Structure formation in cytoskeletal systems and organoids

Or how we manage to end up with ducts, alveoli and acini

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Forces in Biomolecular Systems SFB 863
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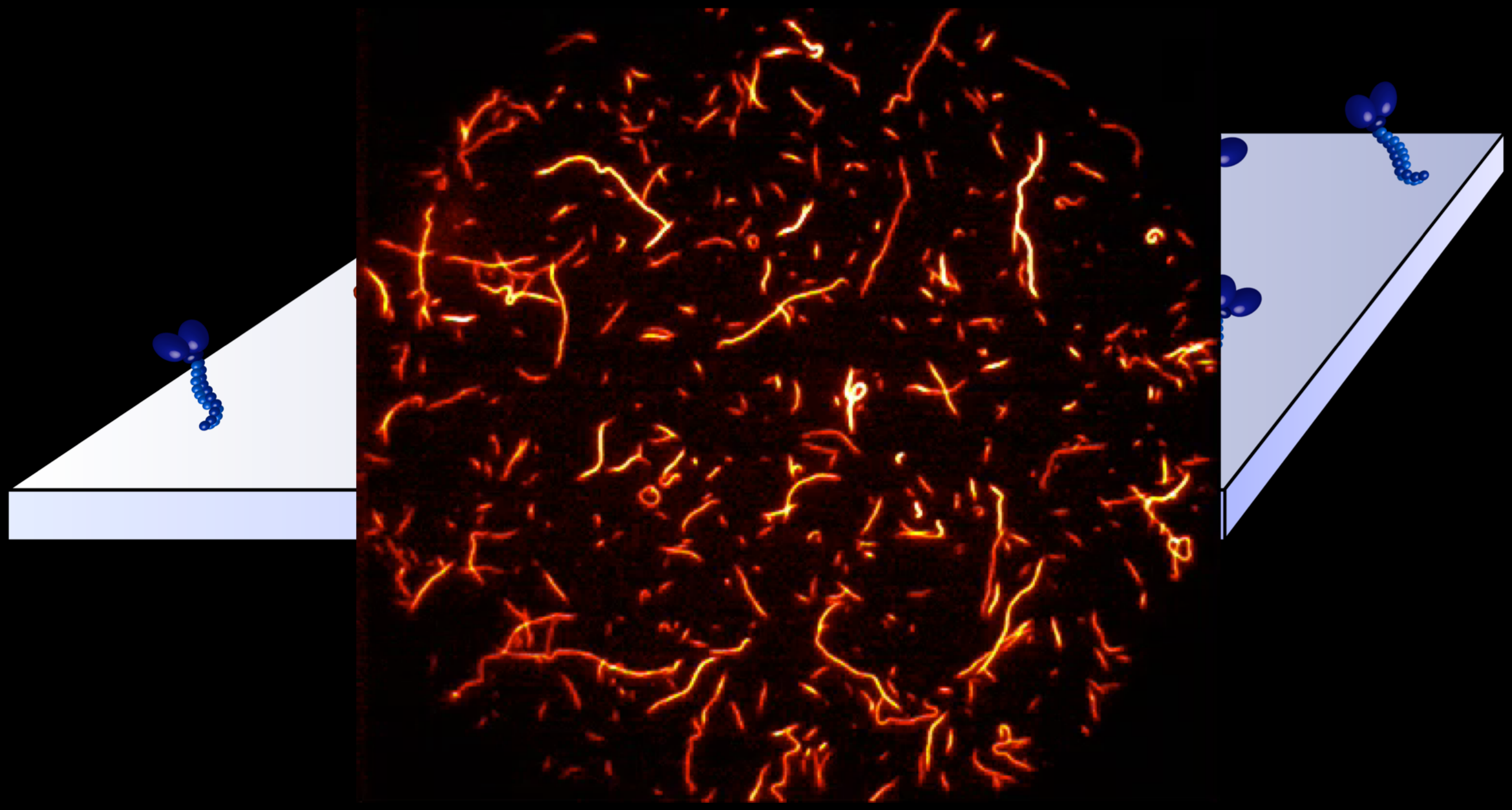
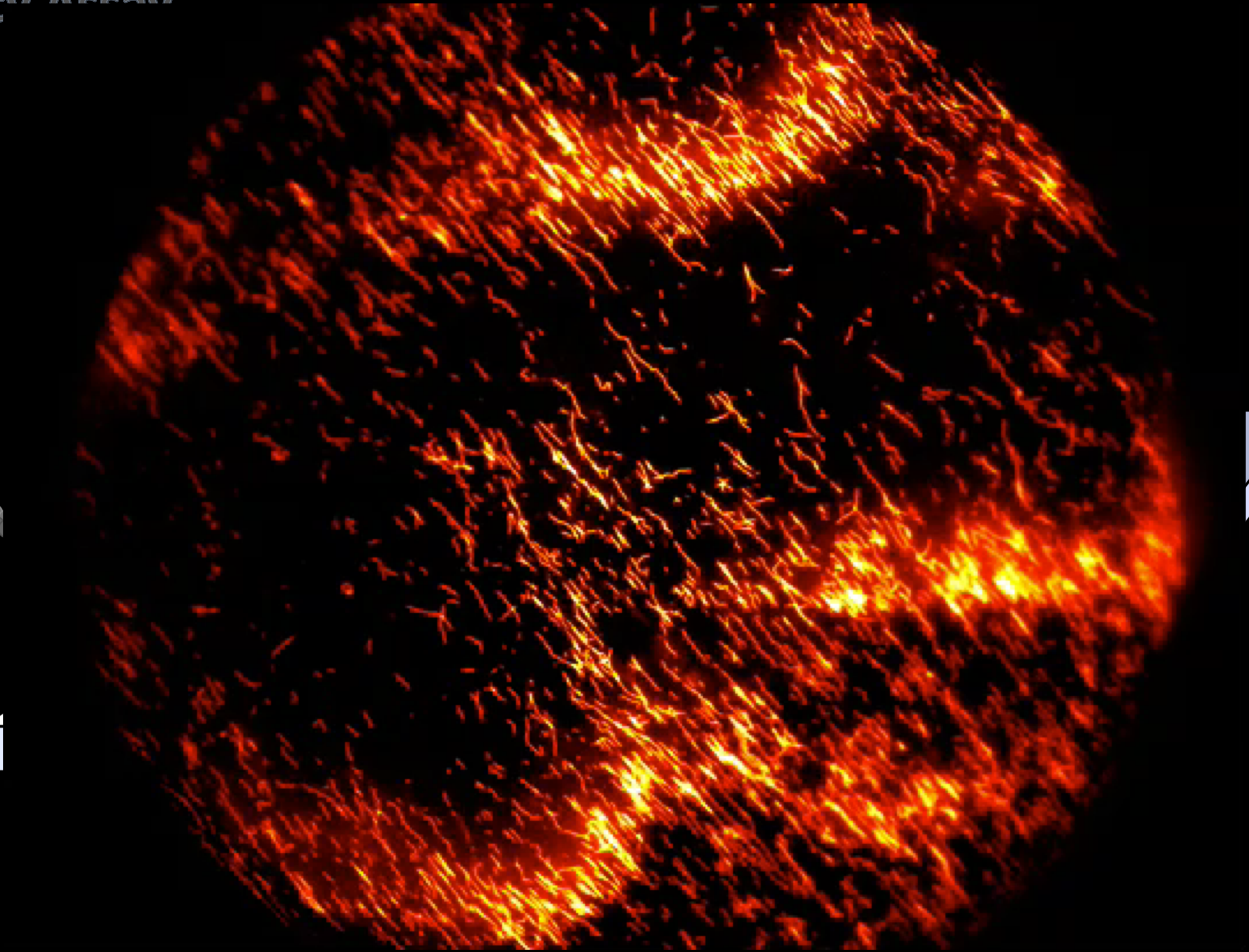
erc
SFB1032 nano agents
Technische Universität München TUM

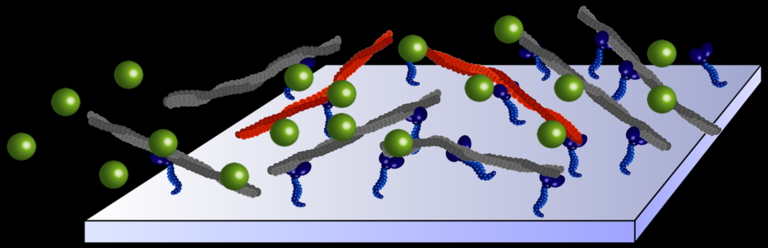
Motility Assay

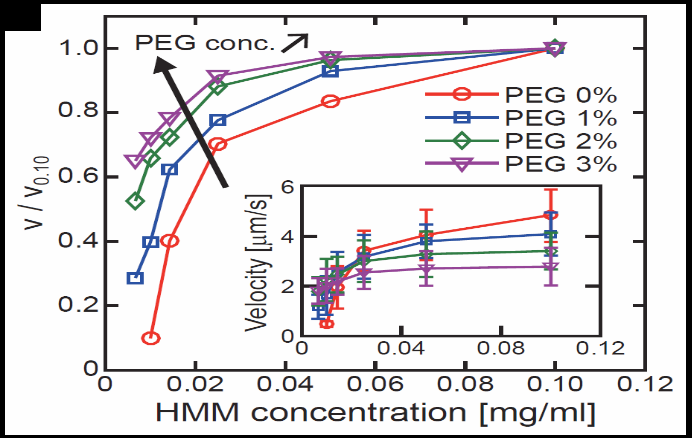


Motility Assay



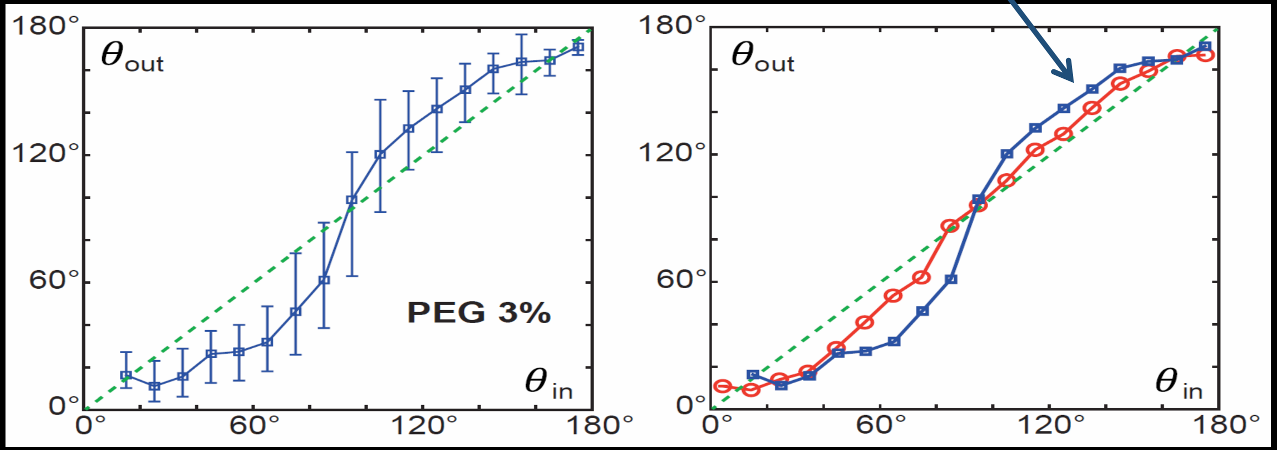
Tuning the processivity of the motors

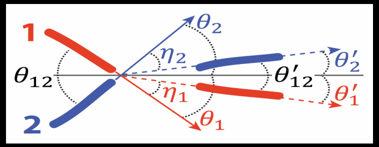




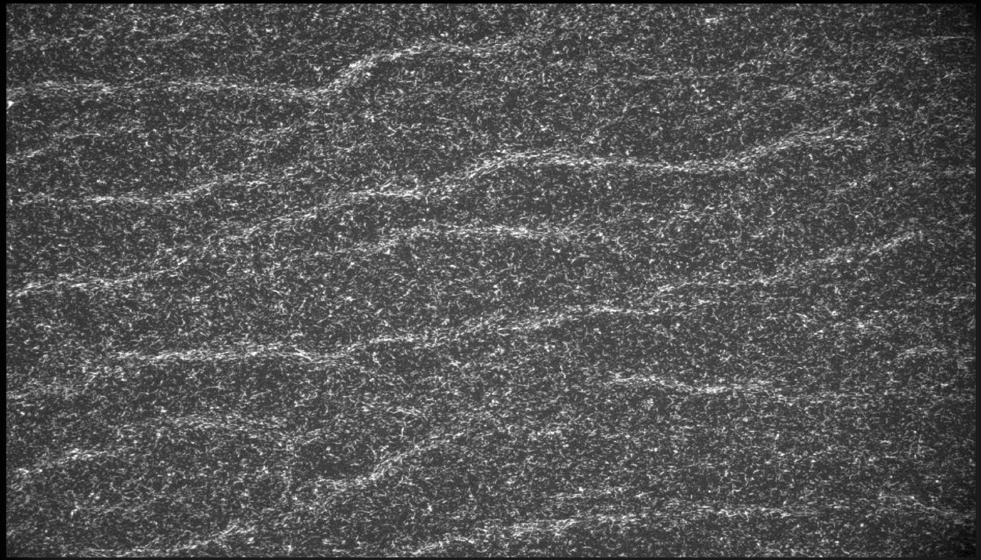
Collision rule between filaments:

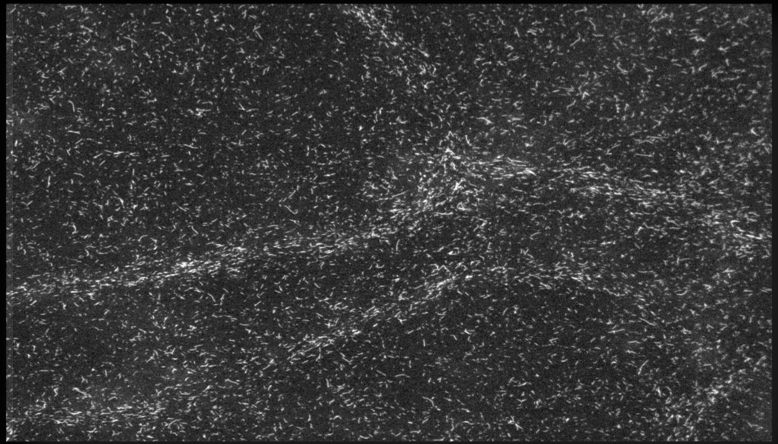
+ PEG





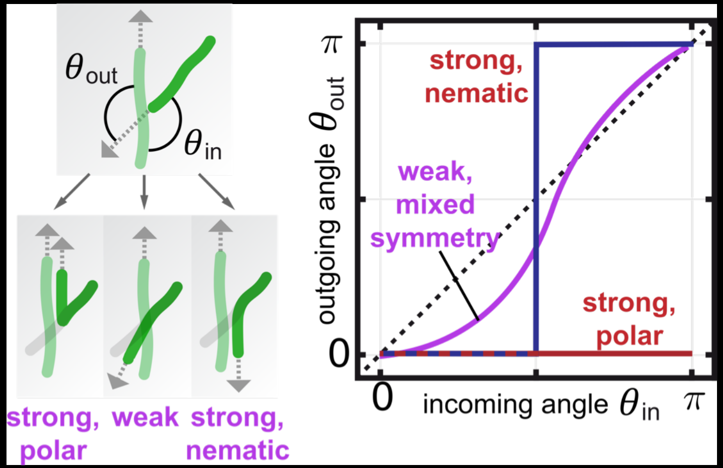
Tuning the processivity of the motors

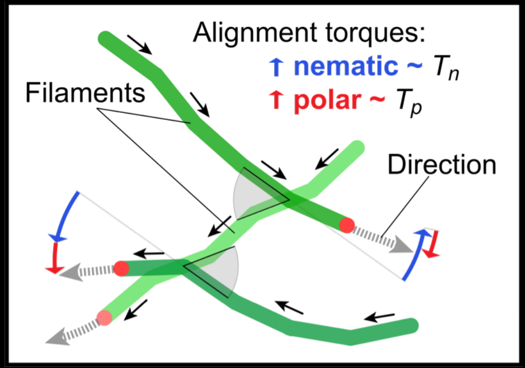


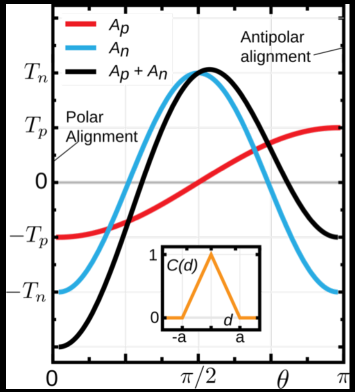


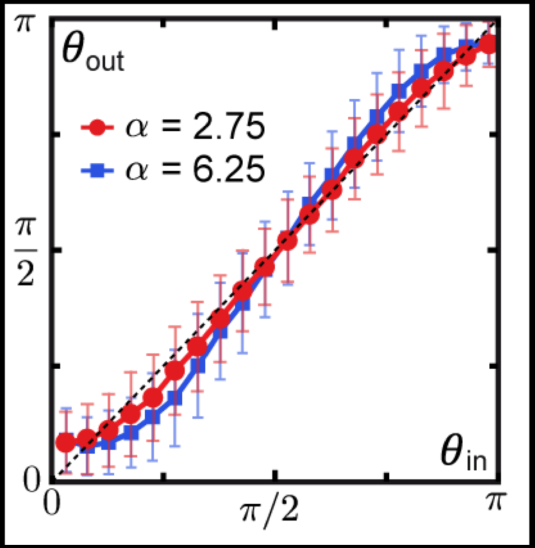
Motility assay simulation

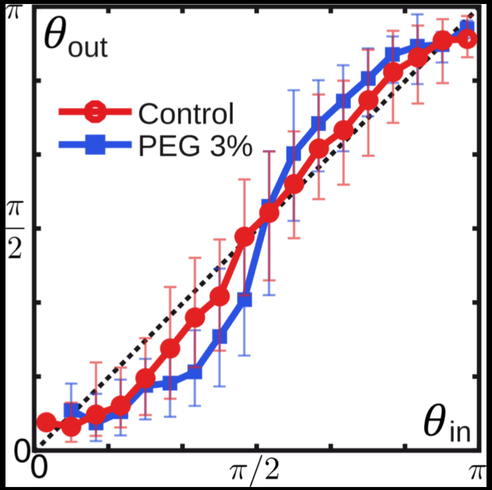
Interaction?





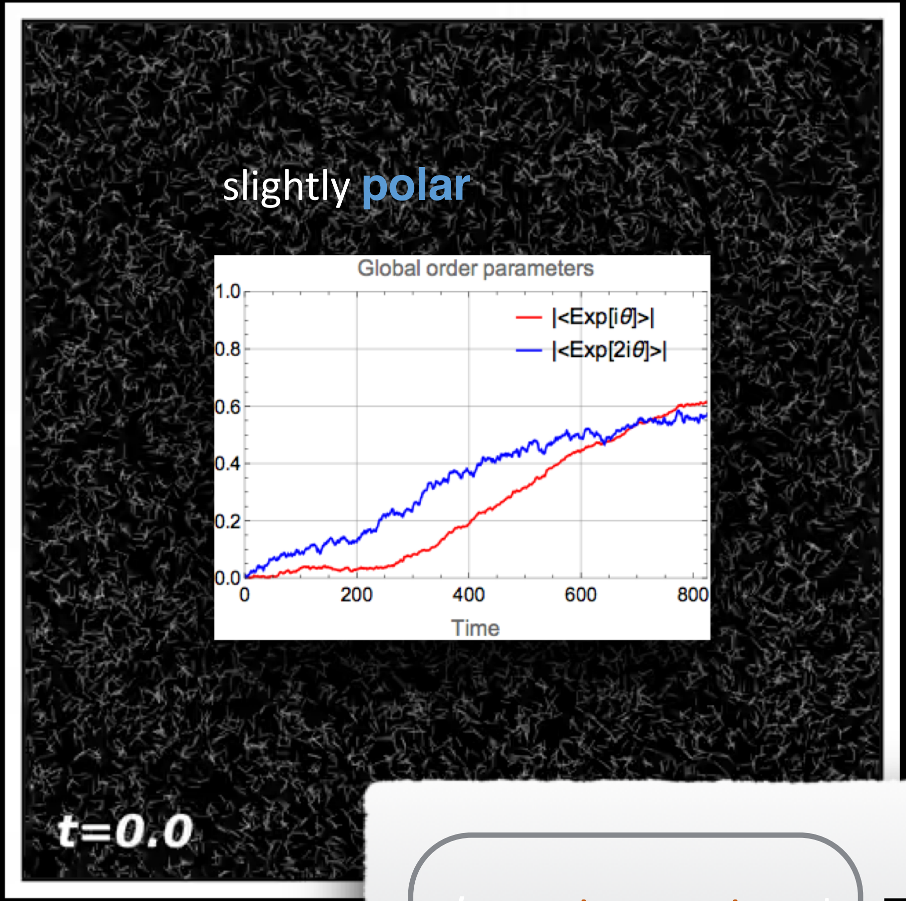


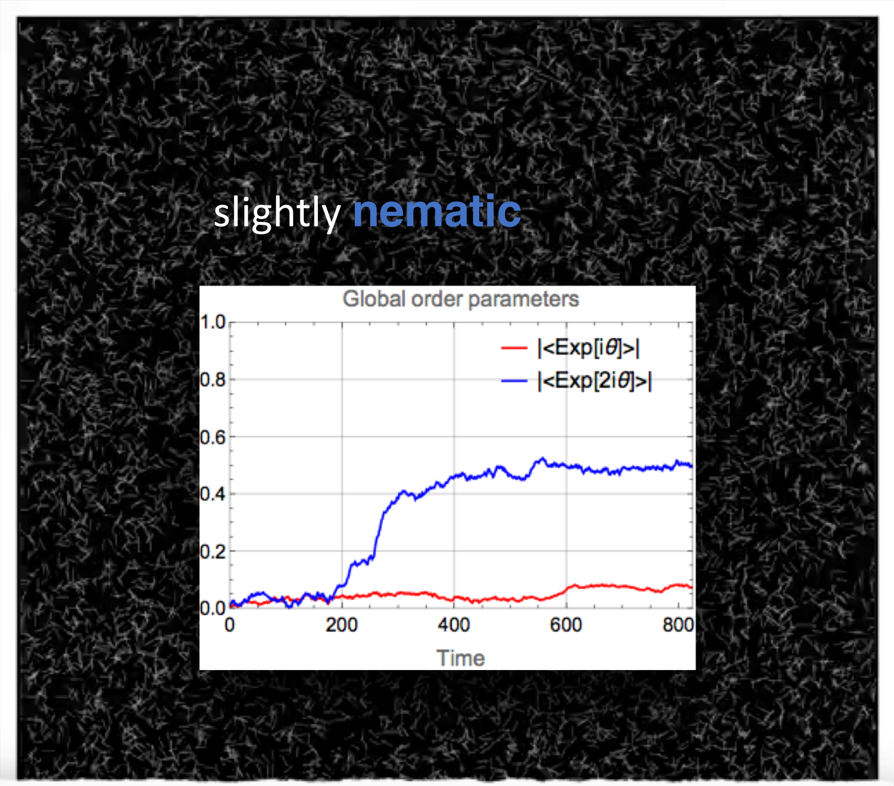


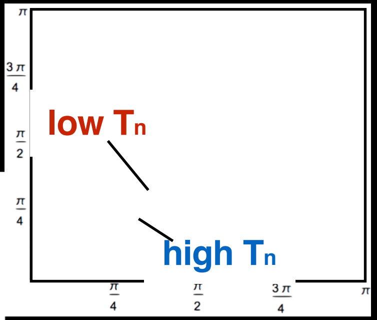


Theory

with 10,000 filaments





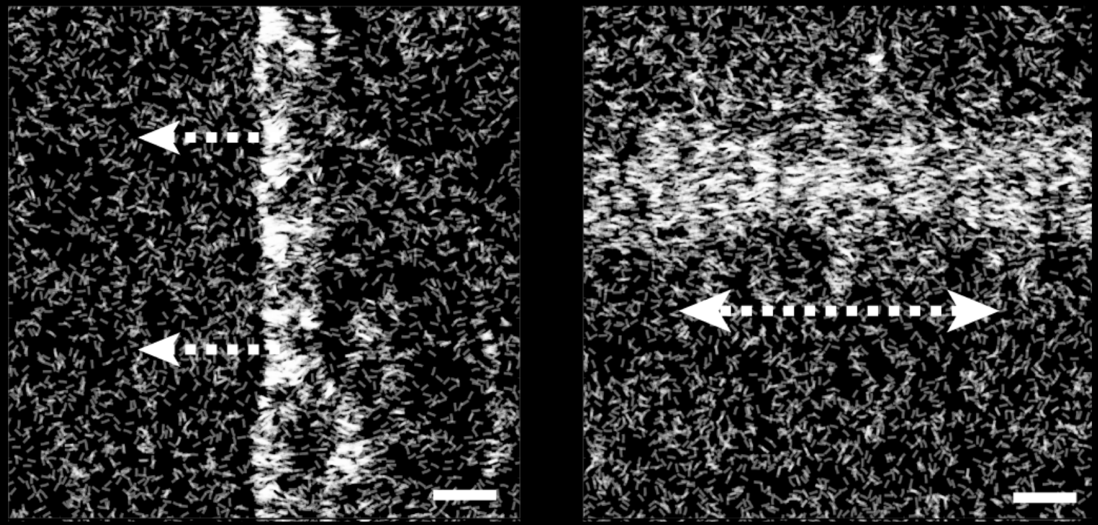


Low microscopic order → *High* macroscopic order

Theory

But something is strange…

Use *identical* parameters, simulate with different initial conditions:



Phase-separation into ***intrinsically conflicting*** types of order

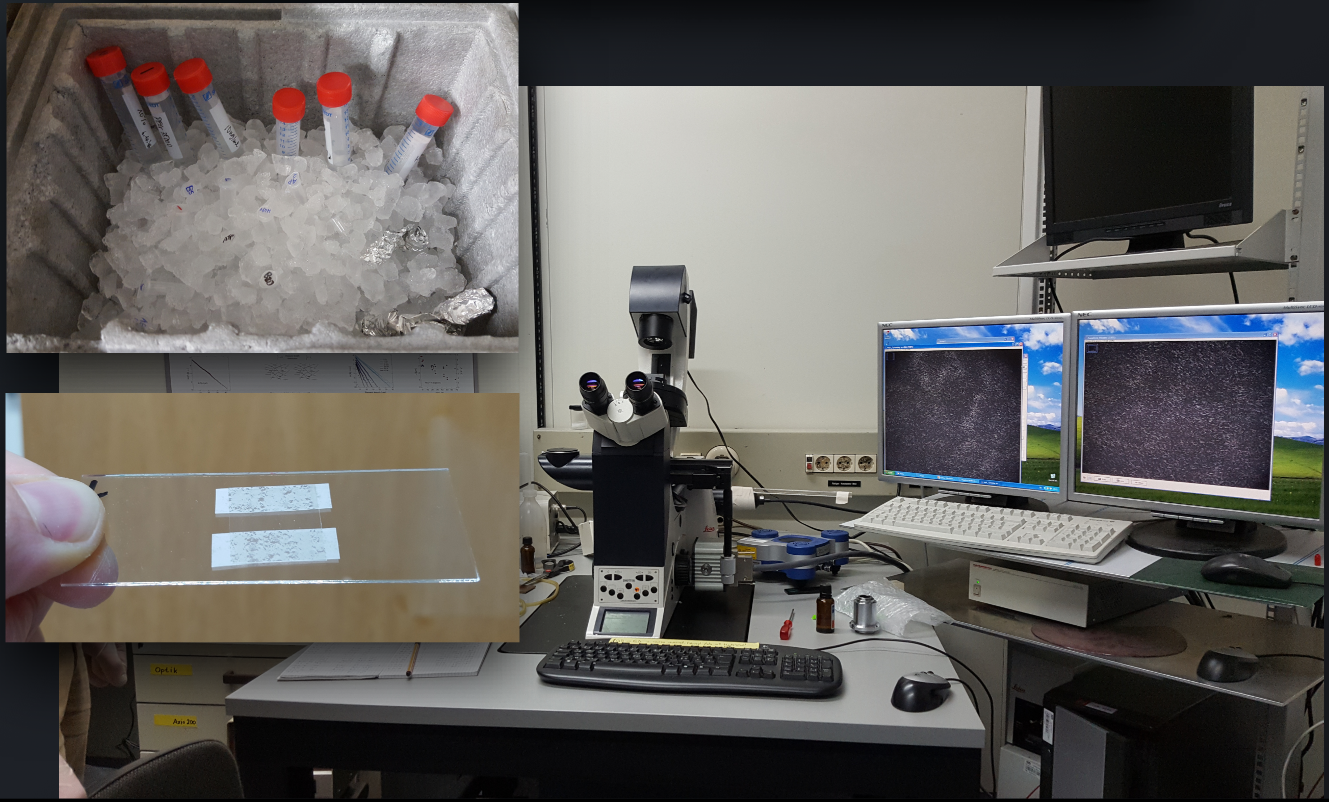
Multistable behavior!

