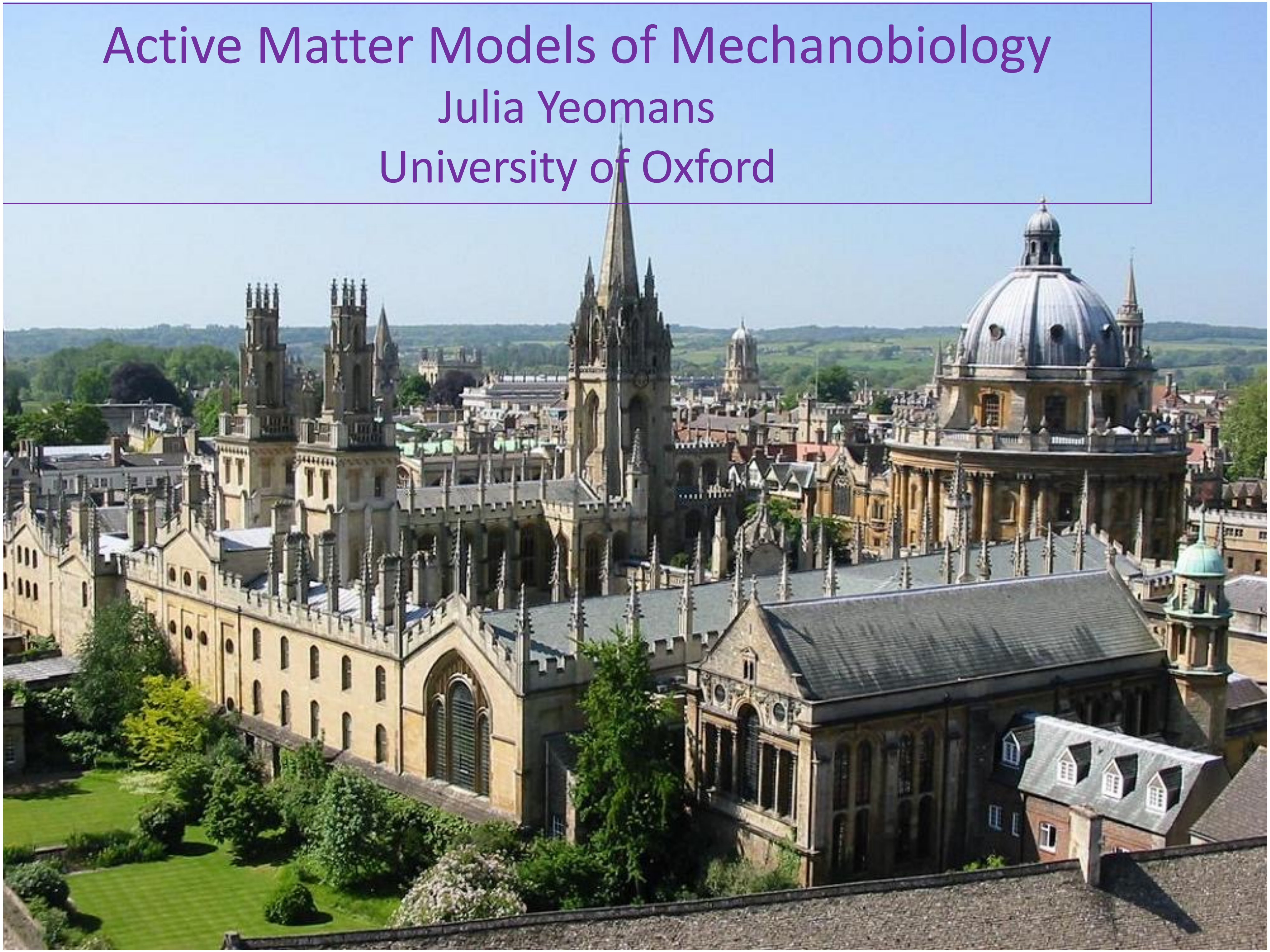
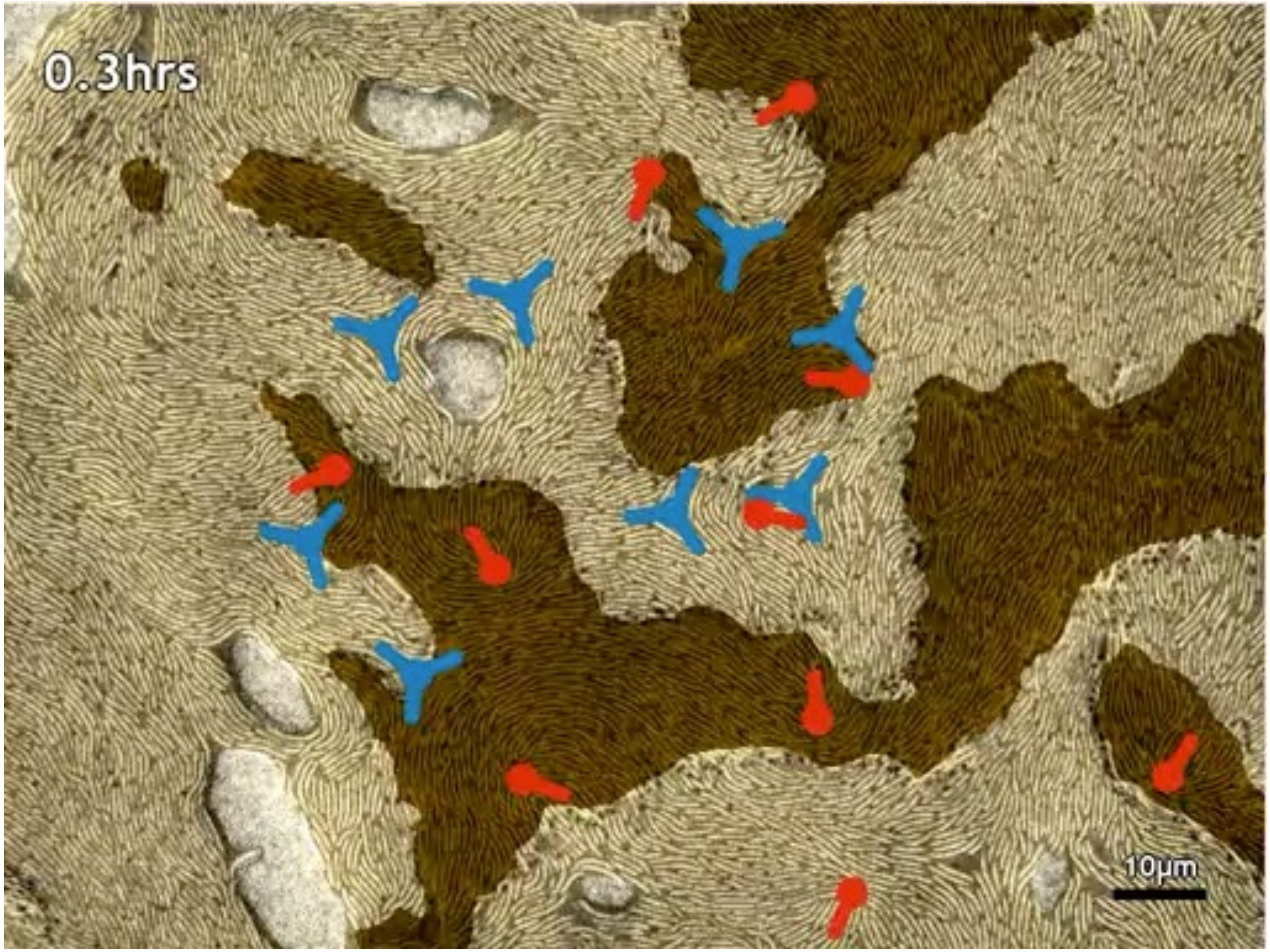
Active Matter Models of Mechanobiology

Julia Yeomans
University of Oxford



Layers form at positions of +1/2 defects, holes at -1/2 defects

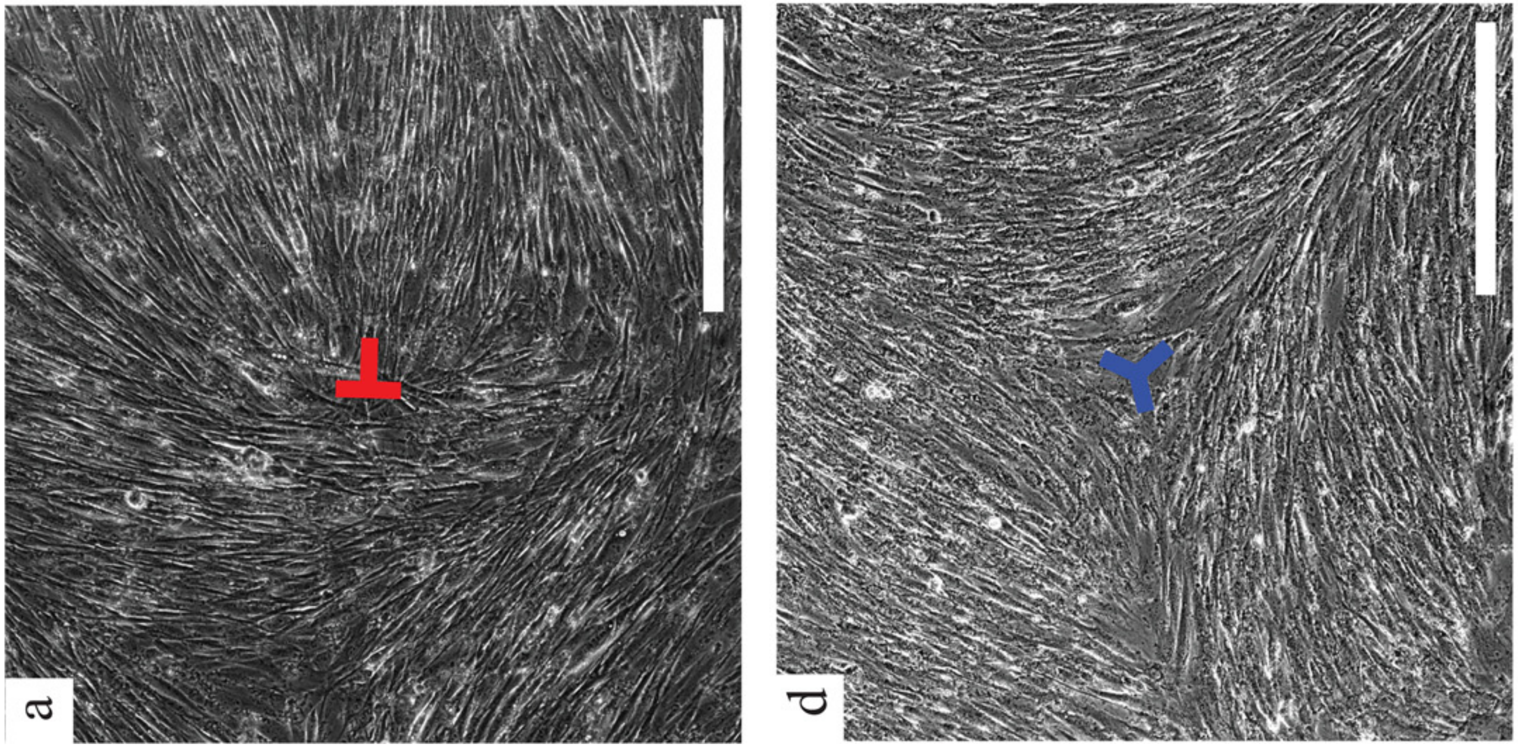


Copenhagen et al, Nature Physics **17** 211 (2021)

Myxococcus xanthus

Topological defects in the mesothelium suppress ovarian cancer cell clearance

Jun Zhang, Ning Yang, Pamela K. Kreeger, Jacob Notbohm   APL BioEng 2021



1. Introduction

2. Active turbulence: the basics

3. Active turbulence: details

4. Mechanobiology

Active anchoring and cell sorting

How do confluent cell layers move?

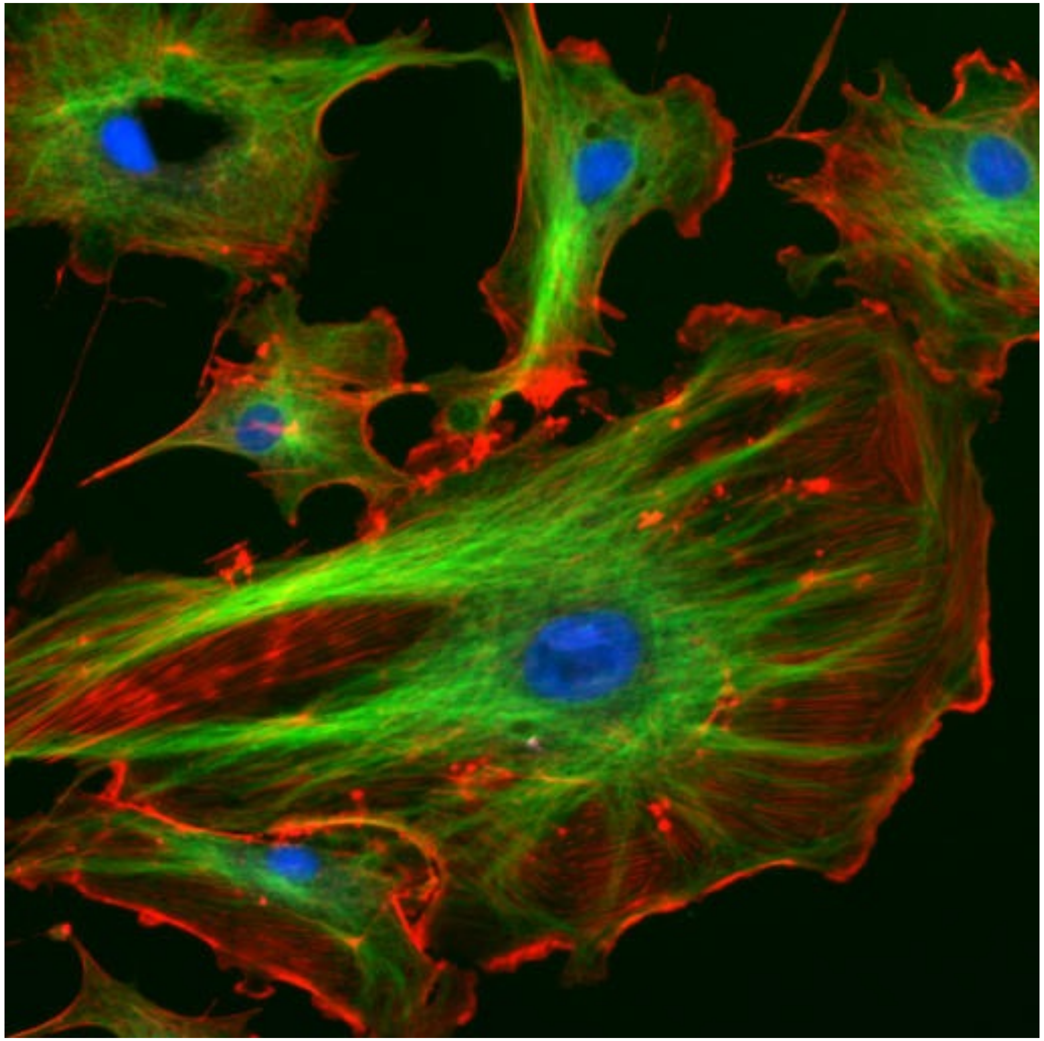
Are cells extensile or contractile?

Phase field models

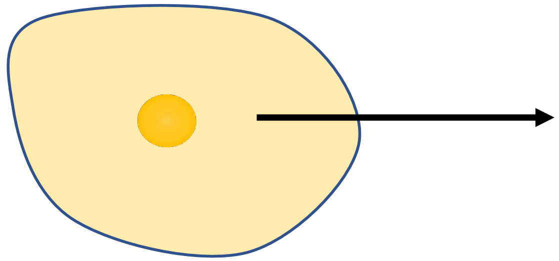
… and a bit more about vertex models

The hare and the tortoise

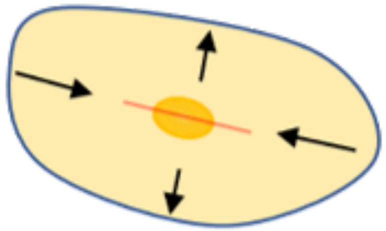
How do individual cells move?



