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Hybrid cellular Potts modeling of cell-ECM interactions

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Mathematical Institute & Institute of Biology Leiden
Leiden University, The Netherlands

Institute of Fundamental Technological Research of the Polish Academy of Sciences

March 27, 2023, online

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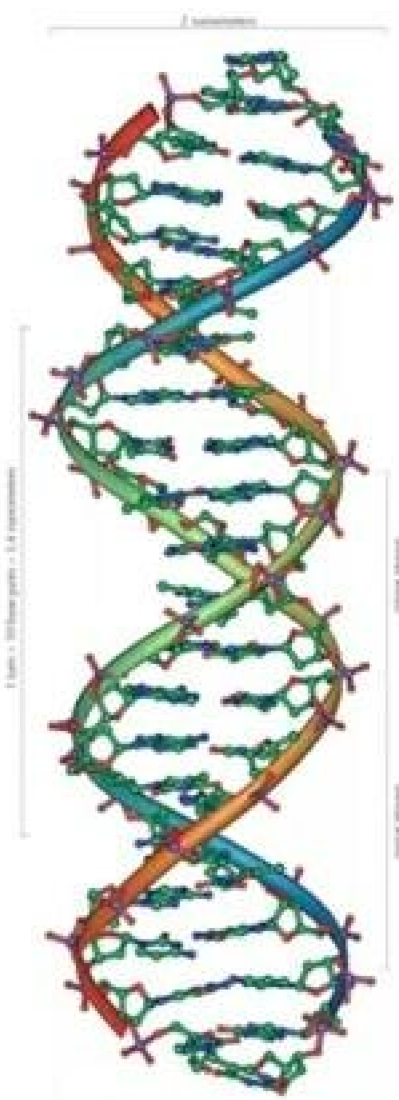
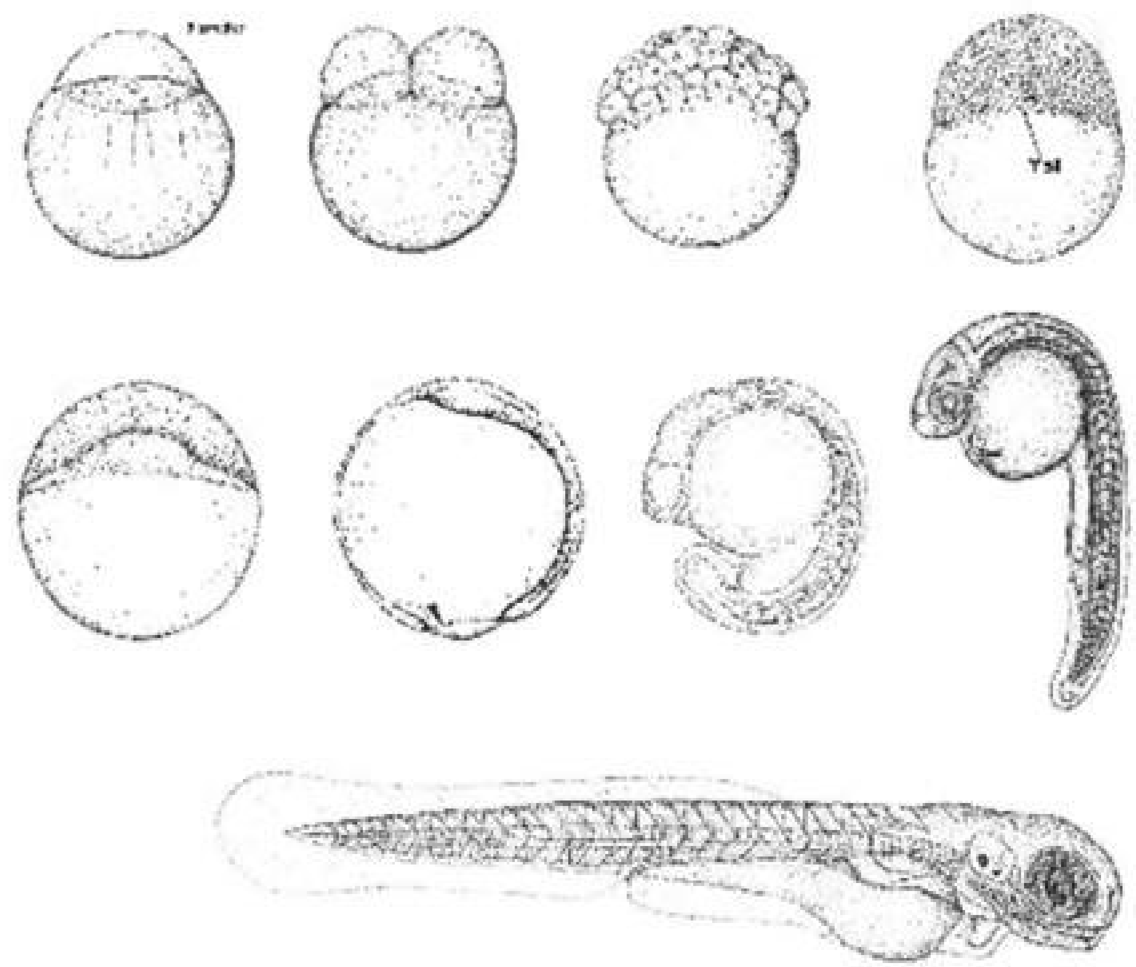
Morphogenesis

How is the **linear** information in the DNA translated into the **three-dimensional** shape of organisms?



DNA



Morphogenesis

Adult

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Morphogenesis
=
Collective behavior

Multicellular organism: a ‘flock’ of cells

- Position in ‘flock’ may feed back on cell behaviour
- Study interaction of collective behavior and intracellular dynamics
- **Multiscale mathematical biology**

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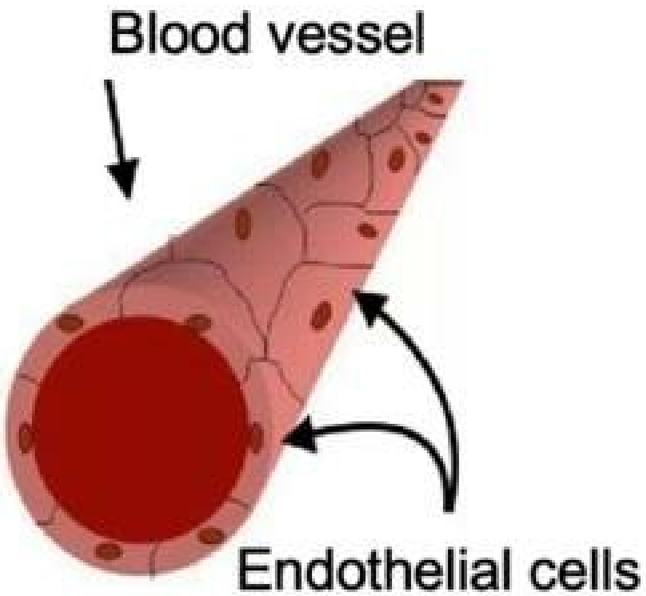
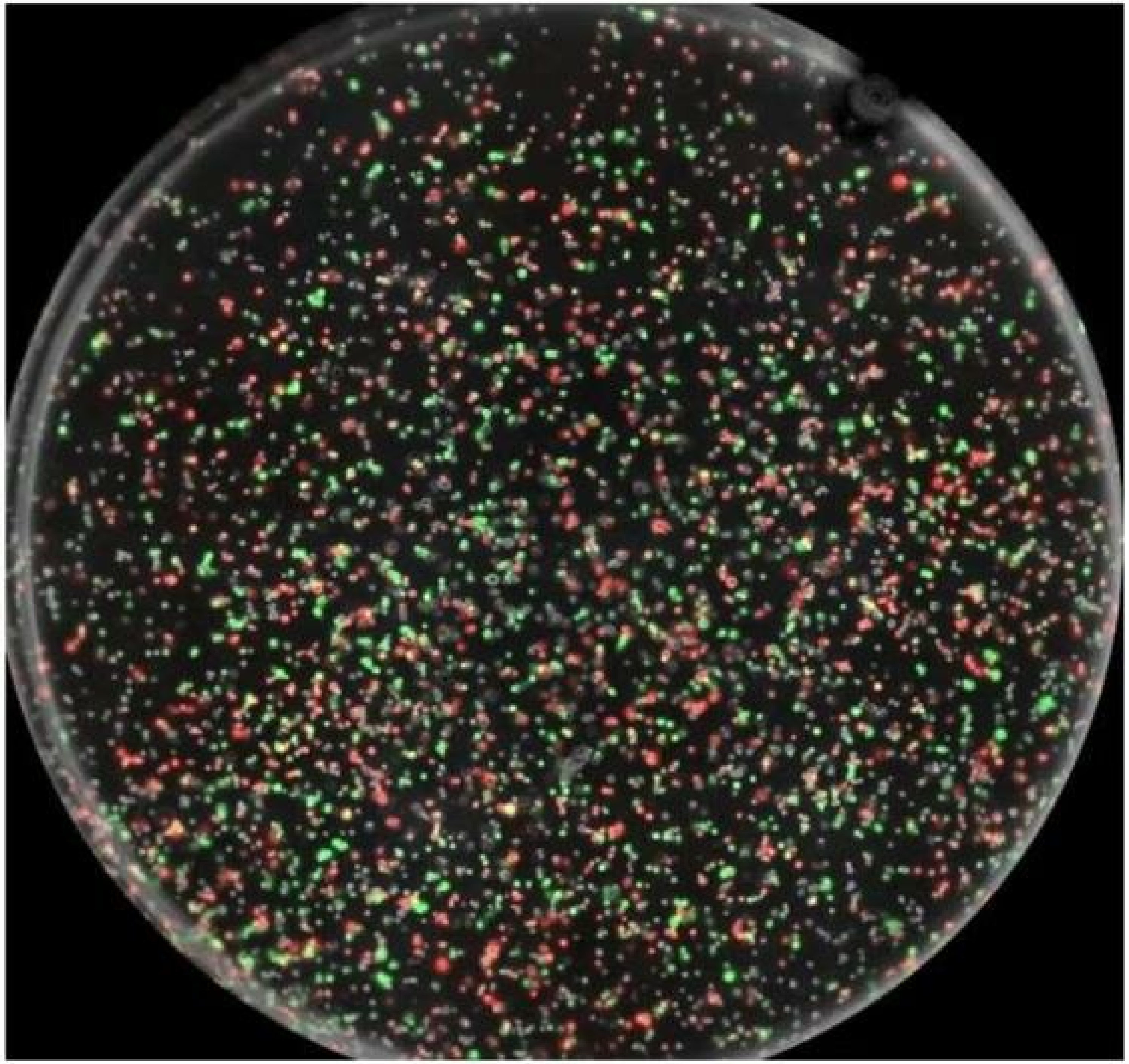
Our favorite problem: Cell-ECM interactions driving angiogenesis





HMEC-1 in Matrigel; Tessa Vergroesen

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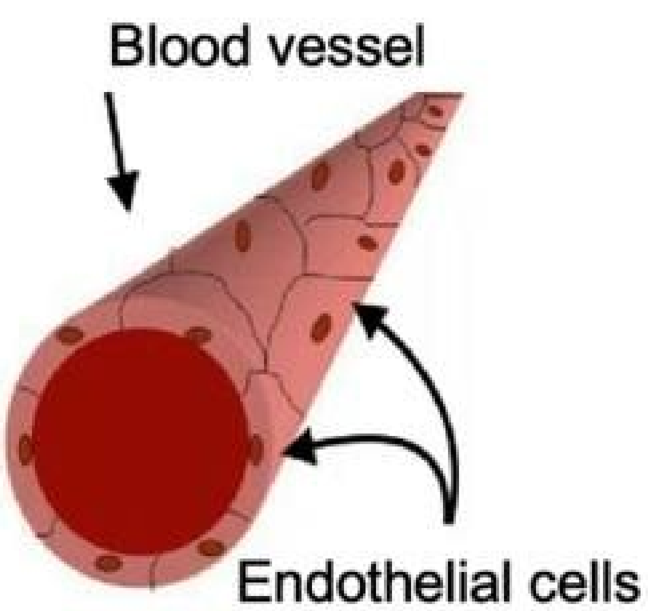
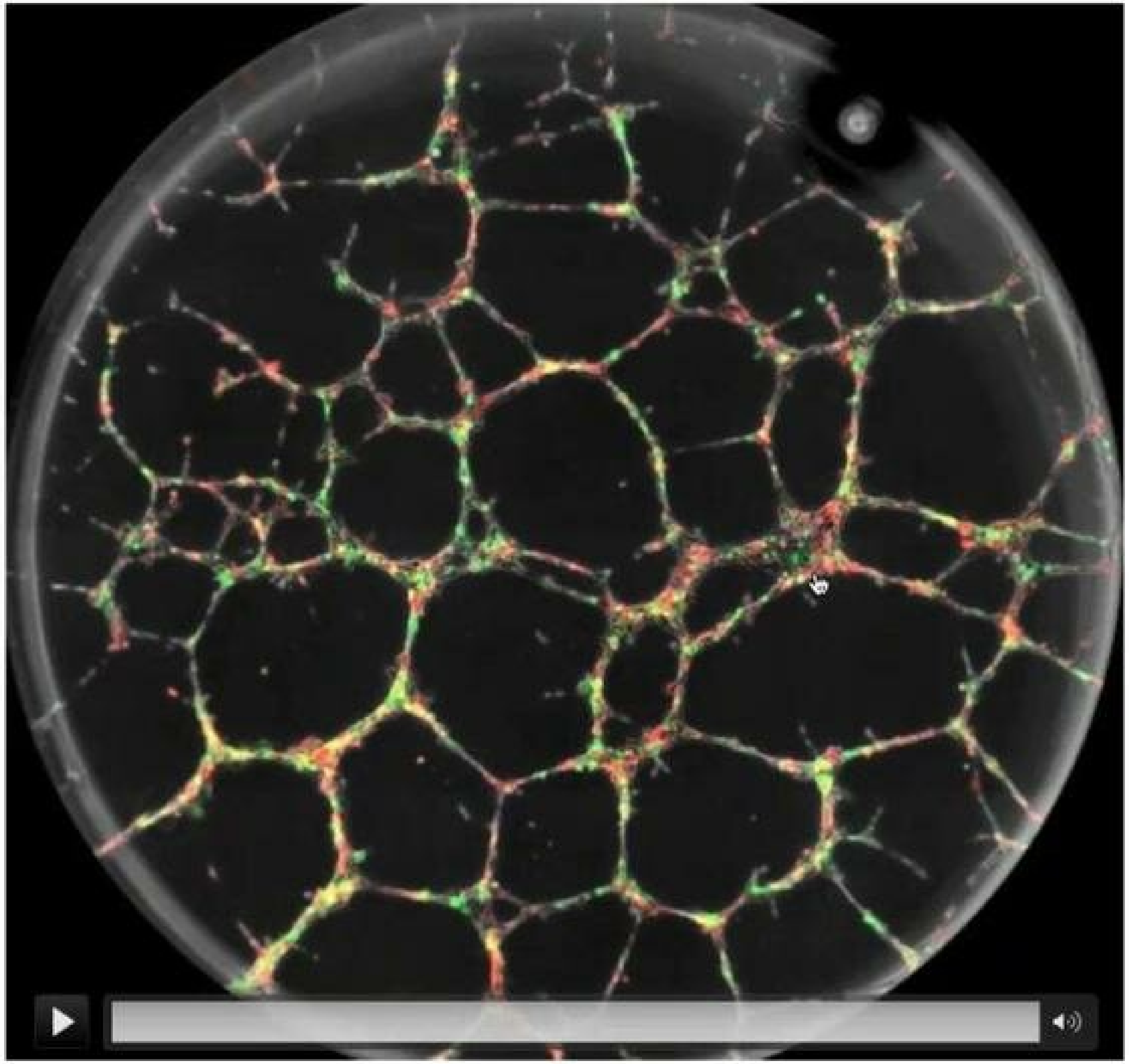
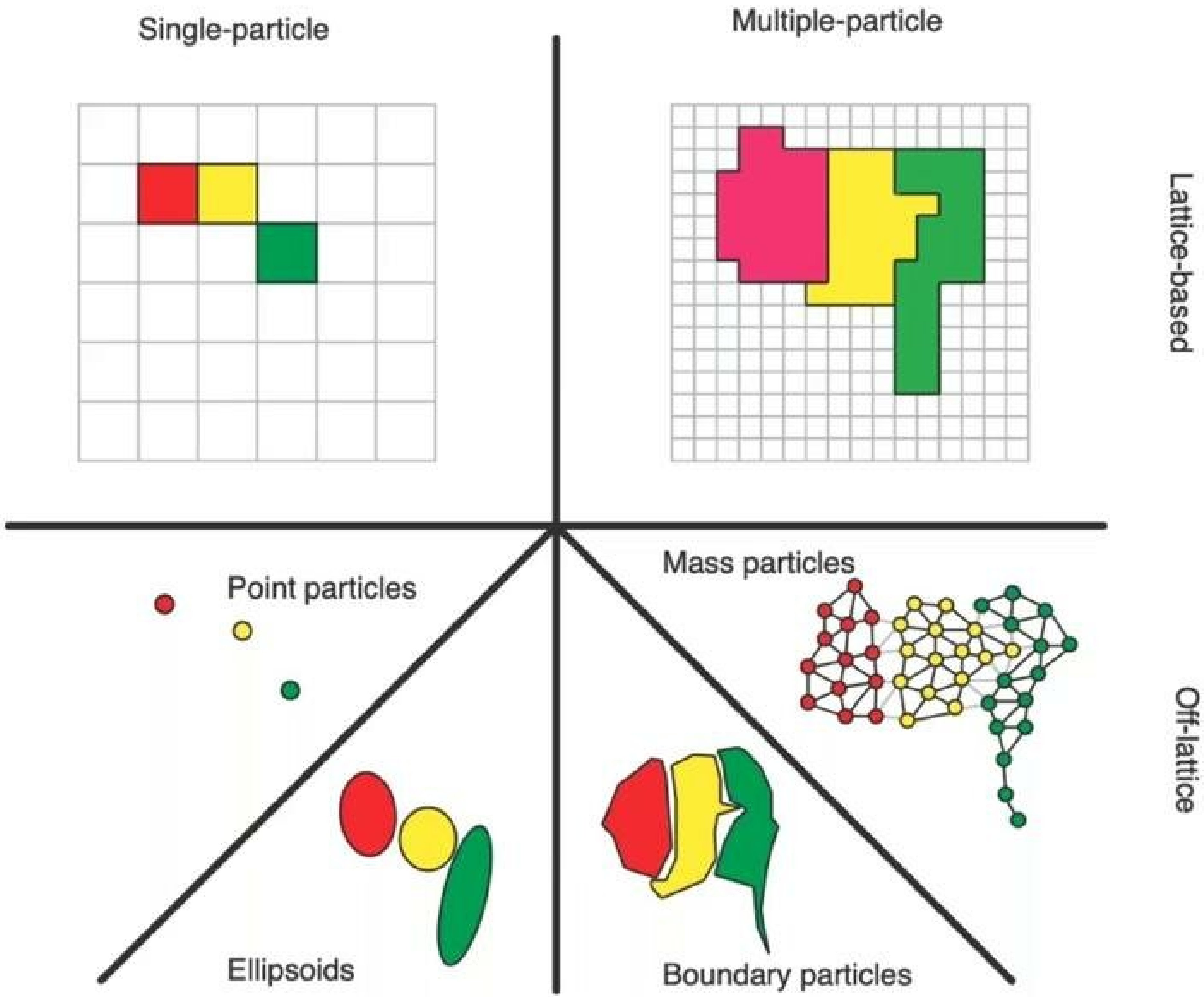
Our favorite problem: Cell-ECM interactions driving angiogenesis





HMEC-1 in Matrigel; Tessa Vergroesen

Cell-based models and the CPM



Cellular Potts Model (Graner & Glazier, 1992)

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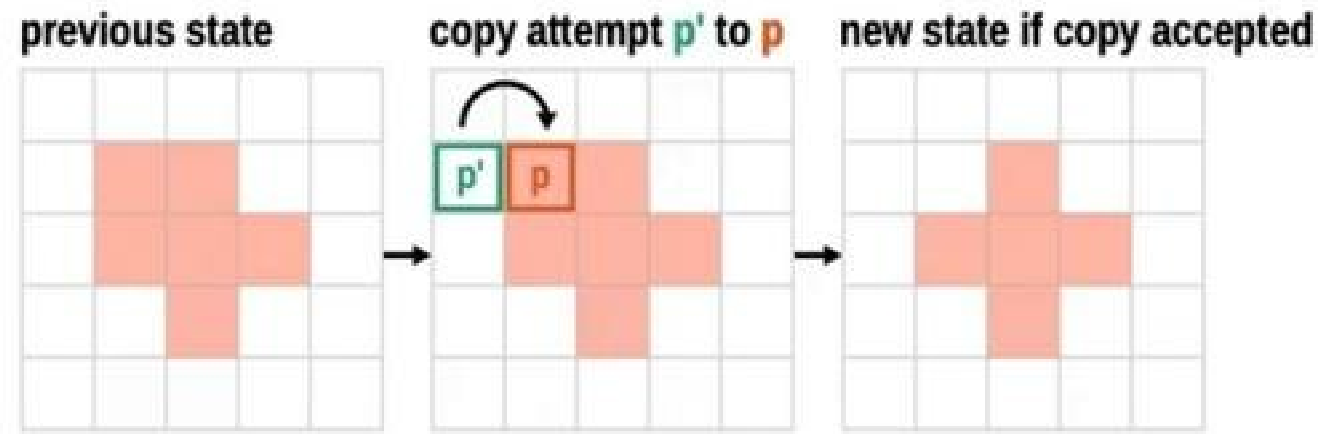
- Describes **random** cell motility
- Cells live on a grid
- One cell covers multiple grid points
- Cells move due to balance between active and reactive **cellular forces**:
  - **Reactive:** e.g, drag forces, adhesion to cells and matrix, strains in matrix based on Hamiltonian
  - **Active:** e.g., random extension/retraction of pseudopods, interaction with **external fields**
- Forces given by system energy, e.g.,:

$$H = \sum_{(\vec{x},\vec{x}')} J\left(\sigma_{\vec{x}}, \sigma_{\vec{x}'}\right) \mathbb{1}_{\sigma_{\vec{x}} \neq \sigma_{\vec{x}'}} + \lambda_A \sum_{\sigma} \left(A_T(\sigma) - a(\sigma)\right)^2$$

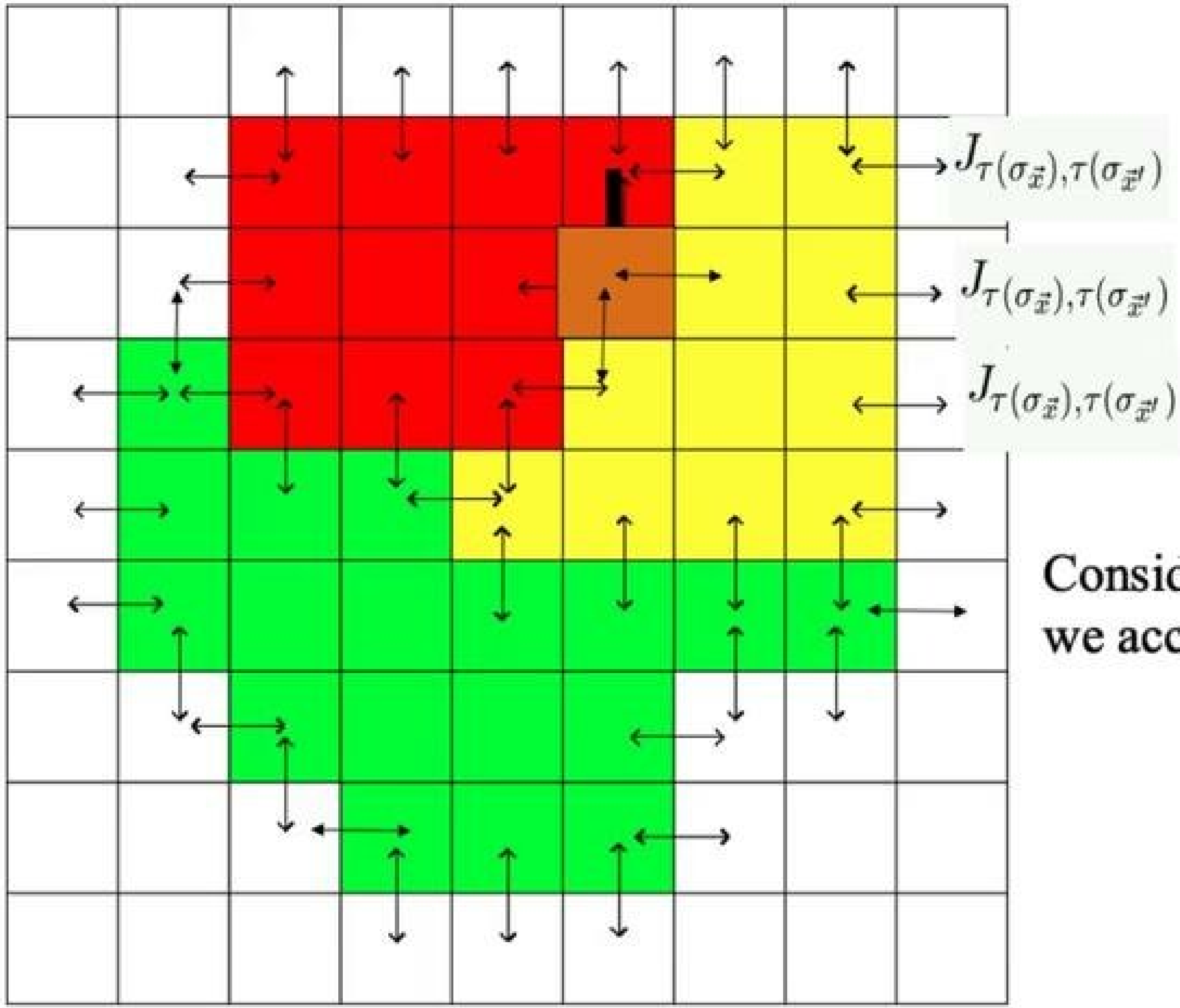


- Monitor energy change ΔH resulting from attempted copy
- Copy with probability:

$$P_{\text{copy}} = \begin{cases} 1 & \Delta H < 0 \\ \exp(-\Delta H/\mu) & \Delta H \geq 0 \end{cases}$$

μ "Cellular temperature"
Or: "Motility parameter"

Cellular Potts Model



Consider energy change ΔH if we accepted this copying

$$H = \sum_{(\vec{x},\vec{x}')} J\left(\tau\left(\sigma_{\vec{x}}\right), \tau\left(\sigma_{\vec{x}'}\right)\right) \mathbb{1}_{\sigma_{\vec{x}} \neq \sigma_{\vec{x}'}} + \lambda_A \sum_{\sigma} \left(A_T(\sigma) - a(\sigma)\right)^2$$

Cell adhesion | Volume conservation

Plus additional constraints, e.g. cell shape constraint: $+\lambda_L \left(L_T - l(\sigma)\right)^2$

Coupling with external fields

- Hybrid CPM-PDE model
  - Example: cell secrete a growth factor that diffuses and is degraded.

$$\frac{\partial c(\vec{x},t)}{\partial t} = \underbrace{D\nabla^2 c(\vec{x},t)}_{\text{Diffusion}} - \underbrace{\varepsilon c(\vec{x},t)}_{\text{Degradation}} + \underbrace{\mathbb{1}_{\sigma(\vec{x})>0}s}_{\text{Secretion by cells}}$$

  - Chemotactic force along chemical gradients

$$\Delta H_{\text{work}} = -\chi_{\tau,i}\left(c_i(\vec{x}) - c_i(\vec{x}\prime)\right)$$

Note, ΔH describes **work**:

  - Force over Distance = Work = Energy

$$P_{\text{copy}} = \begin{cases} 1 & \Delta H + H_{\text{work}} < 0 \\ \exp(-(\Delta H + H_{\text{work}})/\mu) & \Delta H + H_{\text{work}} \geq 0 \end{cases}$$

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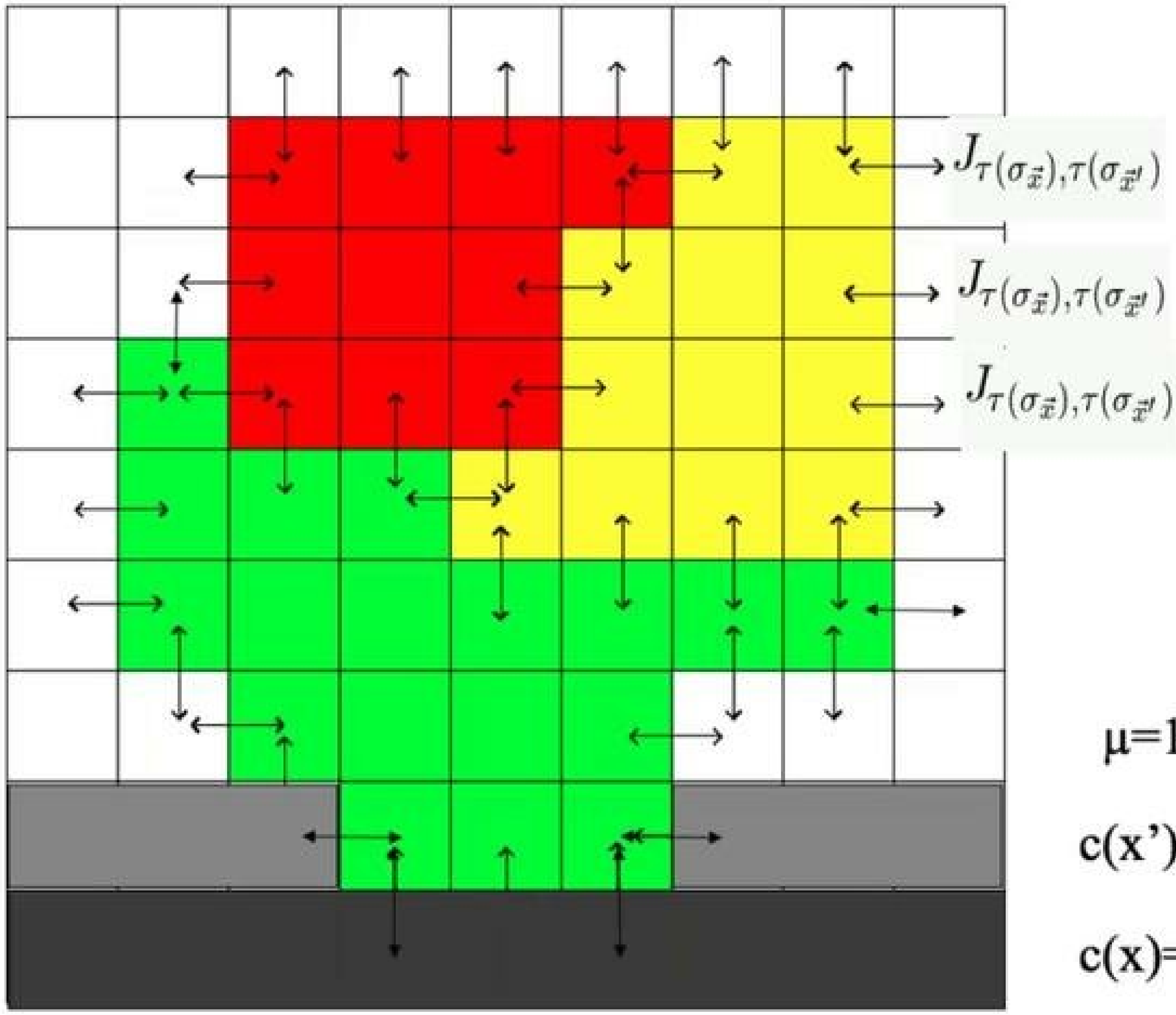
Coupling with extracellular fields

Pseudopods extend and retract more likely up chemical gradients



μ=100

c(x')=0.5

c(x)=1

ΔH -= 50

Savill and Hogeweg, J Theor Biol 1997

Example: mutual attraction of elongated cells

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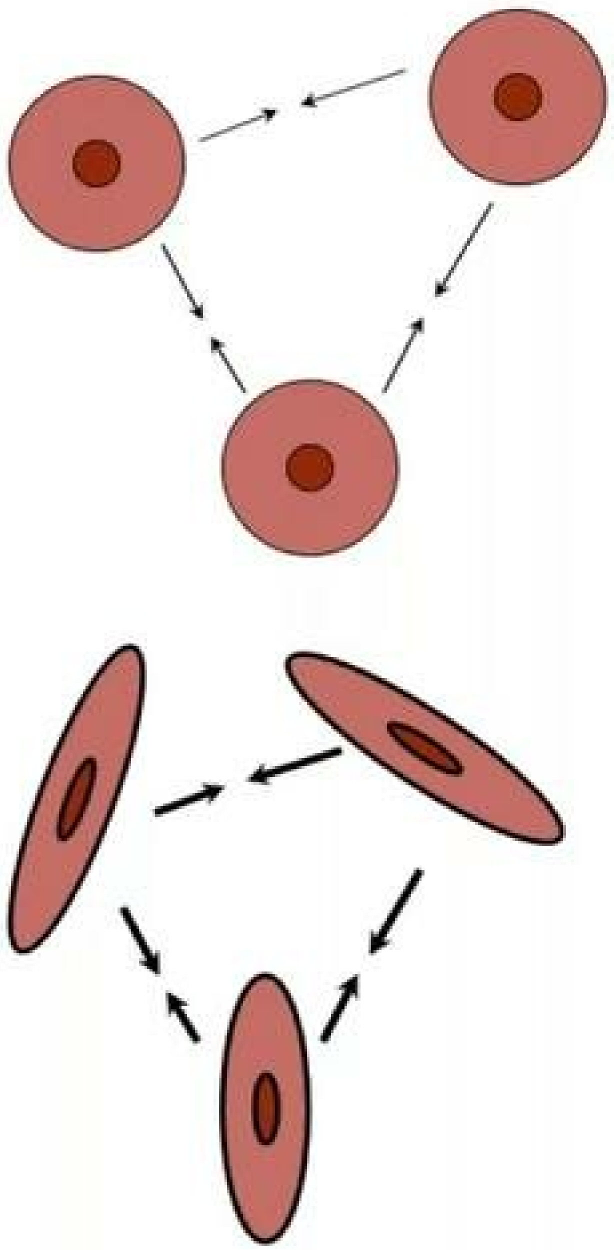

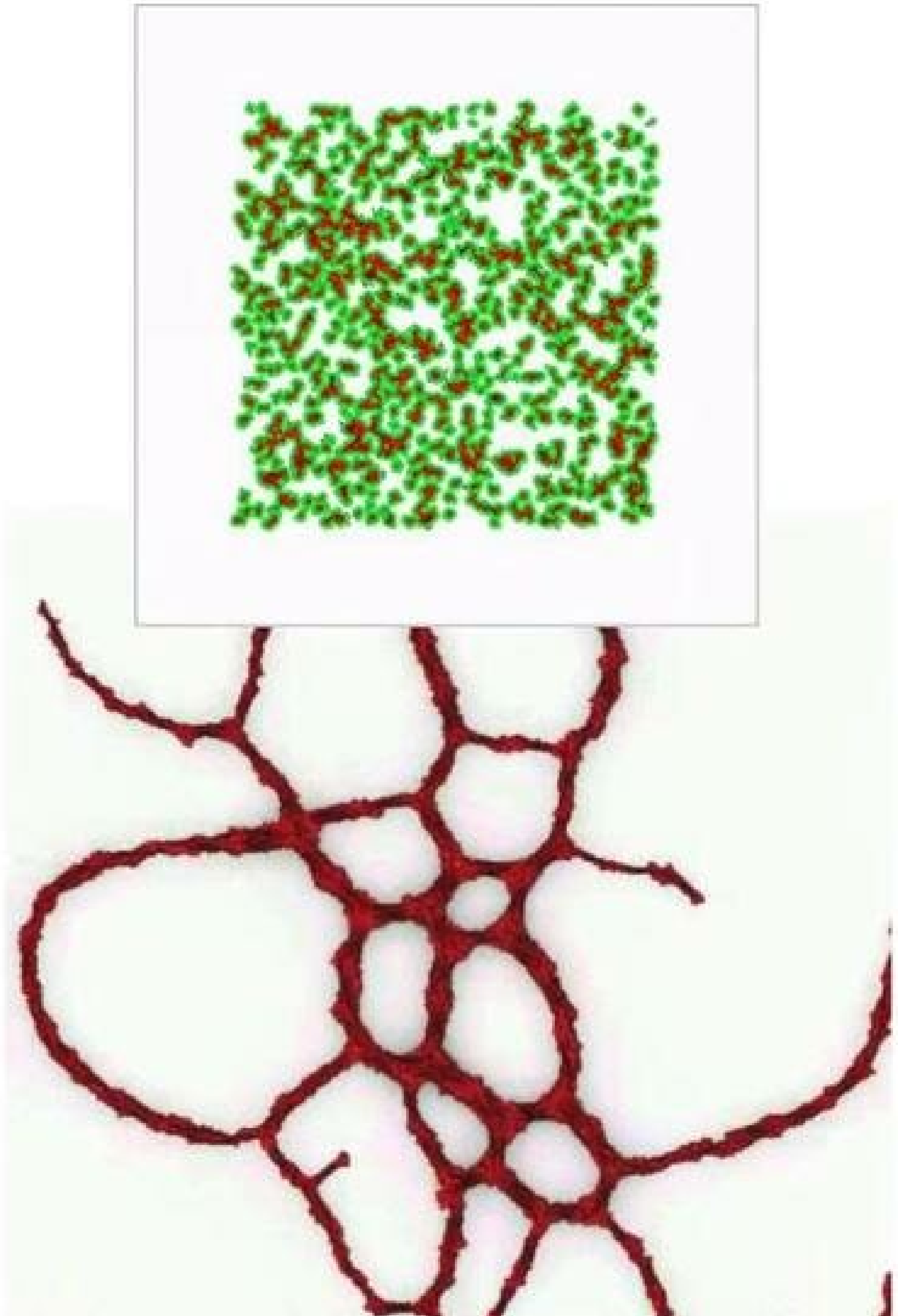

Merks et al. Dev Biol 2006; Palm and Merks, Phys Rev E 2013; Palachanis, Szabó, Merks. Comp. Part. Mech. 2015

