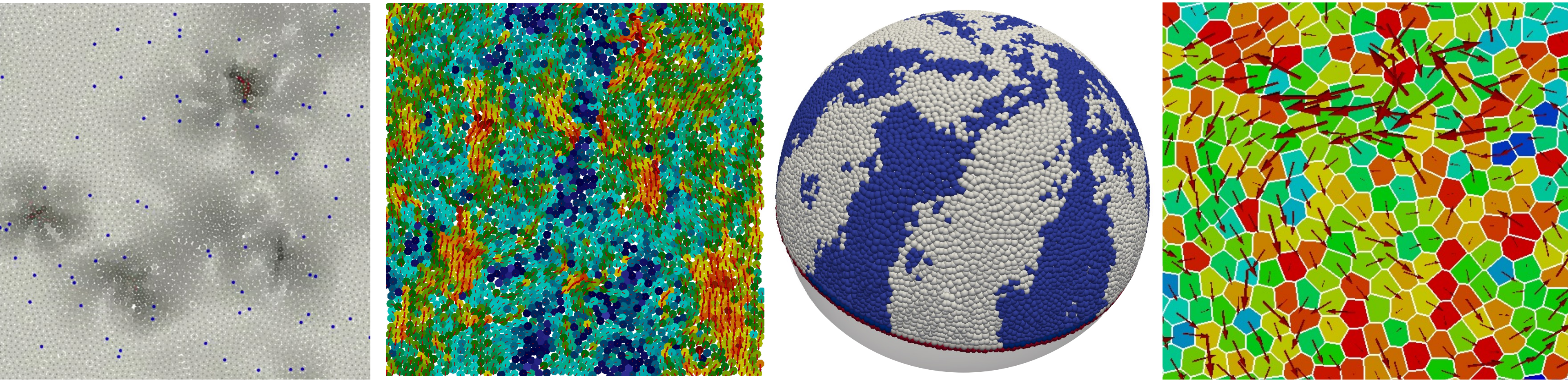
Epithelial cell sheets as a soft active material

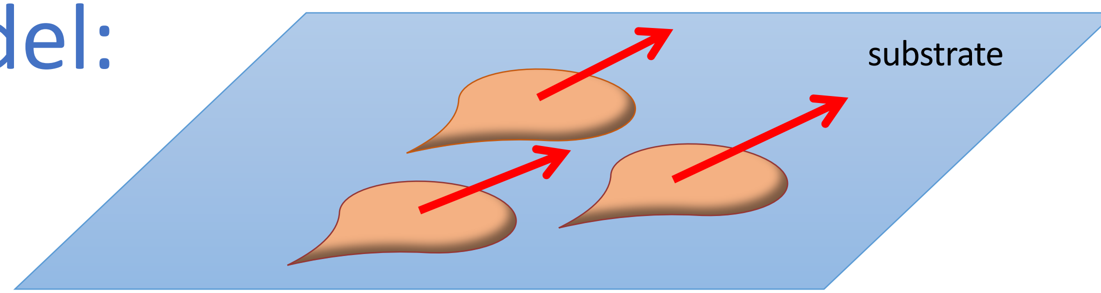
Silke Henkes

& from review paper: Alert & Trepat, Annu. Rev. Condens. Matter Phys. 2020. 11:77–101



Collective motion of ABPs

Particle based model: Active brownian particles (ABPs)



- Dissipative motion on a substrate, no momentum conservation,
- Incorporate self-propulsion as a force
- Separate velocity field and polar director fields

Fully overdamped

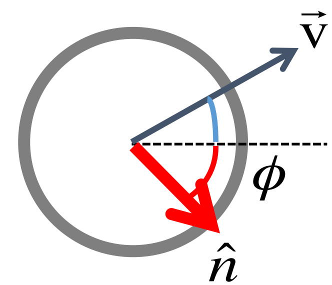
$$\dot{\mathbf{r}}_i = v_0 \hat{\mathbf{n}}_i + \mu \sum_j \mathbf{F}_{ij}$$

self-propulsion

short-range repulsion/attraction forces

$$\dot{\phi} = \eta, \quad \langle \eta(t)\eta(t') \rangle = \frac{1}{\tau}\delta(t-t')$$

siffusive angular dynamics



τ : orientational persistence time

(inverse rotational diffusion constant)

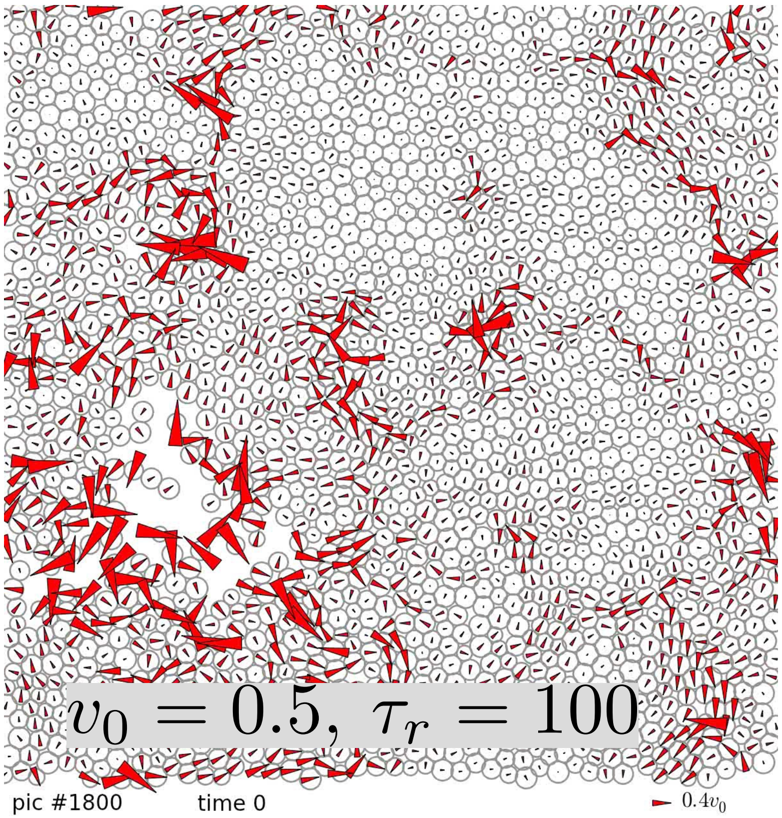
Review article:

MC Marchetti, Y Fily, SH, A Patch, D Yllanes

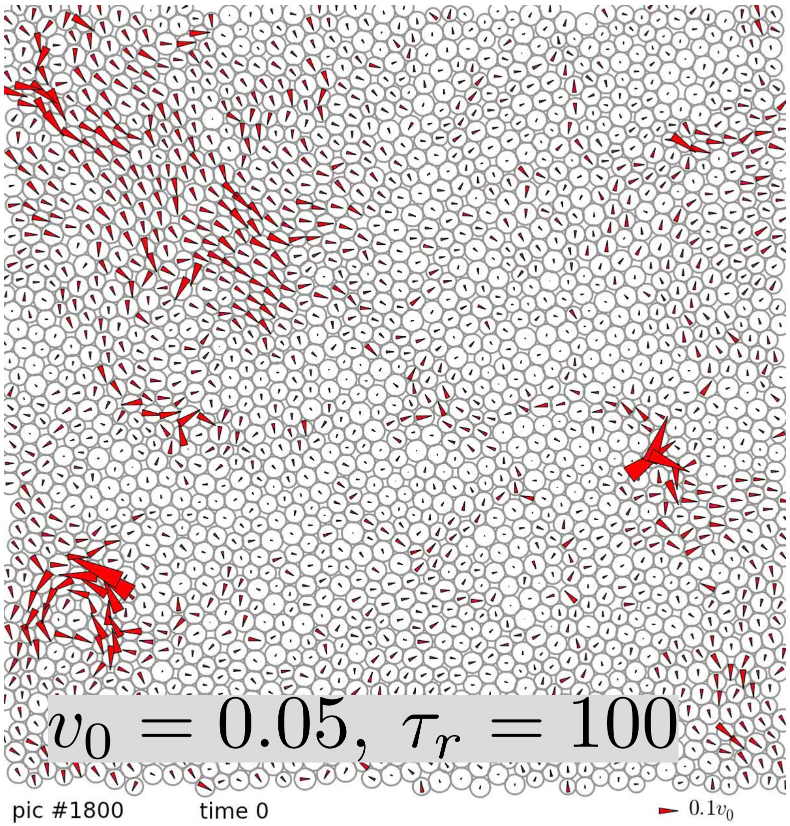
Current Opinion in Colloid & Interface Science 21, 34-43 (2016)

