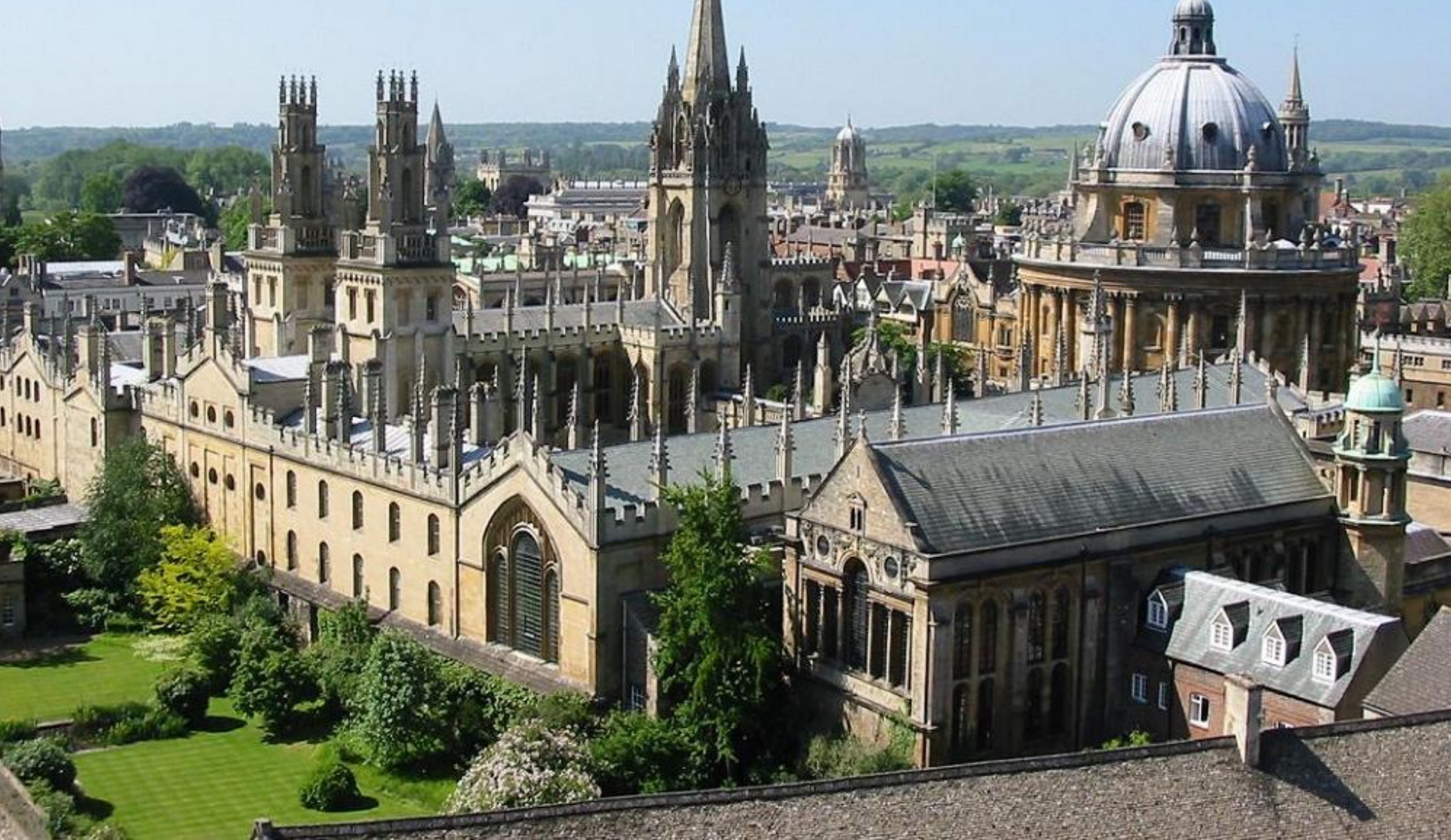
MODELLING CONFLUENT CELL LAYERS AS ACTIVE NEMATICS

Julia Yeomans
University of Oxford



Thank You

Amin Doostmohammadi

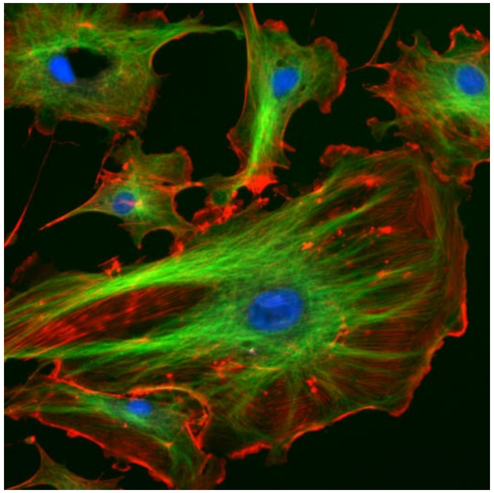
Guanming Zhang

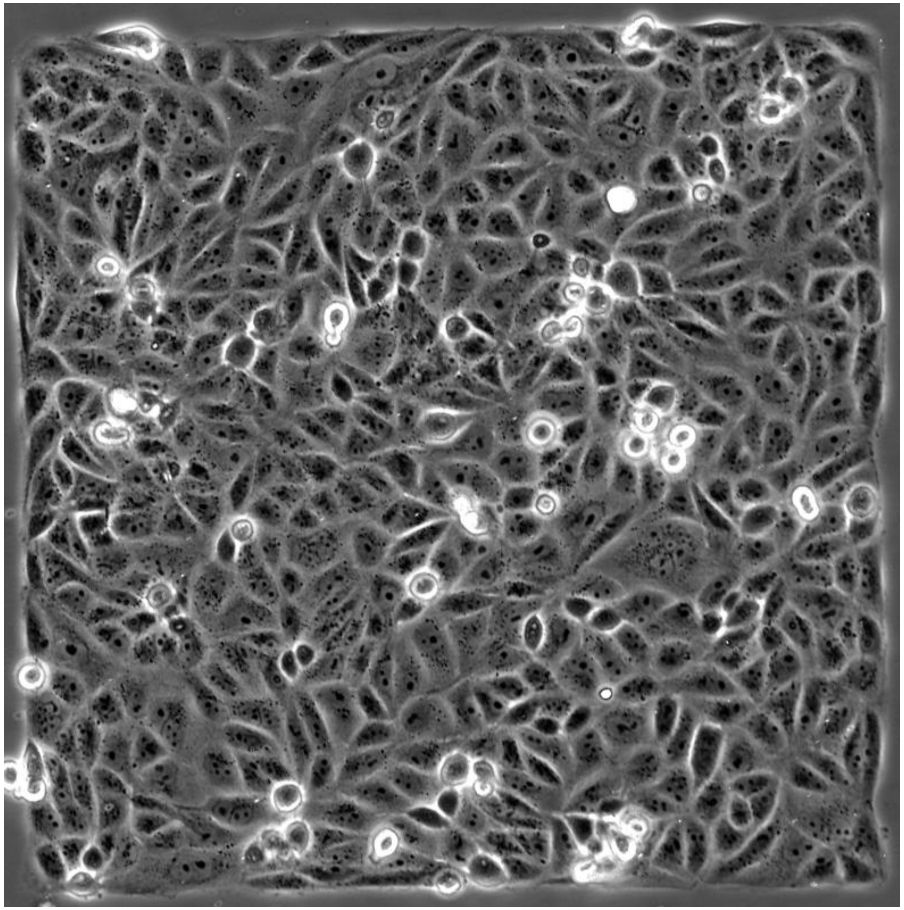
Romain Mueller

Rian Hughes
James Graham
Mehrana Nejad

Thuan Ben Saw
Benoit Ladoux
Lakshmi Balasubramaniam

Confluent cell layers





1. What sort of questions are we trying to answer?

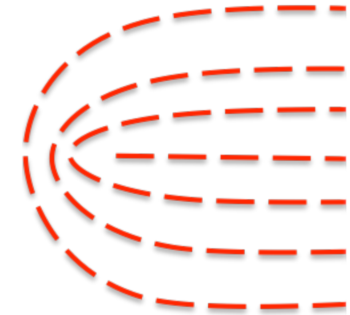
2. Models

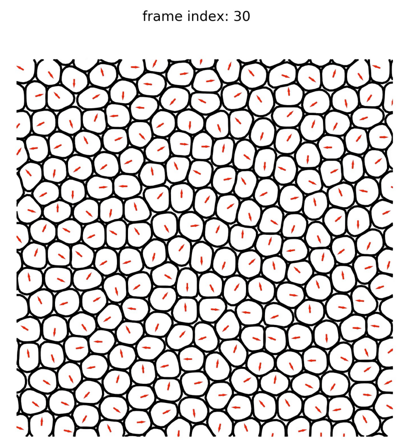
3. The phase field model for confluent cell layers

a. Passive forces

b. Active forces, single cells, polar
contractile dipolar

c. Active forces, confluent layers, extensile dipolar





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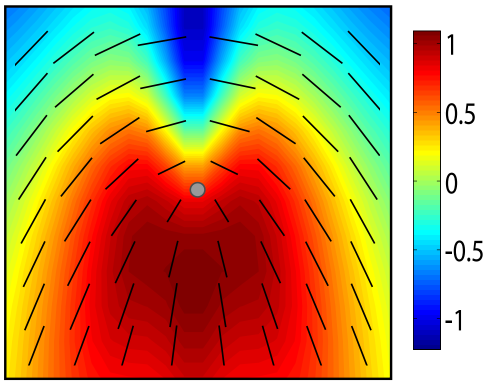
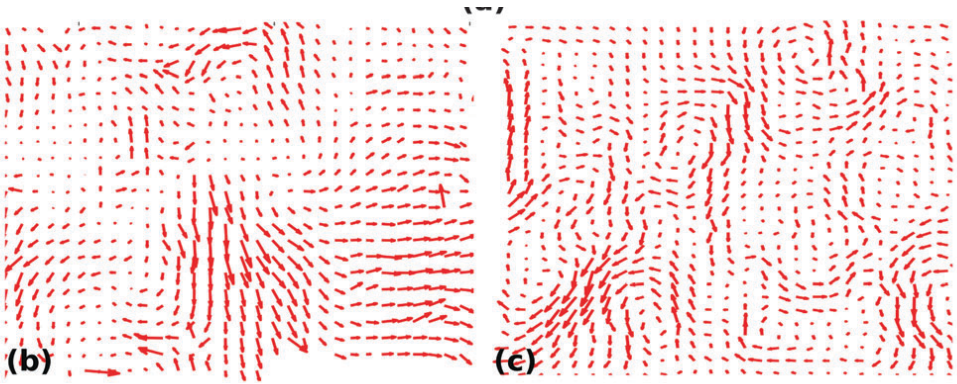
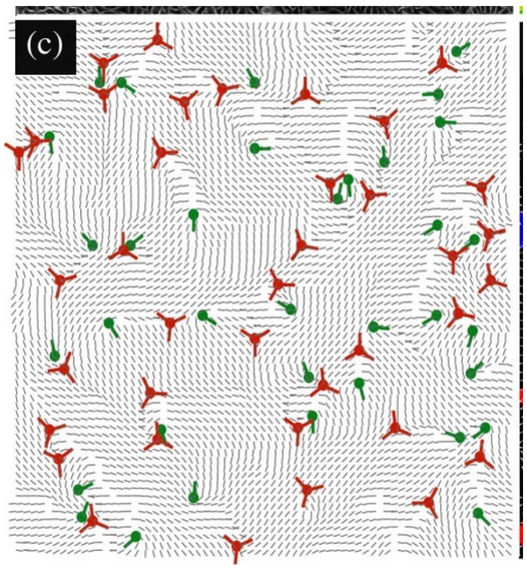


Can we model cell layers as active nematics?



