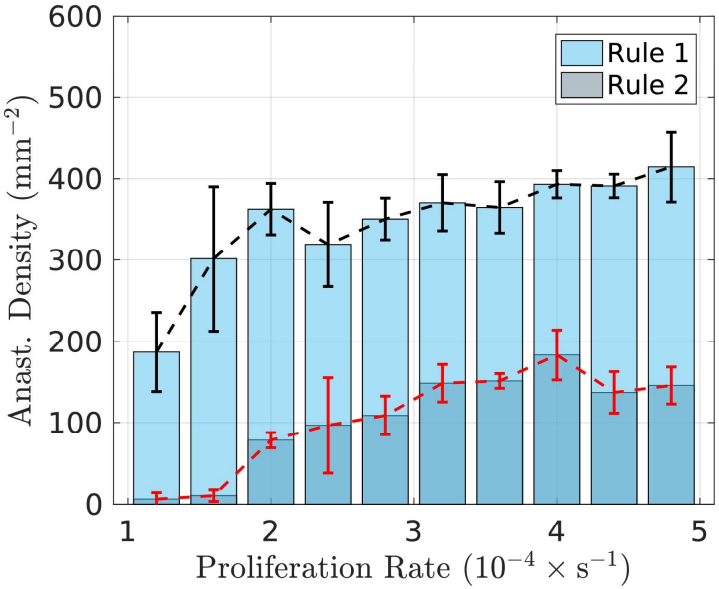
Rule 1





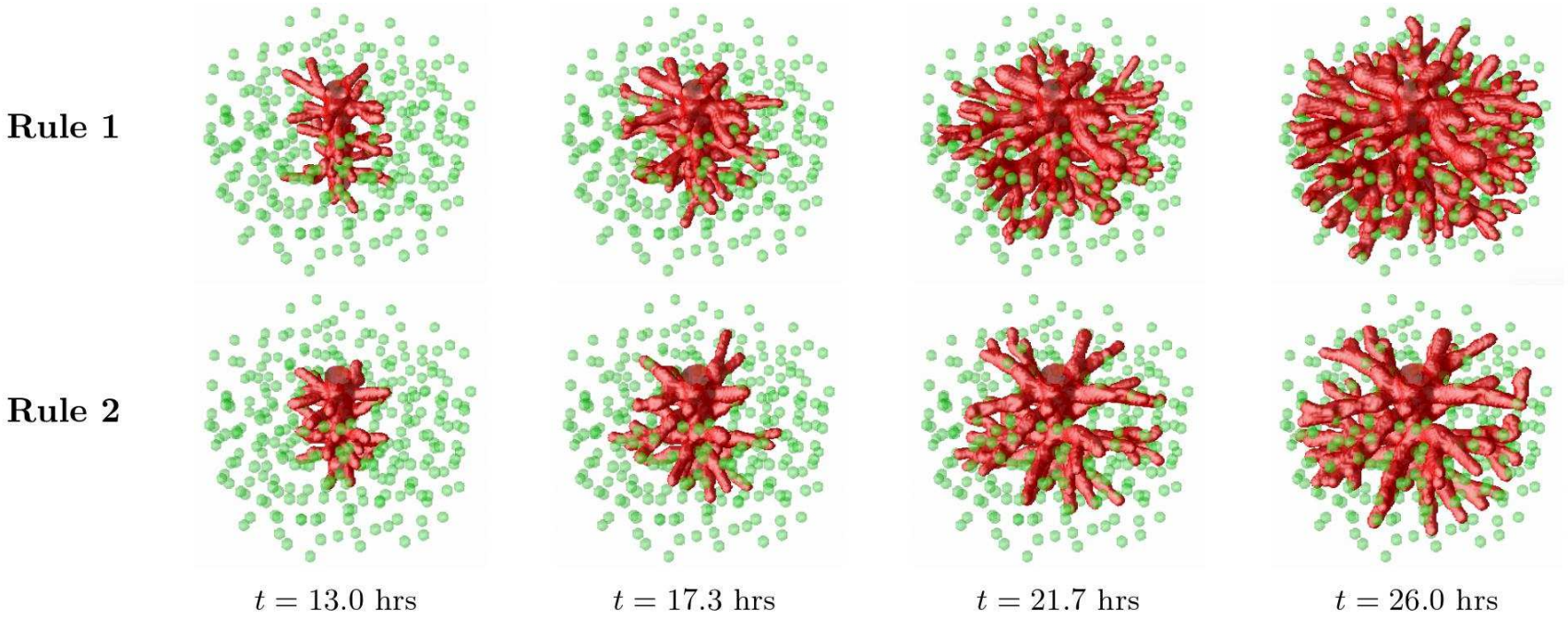
Rule 2