Polar driving

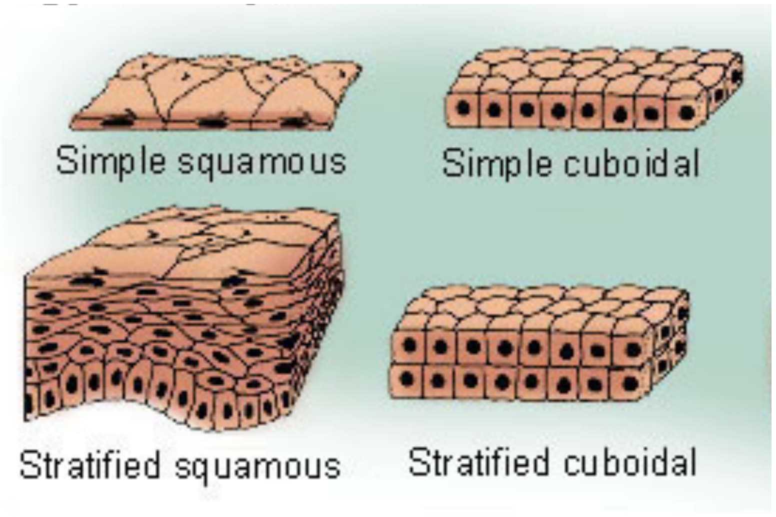


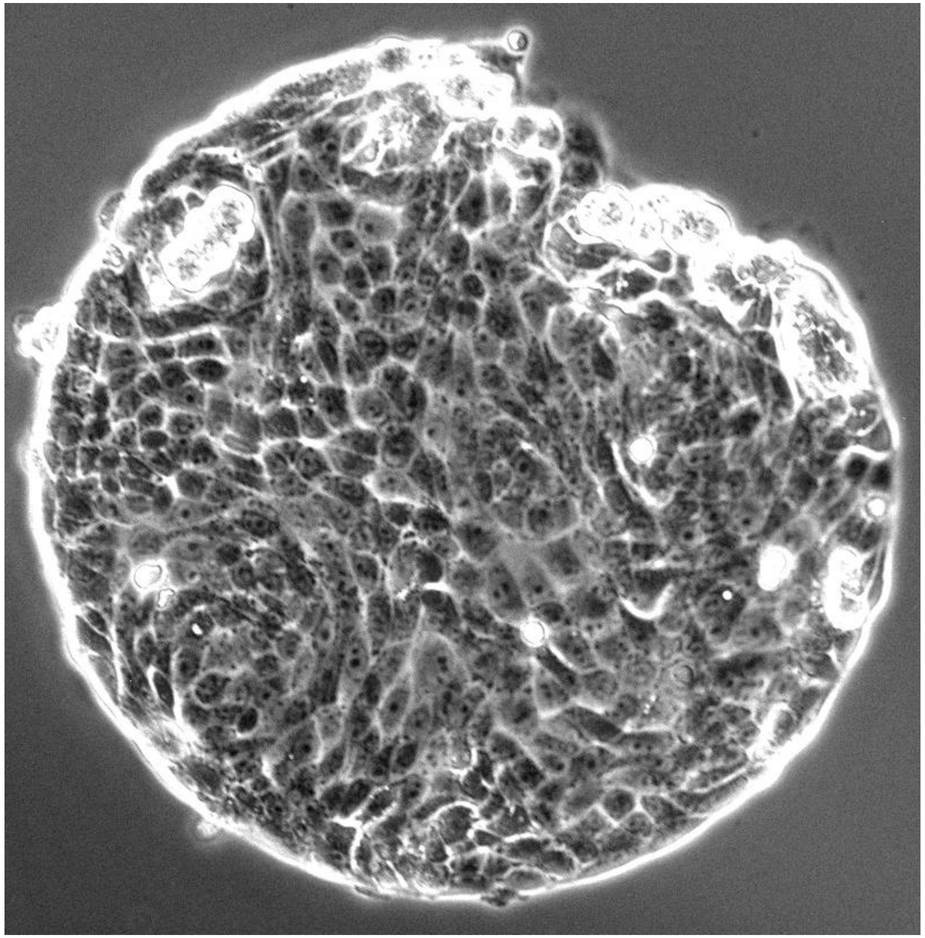
Self contractile activity



How do monolayers of cells move?

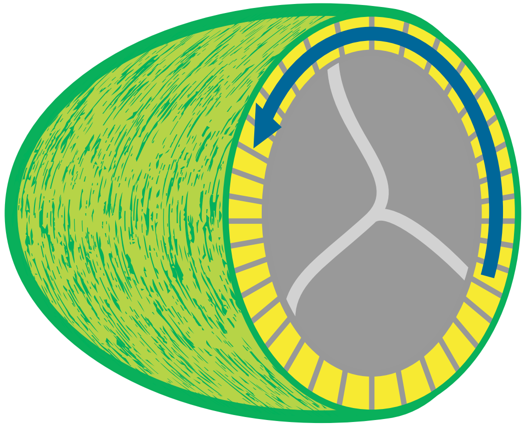
epithelial cells

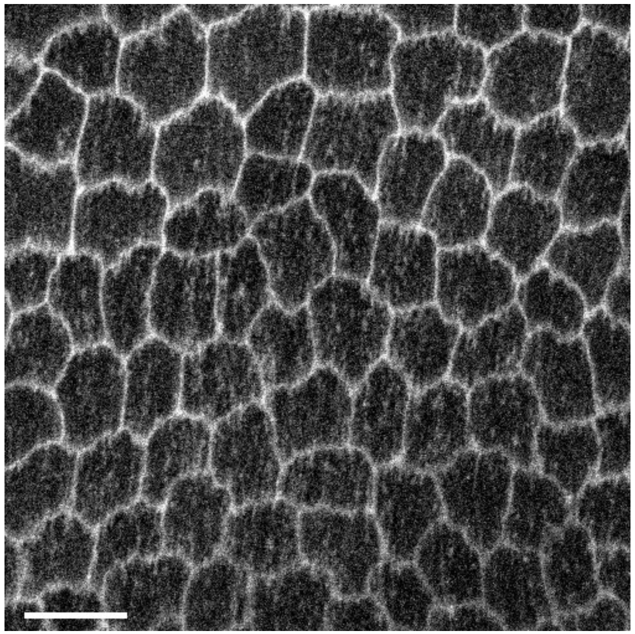


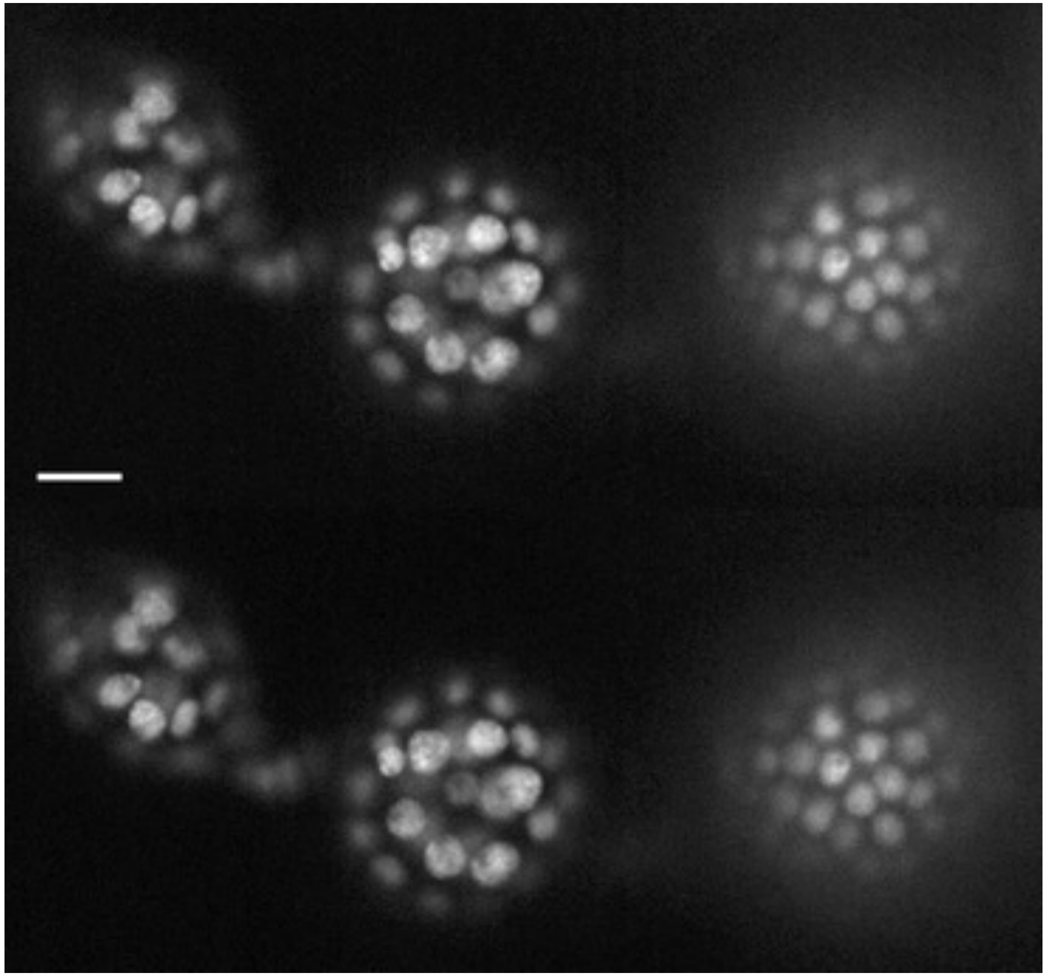


How do layers of cells move? Jamming, Flocking

Egg chamber rotation

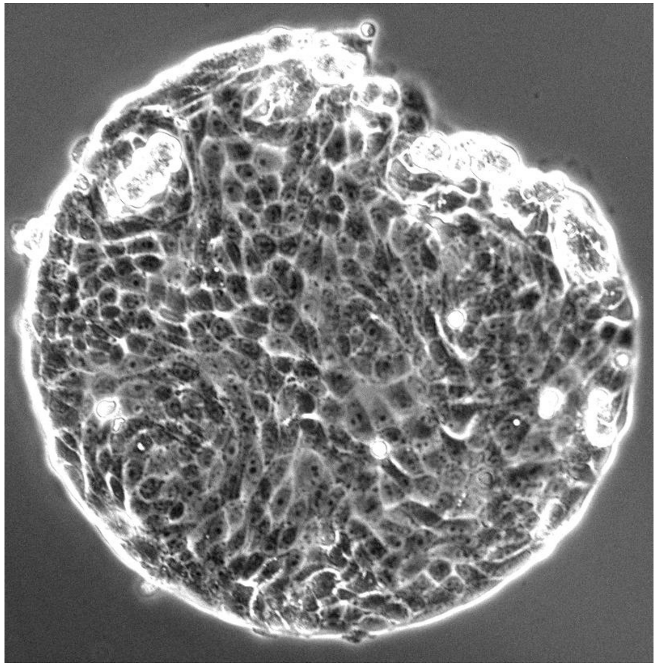


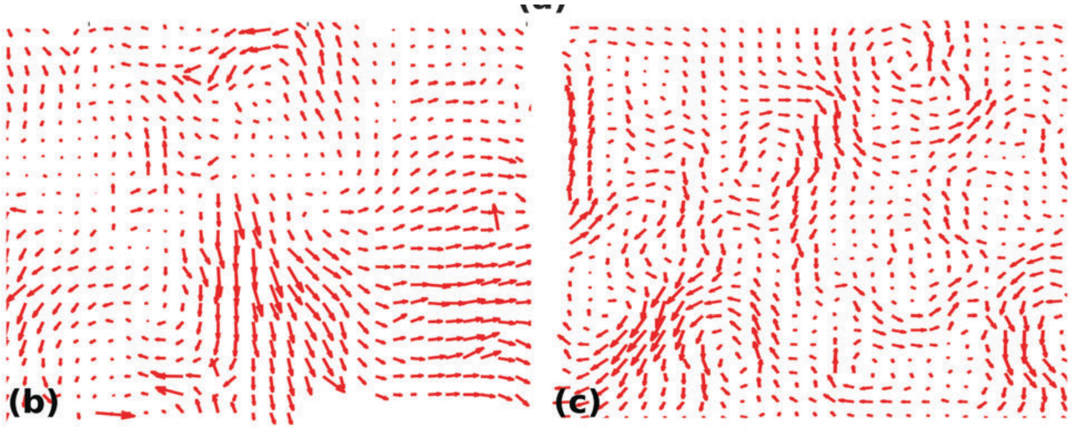




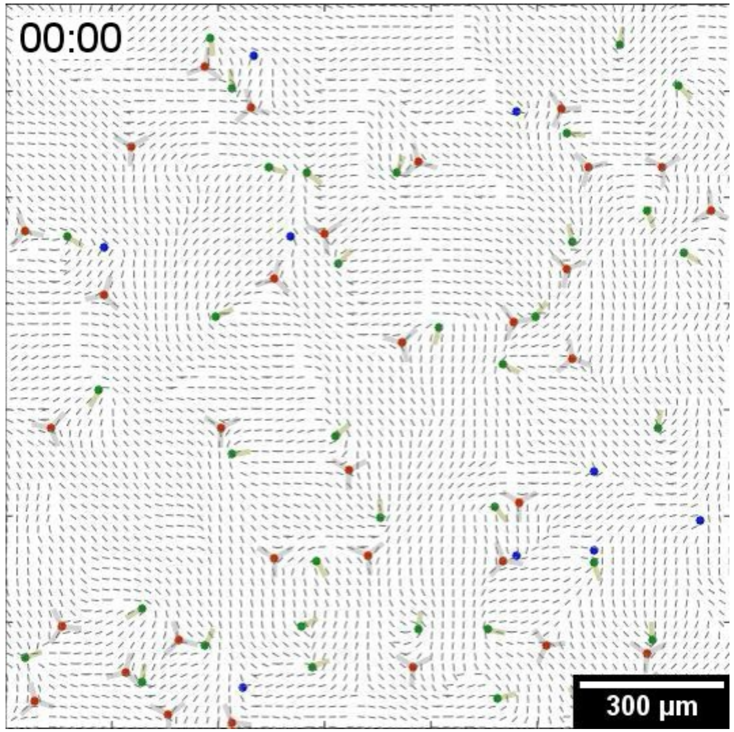
Cetera et al. Nature Comms. 5, 5511 (2014)

How do layers of cells move? Active turbulence?





velocity fields reminiscent
of active turbulence

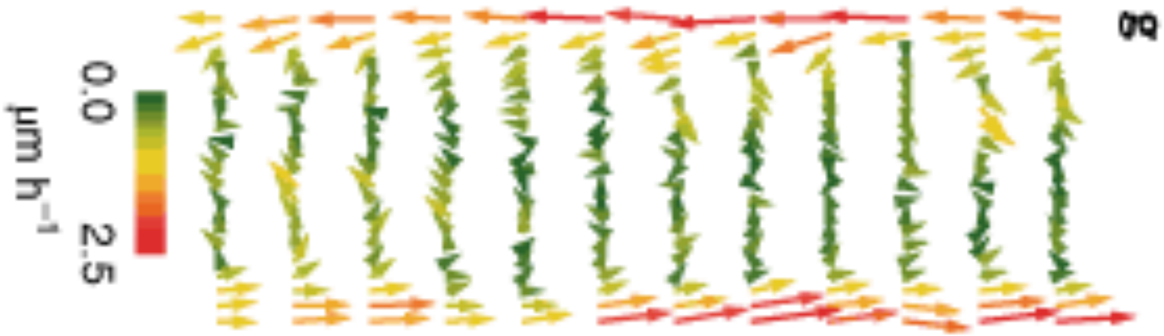


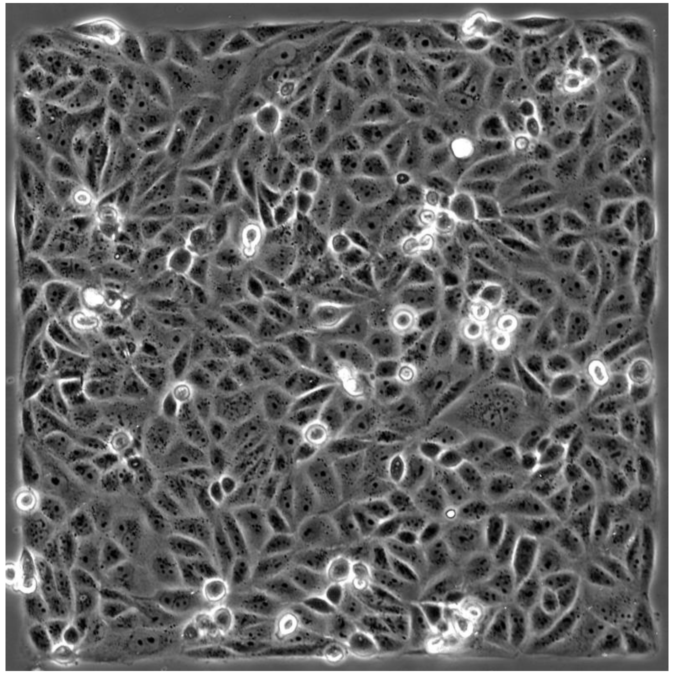
topological defects in human
bronchial epithelial cells
Blanch-Mercader et al PRL 2018

Regular flow when confined at scales below the active length

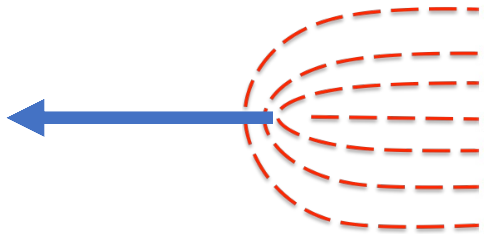
shear flow in confined channels

retinal pigment epithelial (RPE1) cells
and C2C12 mouse myoblasts
(Duclos et al Nat Phys 2018)