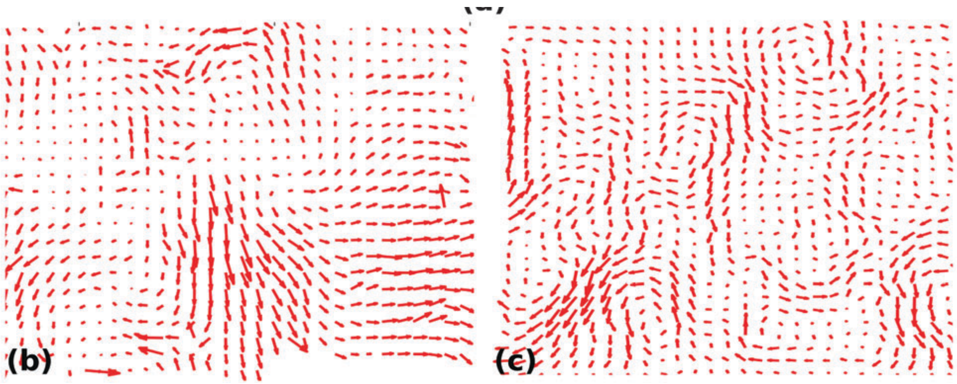
velocity fields reminiscent
of active turbulence



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

shear flow in
confined channels
(Duclos et al Nat Phys 2018)

Can we model cell layers as active nematics?



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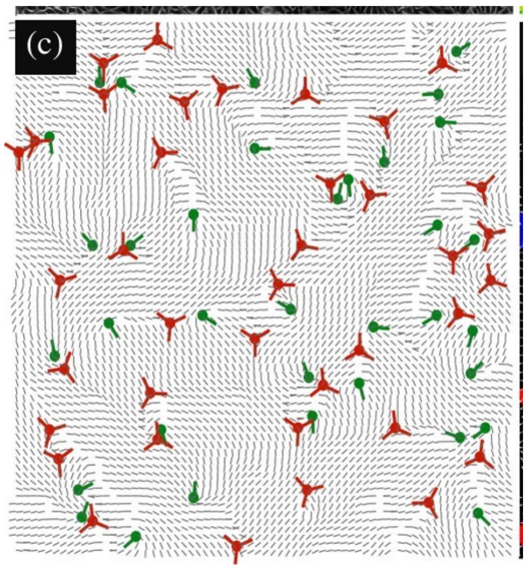


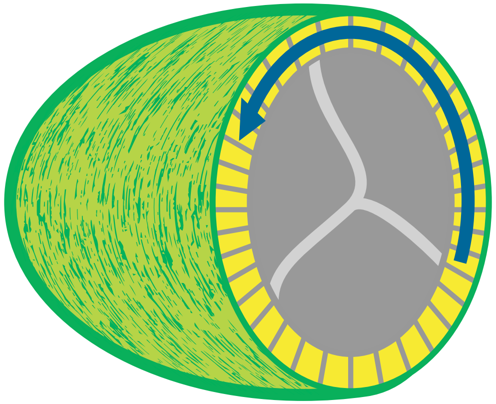
Why can isotropic cells
give nematic behaviour?

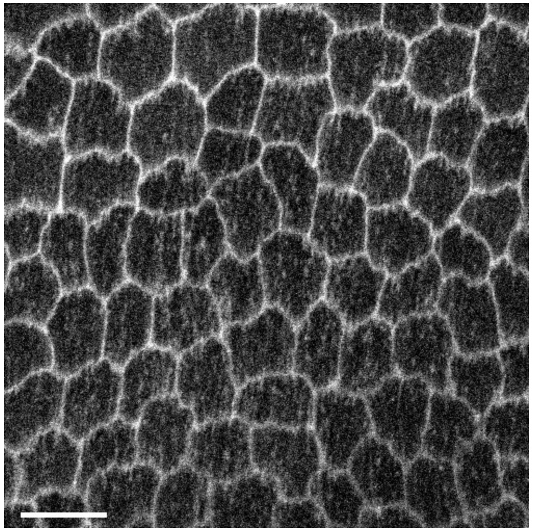
topological defects in human
bronchial epithelial cells
Blanch-Mercader et al PRL 2018

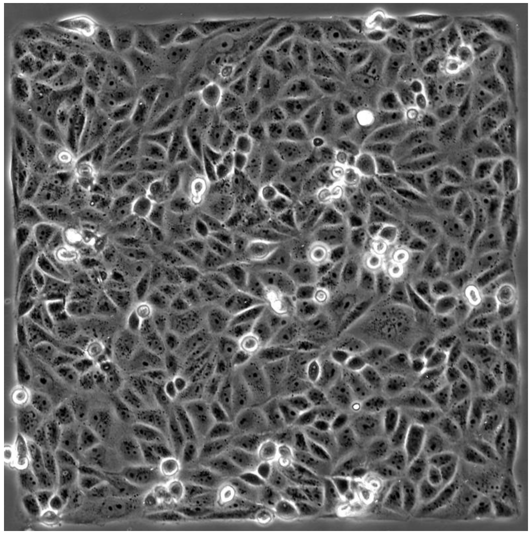
shear flow in
confined channels
(Duclos et al Nat Phys 2018)

Drosophila egg chamber: active turbulence vs flocking

Egg chamber rotation

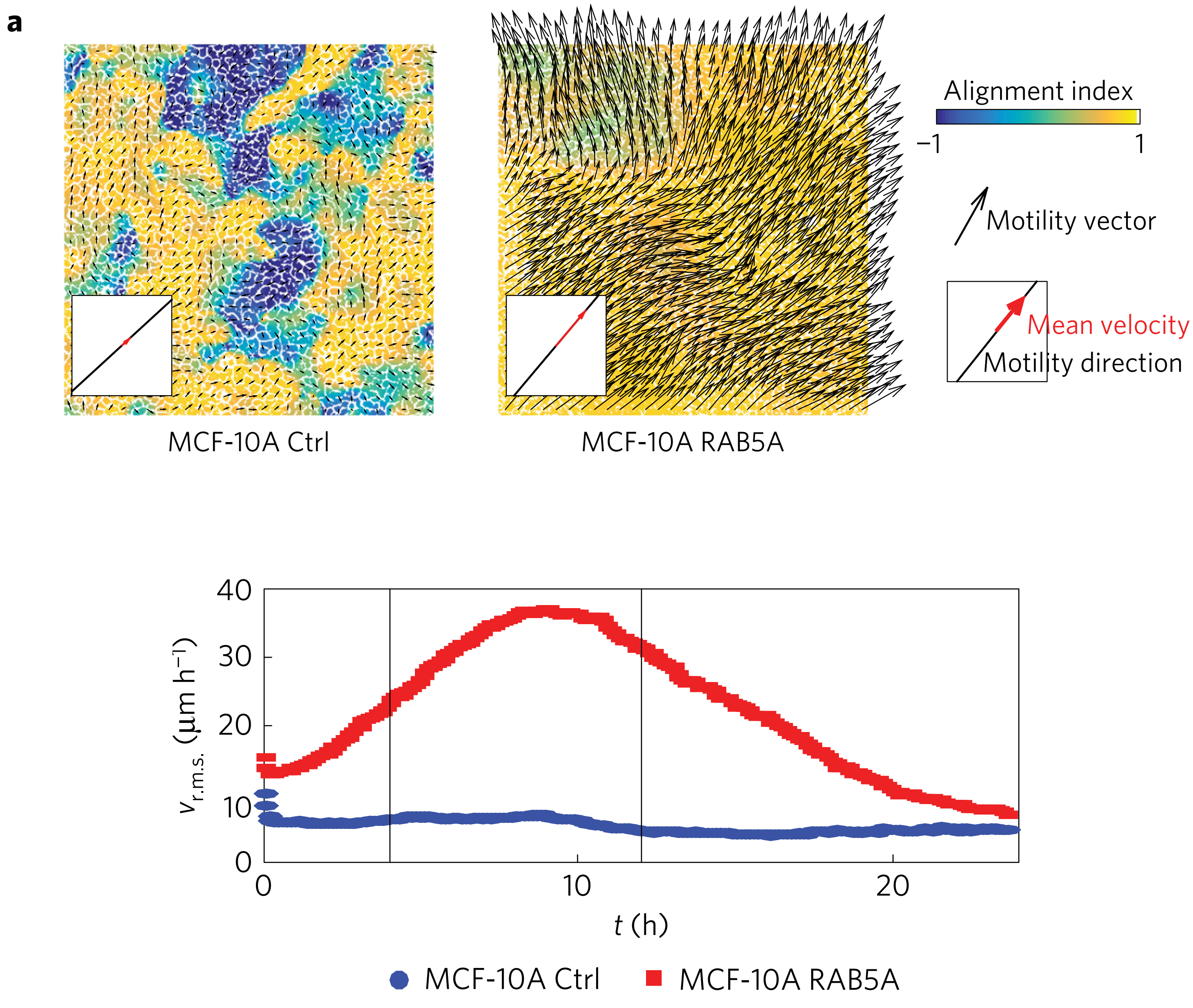


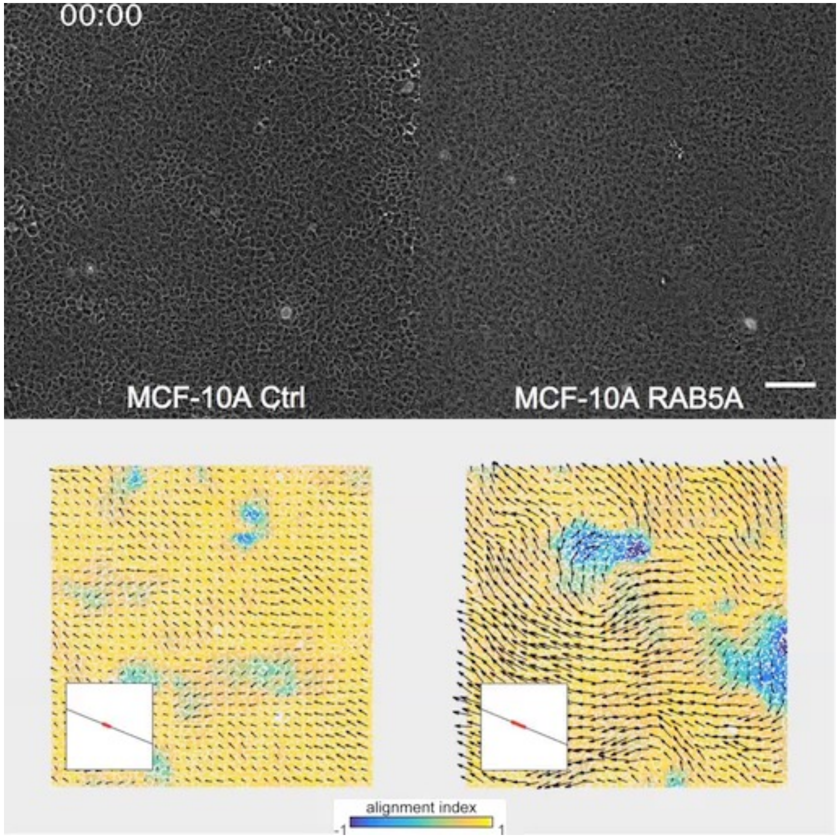




From Sally Horne-Badovinac's lab:
Cetera et al. Nature Comms. 5, 5511 (2014)

Malinverno et al Nature Materials 16 (2017)





Flocking or active turbulence?

polar force or dipolar force

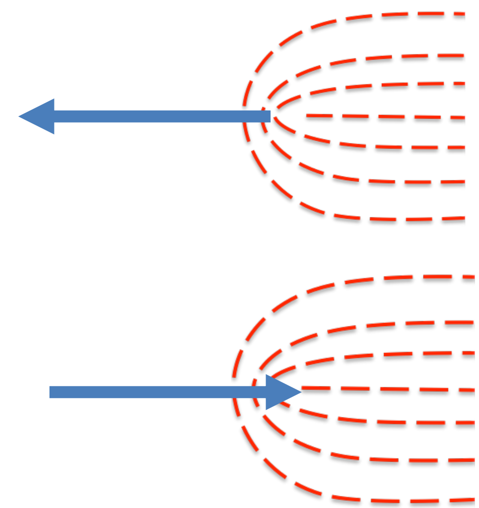
If there are dipolar forces are they extensile or contractile?