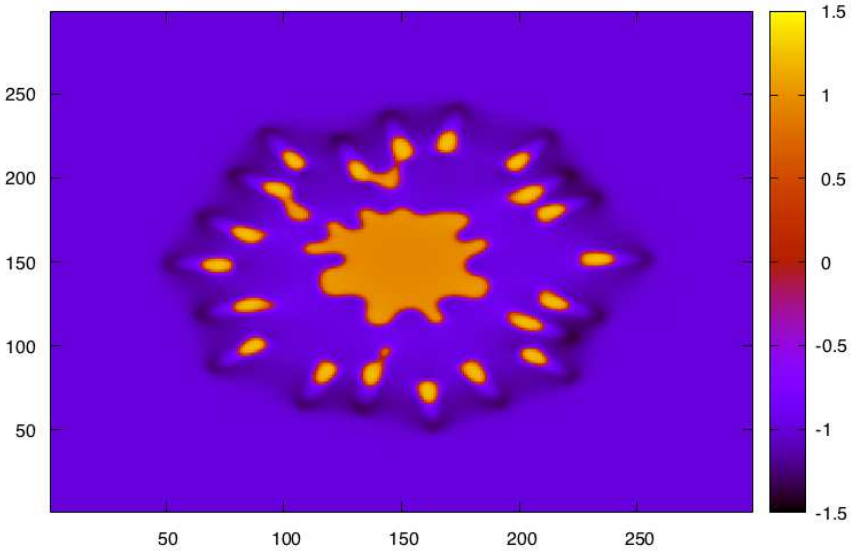
Vessel Growth in 3D

- The rules for cell deactivation also affect the network