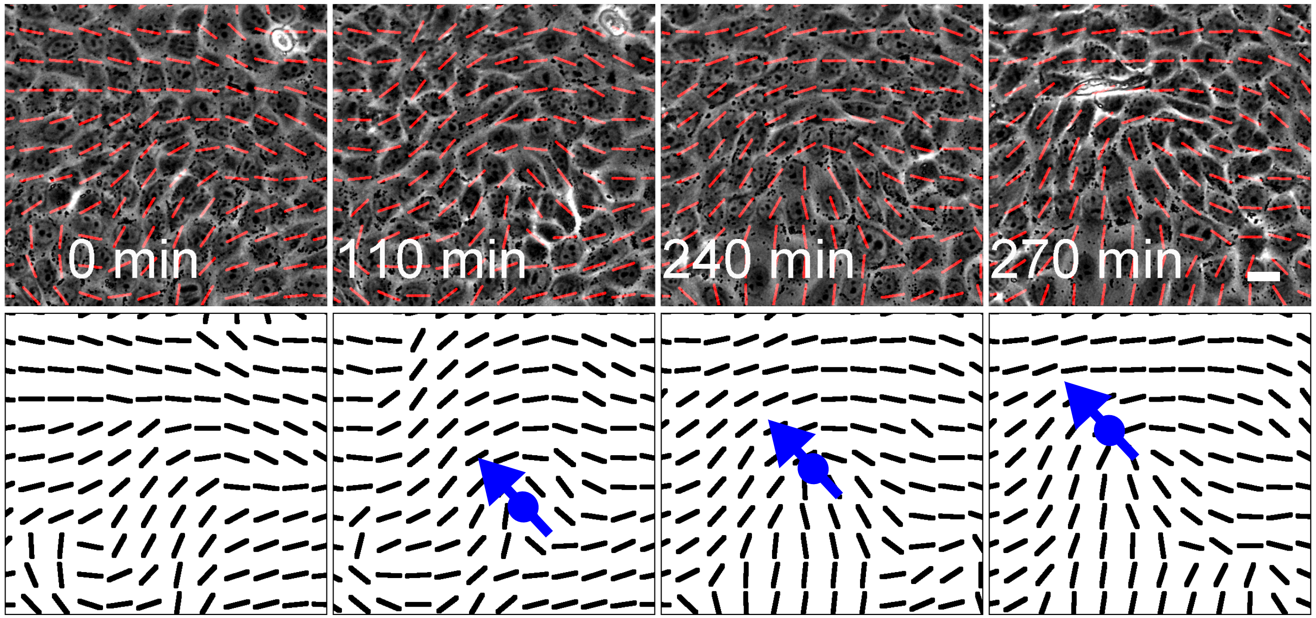




MDCK monolayers



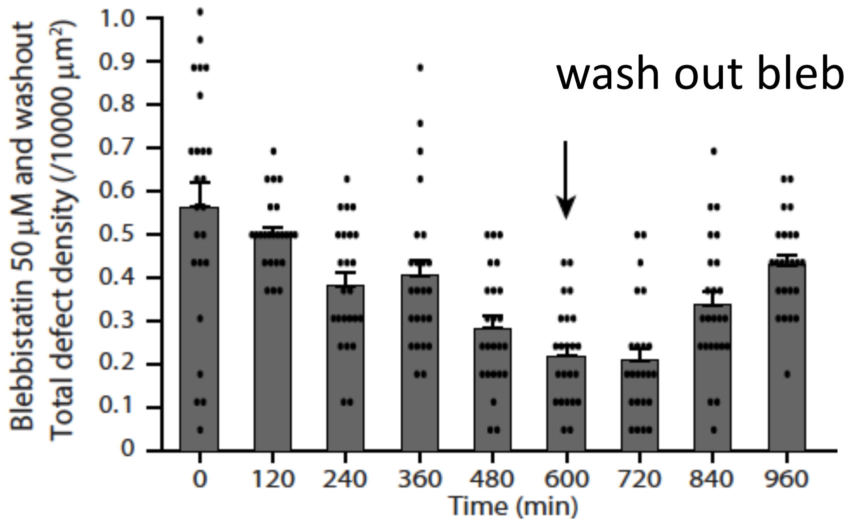
+1/2



topological defects in MDCK cells Saw et al., Nature 2017

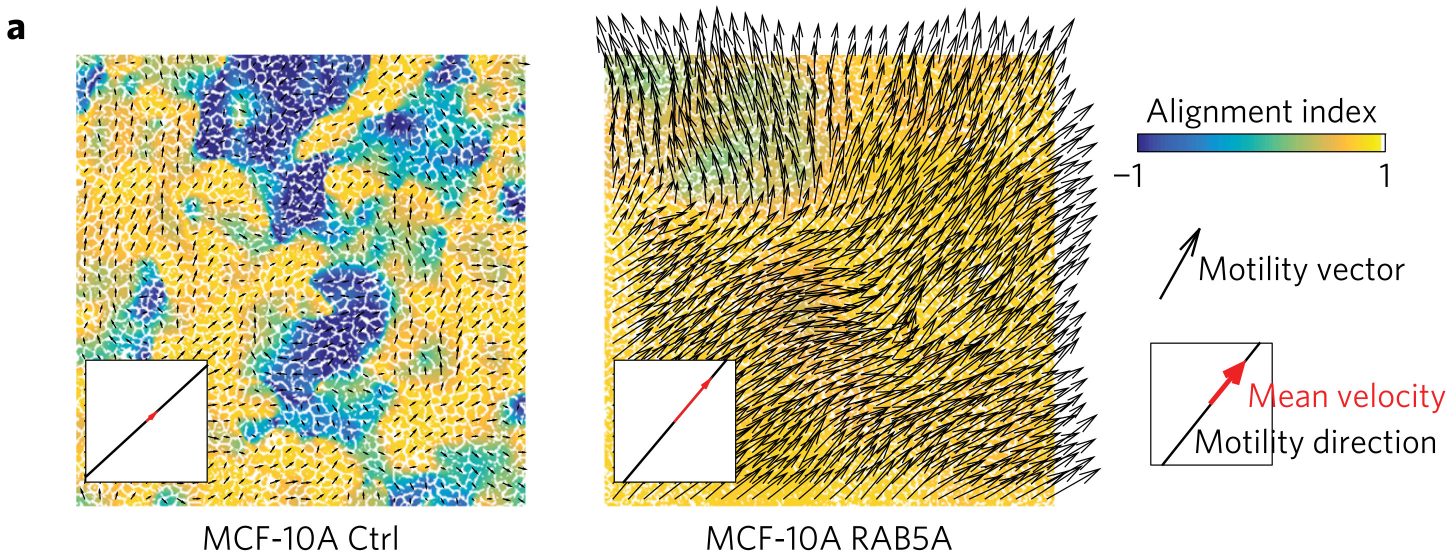
Number of defects

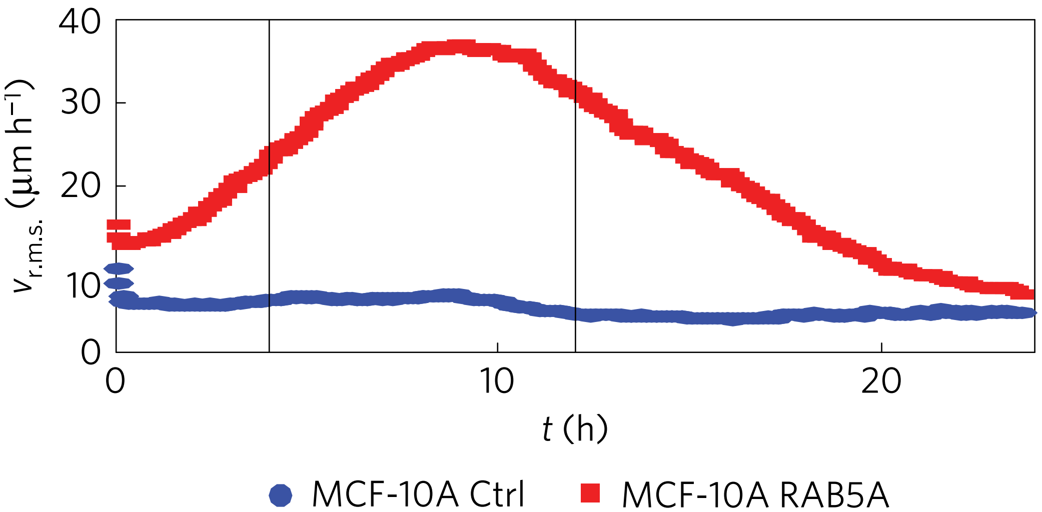
wash out blebbistatin



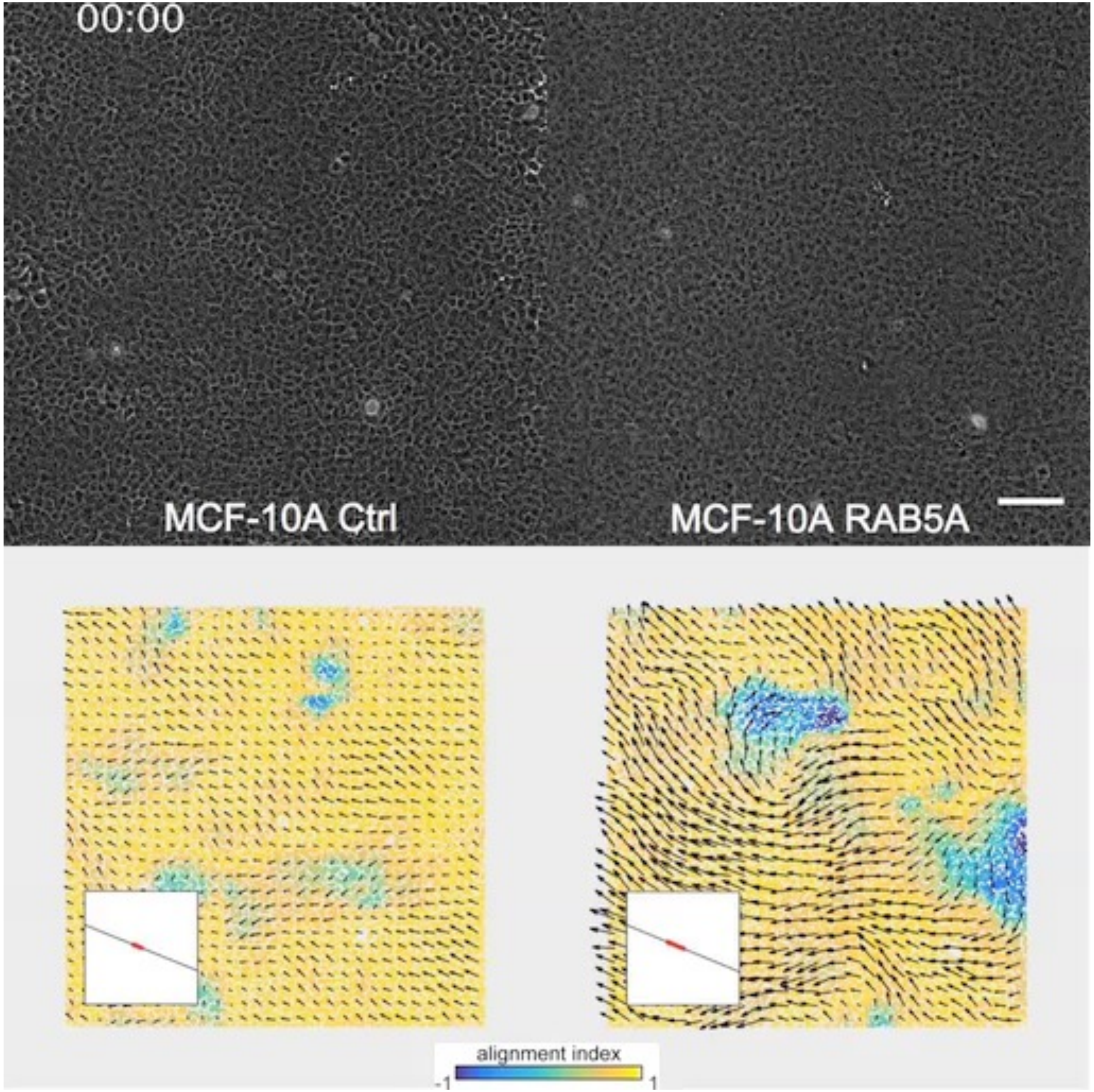
time

Malinverno et al Nature Materials 16 (2017)





Malinverno et al Nature Materials 16 (2017)



Contact inhibition of locomotion (Abercrombie, 1953)

If two cells come into contact they tend to move away from each other –
cells prefer to move into free space
colony expansion / wound healing

Polarisation tends to point away from the direction of greatest cell-cell overlap

Cells within a colony are much less likely to form lamellopodia

Strength of the polarization decreases with increasing cell-cell overlap

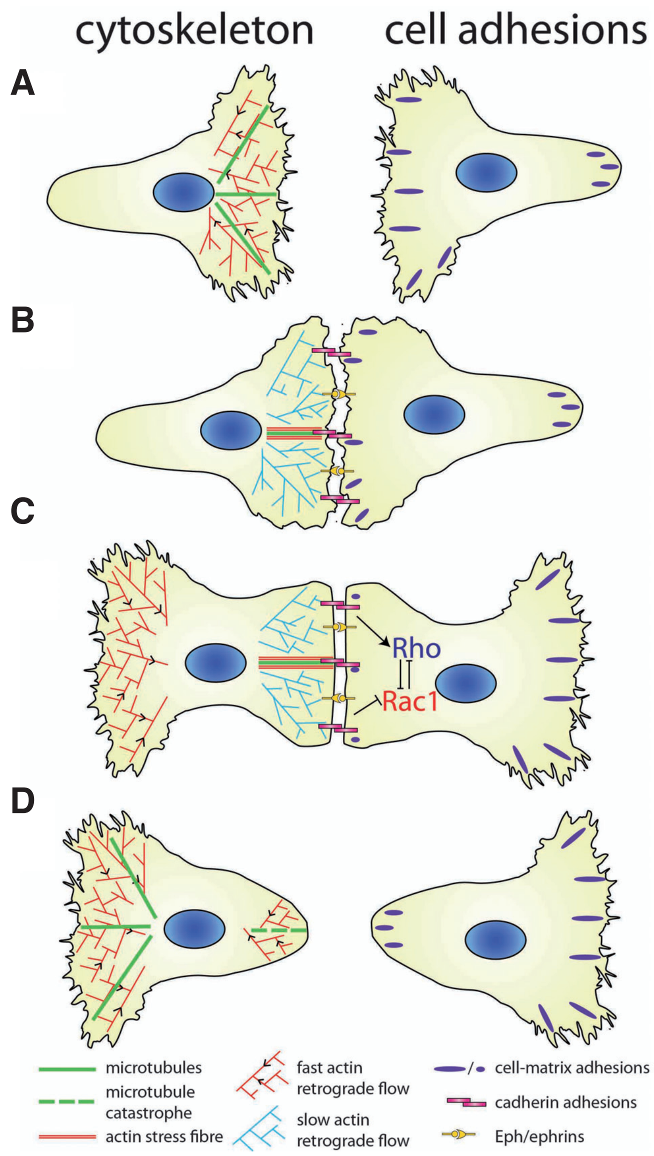
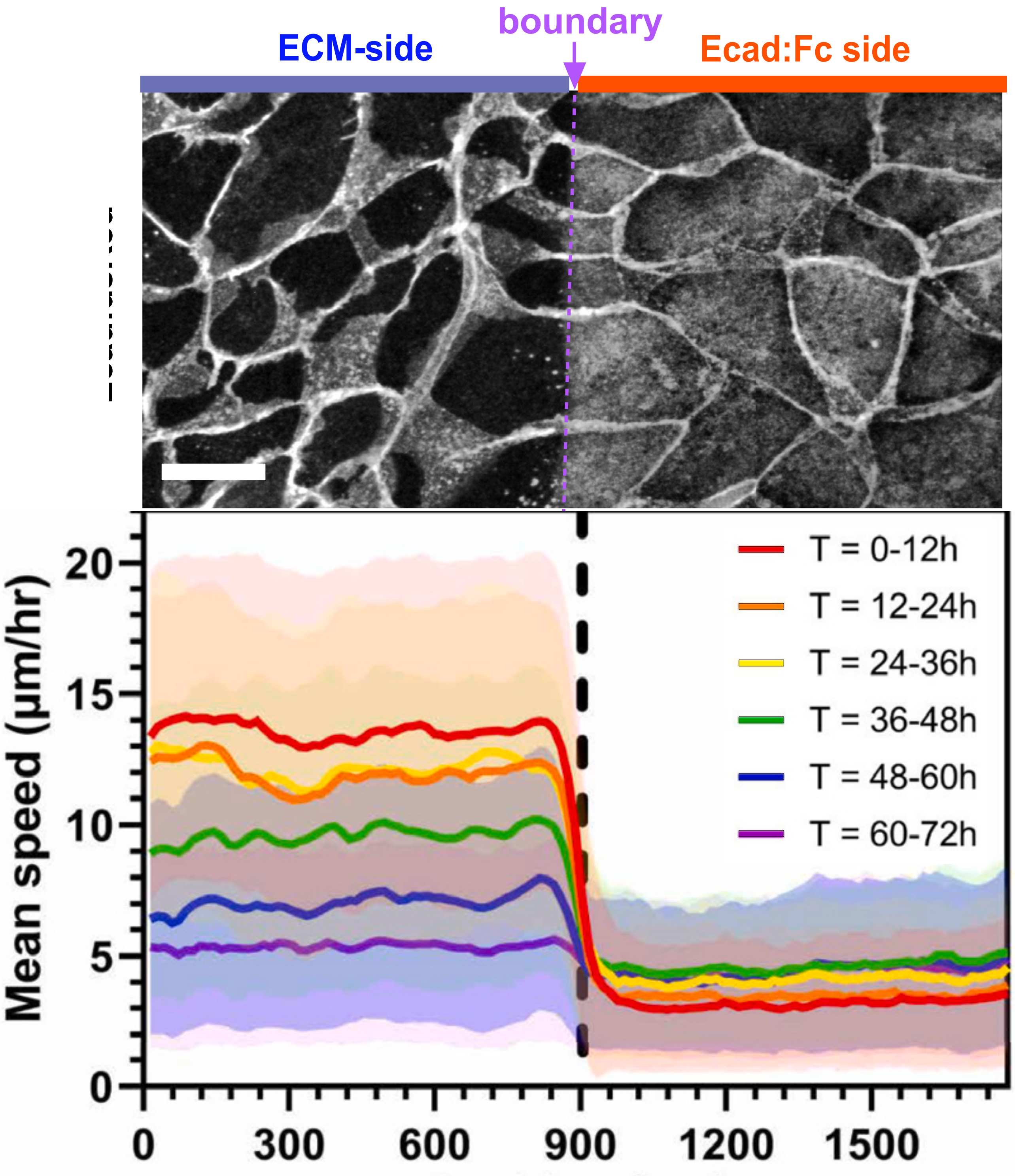


Fig from Int. J. Dev. Biol. 62: 5-13 (2018)



Suh et al, Cell Reports, 2024

Are cell forces polar, fluctuating polar or nematic?