Let's analyze this systematically!

Results

Prediction

multistable/coexisting *states* of polar & nematic order at ***intermediate*** PEG concentration

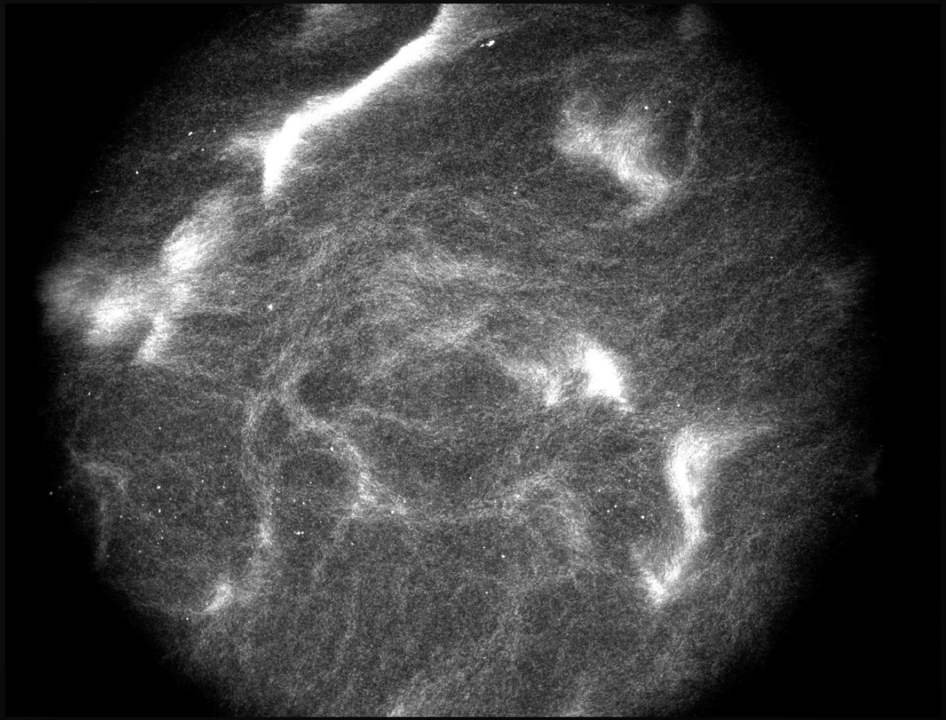


Theory

Experiment

Results

Experiment: (at some intermediate values actin and PEG concentration)



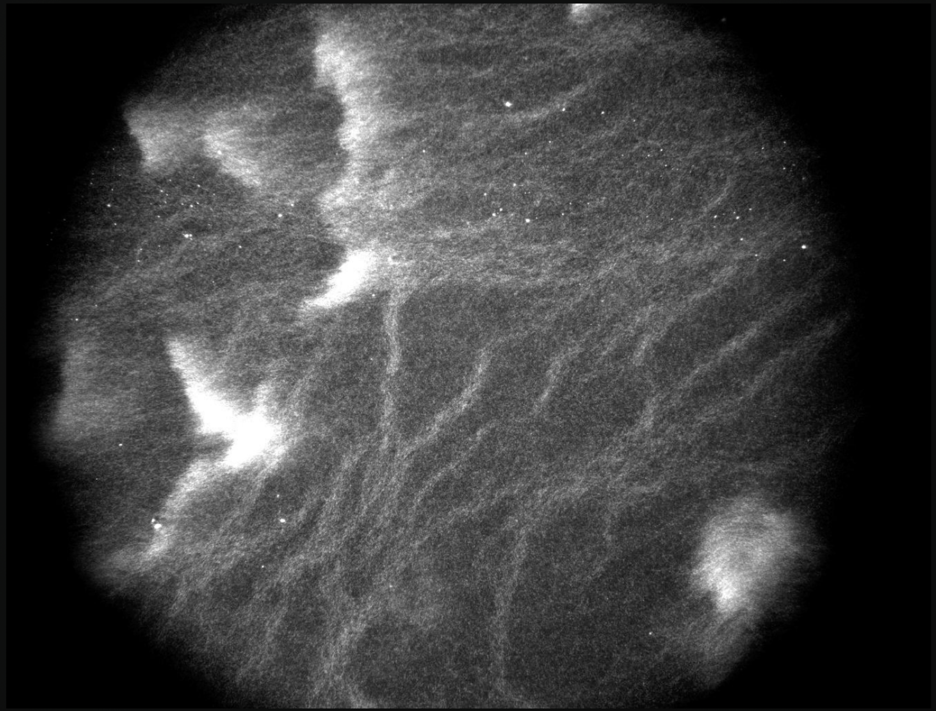
- **Coexistence** of polar waves & nematic lanes!
- **Competition** of patterns by kinetics

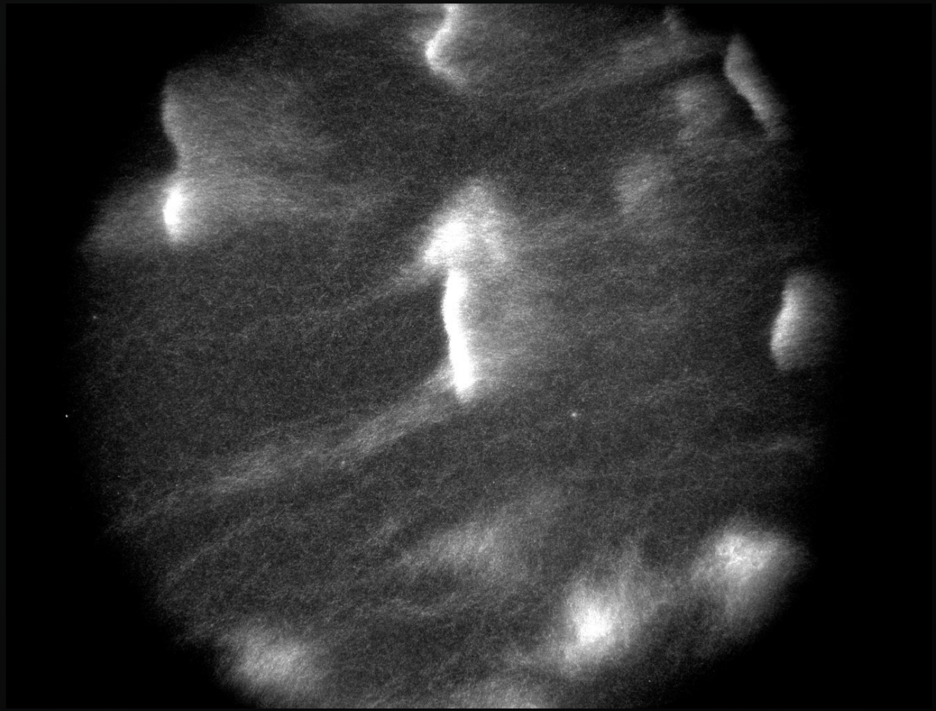
Science (2018): 361:255-

Even experiments by Lorenz Huber, Timo Krüger

Results

Experiment: (at some intermediate values actin and PEG concentration)

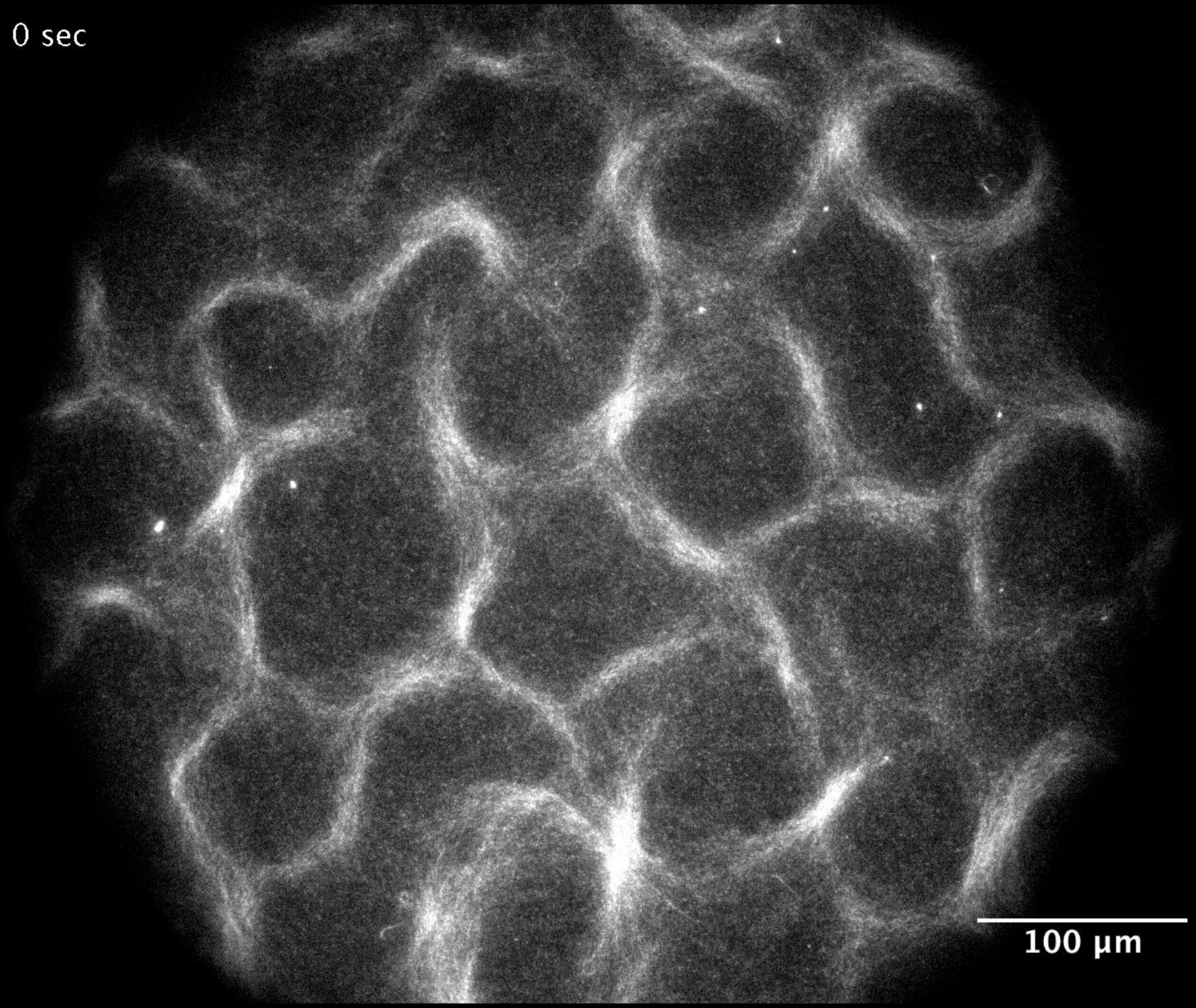




- Wave „eats“ lane
- Wave looses „trails“

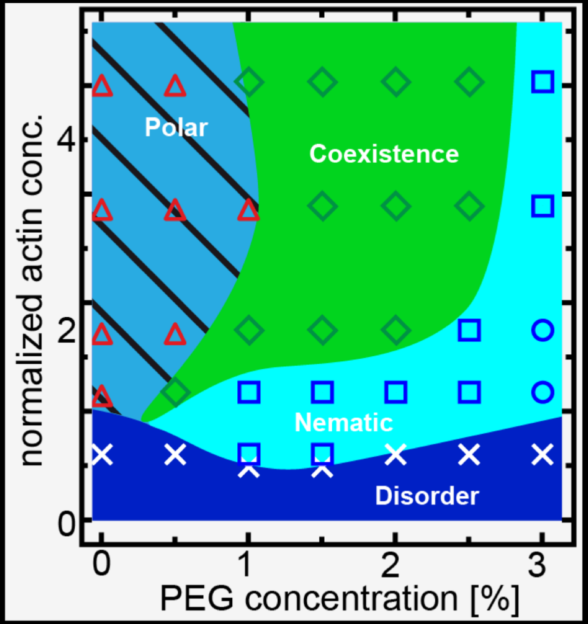
Science (2018): 361:255-

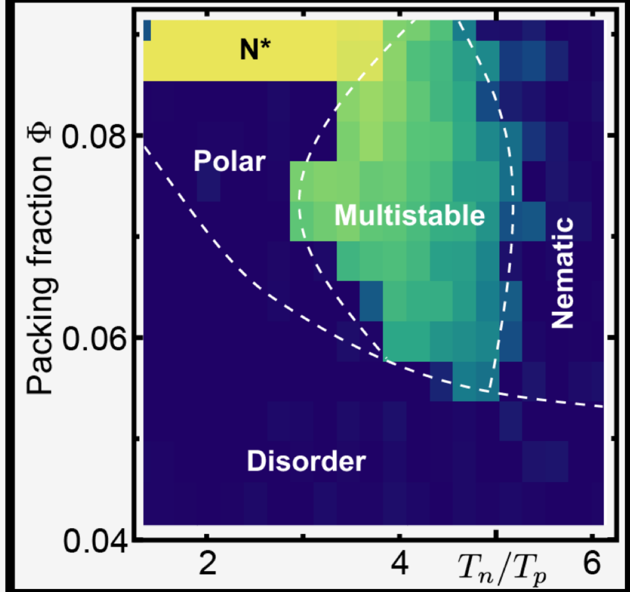
Even experiments by Lorenz Huber, Timo Krüger

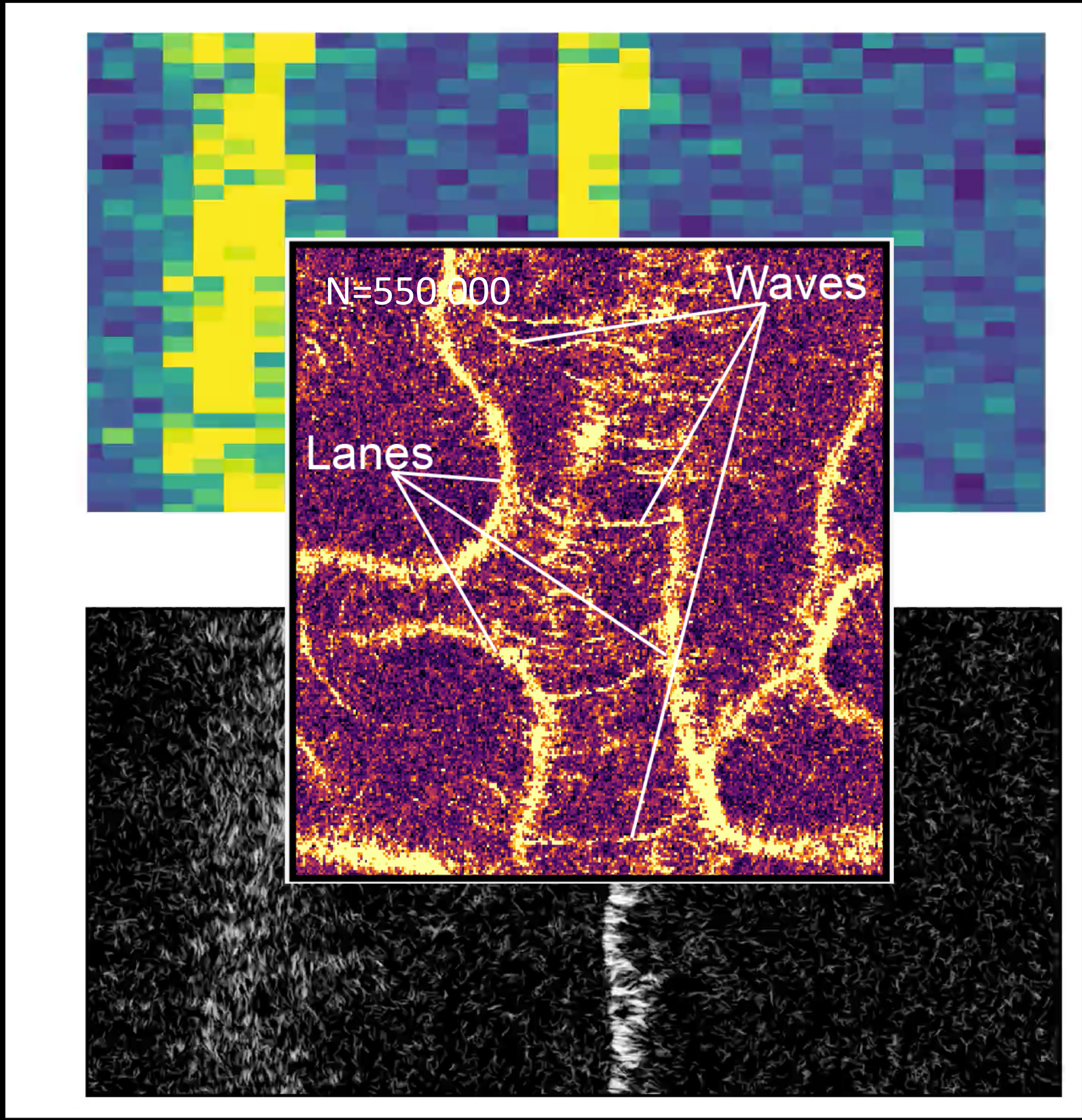

0 sec
100 µm

Results

Phase diagram





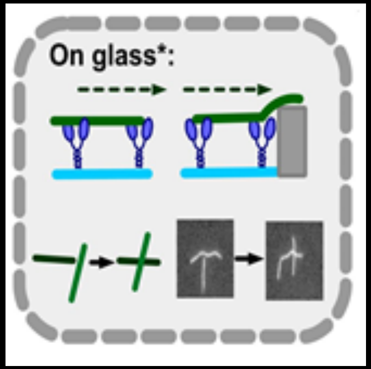


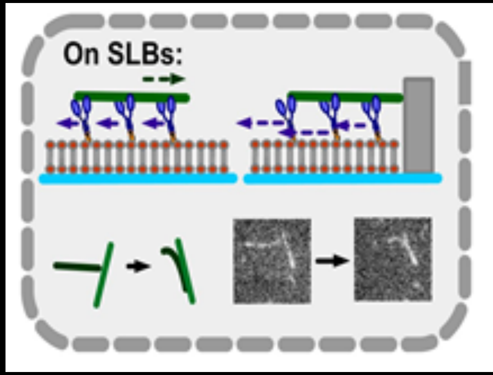
Very similar phase diagram

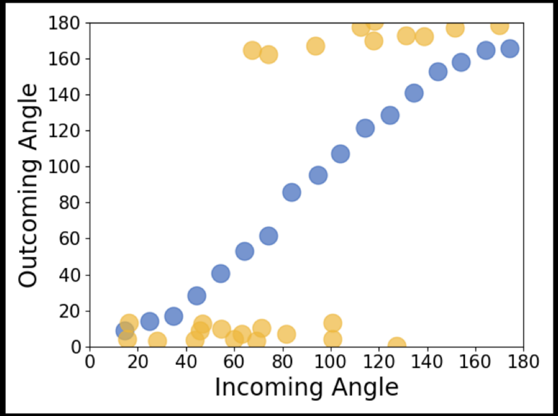
Multistability = Coexistence?