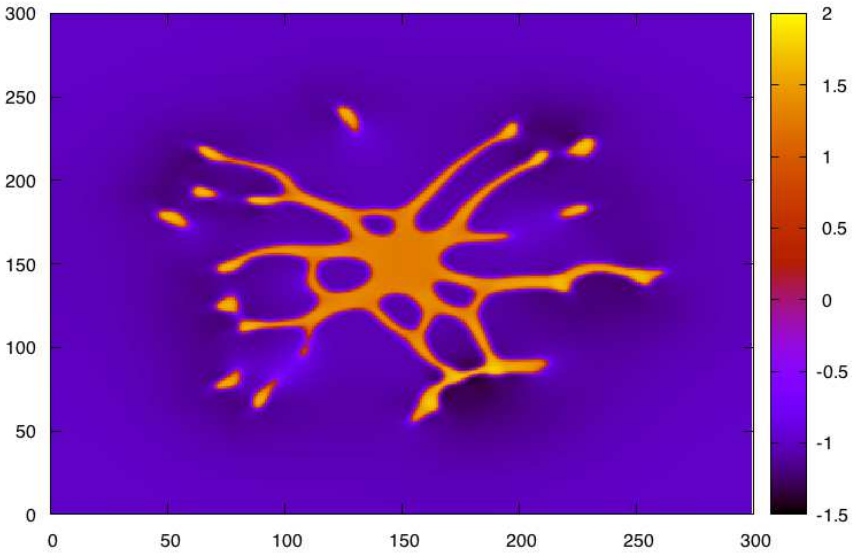


Morphology

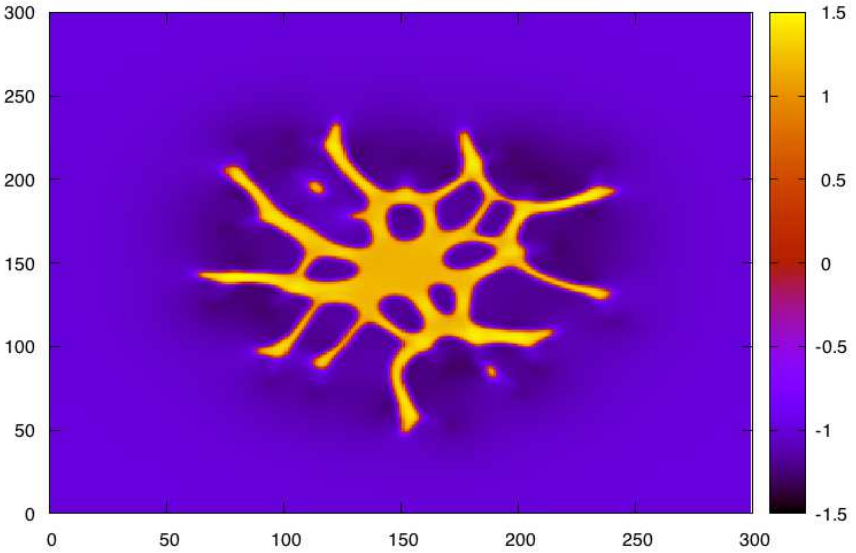
Low rigidity