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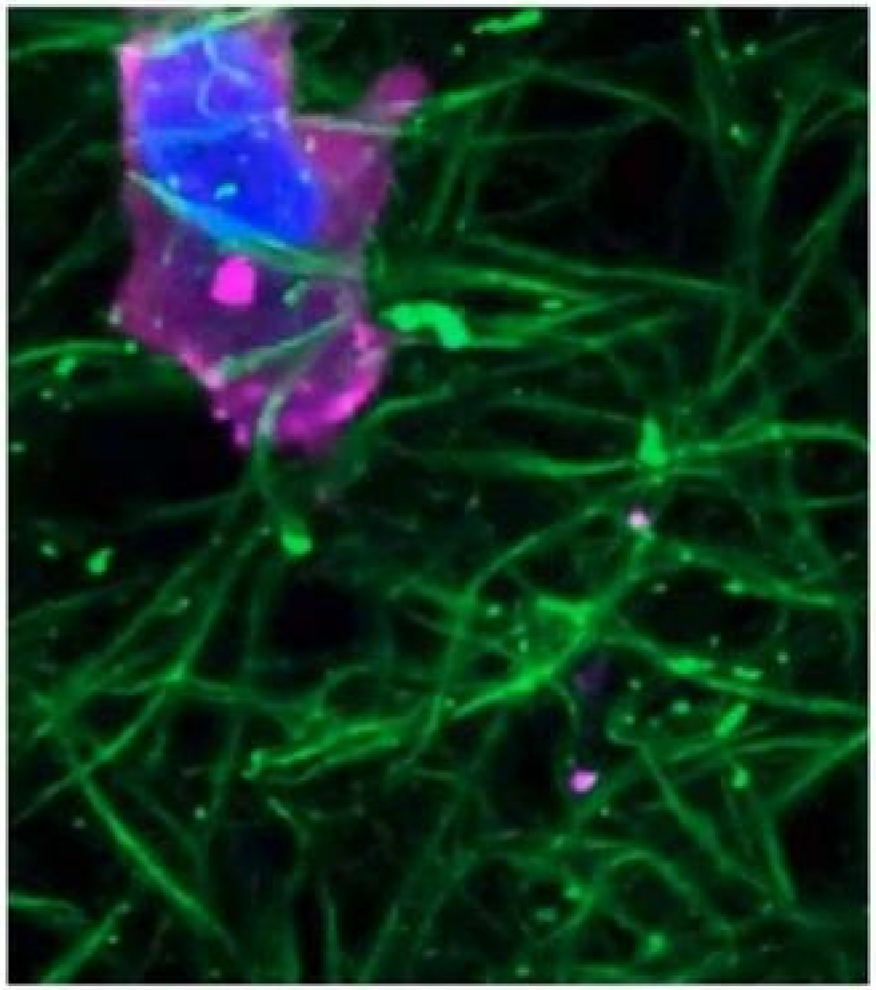
Extracellular matrix (ECM) in morphogenesis

- Extracellular matrix: network of materials that cells produce, for:
  - Mechanical support
  - Signaling

- Signals in ECM can be long-lived and long-distance
  - ECM binds chemical signals
  - Cells respond to strains in ECM

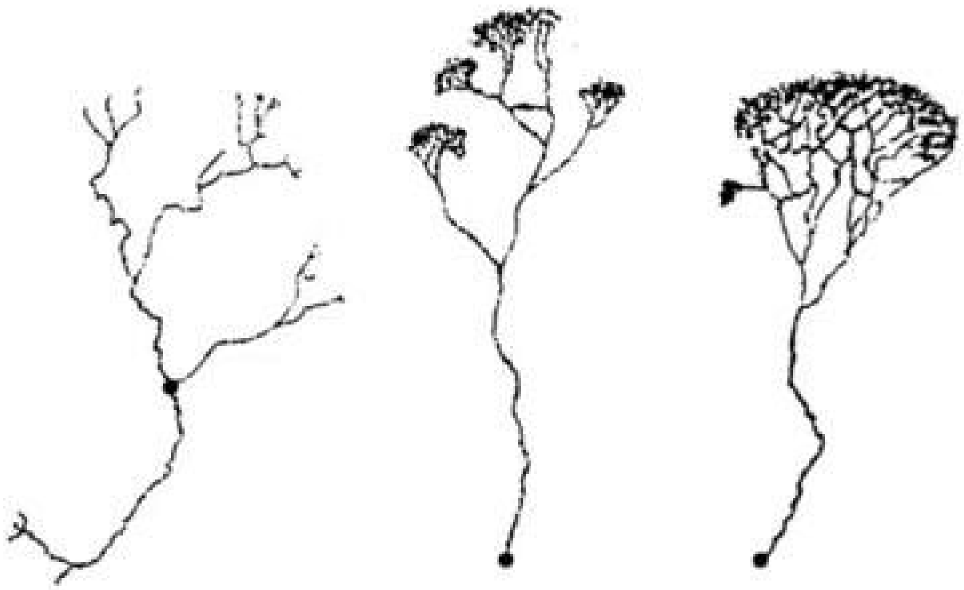
- Thus: ECM is key to tissue morphogenesis



Doyle et al (2021) *Developmental Cell*

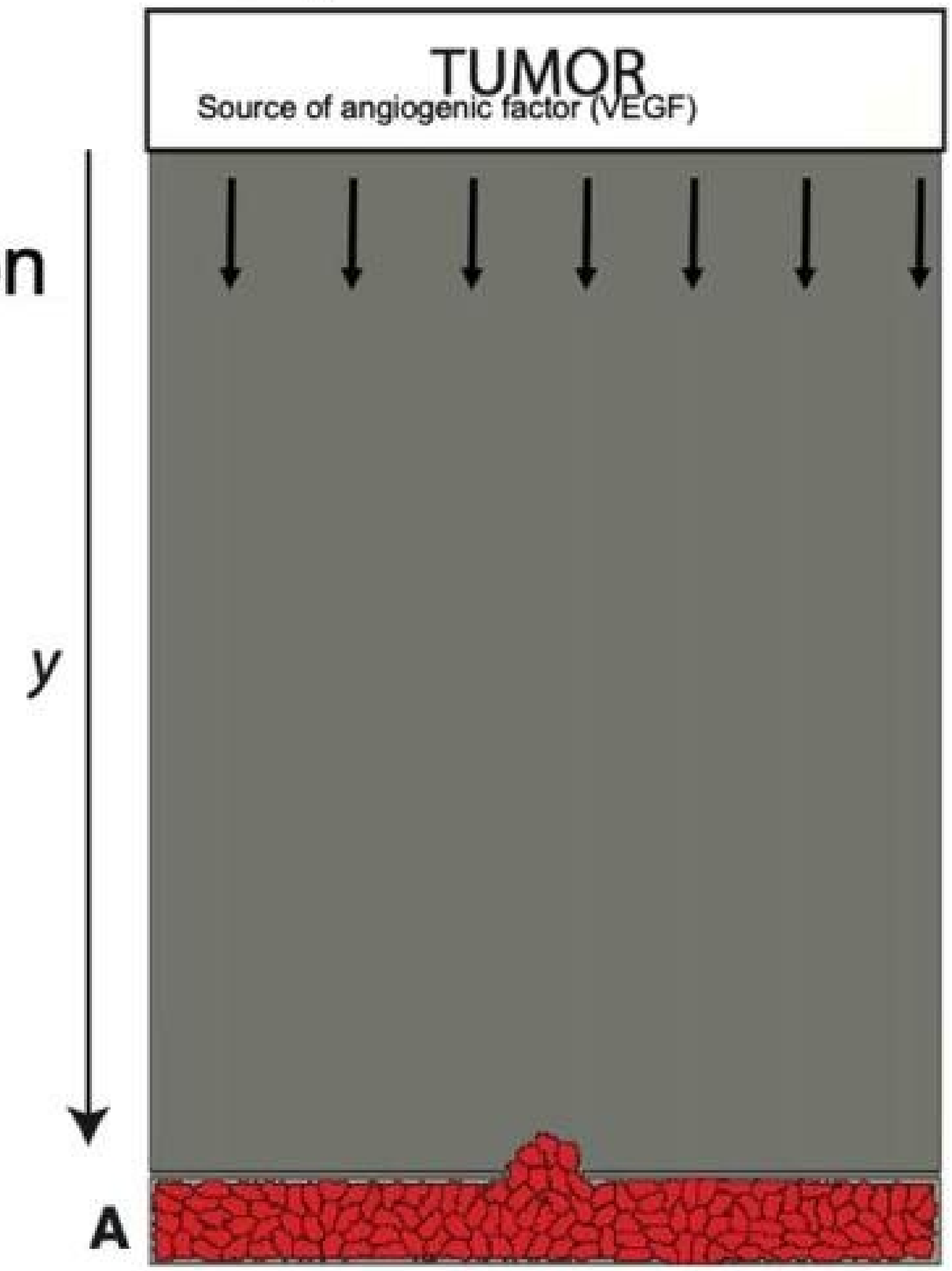
Extracellular matrix (ECM) coordinates angiogenesis

- ECM coordinates cells
  - ECM acts as "stigmergic" signal
  - *cf.* Pheromones in ant trail formation



Deneubourg et al. J. Insect Behav., 1989

Explorative model:



Daub and Merks, 2013. Bull. Math. Biol. 75(8): 1377

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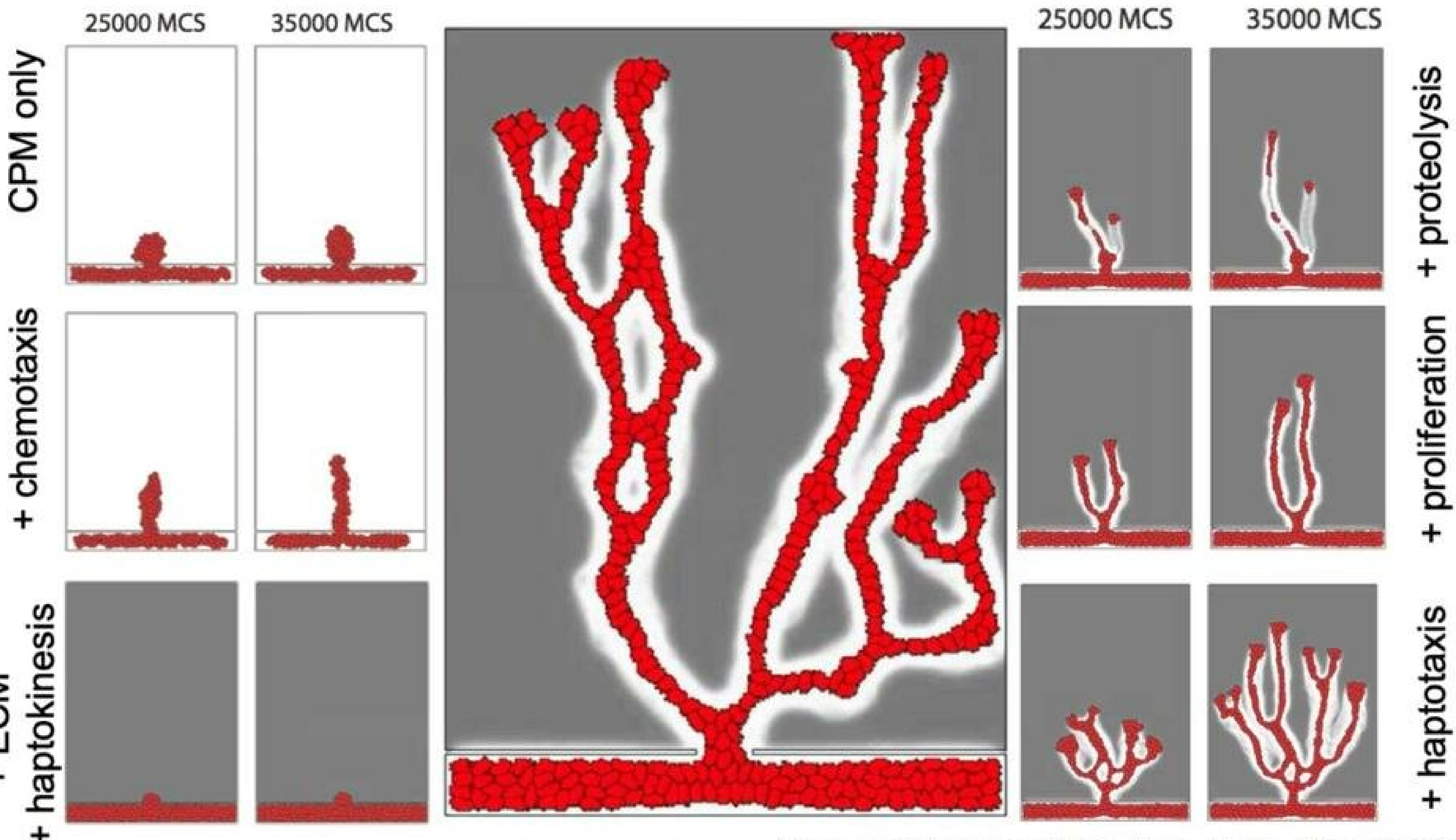
ECM as **chemical** signal:
coordination of cell behavior during angiogenesis



Daub and Merks, 2013. Bull. Math. Biol. 75(8): 1377

To build this model by yourself: Daub and Merks, *Methods in Molecular Cell Biology*, 2015

ECM as cell-cell signal in human cell cultures *fibrin-hMVEC assay*

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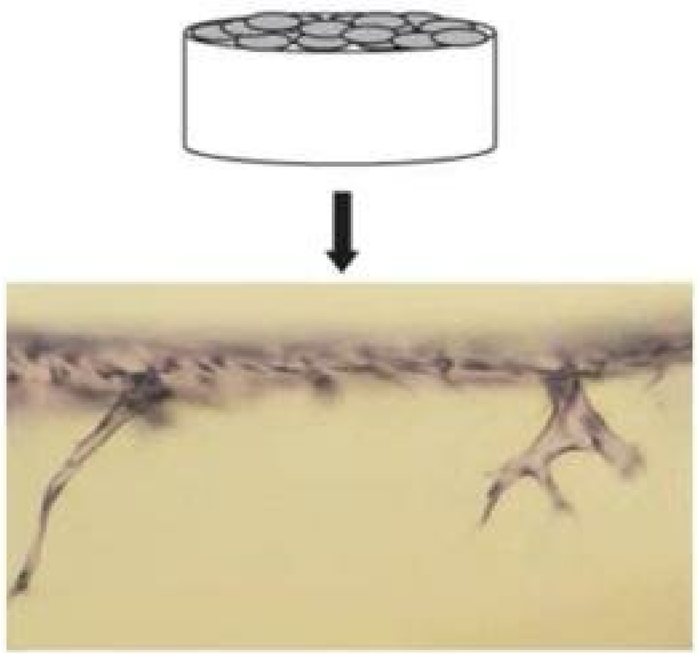
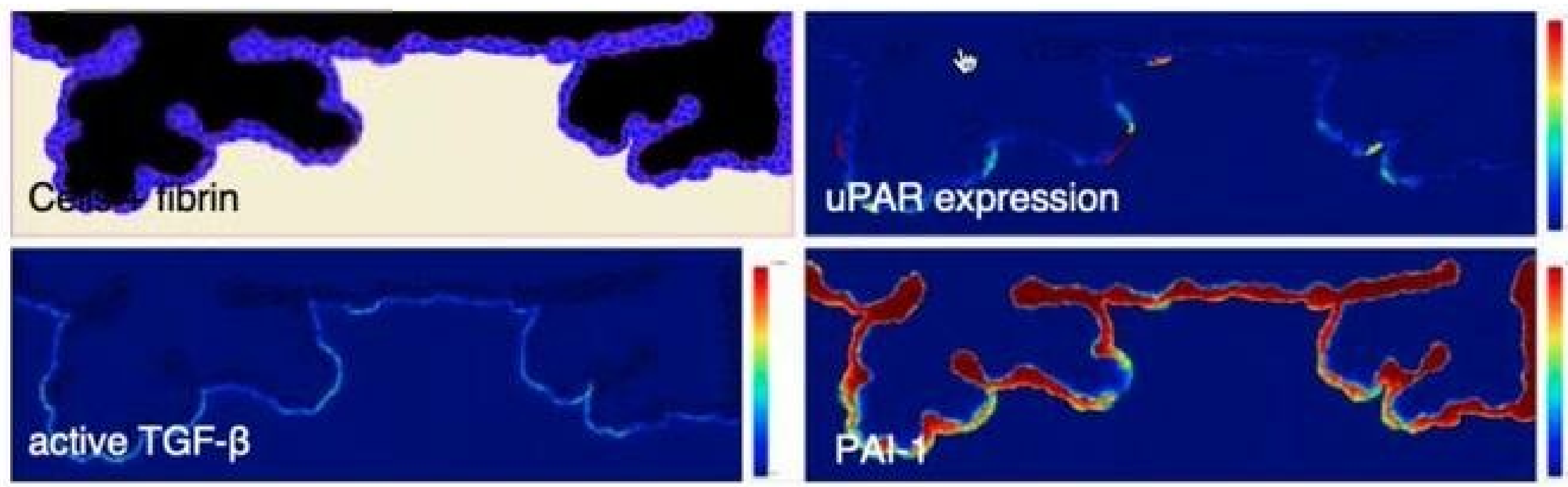
Monolayer of human microvascular endothelial cells on fibrin



Koolwijk *et al.* 1996



Boas et al. PLOS Computational Biology 2018

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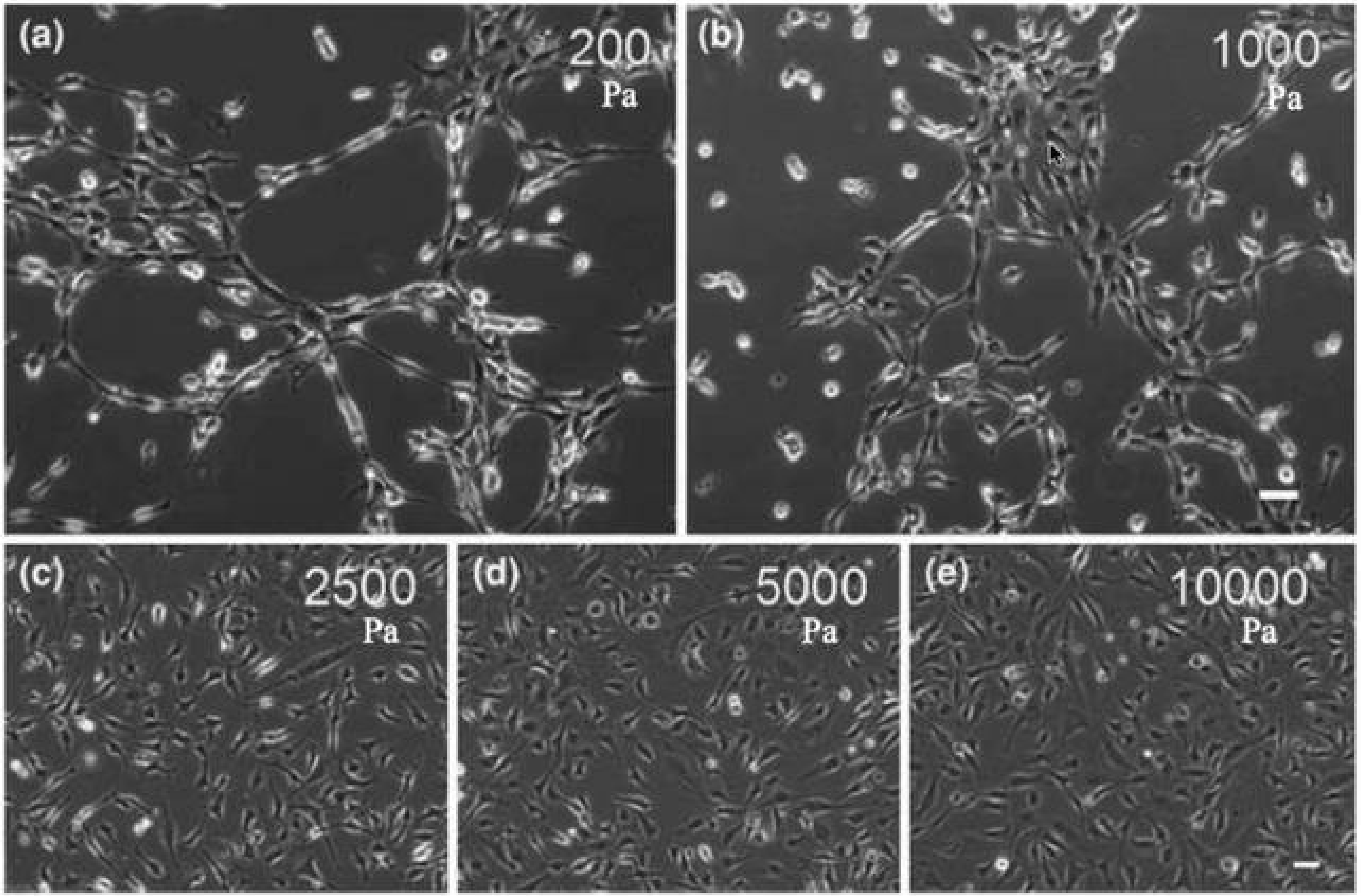
Stiffness of ECM affects vascular patterning

Soft matrix

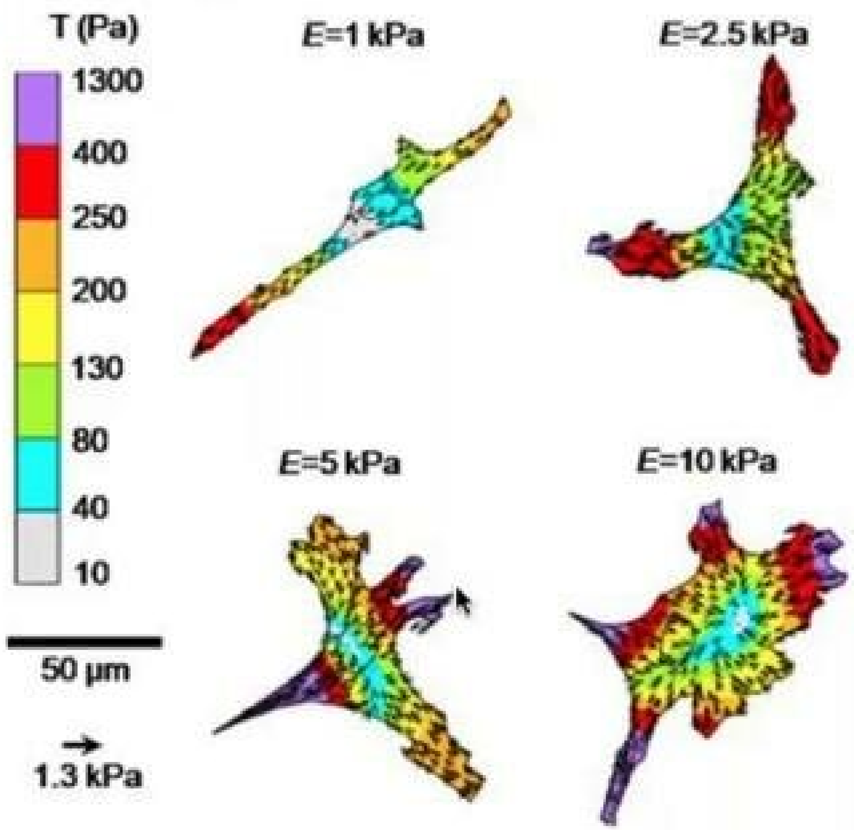


Stiff matrix

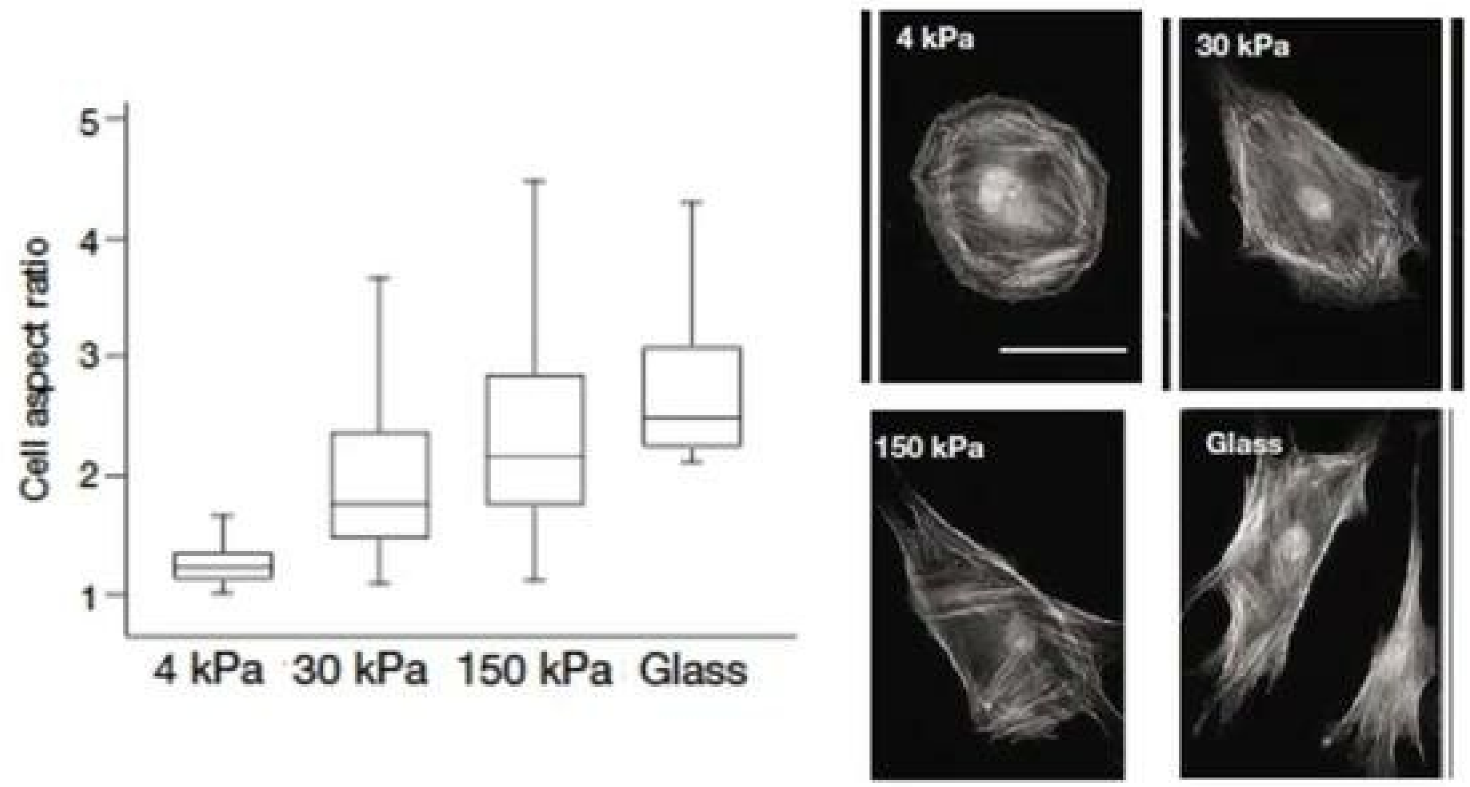
Califano and Reinhart-King, 2008

- **So:** models must include **substrate mechanics**

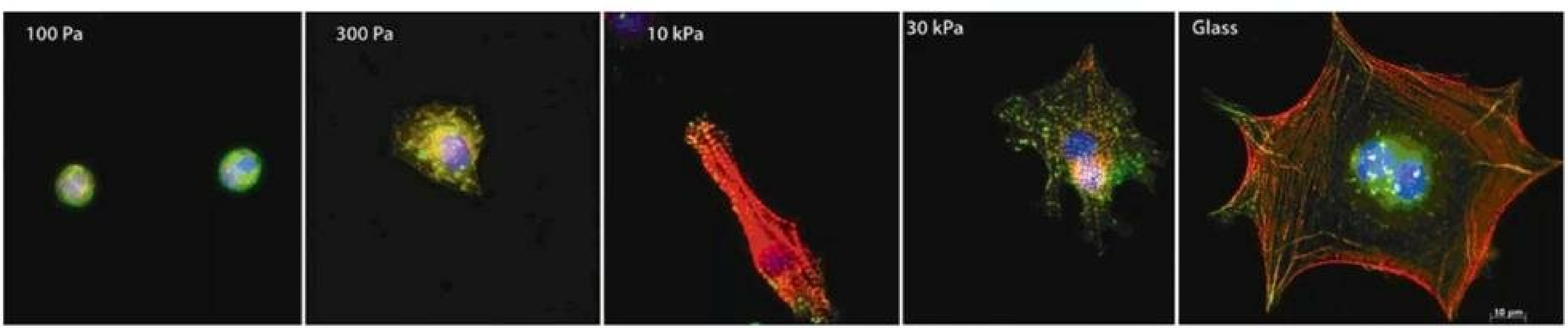
ECM stiffness affects cell shape



Endothelial cells: Califano & Reinhart-King
Cell and Molecular Bioengineering 2010



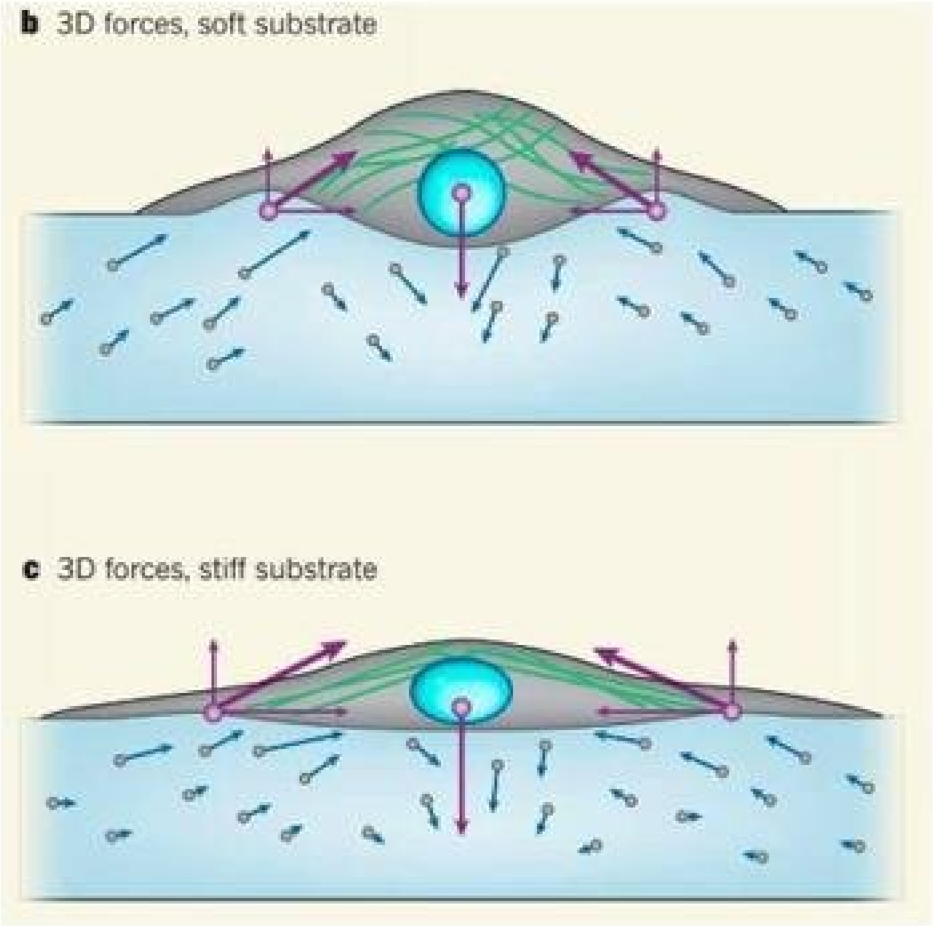
Fibroblasts: Prager-Khoutorsky et al.
Nature Cell Biology *2011* (n=50)



Cardiomyocytes: Winer et al. , in: Wagoner et al. (eds.), 2011

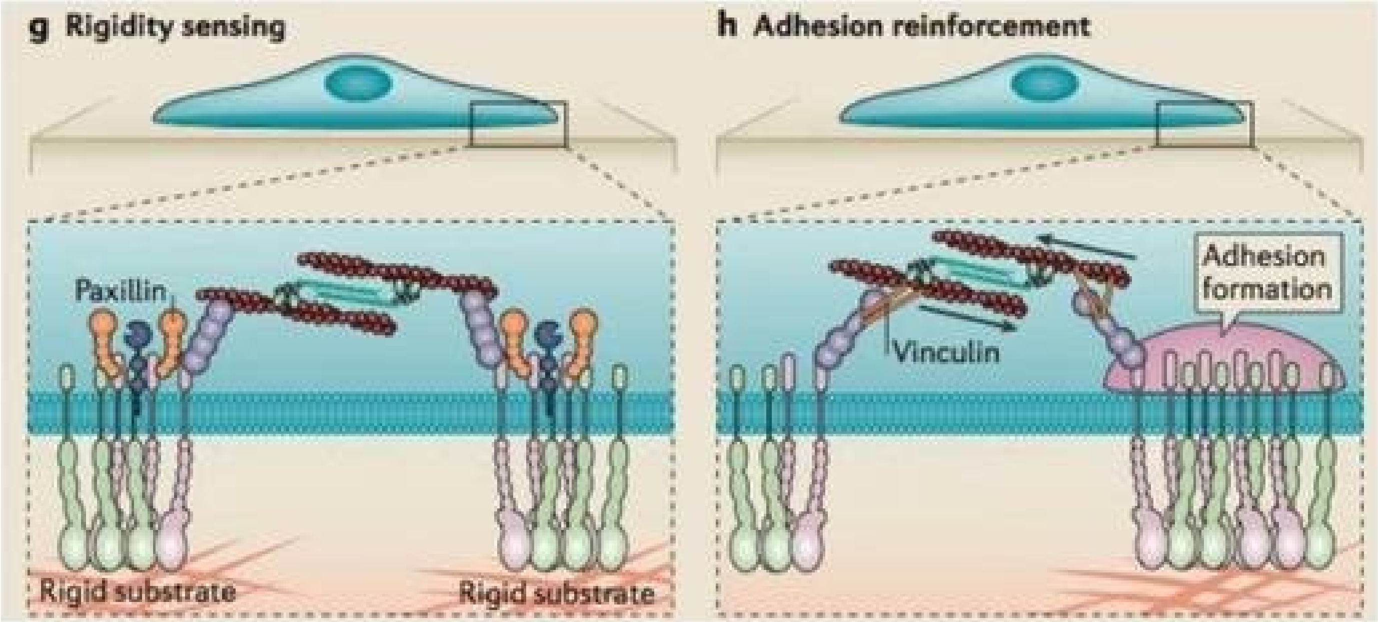
Mechanism: Mechanical reciprocity between cells and substrate

- (1) Cells pull on substrate



Hersen & Ladoux, Nature (2011)

- (2) Cell-substrate connections stabilize on strained substrate



Iskratsch et al. Nat. Rev. Mol. Cell. Biol. (2014)