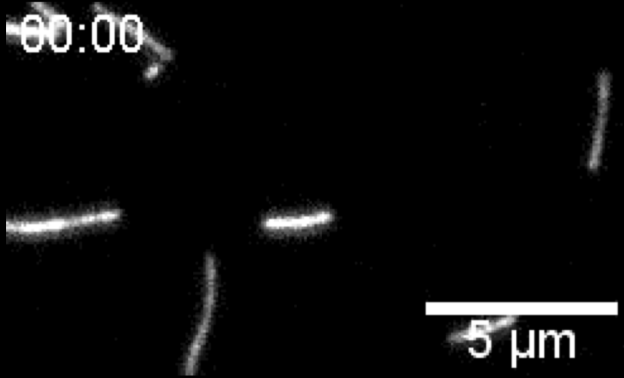
Science (2018): 361:255-

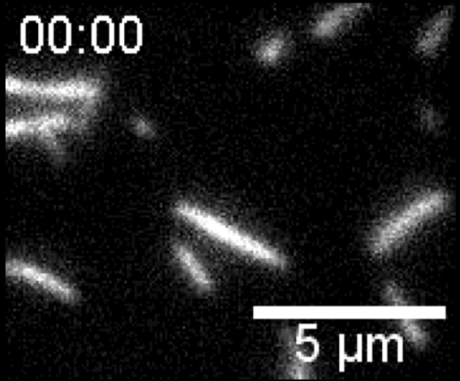
A softer hard interaction

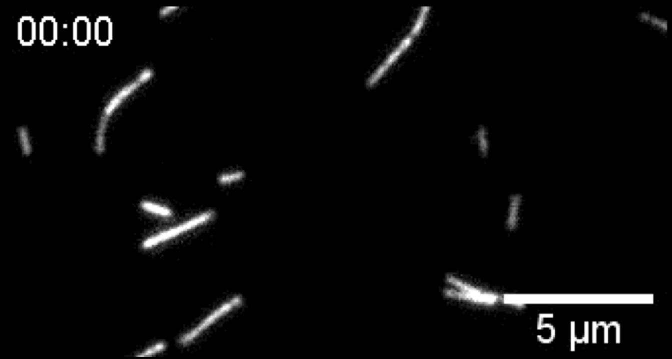




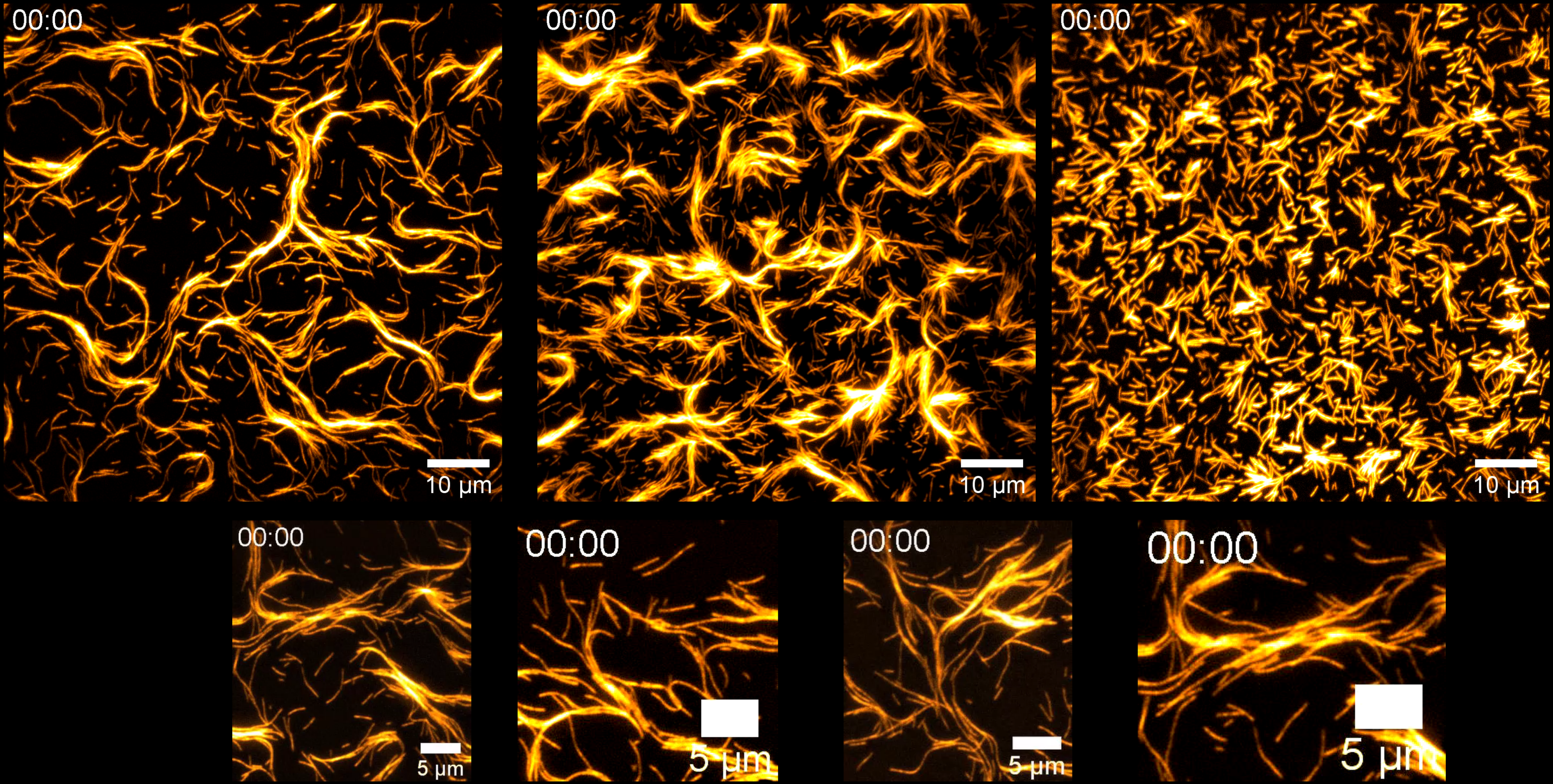




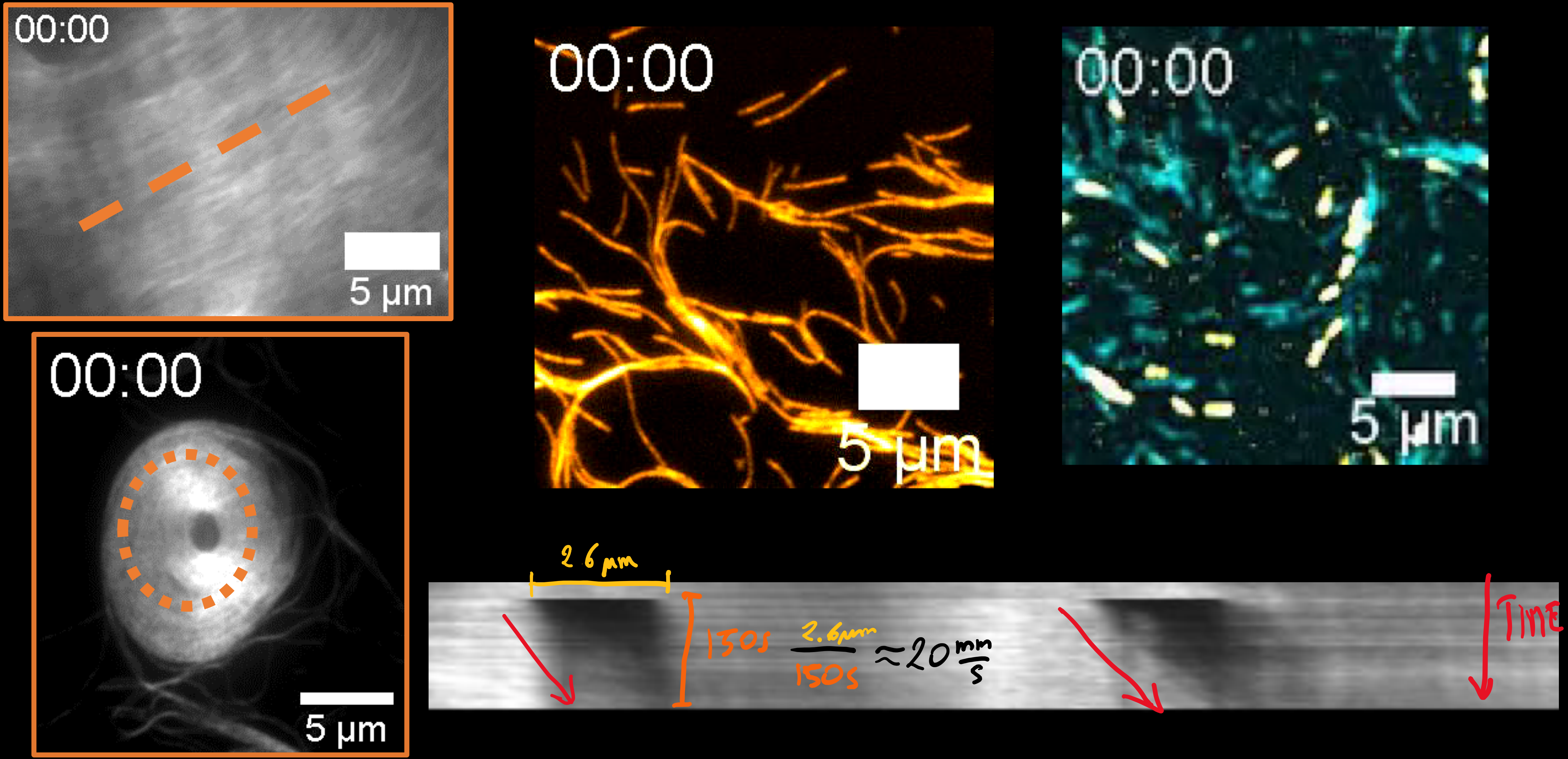




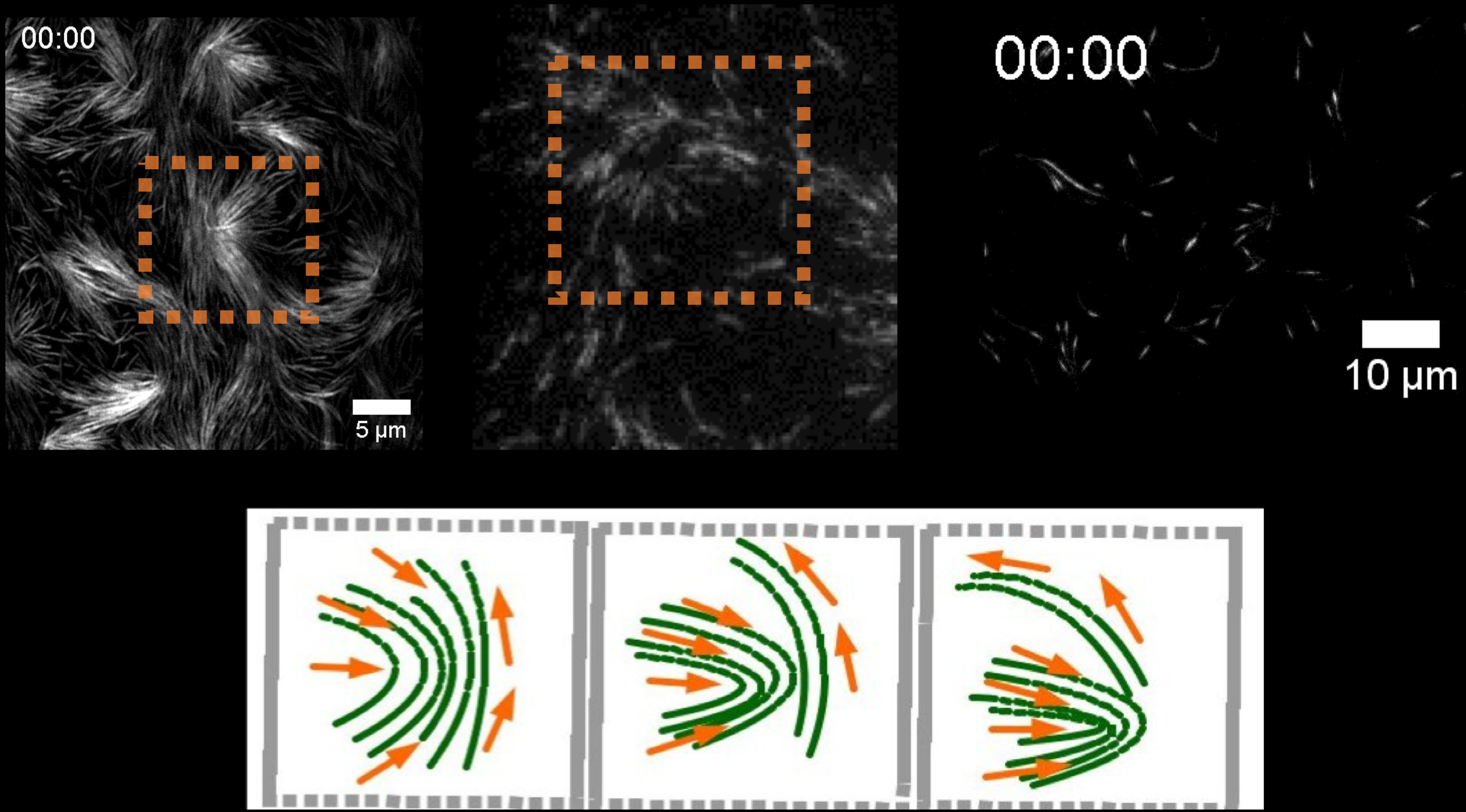
0.4 fil/um2 0.65 fil/um2 0.83 fil/um2



Is it really nematic..?



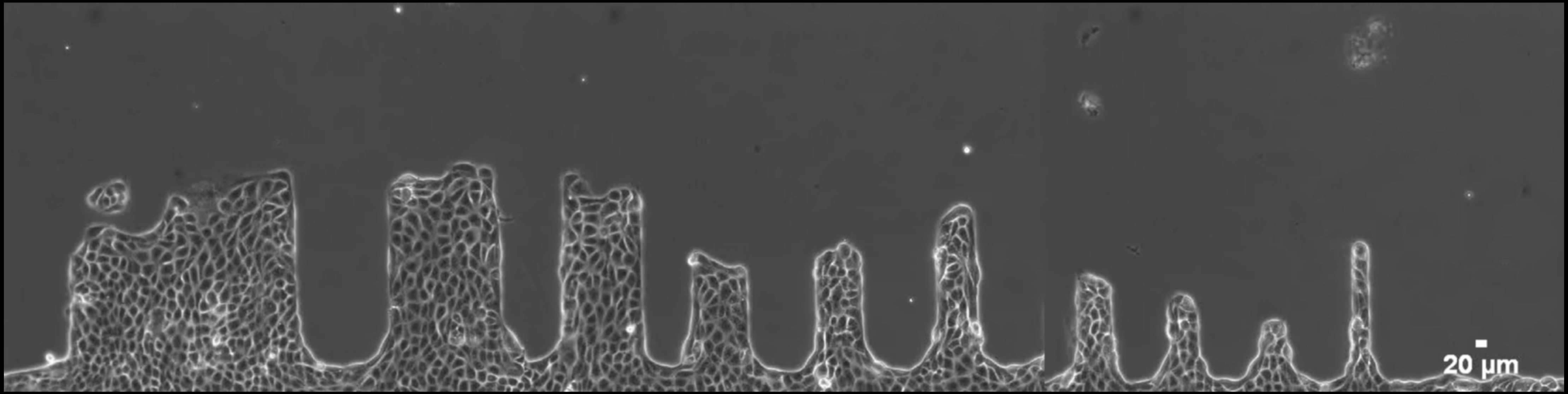
Comets



Pattern formation in active cytoskeletal and organoids

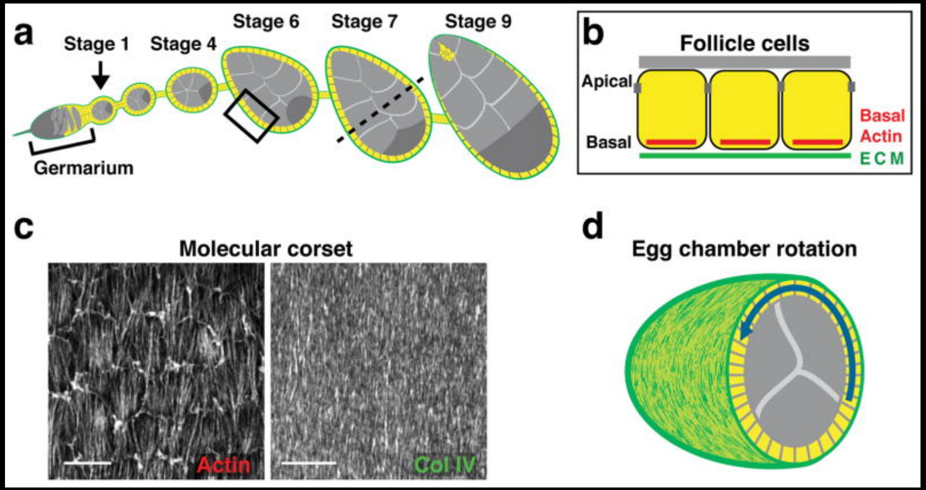
Or how we manage to end up with ducts and acini

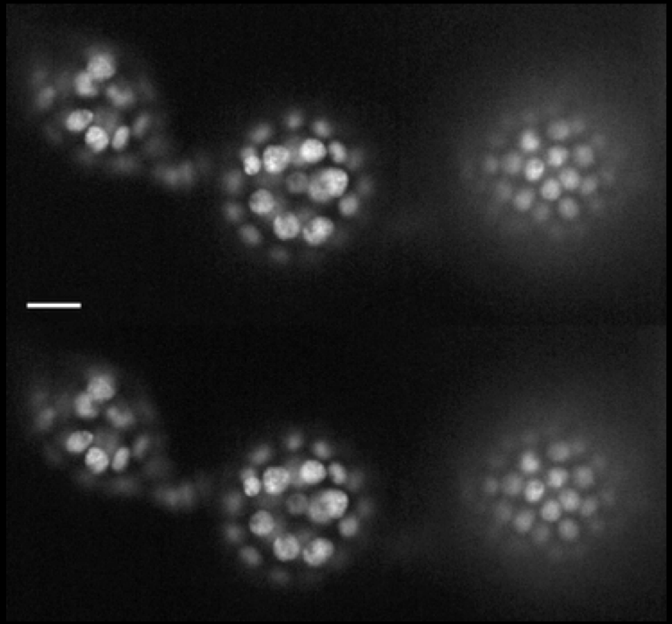
Migration in 2D

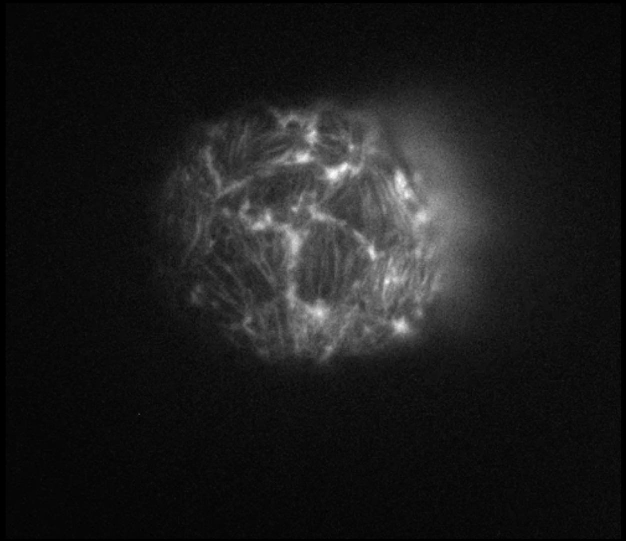


Vedula et al. www.pnas.org/cgi/doi/10.1073/pnas.1119313109

Drosophila egg chamber forms an elliptical egg



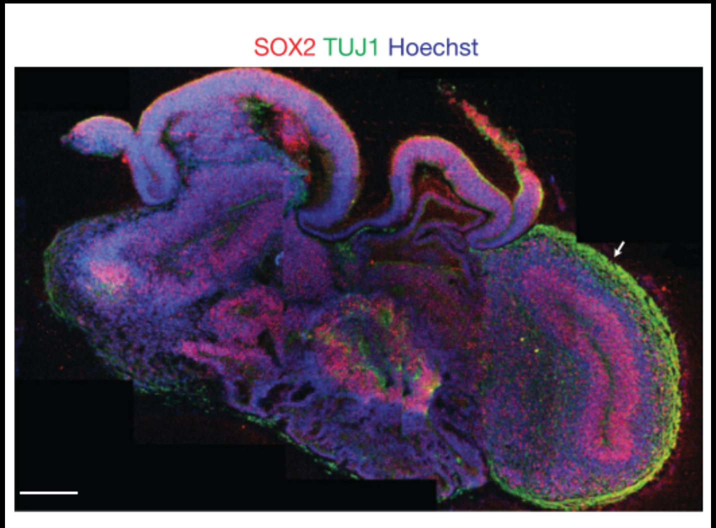




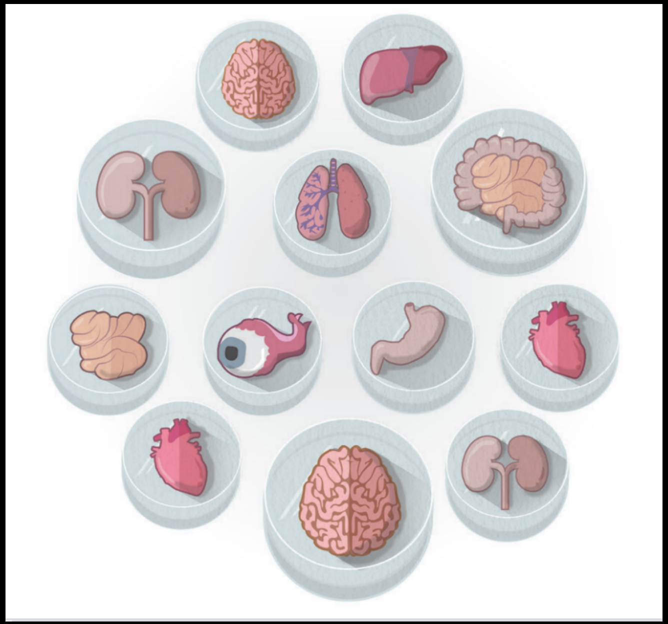
[Nat Commun. 2014; 5: 5511.]

Organoids

An **organoid** is a miniaturized and simplified version of an organ produced in vitro in three dimensions that shows realistic micro-anatomy

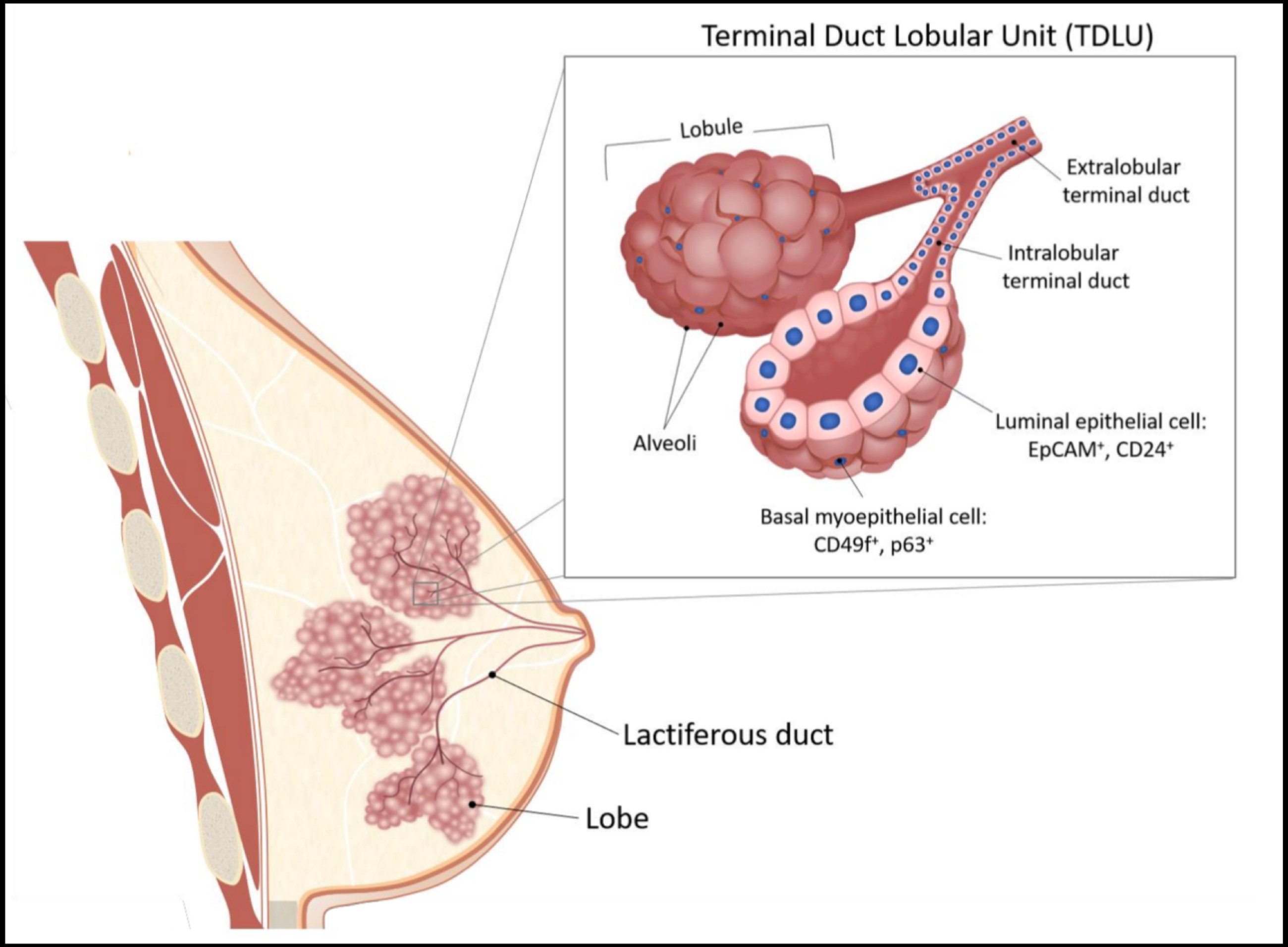


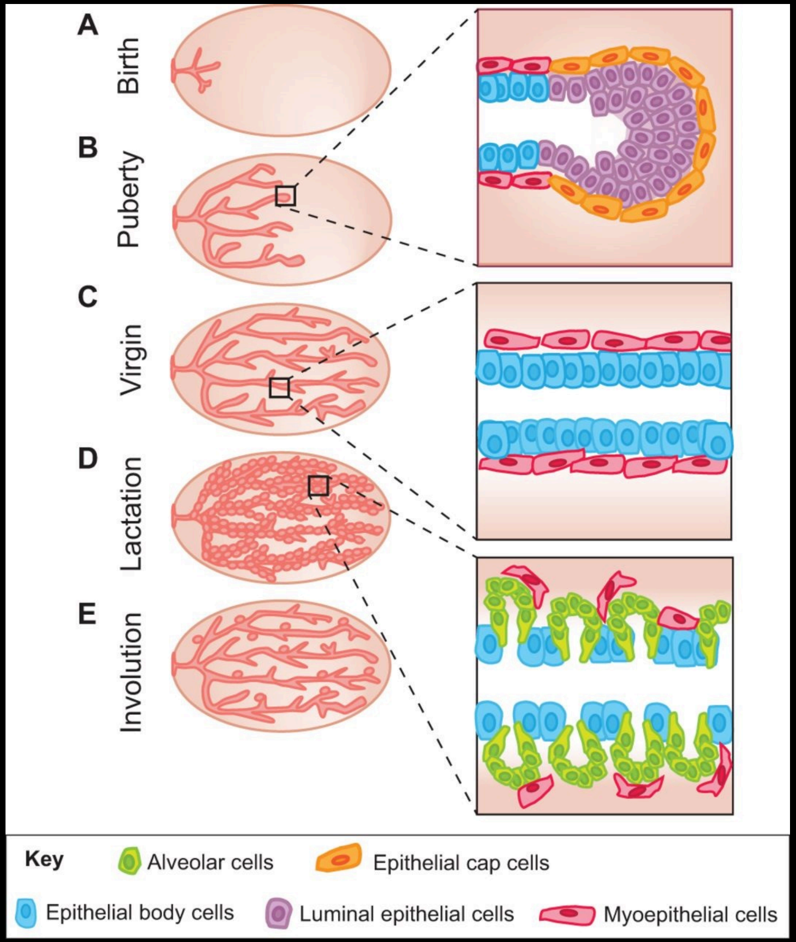
Cerebral organoids model human brain development and microcephaly.
Lancaster et al. *Nature (2013).*



Rise of the organoids.
Willyard. *Nature (2015).*

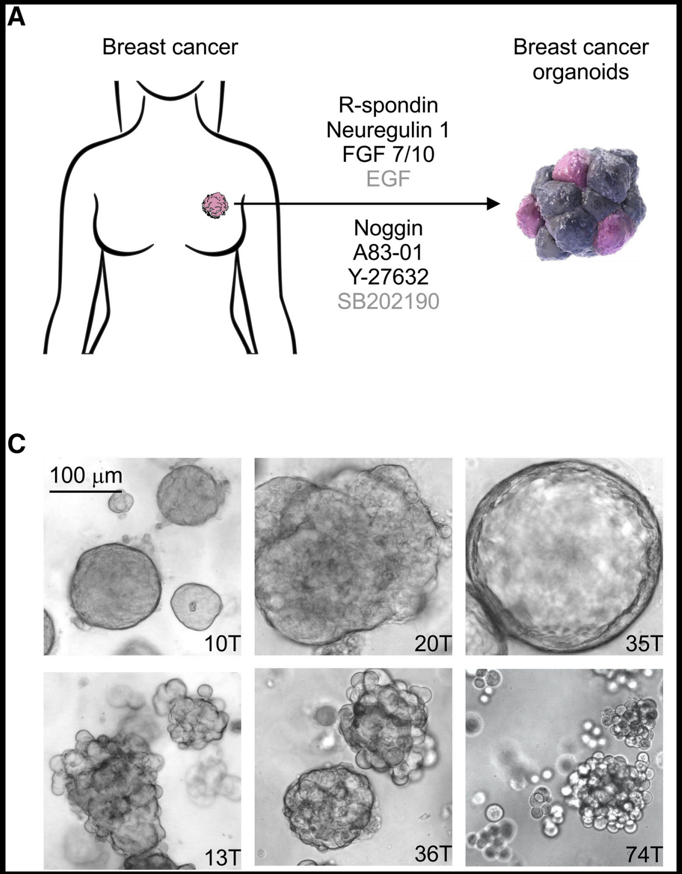
Human Mammary Gland





Mammary gland development: cell fate specification, stem cells and the microenvironment; Jamie L. Inman,i.a. *Development (Cambridge, England)*, 142(6):1028–1042, 2015.