Polar force

Dipolar force

extensile

contractile



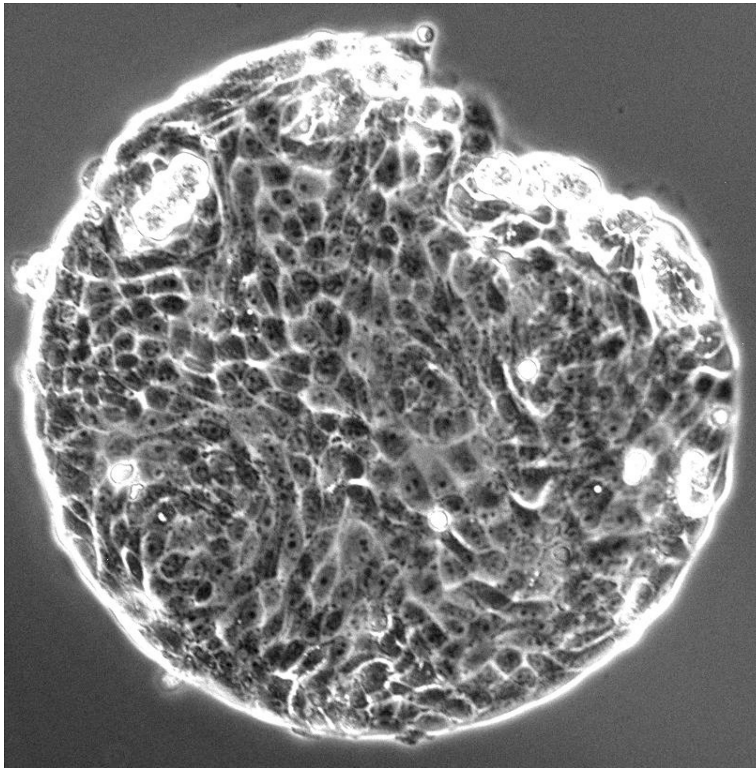
Questions:

Why do circular cells give active turbulence?

Flocking or active turbulence?

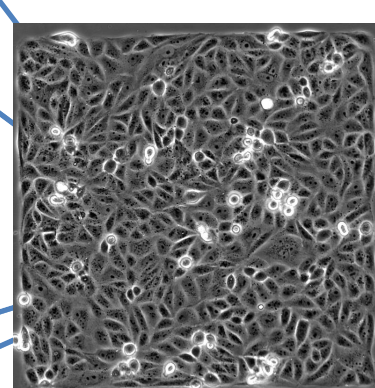
Polar or dipolar driving?

Extensile or contractile dipolar driving?



continuum models:
active nematic /polar
active gels

Vertex + Voronoi models

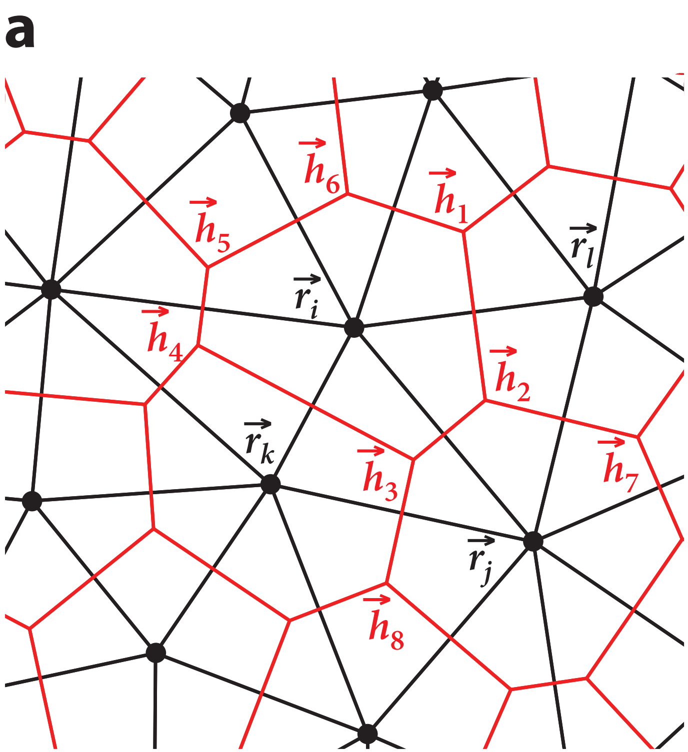


particle models
Vicsek model
cellular Potts model
particles + Voronoi

Phase field models

Alert & Trepat, Annual Review of Condensed Matter Physics 2020

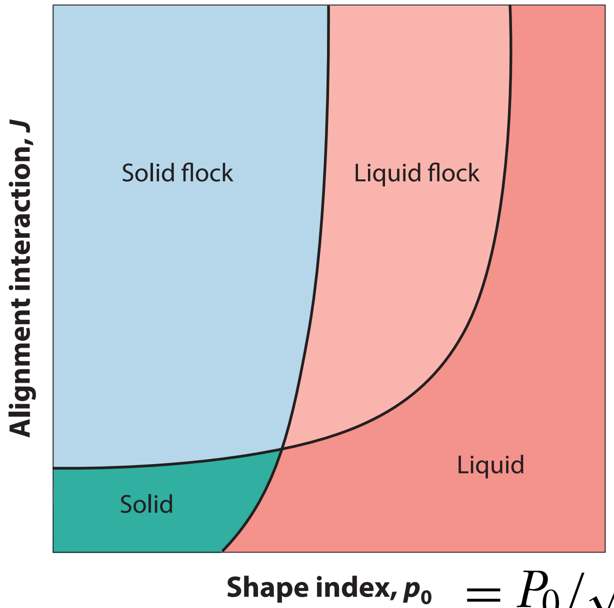
Voronoi models



associate energy with areas and perimeters of the cells

$$\mathcal{F} = \sum_{a=1}^{N} \left[\frac{\kappa}{2} (A_a - A_0)^2 + \frac{\Gamma}{2} (P_a - P_0)^2 \right].$$

add self propulsion by a polar force acting on cell centres of cell vertices



$= P_0/\sqrt{A_0},$

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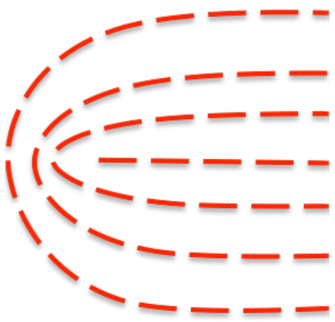
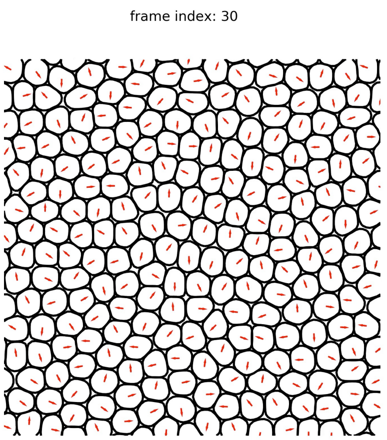
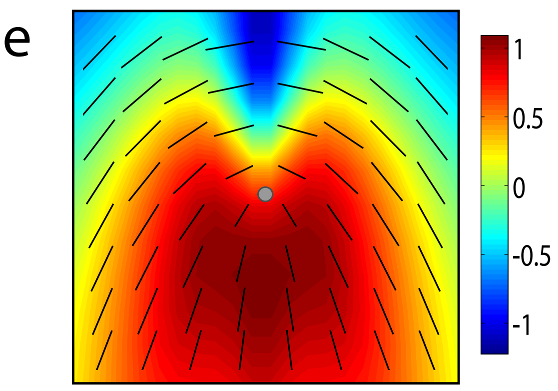
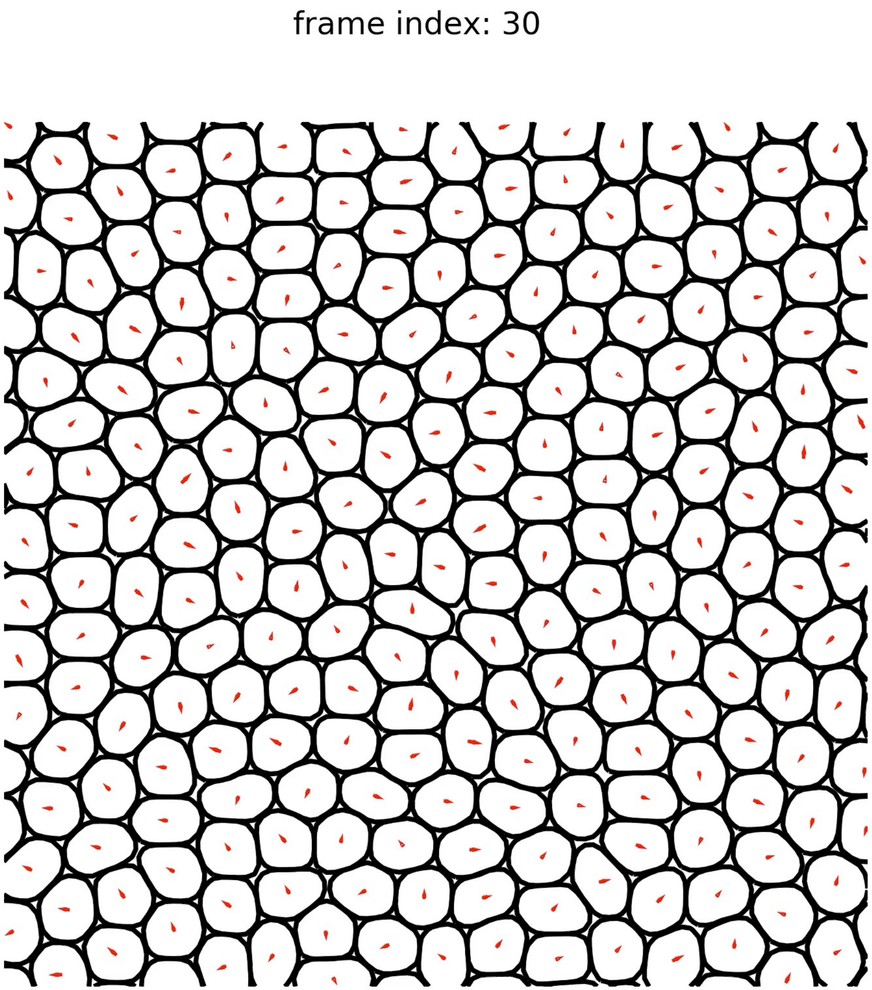






Phase field model



Grant, Aranson

Equations of motion

Each cell is described by a phase field φ_i

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

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

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

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

Passive forces: relax to minimise free energy

penalises overlap between cells

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

favours cell-cell adhesion

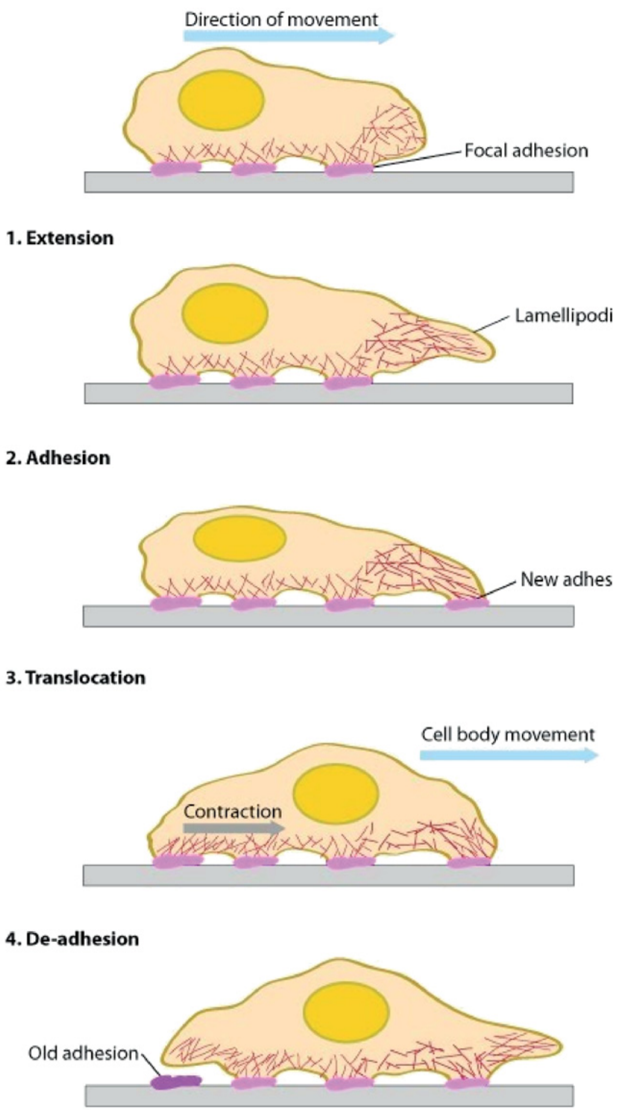
$$\mathcal{F}_{\mathrm{adh}} = \sum_i \sum_{j \neq i} \omega\lambda \int d\mathbf{x}\, \nabla\varphi_i \cdot \nabla\varphi_j$$