Underlying biology?

How much difference does the substrate make?

How much difference do free boundaries make?

Why can squishy cells give active turbulence?

If nematic, are cells extensile or contractile?

Molly McCord

Jay Zhang

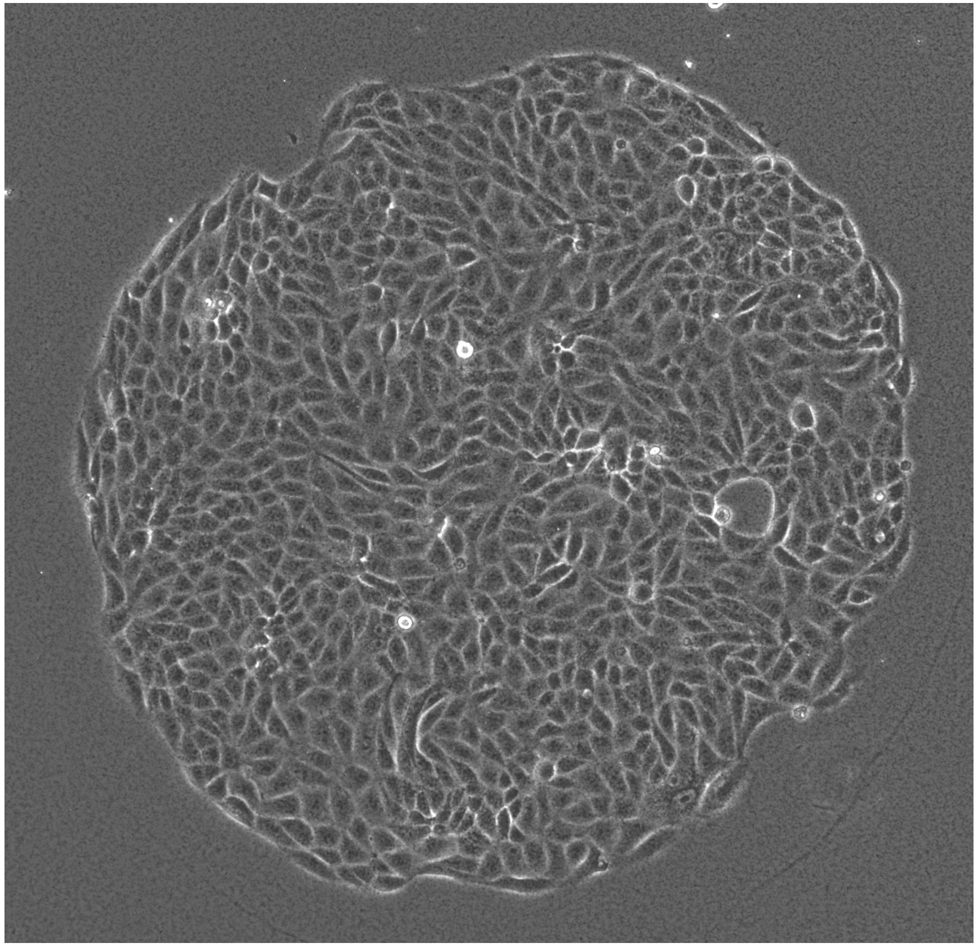
Jacob Notbohm

Mehrana Nejad

Liam Ruske

Guanming Zhang

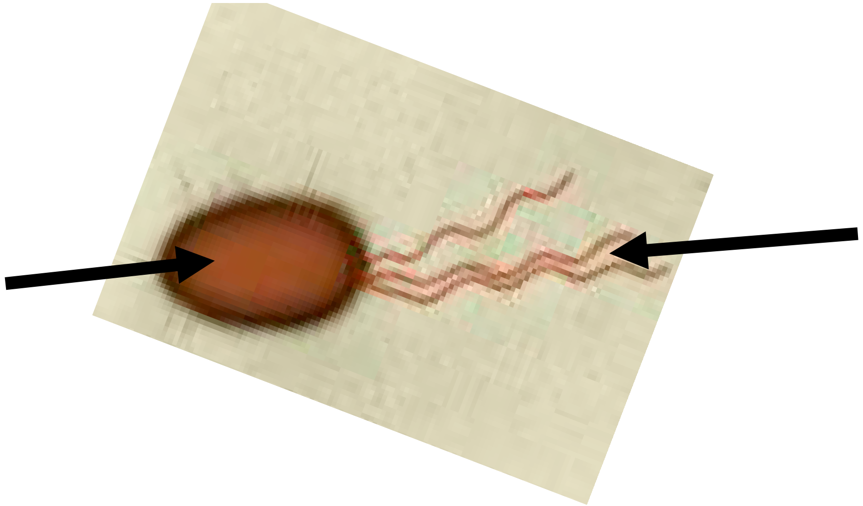
MDCK island

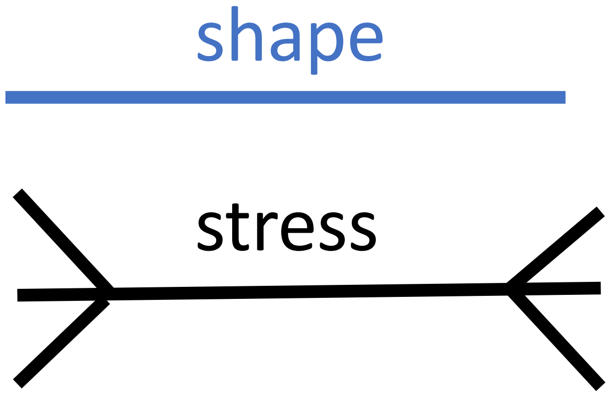


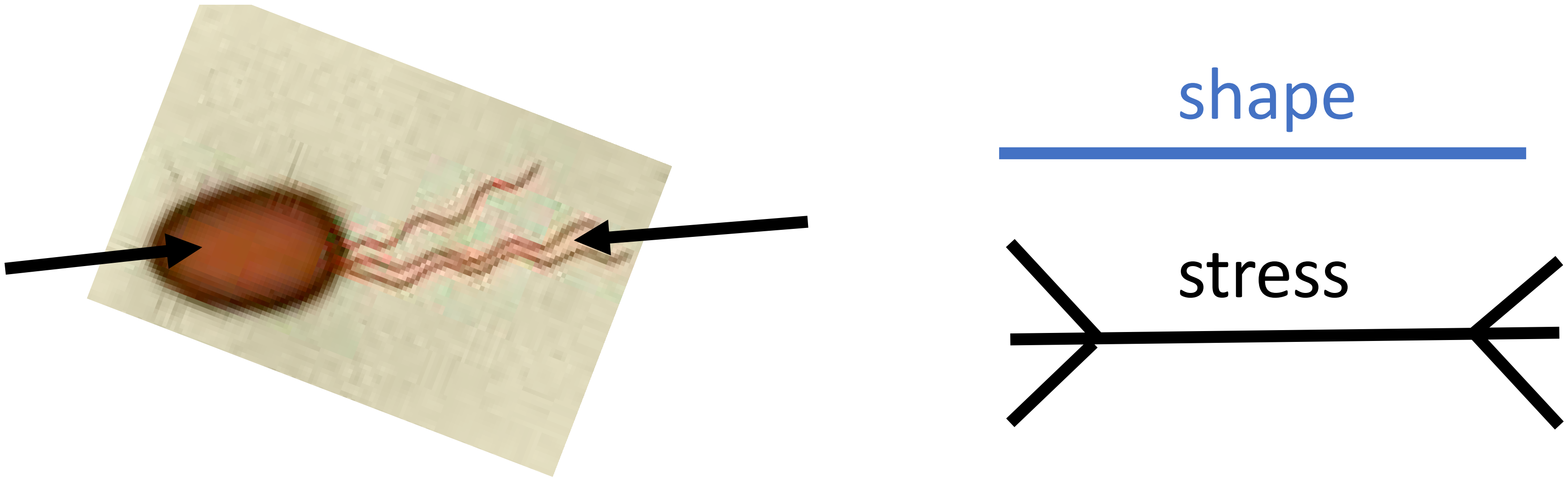
$100\,\mu m$

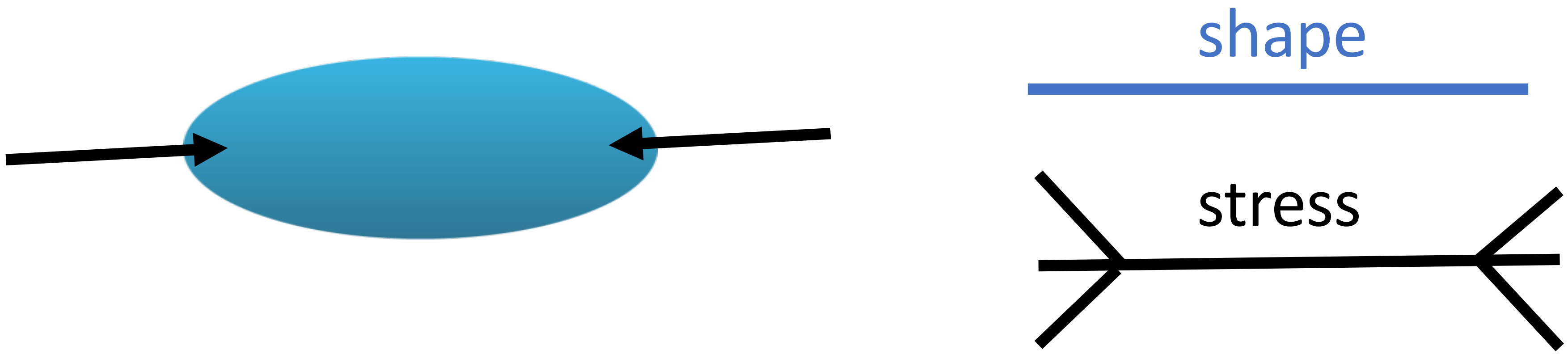
measure shape axis

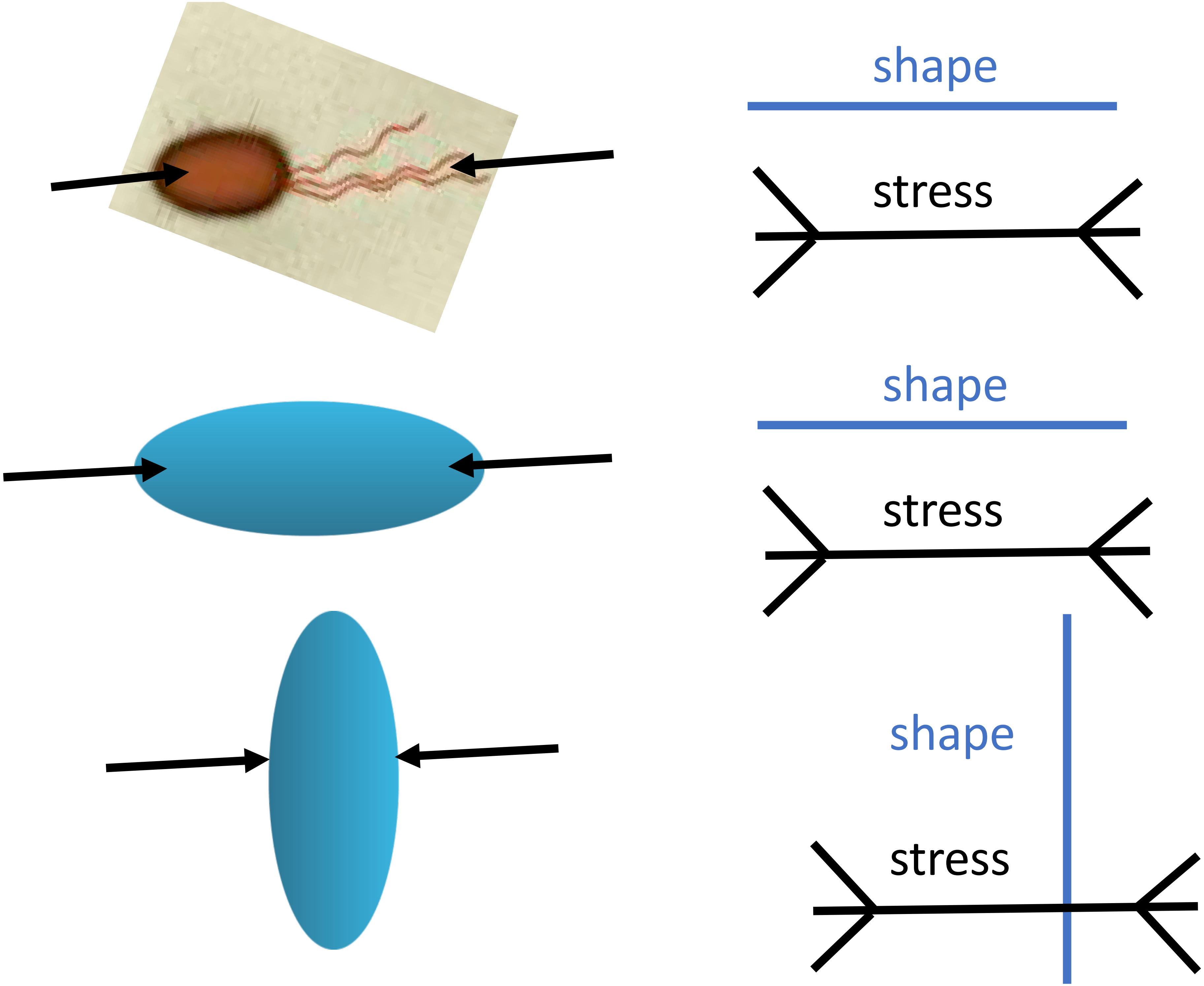
measure direction of principal contractile stress (traction force microscopy)