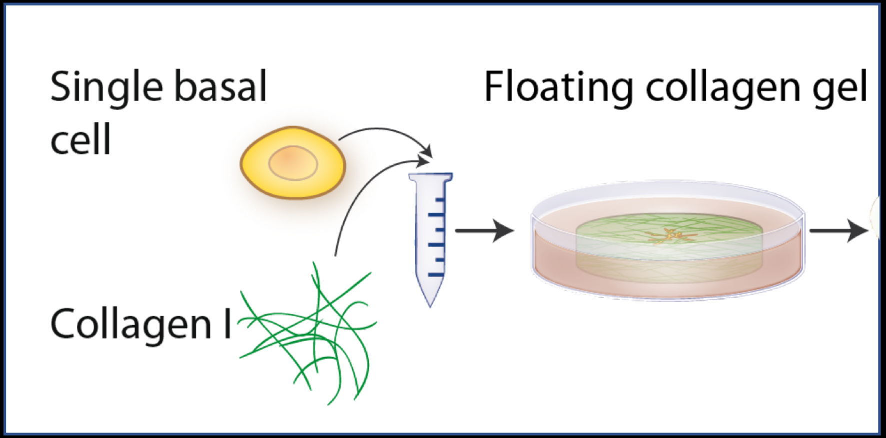
Organoids: no consensus on the role of ECM

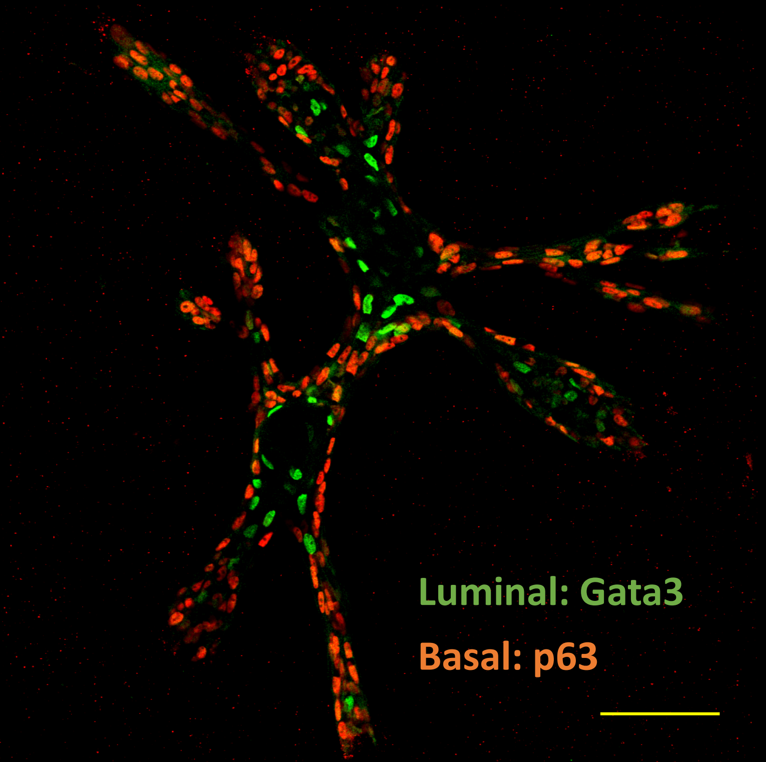


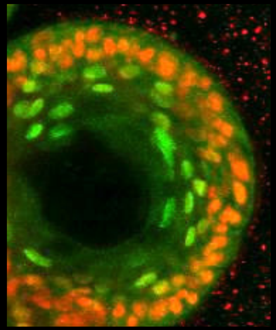
Sachs et al Cell (2018) 172: 373 -

Ewald et al; *Dev. Cell; (2008) 14(4): 570-*

Mammary Gland Organoid in Collagen I
Single cell derived

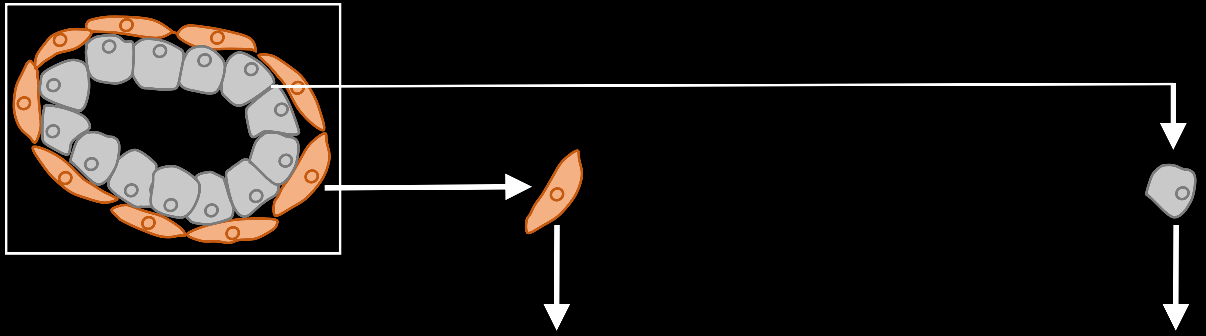




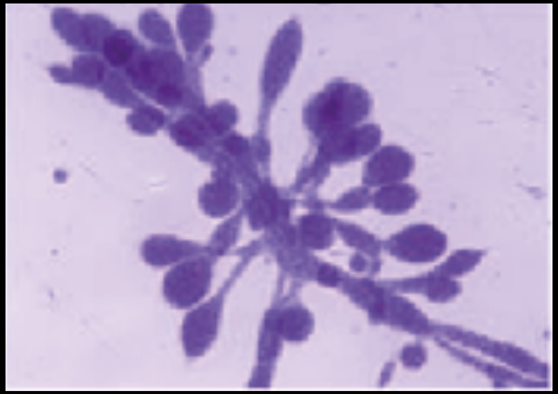


Linnemann JR,…and Scheel CH, Development 2015

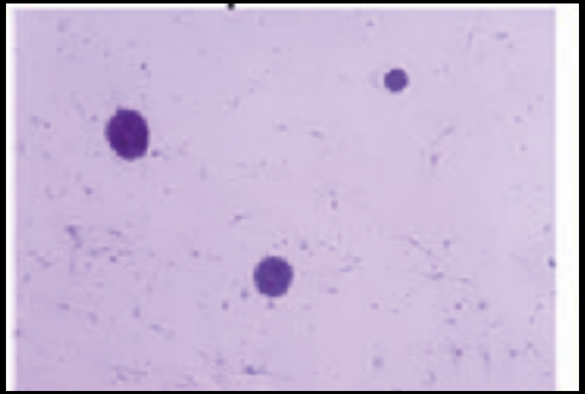
Dynamic interaction of organoids with the collagen matrix



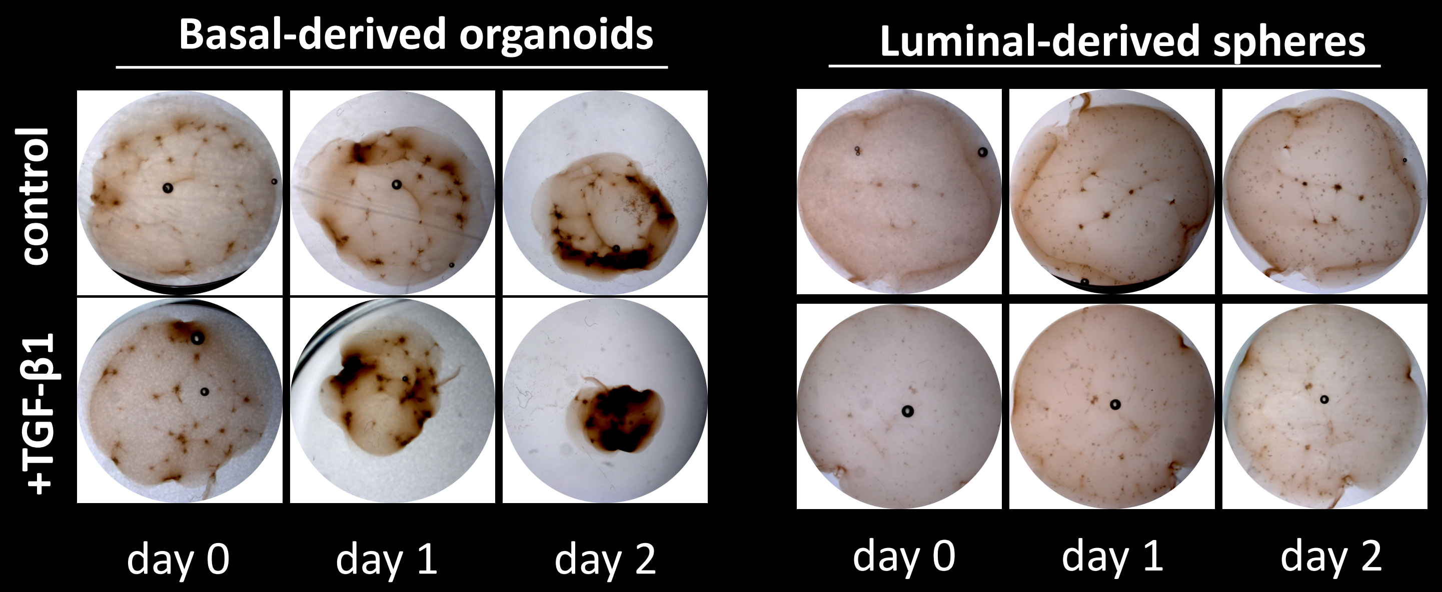
Basal-derived organoids

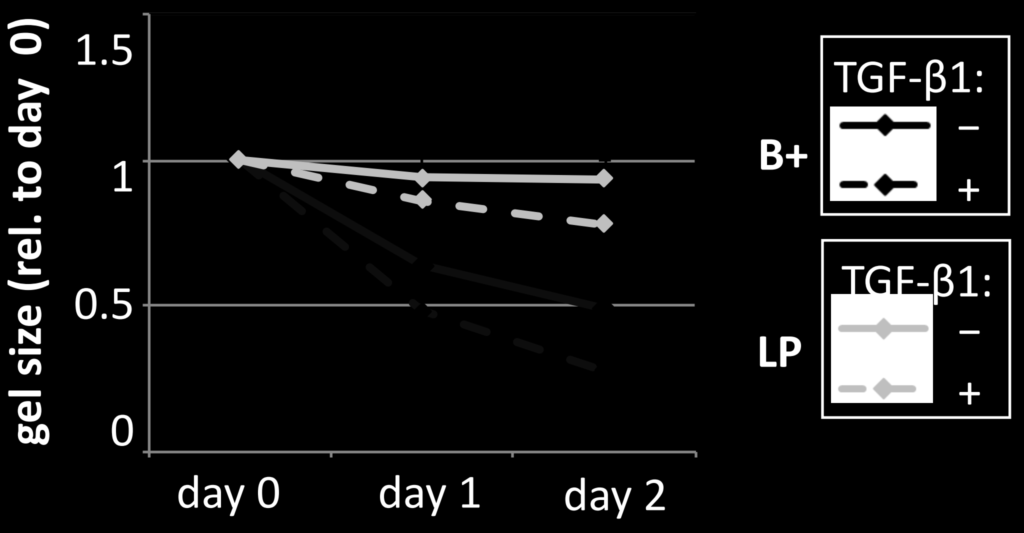


Luminal-derived spheres



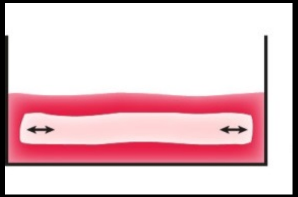
Organoids derived from basal cells contract floating collagen gels

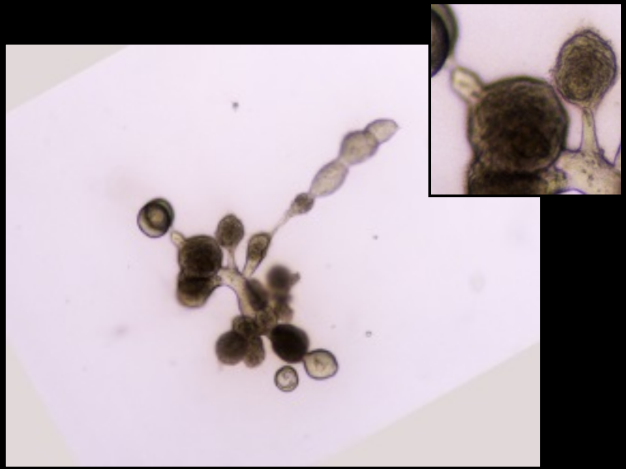




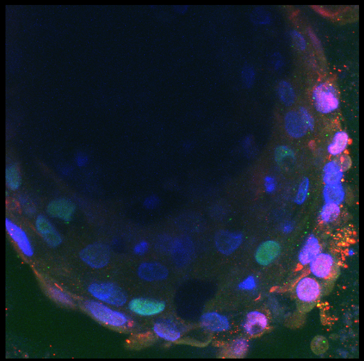
Organoid morphology is impacted by matrix attachment