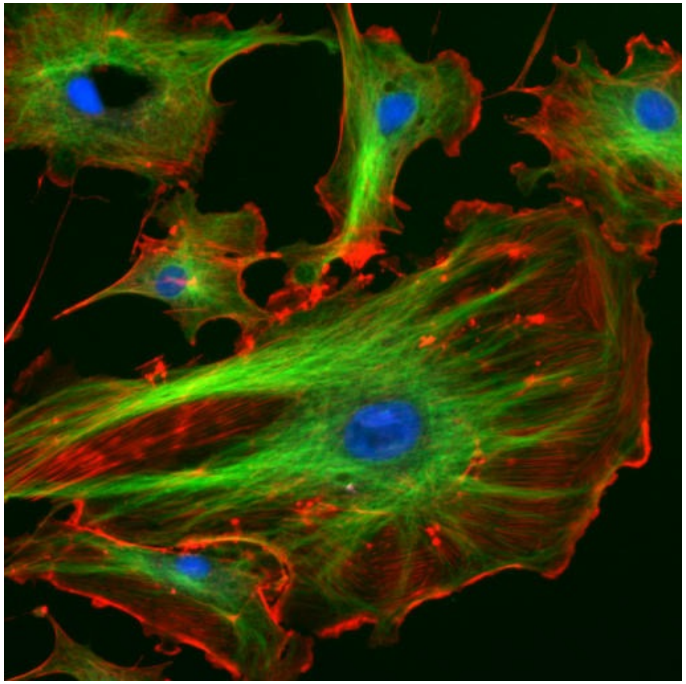
Passive forces: relax to minimise free energy

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

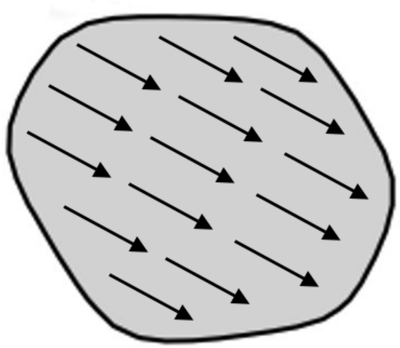
Equilibrium is identical hexagons, but the system can get stuck
In a jammed state.

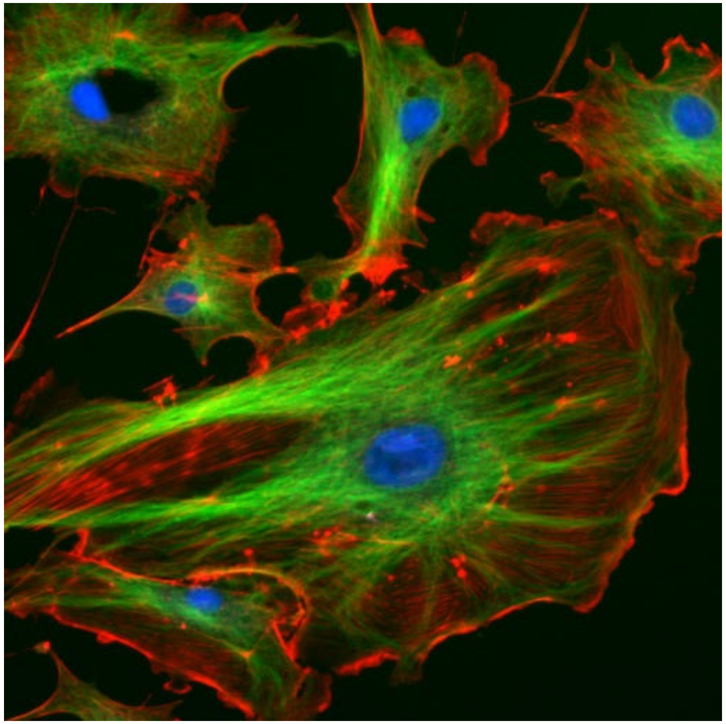
Active polar force (Stokeslet)

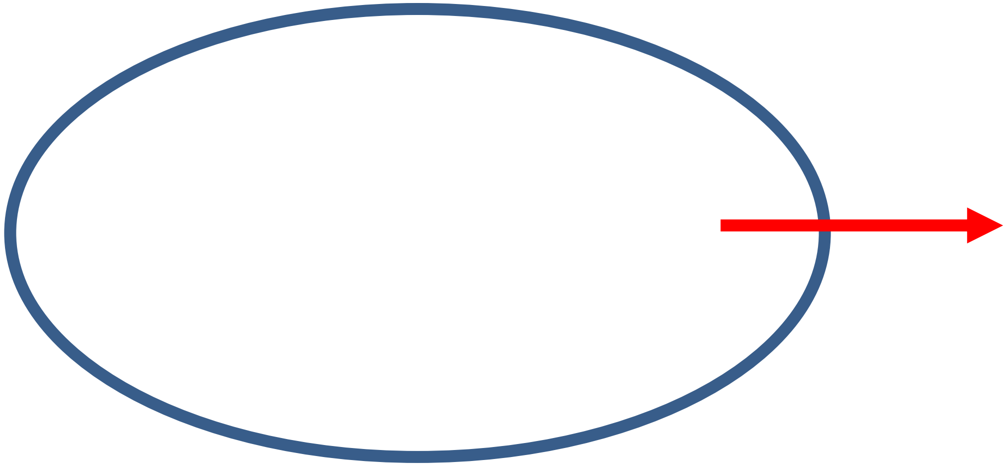




Ladoux and Nicholas Rep Prog Phys 2012

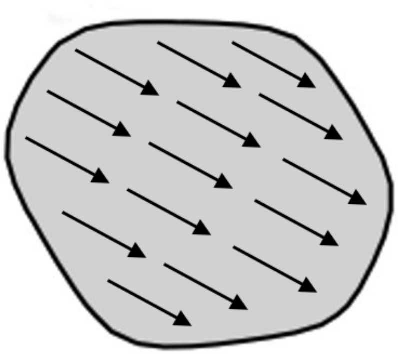






polar force
pulling the cell along

Polar force



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

polarisation of cell i

Choice of polarisation?

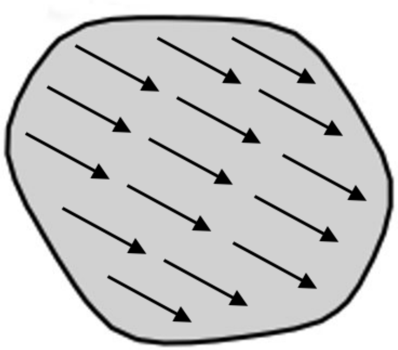
1. Gaussian noise

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



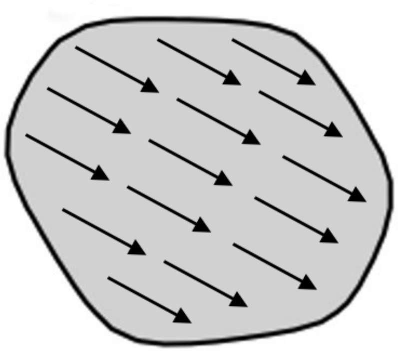
$$\mathbf{f}_i^{\mathrm{pol}}(\mathbf{x}) = \alpha\varphi_i(\mathbf{x})\mathbf{p_i}$$

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 force



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

Choice of polarisation?

So far we have found little difference except that 2 gives flocking.

1. Gaussian noise

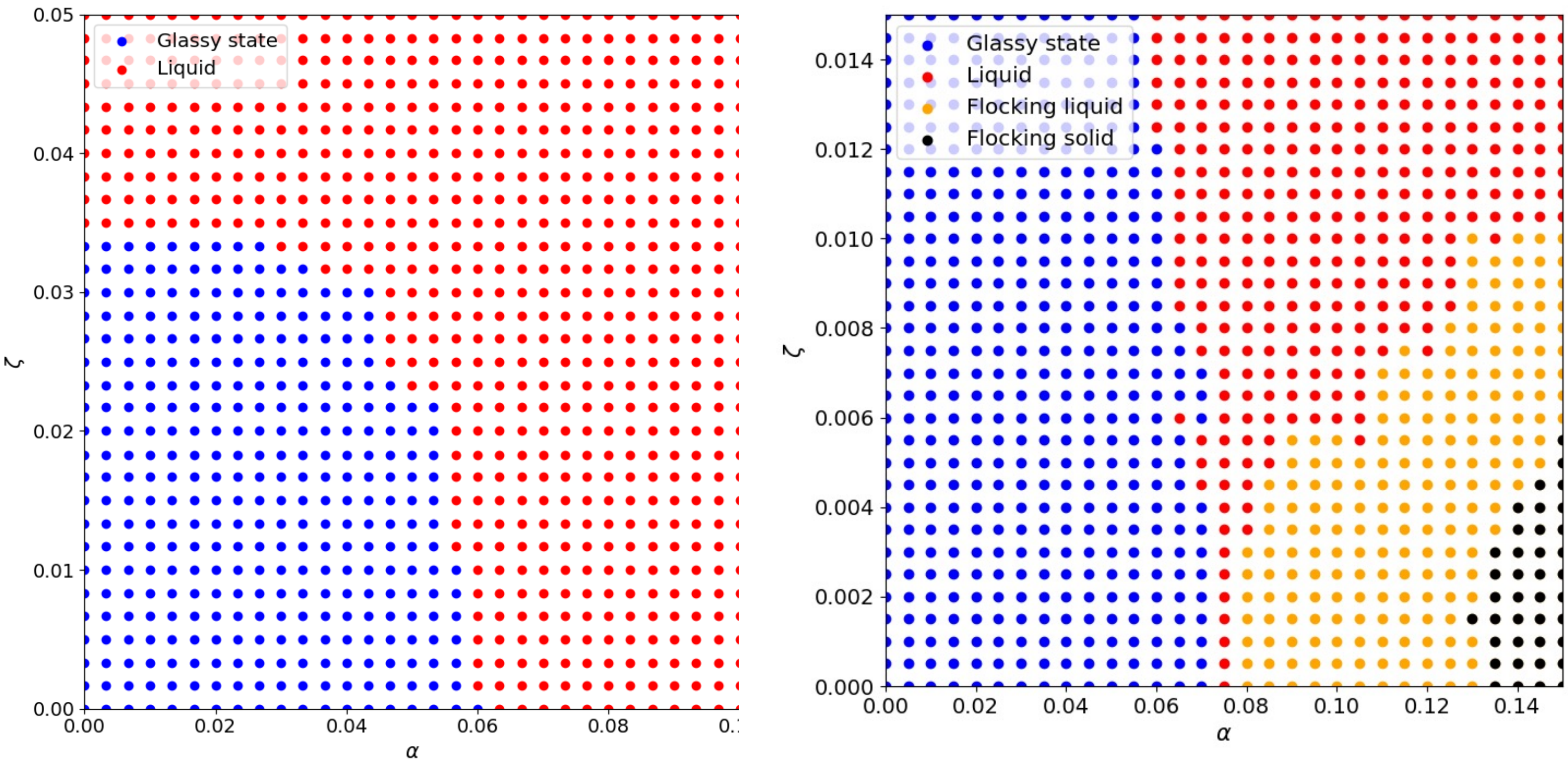
2. Aligns with velocity of cell (+noise)