Extremely simple, but already interesting

Phase separated



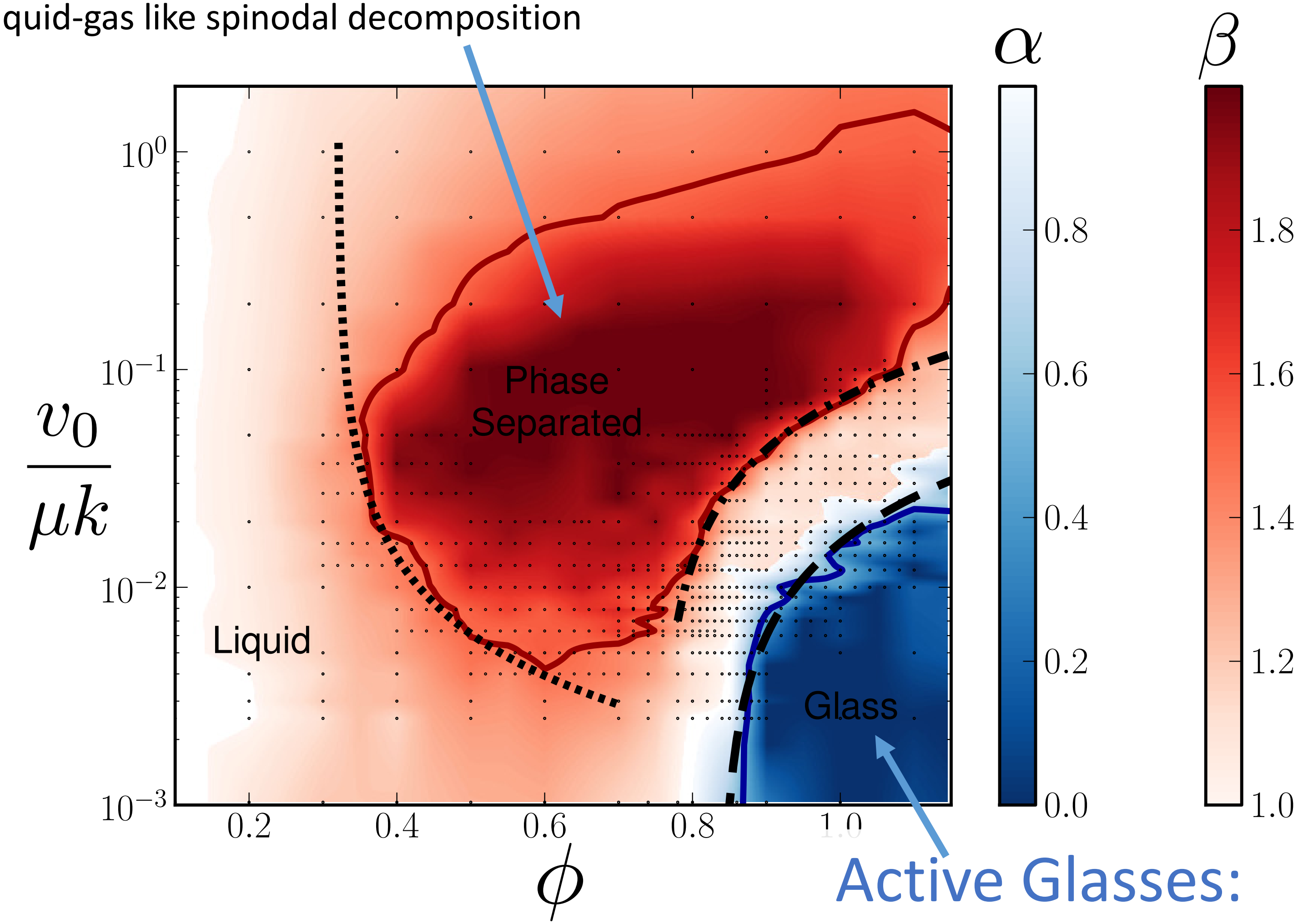
Glass



Where does the 'swirly' motion come from? Generic feature of epithelial cell sheets

Motility-induced phase separation:

Velocity slows down with density due to collisions
Leads to liquid-gas like spinodal decomposition

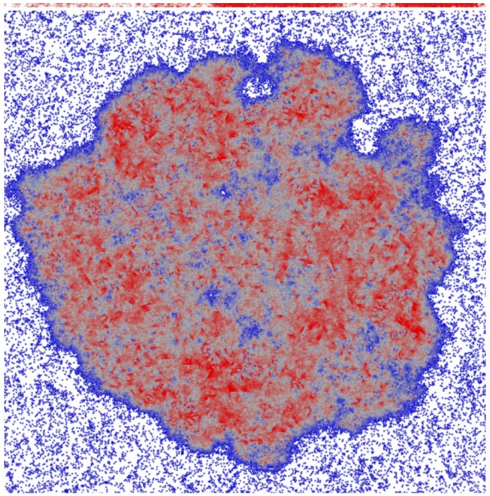


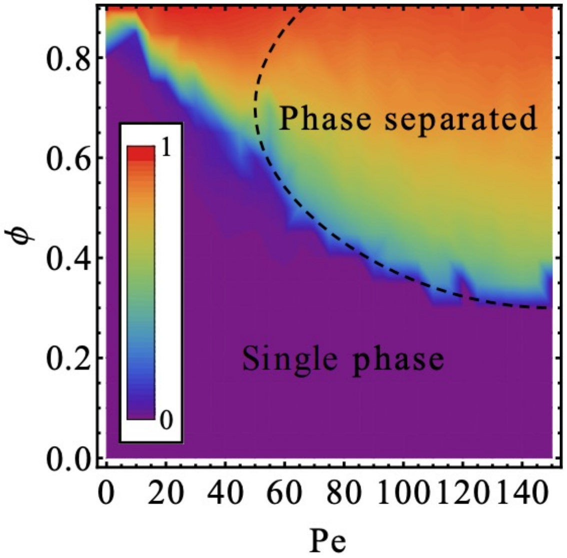
MIPS is still an extremely active field of research, see e.g. M. Cates and J. Tailleur. Motility-induced phase separation, Annu. Rev. Condens. Matter Phys. (2015).

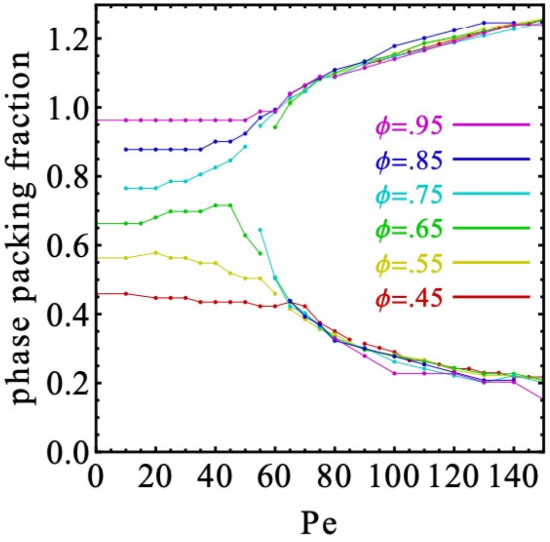
Active Glasses:

Driving too low to push particles past each other at high density. Shares properties with both thermal glasses and sheared athermal packings

Redner, Hagan, Baskaran (2013): Full phase separation, and has all the hallmarks of a liquid-gas transition including a triple point.







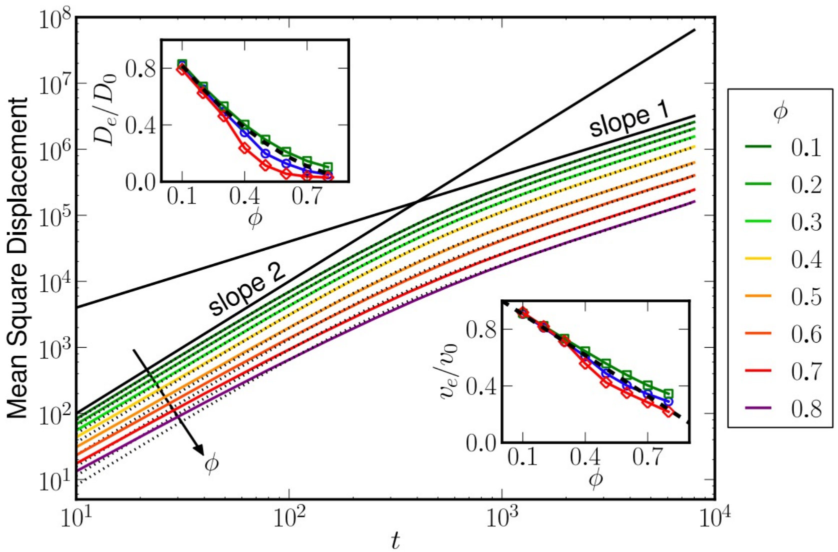
Tuning parameter: Peclet number

$$\mathrm{Pe} = v_0 \tau / a$$

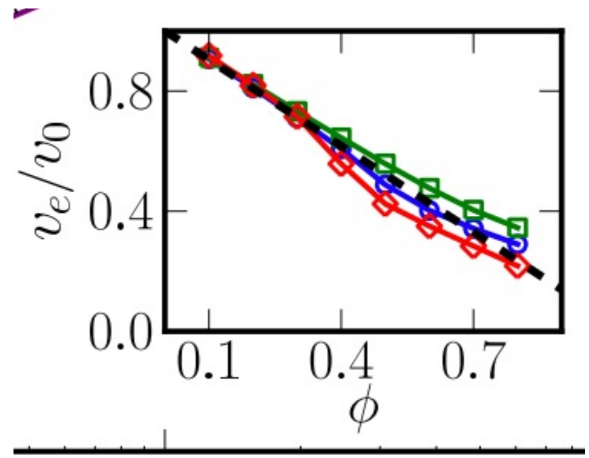
Persistent length scale /
Diffusive length scale

What is happening? (Y. Fily and M.C Marchetti, 2012)

Particles slow down due to collisions: Since they are persistent, they need to either wait to diffuse around each other or squeeze past each other



measure mean square displacement



mean velocity reduces with density!

Effective hydrodynamic equations (based on symmetries, conserved variable ρ and slow variable **p**)

particle current: advection and diffusion

$$\partial_t \rho = -\boldsymbol{\nabla} \cdot [\mathrm{v}(\rho)\mathbf{p} - D(\rho)\boldsymbol{\nabla}\rho] \ ,$$

$$\partial_t \mathbf{p} = -\nu_r \mathbf{p} - \frac{1}{2}\boldsymbol{\nabla}[\mathrm{v}(\rho)\rho] + K\nabla^2\mathbf{p} \ ,$$

What is happening?