floating
collagen gel

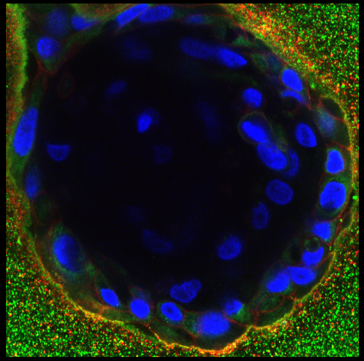




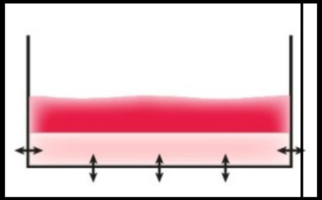
p63
Gata3
DAPI

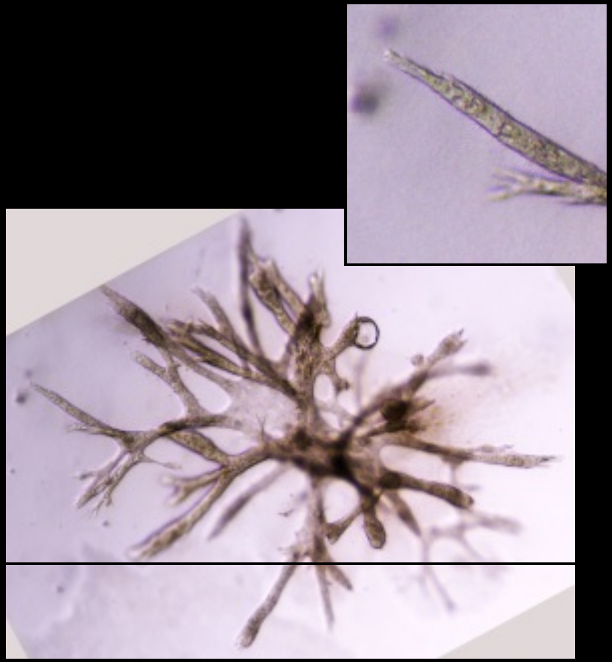


integrin-α6
laminin
DAPI

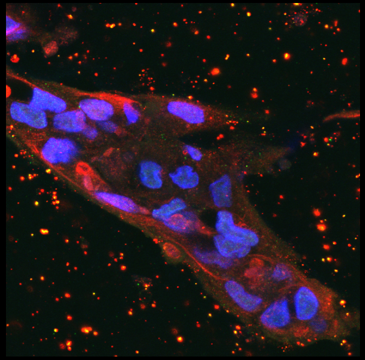


adherent
collagen gel

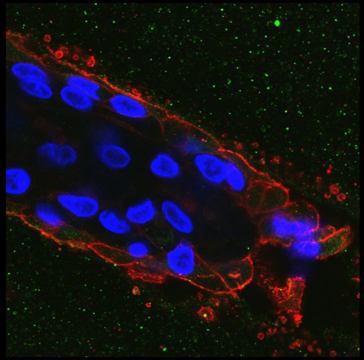


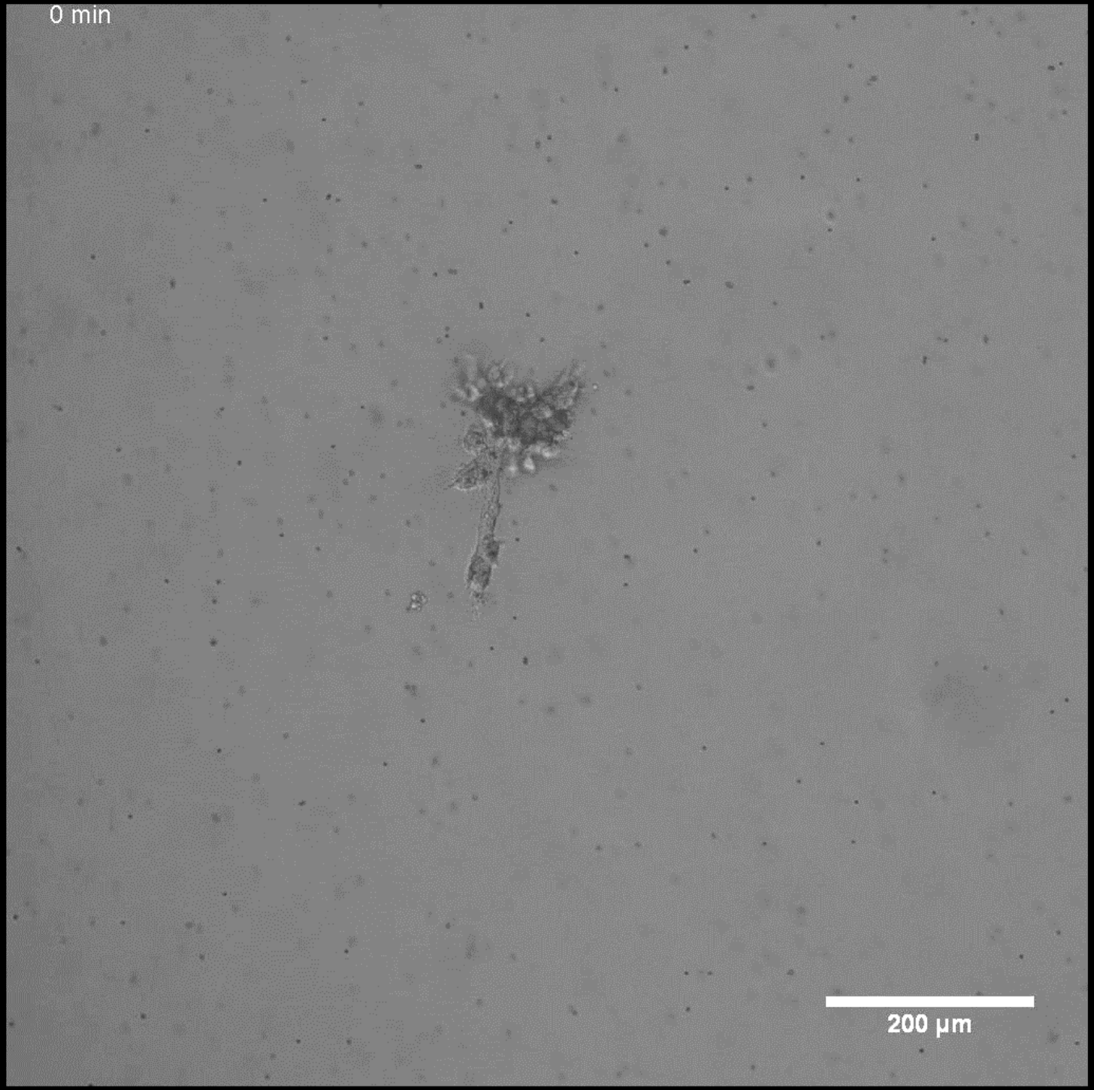


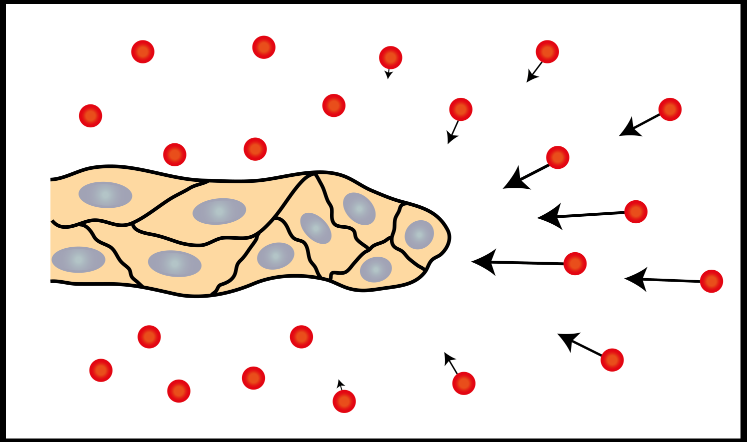
p63
Gata3
DAPI



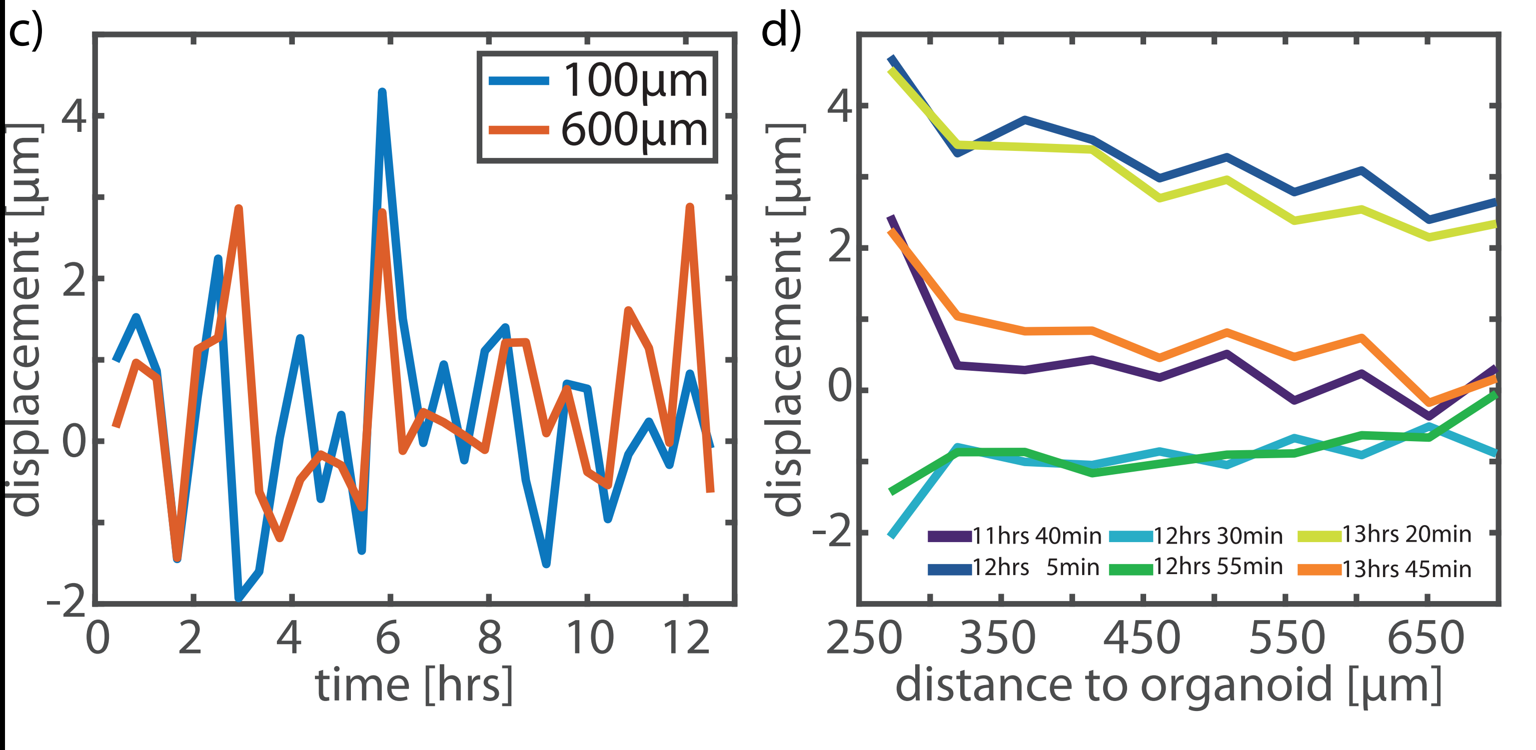
integrin-α6
laminin
DAPI



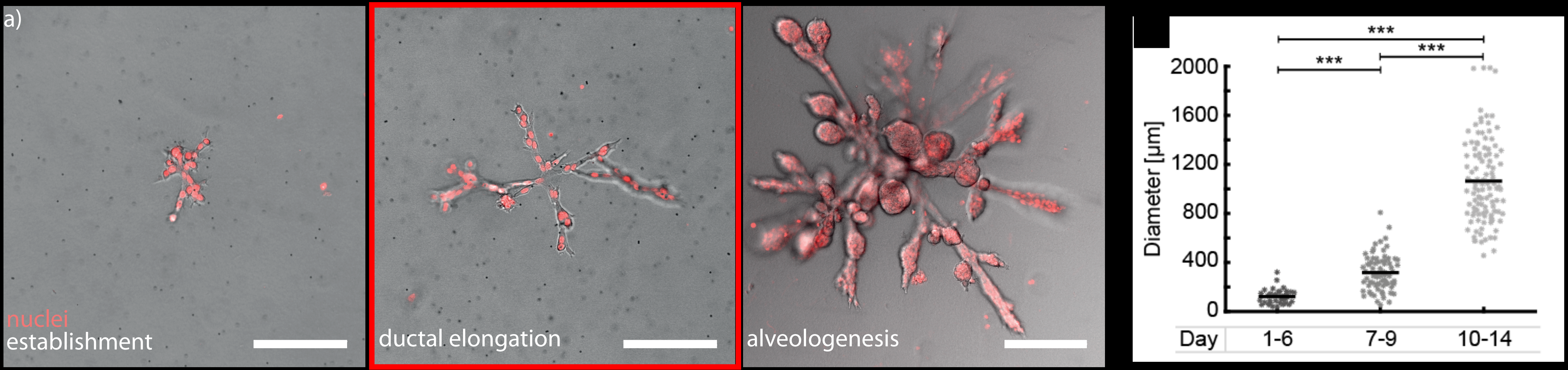

0 min
200 µm



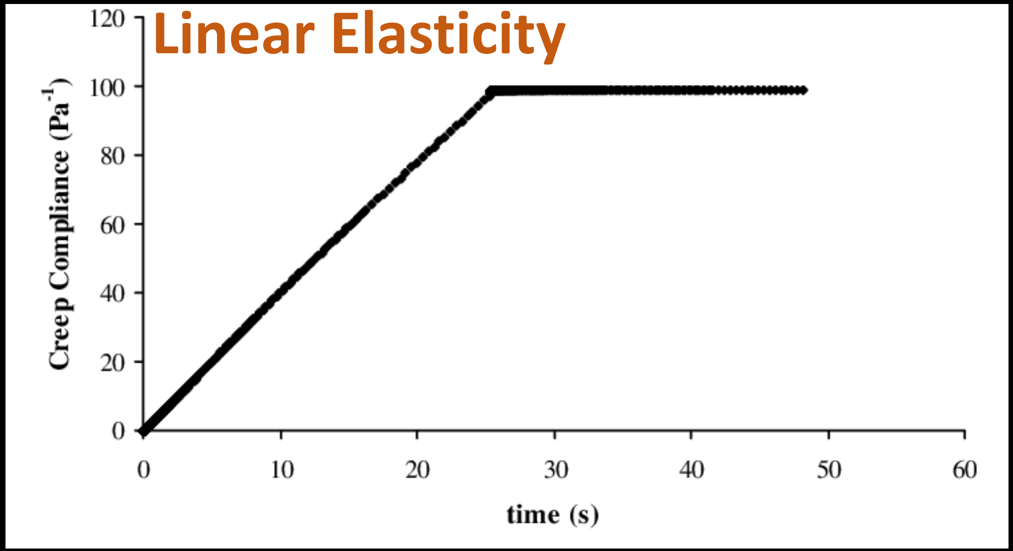
Large scale matrix deformations with oscillatory behaviour

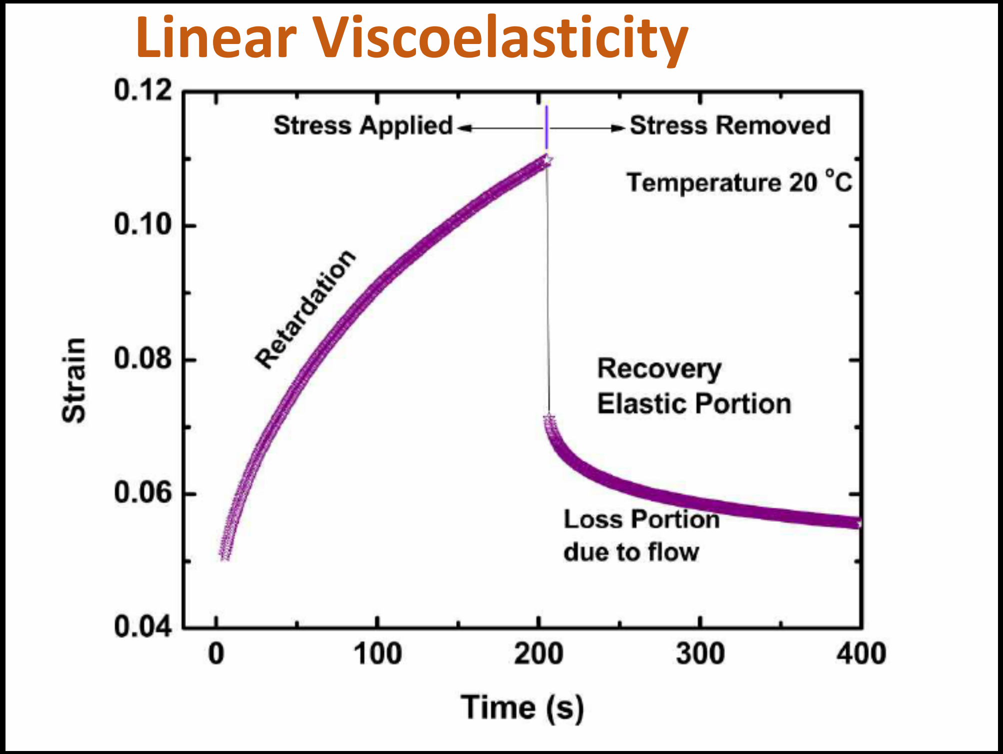


Three phases of organoid development



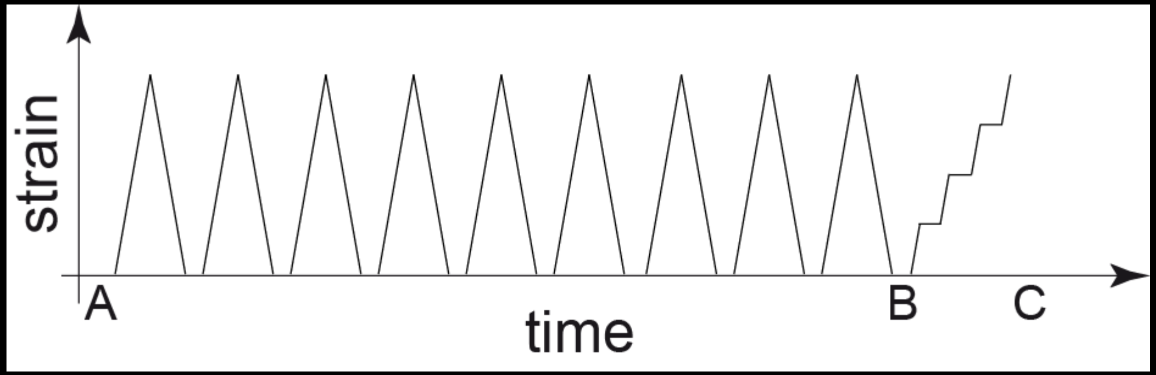
Elasticity 101



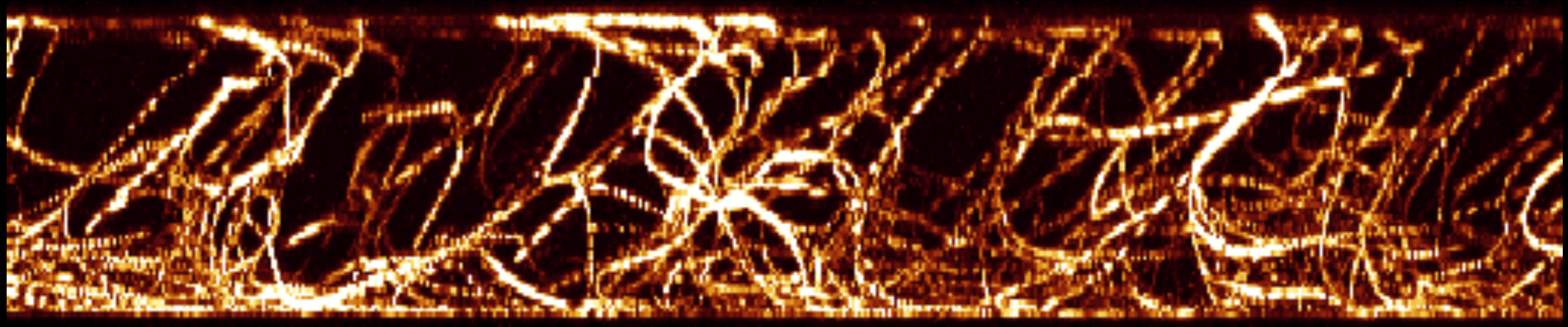


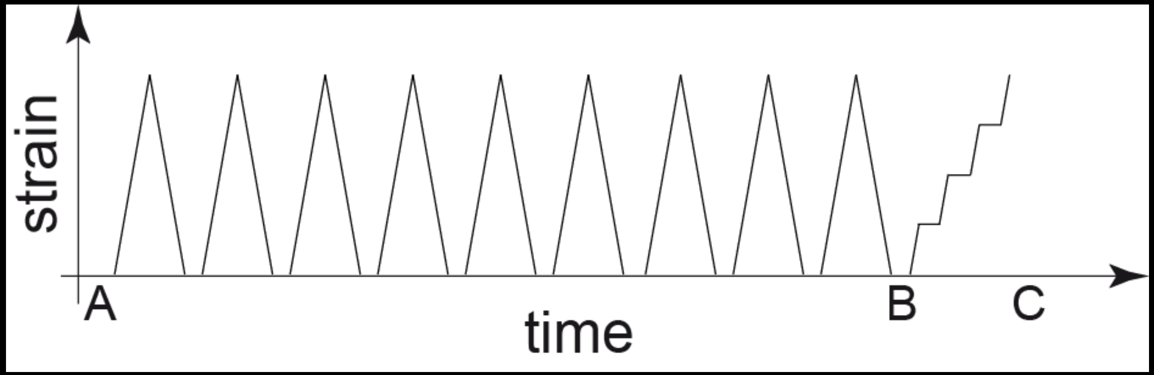
More controlled experiment: shear cell

Confocal microscope



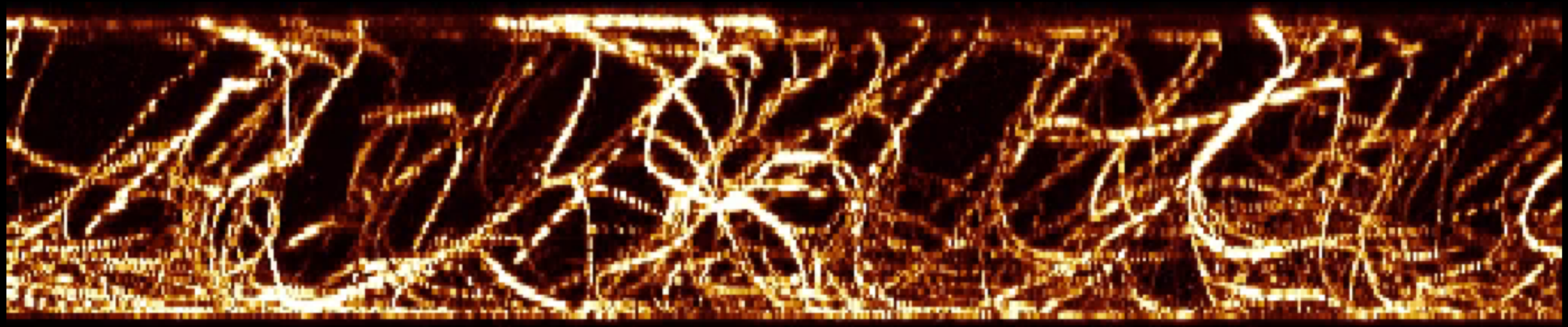
Shear Cell

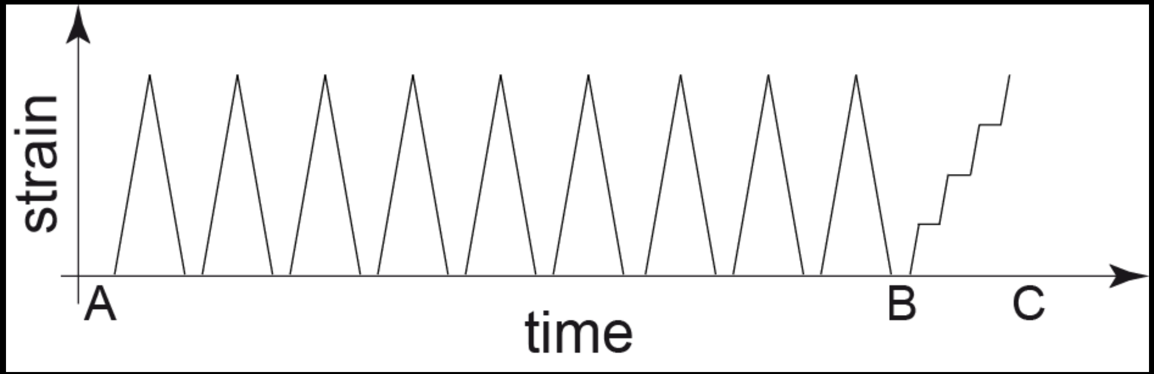




For actin: Schmoller et al, Nat Comm (2010) 1:134

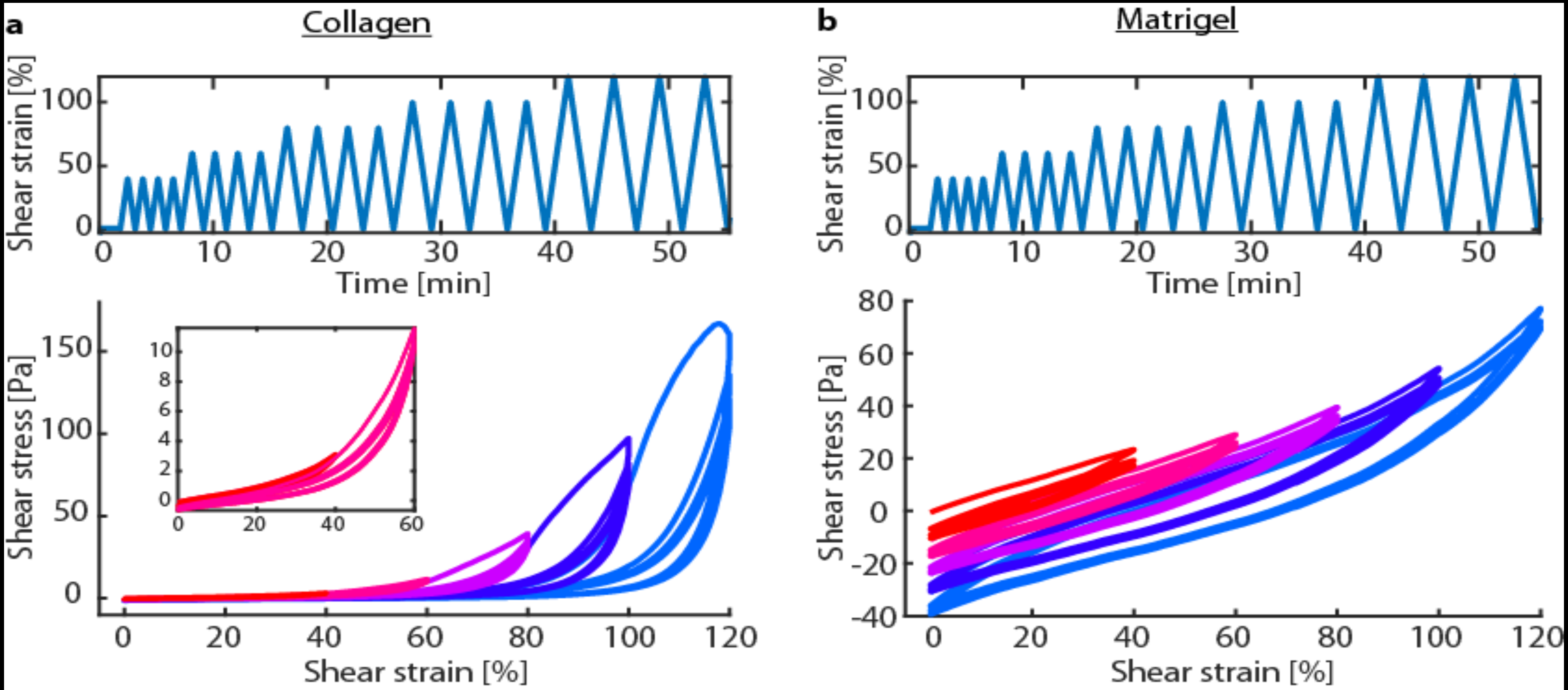
Shear Cell Video





For actin: Schmoller et al, Nat Comm (2010) 1:134

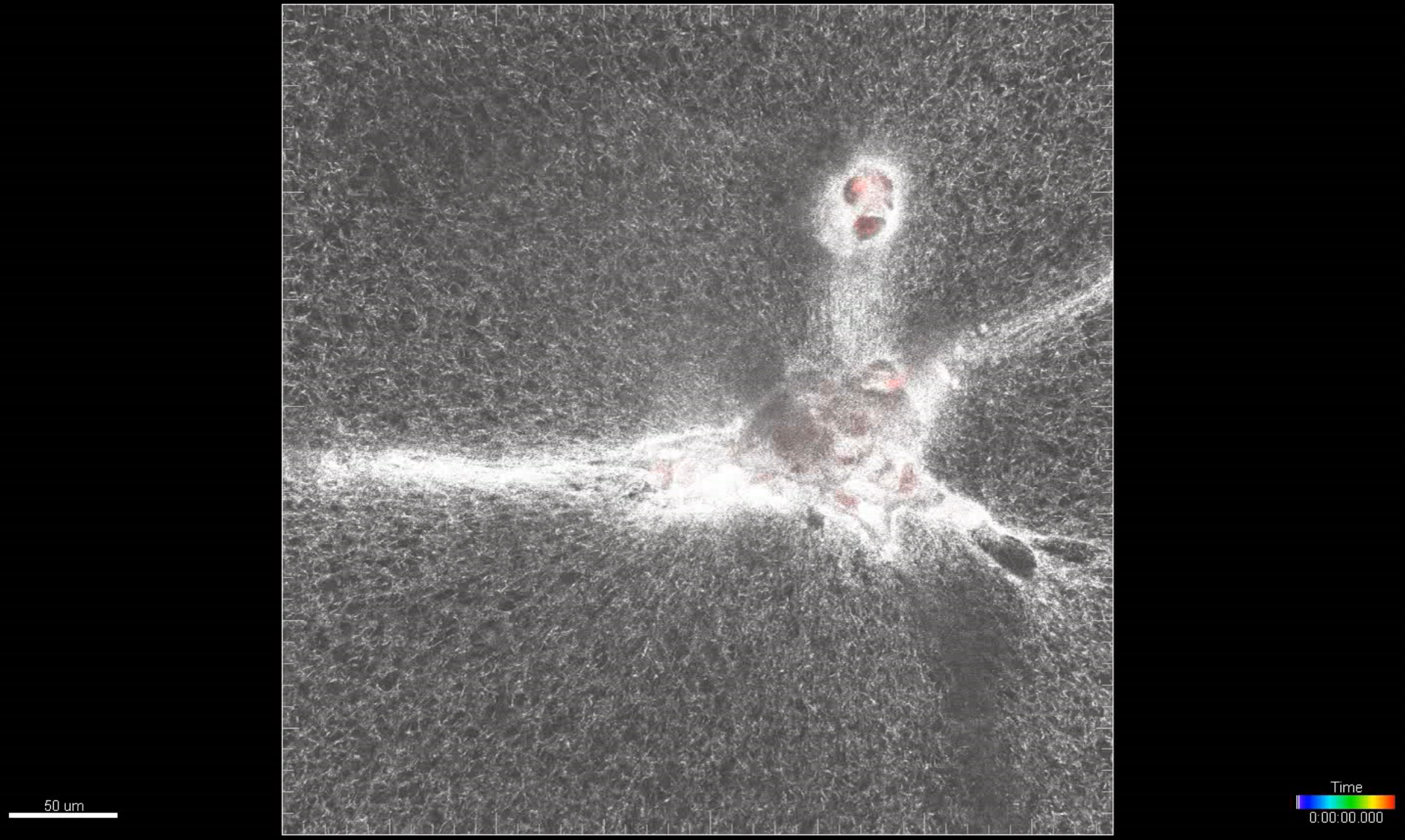
Collagen hass highly <u>plastic</u> <u>nonlinear</u> response – Mullins effect



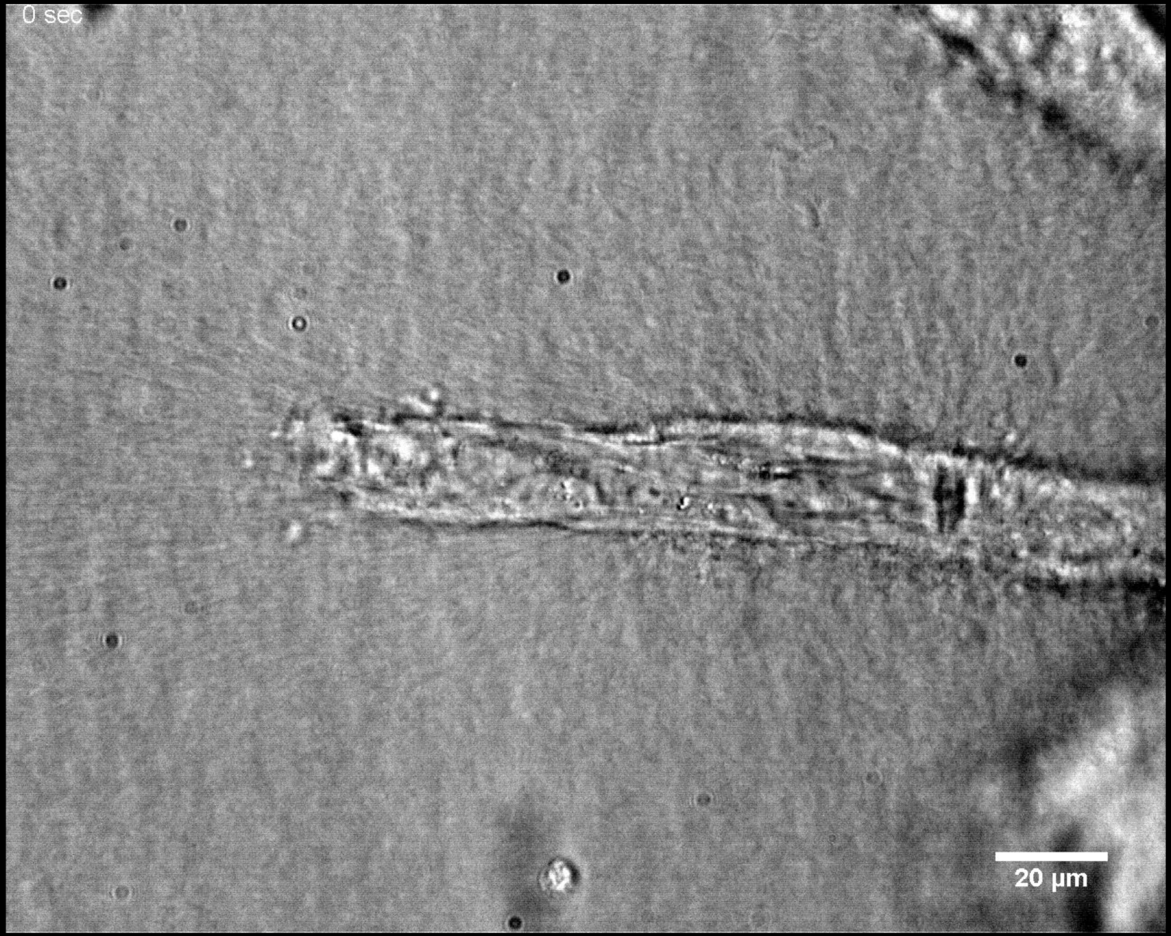
Plastic deformation of the ECM by organoid dynamics