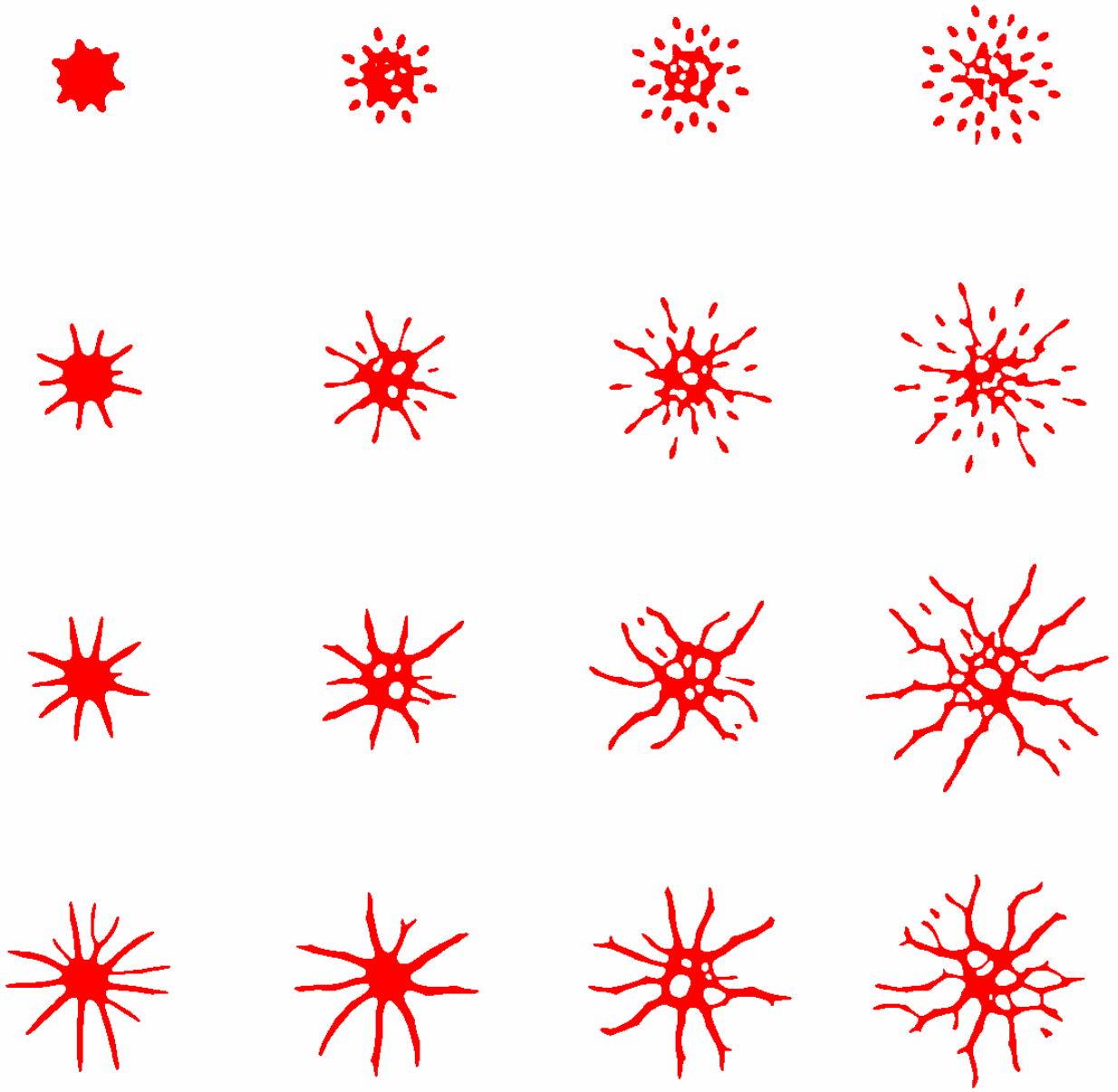
Medium Rigidity



High rigidity



Force vs. Medium Rigidity



What can be seen here?