3. Aligns with long axis of cell (+noise)

4. Aligns and is proportional to the elongation of the cell (+noise)

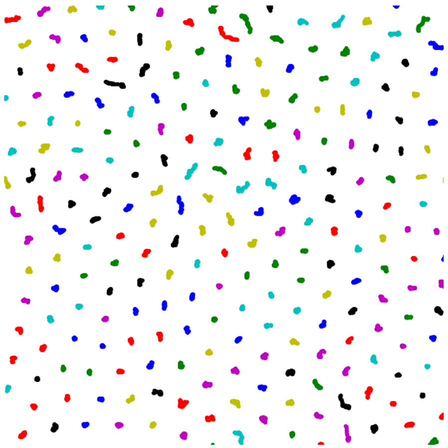
Phase diagram

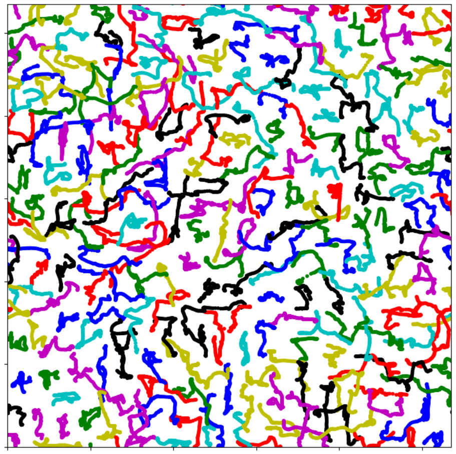
strength of
dipolar force



strength of
polar force

unjamming



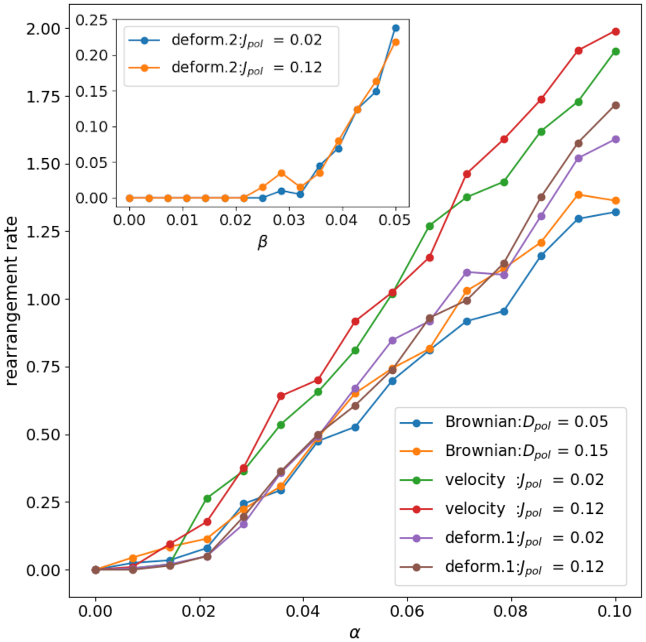


jammed state

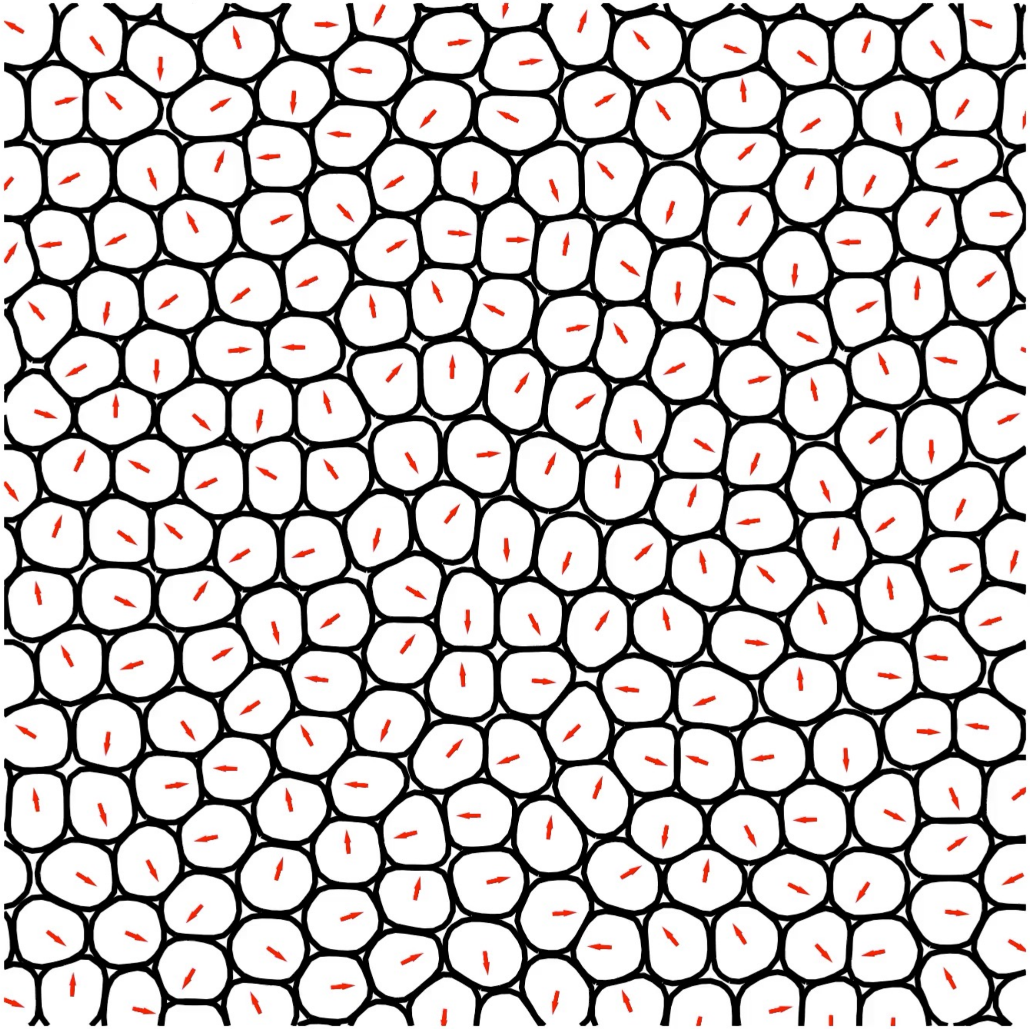
liquid

centre of mass trajectories of the cells

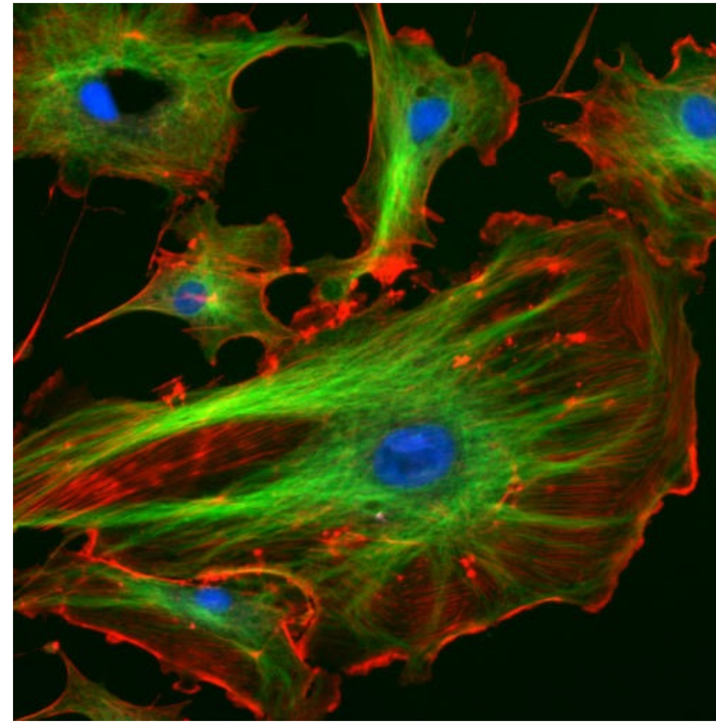
rearrangement rate of cells against strength of polar force

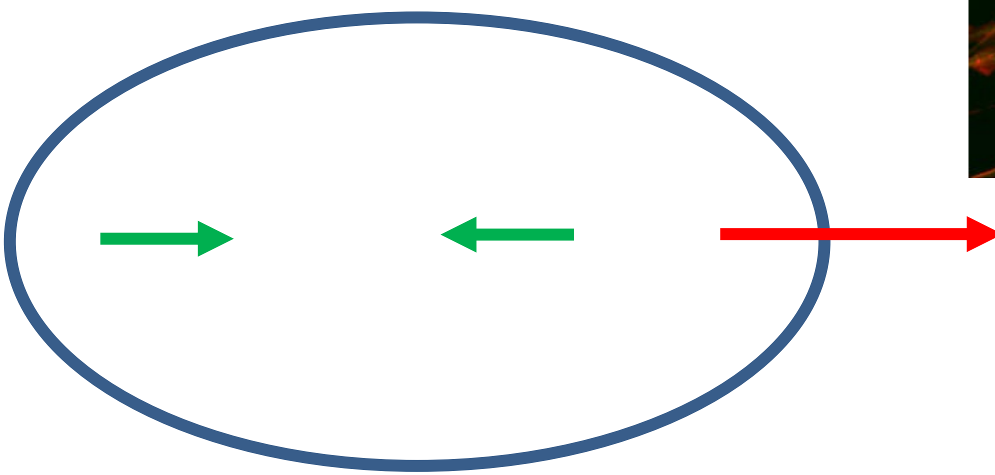


Flocking: polar force aligns to velocity



Contractile (intra-cellular) dipolar force





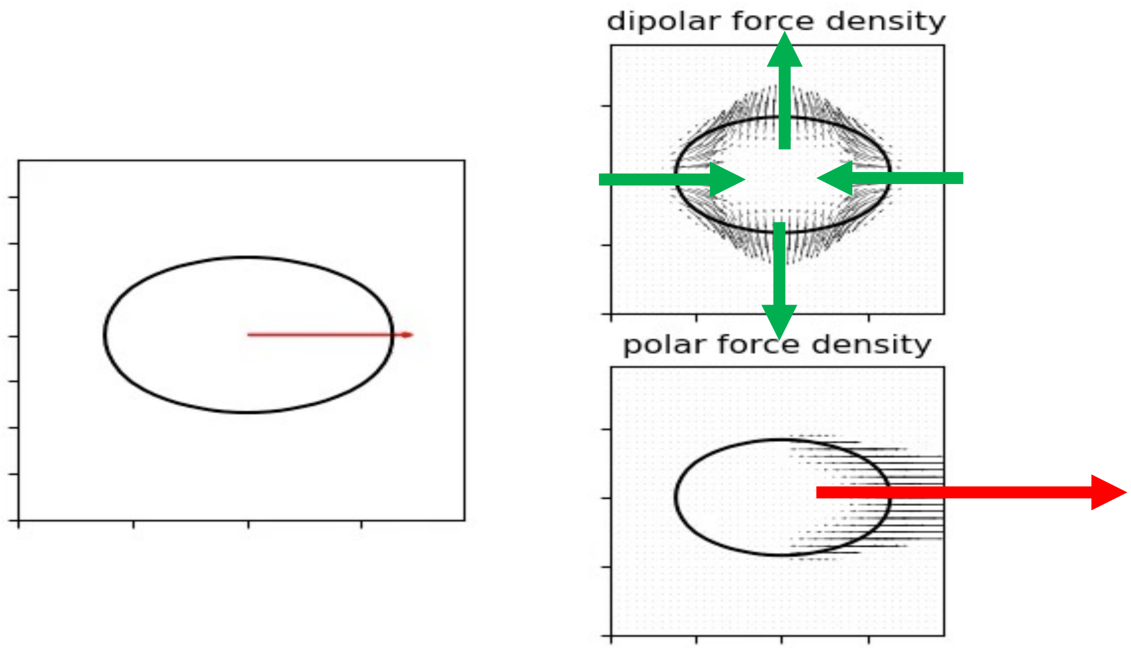
contractile dipolar force
restoring the cell to circular

polar force
pulling the cell along

polarity tensor $\mathcal{P}_i = \vec{p}_i^{\mathrm{T}} \vec{p}_i - \frac{\mathbb{I}}{2} \vec{p}_i^2$

dipolar stress $\sigma_D = -\zeta \sum_i \varphi_i(\mathbf{x}) \mathcal{P}_\mathrm{i}$