This is a macroscopically isotropic system: no mean polarization. Integrate out polarization field and obtain effective equation for density (Cates, Tailleur, Marchetti, ….)

$$\partial_t \rho = \boldsymbol{\nabla} \cdot [\mathcal{D}(\rho) \boldsymbol{\nabla} \rho]$$

Effective diffusion constant which depends on effective velocity as a function of density

$$\mathcal{D}(\rho) = D(\rho) + \frac{\mathrm{v}^2(\rho)}{2\nu_r}\left(1 + \frac{d \ln \mathrm{v}}{d \ln \rho}\right)$$

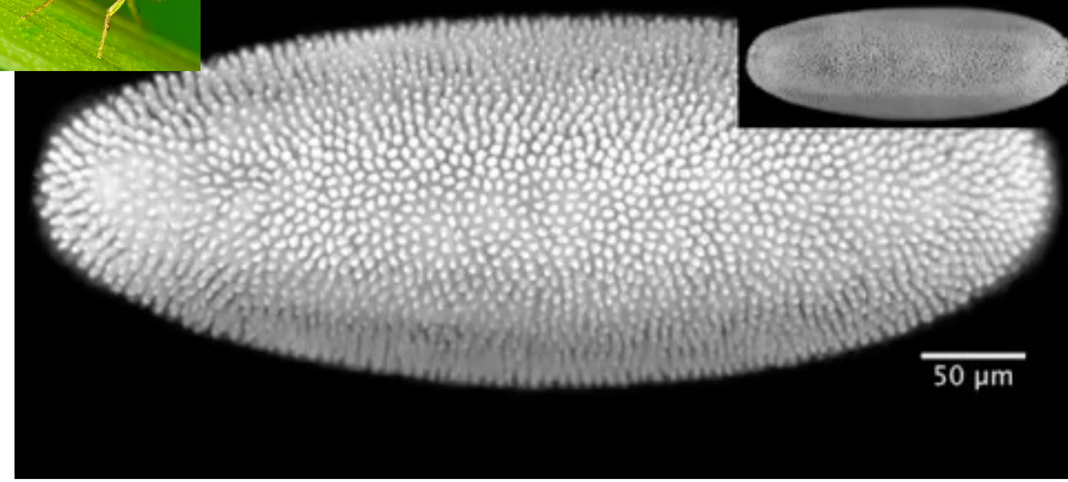
This term is generally negative, and if v(ρ) decreases sufficiently quickly:

Diffusion constant becomes negative!
Thermodynamically unstable, full phase separation.

Models of cell sheets

Collective cell mechanics in development

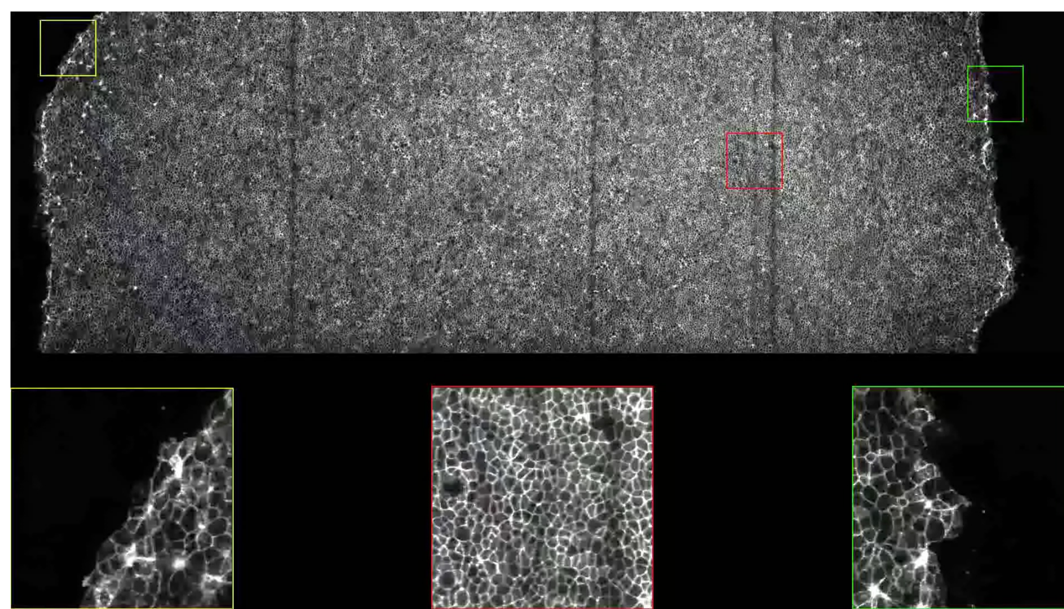
Fruit fly (drosophila) gastrulation



First step in the development of the embryo

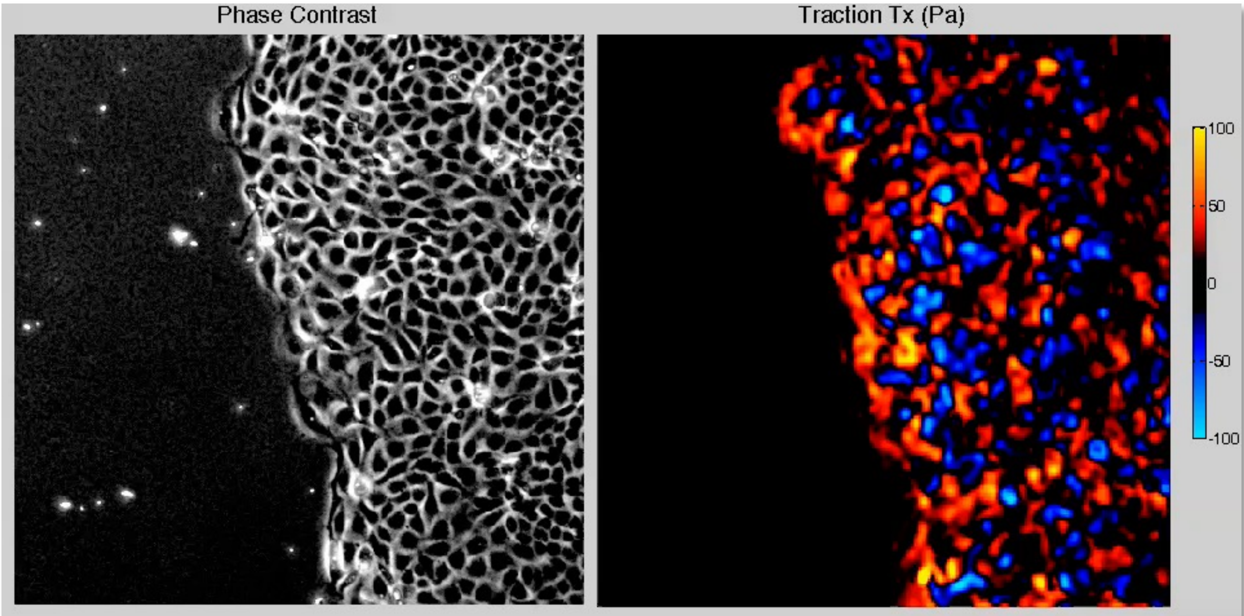
European Molecular Biology Laboratory (EMBL)

Primitive streak formation (gastrulation in the chick embryo)



E. Rozbicki et al, Nature Cell Biology 17, 397–408 (2015)

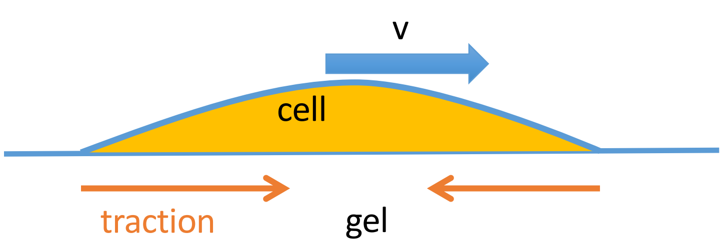
Migration patterns in confluent cell layers



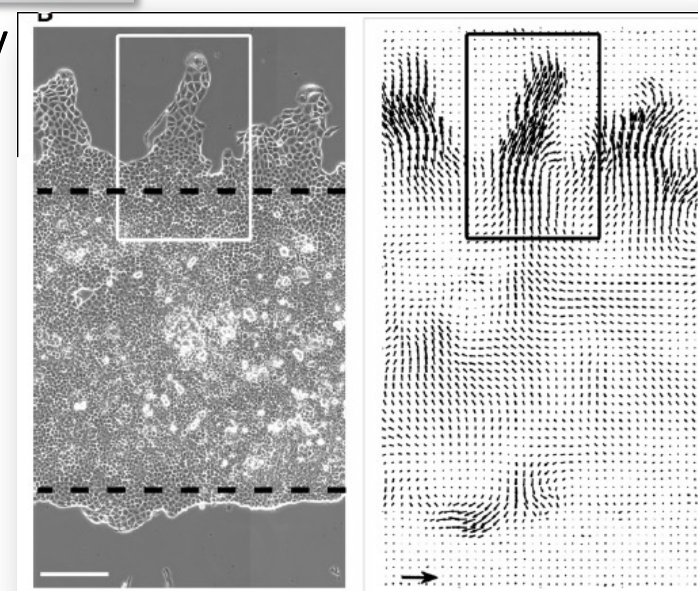
X. Trepat et al., Nature Physics, 5, 426 (2009)