Controlled sprouting activity

Tip cells move towards each other

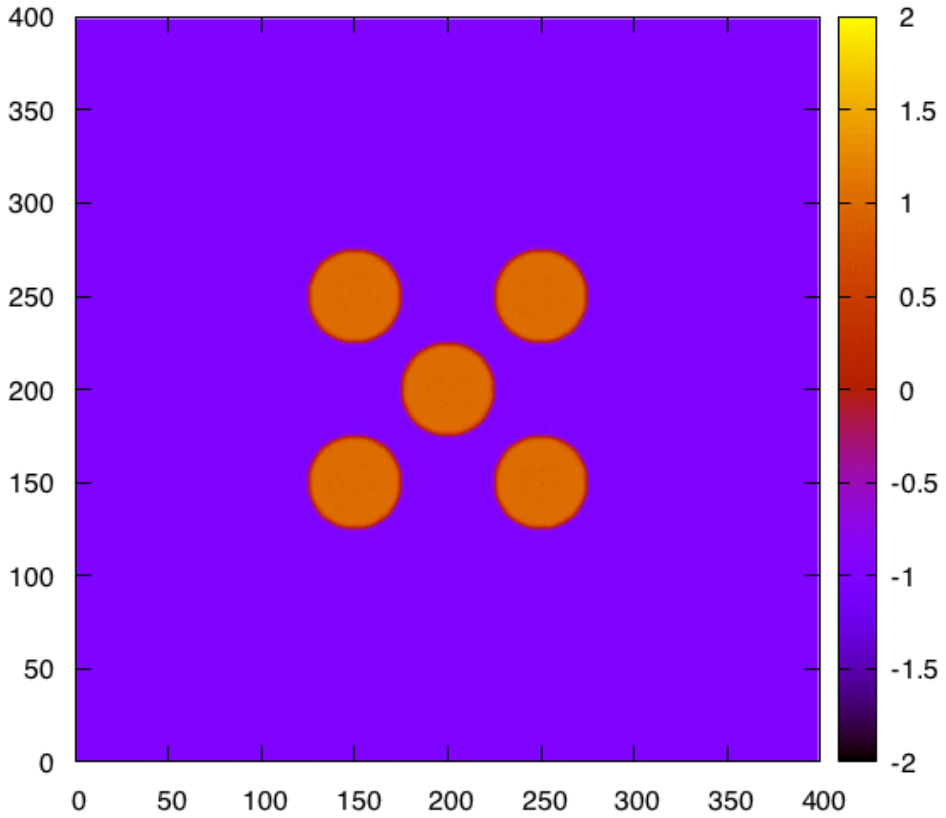
Anastomosis

Long and robust vessels

Ramifications

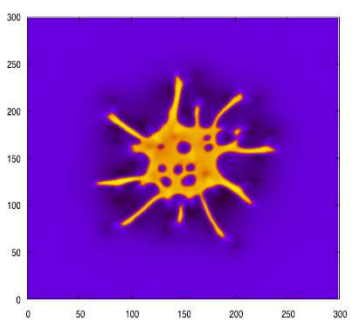
Result

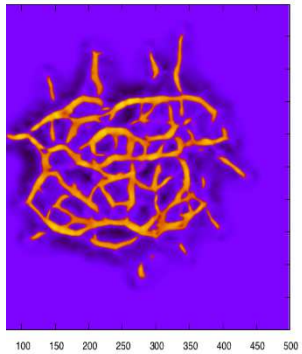
Complex vascular network!