dipolar force $\mathbf{f}(\mathbf{x})^{\text{dipolar}} = \nabla \cdot \sigma_D$



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

Cells within a colony are much less likely to form lamellopodia

Strength of the polarization decreases with increasing cell-cell overlap

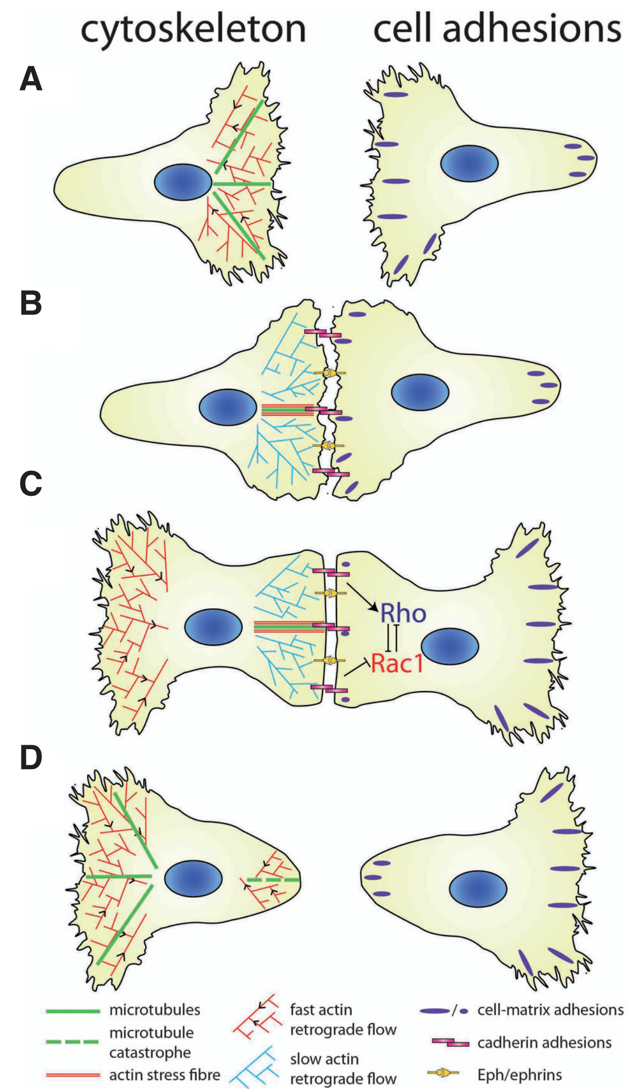
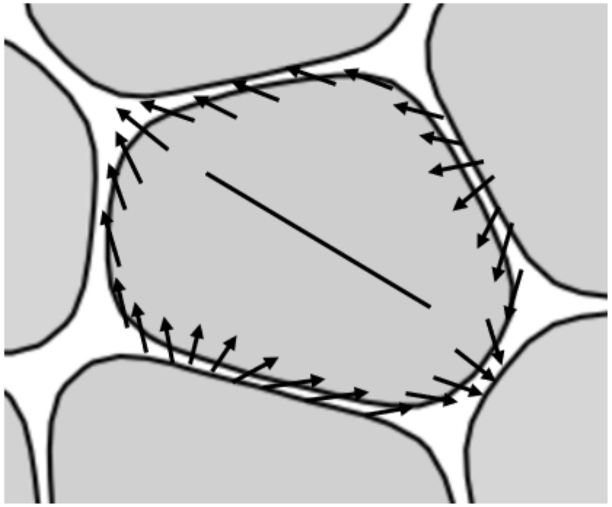
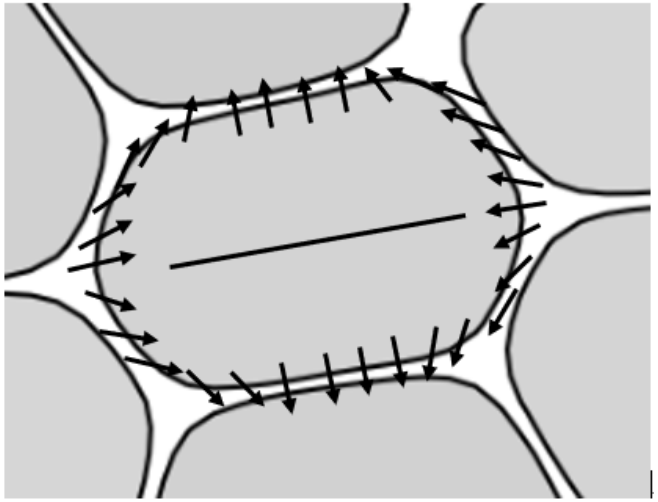


Fig from Int. J. Dev. Biol. 62: 5-13 (2018)

But can also have dipolar forces due to cell-cell junctions: these are probably extensile

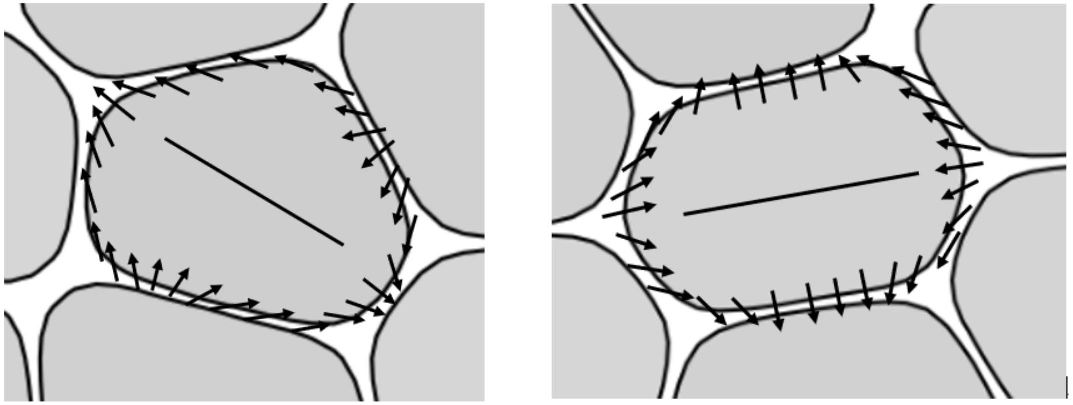


(a) extensile



(b) contractile

But can also have dipolar forces due to cell-cell junctions: these are probably extensile



(a) extensile (b) contractile

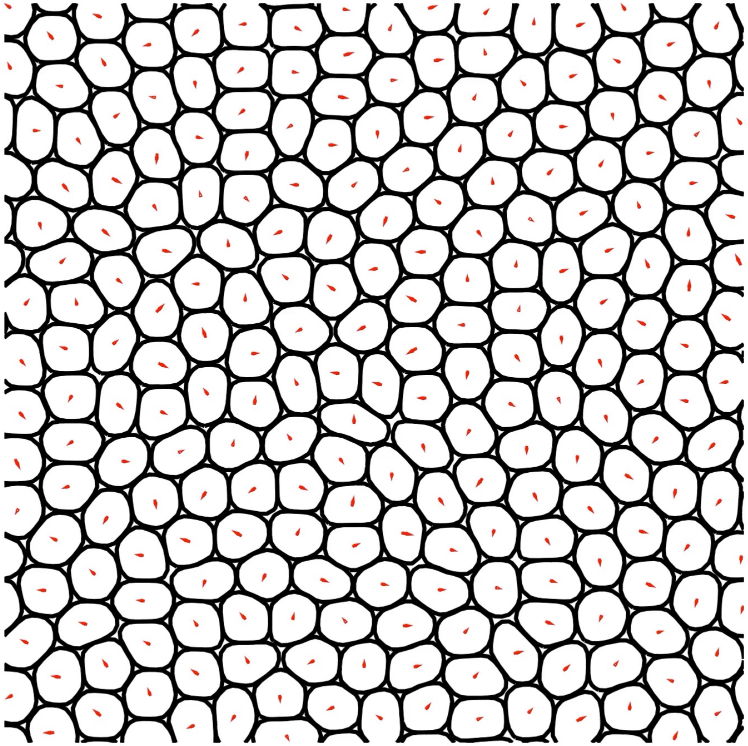
deformation tensor
$$\mathcal{D}_i = -\frac{1}{2}\int d\mathbf{x}\left\{\nabla\varphi_i\nabla\varphi_i^T - \mathrm{Tr}(\nabla\varphi_i\nabla\varphi_i^T)\right\}$$

dipolar stress
$$\sigma_D = -\zeta\sum_i \varphi_i(\mathbf{x})\mathcal{D}_i$$

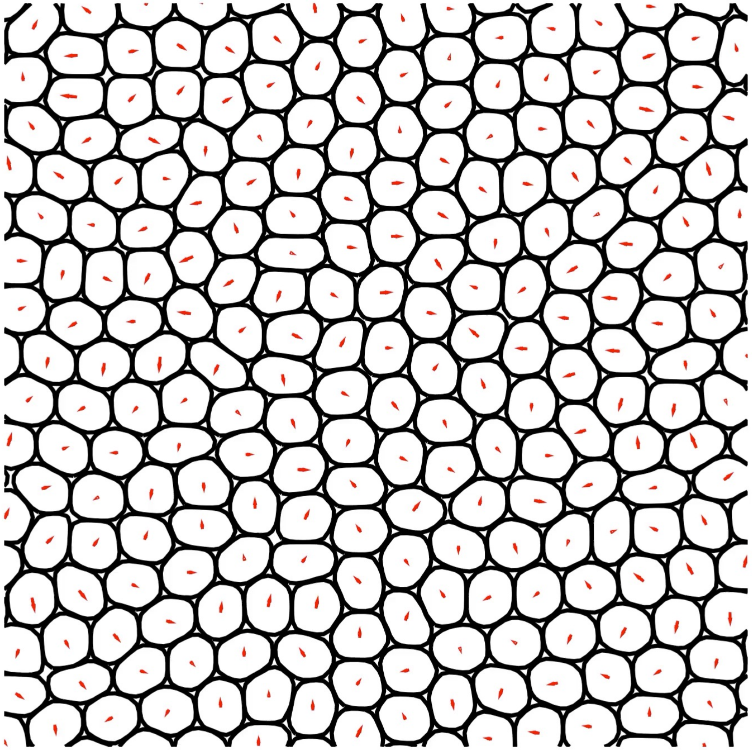
dipolar force
$$\mathbf{f}(\mathbf{x})^{\text{dipolar}} = \nabla\cdot\sigma_D$$