Traction forces at the interface of the cell layer with the substrate

Experimental stresses via force traction microscopy

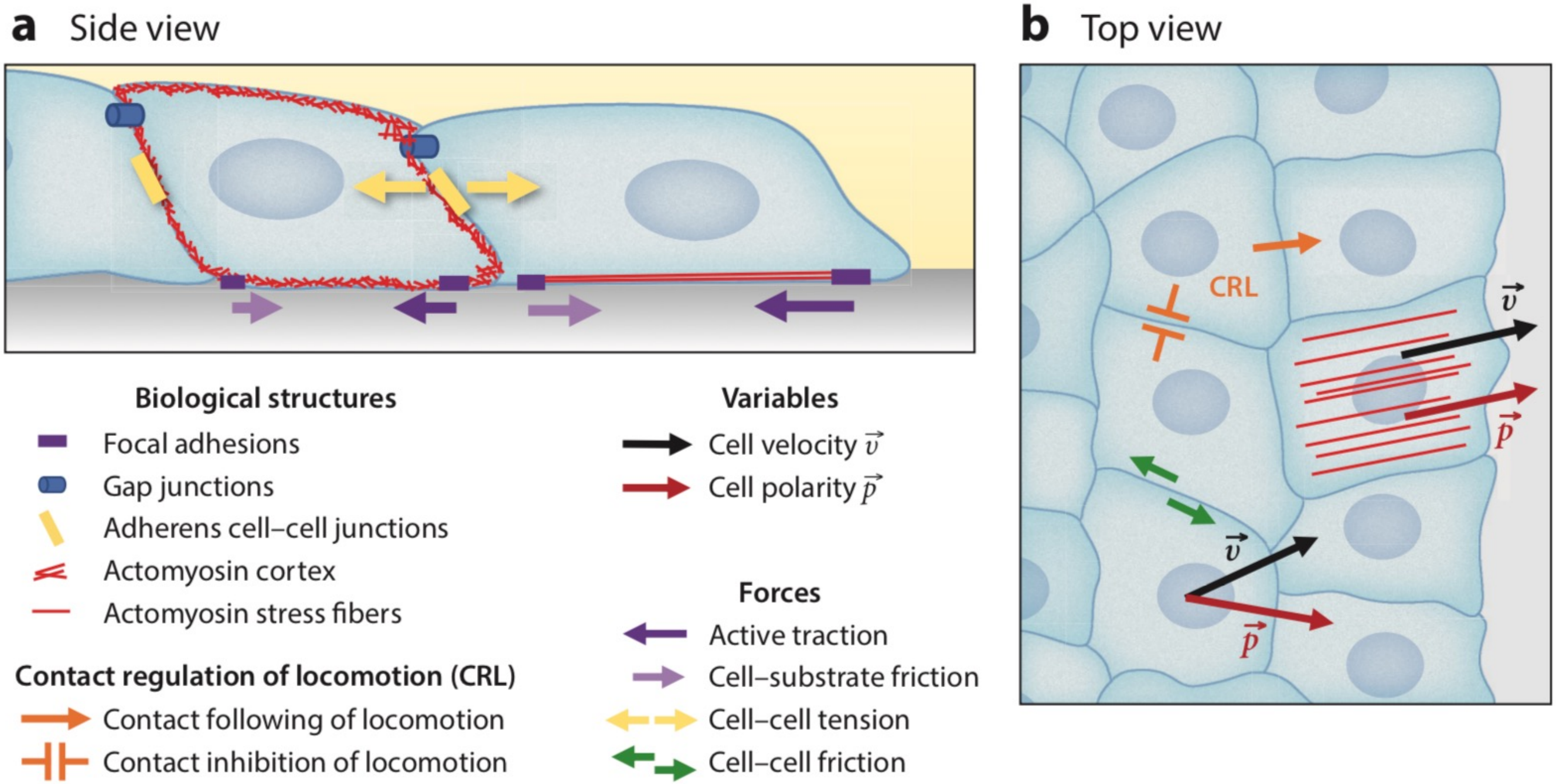


“Cell on a gel” setup

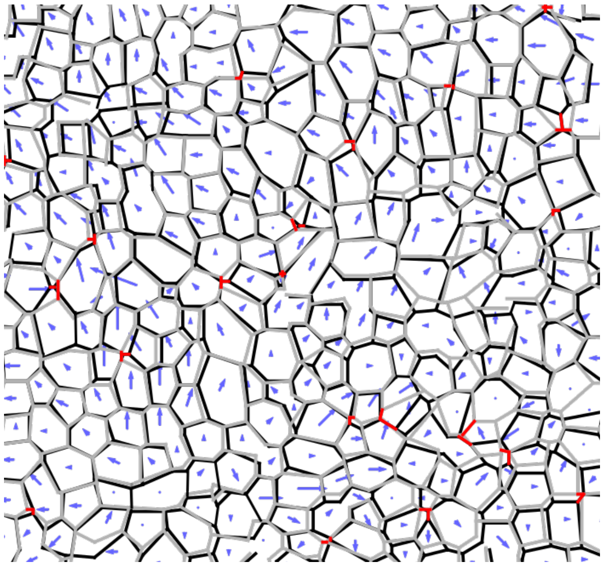


Fingering instability at the edges of the cell layer
L. Petitjean et al., Biophys. J., 98 1790–1800 (2010)

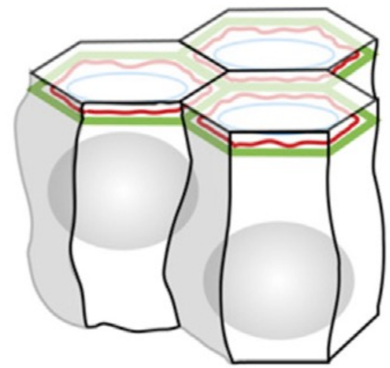
Active drivers in epithelial tissues



Active drivers in epithelial tissues

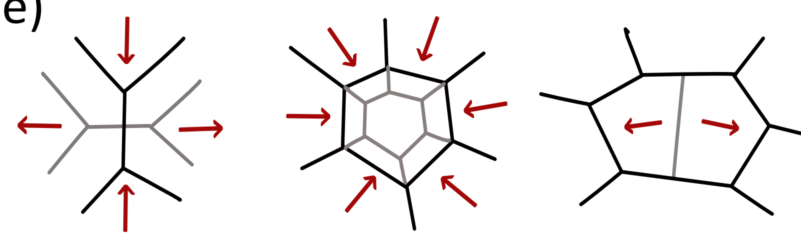


Migration and T1s in chick embryo



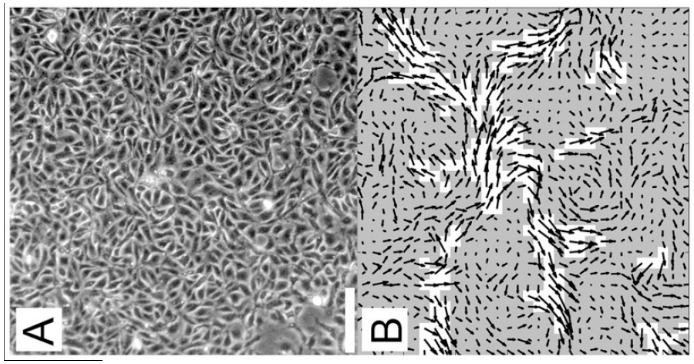
Schematic representation of the organization of neighboring cells in an epithelial sheet. (from R. Farhadifar, et al., Current Biology 2007)

- Cell migration on substrate (if there is one)
- Junction contractions
- Cell division and death
- Shape fluctuations
- Chemical signaling
- Interactions of different cell types
- Boundaries and topology



Microscopic nonaffine processes – cell intercalation (T1 event), ingression or apoptosis and division

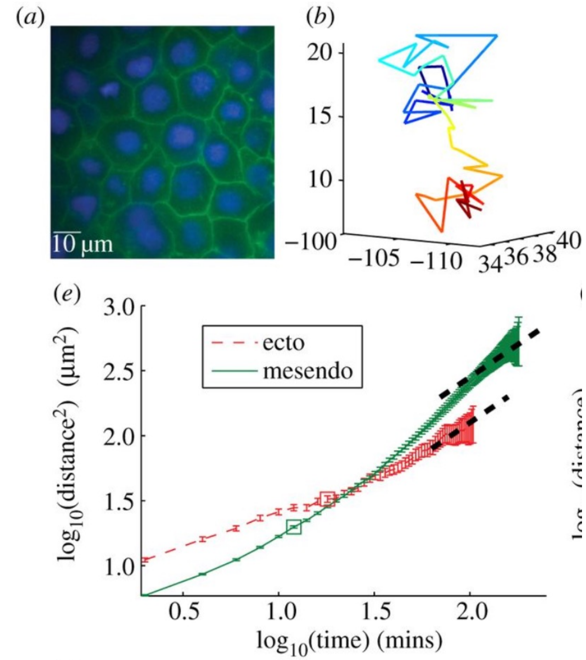
Swirling / sheared / glassy dynamics



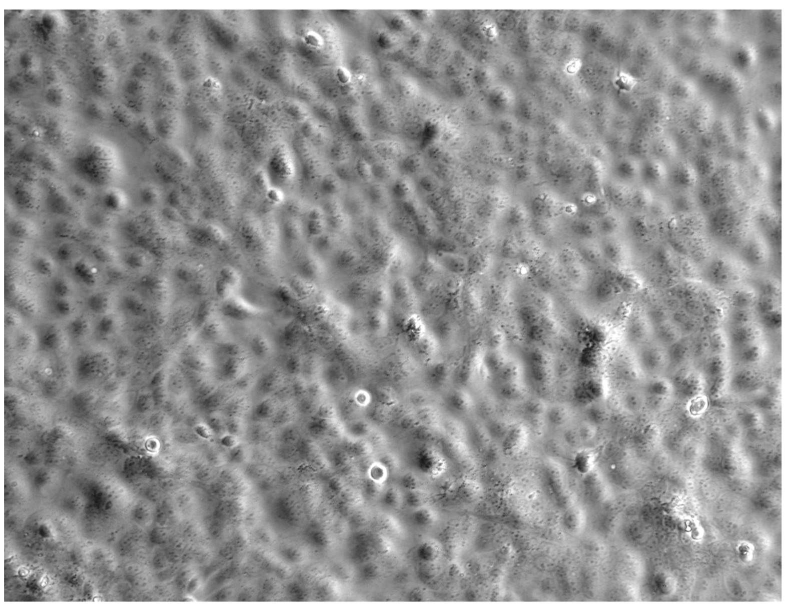
T. Angelini et al., PNAS 108 4714 (2011)

'Swirly' patterns resembling both sheared materials and dynamical heterogeneities