Mechanical reciprocity: Focal adhesions mature under force

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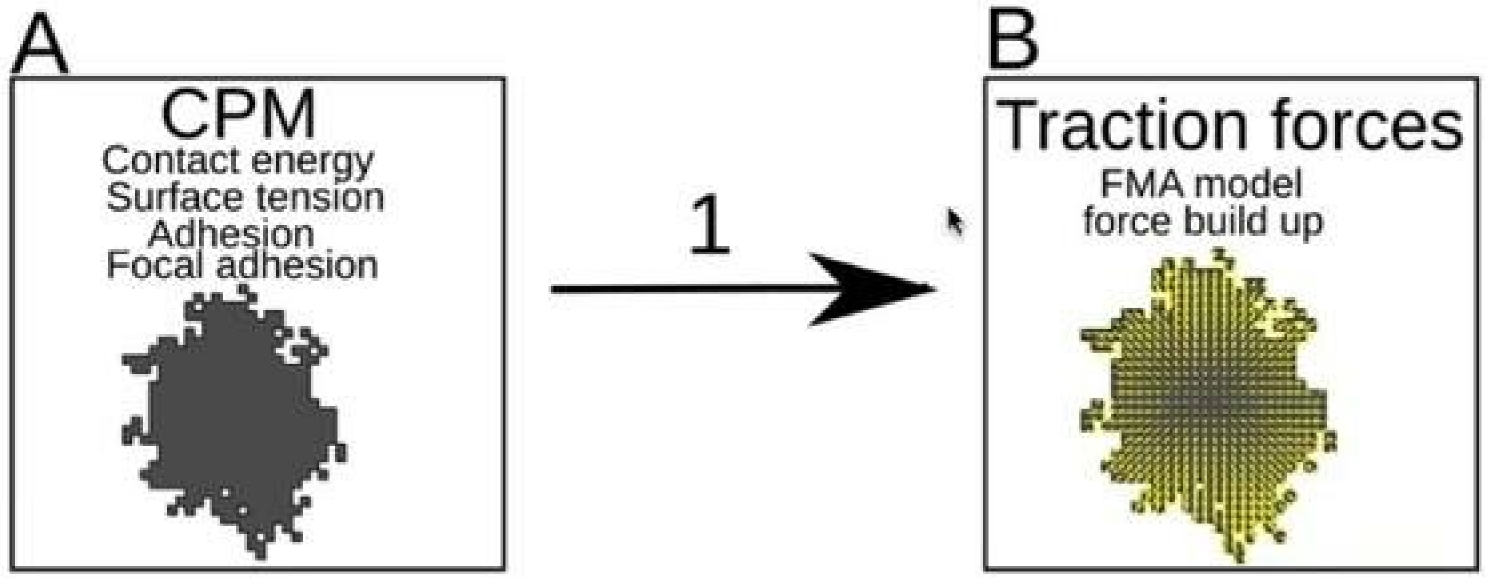
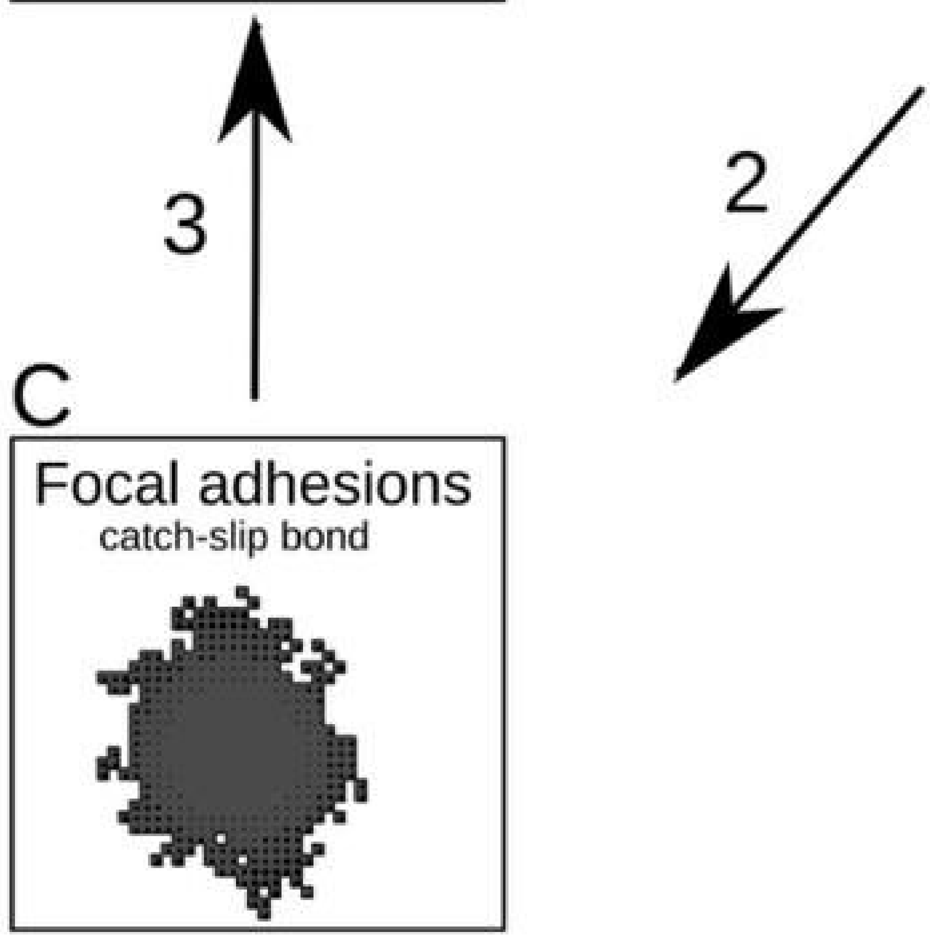
Lisanne Rens





Focal adhesions (FAs):

- Act as cluster of 'catch-slip bonds' (Novikova and Storm, Biophys J 2014)
- Mechanical tension builds up over time (Schwarz et al., Biosystems 2006)
- Mechanical equillibrium reached faster on stiff substrates

Result: on stiff substrates FAs grow stronger, so are ripped from substrate less easily

Rens & Merks (2020) *iScience* 9: 101488
https://doi.org/10.1016/j.isci.2020.101488

Each focal adhesion (FA) is described by an ODE model

- Each FA of size $N_e(t)$ is a cluster of catch-slip bonds
  (Novikova and Storm, *Biophys. J.* 2013: continuous assembly/disassembly

$$\frac{dN_e(t)}{dt} = g(N_e(t) - N_t) - b(\phi_e(t))N_e(t)$$

- Mechanical tension **inhibits** degradation of FAs
- Tension builds up **over time**, as (Schwarz et al. Biosyst. 2006),

$$\phi_e(t) = \left| F_s \left(1 - e^{-t/t_k}\right) \right|$$

- with $t_k = F_s / v_0 K$; function of stall force F_s , contraction velocity of actomyosin cables v_0 and K, matrix stiffness
- Within a fixed time interval, FAs experience **less tension on soft matrices** than on stiff matrices

Rens & Merks (2020) *iScience* 9: 101488
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Detailed model explains cell spreading, but not elongation

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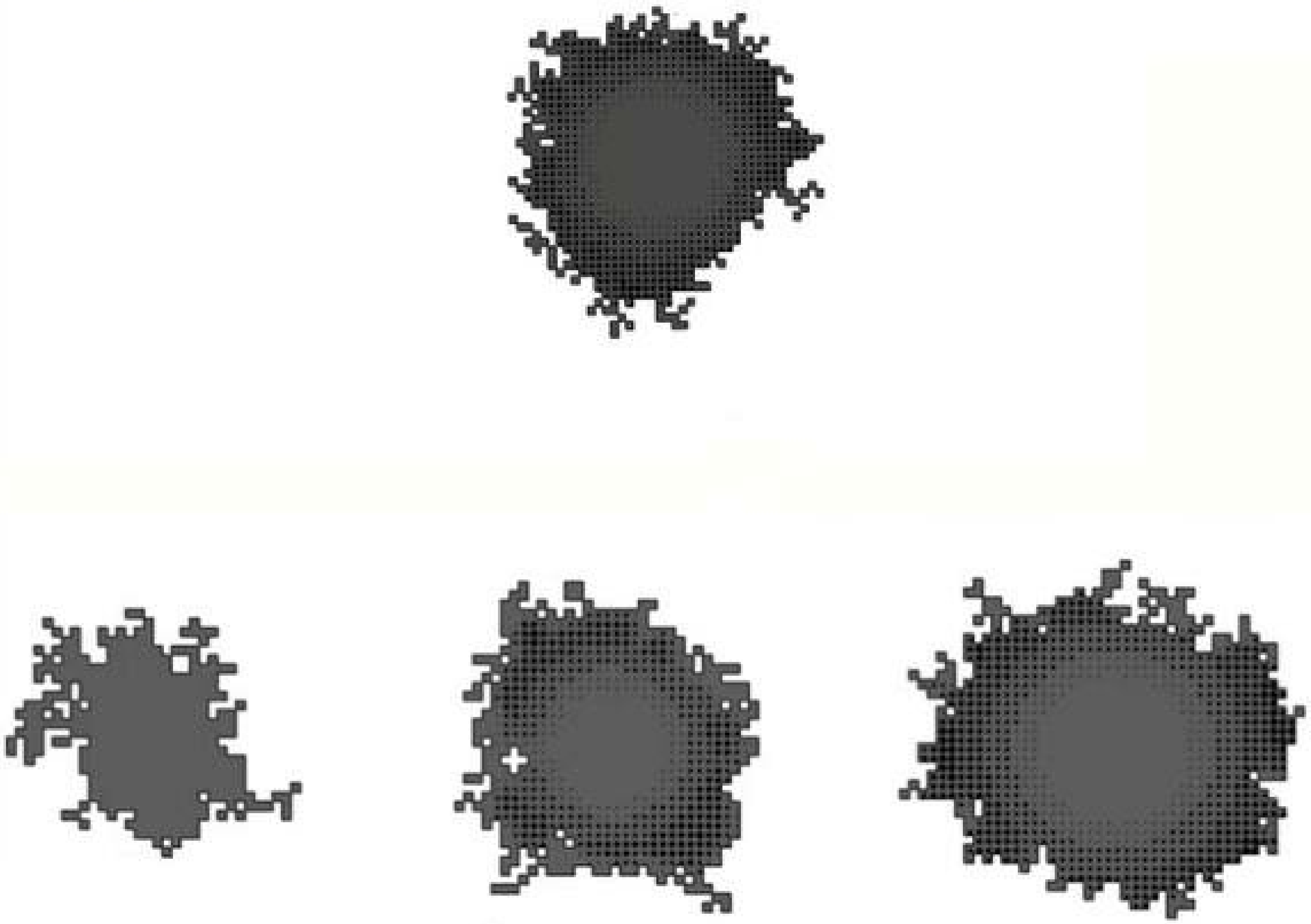
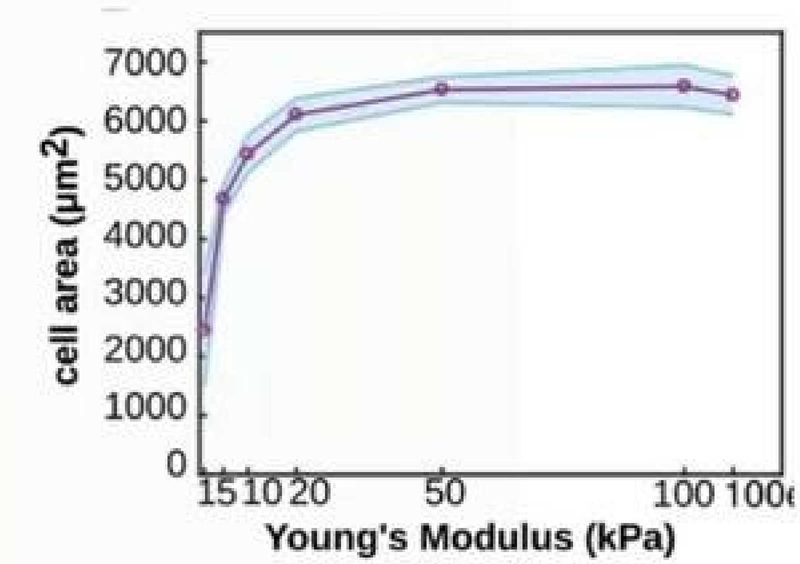
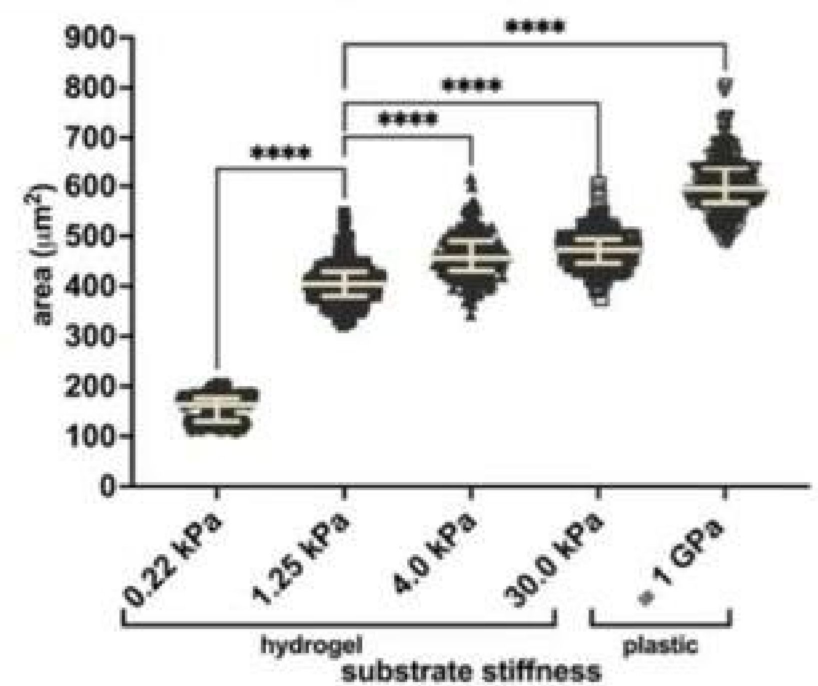


1kPa 5kPa 50kPa

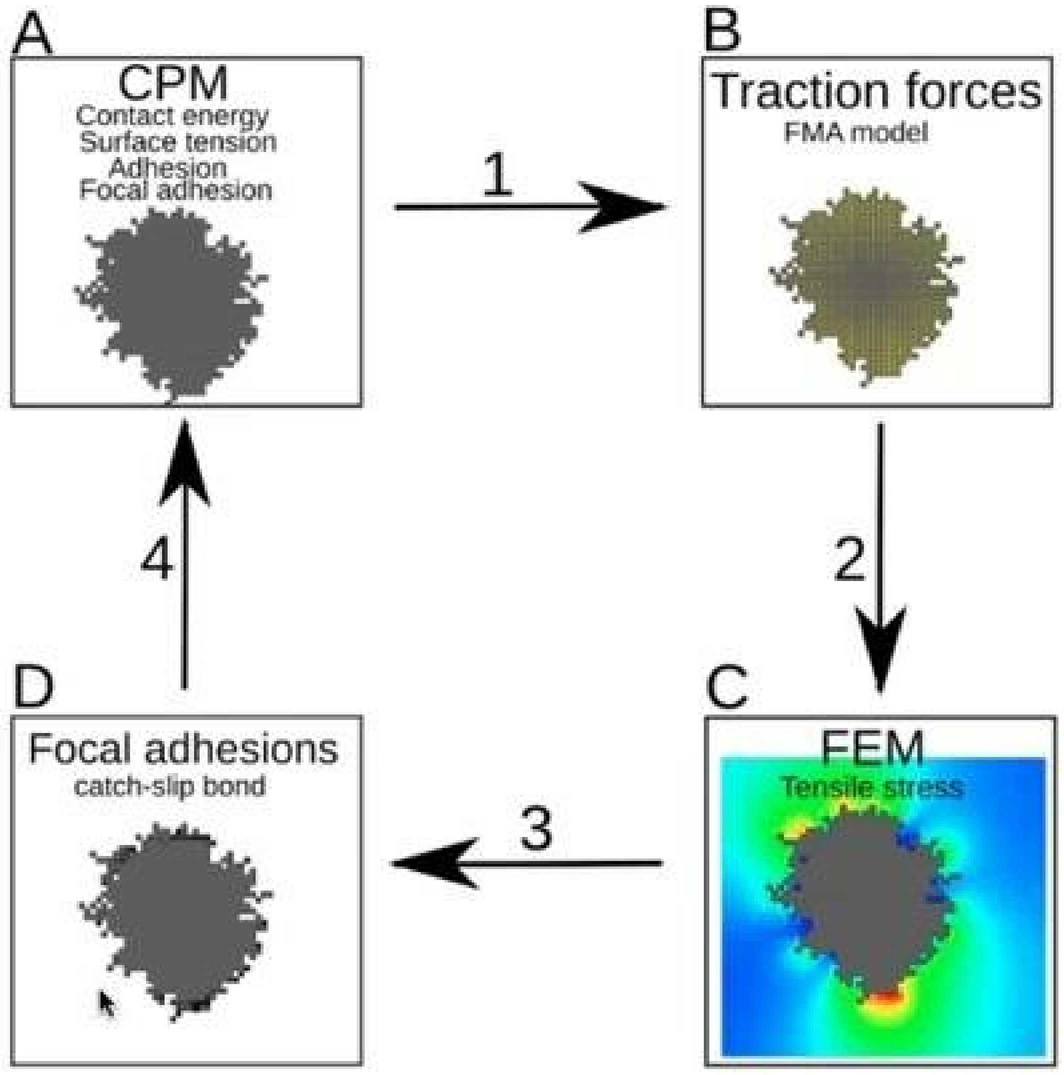




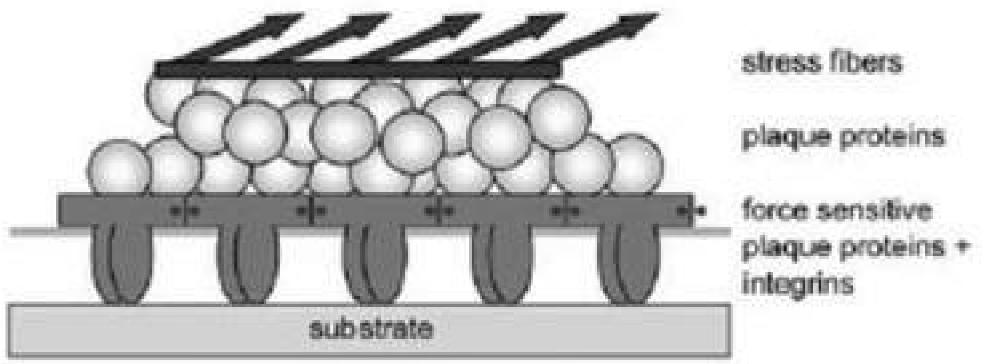
Rens & Merks (2020) *iScience* 9: 101488
https://doi.org/10.1016/j.isci.2020.101488

Pulmonary endothelial cells, Paudel et al. AJP Cell Physiol. 2022

Feedback from ECM-deformation required for cell elongation



Planar substrate stress strengthens adhesions



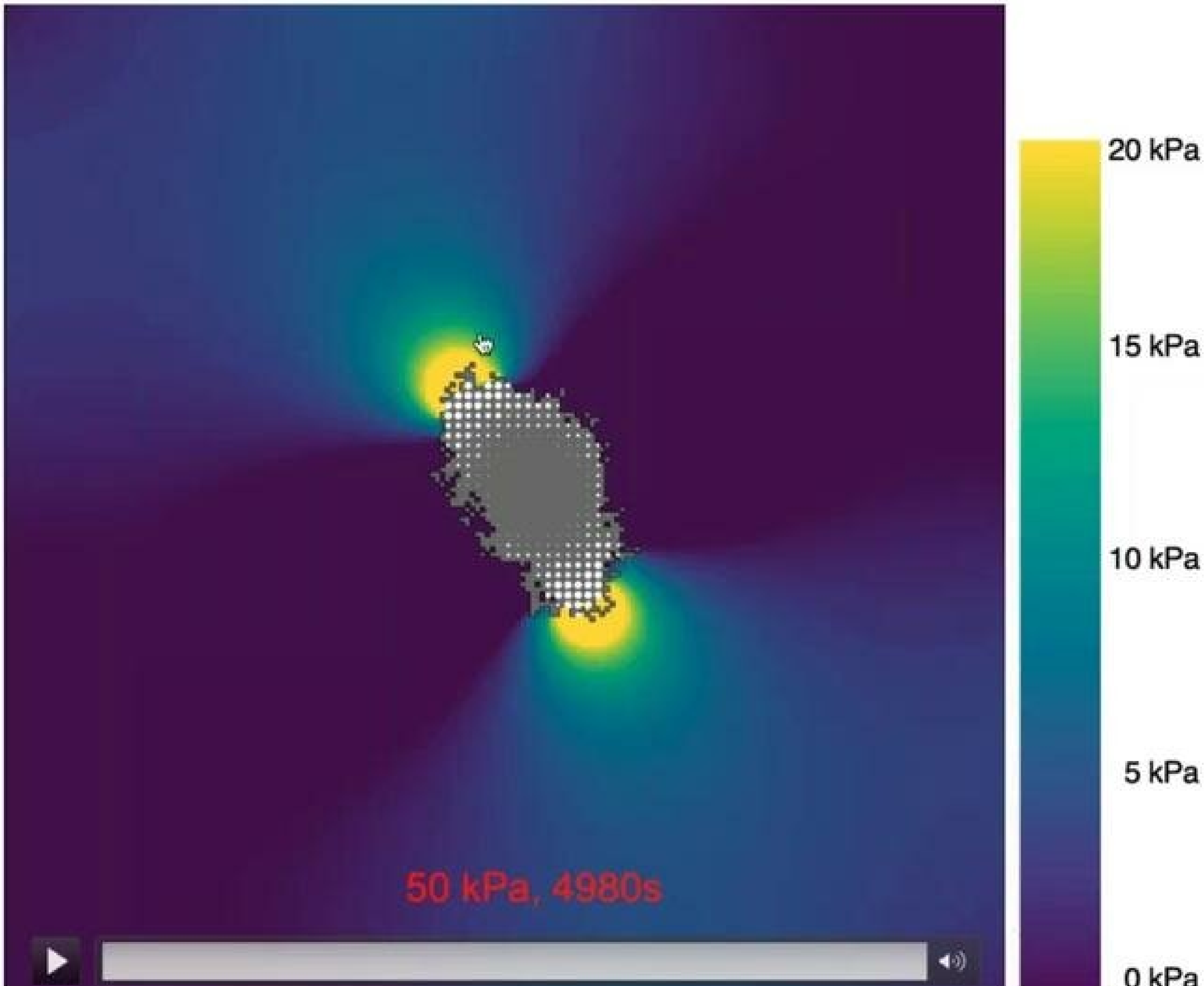
Besser et al. 2006

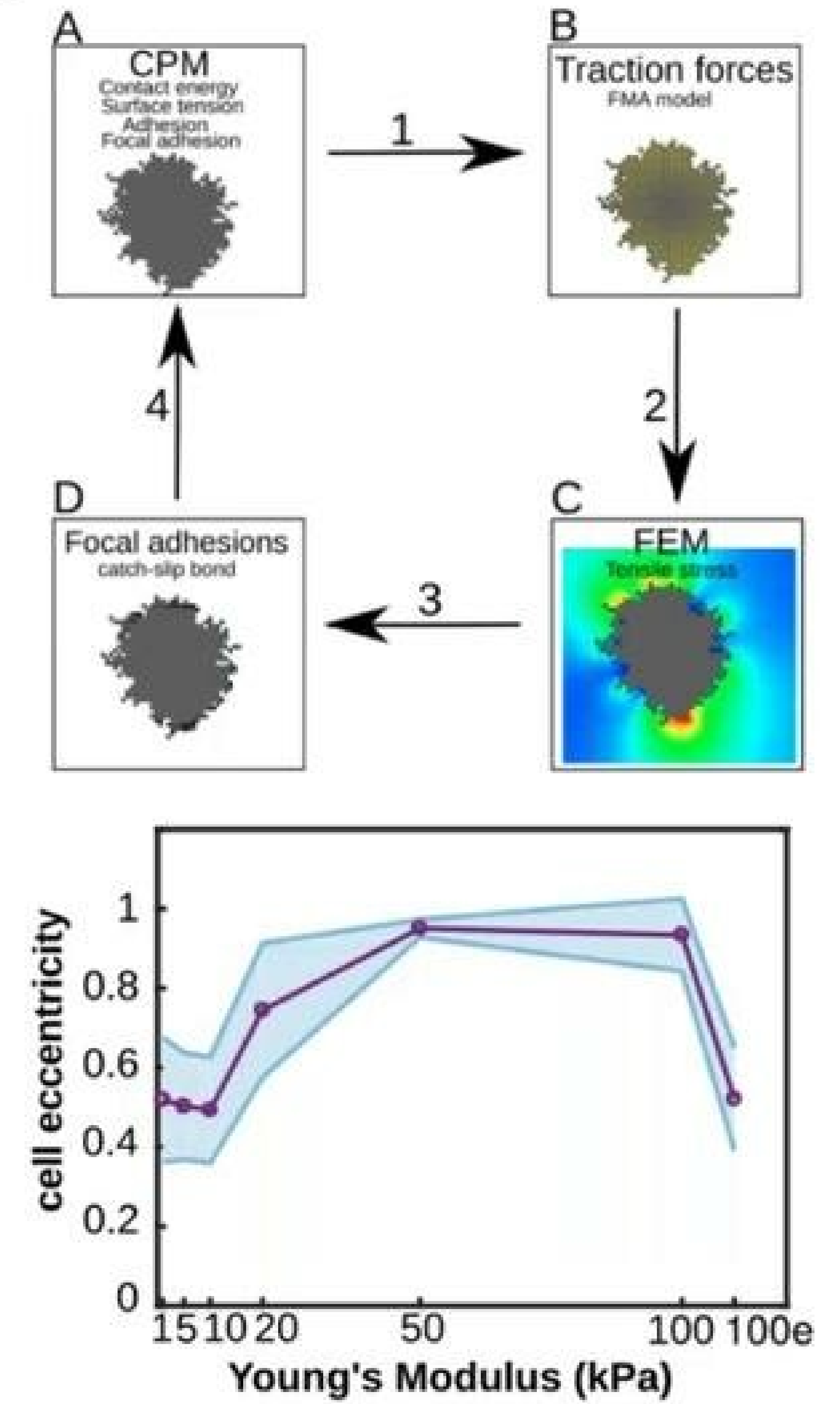
$$\Delta H_{\text{work}} = \lambda_N \frac{N(\vec{x})}{N_h + N(\vec{x})}\left(1 + p\frac{h(s(\vec{x}))}{s_o + h(s(\vec{x}))}\right)$$

with $h(s(\vec{x})) = \frac{1}{2}\left(s_{xx} + s_{yy}\right)$ the hydrostatic stress of the substrate

Rens & Merks (2020) *iScience* 9: 101488
https://doi.org/10.1016/j.isci.2020.101488

Cells elongate with substrate reciprocity





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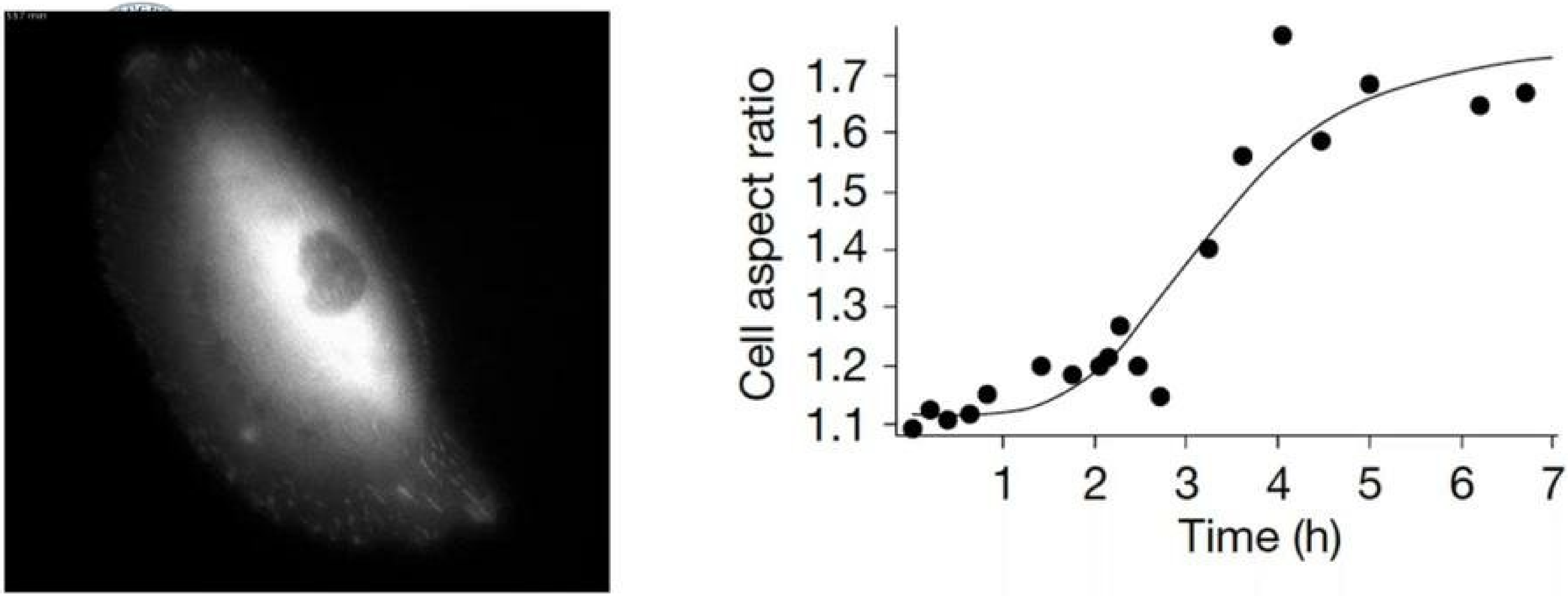
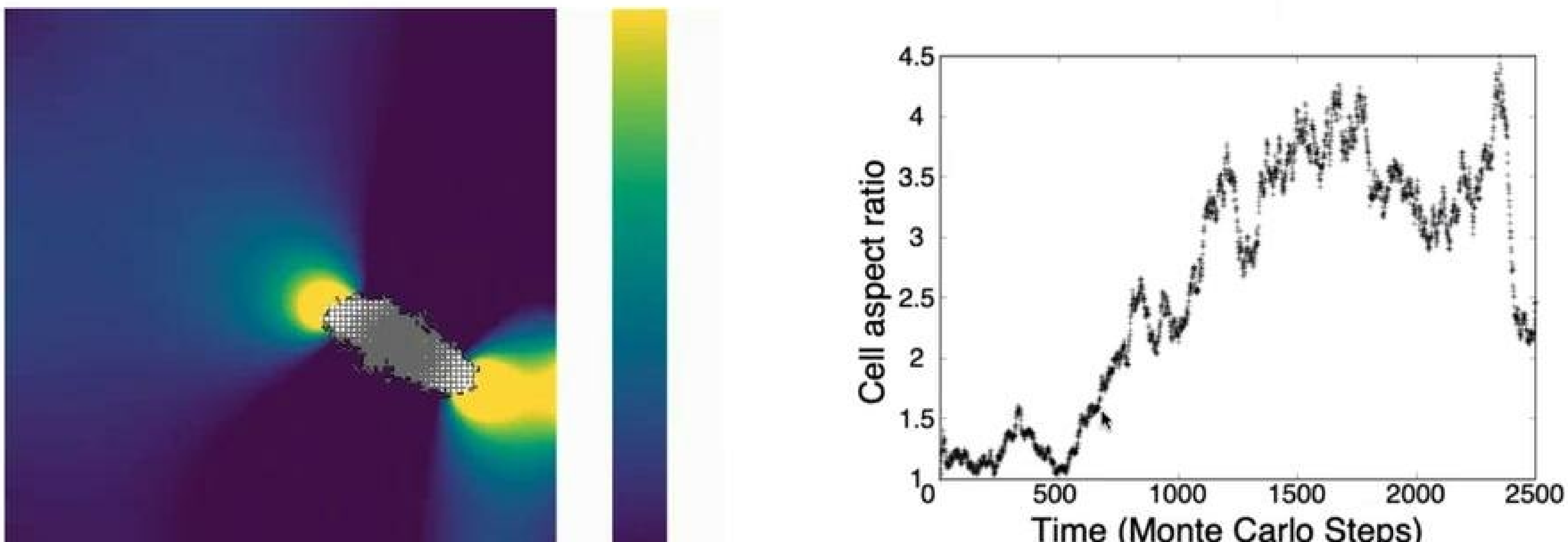


Fibroblast on 2 MPa substrate; Prager-Khoutrosky … Bershadsky, Nature Cell Biology 2011



Simulated cell on ‘stiff’ substrate (qualitative!)

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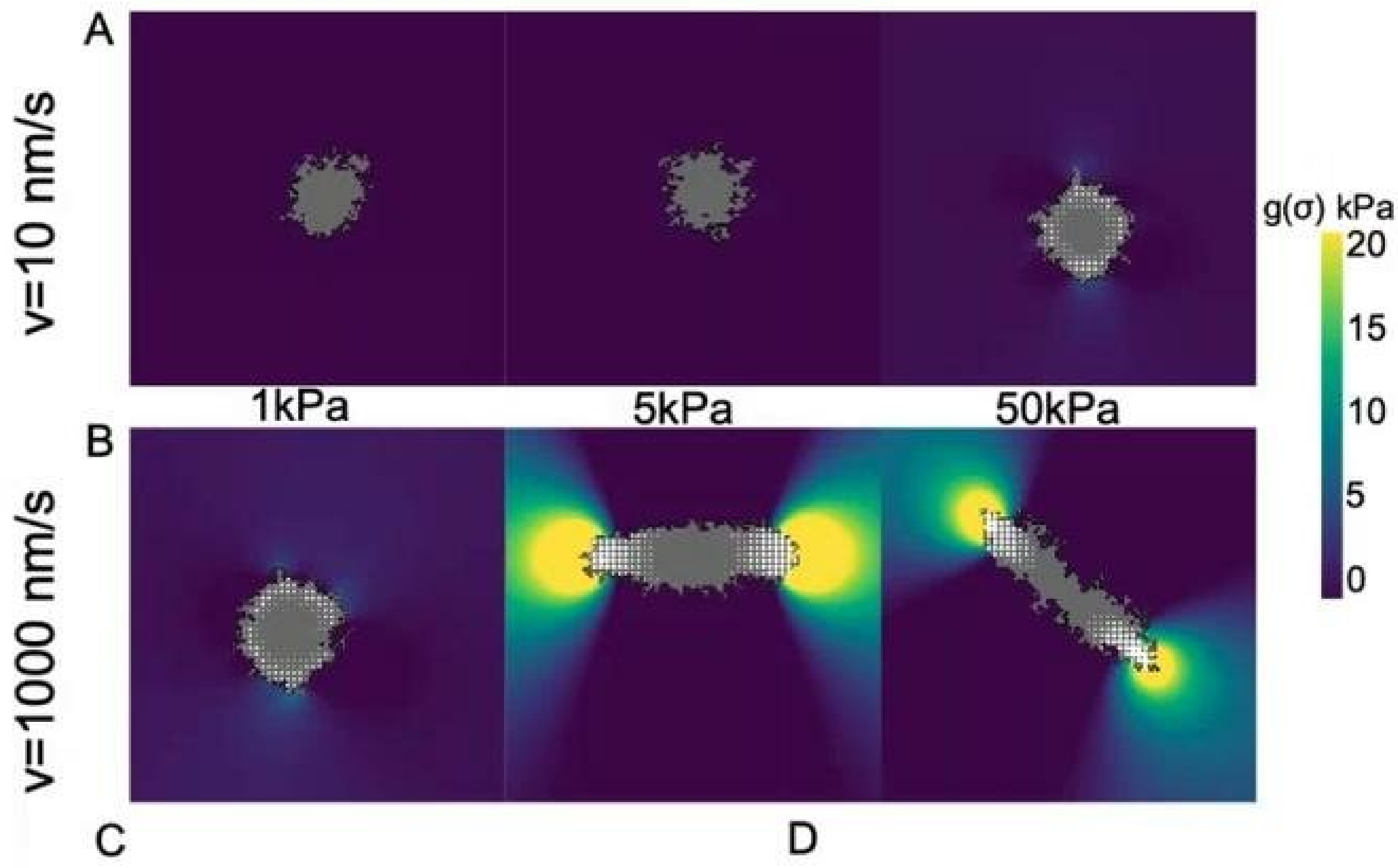
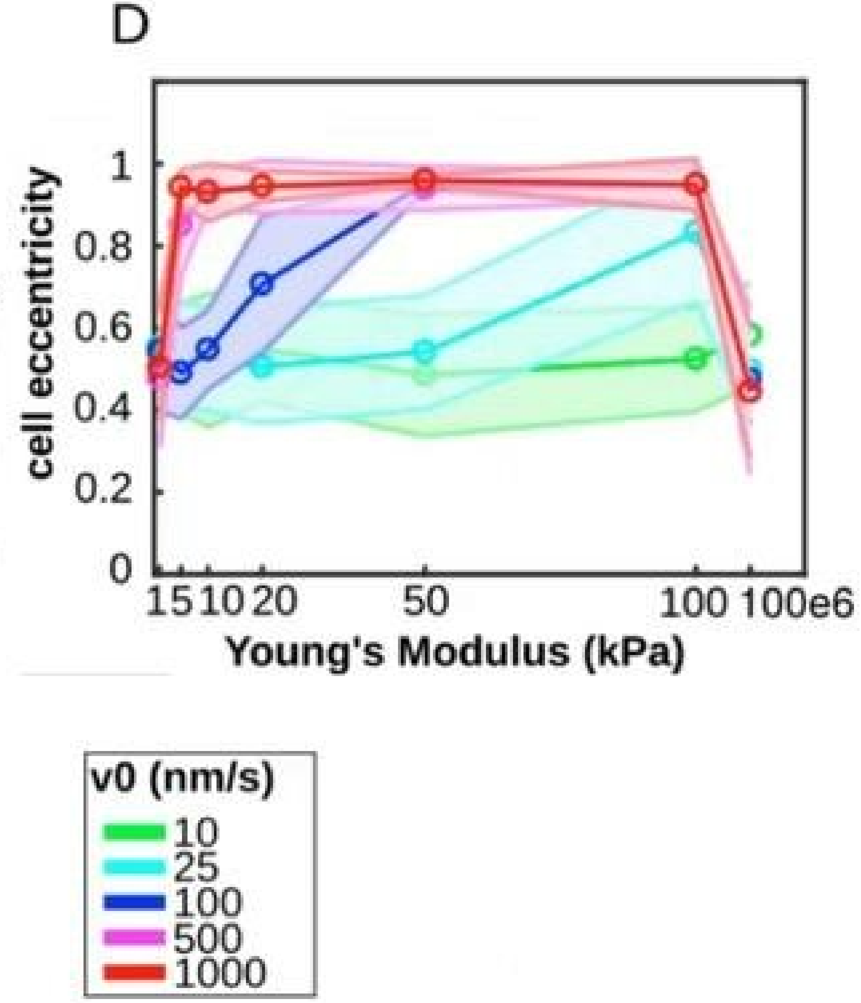
Speed of actomyosin contraction determines at what stiffness cells elongate