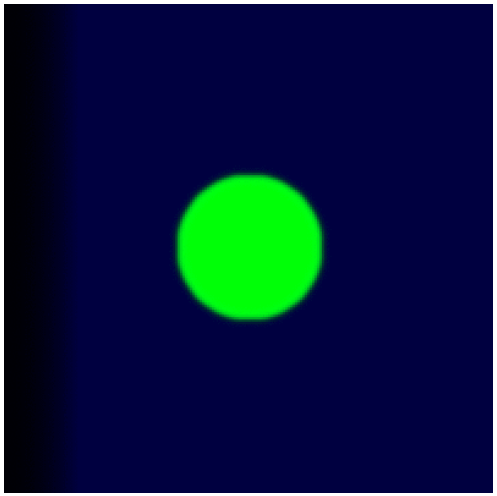
Sprout Formation *in Silico*

- Formation of vascular networks coupled with tissue mechanics



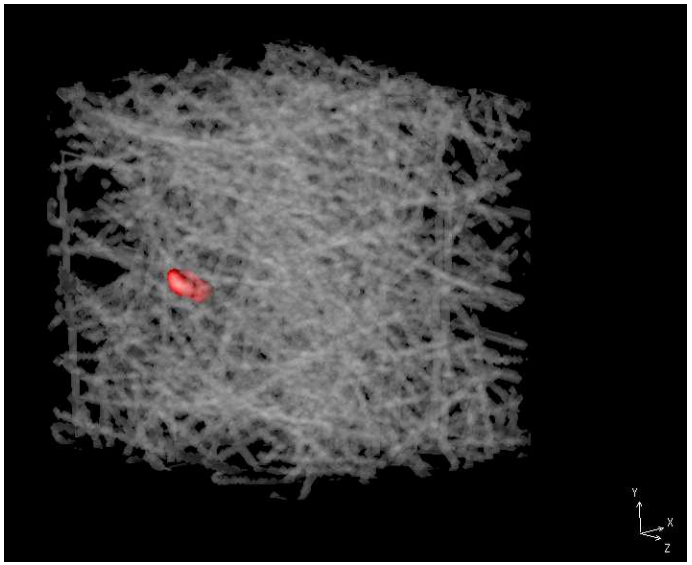


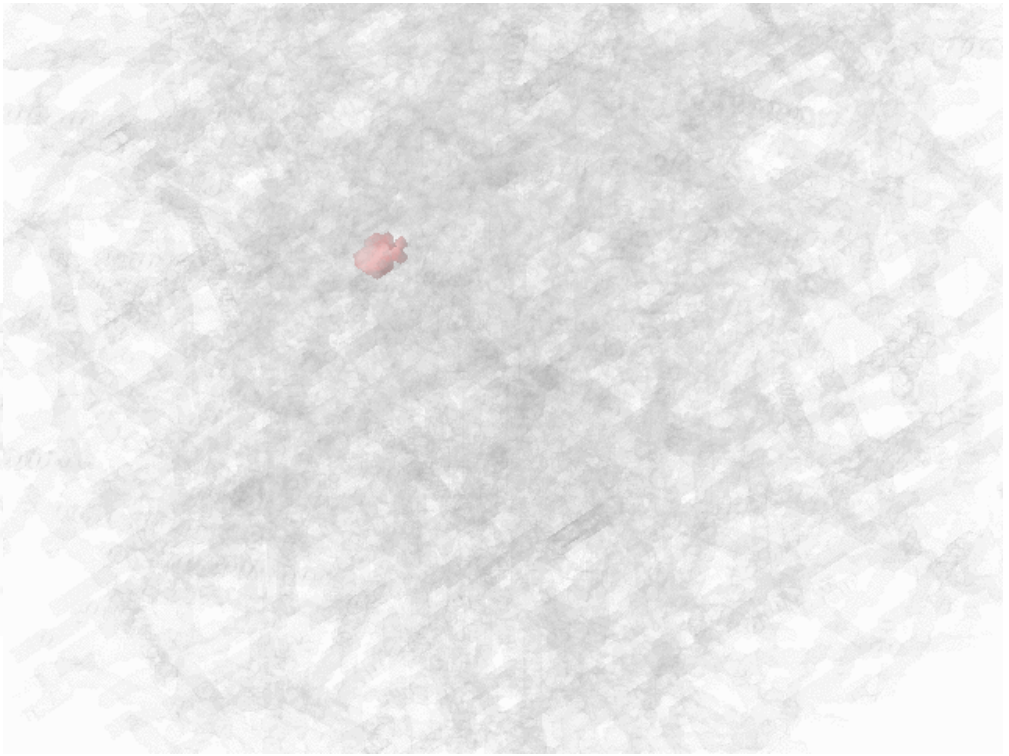
+ **Model now includes**
  - Both ECs and tissue cells
  - Forces exerted by cells on the matrix
  - EC proliferation dependent on both VEGF levels and local stresses
  - Mechanical properties depend on position
  - Degradation of matrix
  - Matrix remodeling
  - VEGF release from the matrix