Three-dimensional cell balls are liquid, but show evidence of dynamical slowing-down



E. Schötz et al, J. Roy. Soc. Int (2013)

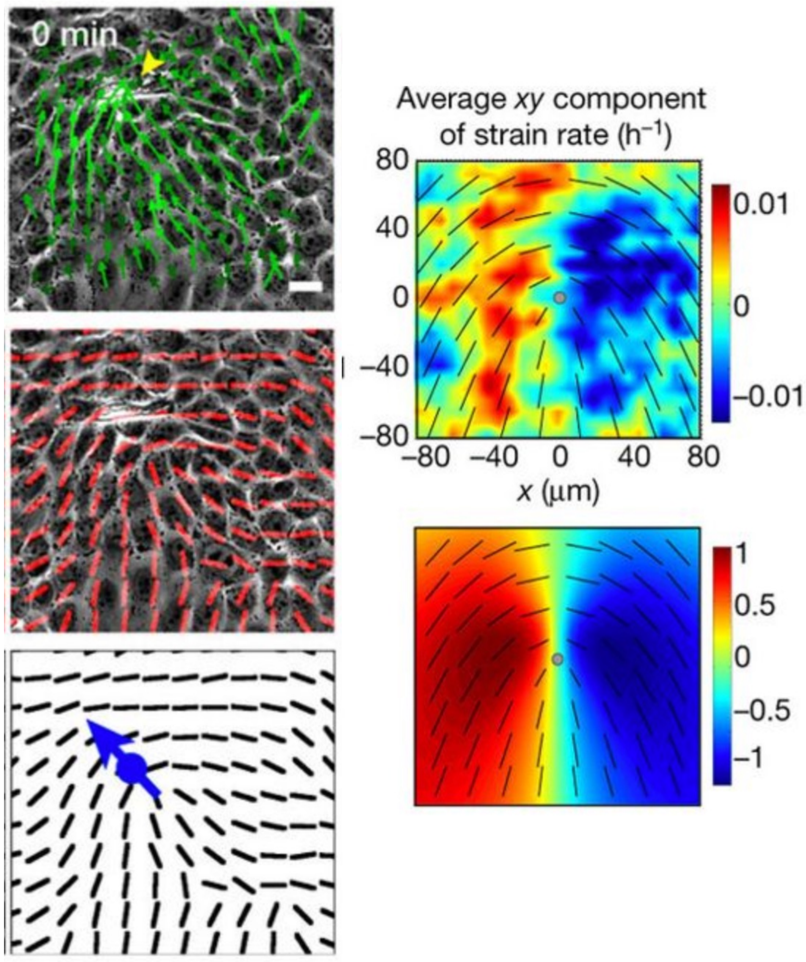


Kaja Kostanjevec

Generic feature of all types of epithelial cells. Here: Human corneal epithelial cell sheet

Additionally: active nematic properties

T. B. Saw et al, Nature 544, 212 (2017)



Continuum hydrodynamic theory is incomplete:

- Cells are disordered, soft material
- Defects scale similar to cell scale
- Fluctuations are large, active nematic motion is on average only

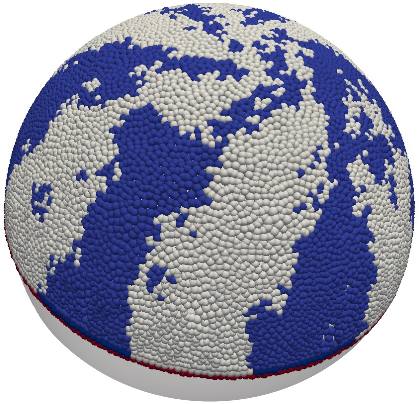
First part of this talk:

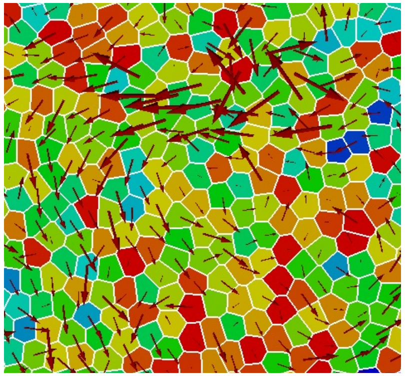
- Construct a truly minimal model of dense active cell sheets
- correlations in the absence of active alignment
- Fit to experimental cell sheets

Building models: What tools do we need?

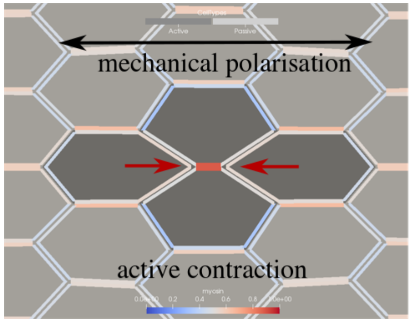
1. Continuum models (active gel and active nematic) & extensions, like phase field models

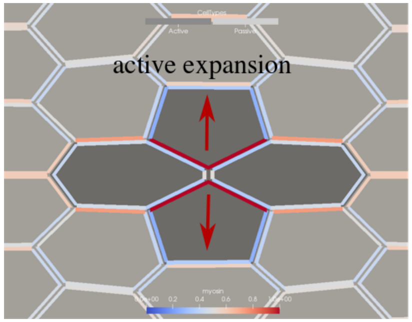
2. Cellular Potts model & other lattice based models





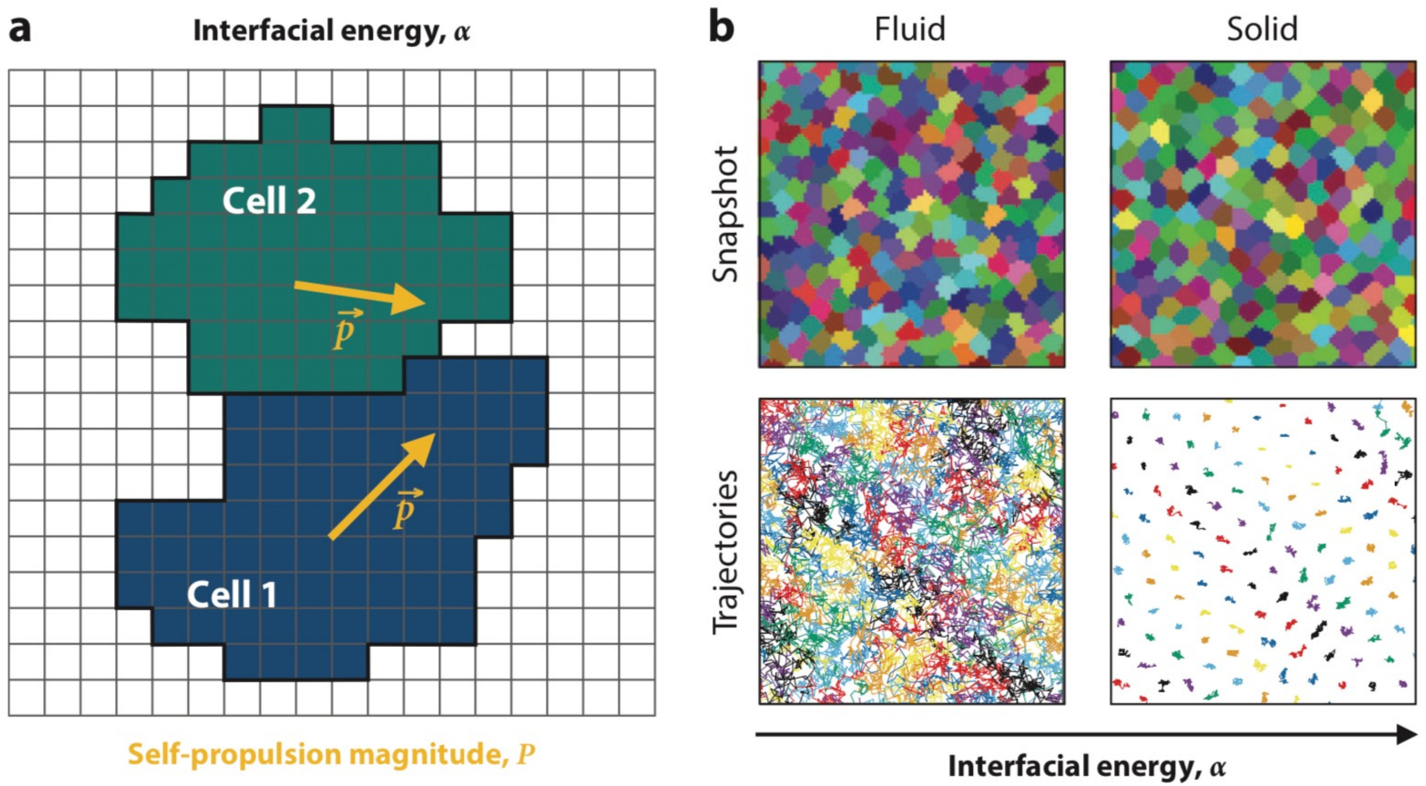
3. Particle based models and Voronoi Vertex models:
   - Large scale flow properties
   - Link to rheology, granular and glass physics literature





4. Active junction vertex models:
   - Cell junction properties
   - Understand polarization in tissues
   - Link to Biology

Cellular Potts models



Minimise effective Hamiltonian, Monte Carlo approach, not true dynamics (in its simplest forms)

$$\mathcal{H} = \sum_{\langle i,j \rangle} J(\sigma_i, \sigma_j) + \lambda \sum_{\sigma=1}^{m-1} (A_\sigma - A_0)^2 - P \sum_{\sigma=1}^{m-1} \vec{R}_\sigma \cdot \vec{p}_\sigma \, .$$

Interaction (spins) Area constraint Migration / polarity

Phase field models

Different scalar field ϕ_i for every cell. Simulate overdamped dynamics of many interacting cells:

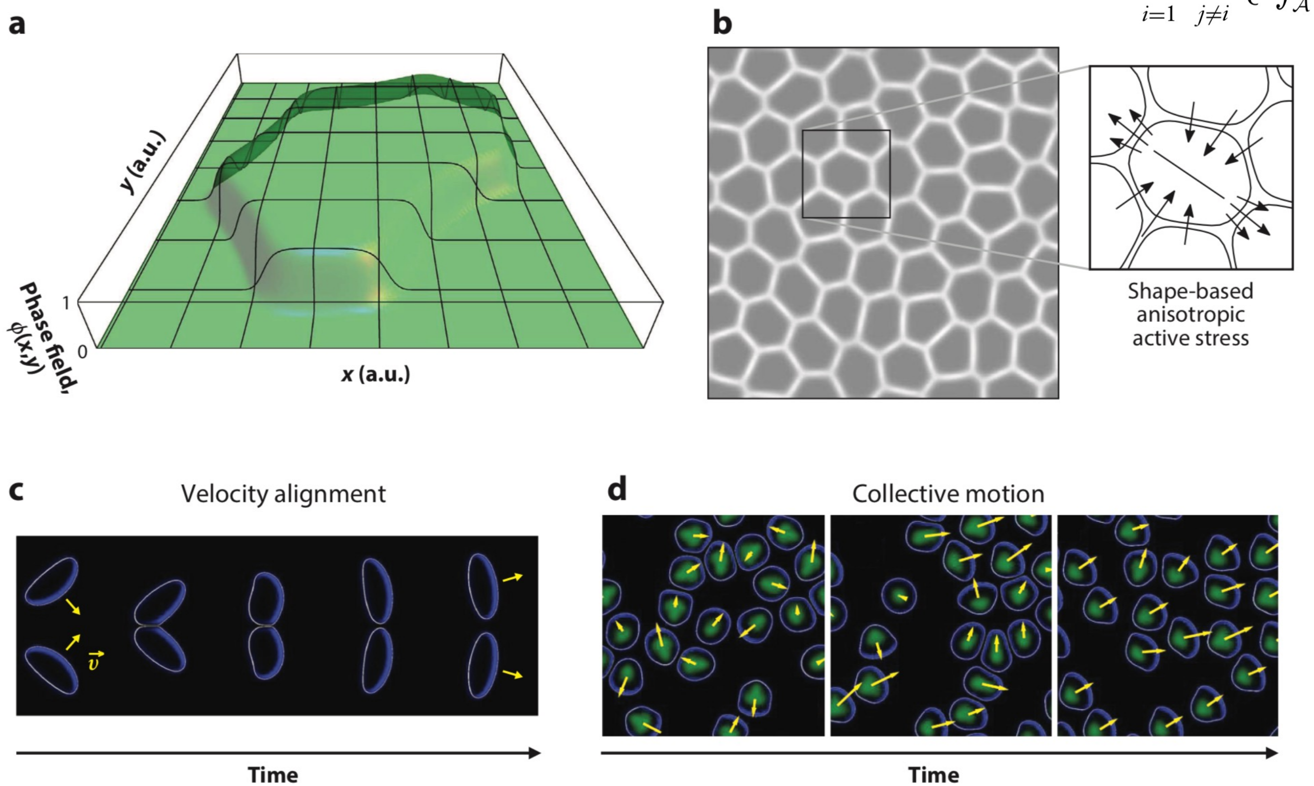
$$\partial_t \phi_i + \vec{v}_i \cdot \vec{\nabla} \phi_i = -\frac{\delta \mathcal{F}}{\delta \phi_i}$$

Total free energy is sum of Cahn-Hilliard (phase separation), area constraint and cell-cell interaction terms:

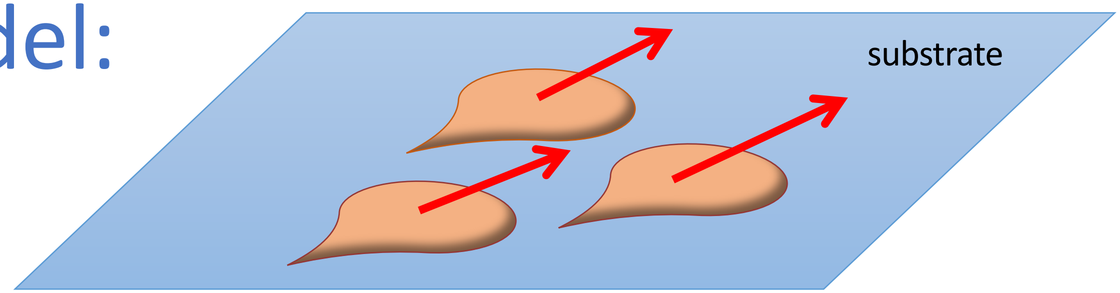
$$\mathcal{F}_{\mathrm{CH}} = \sum_{i=1}^{N} \frac{\gamma}{\epsilon} \int_{\mathcal{A}} \left[4\phi_i^2 (1-\phi_i)^2 + \epsilon^2 |\vec{\nabla}\phi_i|^2 \right] \mathrm{d}^2\vec{r},$$

$$\mathcal{F}_{\mathrm{area}} = \sum_{i=1}^{N} \mu \left(1 - \frac{1}{\pi R^2} \int_{\mathcal{A}} \phi_i^2 \, \mathrm{d}^2\vec{r} \right)^2,$$

$$\mathcal{F}_{\mathrm{cell-cell}} = \sum_{i=1}^{N} \sum_{j \neq i} \frac{\kappa}{\epsilon} \int_{\mathcal{A}} \left[\phi_i^2 \phi_j^2 - \tau \epsilon^4 |\vec{\nabla}\phi_i|^2 |\vec{\nabla}\phi_j|^2 \right] \mathrm{d}^2\vec{r}.$$



Particle based model: Active brownian particles (ABPs)



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Fully overdamped

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self-propulsion

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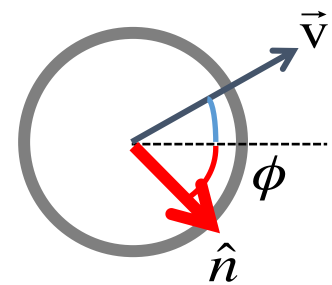

τ : orientational persistence time

(inverse rotational diffusion constant)

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Velocity slows down with density due to collisions
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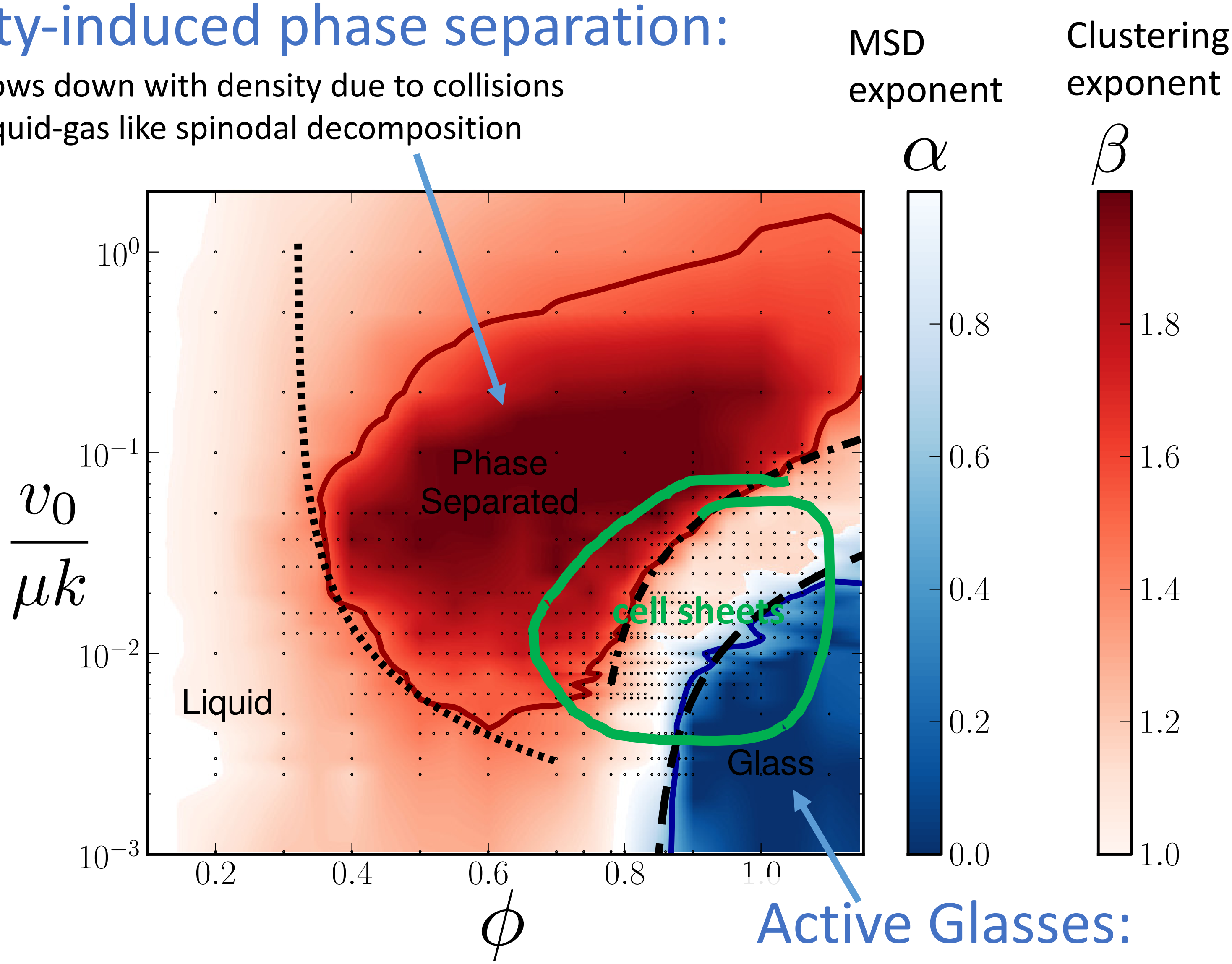