Increasing the magnitude of the extensile dipolar forces – no polar driving

frame index: 30

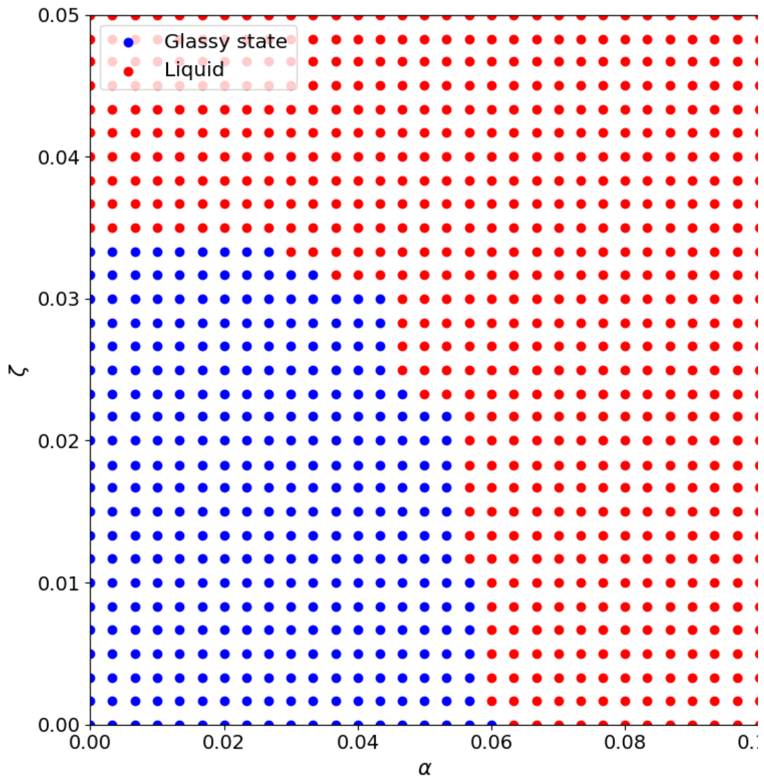


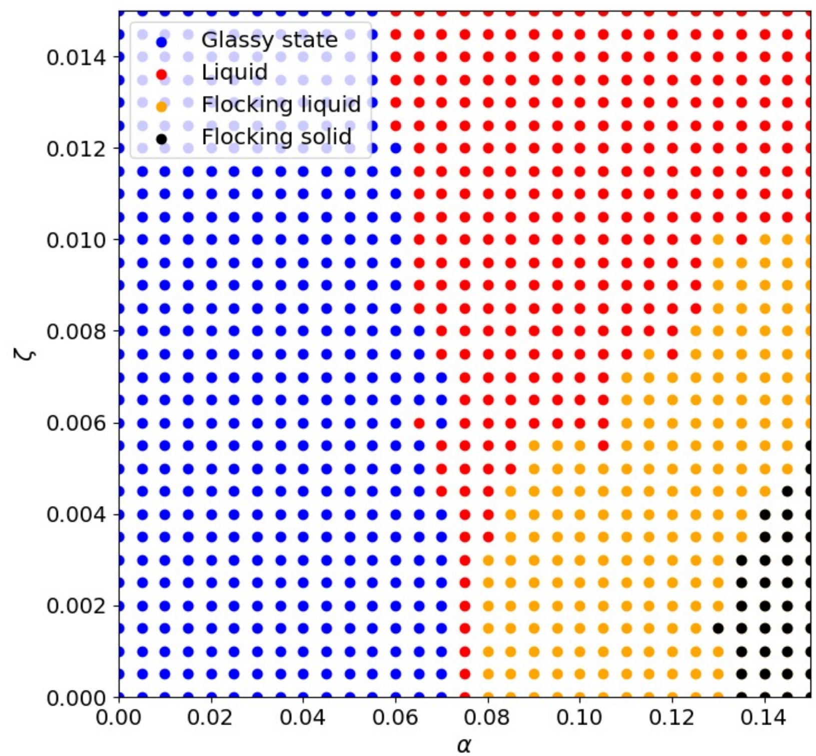
frame index: 30



Phase diagram

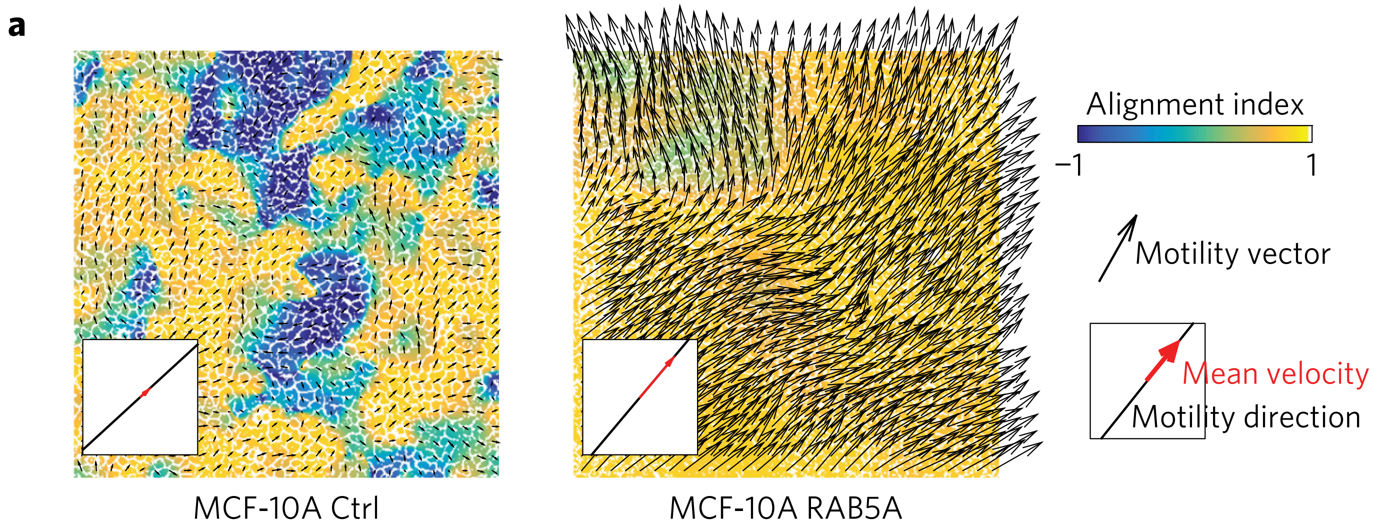
strength of extensile
dipolar force

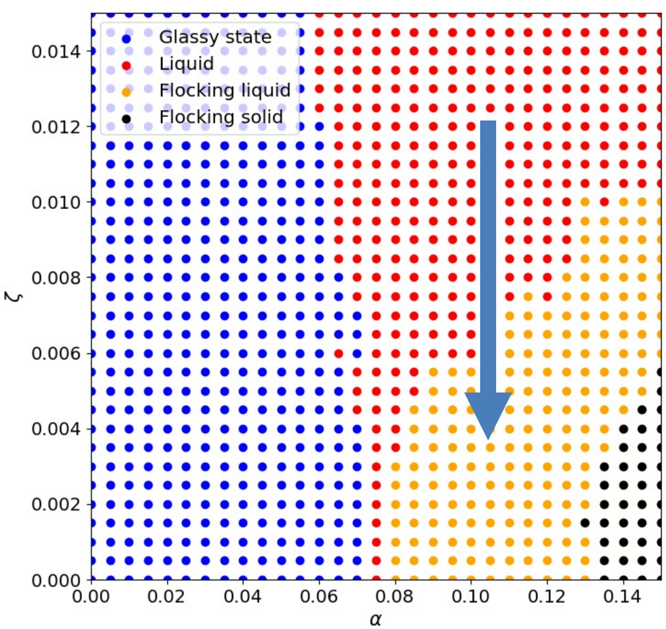




strength of
polar force

Malinverno et al Nature Materials 16 (2017)

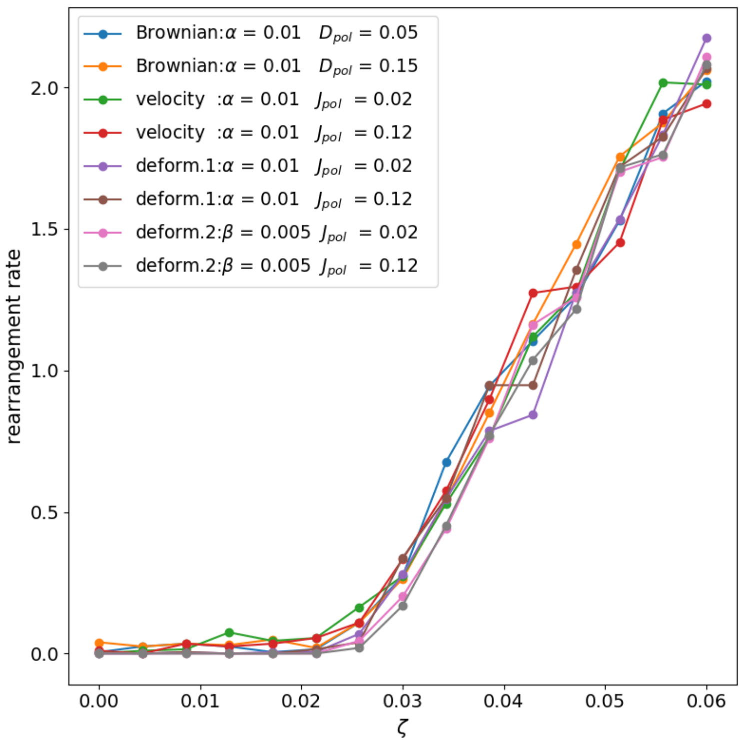




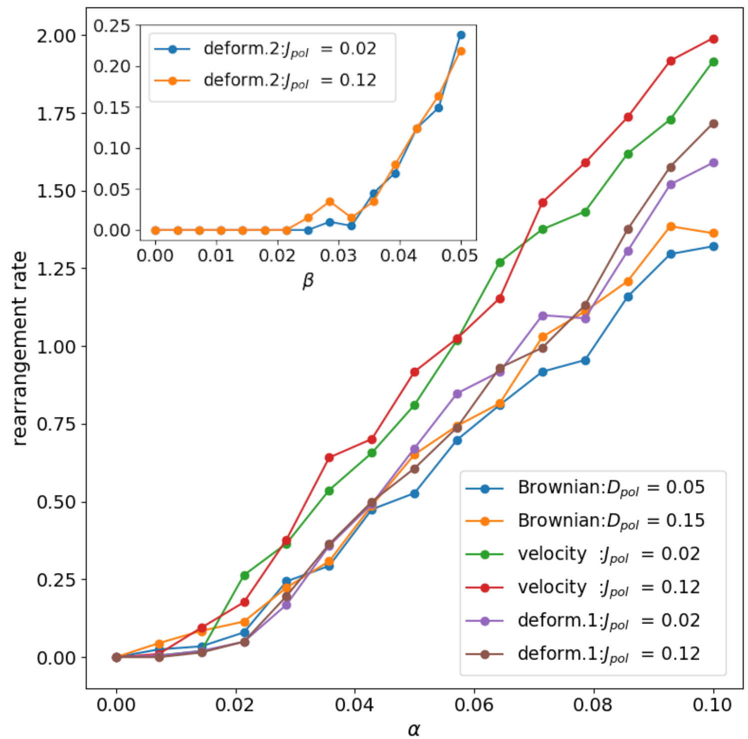
RAB5A ⇔ turning off intercellular interactions

unjamming

dipolar

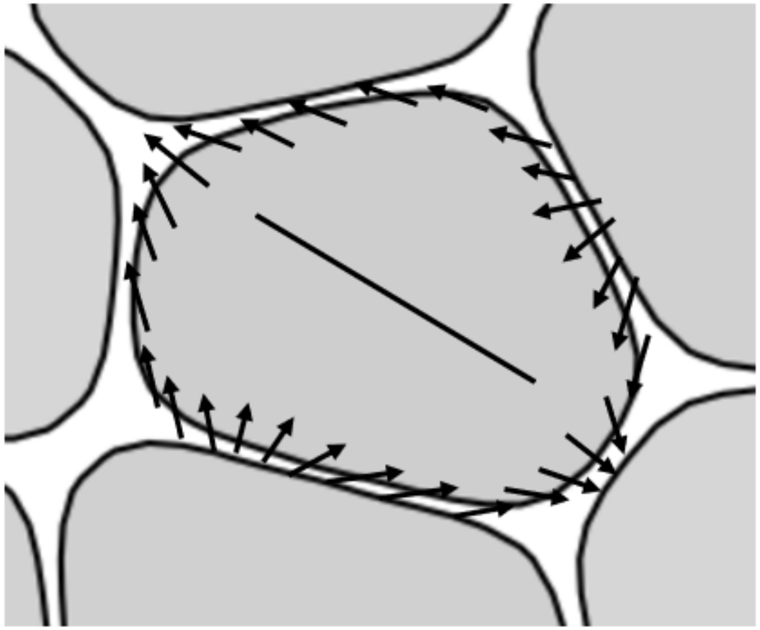


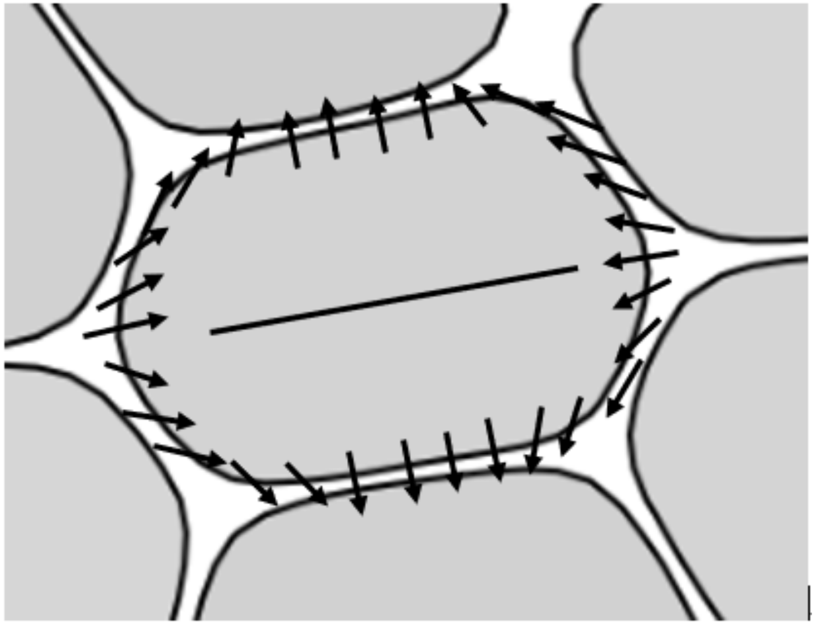
polar



rearrangement rate: average number of cells that change neighbours at each time step