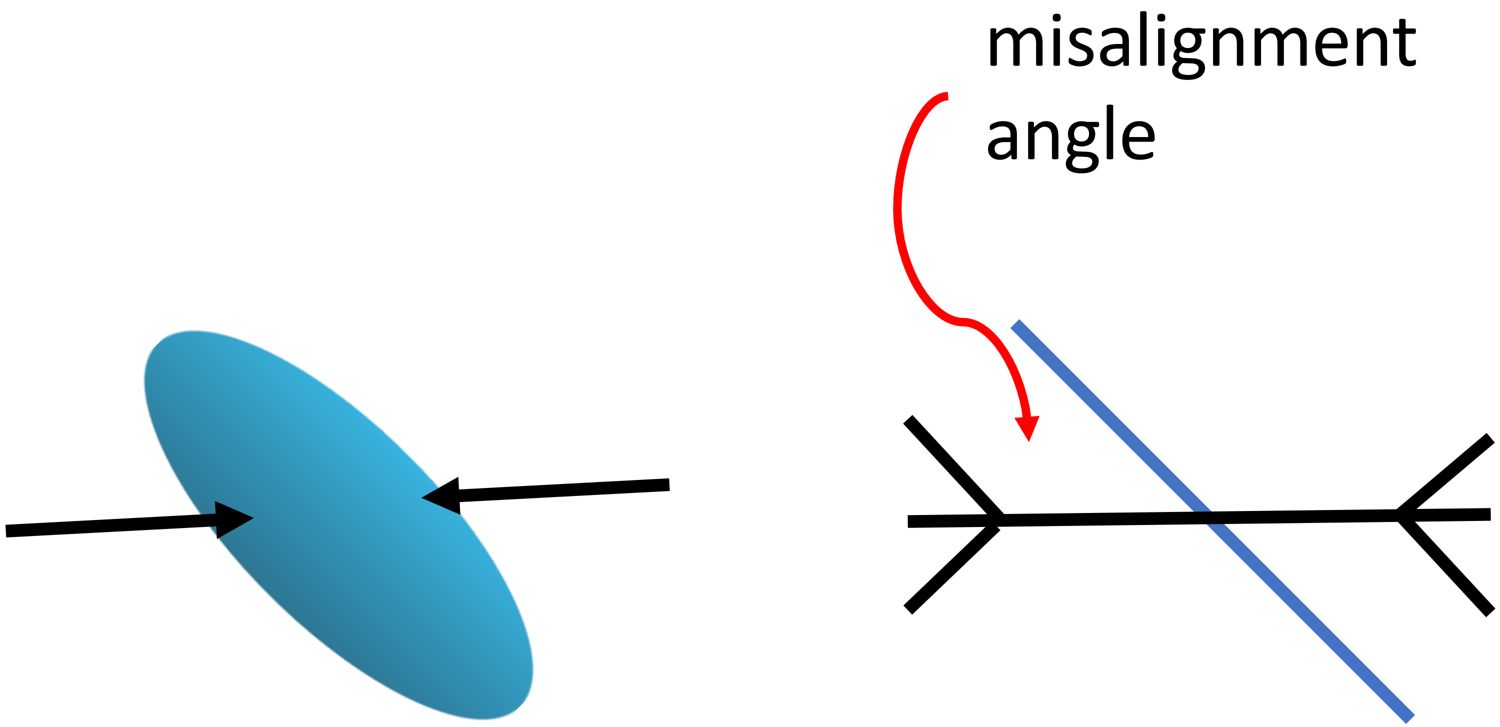



shape
stress


shape
stress

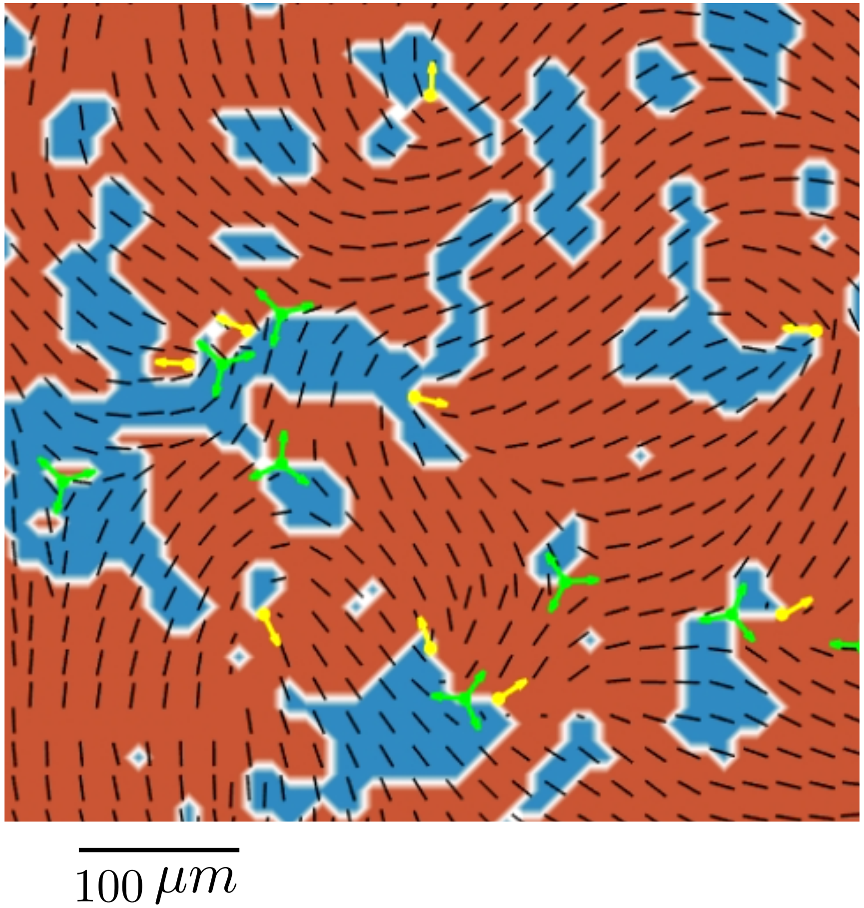

shape
stress

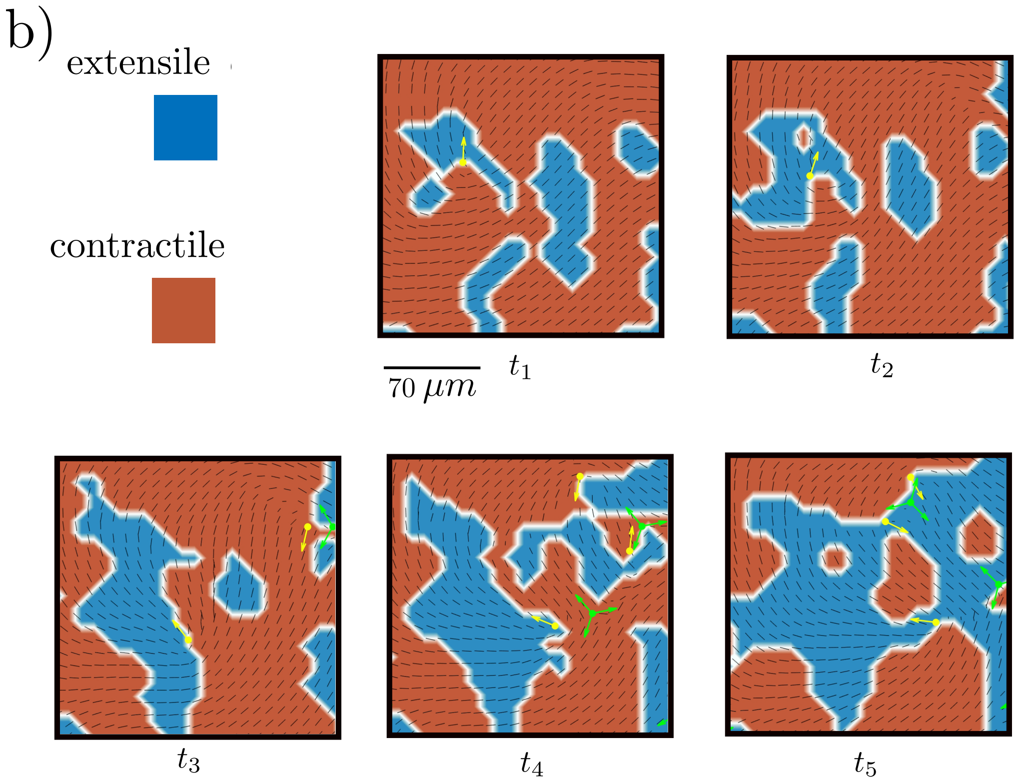

shape
stress
shape
stress
shape
stress



misalignment angle: angle between shape and stress

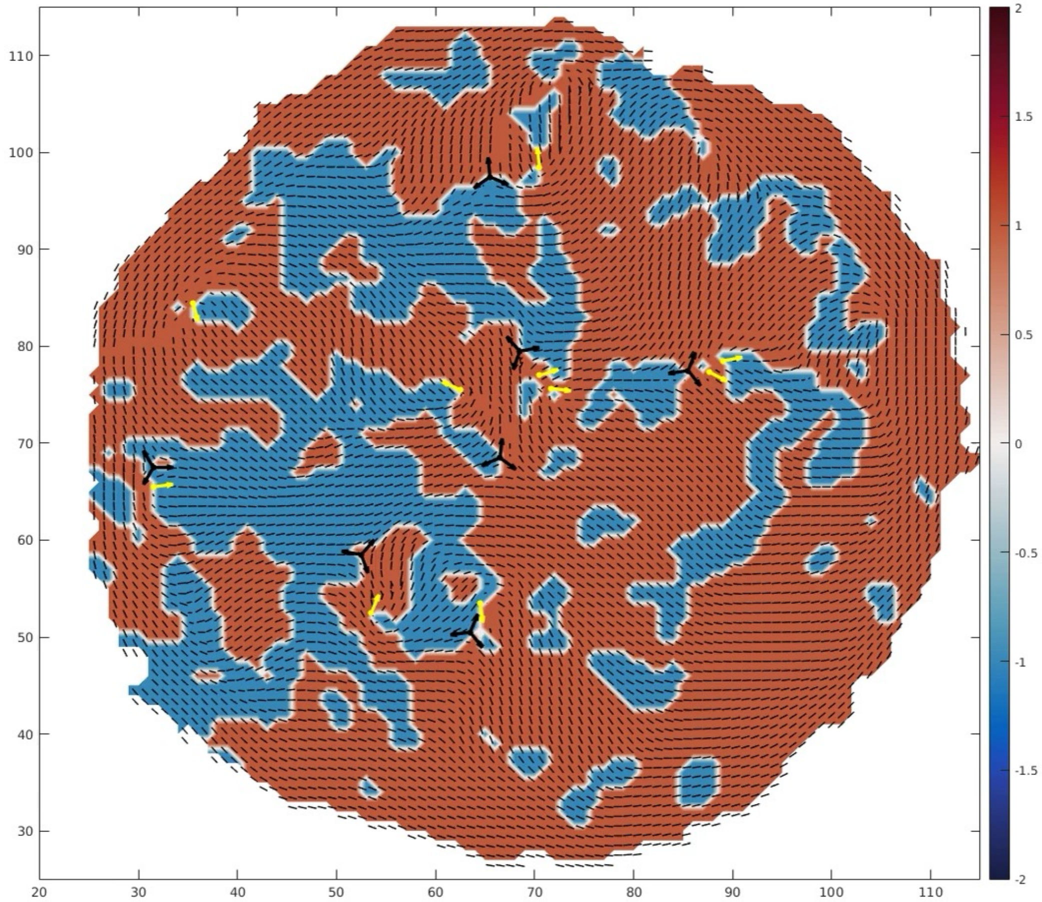
Misalignment angle in an MDCK monolayer





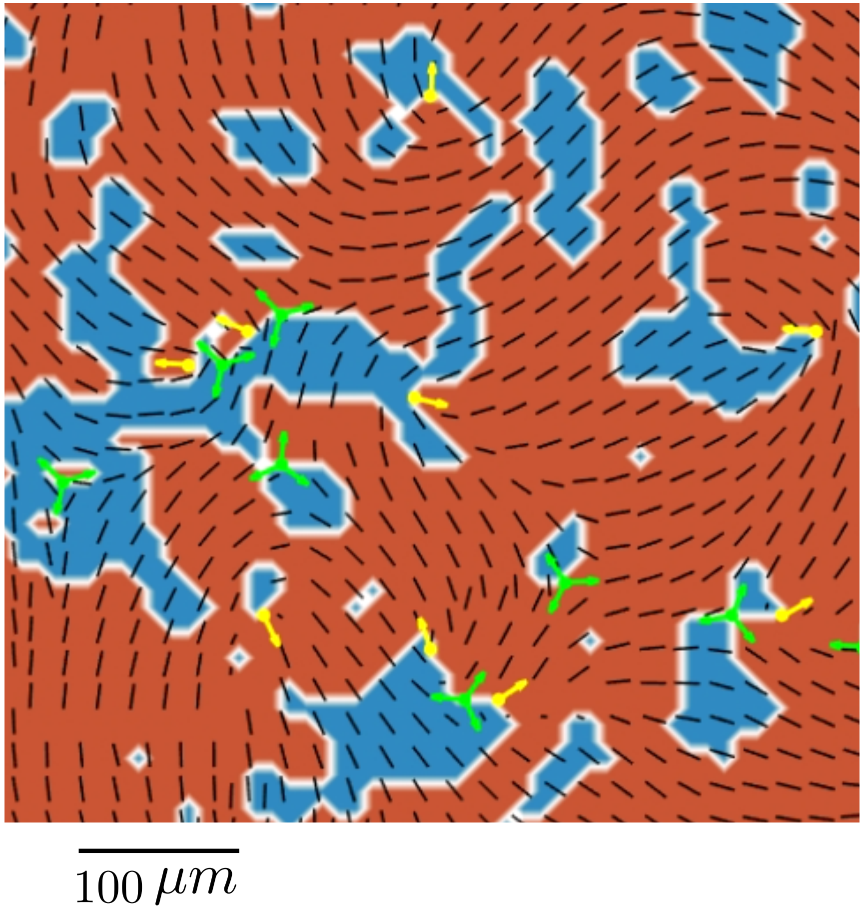
Angle between contractile stress axis and shape axis small (0 to 45°) (red)
large (45° to 90°)(blue)

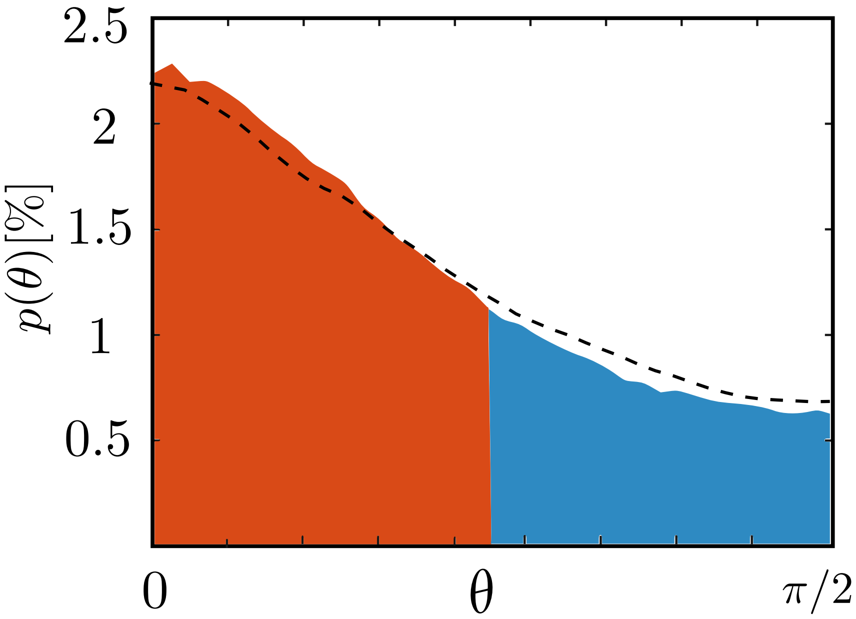
Misalignment angle in an MDCK monolayer



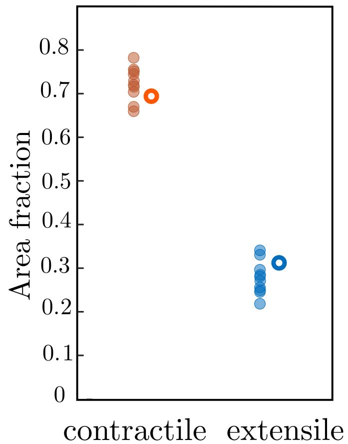
misalignment angle small (red); large (blue)

Misalignment angle in an MDCK monolayer





distribution of angle betweer shape and stress axes



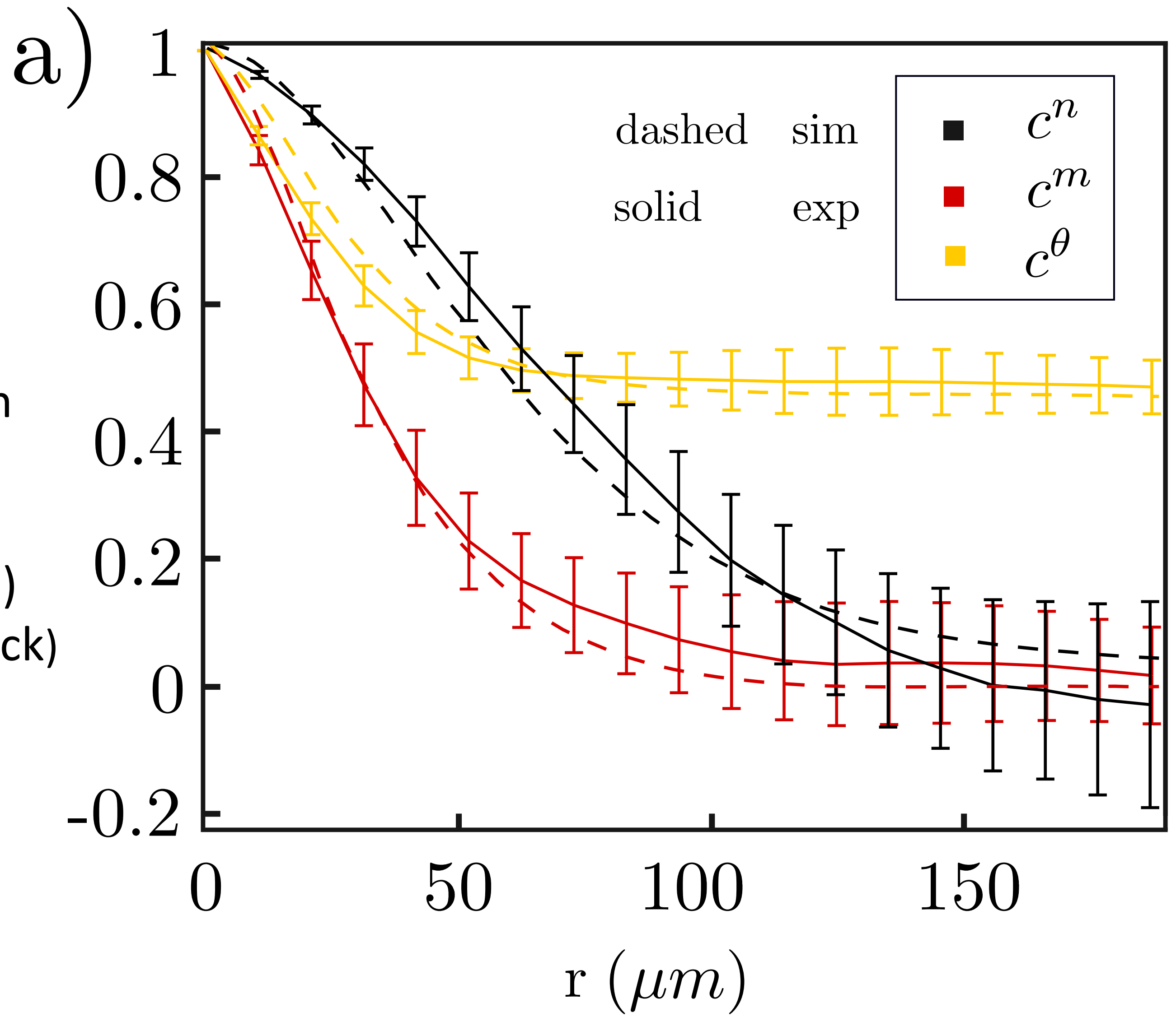
Angle between stress axis and shape axis
small (red)
large (blue)

area fraction of red
& blue cells to show
variation by MDCK sample

Shape and stress respond in different ways to strong active flows

spatial correlation functions

stress (red)
shape (black)



$$C^x(r) = \langle \cos 2[\psi_x(r + r_0, t_0) - \psi_x(r_0, t_0)] \rangle_{t_0, r_0}$$