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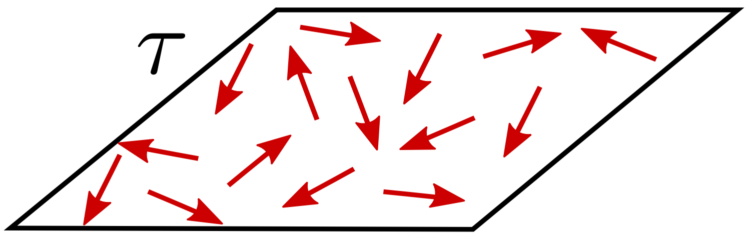
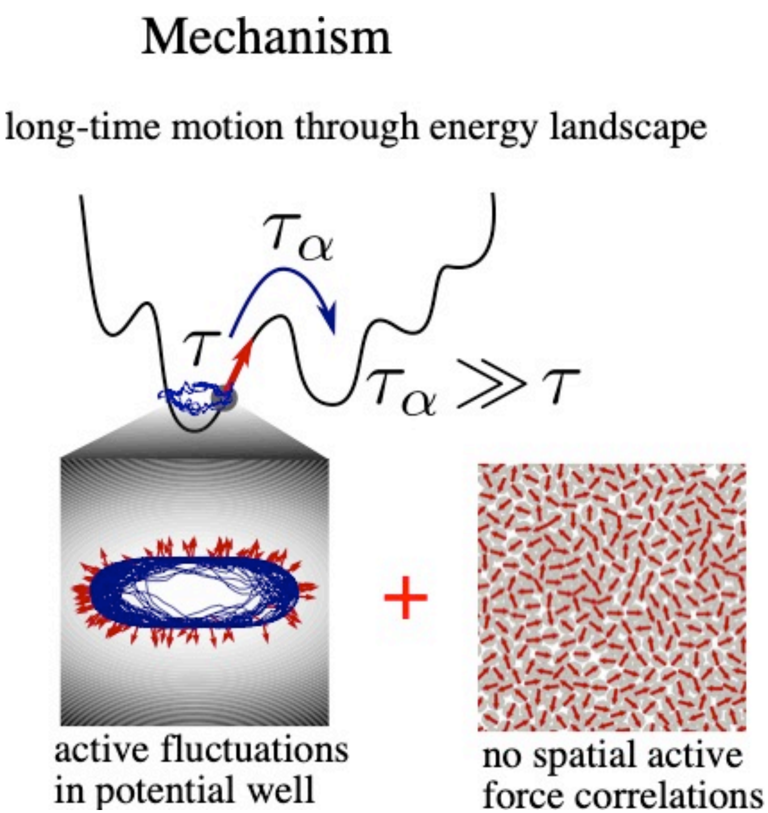
Active Glasses:

Driving too low to push particles past each other at high density. Shares properties with both thermal glasses and sheared athermal packings

Physical picture for swirling motion

SH, K Kostanjevec, JM Collinson, R Sknepnek, E Bertin,
Nature Communications 11 (1), 1-9 (2020)





Short and intermediate times: elastic sheet with random forces of magnitude v_0 acting on it. Change direction with persistence time τ.

Long times: system rearranges at time scale τ_α. We traverse a series of distinct, but statistically similar minima where the elastic sheet approximation is valid.
Work in the regime where $\tau < \tau_\alpha$

Active Brownian particles in linear response:

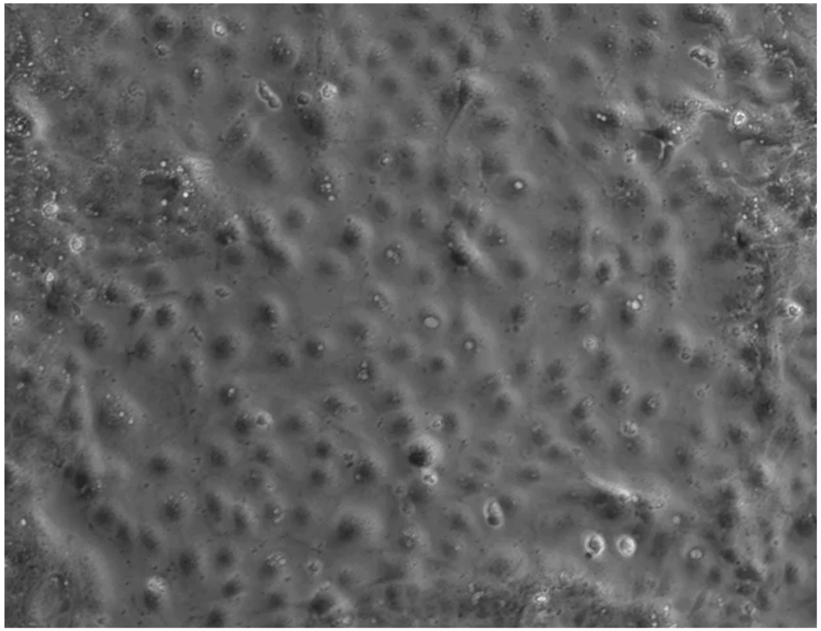
$$\delta \dot{\mathbf{r}}_i = v_0 \hat{\mathbf{n}}_i - \mu \sum_j \mathbf{K}_{ij} \cdot \delta \mathbf{r}_j$$

Active forces are randomly oriented, time-correlated forces applied at every particle level.

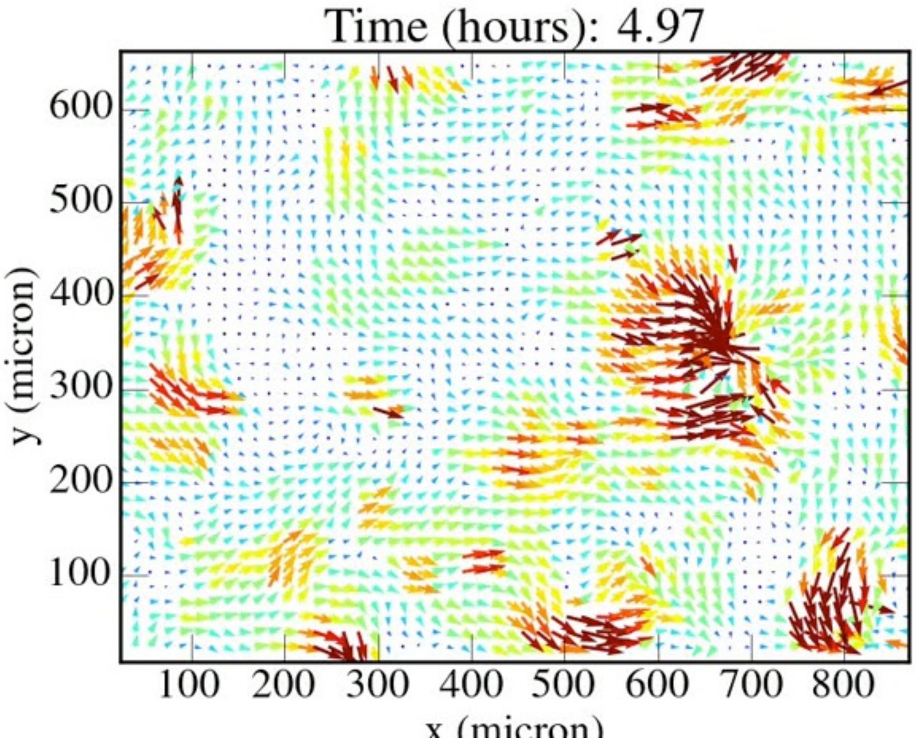
Solve using normal modes

Following same approach in sheared granular materials, C. Maloney, PRL 2006, and later with A. Lemaitre

Experimental cell dynamics



Kaja Kostanjevec



In vitro HCE (human corneal epithelial) cells on a substrate.

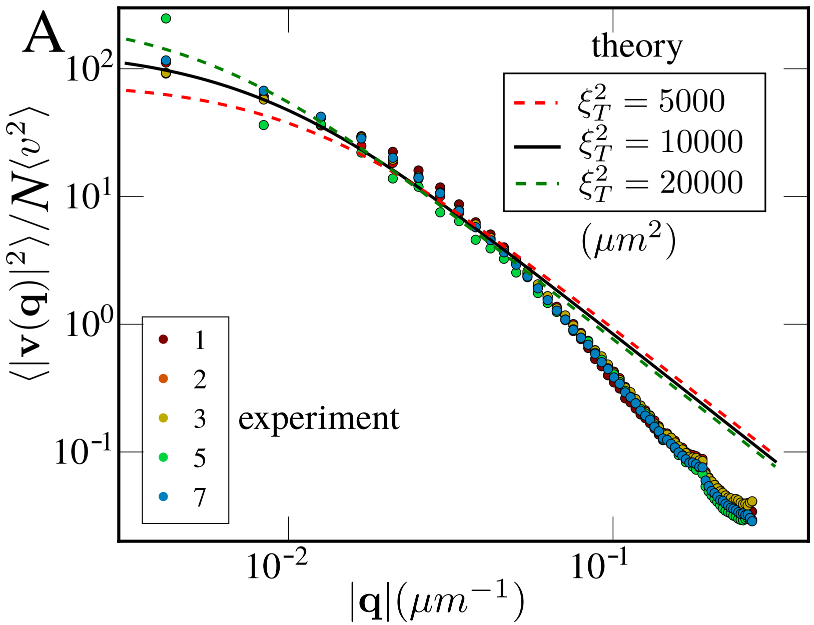
Measure

- Cell velocities and correlations
- Division and death rate

Migration patterns resemble other epithelial cell lines, e.g. in vitro MDCK

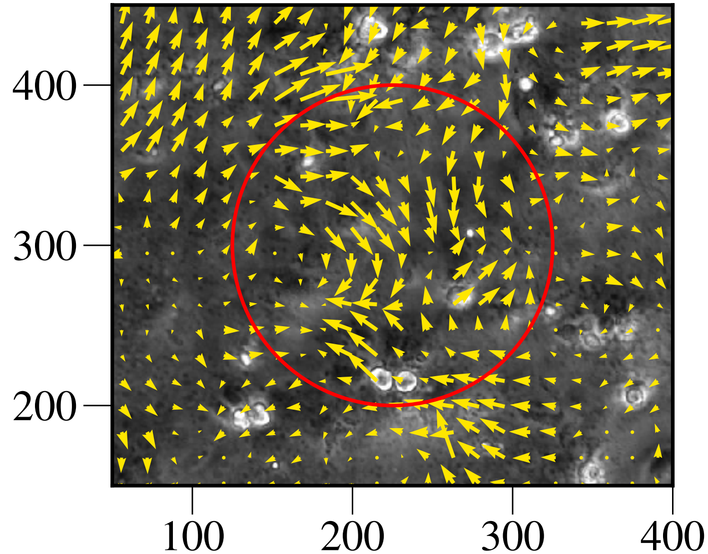
Use particle image velocimetry (PIV) to extract velocity fields.