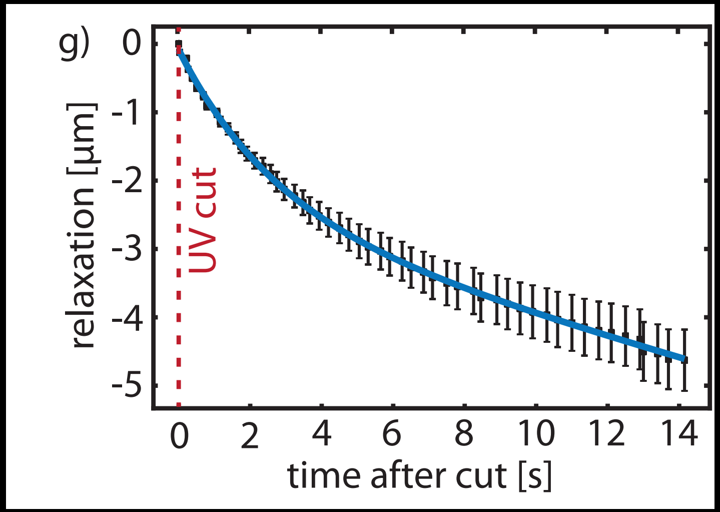
Fibre alignment

Collagen cage



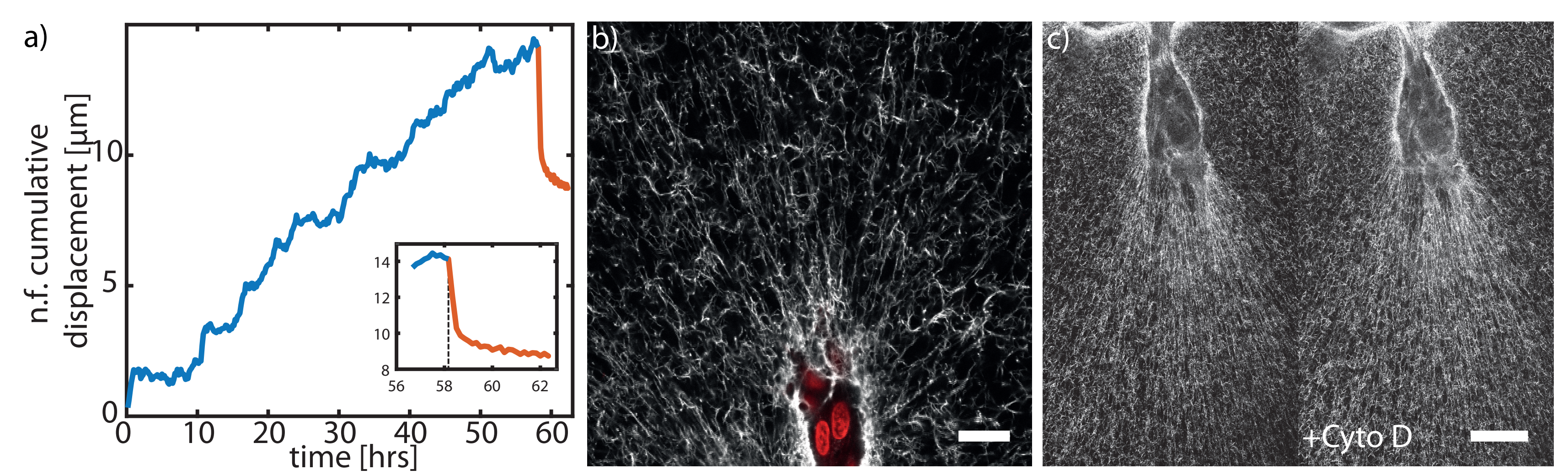
Laser-cut in front of branch-tip: instant relaxation





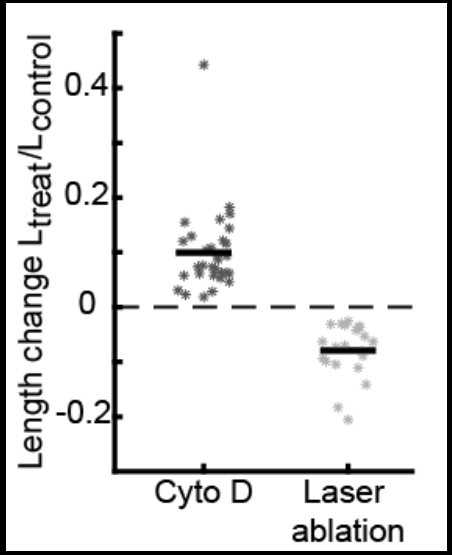
What happends to the collagen matrix when active pulling stops?

+Cytochalasin D

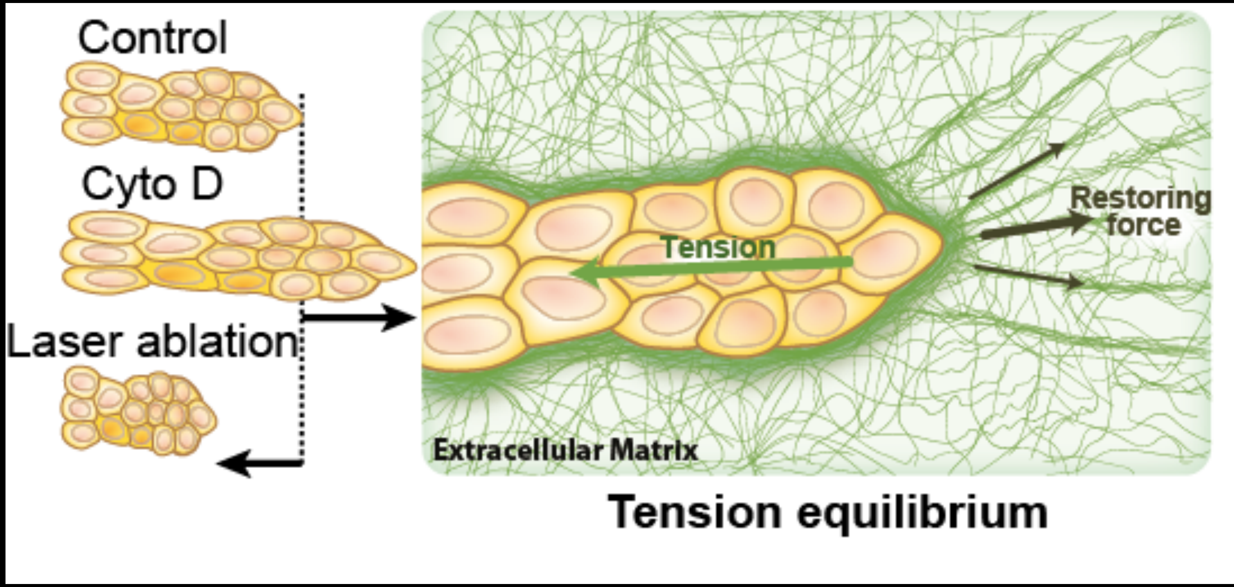


Fluorescent collagen

Plastic deformation of the collagen matrix in front of the tip cells

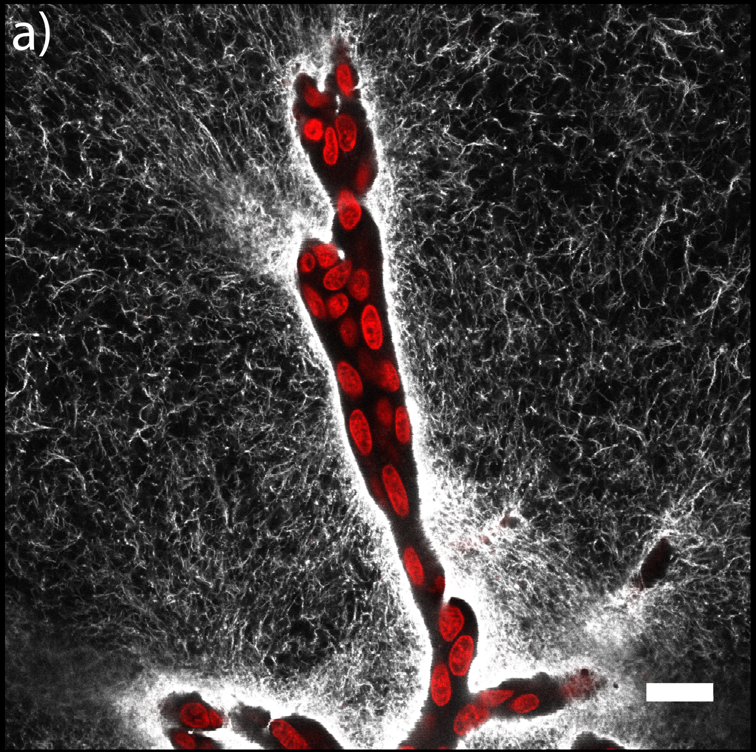


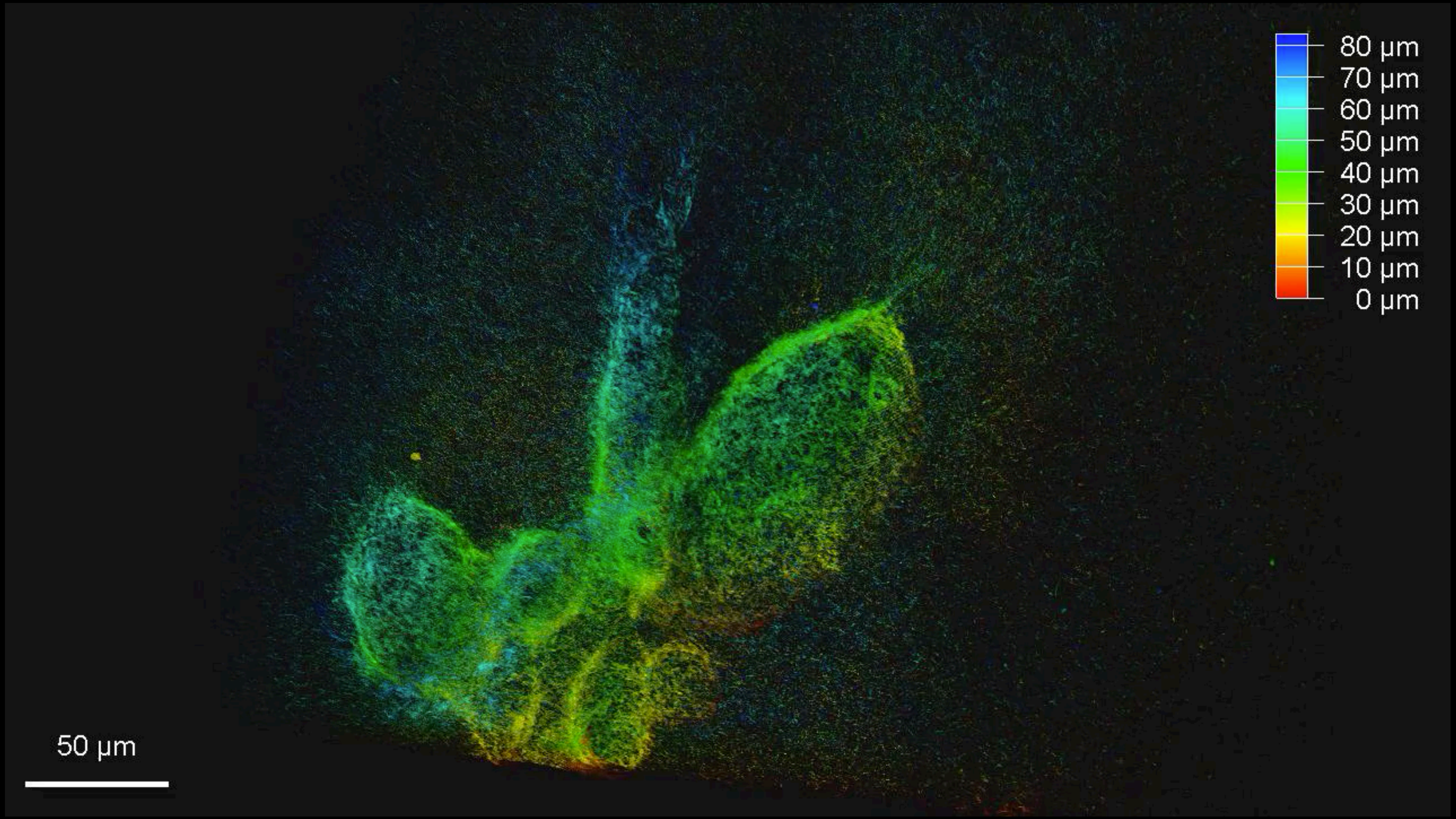
Length change $L_{treat}/L_{control}$
0.4
0.2
0
-0.2
Cyto D
Laser ablation



Control
Cyto D
Laser ablation
Tension
Restoring force
Extracellular Matrix
Tension equilibrium

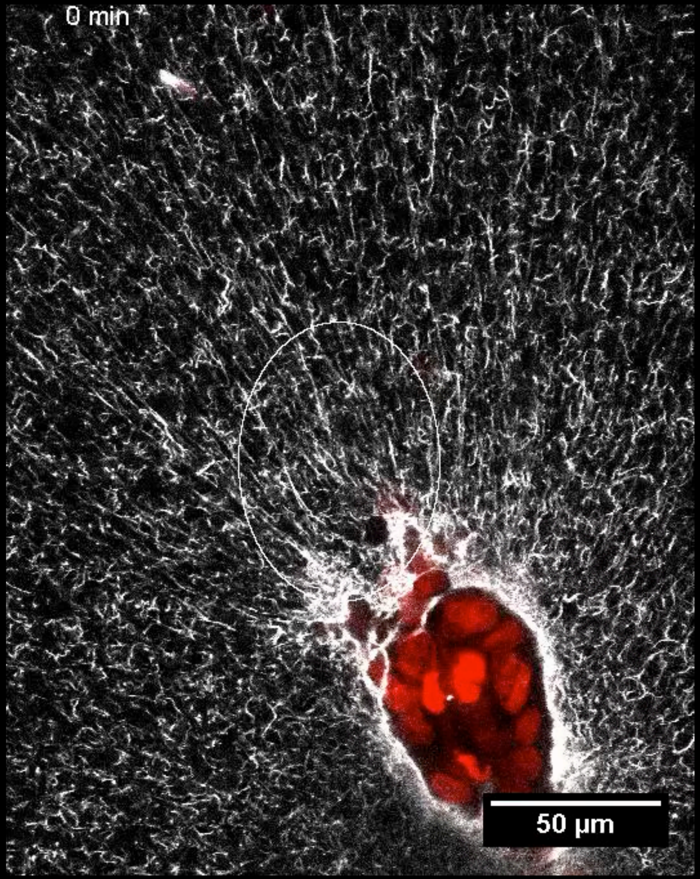
Generation of a stable collagen cage around elongating duct

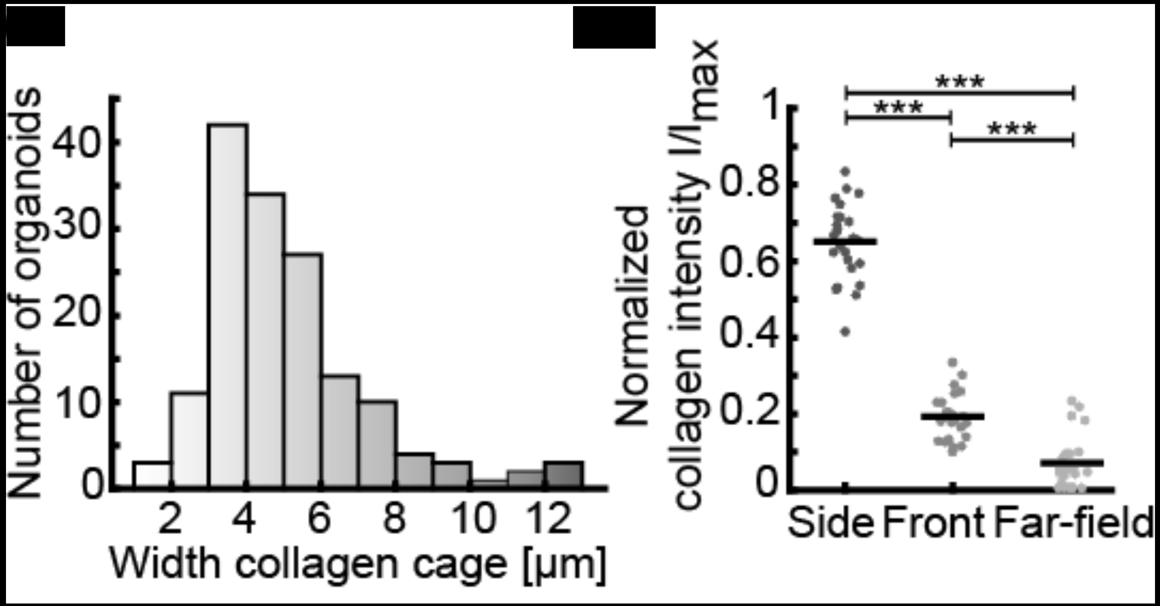




https://biorxiv.org/cgi/content/short/860015v1

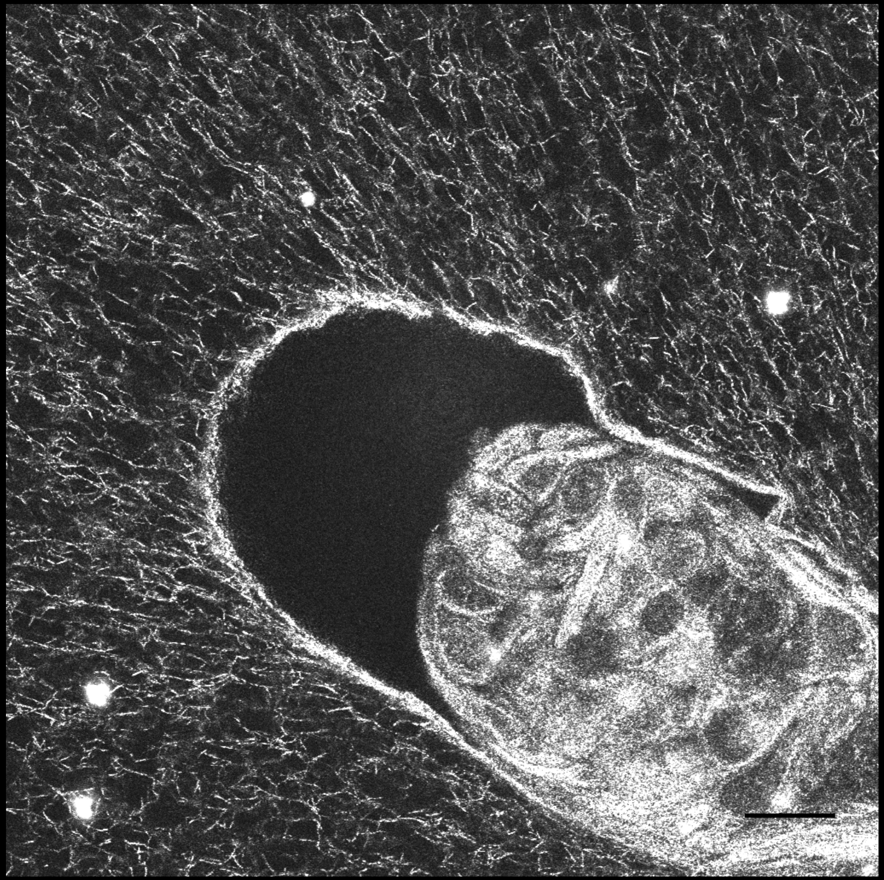
Generation of a stable collagen cage around elongating duct

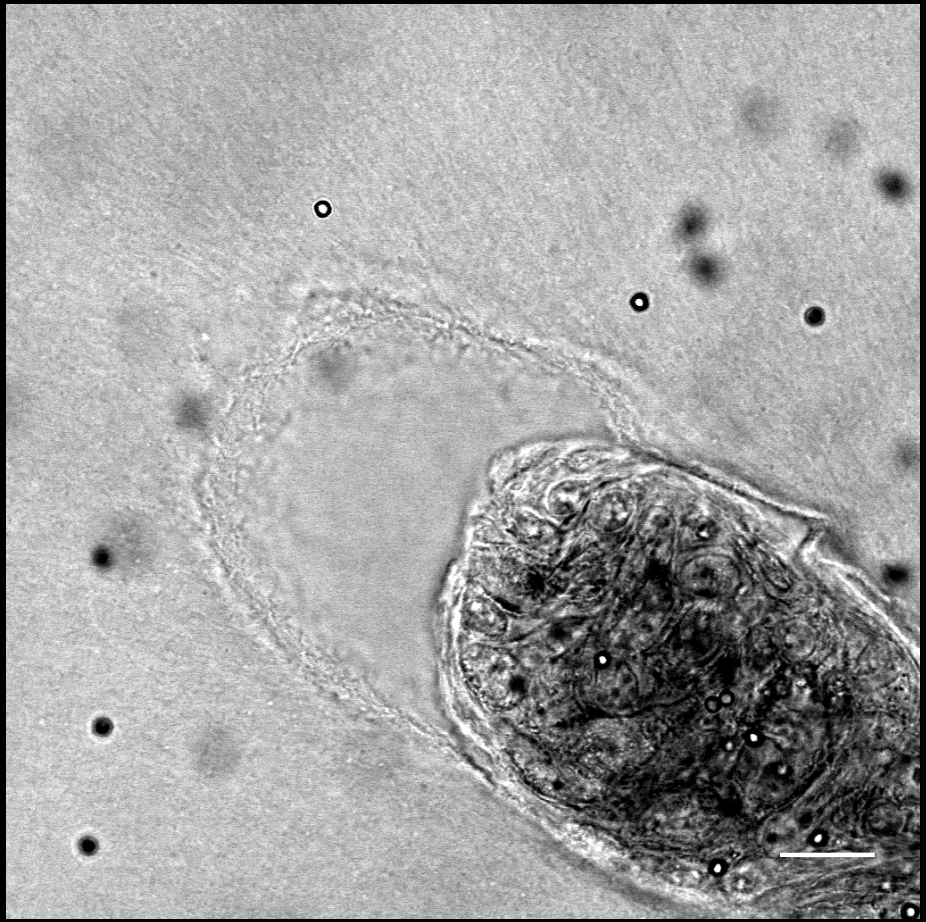




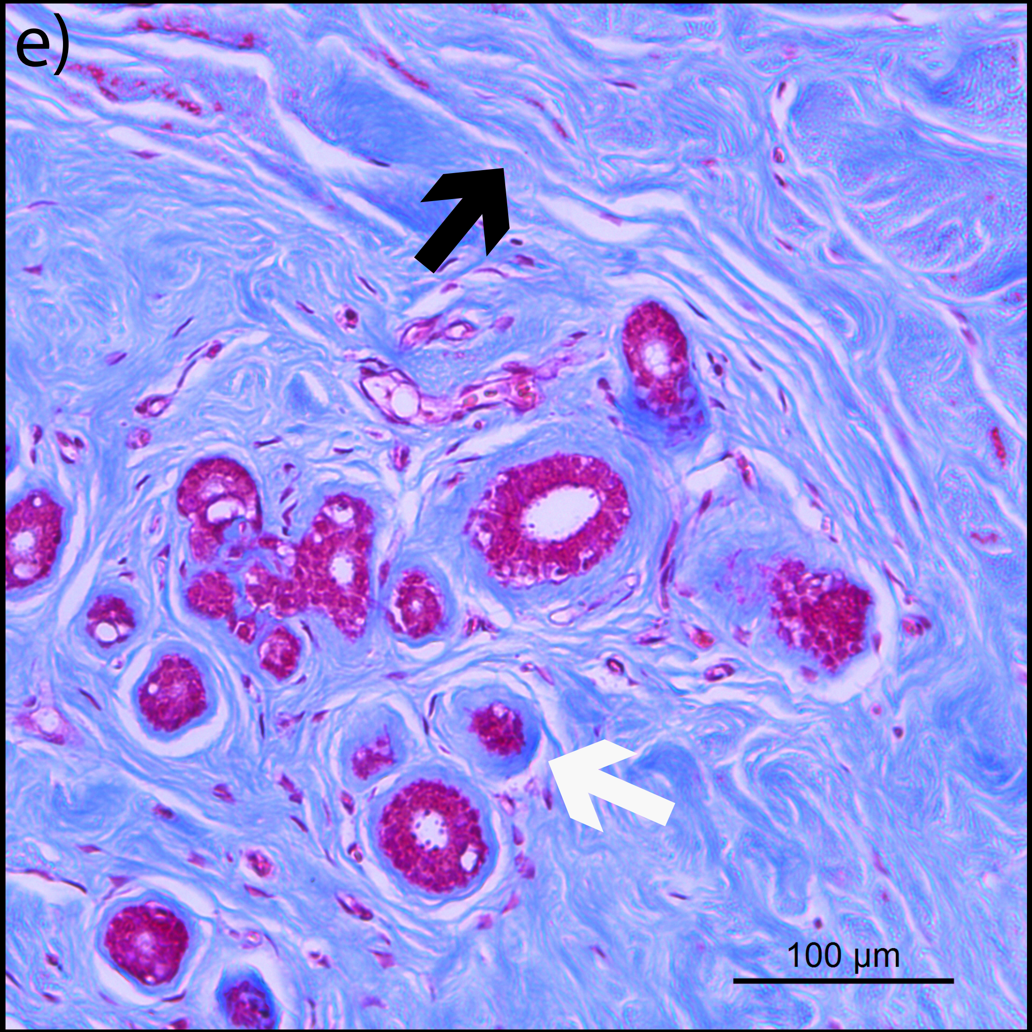
https://biorxiv.org/cgi/content/short/860015v1