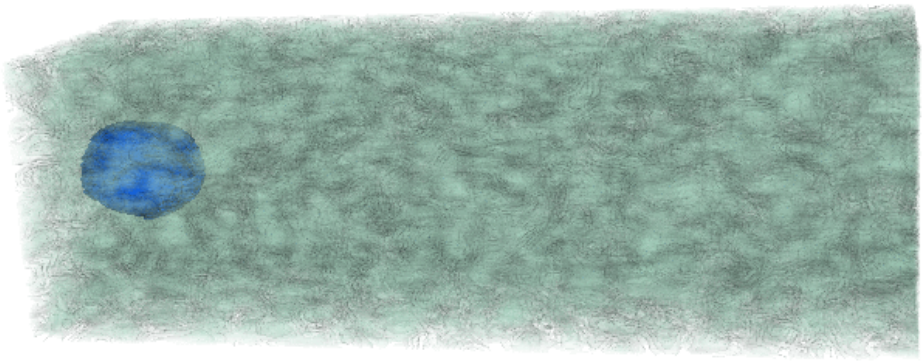


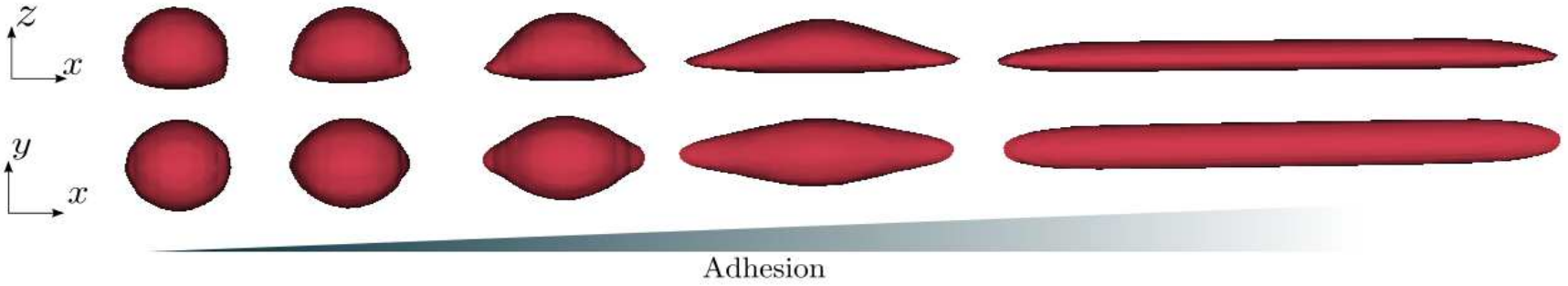
Cell Based Modeling

- Model the **interaction** between individual cells and the tissue
  - 3D cell migration
    - Matrix adhesion and degradation





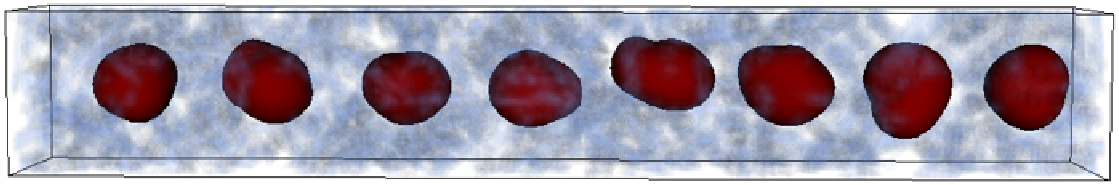



z
x
y
x
Adhesion

Migration Dynamics

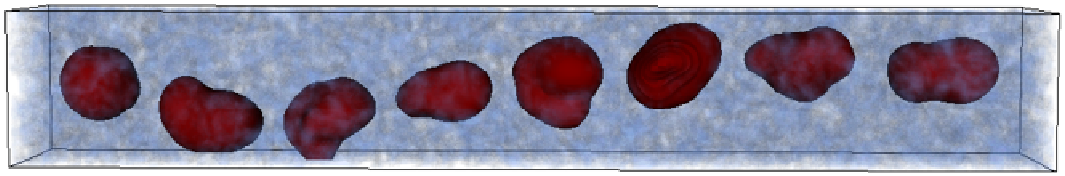
$\rho = 0.2$ Fibers' density

1D

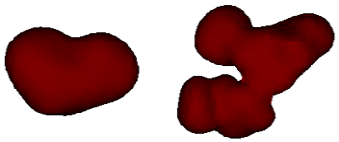


3D

$\rho = 0.54$



A.R = 2.30 - 5.23



Adhesion

Conclusions

For relatively small systems (like *in vitro* tests) a **discrete** approach can be a fast and insightful approach

Takes into account the discrete nature of cells and their **interactions** with the neighborhood (cells, ECM and molecules)

A **Cellular Potts Model** is a simple, flexible and powerful approach that can be applied to many biological systems (with limitations, in particular on the system size)

Continuous models are more feasible for extended systems

Biology can advance faster with computer **modeling**, and modeling can be more **accurate** with more biological data

Age of quantitative biology

University of Coimbra

Soft and Biological Matter Group: Biological Modeling

Rui Travasso

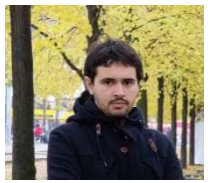
João Carvalho

Fernando dos Aidos

Postdoc

Teresa Grilo

Ph.D. Students



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Thank you for your attention

Any questions?