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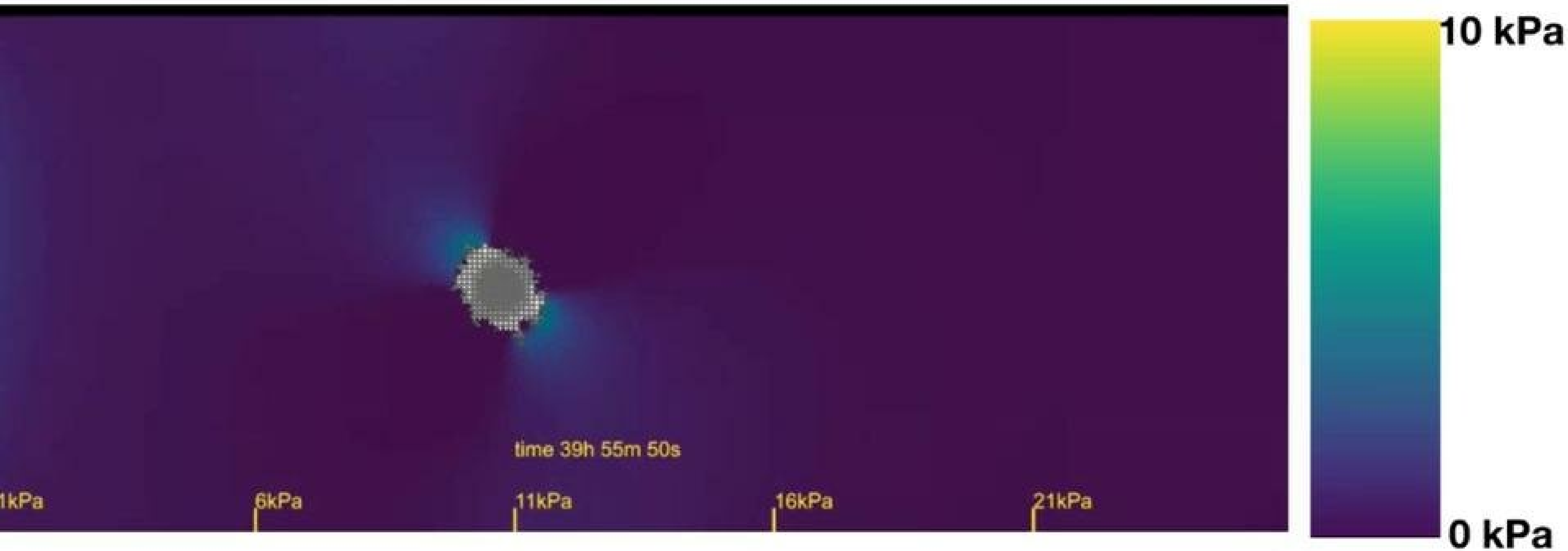
https://doi.org/10.1016/j.isci.2020.101488

Durotaxis

Cells move to higher stiffness



Rens & Merks (2020) *iScience* 9: 101488
https://doi.org/10.1016/j.isci.2020.101488

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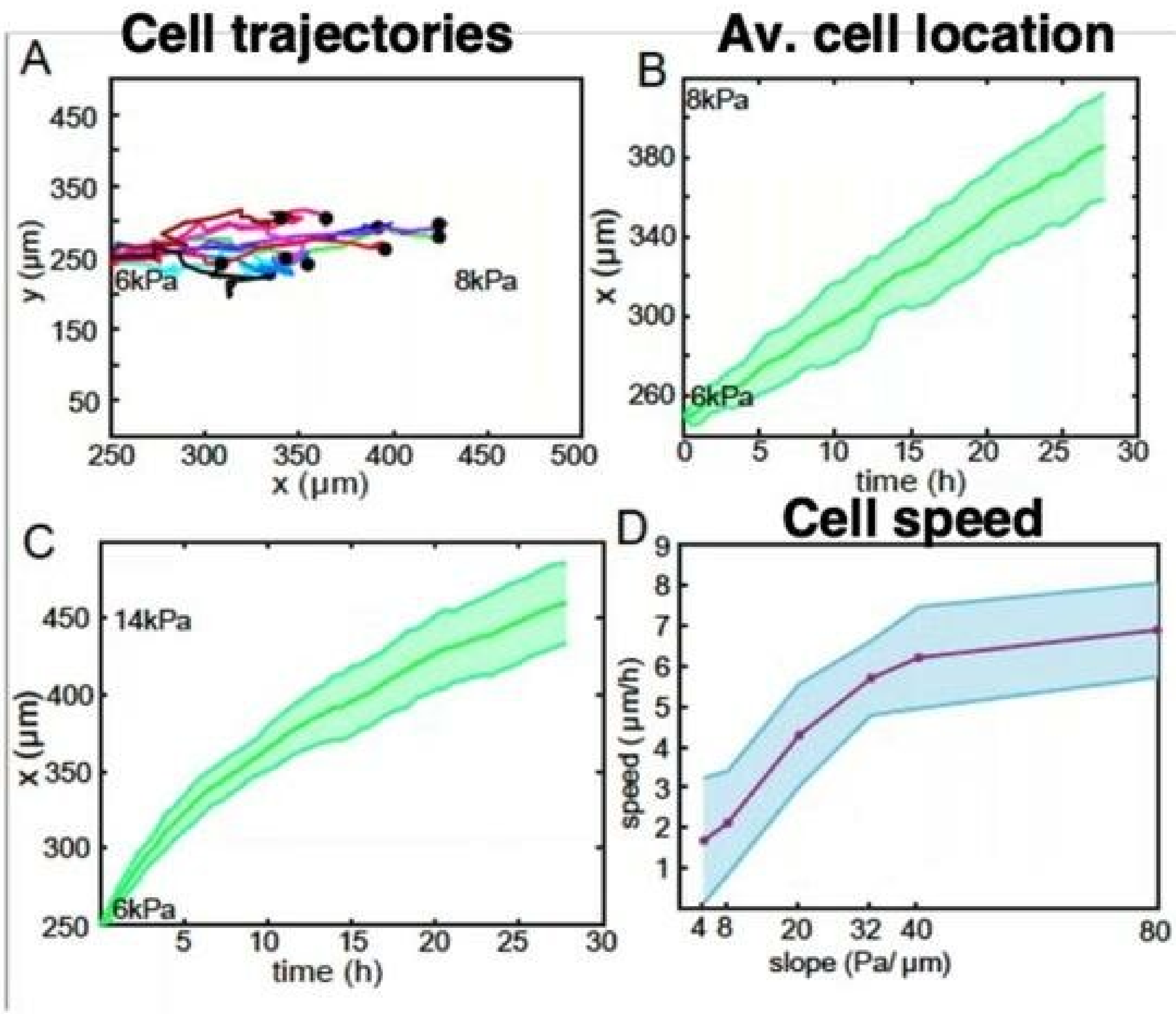
Durotaxis:

Faster movement on steeper slopes



Rens & Merks (2020) *iScience* 9: 101488
https://doi.org/10.1016/j.isci.2020.101488

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From **isotropic** ECMs to **fibrous** ECMs

Is it correct to model the ECM as an isotropic material?

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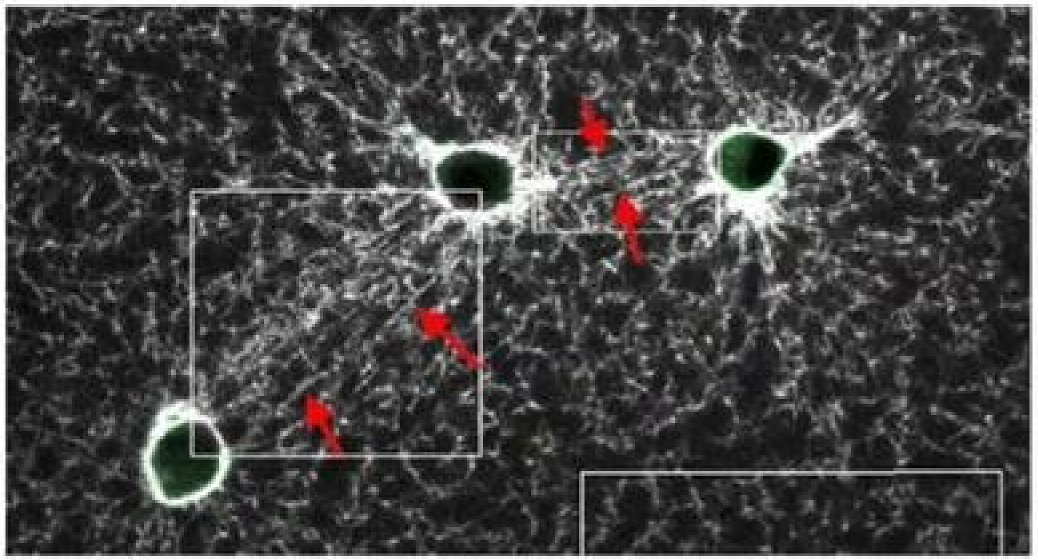
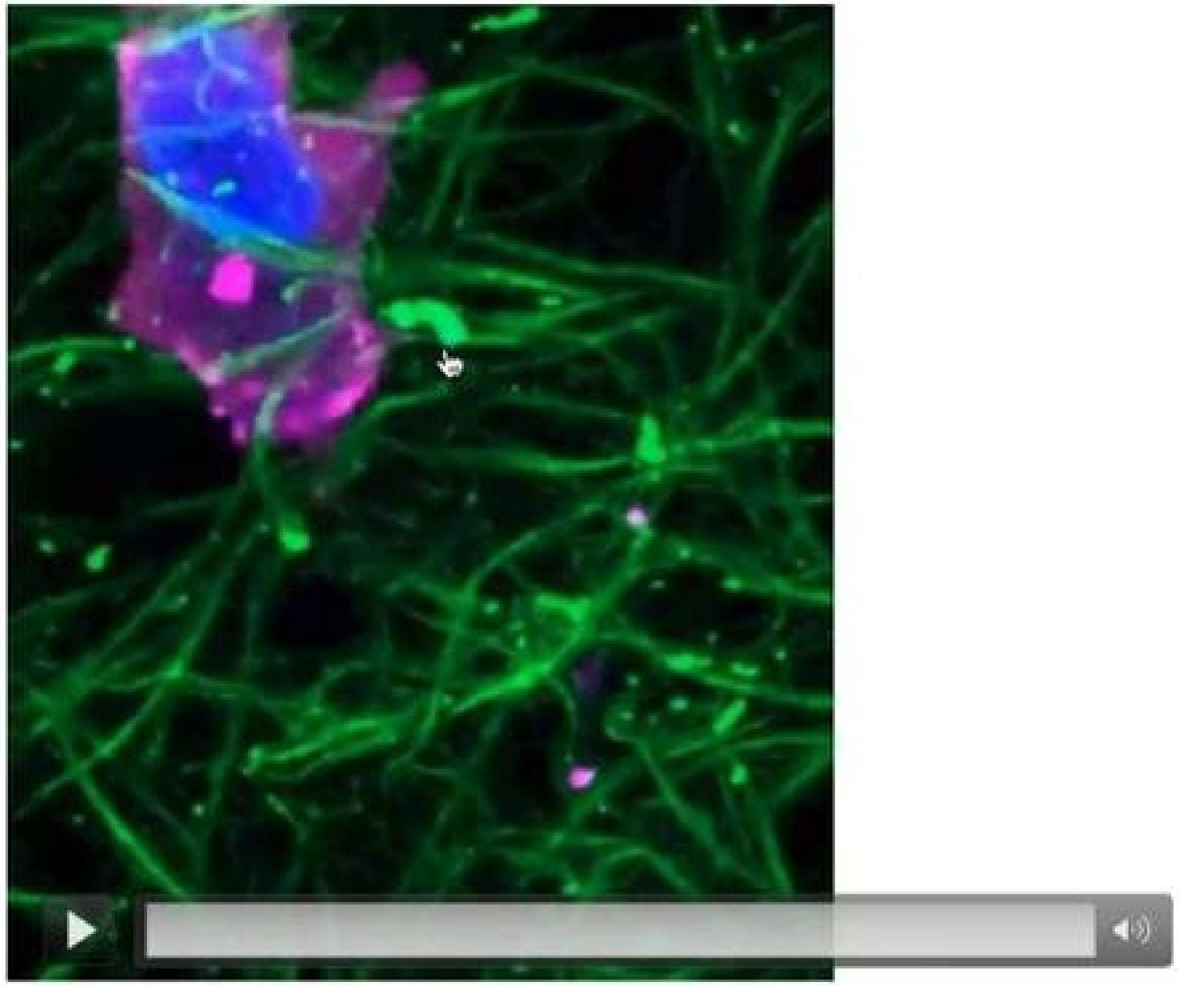
Was it correct to model ECMs as an isotropic material?



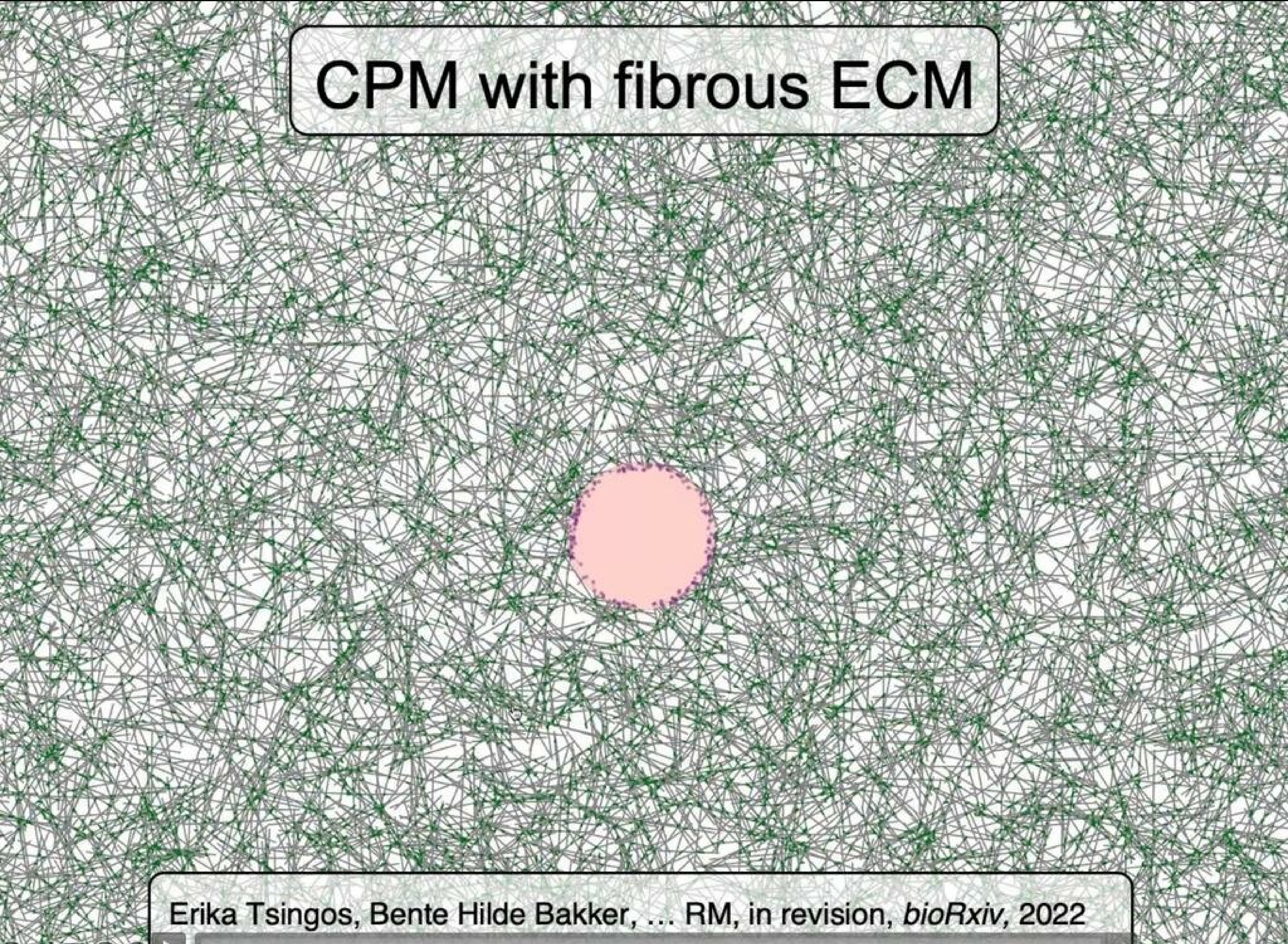
Mann et al. (2019) *Journal of the Royal Society Interface*



Doyle et al (2021) *Developmental Cell*

Erika Tsingos, Bente Hilde Bakker, … RM, in revision, *bioRxiv*, 2022

CPM with fibrous ECM



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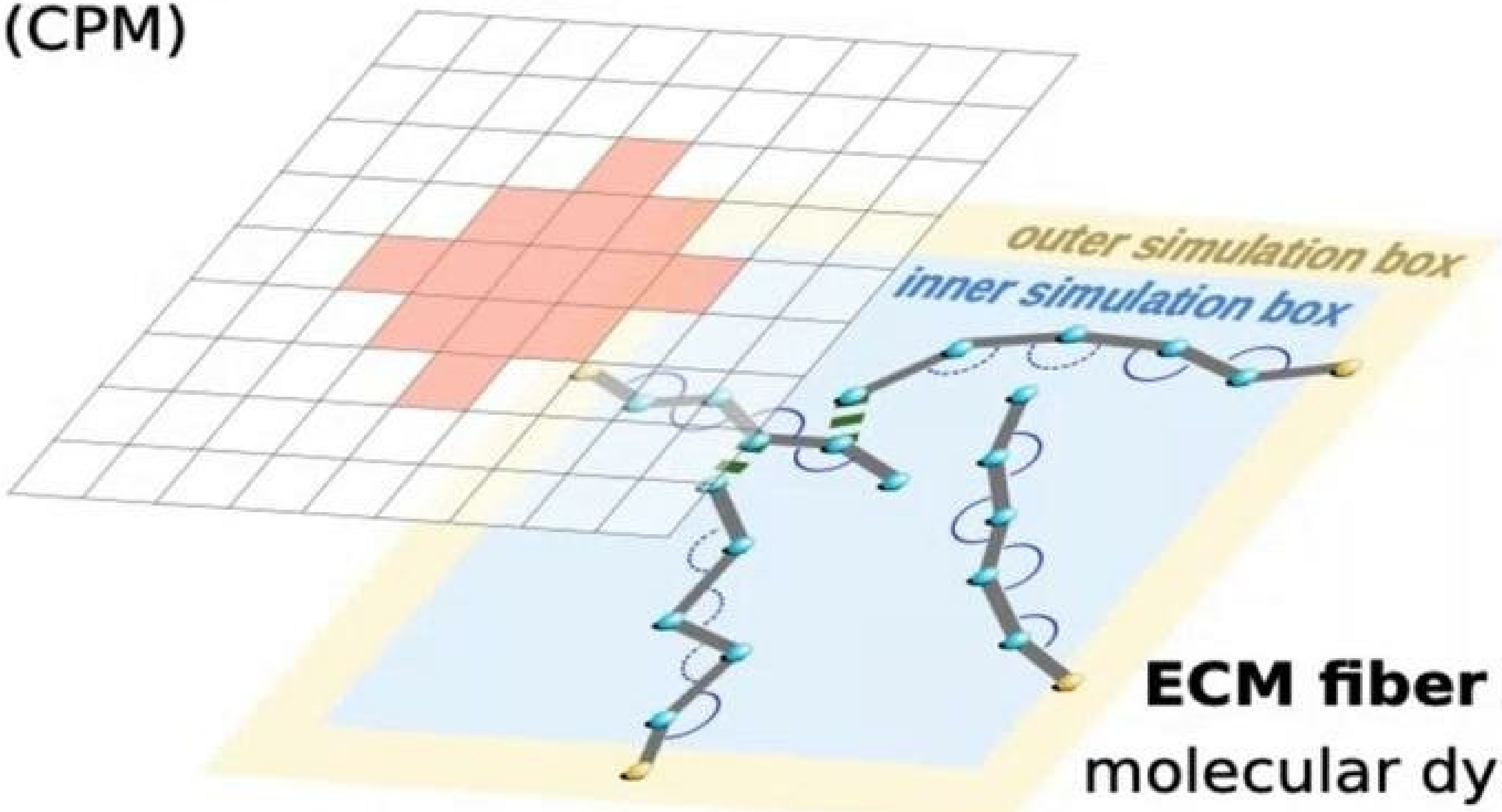
CPM with fibrous ECM

Bente Hilde Bakker Erika Tsingos

cell model
cellular Potts model
(CPM)



ECM fiber model
molecular dynamics
bead-chain model

Erika Tsingos, Bente Hilde Bakker, Koen Keijzer, HJ Hupkes, RM, in revision, *bioRxiv*, 2022

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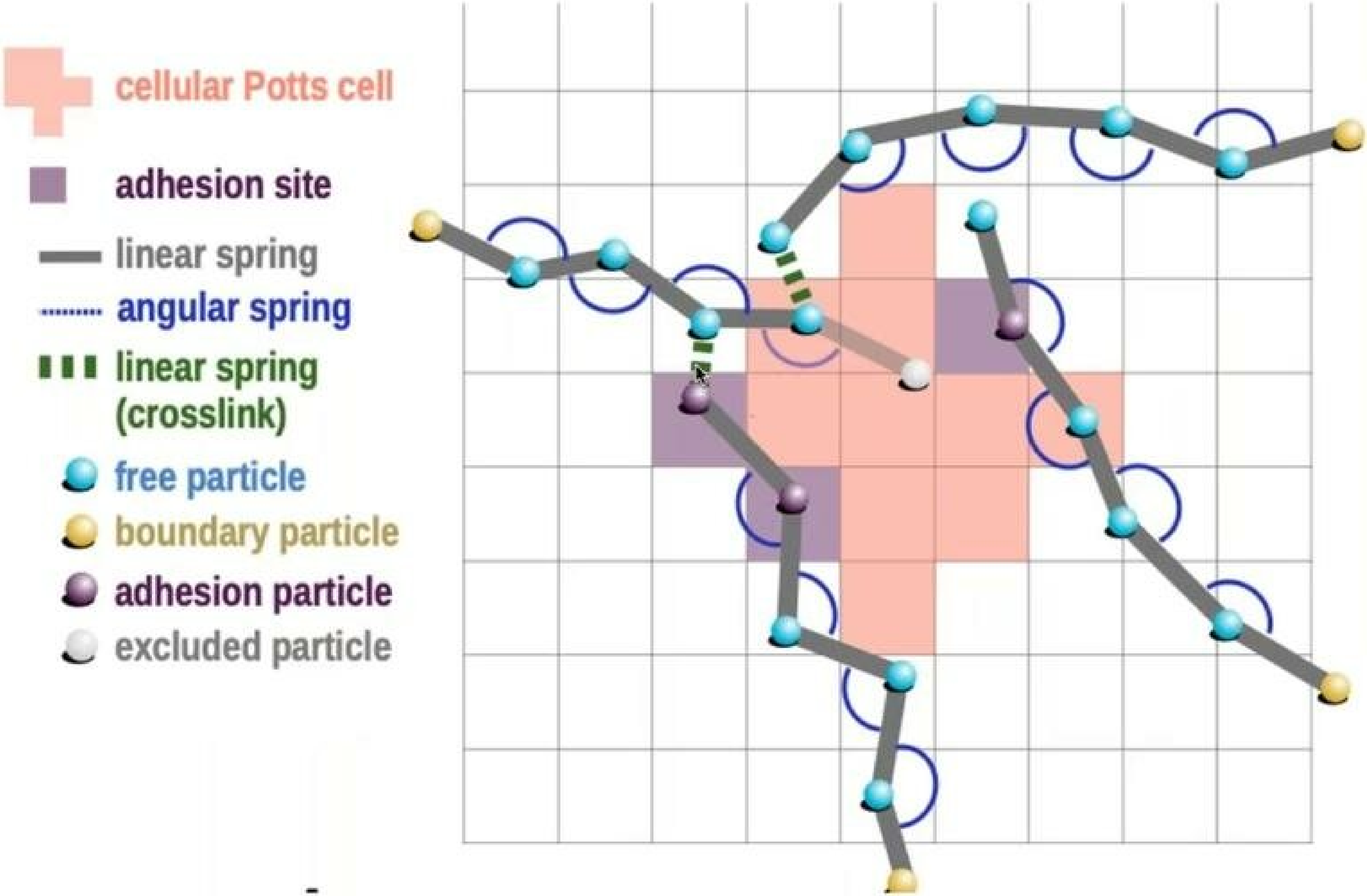
CPM with fibrous ECM

Bente Hilde Bakker

Erika Tsingos



Erika Tsingos, Bente Hilde Bakker, Koen Keijzer, HJ Hupkes, RM, in revision, *bioRxiv,* 2022

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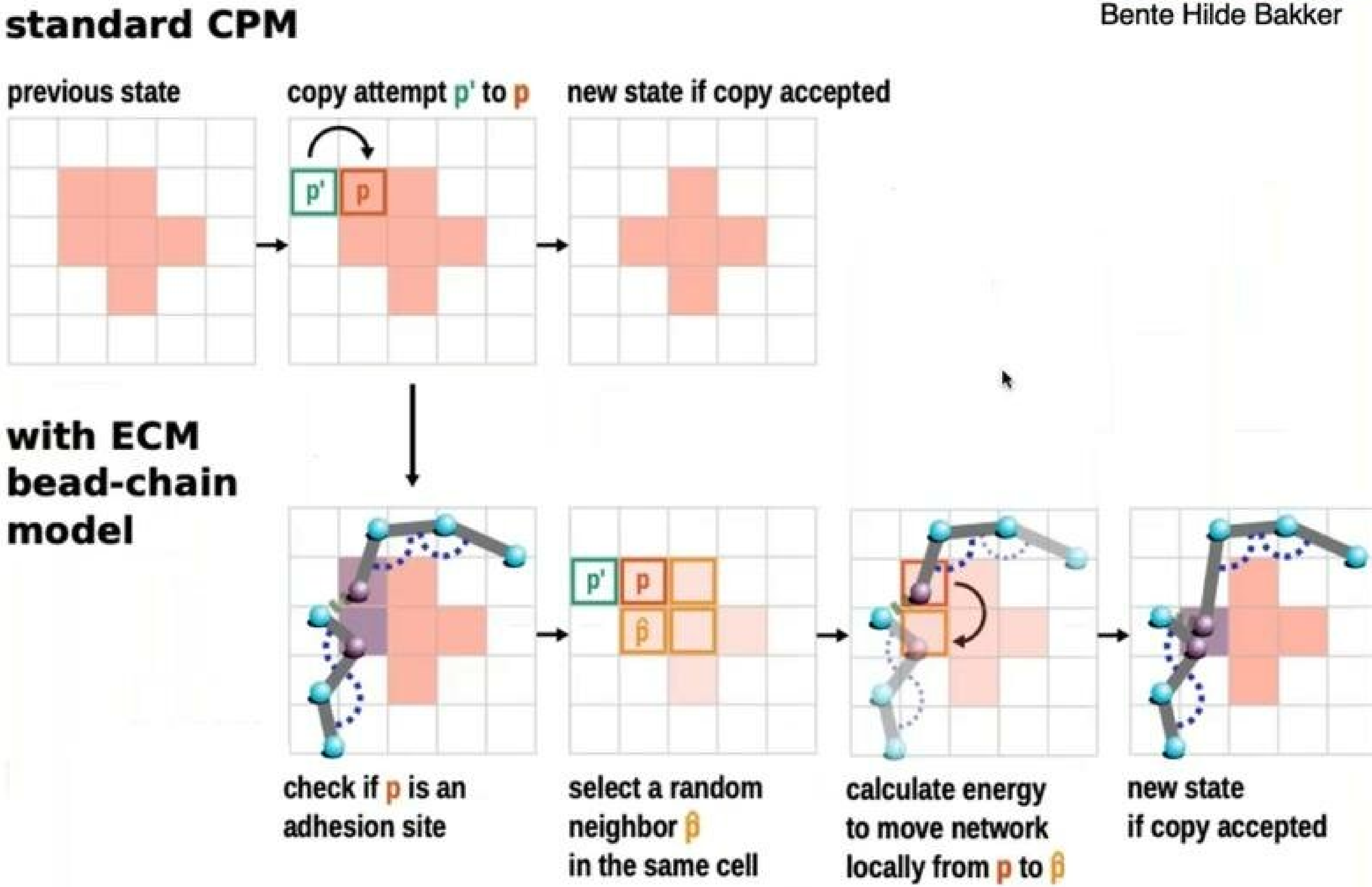
CPM with fibrous ECM


Bente Hilde Bakker


Erika Tsingos



Erika Tsingos, Bente Hilde Bakker, … RM, in revision, *bioRxiv,* 2022

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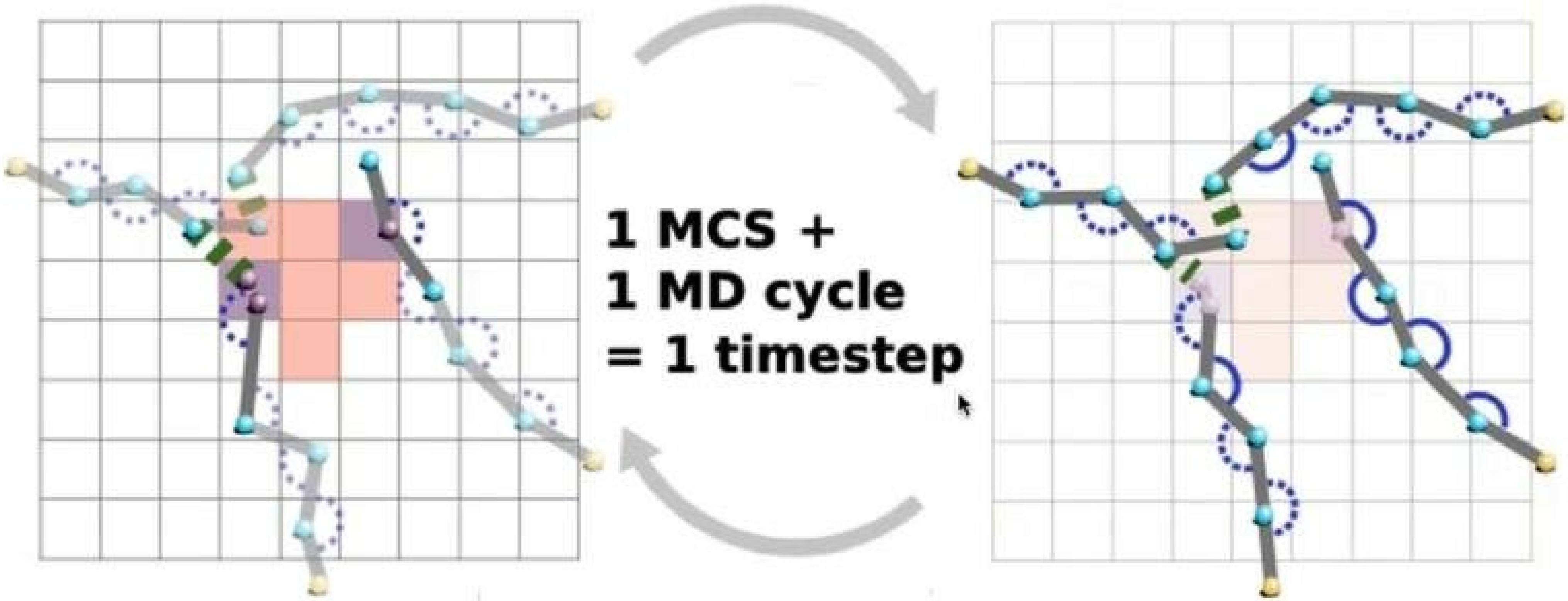
CPM with fibrous ECM

Bente Hilde Bakker

Erika Tsingos

1 MCS

- Assume network quasi-steady state
- Compute CPM Hamiltonian



1 MD cycle

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Effect of fiber density and cross-linker density

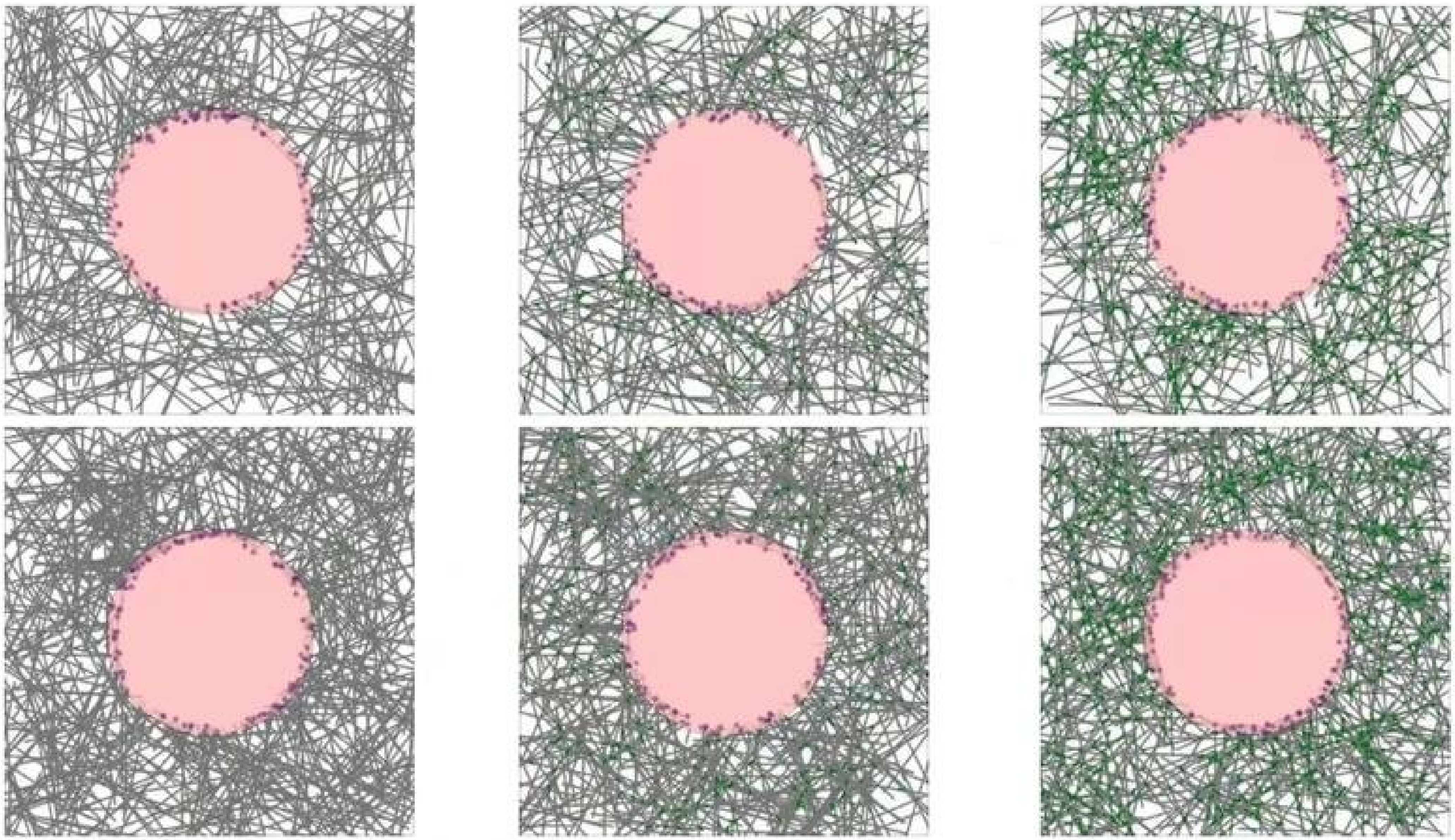
Cross-linker density

0 per μm^2 | 0.2 per μm^2 | 0.8 per μm^2

Fiber density:

~9.4 % v/v
~1.0 mg/ml
collagen [1]

~14.1 % v/v
~2.0 mg/ml
collagen [1]



Assuming fiber diameter of 0.25 μm and length of 12.5 μm; domain height = 1 μm. [1] Kreger et al. Biopolymers 93.8 (2010): 690-707.