Why can circular cells show topological defects



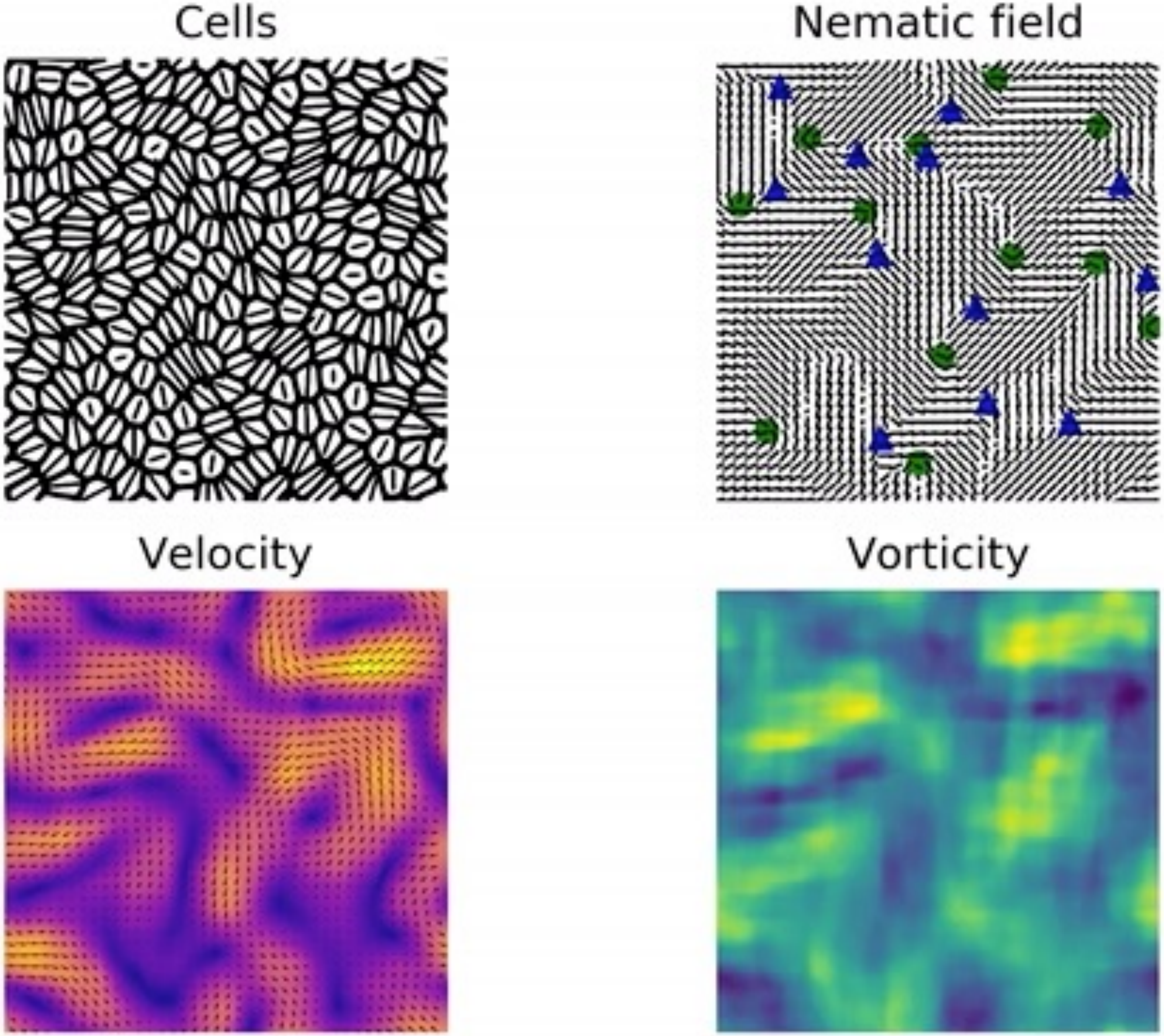


extensile

contractile

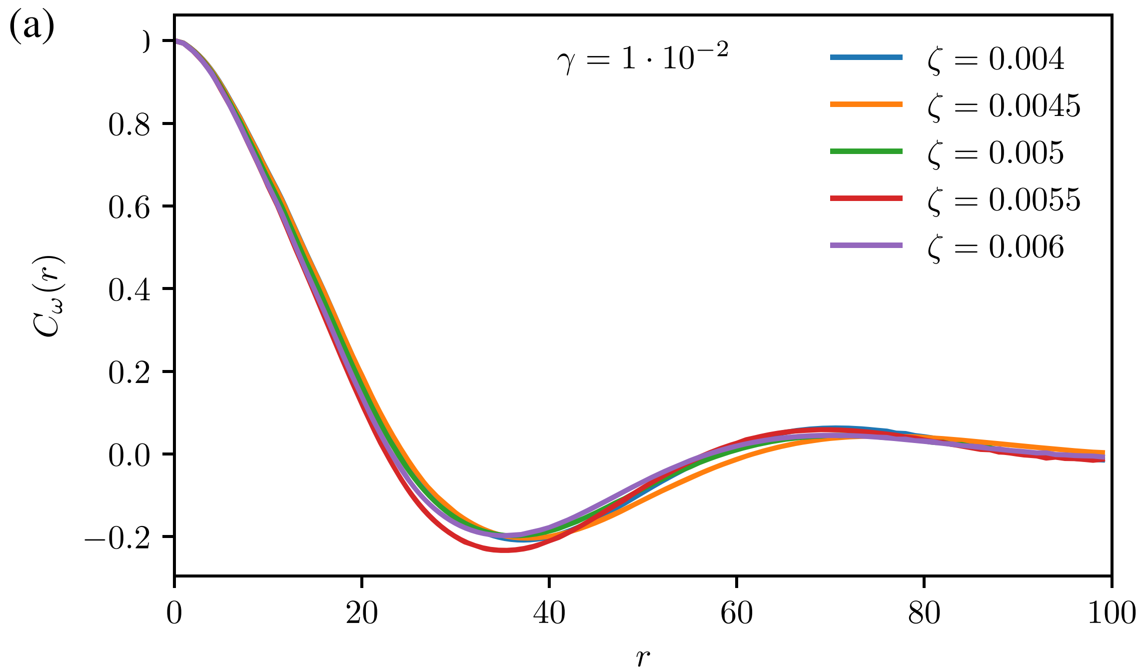
extensile cell-cell interactions => nematic ordering => active turbulence

(NB cf shear flows in continuum active nematics)


Cells
Nematic field
Velocity
Vorticity

Active turbulence

vorticity-vorticity correlation function



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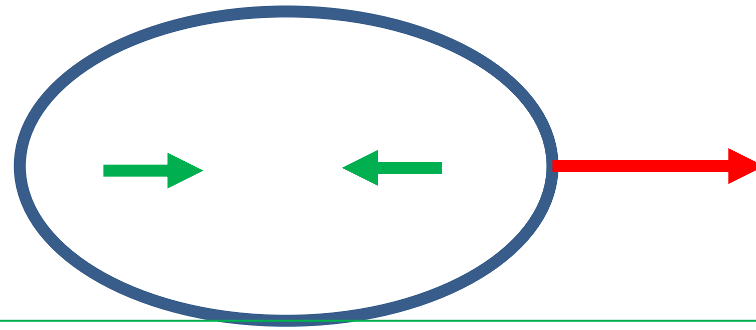
Round up of forces

Passive: distinguishes different cells, determines their size
adhesion

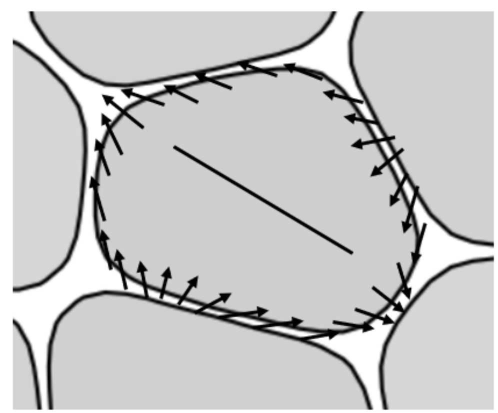
Active single cell forces



contractile dipolar force (stresslet)
restoring the cell to circular

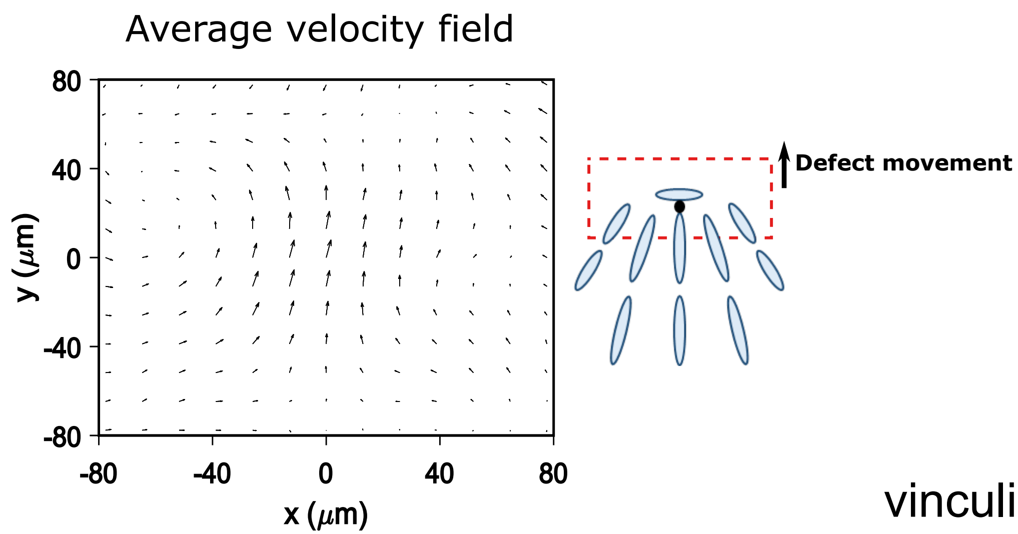
polar force
pulling the cell along

Active forces due to cell junctions
(probably) extensile dipole



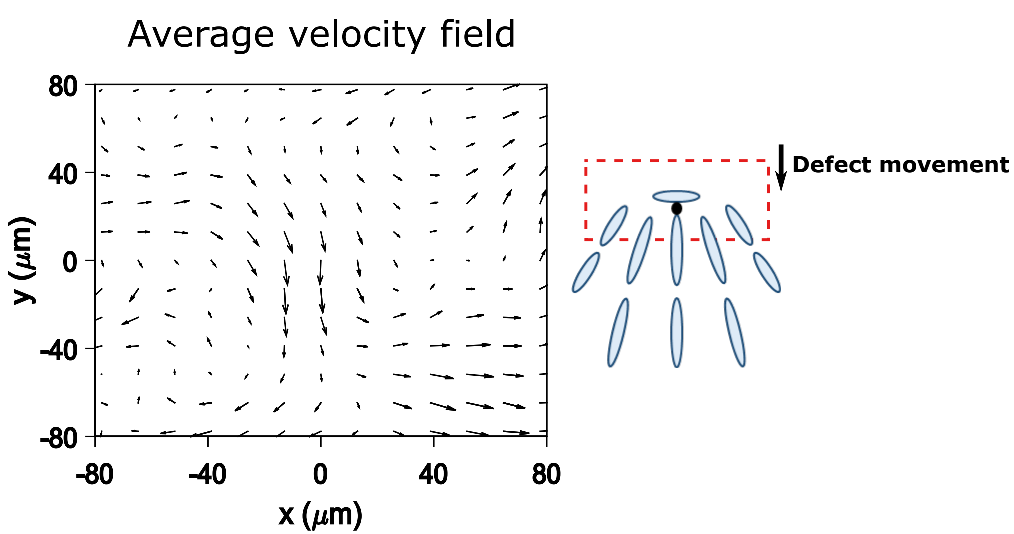
(a) extensile

Why are the defects extensile?



MDCK cells

vinculin relocates from cell-cell boundaries to cell-substrate boundaries



MDCK cells with
cell junctions
Weakened
E-cadherin knock-out

Balasubramaniam et al.
Nature Materials, in press
bioRxiv 2020.10.28.358663

Questions:

Why do circular cells give active turbulence?
Extensile inter-cellular interactions

Flocking or active turbulence?
Polar or dipolar driving?
Contact inhibition of locomotion
activated or not

Extensile or contractile dipolar driving?
Extensile wins for strong cell-cell junctions