Cage is mechanically stable – Triton X treatmeant



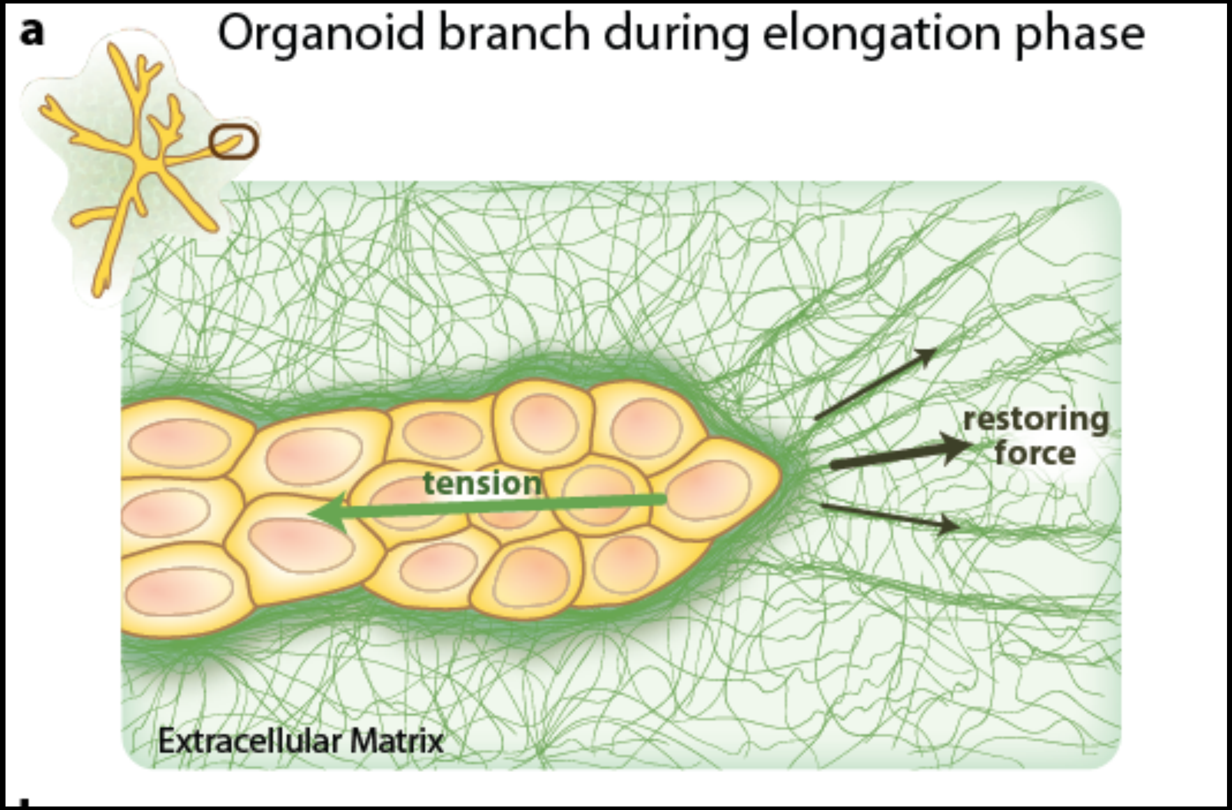


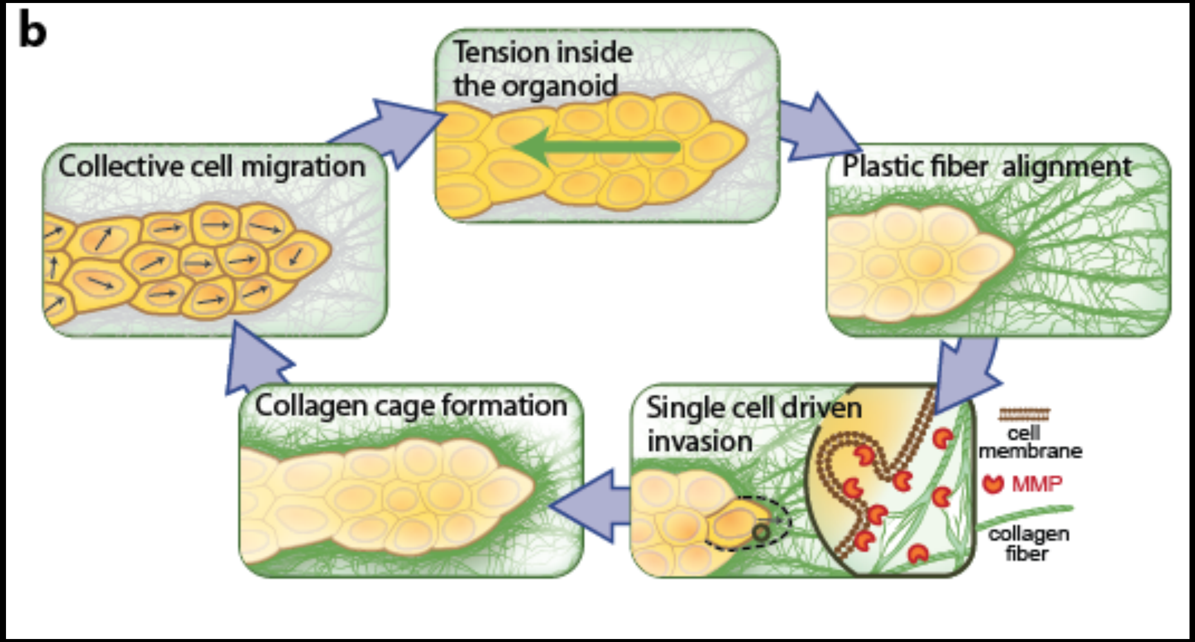
Are mammary ducts embedded in collagen cage in vivo?



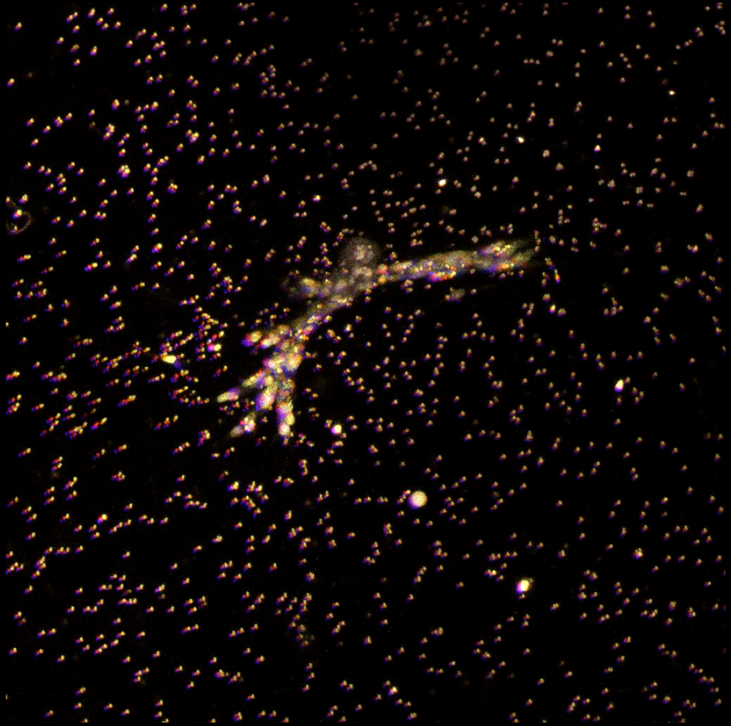
Trichrome staining, human breast tissue

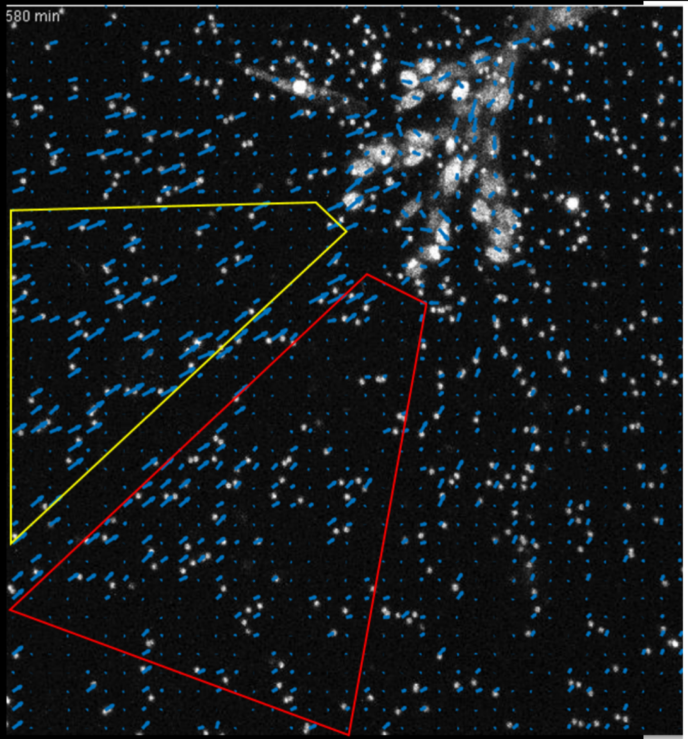
Tension Feedback Loop

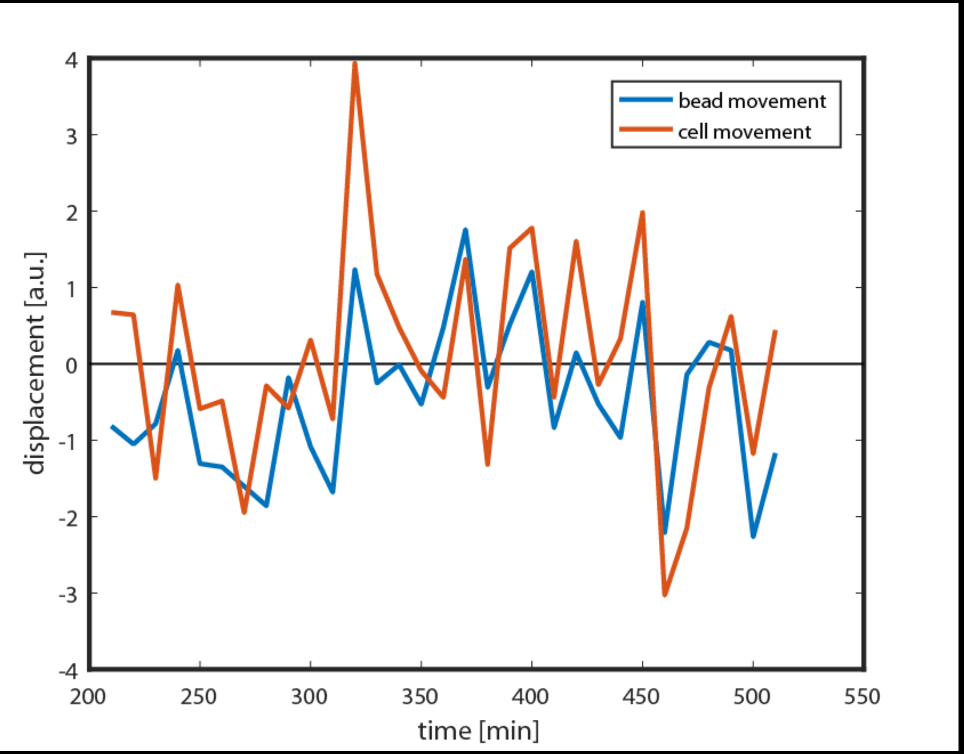




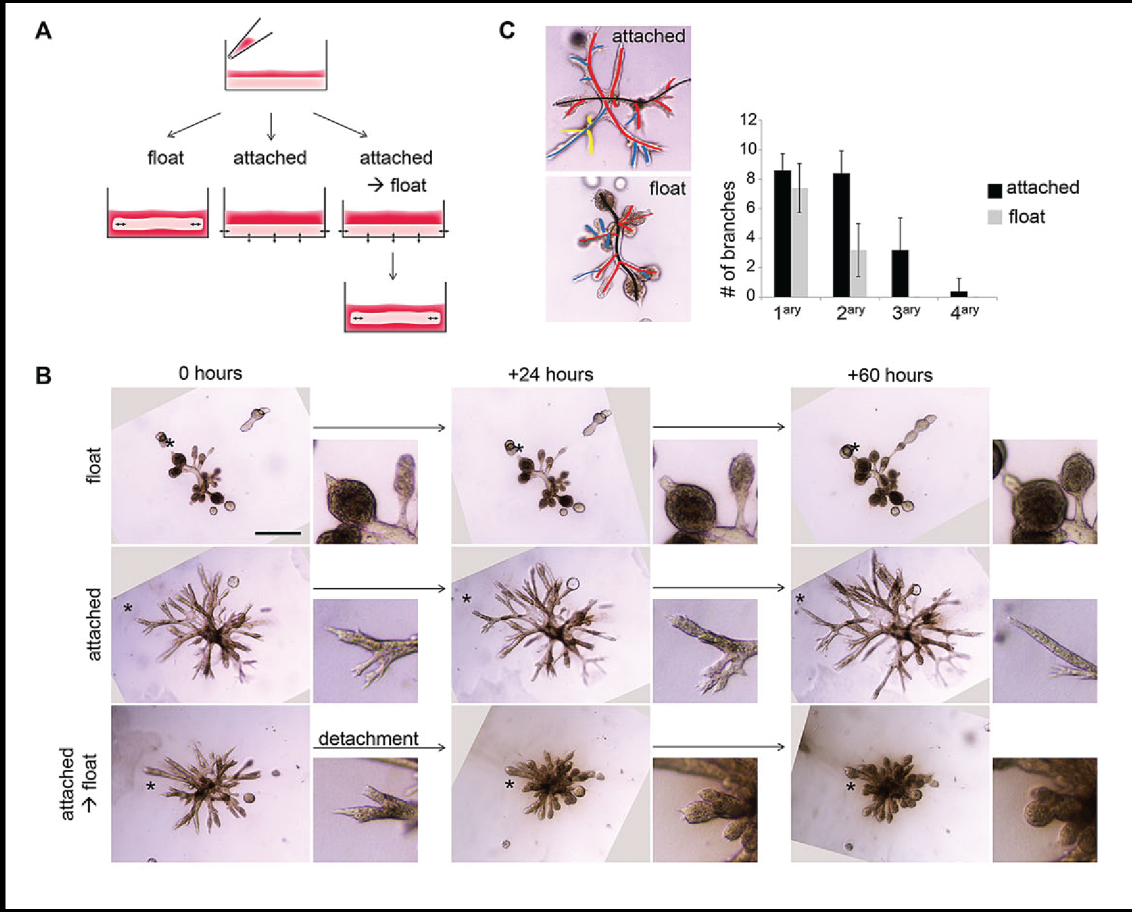
Cell movement and strain field correlate



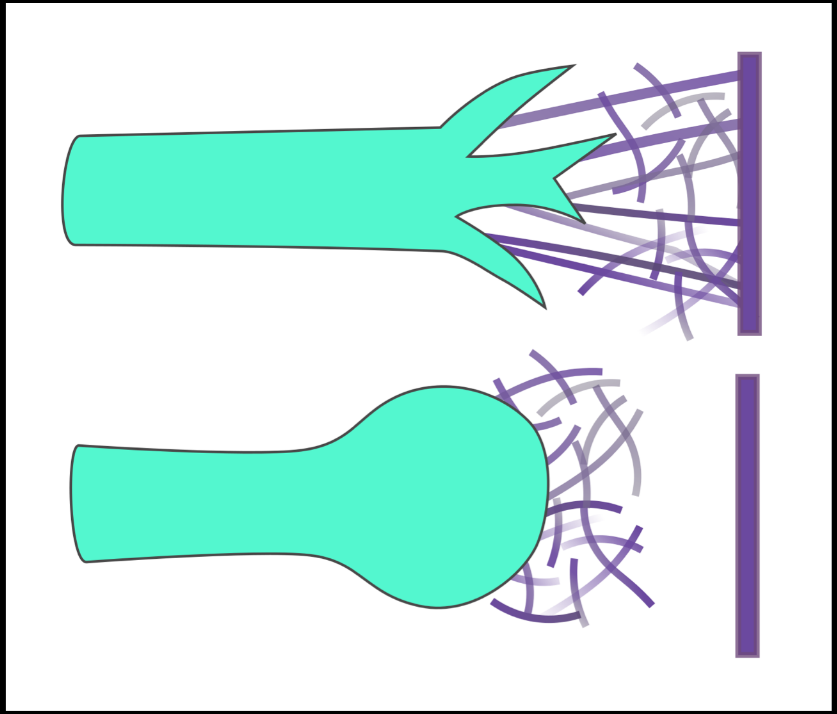




Organoids from human mammary gland cells develop alveoli-like branches in compliant gels



From a physical perspective: a transition from cylindrical to spherical geometry that requires low extracellular forces.

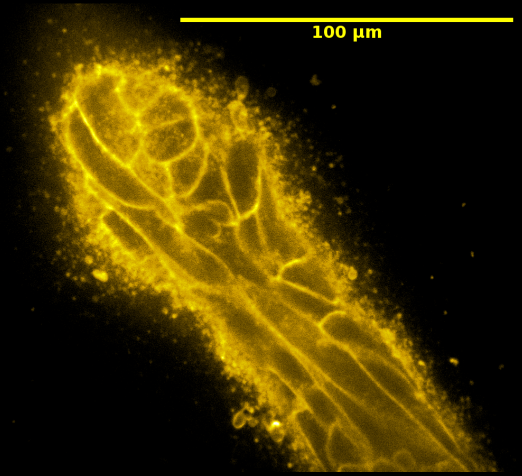


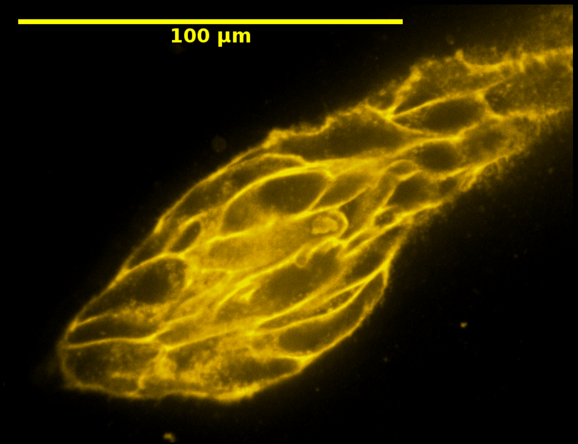
Linnemann et al, Development (2015) 142, 3239-3251

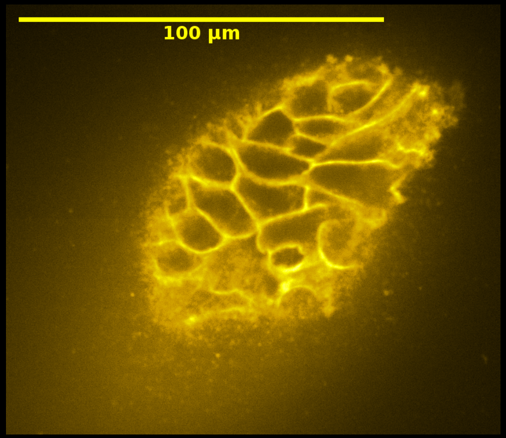
Idea: anisotropic Laplace law

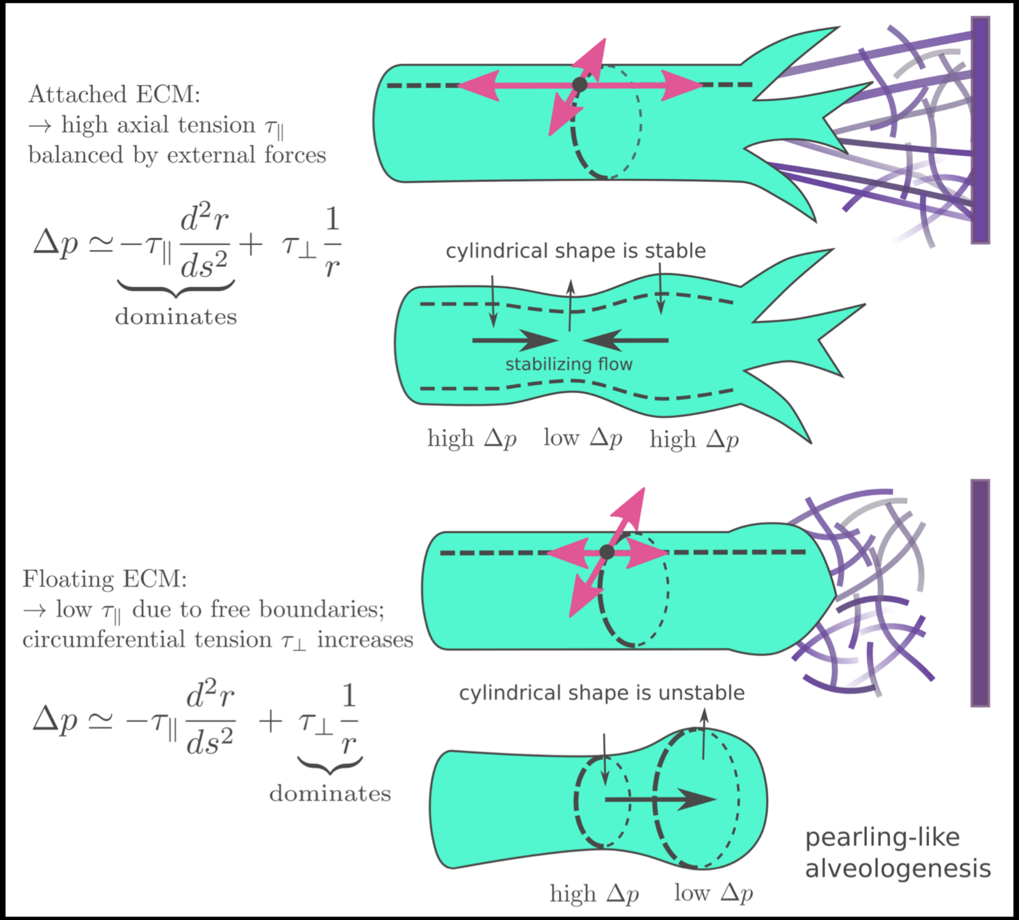
Cells are elongated
in the axial direction
in cylindrical branches.

In contrast, in round
alveoli they
are less elongated
and more isotropically
distributed.