Erika Tsingos, Bente Hilde Bakker, Koen Keijzer, HJ Hupkes, RM, in revision, *bioRxiv*, 2022

Effect of fiber density and cross-linker density

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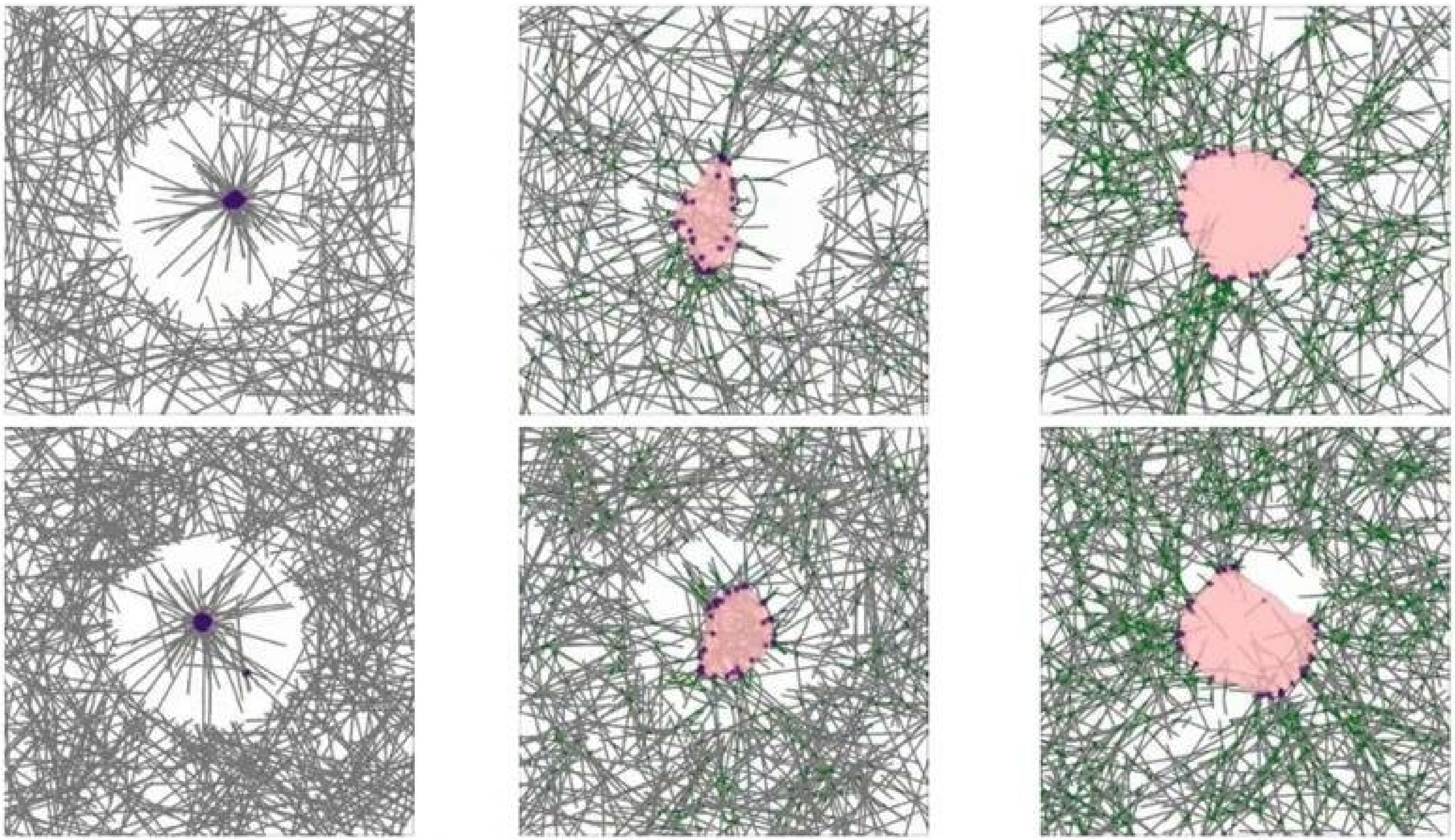
Cross-linker density

0 per μm^2 | 0.2 per μm^2 | 0.8 per μm^2

Fiber density:

~9.4 % v/v
~1.0 mg/ml
collagen [1]

~14.1 % v/v
~2.0 mg/ml
collagen [1]



Assuming fiber diameter of 0.25 μm and length of 12.5 μm; domain height = 1 μm. [1] Kreger et al. Biopolymers 93.8 (2010): 690-707.

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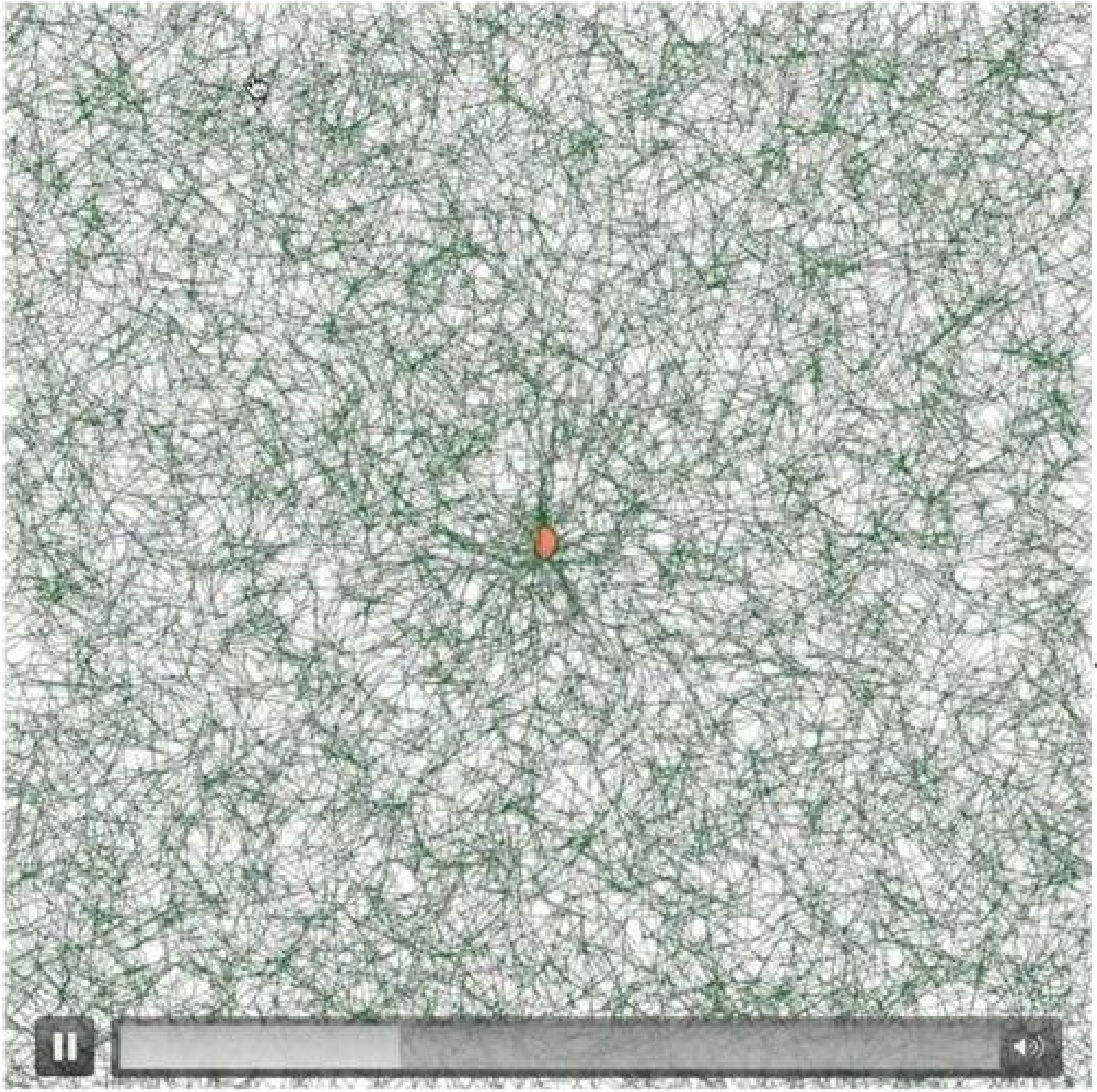
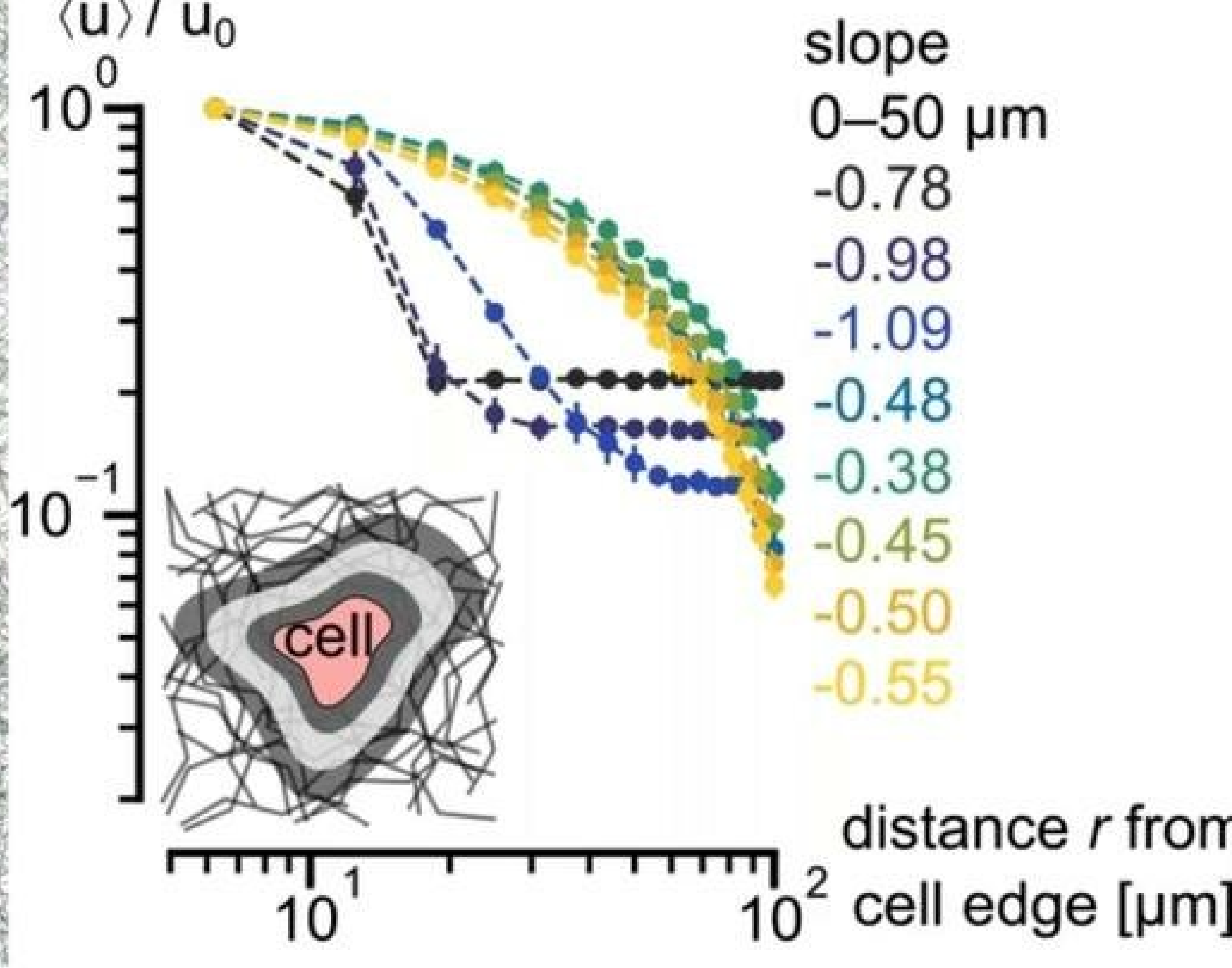
Cells remodel matrix up to 4 cell diameters away





Contractile cells in fibrous extracellular matrices

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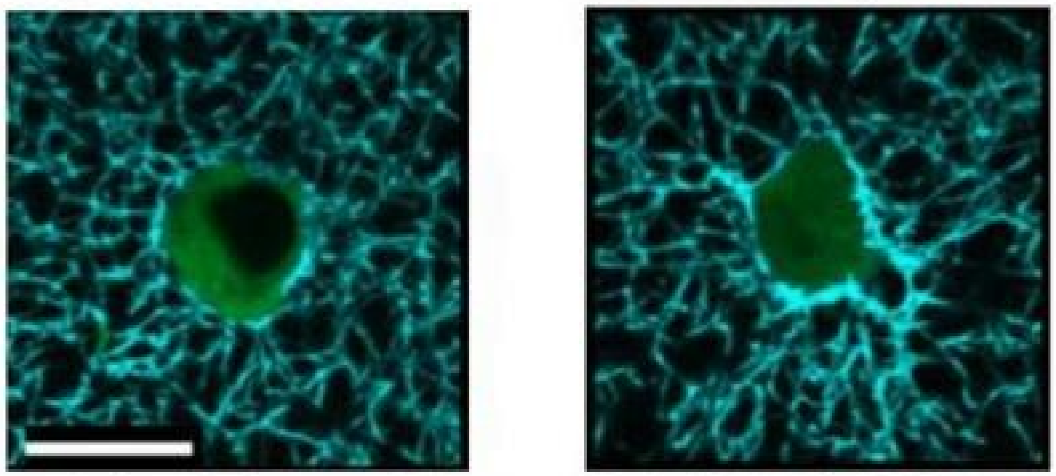
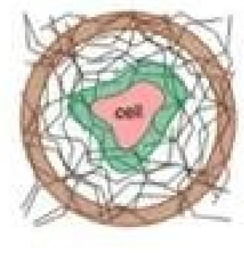
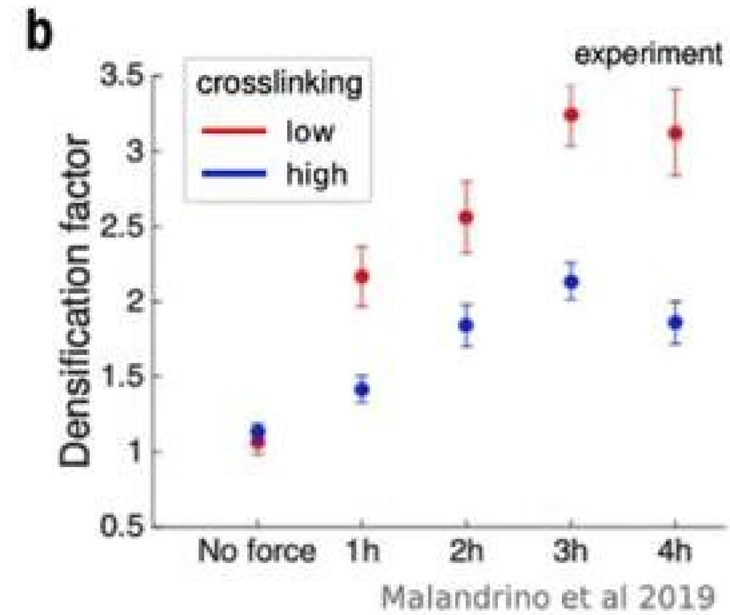
Experiment

high-crosslinking fibrin   low-crosslinking fibrin



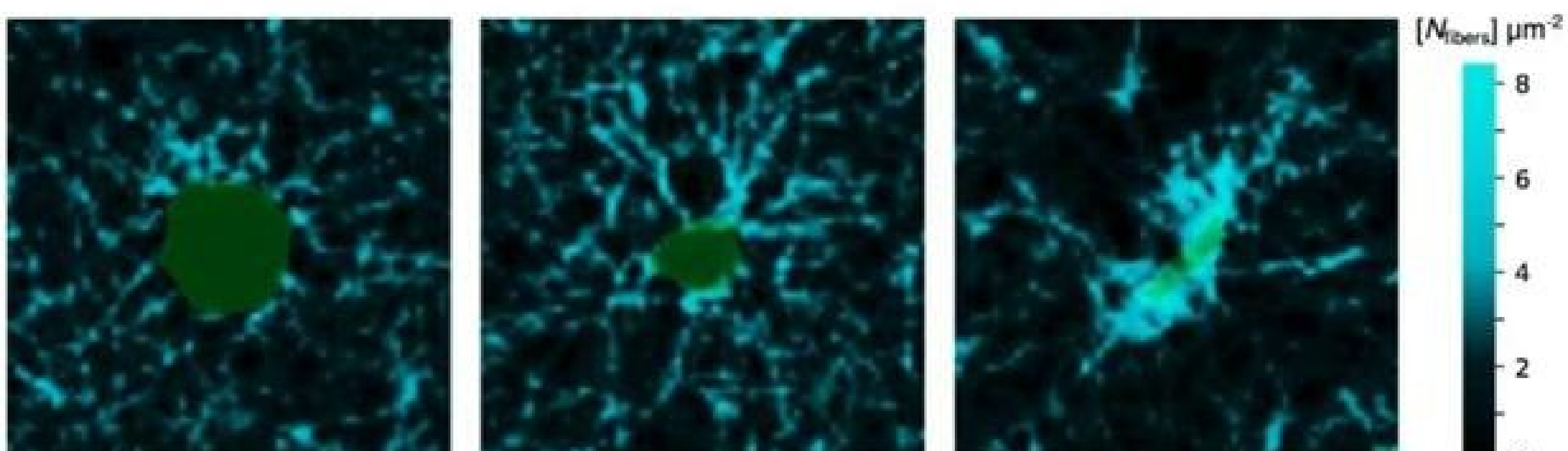
Malandrino, Trepat, Kamm, Mak (2020) P Comput Biol

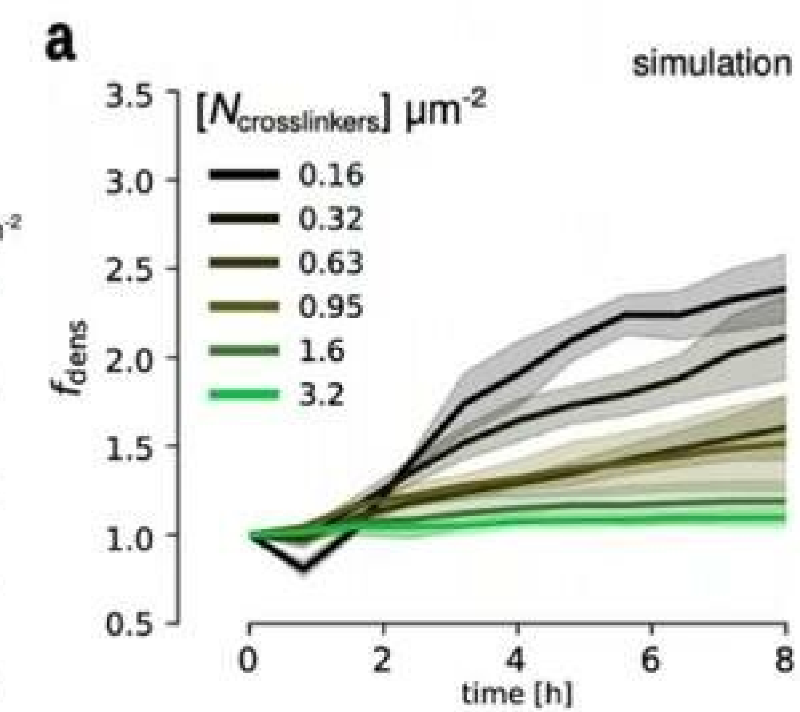




Time-averaged fiber density after ~8h simulated time

Simulation





Erika Tsingos, Bente Hilde Bakker, Koen Keijzer, HJ Hupkes, RM, in revision, *bioRxiv*, 2022

In silico atomic force microscopy

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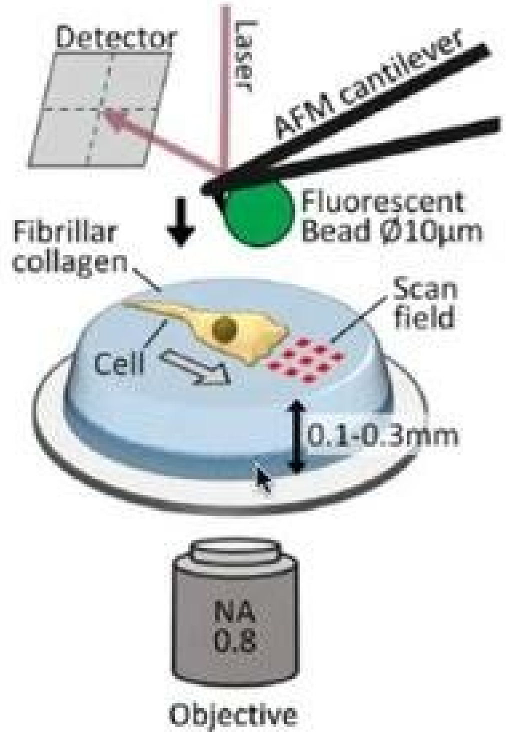
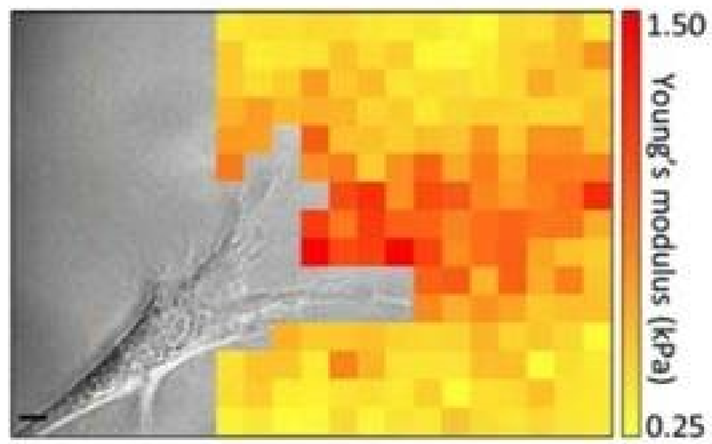
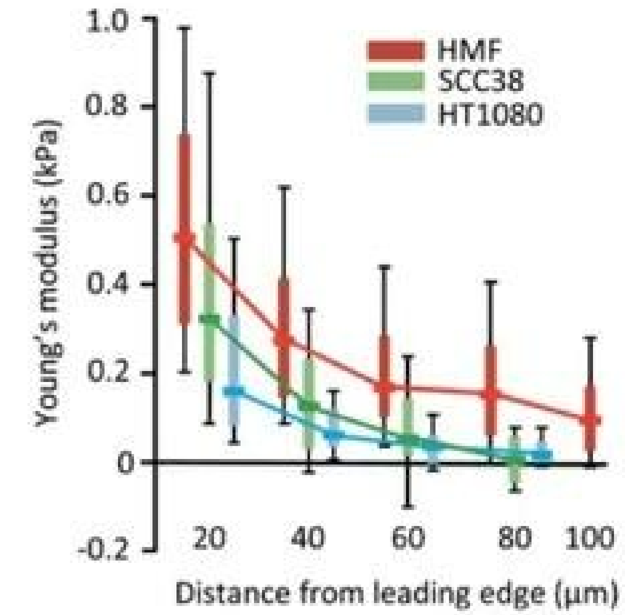
Experiment

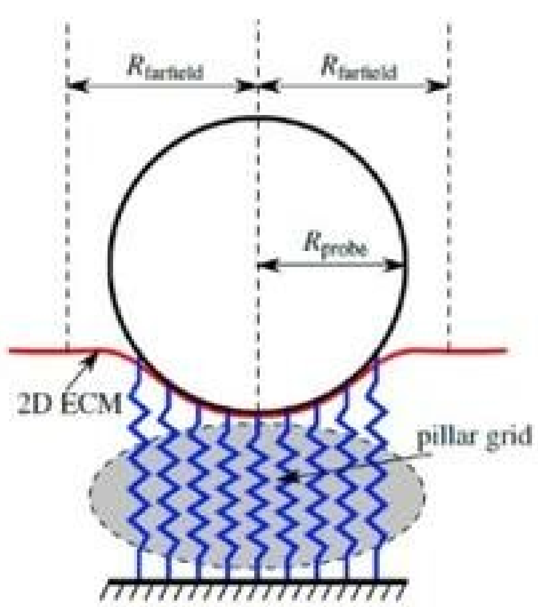


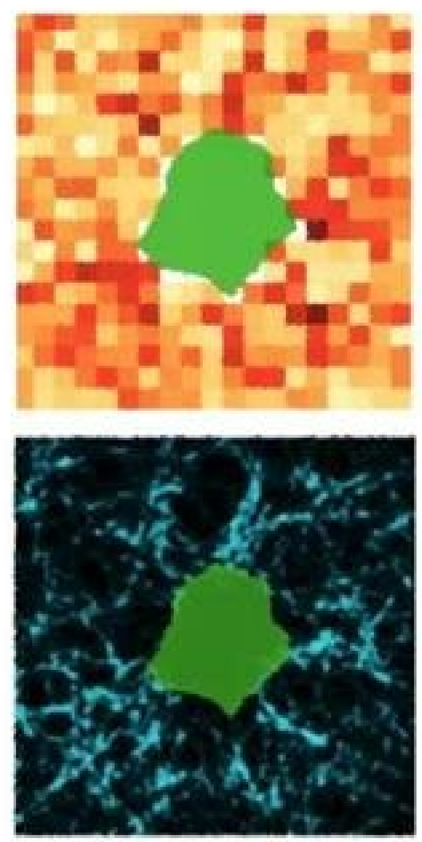


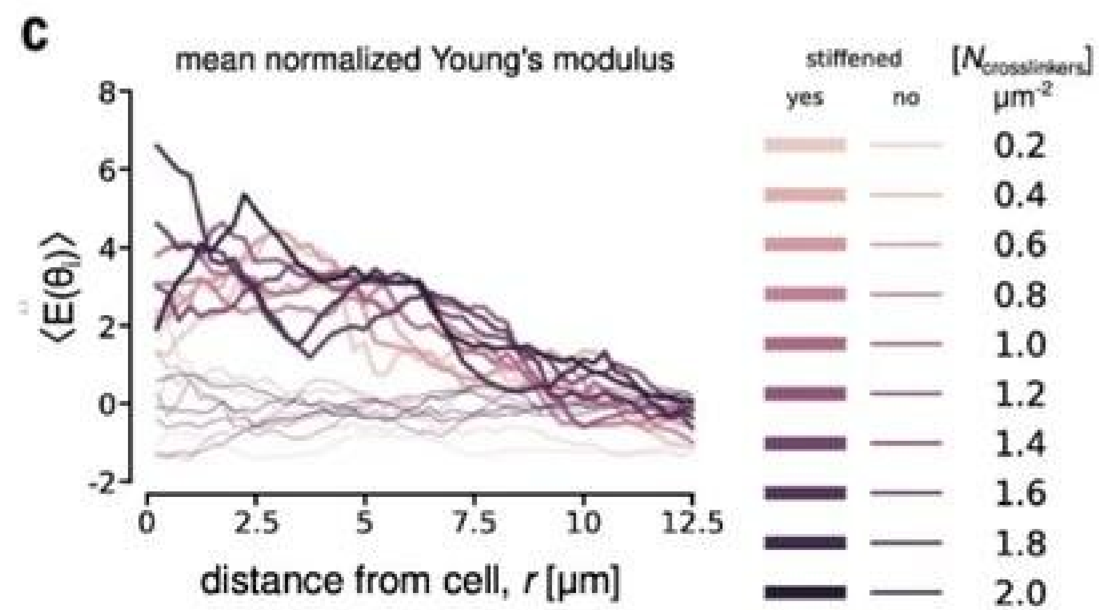
Van Helvert ... Friedl et al. (2016)
ACS Applied Materials & Interfaces



Simulation







Erika Tsingos, Bente Hilde Bakker, Koen Keijzer, HJ Hupkes, RM, in revision, *bioRxiv*, 2022

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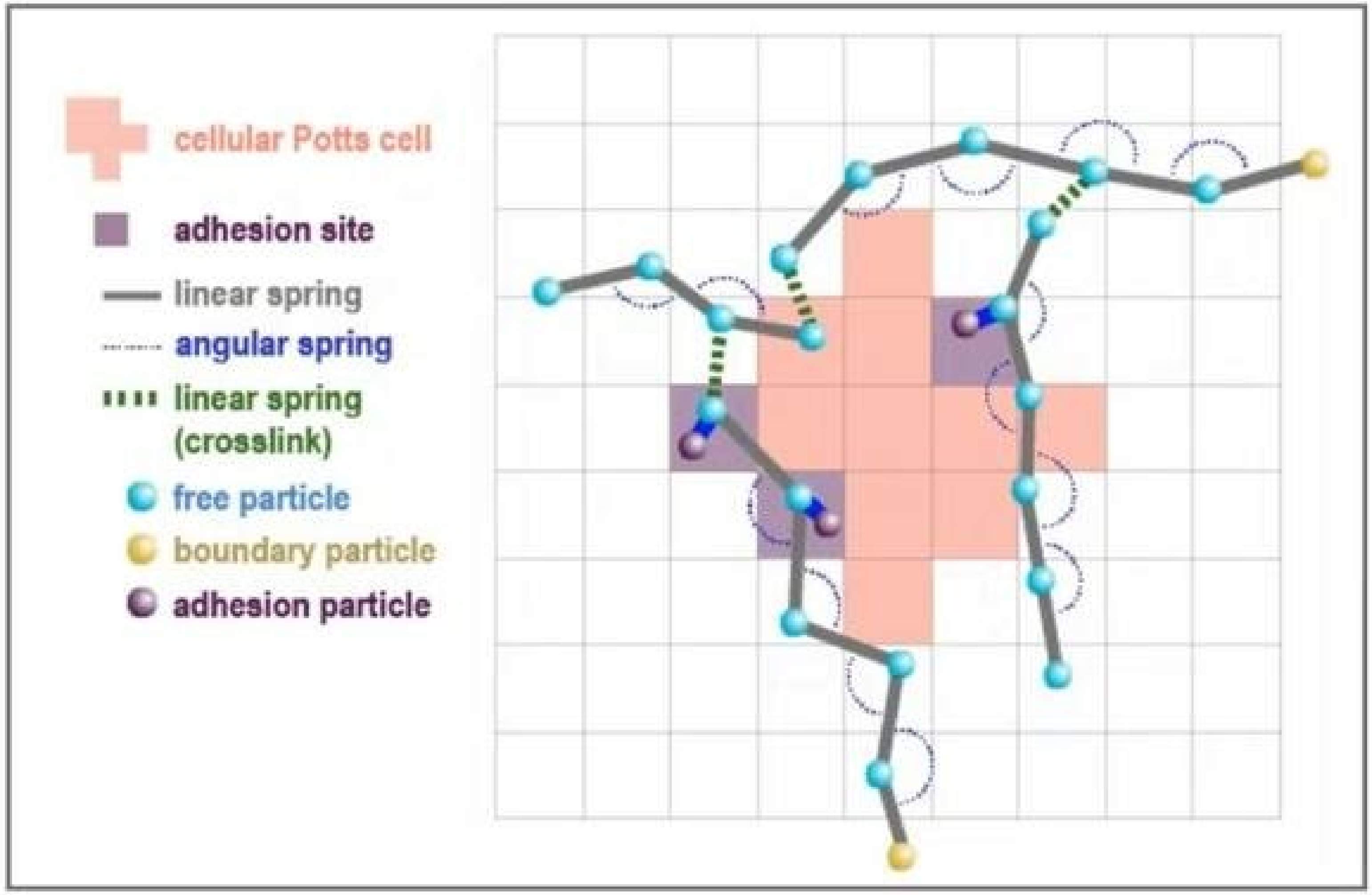

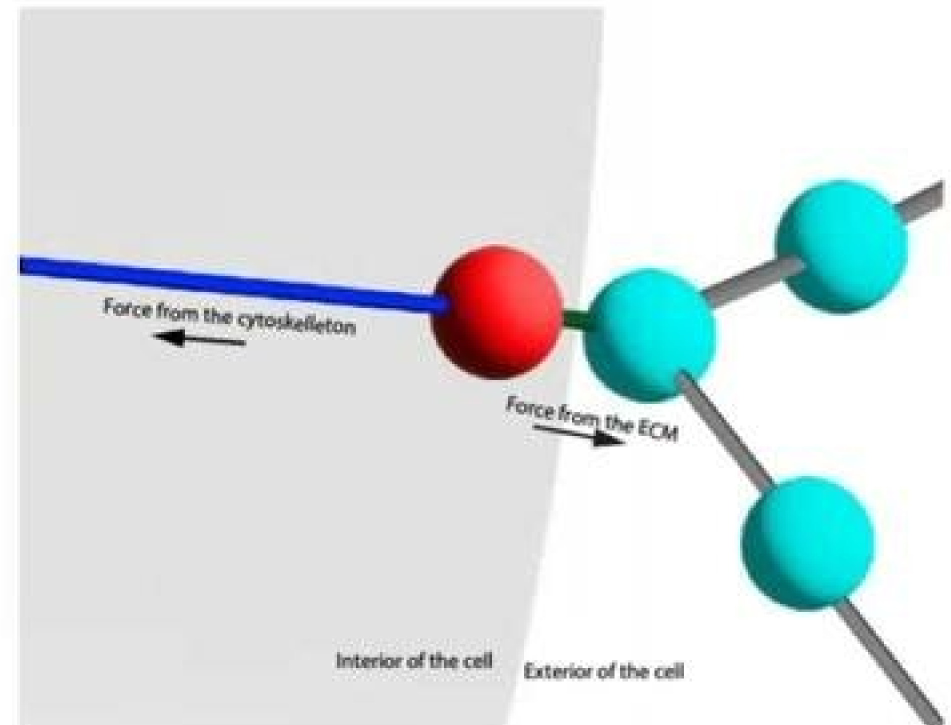

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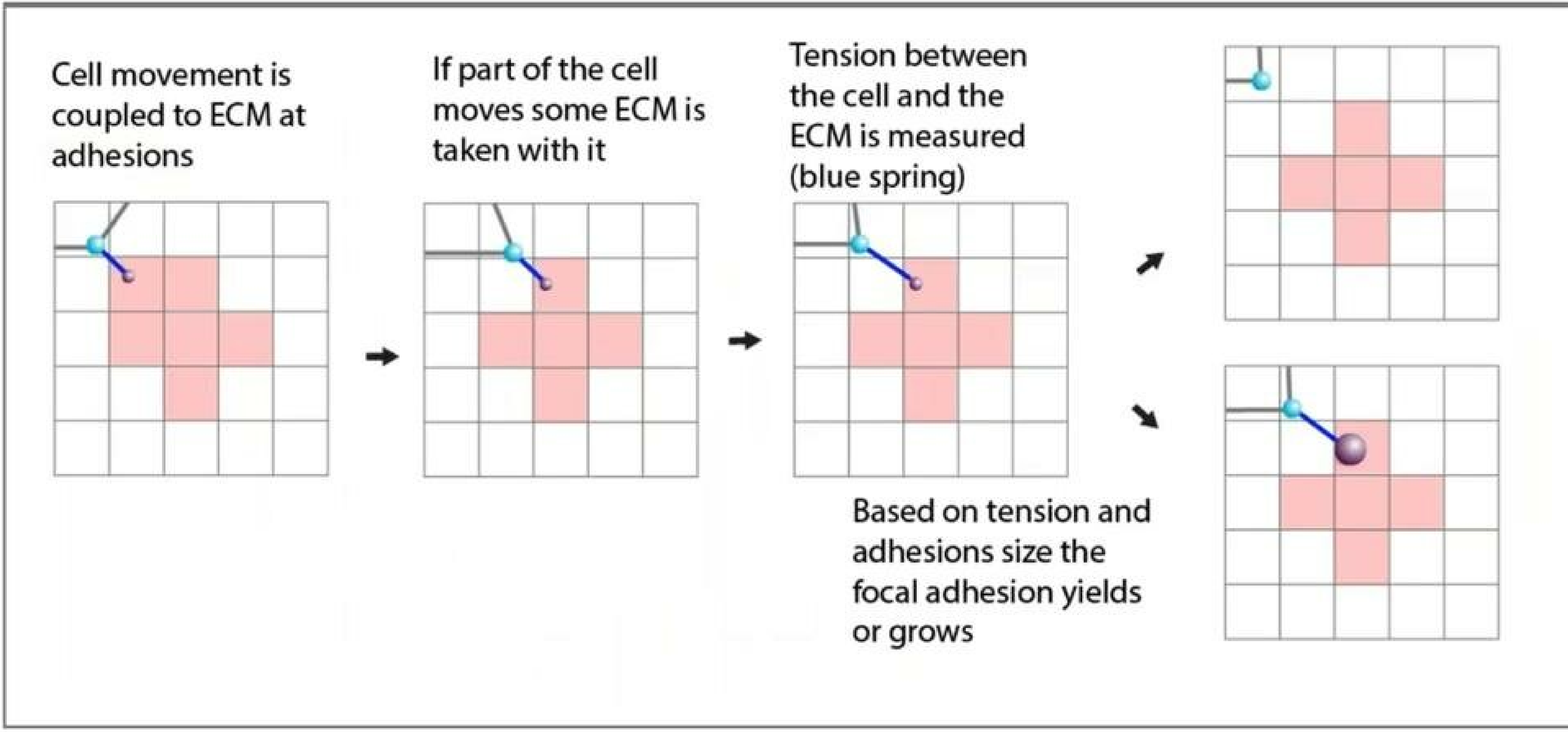
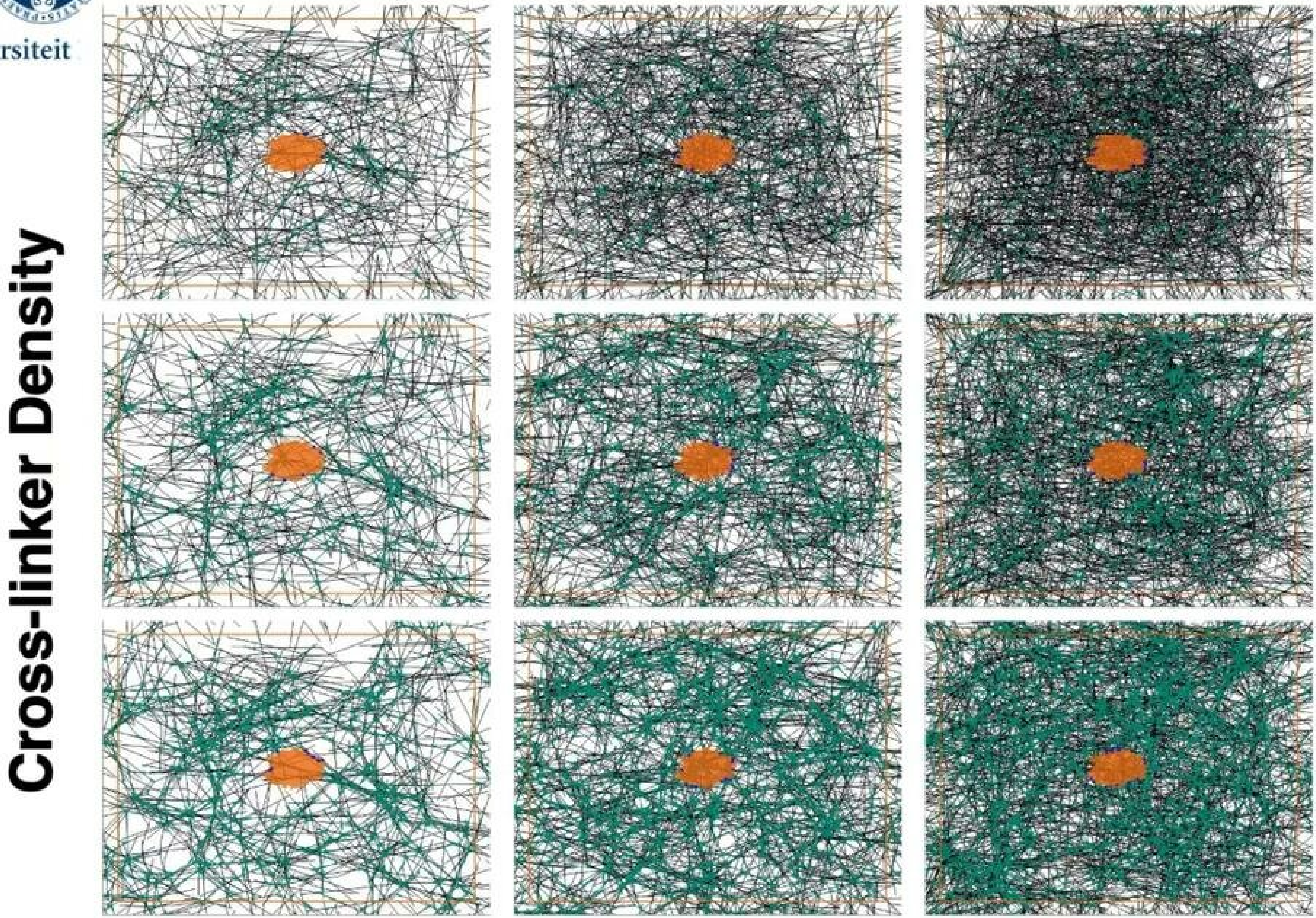