Active stress

$$\boxed{(\partial_t + u_k \partial_k) Q_{ij} - S_{ij} = \Gamma H_{ij}}$$

couples nematic order and shear flows

relaxation to minimum of Landau-de Gennes free energy

$$\boxed{\rho(\partial_t + u_k \partial_k) u_i = \partial_j \Pi_{ij}}$$

viscous + elastic + active stress

$$\boxed{\Pi_{ij}^{active} = -\zeta Q_{ij}}$$

Continuum equations of active liquid crystal hydrodynamics

Two different order parameters: one for shape, one for stress:

$$(\partial_t + u_k\partial_k)Q_{ij}^{stress} - S_{ij}^{stress} = \Gamma H_{ij}^{stress}$$

$$(\partial_t + u_k\partial_k)Q_{ij}^{shape} - S_{ij}^{shape} = \Gamma H_{ij}^{shape}$$

$$\boxed{\rho(\partial_t + u_k\partial_k)u_i = \partial_j \Pi_{ij}}$$

$$\boxed{\Pi_{ij}^{active} = -\zeta Q_{ij}}$$

Continuum equations of active liquid crystal hydrodynamics

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$$(\partial_t + u_k \partial_k) Q_{ij}^{shape} - S_{ij}^{shape} = \Gamma H_{ij}^{shape}$$

$$\boxed{\rho(\partial_t + u_k \partial_k) u_i = \partial_j \Pi_{ij}}$$

Active forces produced by the stress fibres

$$\boxed{\Pi_{ij}^{active} = \zeta Q_{ij}^{stress}}$$

Changes in the free energy

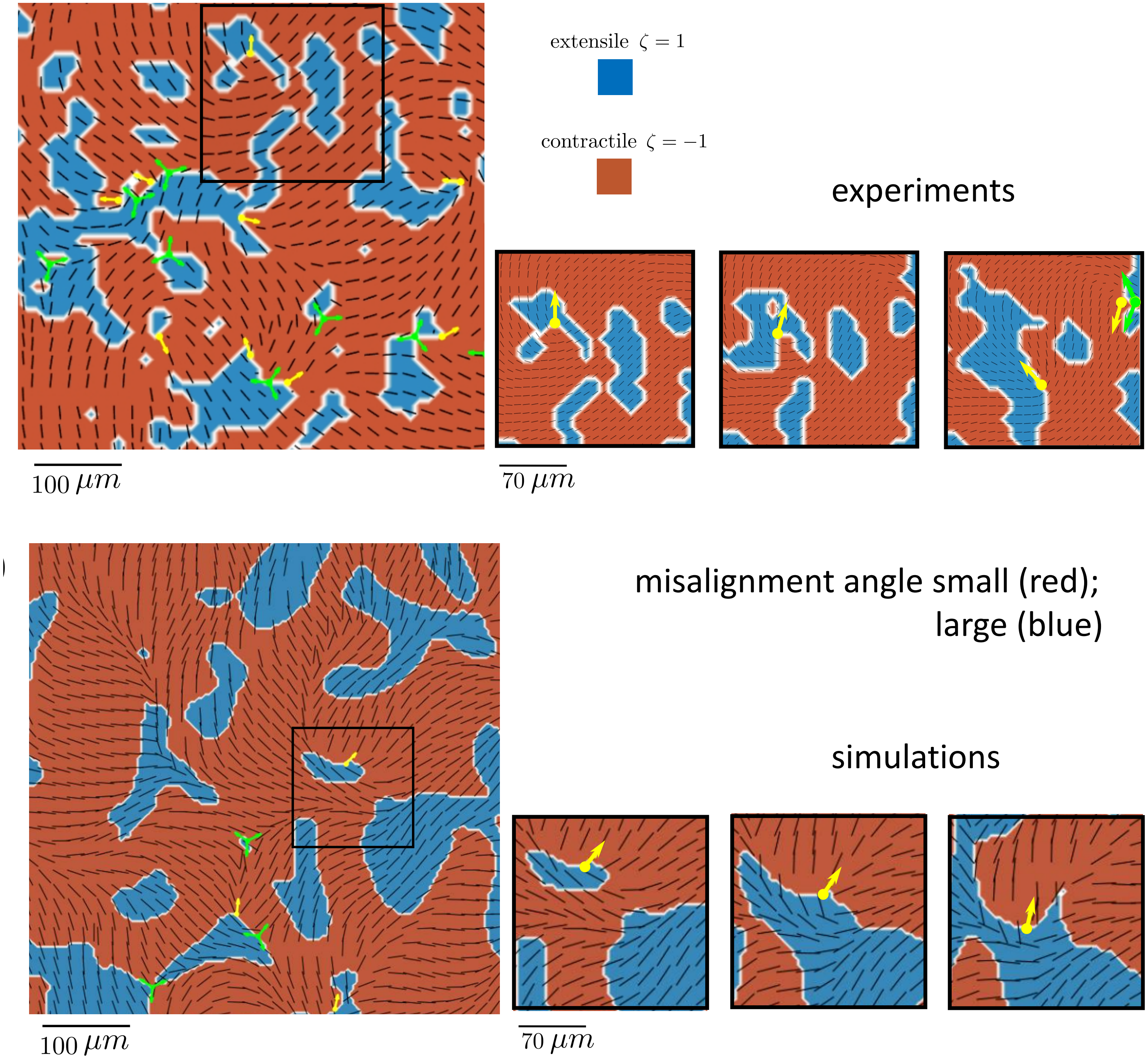
$$\mathcal{F} = \text{bulk terms} \quad +$$

$$K^{stress}(\partial_k Q_{ij}^{stress})^2/2 \quad +$$

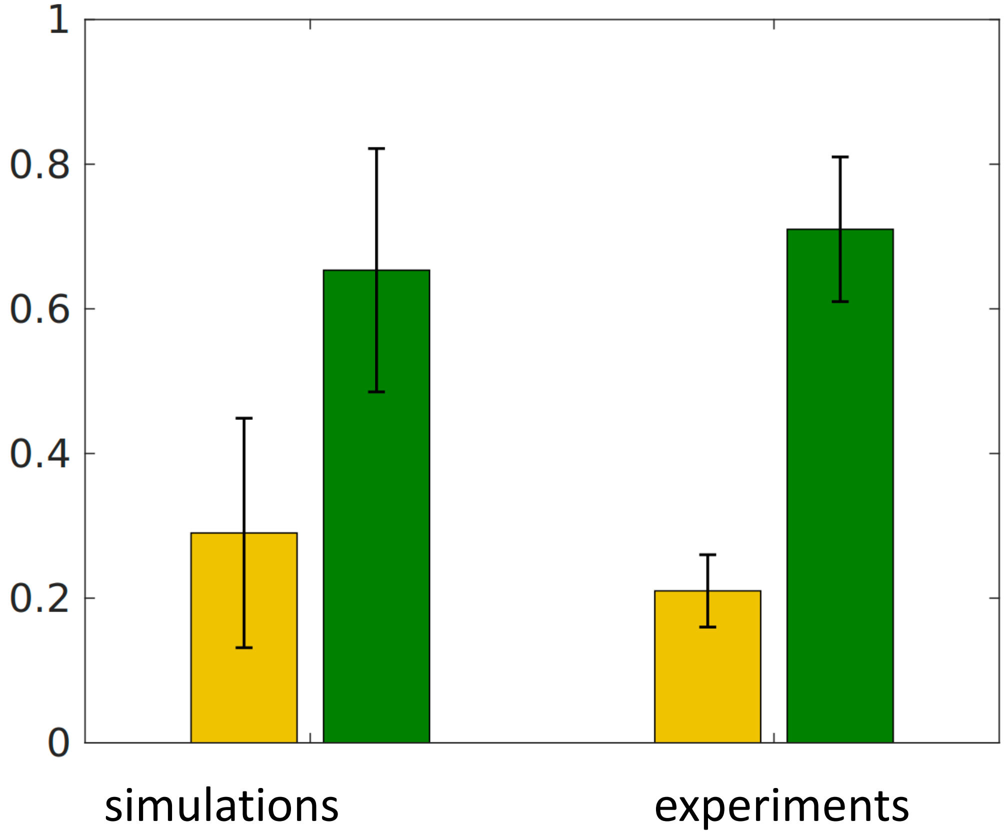
different elastic constants for stress and shape

$$K^{shape}(\partial_k Q_{ij}^{shape})^2/2 \quad +$$

term that aligns stress to shape


extensile $\zeta = 1$
contractile $\zeta = -1$
experiments
100 μm
70 μm
misalignment angle small (red);
large (blue)
simulations
100 μm
70 μm

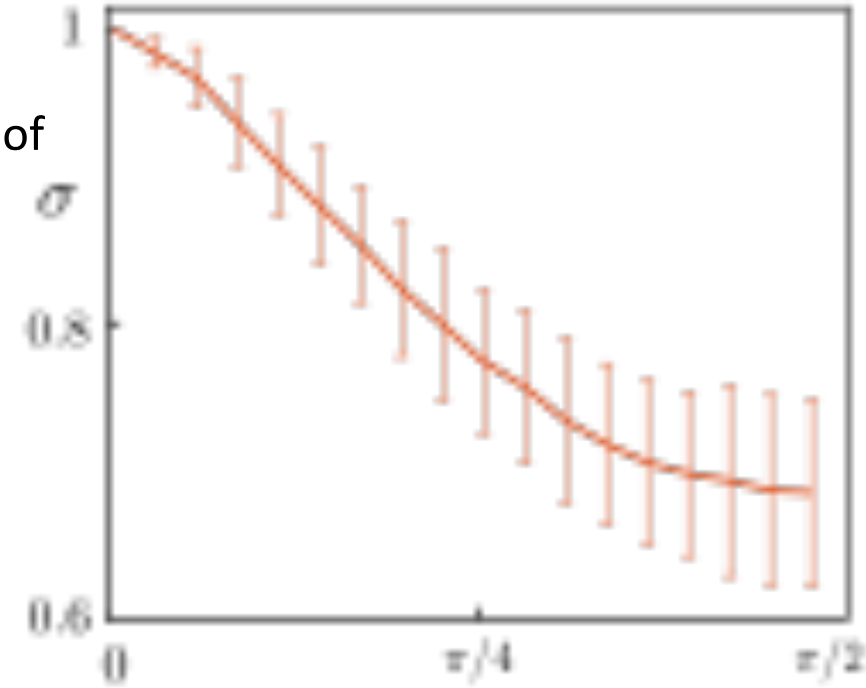
Defects sit at interfaces where misalignment angle approx. 45^o



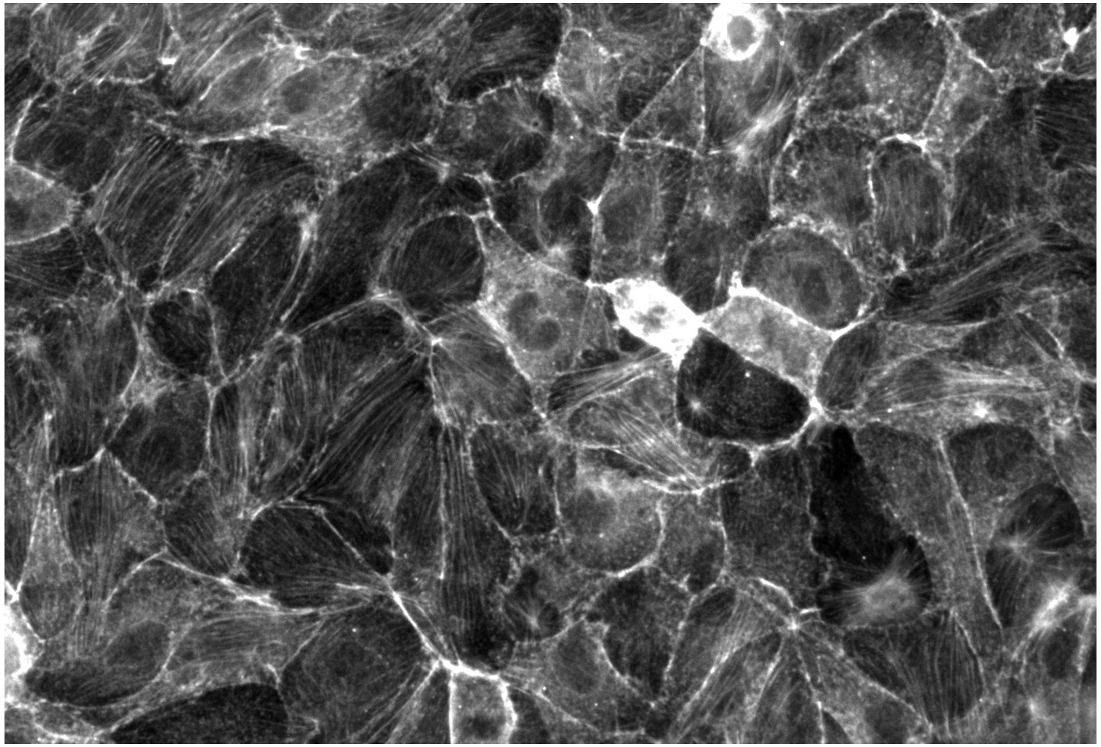
Yellow: area fraction of interface

Green: fraction of defects at interface

magnitude of the stress



misalignment angle θ



1. Introduction

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Active anchoring and cell sorting

How do confluent cell layers move?

Are cells extensile or contractile?