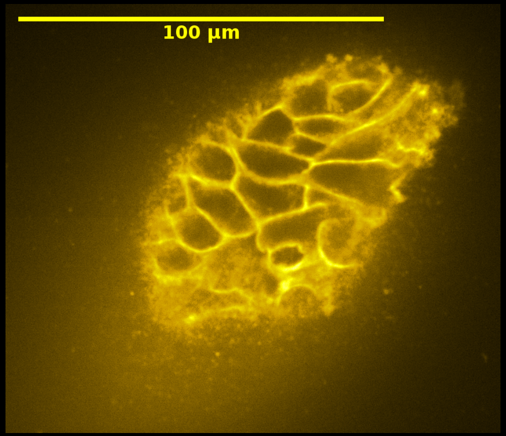


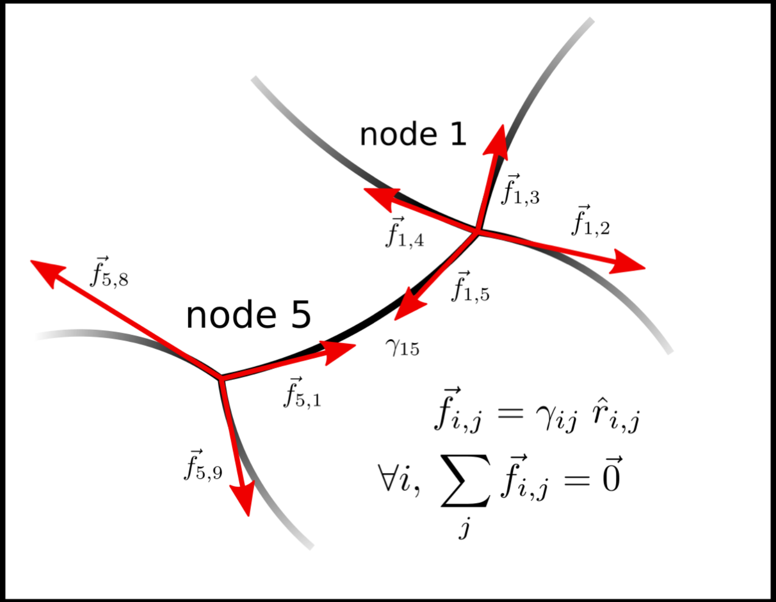


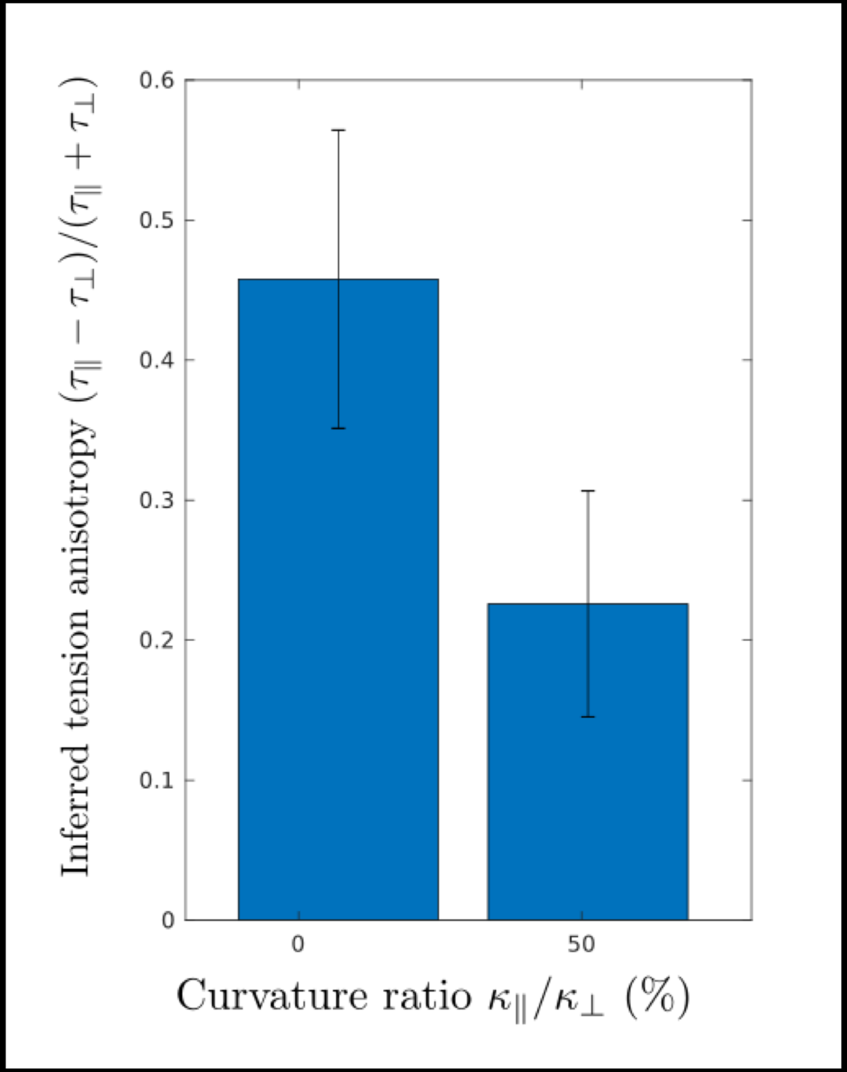




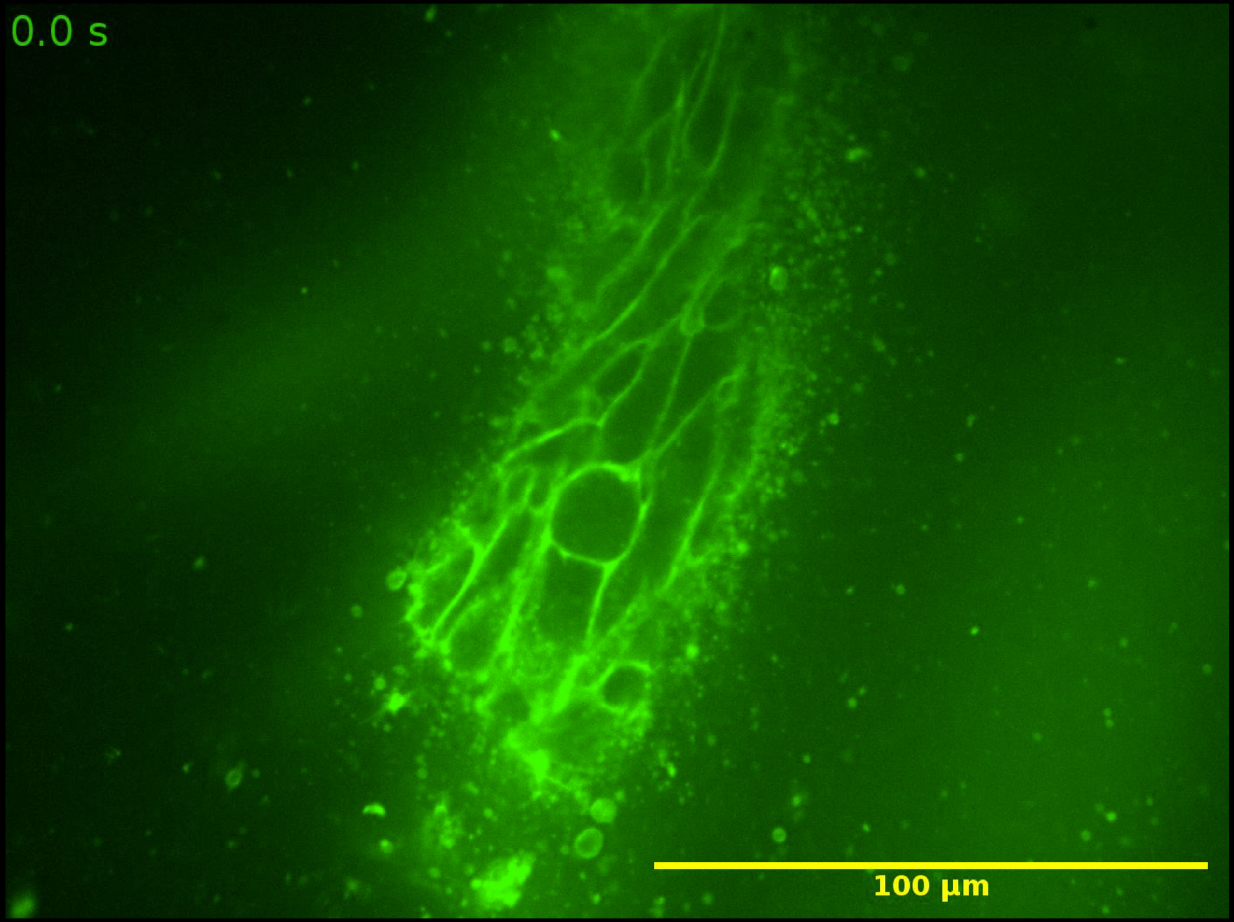
Anisotropy from curvelinear boundary method

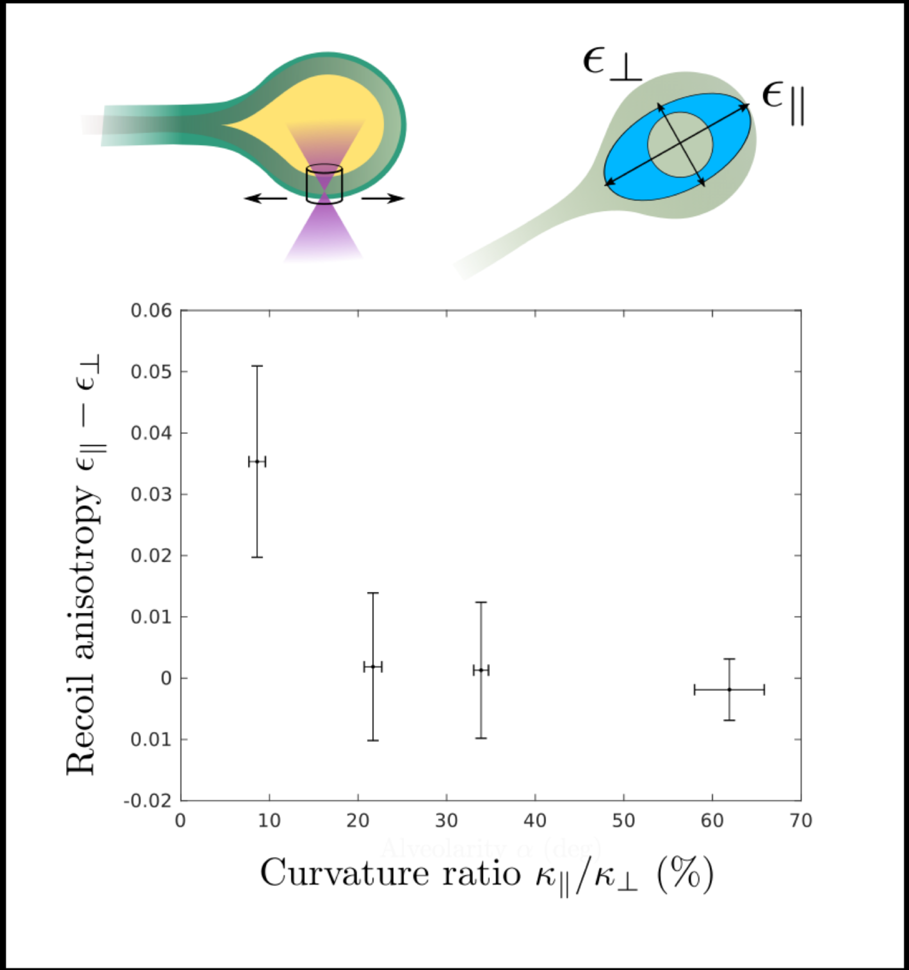




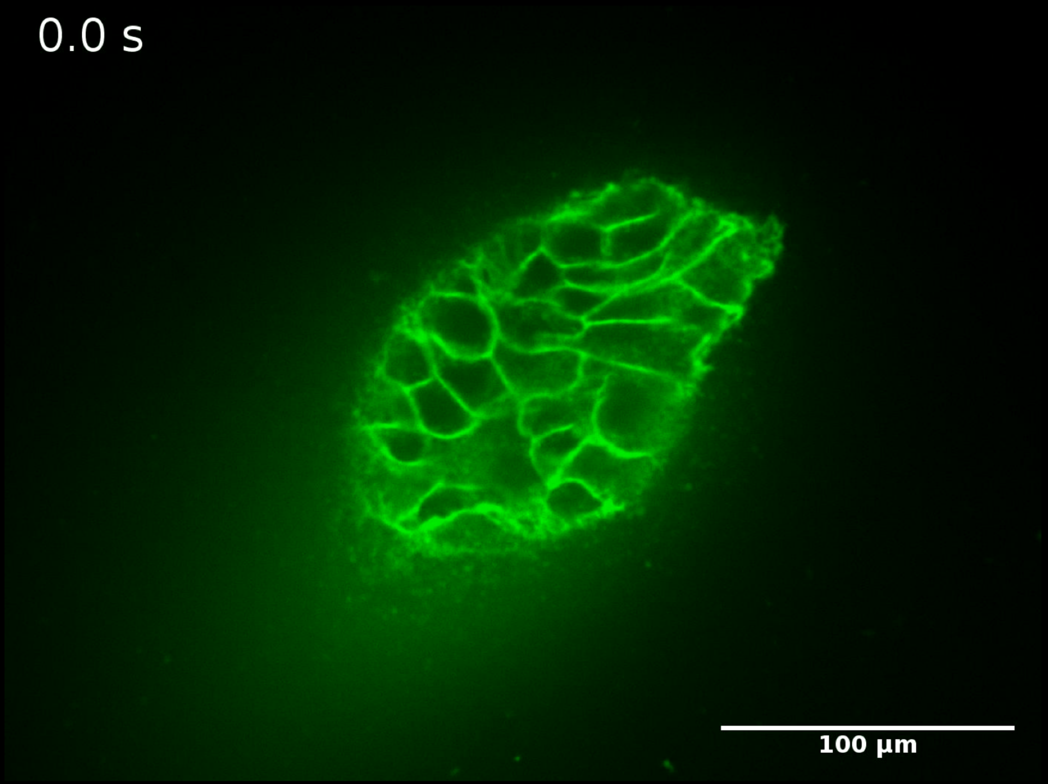


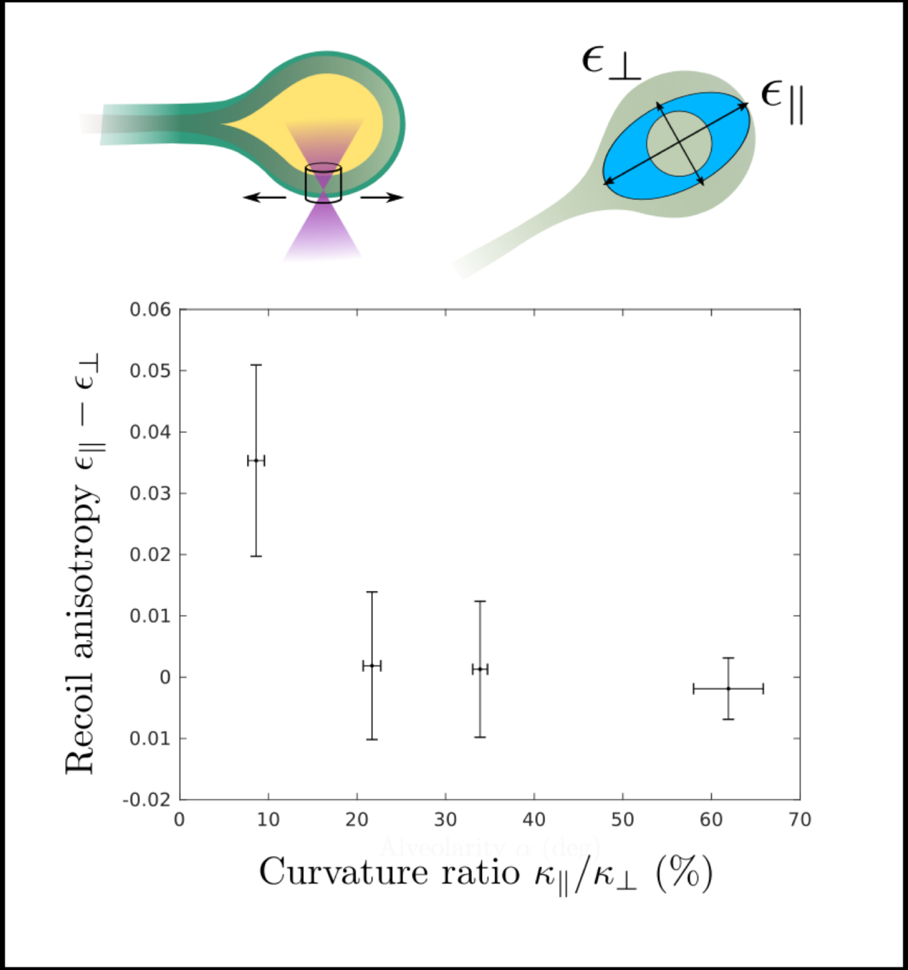
Laser ablation shows anisotropic reactions only in highly cylindrical branches



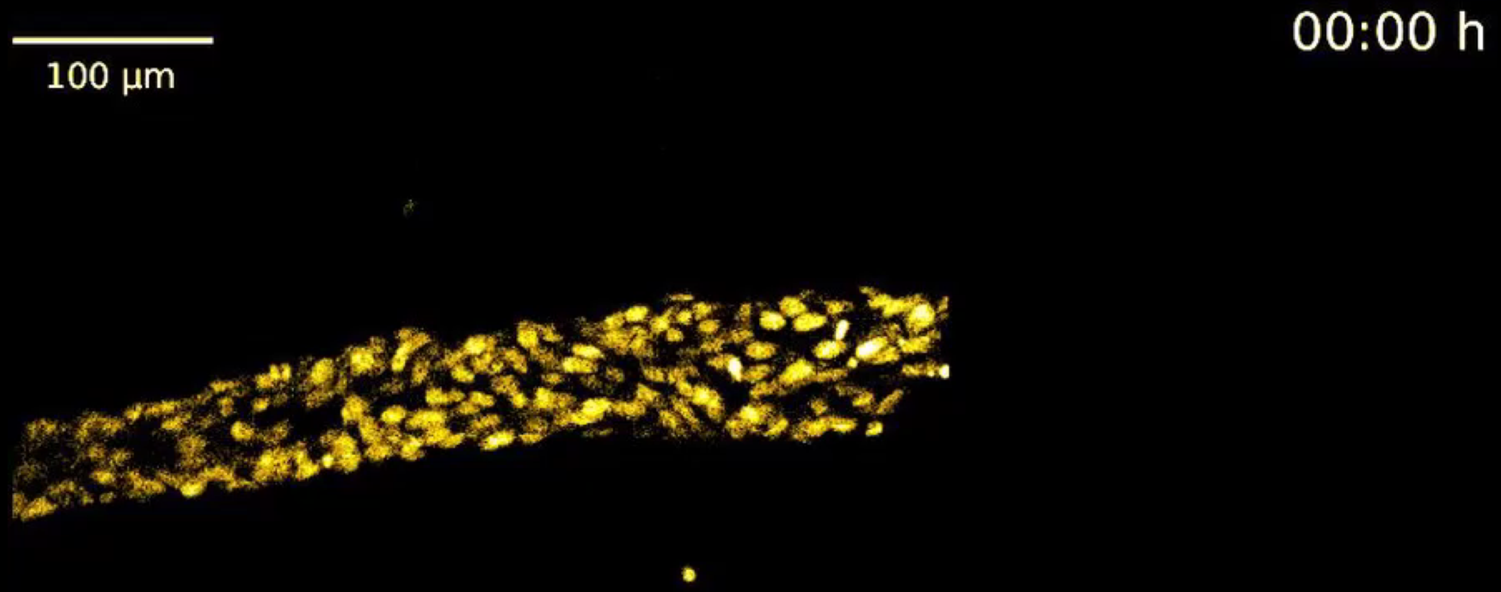


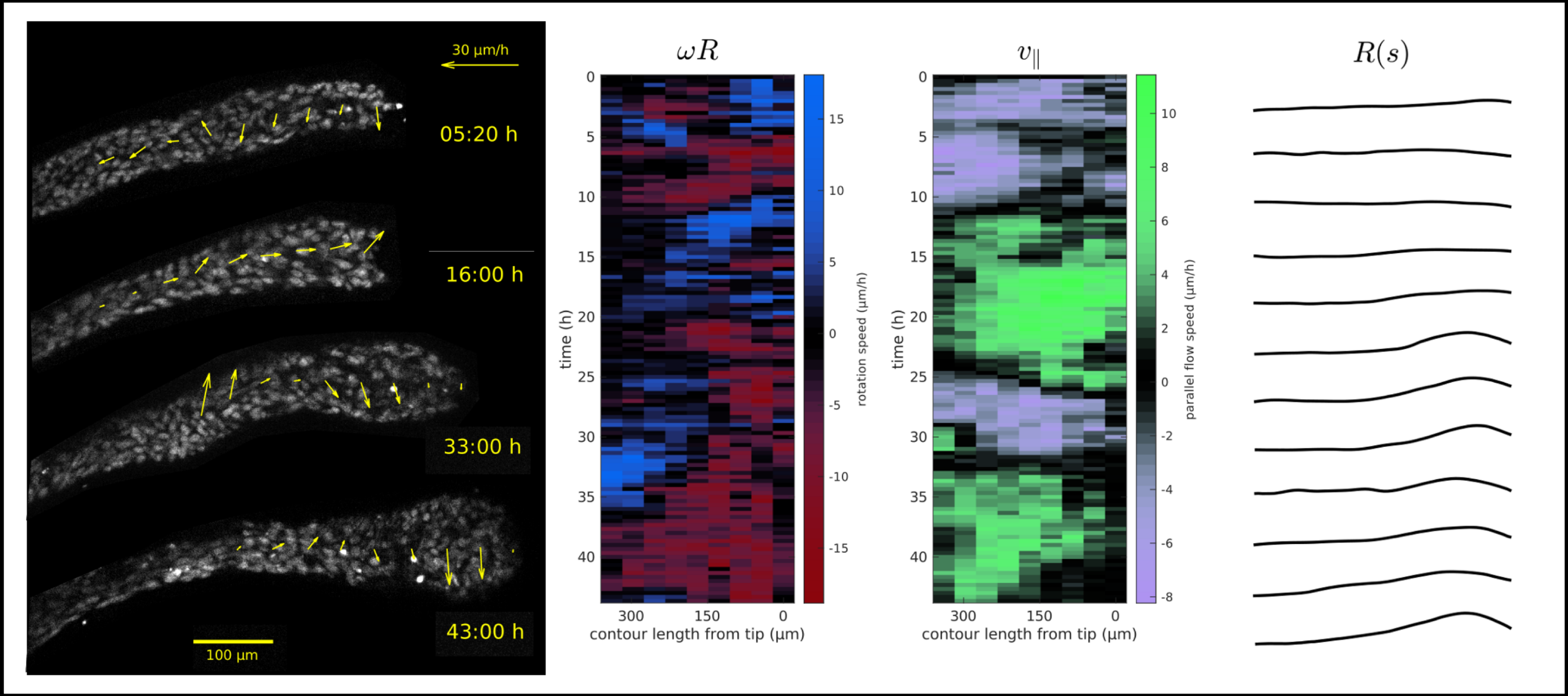
Laser ablation shows anisotropic reactions only in highly cylindrical branches





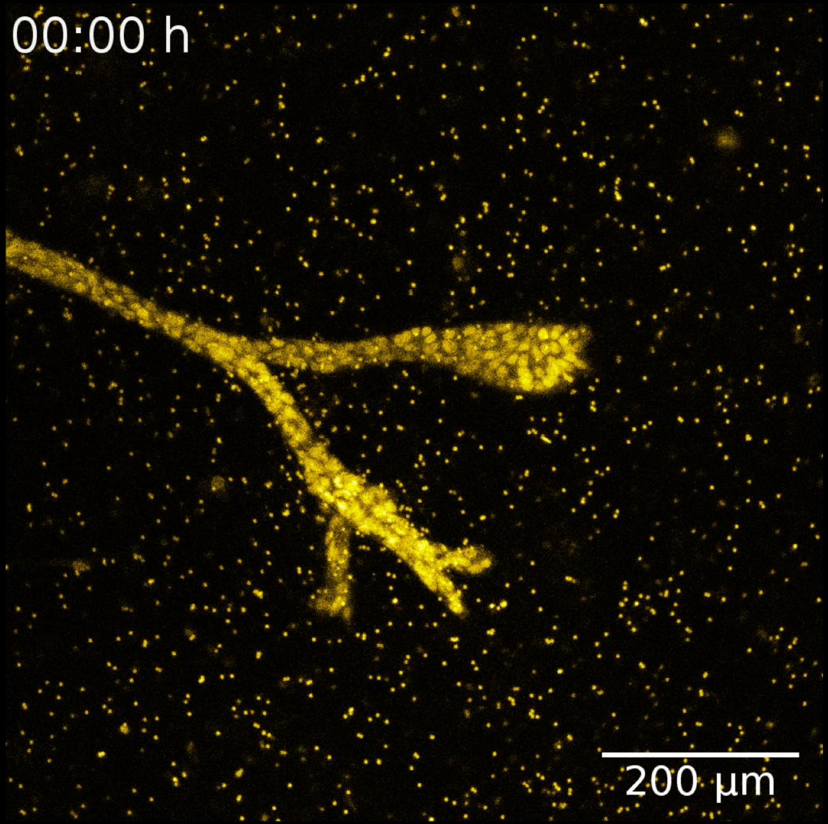
What triggers isotropification?

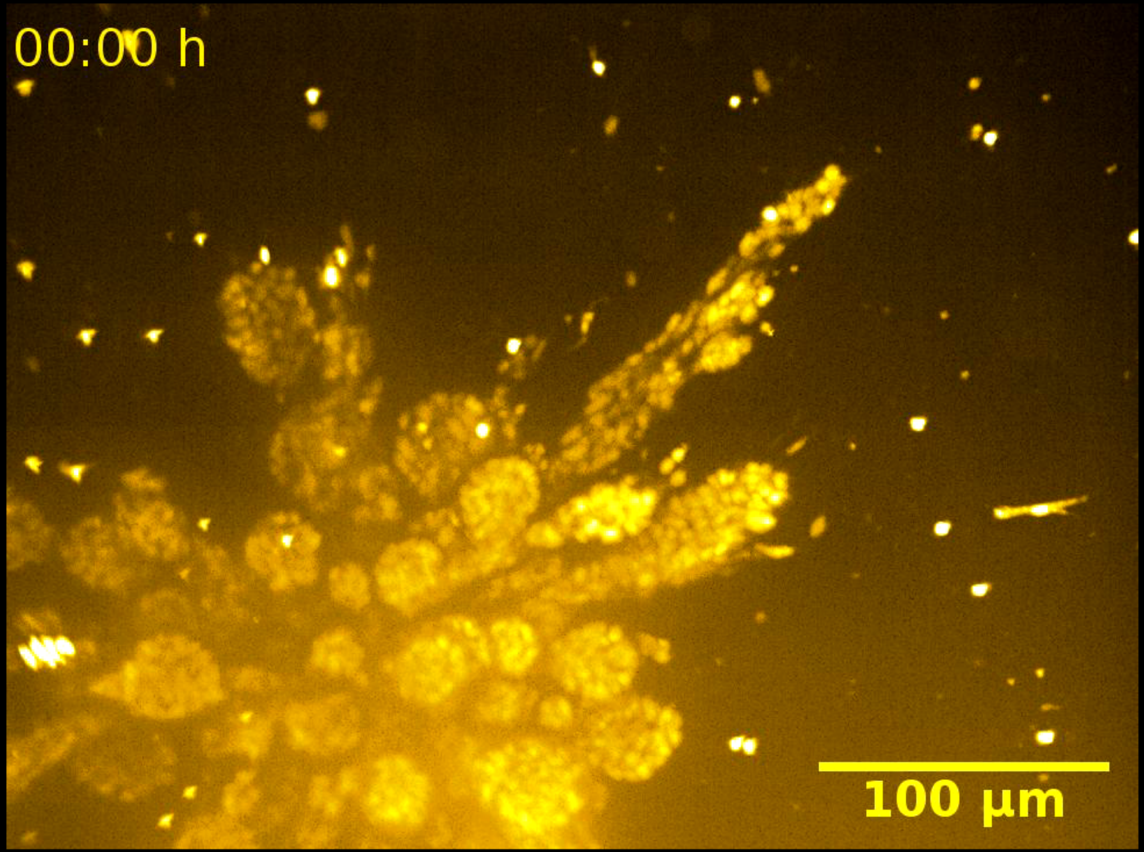




30 µm/h
05:20 h
16:00 h
33:00 h
43:00 h
100 µm
ωR
time (h)
contour length from tip (µm)
rotation speed (µm/h)
$v_\parallel$
time (h)
contour length from tip (µm)
parallel flow speed (µm/h)
$R(s)$

All Alveoli rotate!





Pancreas

E27
Benedikt Buchmann
Samuel Randriamanantsoa
Pablo Fernandez

Brains:
Lorenz Huber
Timo Krüger
Christoph Weber
Erwin Frey

Organoids:
Lisa Meixner
Christine Scheel

Papargyriou, Aristeidis
Maximilian Reichert

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