ECM Density



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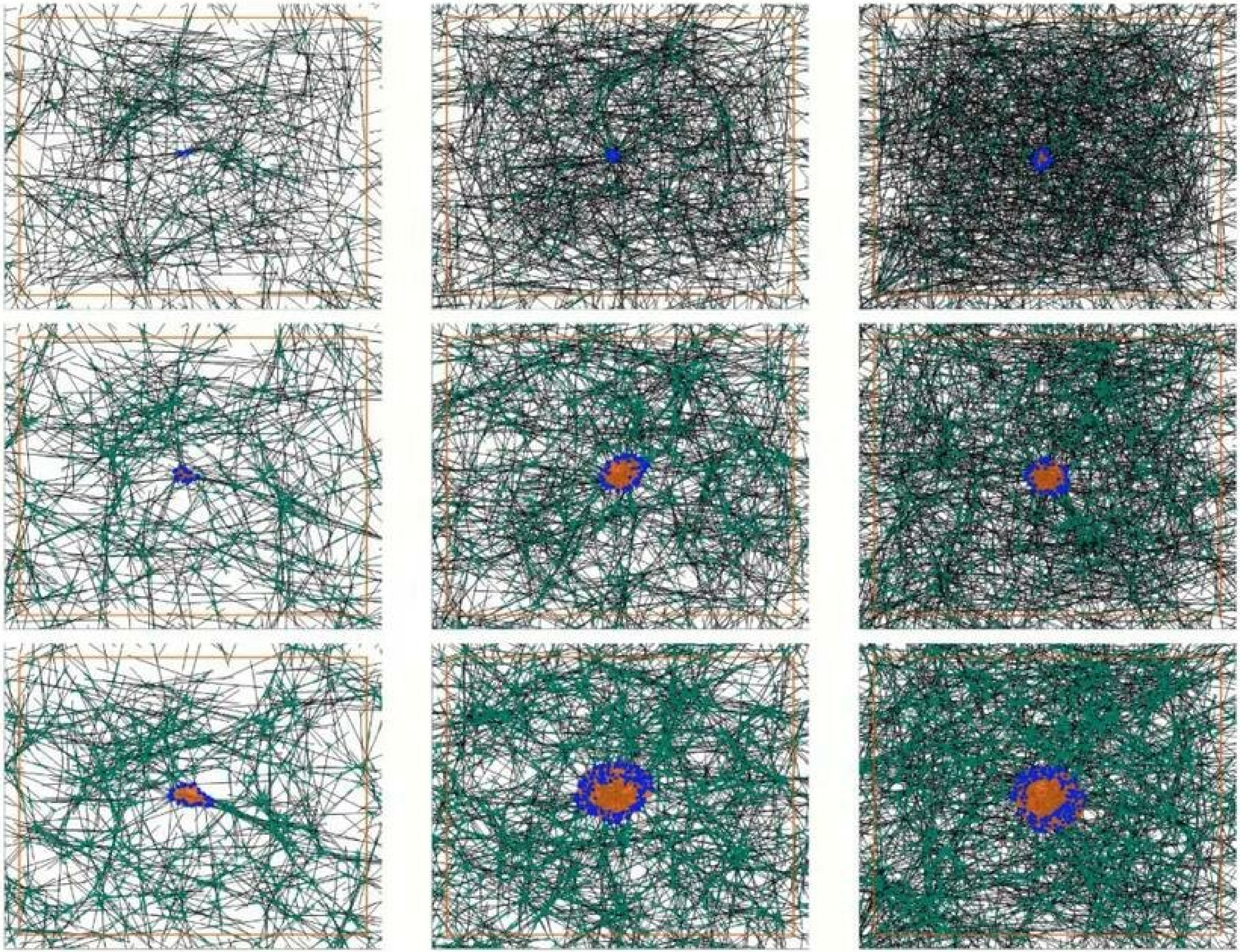
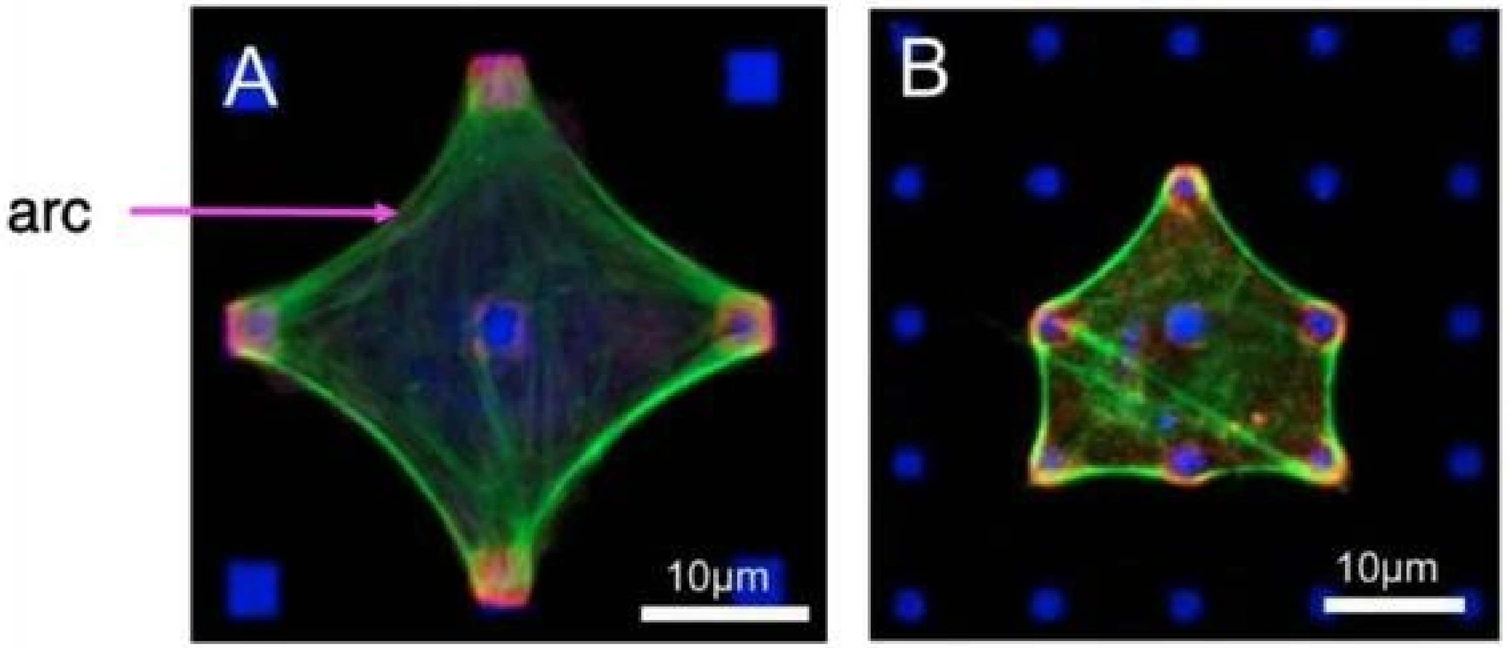
ECM Density



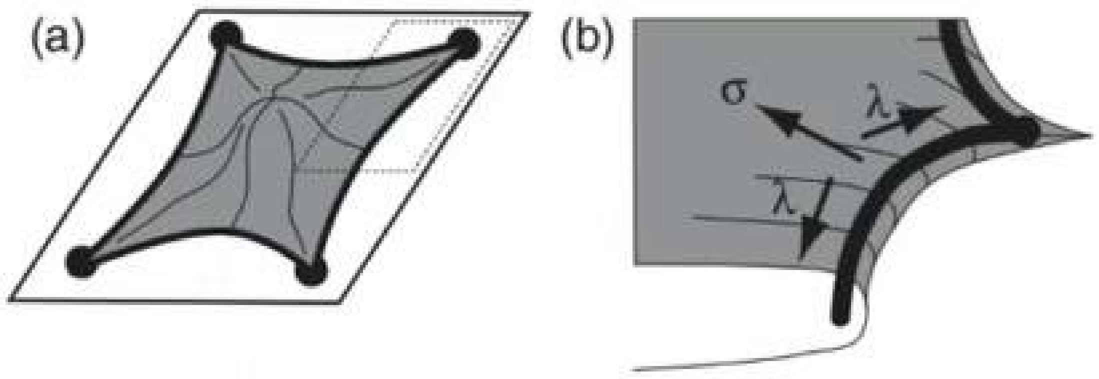
Cross-linker Density

Effect cytoskeletal contractility on cell shape

- Cells adhering on patterned substrates



Bischofs et al. Biophys J 2008



Bischofs et al. PRL 2009

- What is the shape of the free hanging 'arcs'?

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Cross-talk between cell shape and cytoskeletal organization

- **Approach:** let a coarse-grained model of the actin cytoskeleton control the CPM and *vice versa*
  - Q-tensor describes actin orientation at each location

$$\hat{Q} = \begin{bmatrix} Q_{xx} & Q_{xy} \\ Q_{xy} & -Q_{xx} \end{bmatrix} = \frac{S}{2} \begin{bmatrix} \cos 2\theta_{\mathrm{SF}} & \sin 2\theta_{\mathrm{SF}} \\ \sin 2\theta_{\mathrm{SF}} & -\cos 2\theta_{\mathrm{SF}} \end{bmatrix}$$

  - With $S = \sqrt{2 \operatorname{tr} Q^2}$, the nematic order parameter (S=0 isotropic, S=1 fully aligned)
- Dynamics:
  - tendency of actin fibers to **align with one another (K)** versus **alignment of fibers with cell boundary (W)**

Schakenraad... **Giomi**. Soft Matter, 16(27), 6328–6343.
http://doi.org/10.1039/d0sm00492h

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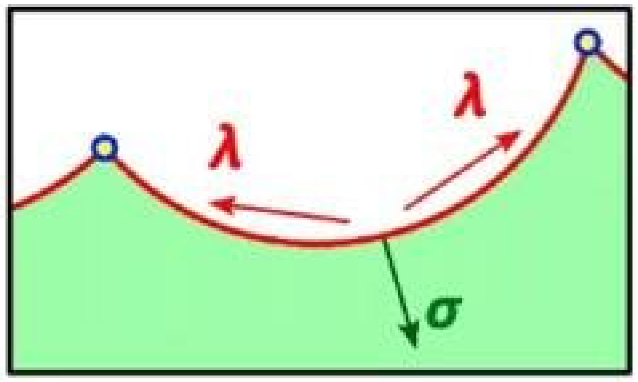
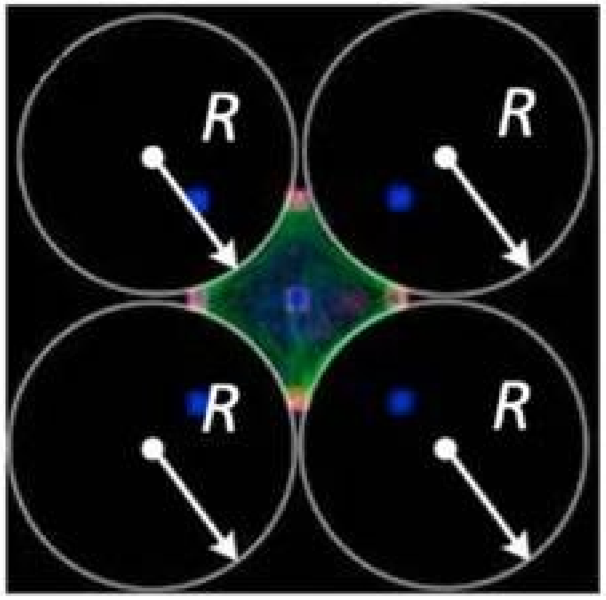
From **isotropy** to **anisotropy**

Is the model of
intracellular contractility correct?

Isotropic contraction: circular arcs

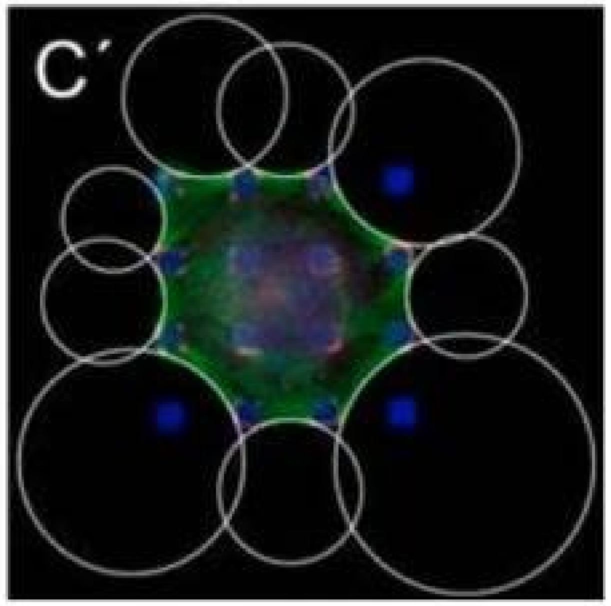
- Young-Laplace law predicts circular arcs (Bar-Ziv et al. PNAS 1999)
  - Minimize $H = \sigma A + \int \lambda(s) ds$
  - Gives $R = \lambda/\sigma$



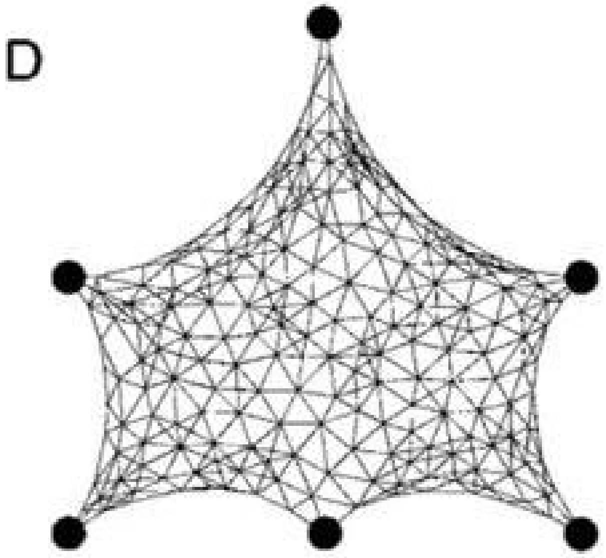


Bischofs et al. Biophys J 2008

- Cell bulk is elastic and cortex contracts actively:
  - Curvature depends on distance between adhesion points (Bischofs et al. Biophys J 2008)



Bischofs et al. Biophys J 2008



$$R = l_t \left(\frac{2R}{\alpha d} \arcsin\left(\frac{d}{2R}\right) - 1 \right).$$

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Isotropic cell contraction in the CPM

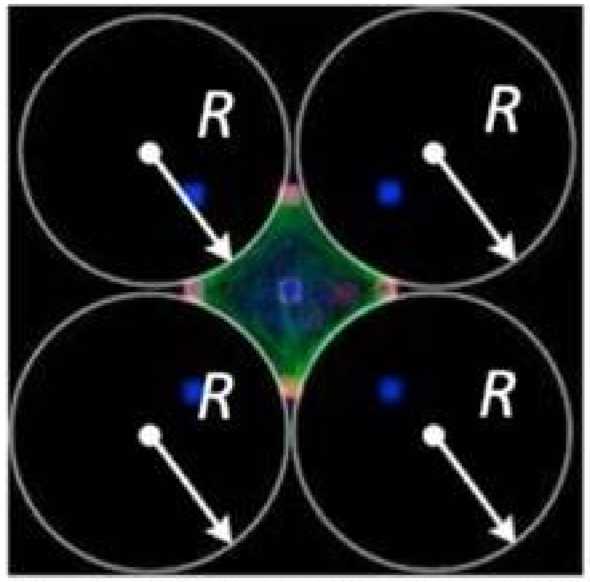
Koen Schakenraad

- Cortex is elastic and cortex and cell bulk contract actively:

$$H = \sigma A + \lambda P - \frac{E_0}{A_{\mathrm{ref}} + A_{\mathrm{ad}}} A_{\mathrm{ad}}$$

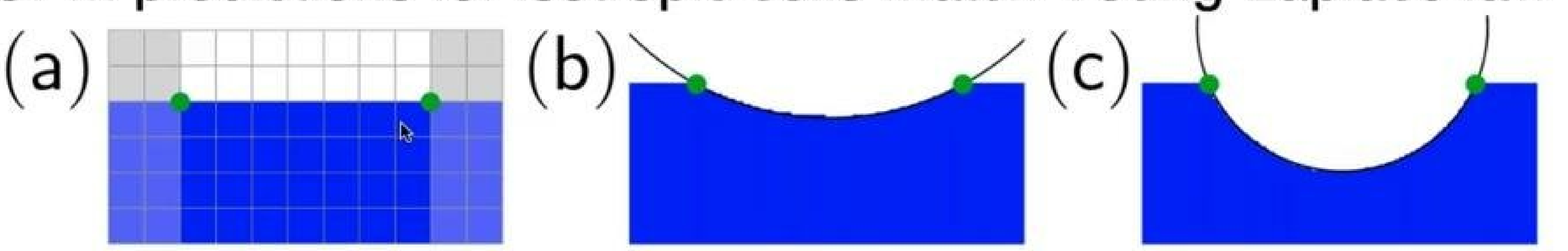
H = contraction + line tension - adhesion to patterned substrate

- Prediction:
  - Young-Laplace law: circular arcs between adhesion sites $R = \lambda/\sigma \quad \lambda = 500$



Bischofs et al. Biophys J 2008

CPM predictions for isotropic cells match Young-Laplace law



Initial configuration

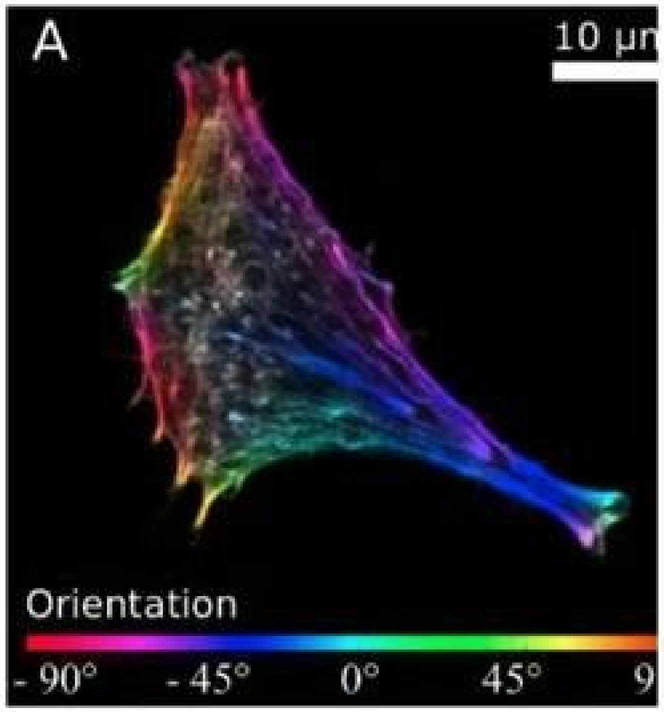
$\sigma = 10, R = 50, R_{\mathrm{CPM}} = 54$

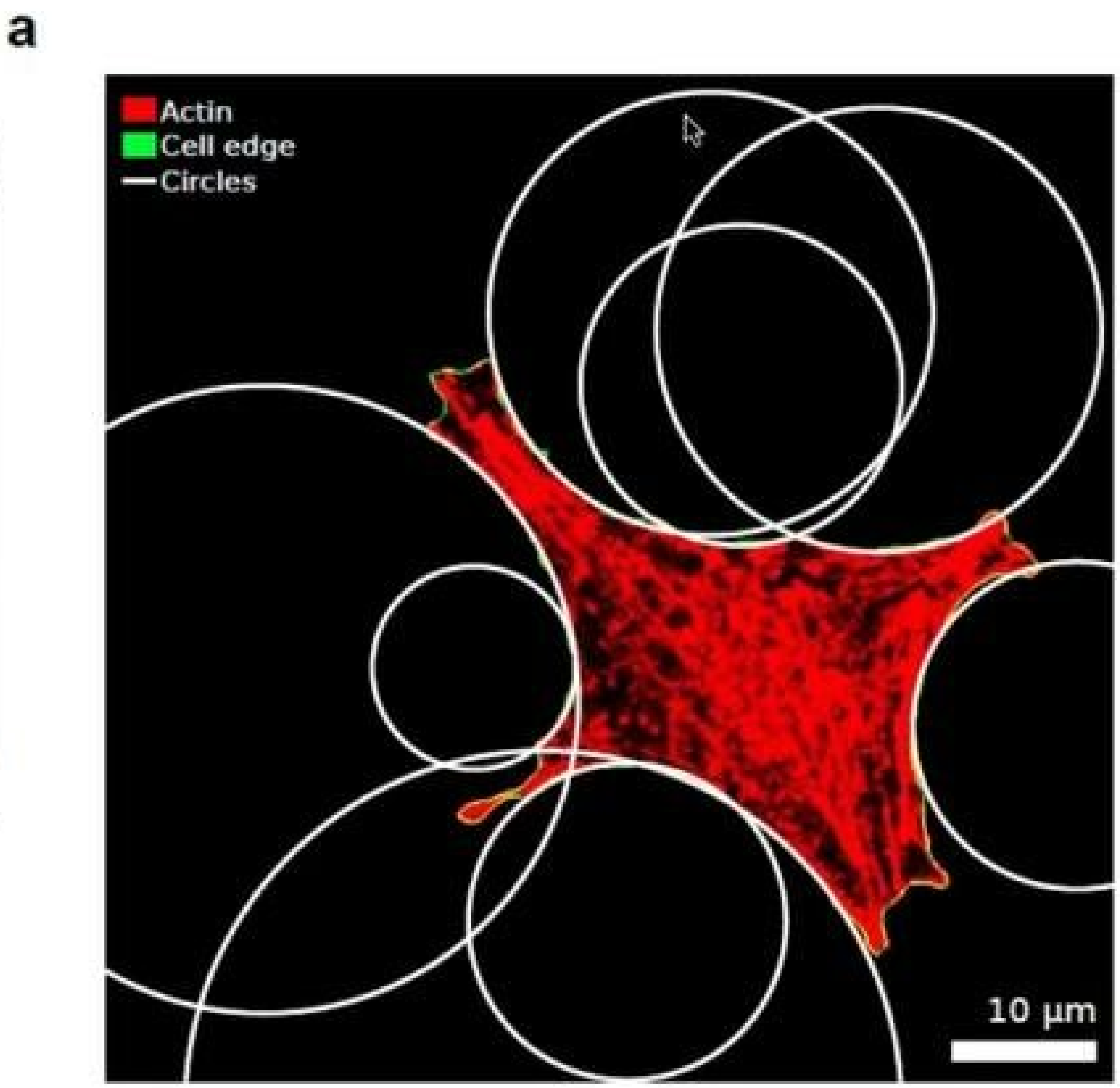
$\sigma = 5, R = 100, R_{\mathrm{CPM}} = 105$

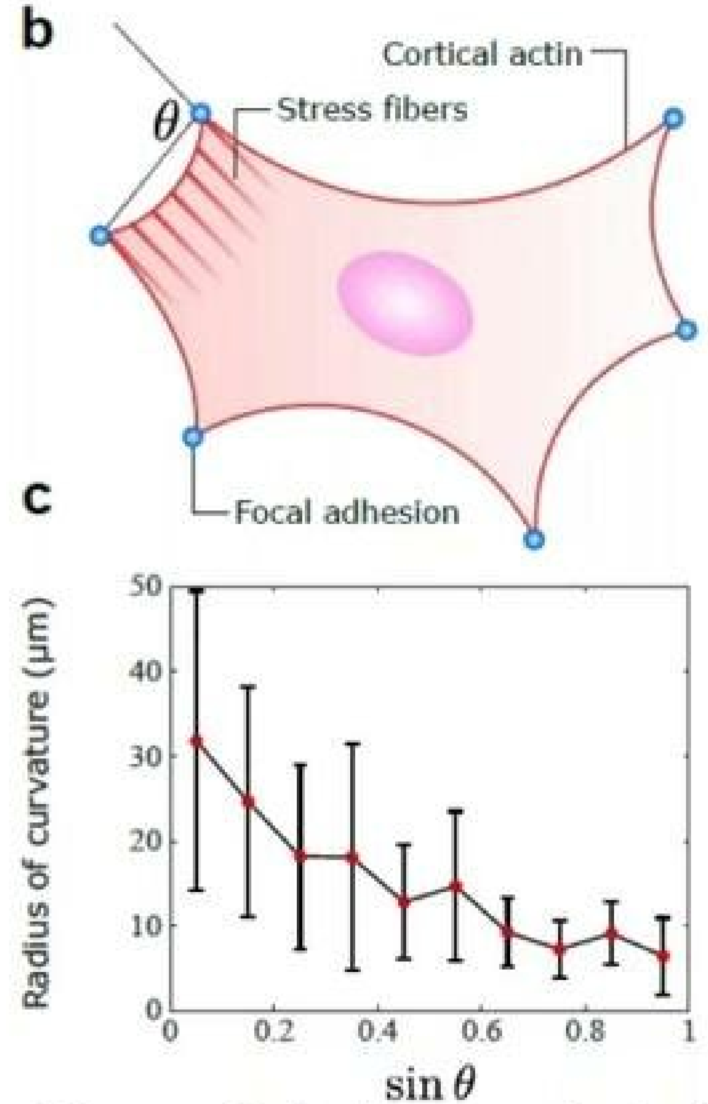
Schakenraad, Martorana, Bakker, Giomi, RM, in revision
bioRxiv, https://doi.org/10.1101/2022.04.18.488715

Anisotropic contraction

- Curvature of cell edge depends on angle θ between stress fibers and lines connecting adhesion points





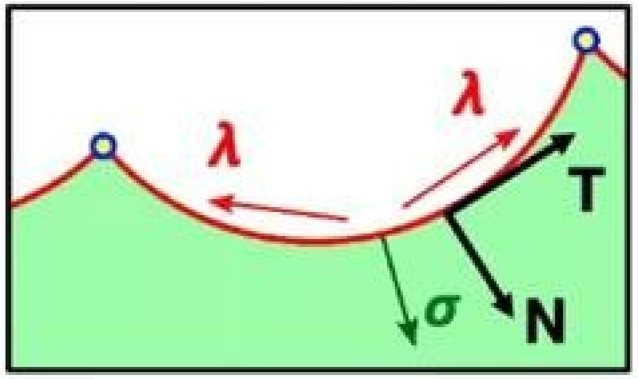


Pomp, Schakenraad et al. Phys Rev Lett 2018

Anisotropic contraction: **elliptic** arcs

Isotropic case

$$\frac{\mathrm{d}\lambda}{\mathrm{d}s}\boldsymbol{T} + (\lambda\kappa + \sigma)\boldsymbol{N} = \boldsymbol{0}$$

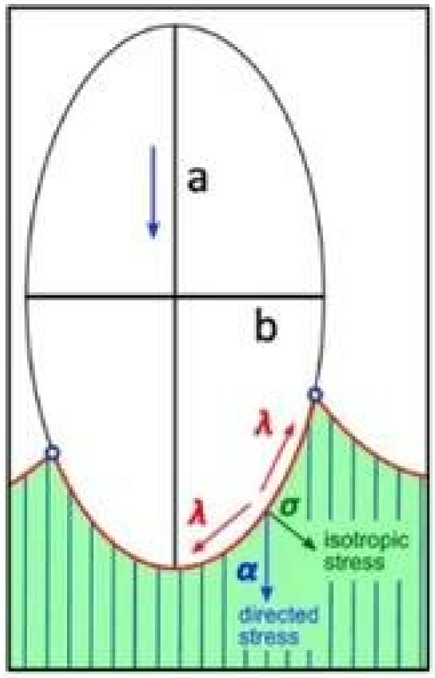


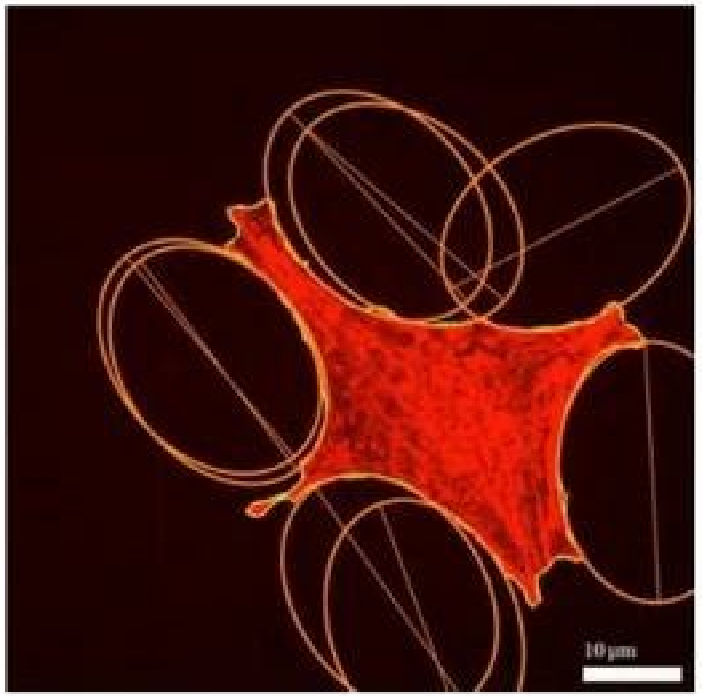
Anisotropic case

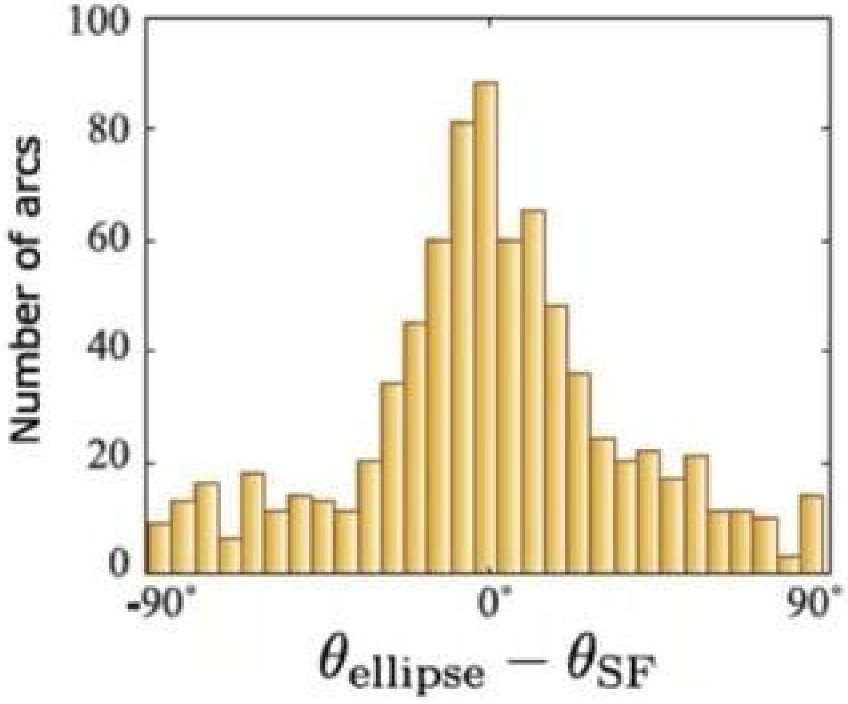
$$\frac{\mathrm{d}\lambda}{\mathrm{d}s}\boldsymbol{T} + (\lambda\kappa + \sigma)\boldsymbol{N} + \alpha(\boldsymbol{n}\cdot\boldsymbol{N})\boldsymbol{n} = \boldsymbol{0}$$

- **Cell shape:** segment of an ellipse.
- **Long axis** aligns with stress fibers
- **Aspect ratio** given by ratio between isotropic (σ) and directed (α) forces

$$\frac{b^2}{a^2} = \frac{\sigma}{\sigma + \alpha}$$







Pomp, Schakenraad et al. Phys Rev Lett 2018

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Schakenraad… **Giomi**. Soft Matter, 16(27), 6328–6343.
http://doi.org/10.1039/d0sm00492h

Anisotropic cell forces in the CPM

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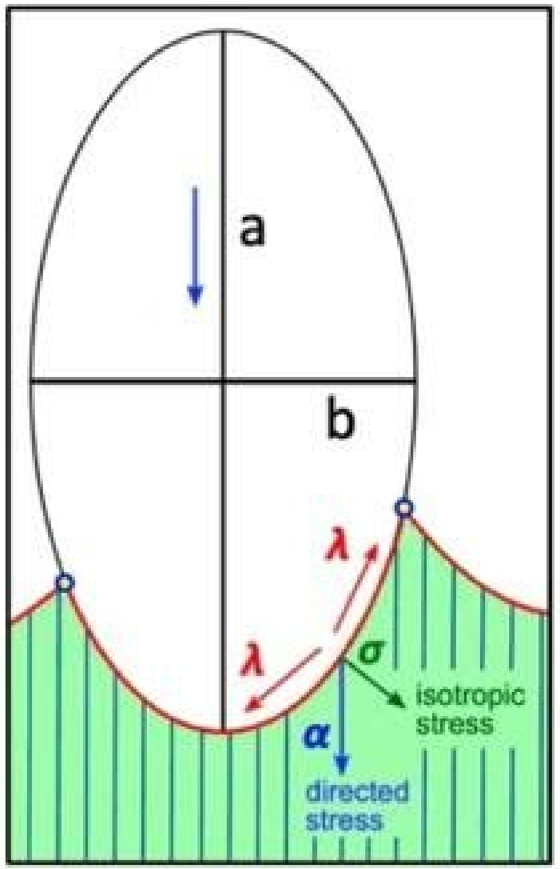
$$\vec{f} = \frac{d\lambda}{ds}\,\mathrm{T} + (\lambda\kappa + \sigma)\vec{N} + \alpha S(\vec{n}\cdot\vec{N})\vec{n}$$

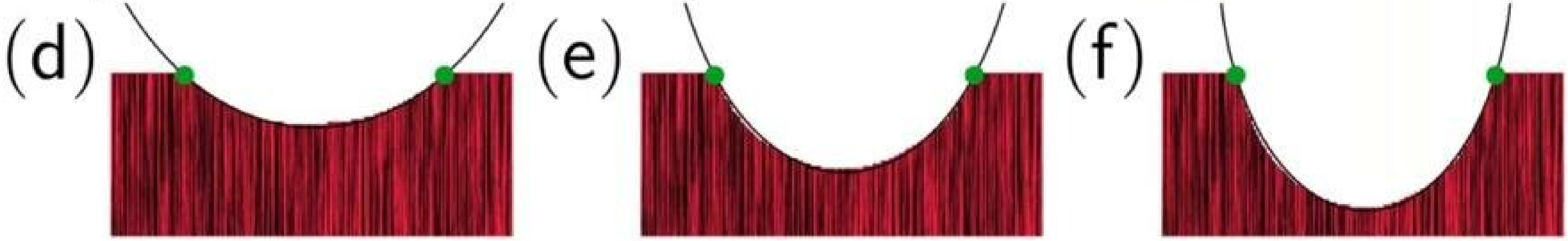
$$\Delta H = \lambda\Delta P + \sigma\Delta A + \Delta H_{\mathrm{work}}$$

$$\Rightarrow \Delta H_{\mathrm{work}} = \alpha S(\vec{n}\cdot\vec{N})^2\Delta \mathrm{A}$$

Additional force along actin fiber orientation



CPM predictions for isotropic cells:



Semi-major axis			
Theory:	120 l.u.	120 l.u	100 l.u
Simulation:	134 l.u	118 l.u.	98 l.u.