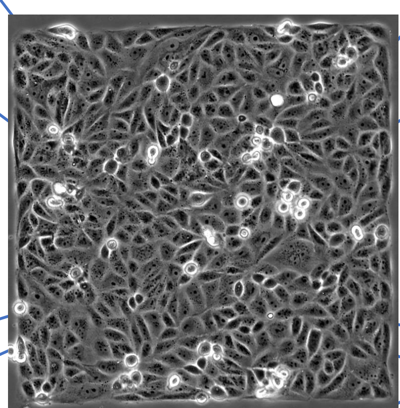
Phase field models

… and a bit more about vertex models

The hare and the tortoise

continuum models:
active nematic /polar
active gels

Vertex + Voronoi models

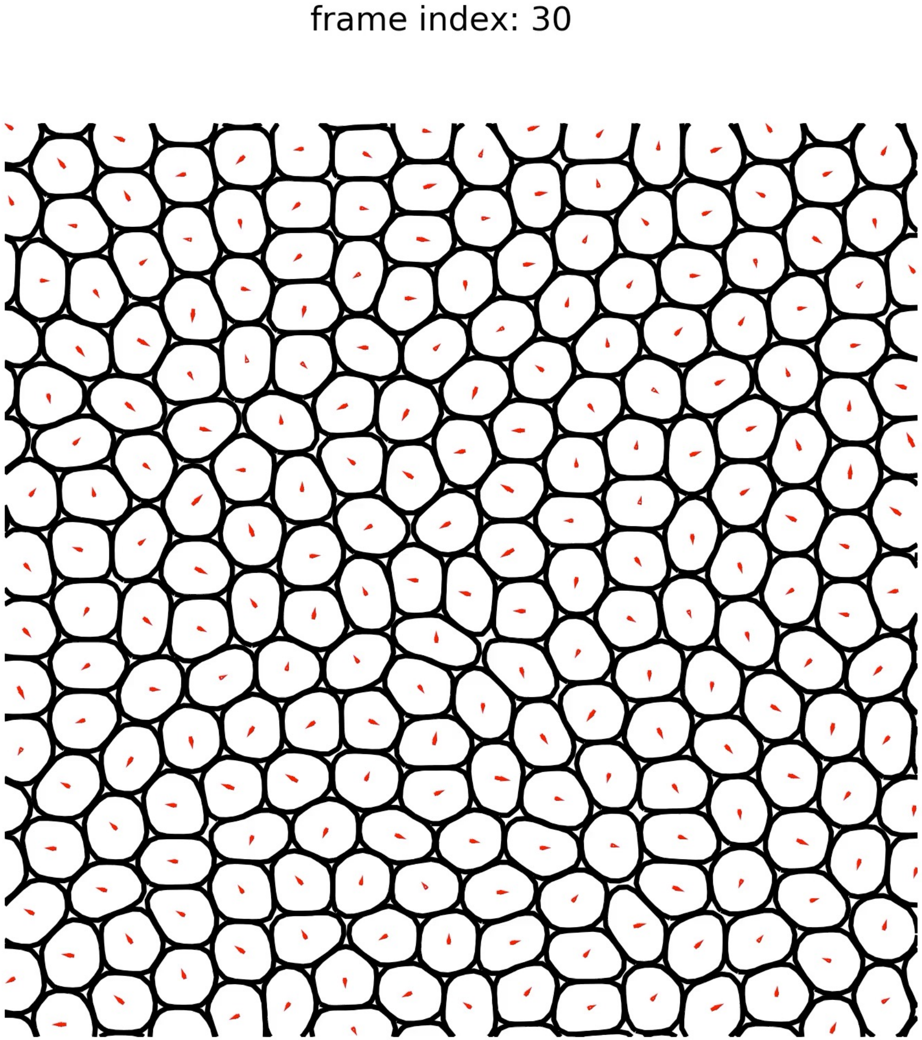


particle models
Vicsek model
cellular Potts model

Phase field models

Alert & Trepat, Annual Review of Condensed Matter Physics 2020

Phase field model



Grant, Aranson

Equations of motion

Each cell is described by a phase field φ_i

$$\partial_t \varphi_i + \mathbf{v}_i \cdot \nabla \varphi_i = -\frac{\delta \mathcal{F}}{\delta \varphi_i}$$

$$\xi \, \mathbf{v}_i(\mathbf{x}_i) = \mathbf{f}_i^{\mathrm{tot}}(\mathbf{x}_i)$$

passive forces + active forces

Passive forces: relax to minimise free energy

Cahn-Hilliard term: fixes φ_i to 1 inside a cell and 0 outside and imposes a surface tension

$$\mathcal{F}_{CH} = \sum_i \frac{\gamma}{\lambda} \int d\mathbf{x} \left\{ 4\varphi_i^2 (1 - \varphi_i)^2 + \lambda^2 (\nabla \varphi_i)^2 \right\}$$

soft constraint on the area

$$\mathcal{F}_{\text{area}} = \sum_i \mu \left\{ 1 - \frac{1}{\pi R^2} \int d\mathbf{x}\; \varphi_i^2 \right\}^2$$

Passive forces: relax to minimise free energy

penalises overlap between cells

$$\mathcal{F}_{\text{rep}} = \sum_i \sum_{j \neq i} \frac{\kappa}{\lambda} \int d\mathbf{x}\, \varphi_i^2 \varphi_j^2$$

favours cell-cell adhesion

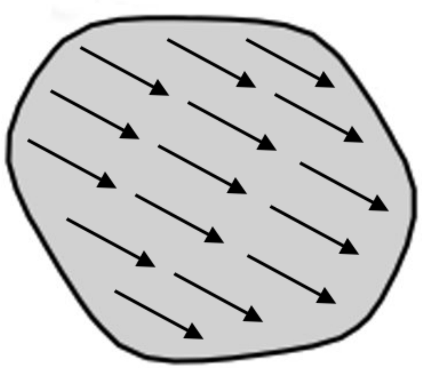
$$\mathcal{F}_{\text{adh}} = \sum_i \sum_{j \neq i} \omega\lambda \int d\mathbf{x}\, \nabla\varphi_i \cdot \nabla\varphi_j$$

Passive forces: relax to minimise free energy

$$\mathbf{f}_i^{passive}(\mathbf{x}) = \frac{\delta \mathcal{F}}{\delta \varphi_i} \nabla \varphi_i$$

Equilibrium is identical hexagons, but the system can get stuck
In a jammed state.

Active polar force



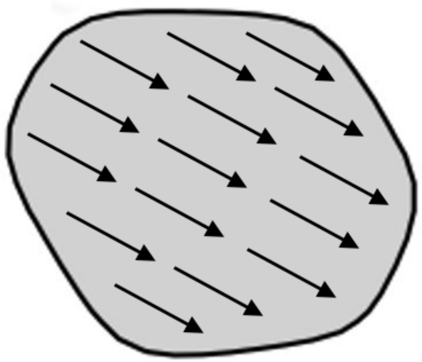
$$\mathbf{f}_i^{\mathrm{pol}}(\mathbf{x}) = \alpha\varphi_i(\mathbf{x})\mathbf{p_i}$$

polarisation of cell i

Choice of polarisation?

1. Gaussian noise
2. Aligns with velocity of cell (+noise)
3. Aligns with long axis of cell (+noise)
4. Aligns and is proportional to the elongation of the cell (+noise)

Polar force



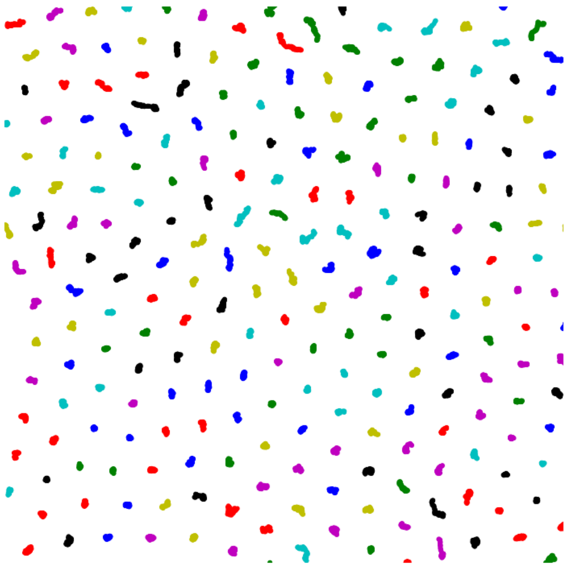
$$\mathbf{f}_i^{\mathrm{pol}}(\mathbf{x}) = \alpha \varphi_i(\mathbf{x}) \mathbf{p_i}$$

Choice of polarisation?

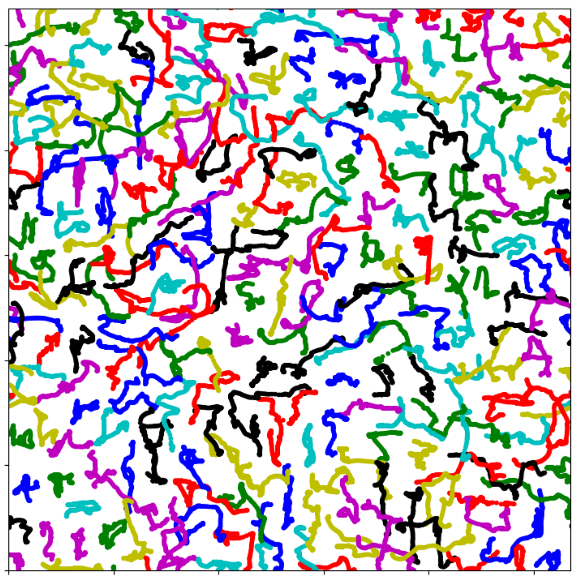
alignment time ~ time to move a cell diameter

1. Gaussian noise
2. Aligns with velocity of cell (+noise)
3. Aligns with long axis of cell (+noise)
4. Aligns and is proportional to the elongation of the cell (+noise)

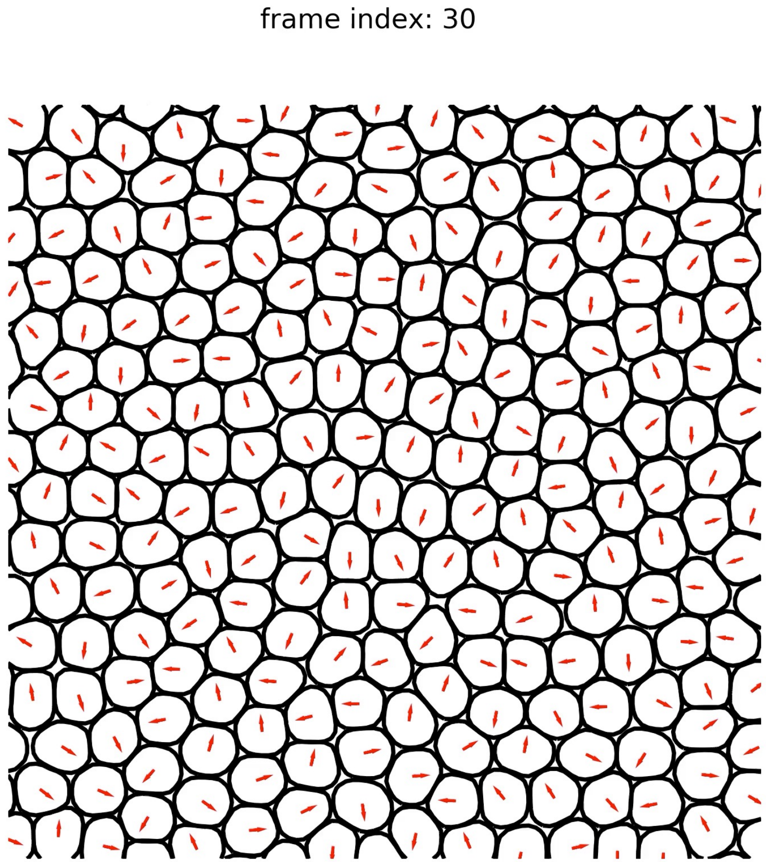
Polar forcing: results



jammed state



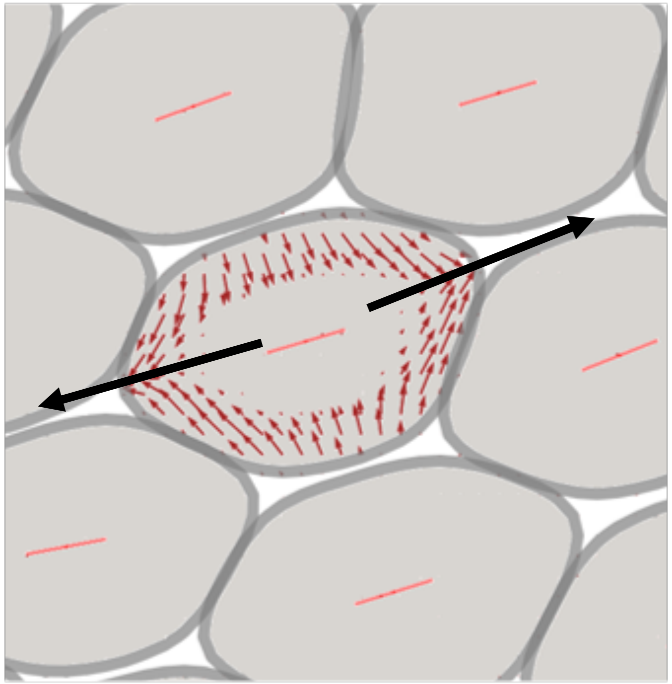
liquid



flocking if the polarisation aligns with the velocity

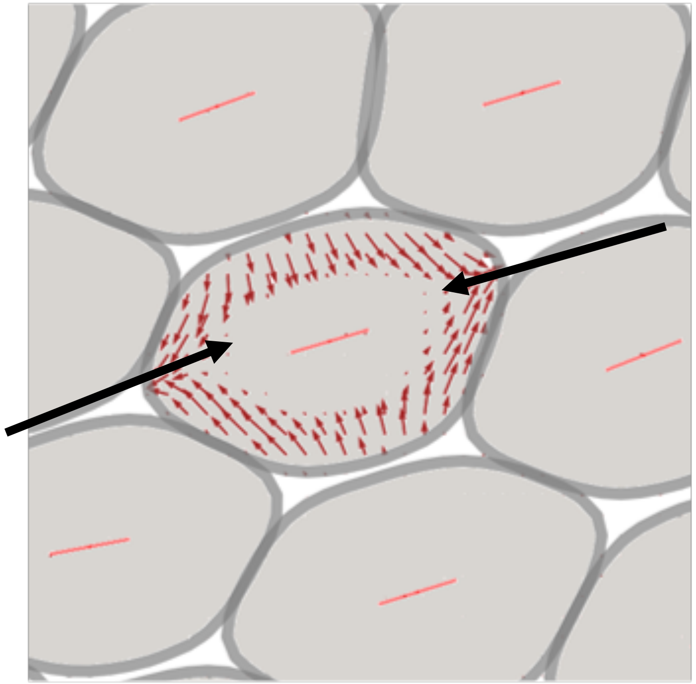
$$\sigma_{\alpha\beta}^{(i)}(\mathbf{x}) = -\zeta_{\mathrm{self}}\, \varphi^{(i)}(\mathbf{x}) Q_{\alpha\beta}^{(i)} - \zeta_{\mathrm{inter}} \sum_{j \neq i} \varphi^{(j)}(\mathbf{x}) Q_{\alpha\beta}^{(j)}$$

$$\Pi_{ij}^{active} = -\zeta Q_{ij}$$



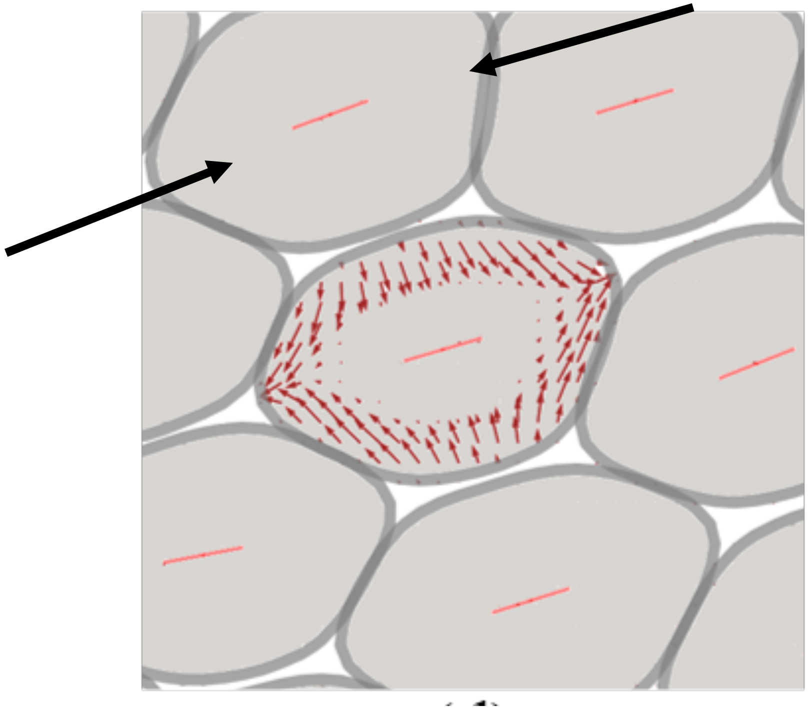
Extensile forces within a cell => active turbulence

$$\boxed{\Pi_{ij}^{active} = -\zeta Q_{ij}}$$



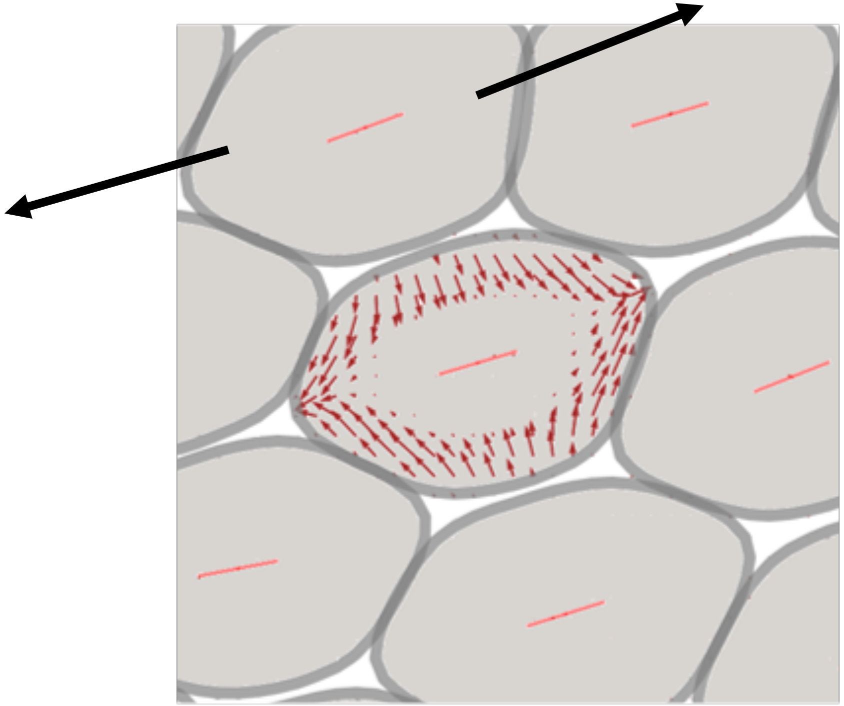
Contractile forces within a cell => nothing moves