Schakenraad, Martorana, Bakker, Giomi, RM, in revision
bioRxiv, https://doi.org/10.1101/2022.04.18.488715

Anisotropic cell forces in the CPM

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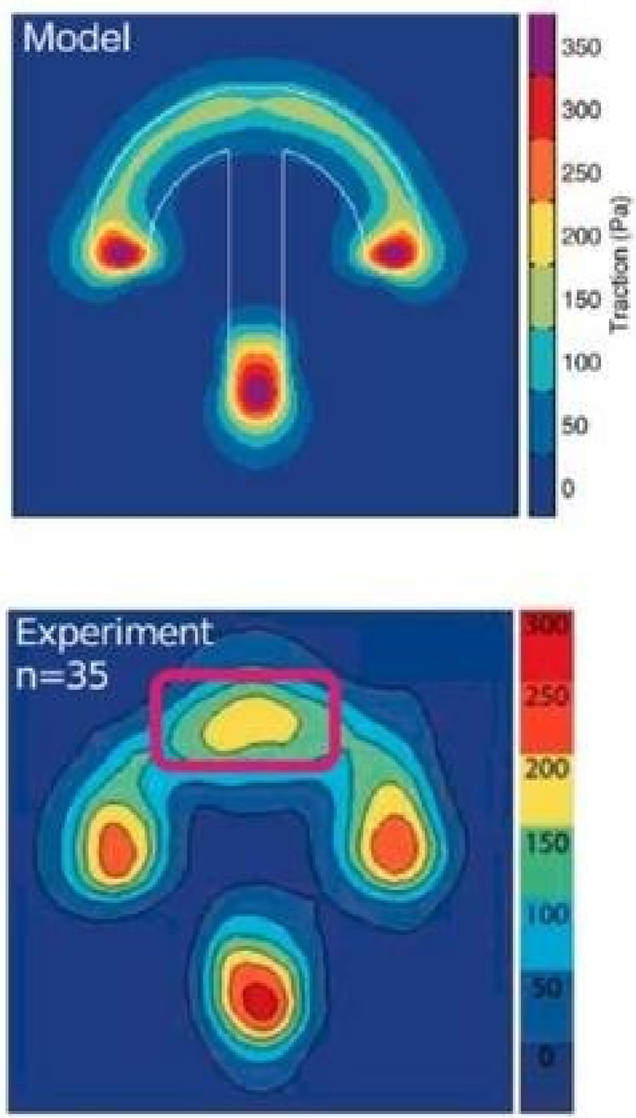
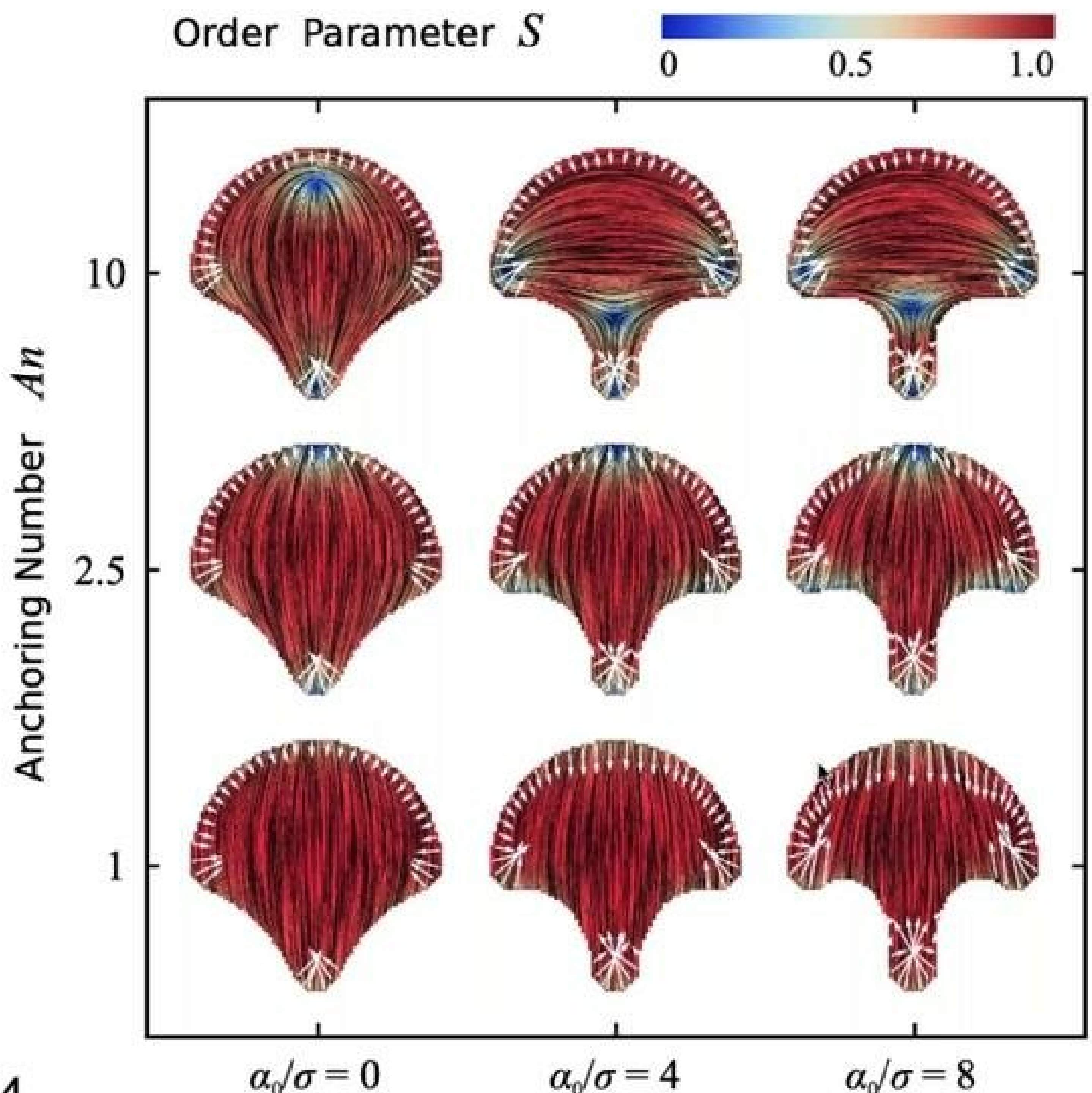


Albert and Schwarz, Biophys J 2014



Schakenraad, Martorana, Bakker, Giomi, RM, in revision
bioRxiv, https://doi.org/10.1101/2022.04.18.488715

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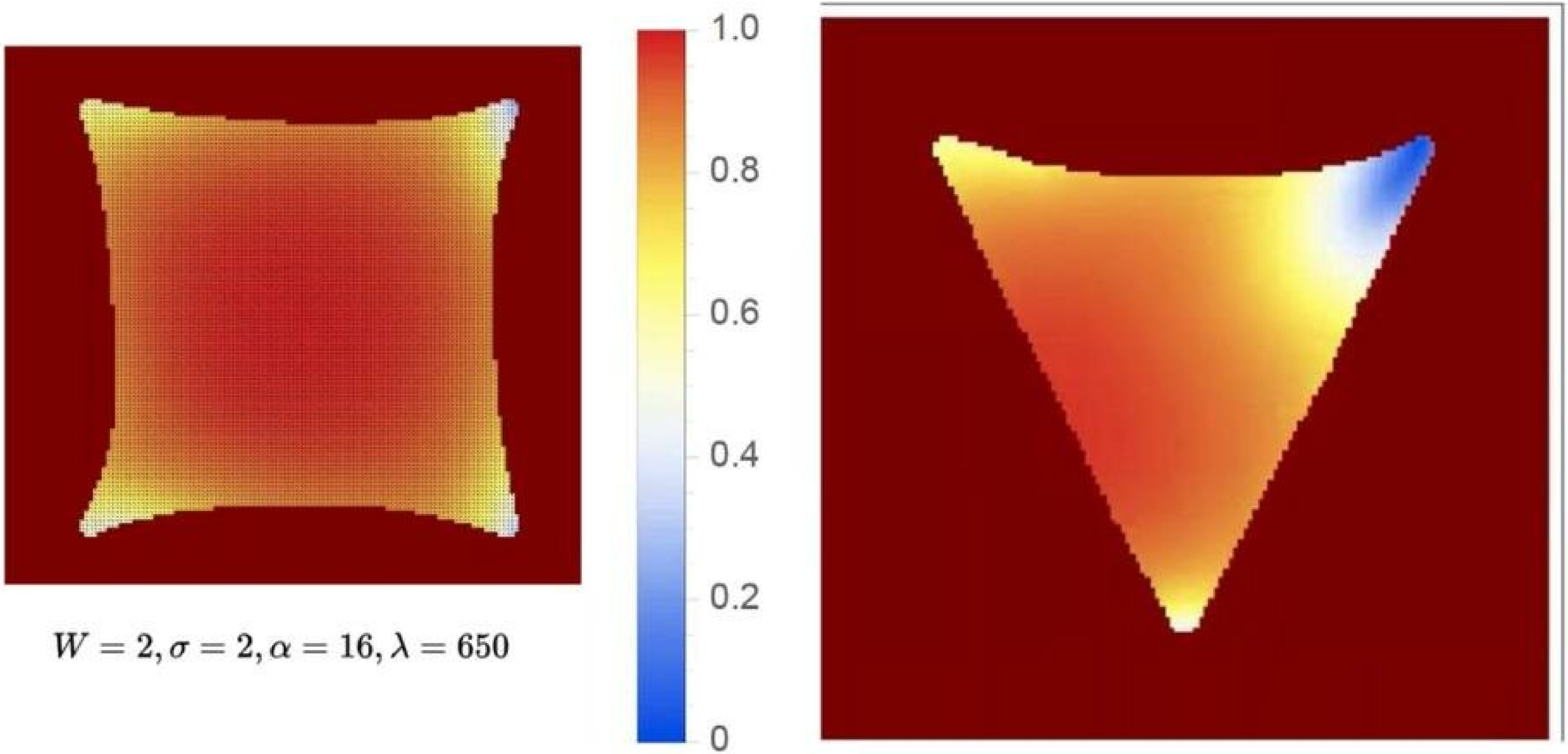
Cell and cytoskeleton cross-talk



$W = 2, \sigma = 2, \alpha = 16, \lambda = 650$

nematic order parameter (S)

Spreading on V-like shape

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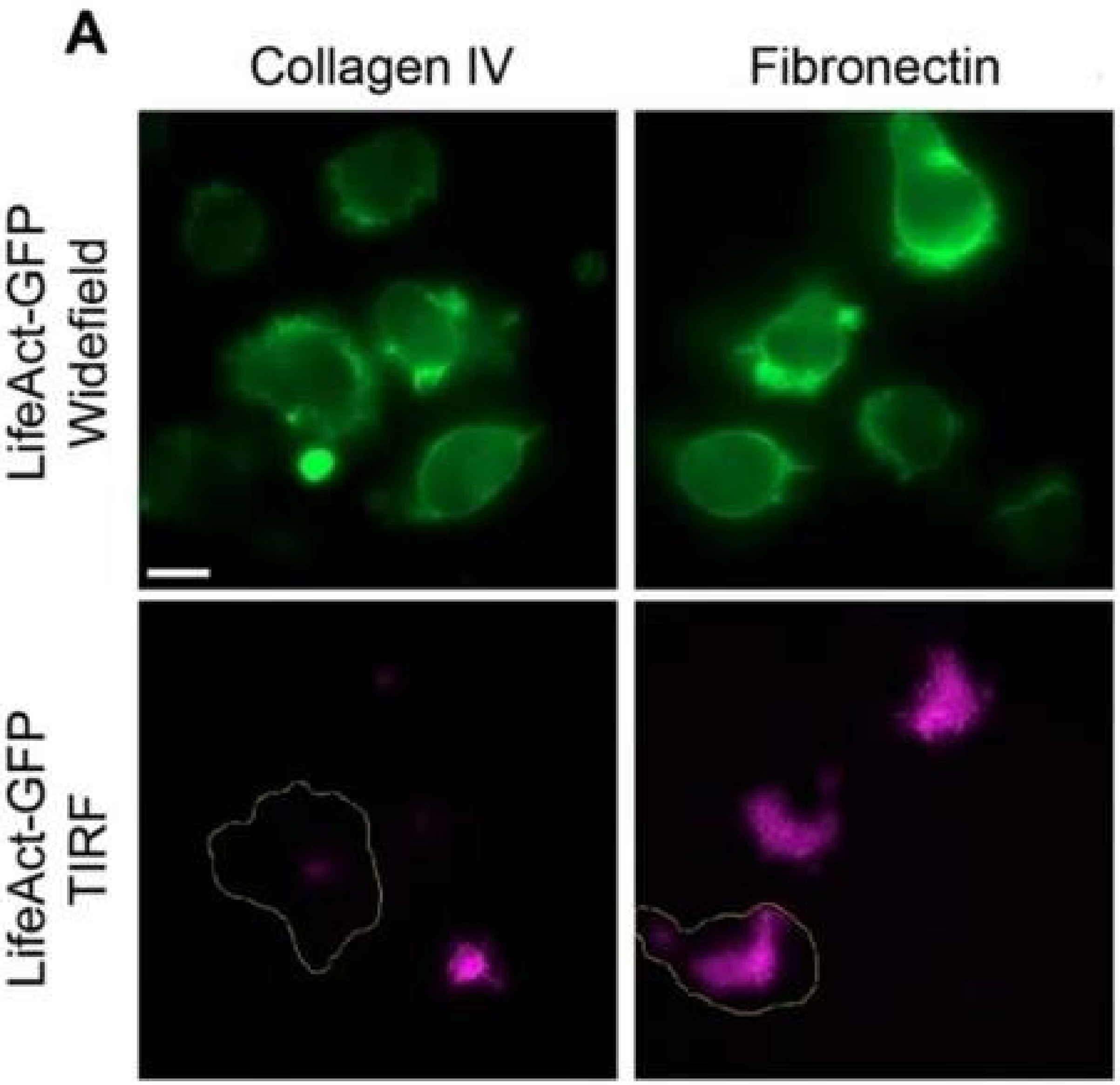
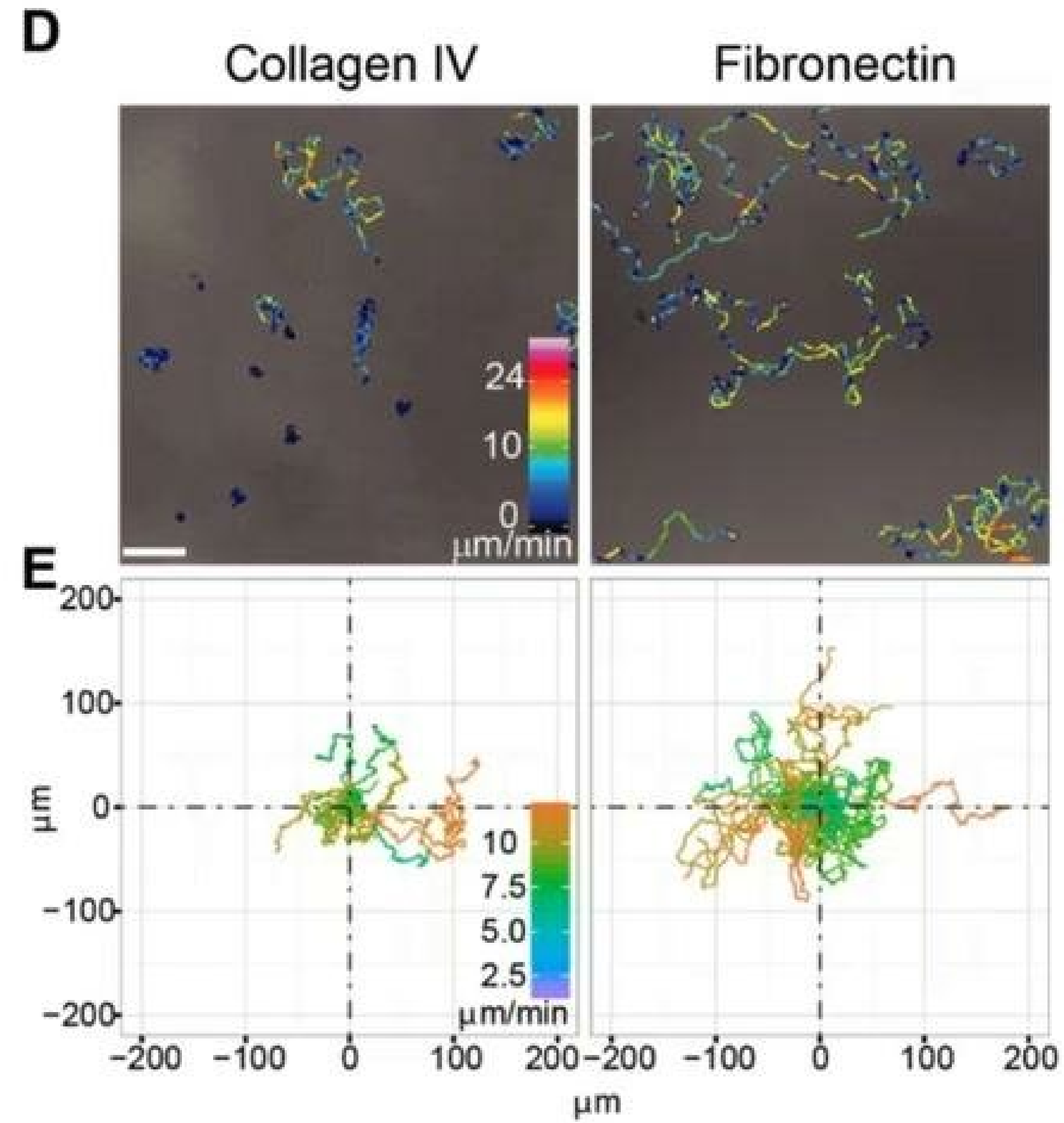
ECM affects B-cell migration





B lymphocytes
(human JY cell line)

Rey-Barroso et al. *Sci Rep* 2018

Simplified model:
Cell-substrate reciprocity partly explains stiffness-dependent cell-cell interactions

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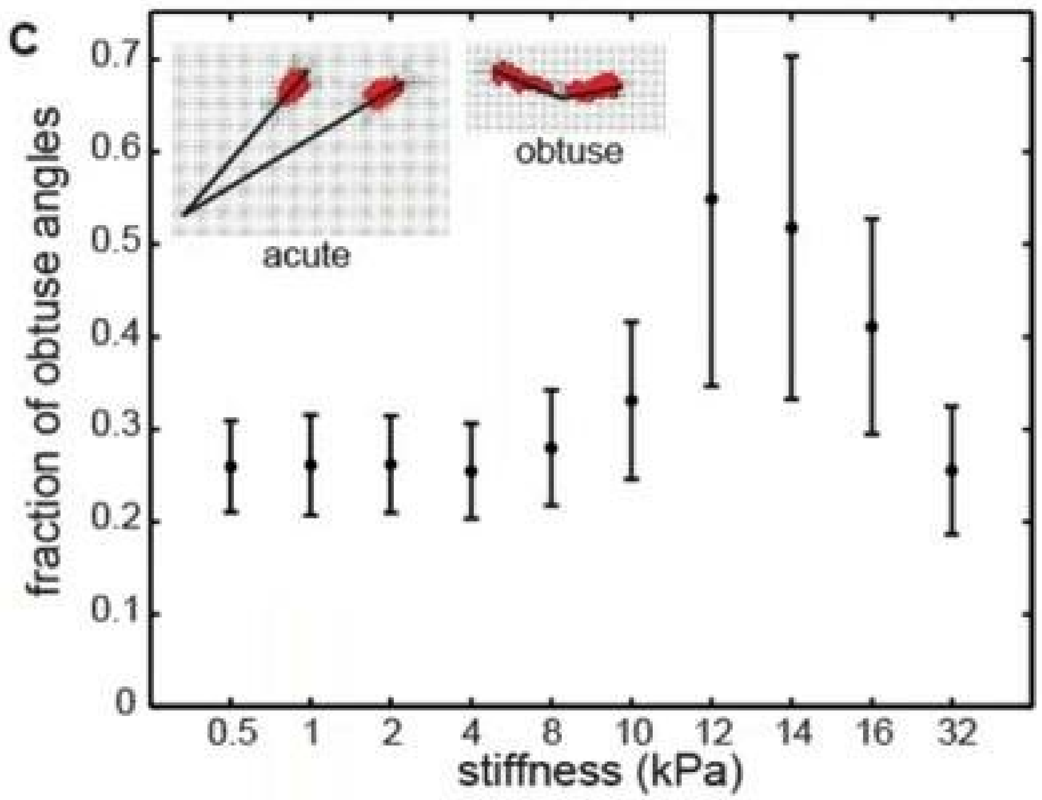
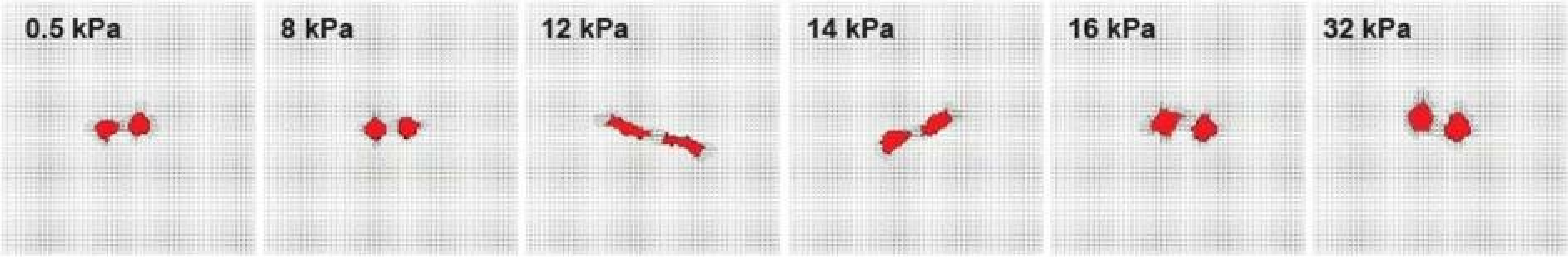
Video S2 - cell pairs

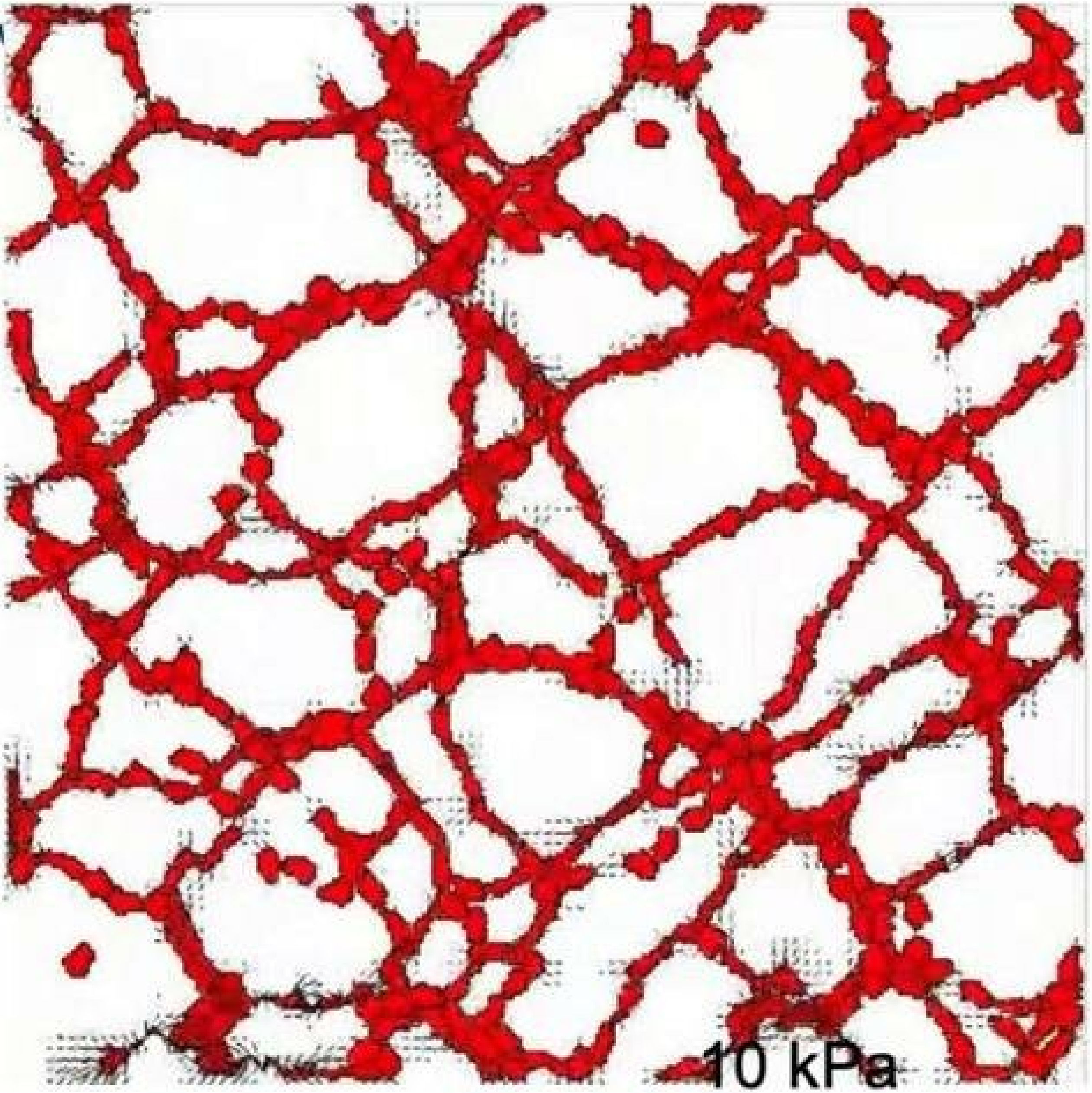
Van Oers, Rens, LaValley, Reinhart-King, and Merks
PLoS Comp Biol 2014

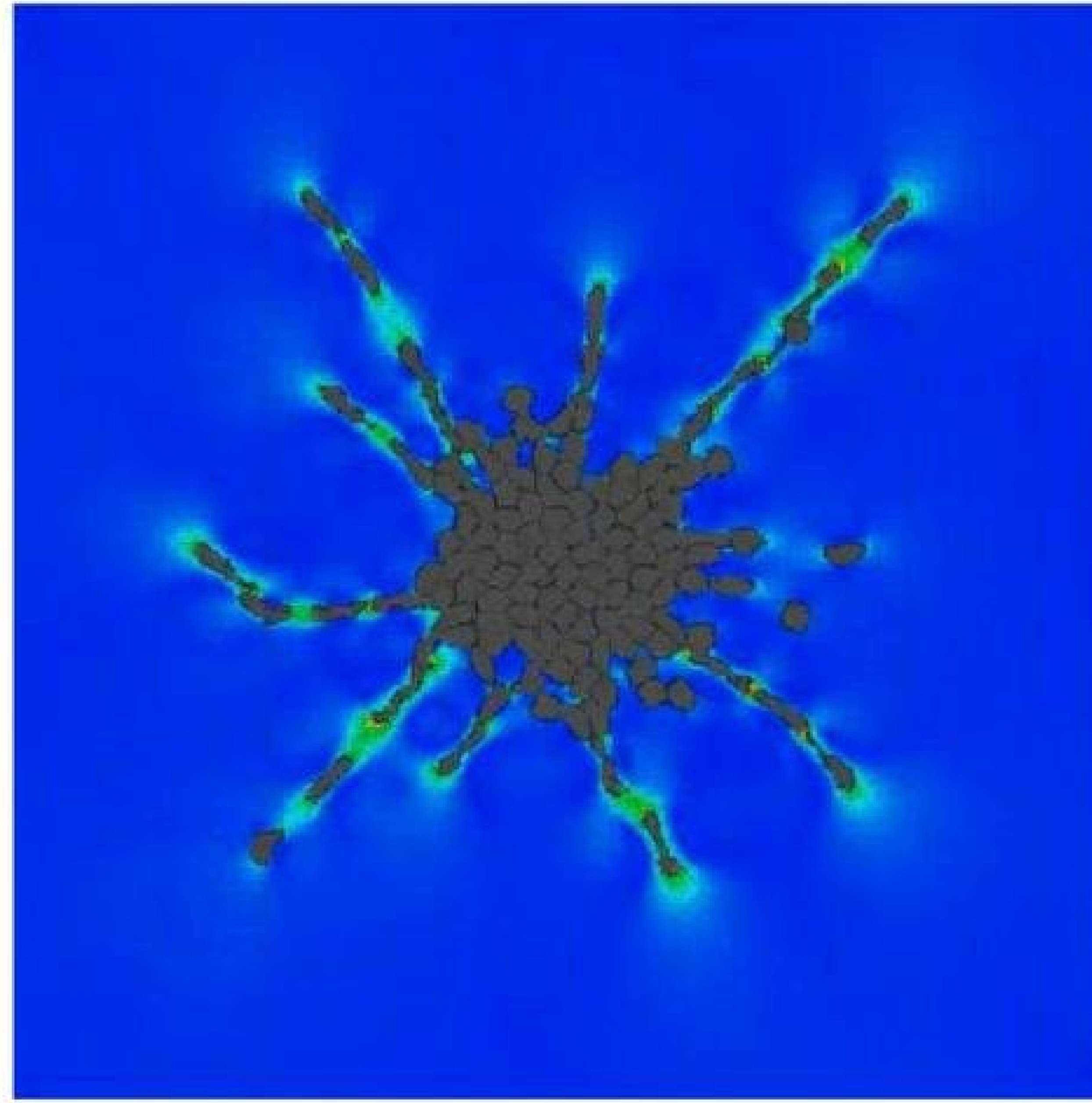


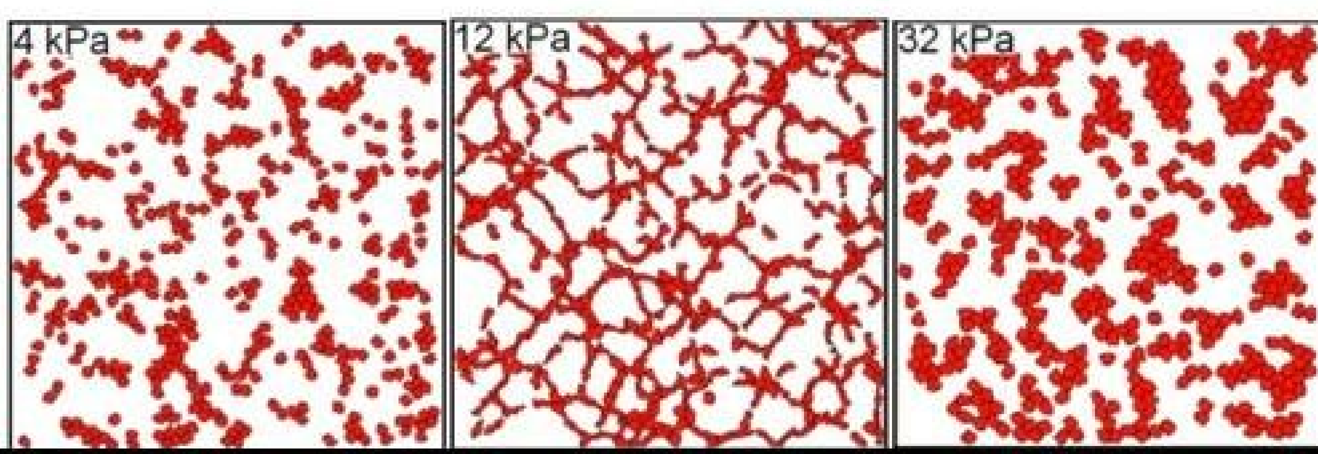


Collective cell behavior

Univ







Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

... but only if cells exert forces on matrix

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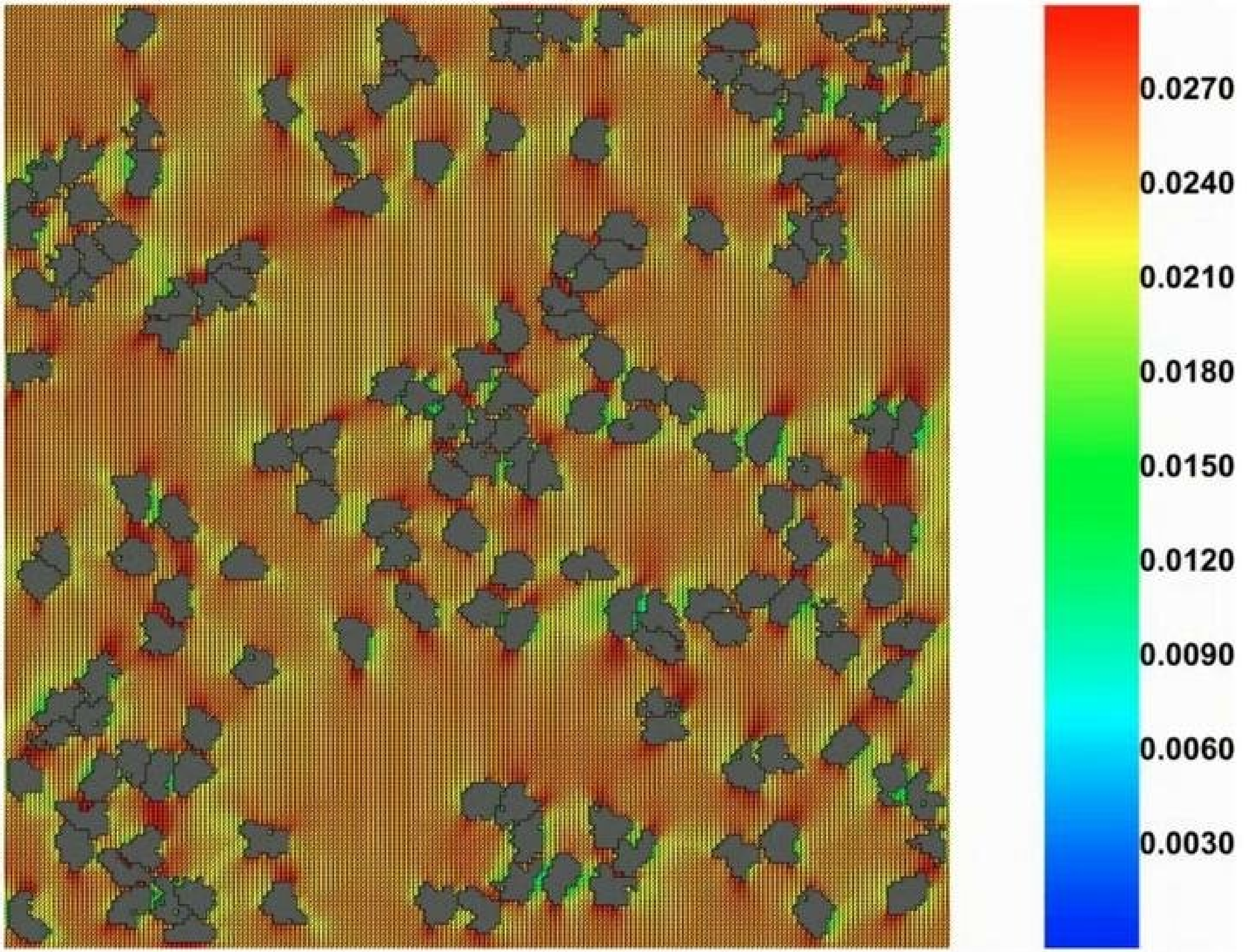

Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

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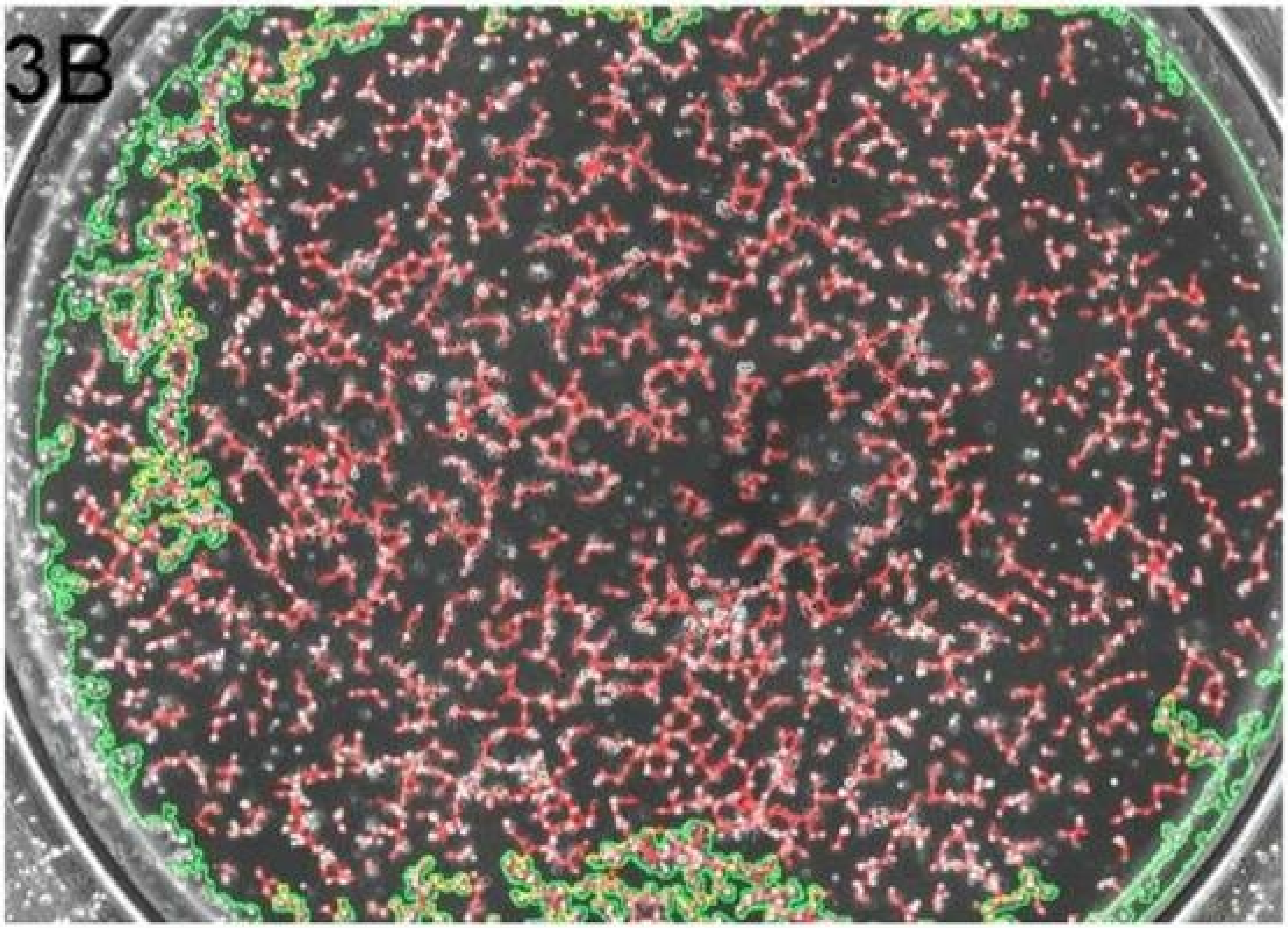
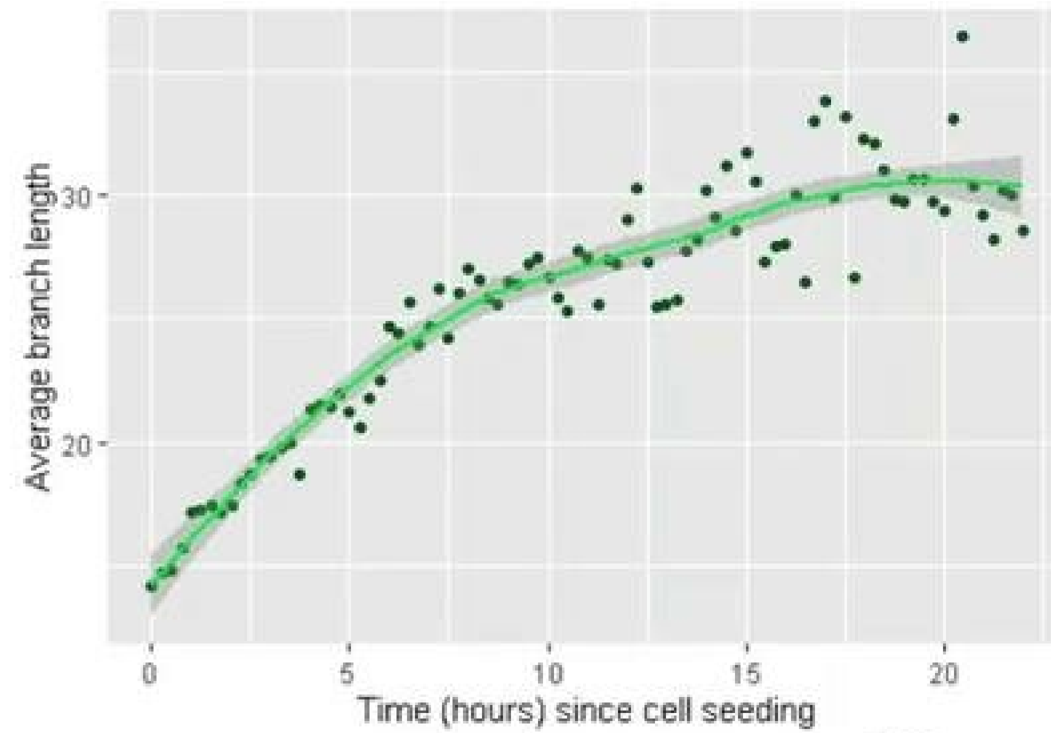
Automated image analysis

Tessa Vergroesen





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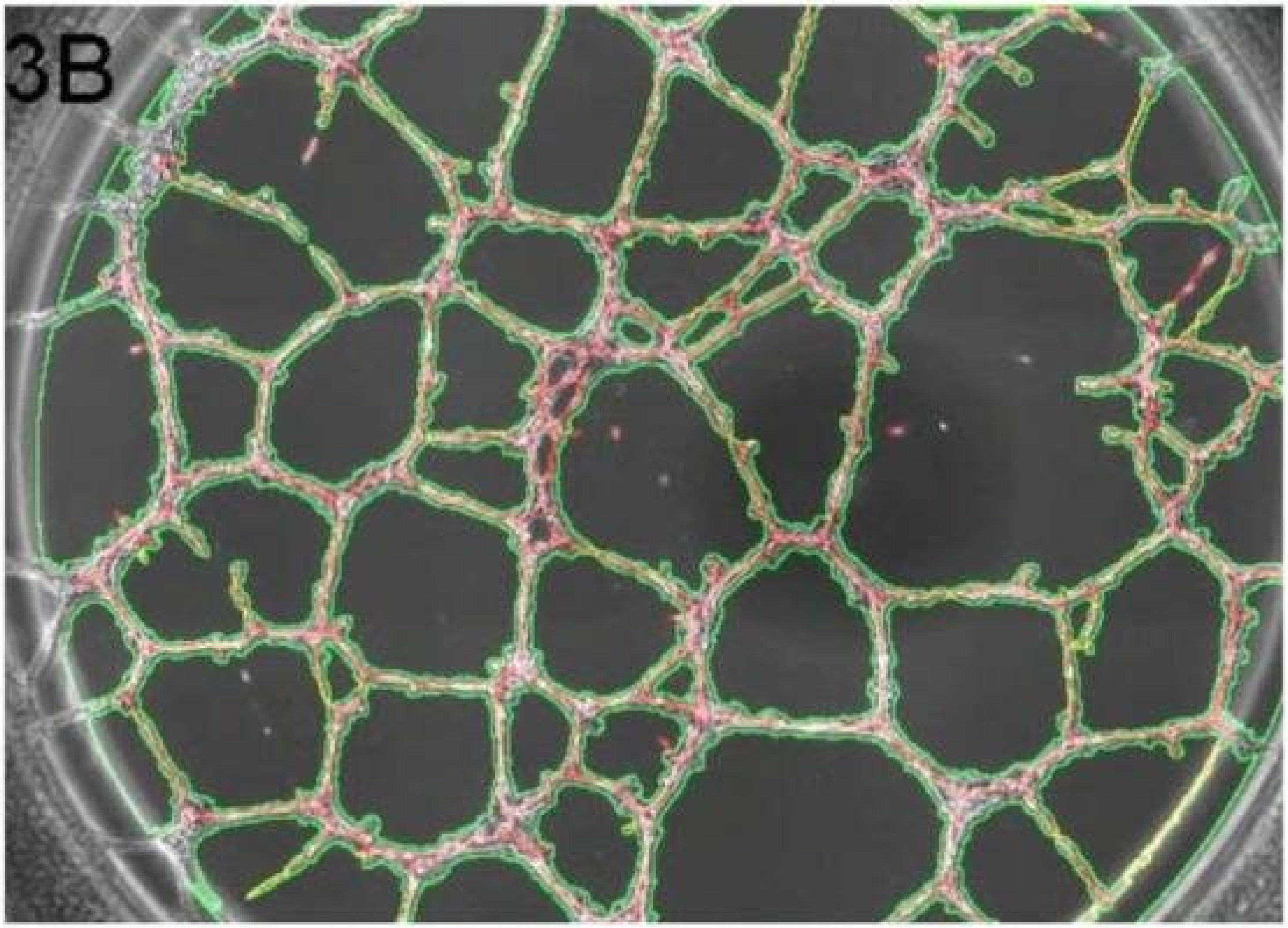
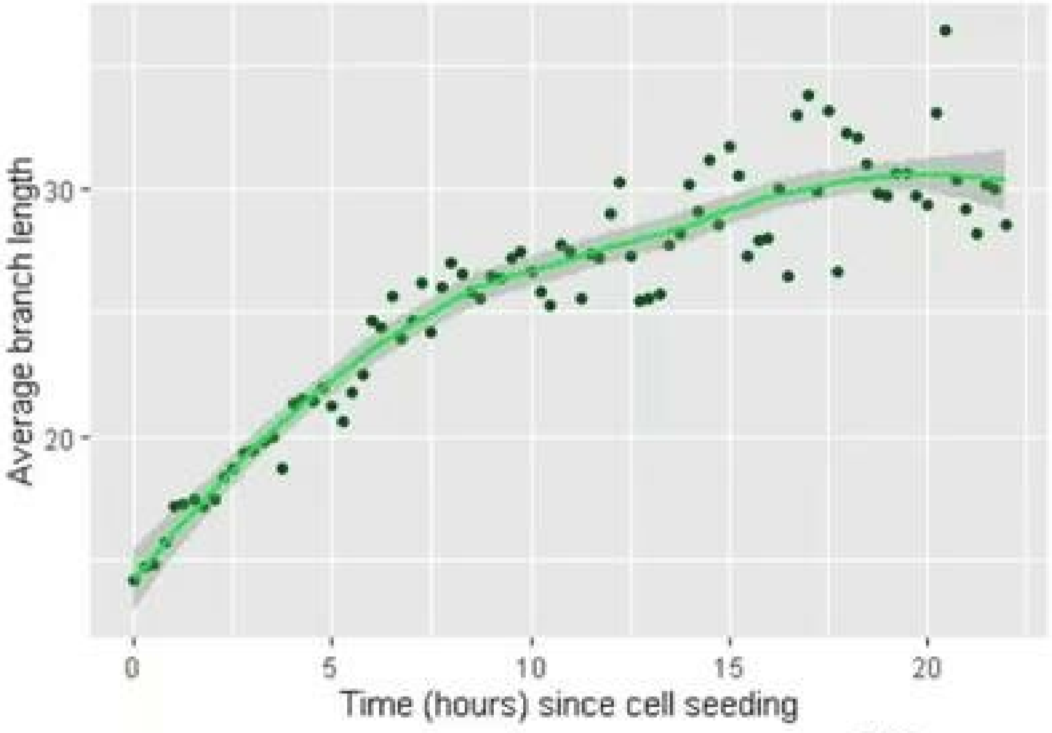
Automated image analysis

Tessa Vergroesen





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Acknowledgments

Not on the picture:
- *Enrico Sandro Colizzi*
- *Koen Schakenraad*

Collaborators:

Leiden University:
- *Luca Giomi*
- *Eric Danen*

Cornell University:
- *Danielle LaValley*
- *Cynthia Reinhart-King*

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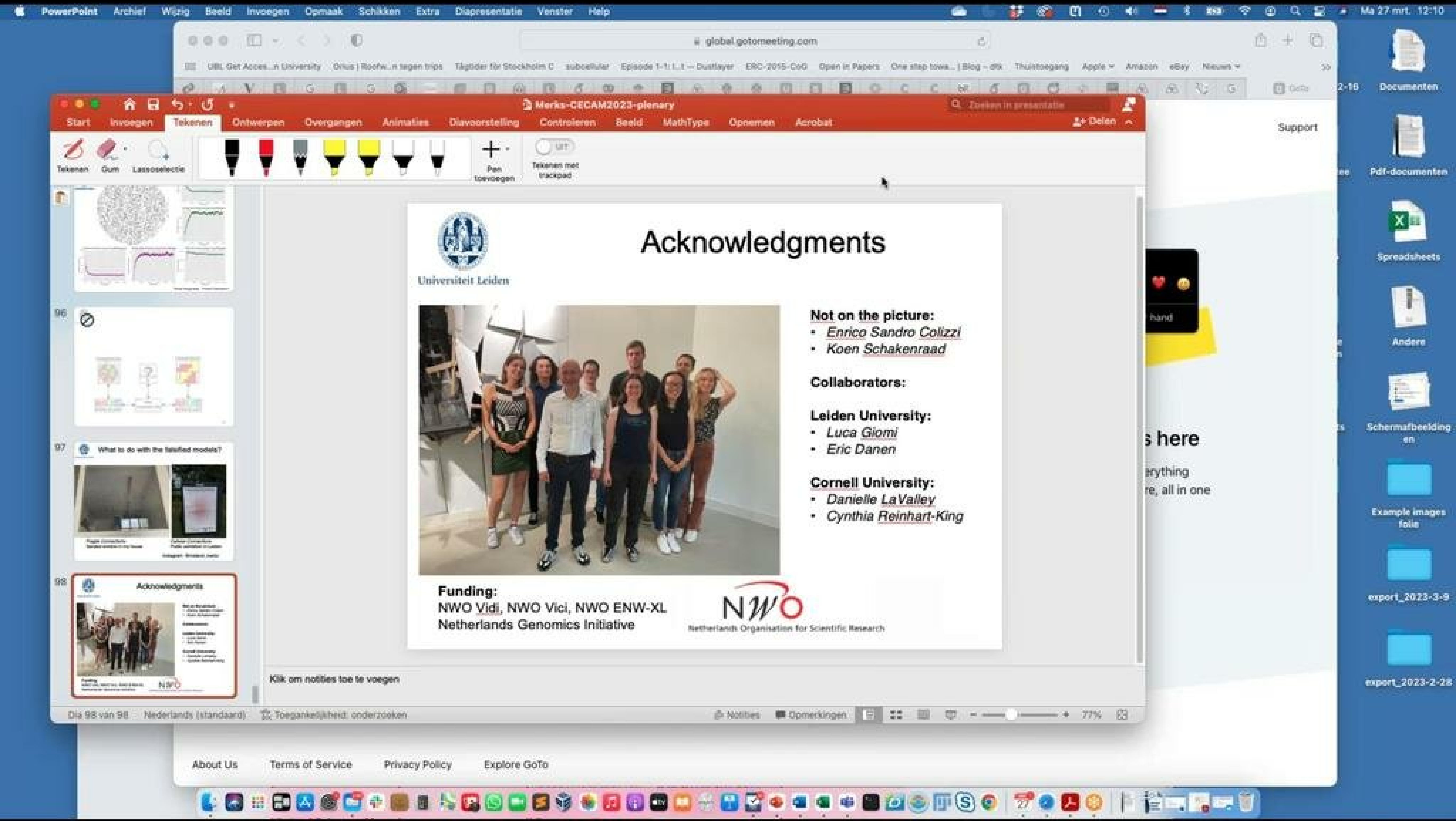
Netherlands Genomics Initiative

NWO
Netherlands Organisation for Scientific Research


Merks-CECAM2023-plenary
Acknowledgments
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Funding:
NWO Vidi, NWO Vici, NWO ENW-XL
Netherlands Genomics Initiative
NWO
Netherlands Organisation for Scientific Research
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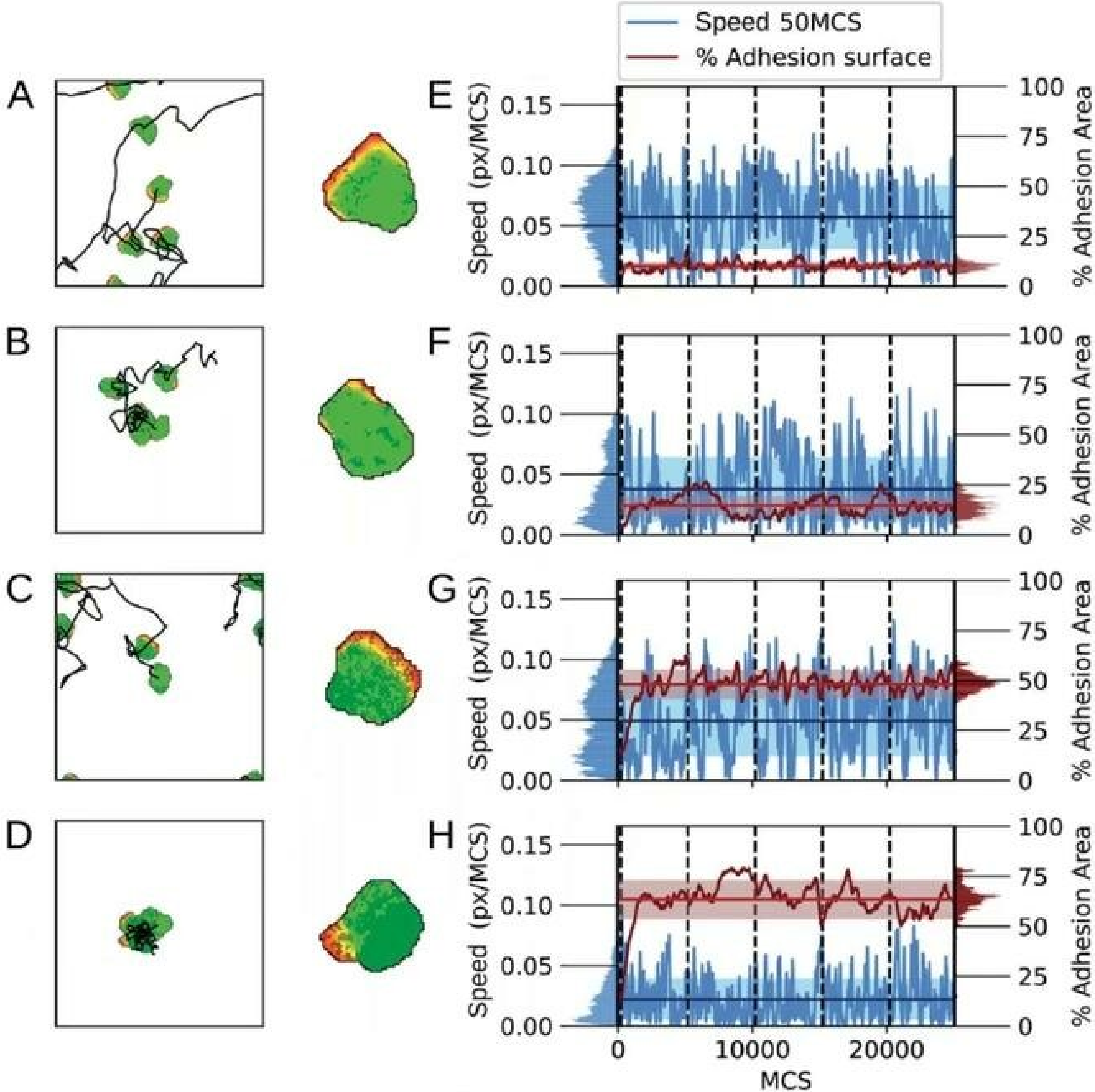

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Van Steijn et al., *PLOS Computational Biology*, 2022

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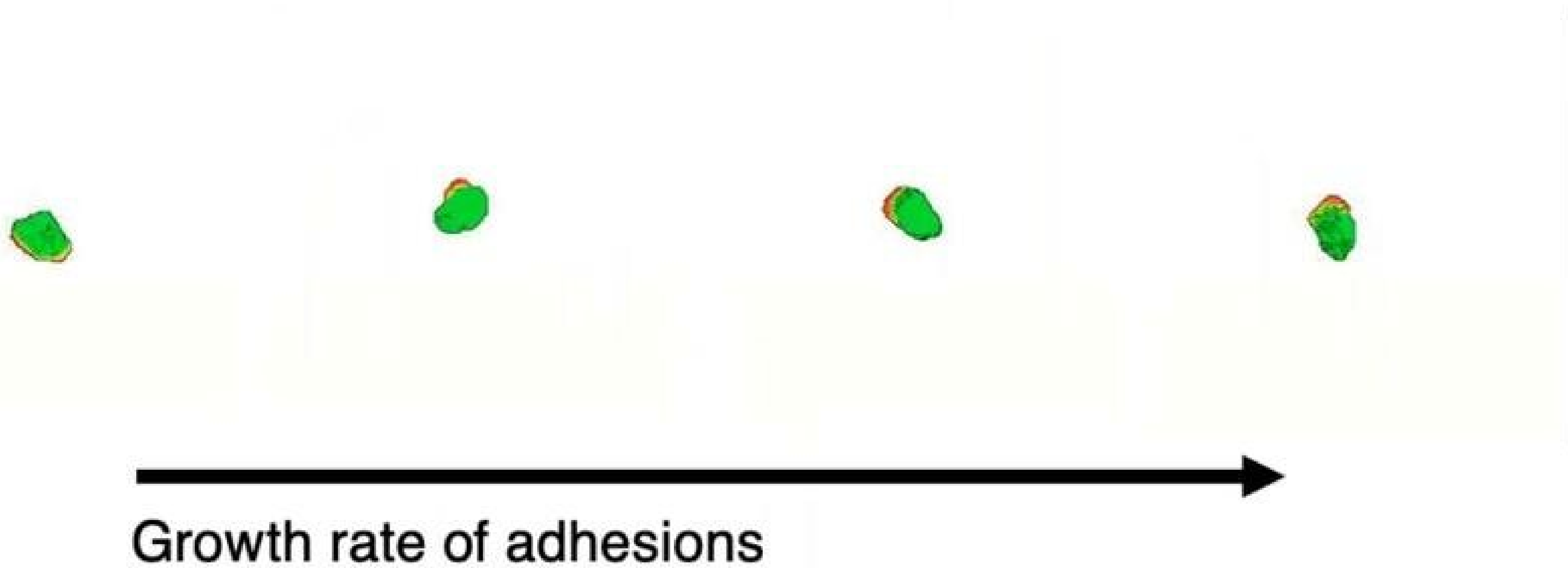

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How do such differences arise?
Hypothesis: **cell-substrate adhesion**

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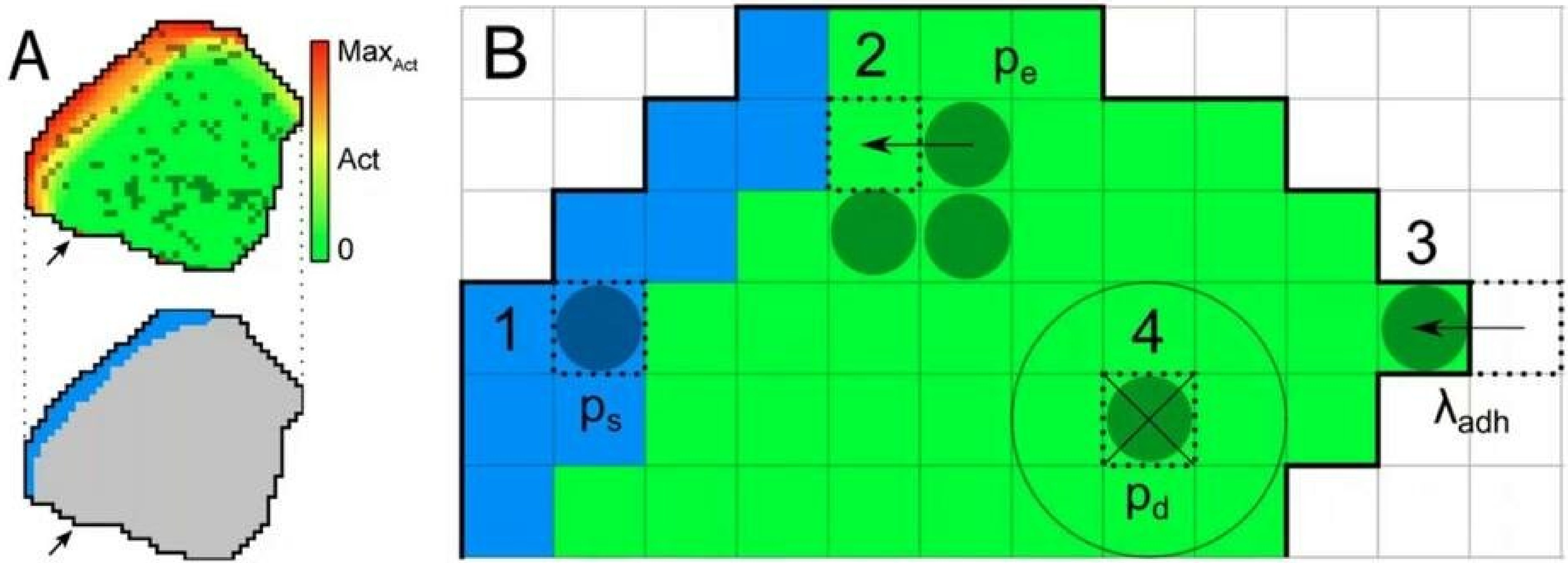

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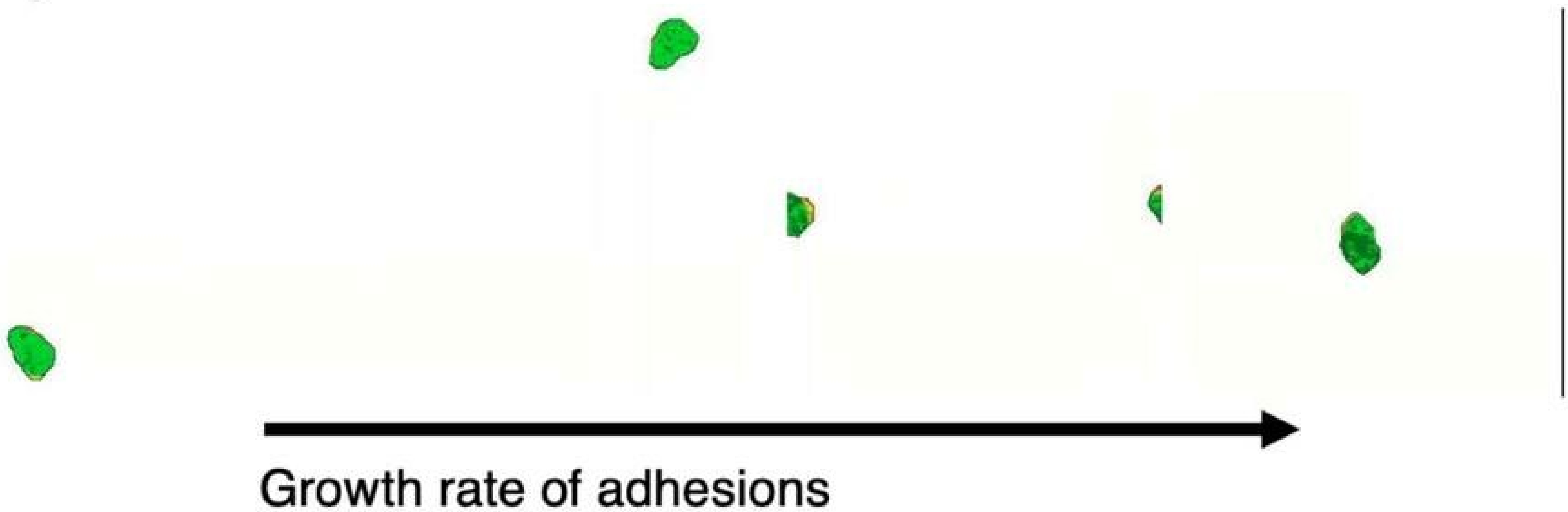

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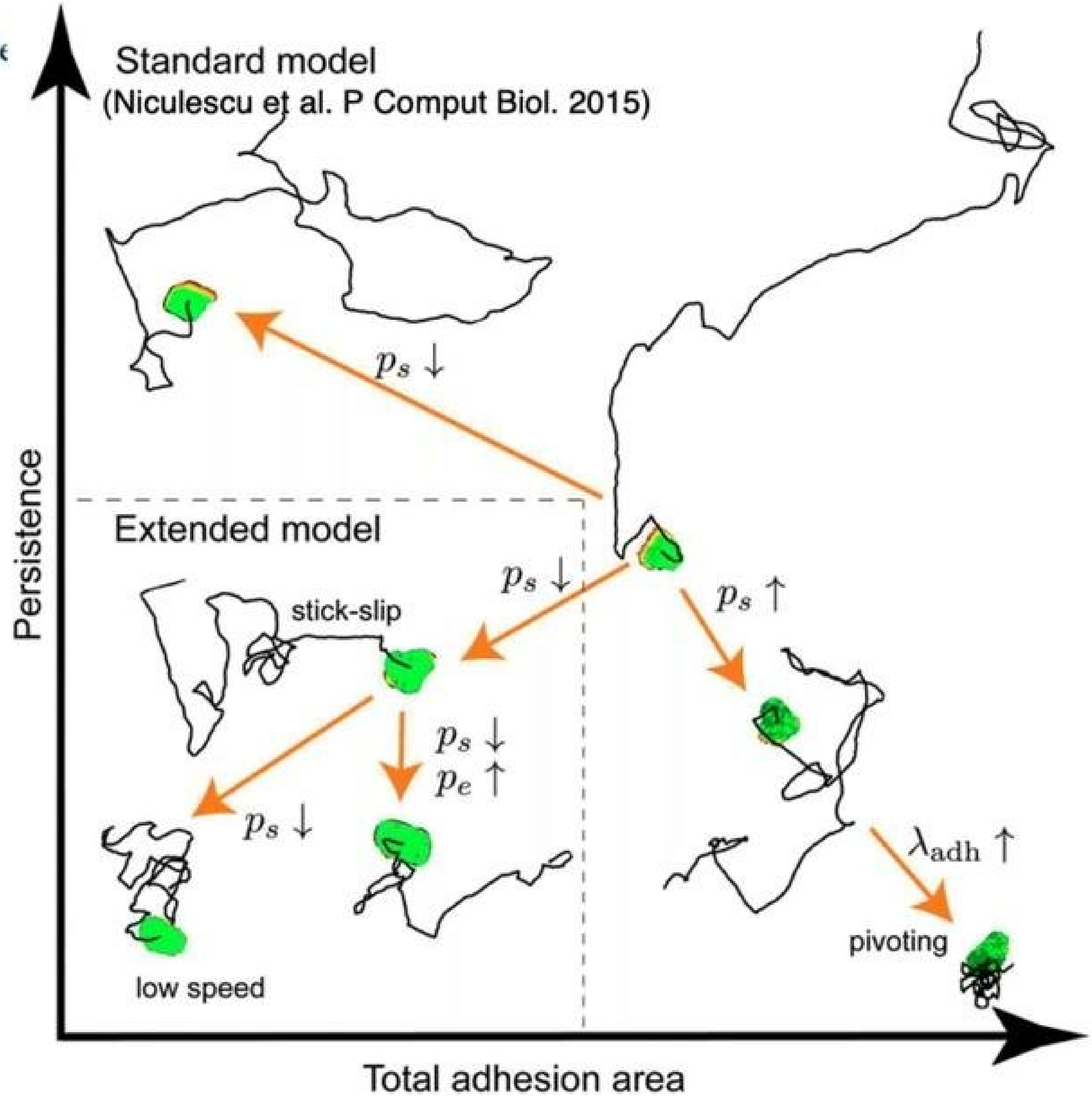

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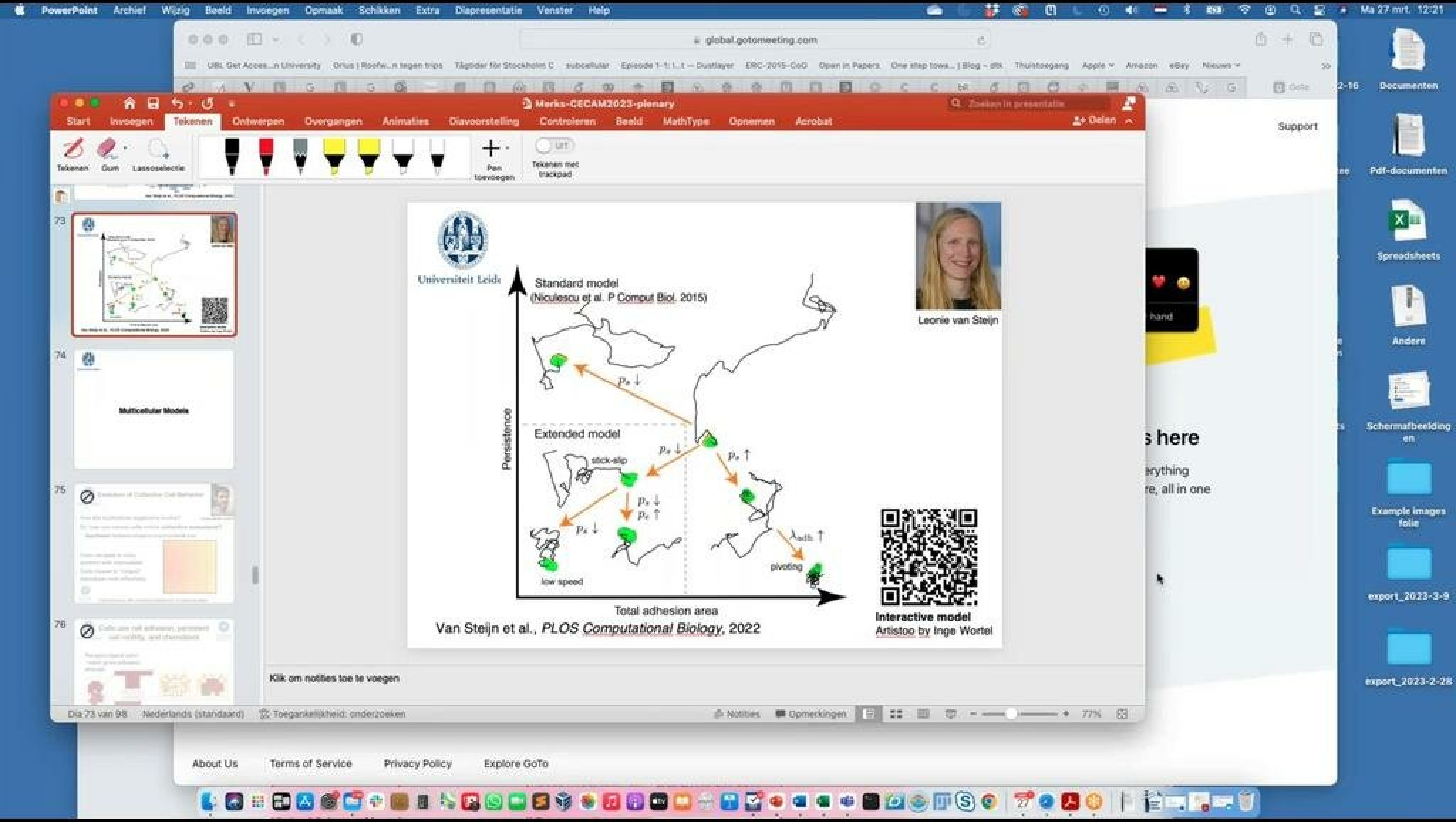
Interactive model
Artistoo by Inge Wortel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Standard model
(Niculescu et al. P Comput Biol. 2015)
Extended model
stick-slip
low speed
pivoting
Persistence
Total adhesion area
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Interactive model
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Multicellular Models

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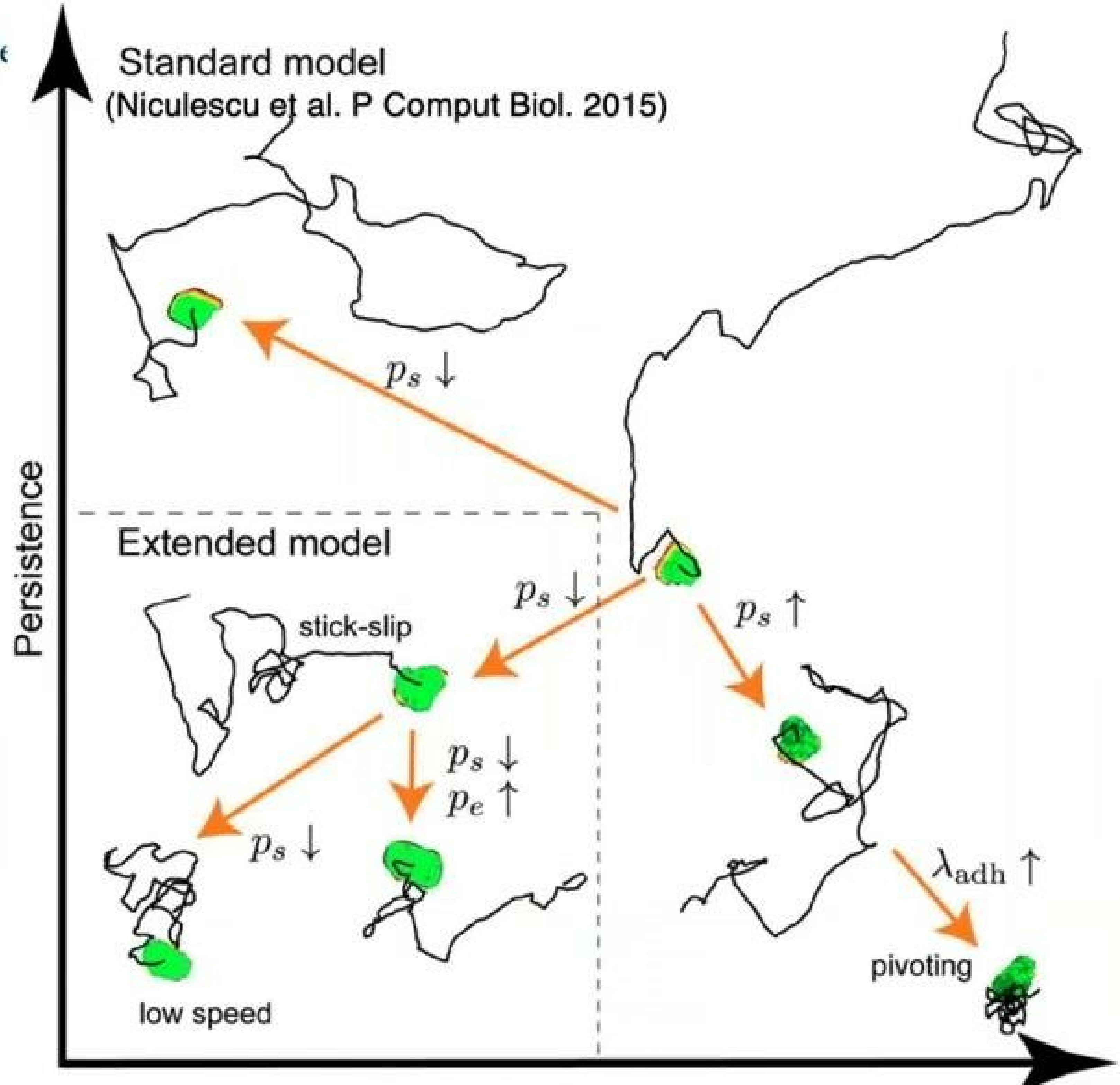

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Interactive model
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