$$\Pi_{ij}^{active} = -\zeta Q_{ij}$$



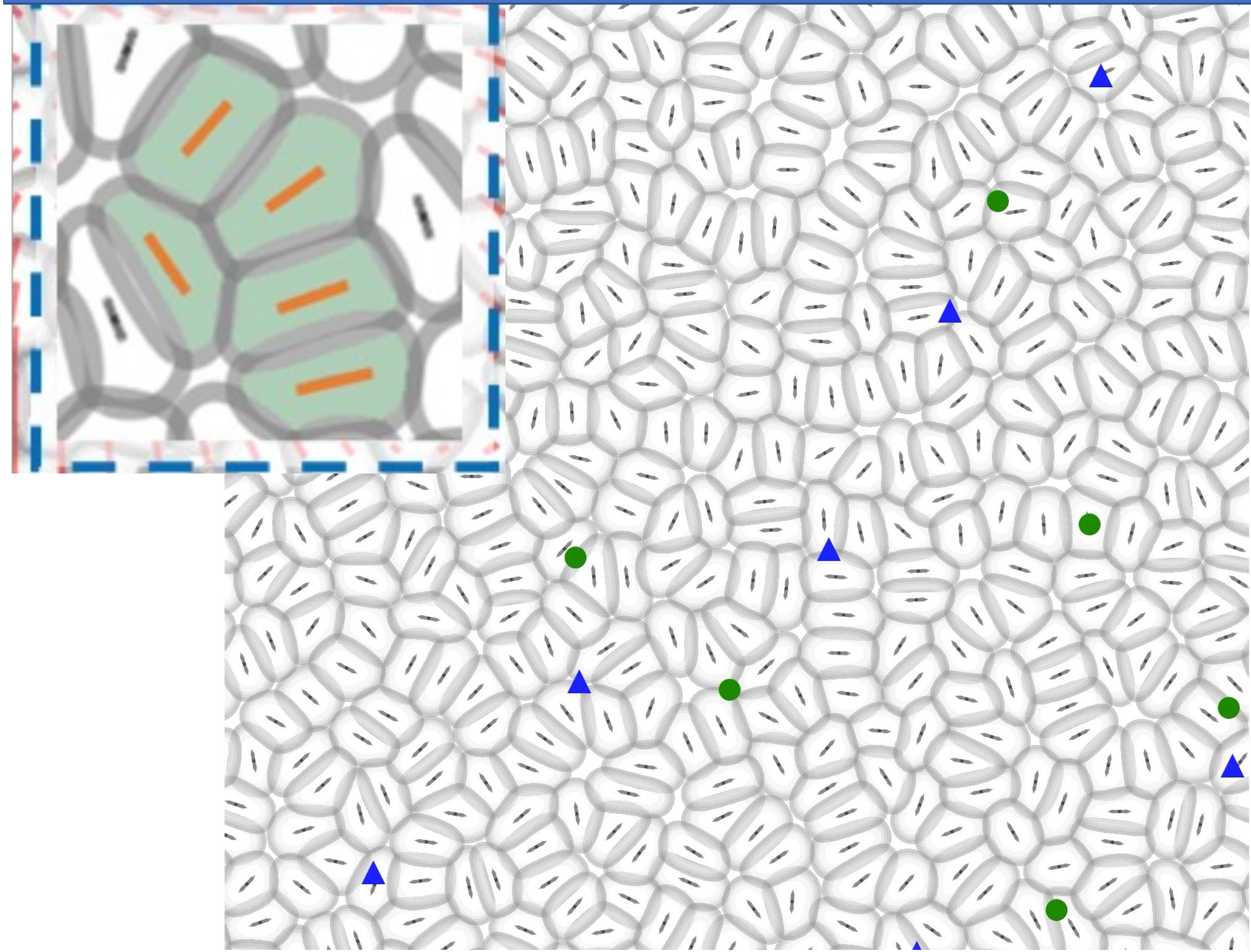
Contractile forces between cells =>
cells elongate and form a nematic-like lattice

$$\Pi_{ij}^{active} = -\zeta Q_{ij}$$



Extensile forces between cells =>
cells elongate and form a “capped line” state

Active, extensile, intercellular forces



Vertex model

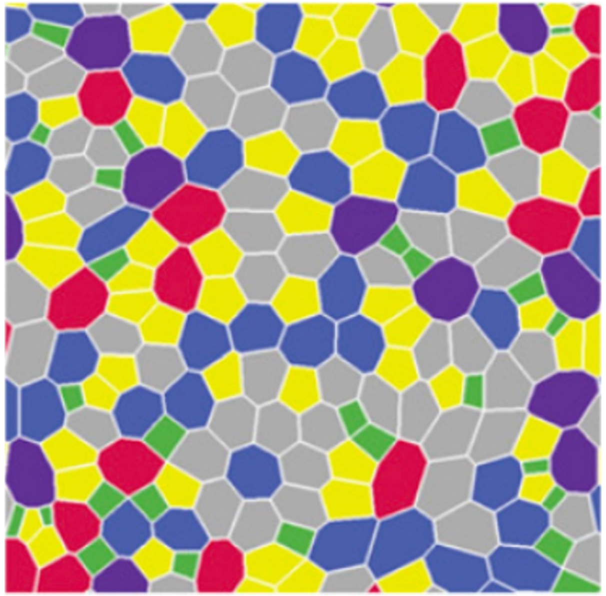
- One of the standard approaches to modelling epithelia

- Area-and-perimeter elasticity

$$E_{\mathrm{VM}} = \sum_c \left[\frac{1}{2} k_A (A_c - A_0)^2 + \frac{1}{2} k_P (P_c - P_0)^2\right]$$

- Vertices follow overdamped dynamics

$$\eta \dot{\mathbf{r}}_i = -\nabla E_{\mathrm{VM}} + \mathbf{f}_i^{\mathrm{active}}$$



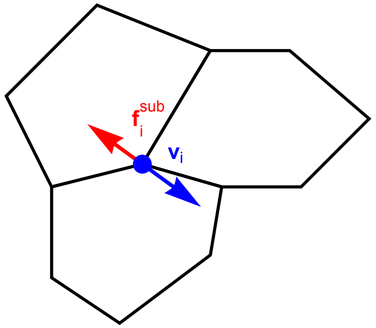
Farhadifar *et al.*
Curr. Biol. (2007)

Jan Rozman

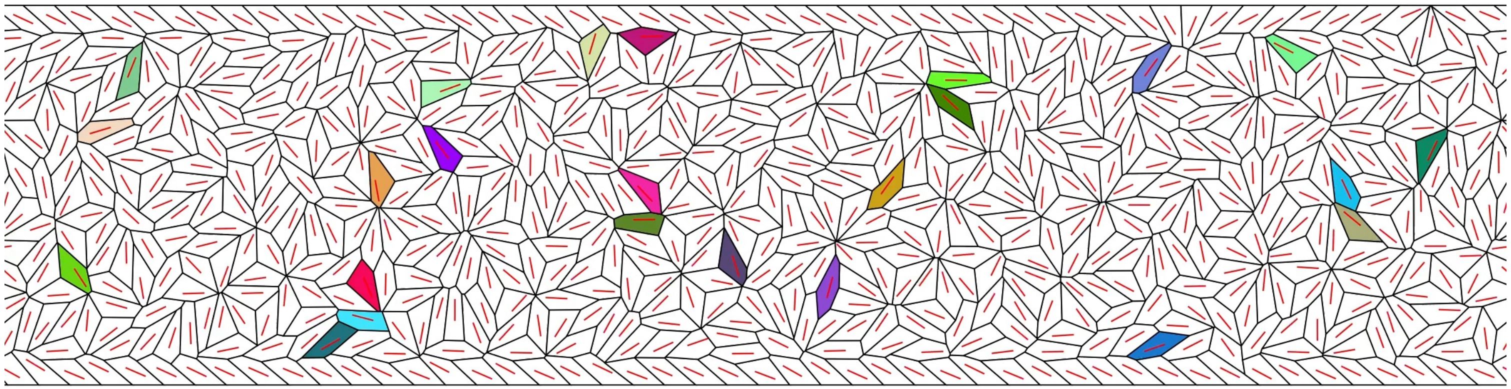
Chaithanya K. V. S.
Rastko Sknepnek

Flows in channel confinement

- Nematic stresses: unidirectional channel flows
- Flows never develop in the vertex model



$$\eta \dot{\mathbf{r}}_i = \mathbf{f}_i$$



Rozman*, Chaithanya*, *et al.* arXiv (2023)

Vertex model

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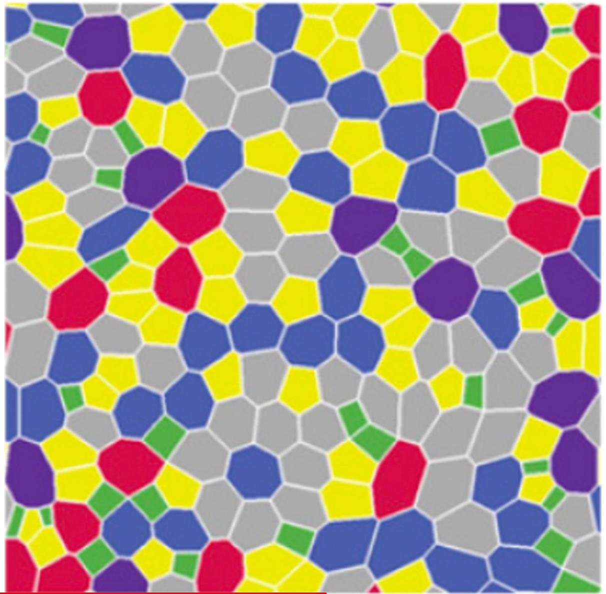


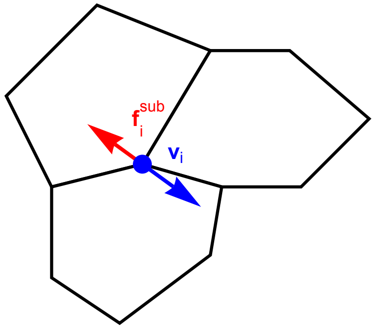
- Separate vertex-substrate (η) and vertex-vertex (ξ) frictions

$$\boxed{\eta \dot{\mathbf{r}}_i + \xi \sum_{S_i} (\dot{\mathbf{r}}_i - \dot{\mathbf{r}}_j) = -\nabla E_{\mathrm{VM}} + \mathbf{f}_i^{\mathrm{active}}}$$

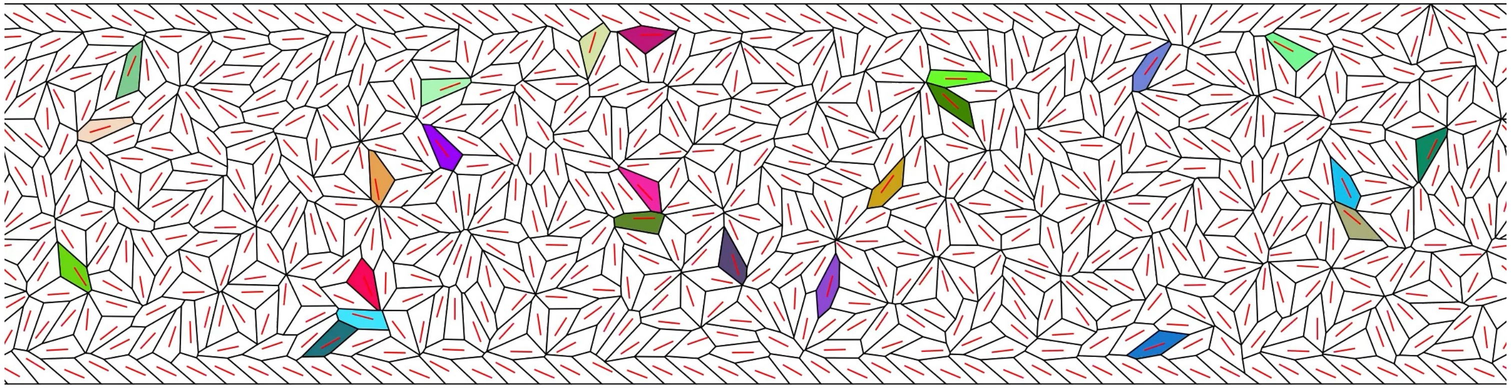
- Dry model for $\xi = 0$
- "Wet" model if $\frac{\eta}{\xi} \ll 1$

Flows in channel confinement

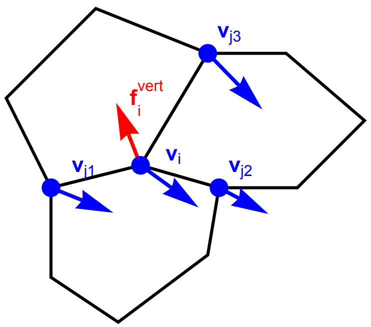
- Dipolar stresses: unidirectional channel flows
- Flows never develop in the vertex model



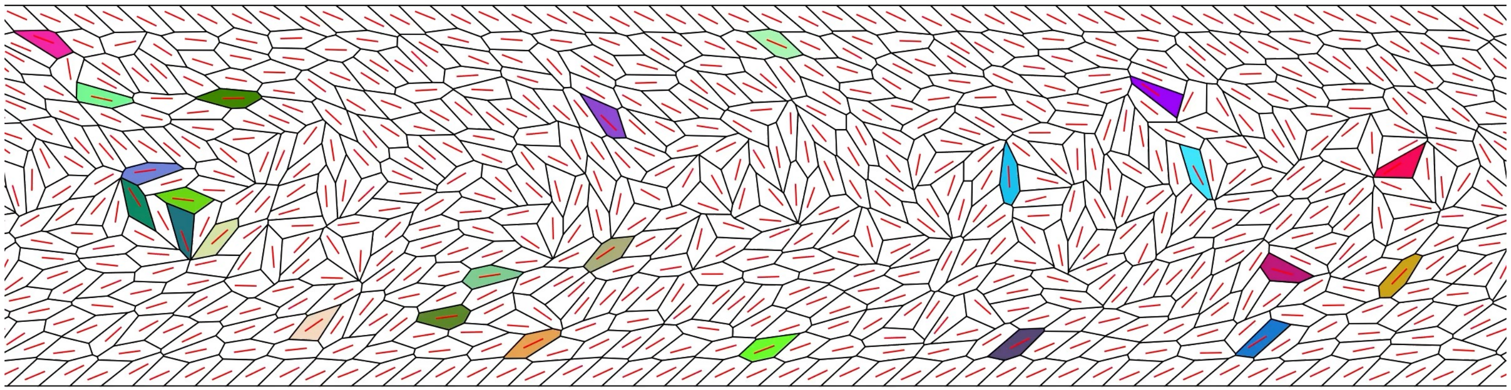
$$\eta \dot{\mathbf{r}}_i = \mathbf{f}_i$$



- Internal dissipation: formation of flows
- Hydrodynamics & long-range correlation



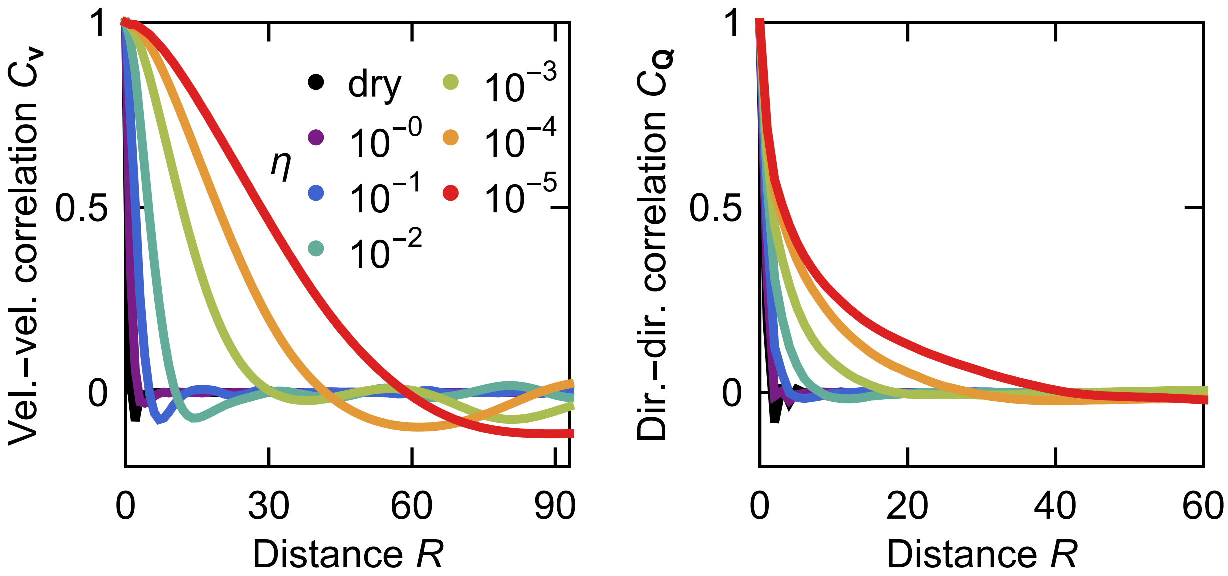
$$\eta \dot{\mathbf{r}}_i + \xi \sum_{s_i} (\dot{\mathbf{r}}_i - \dot{\mathbf{r}}_j) = \mathbf{f}_i$$



Rozman*, Chaithanya*, *et al.* arXiv (2023)

Correlations

- Velocity-velocity and director-director correlations
- $\sim$1 cell range in dry periodic system
- Much longer range in wet model
- Increasing substrate friction reduces correlation



With thanks to

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