Experimental cell dynamics



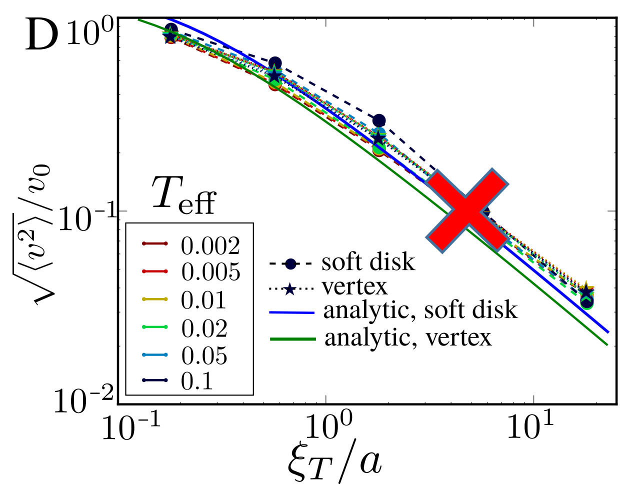
Use a single length scale to fit the velocity correlations.

ξ_T = 5-6 cell diameters, equivalent to ξ_T = 100µm, quantitatively matches S. Garcia et al, PNAS (2015) on MDCK layers



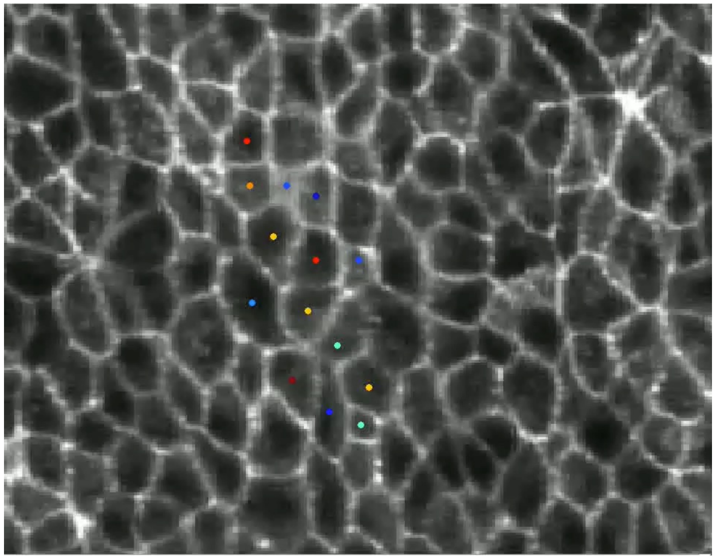
Intersection with *q=0* axis: ratio of v_0^2 to mean square velocity

$$\langle v \rangle = 0.1 v_0$$

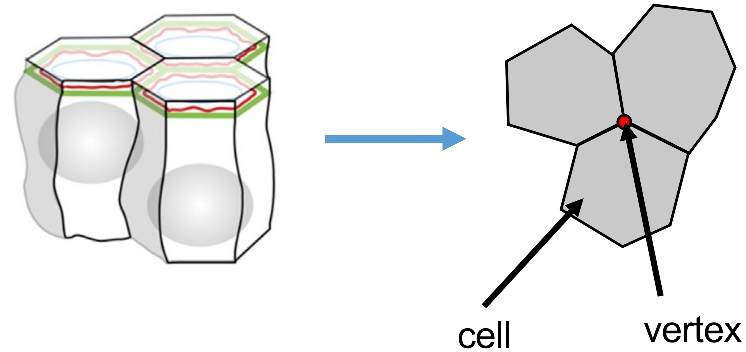


Highly active / out of equilibrium regime!

Appropriate model for realistic tissues?

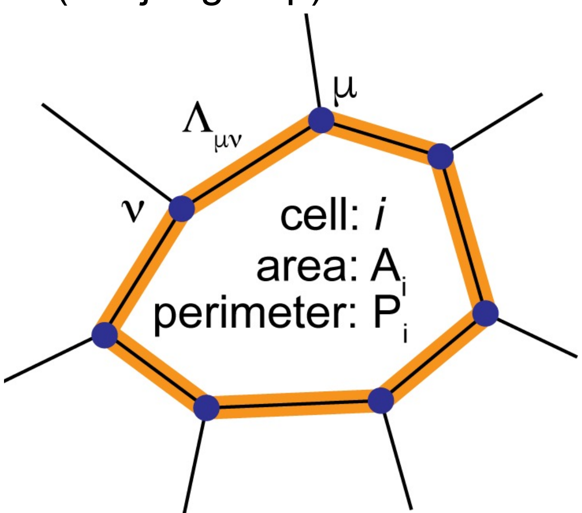


movie curtesy of Antti Karjalainen (Weijer group)



The Vertex model

Ngai and Honda (2000), R. Farhadifar et al. (2007), A. Fletcher et al (2014)



perimeter change penalty (contractility)

$$V_{\text{Vertex}} = \sum_{i=1}^{N} \underbrace{\frac{\kappa}{2}(A_i - A_0)^2}_{\text{area change penalty (compressibility)}} + \overbrace{\frac{\Gamma}{2}(P_i - P_0)^2}^{\text{perimeter change penalty (contractility)}}$$

area change penalty (compressibility)

Tissue conformation determined by energy minimisation.

Active Vertex model (aka self-propelled Voronoi model)

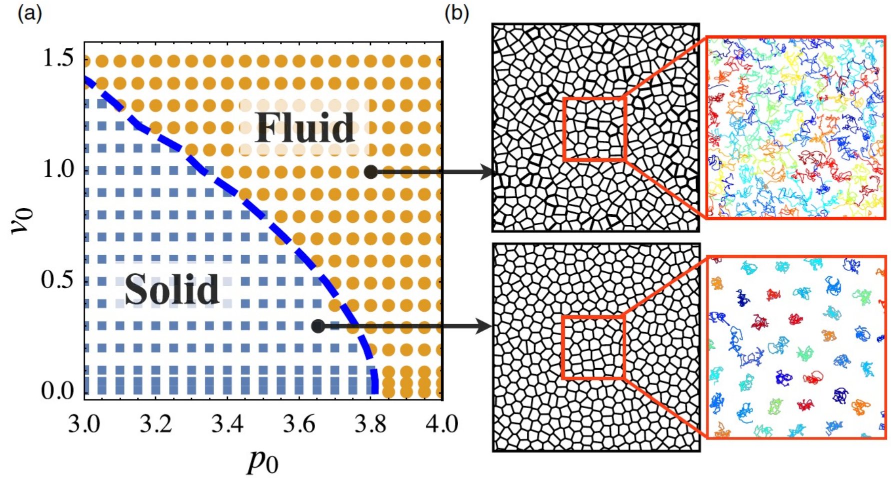
The Vertex model is quasistatic (a descendant of foam models). Not appropriate for most tissues!

Add active dynamics to the Vertex model: Motility of the cell centres

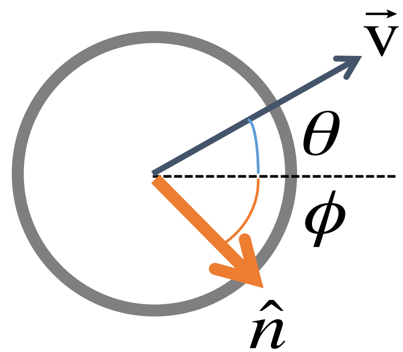
$$\zeta \dot{\mathbf{r}}_i = \mathbf{F}_{\mathrm{act}} - \nabla_{\mathbf{r}_i} V_{\mathrm{Vertex}}$$

Non-aligning self propulsion

$$\mathbf{F}_{\mathrm{act}} = v_0 \mathbf{n}_i$$



D. Bi et al., PRX 6, 021011 (2016)



Diffusive angular dynamics

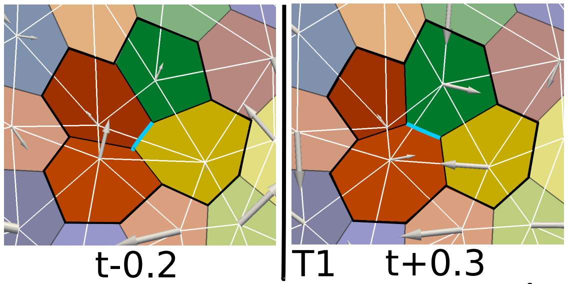
$$\dot{\phi} = \eta, \quad \langle \eta(t)\eta(t') \rangle = \frac{1}{\tau_r}\delta(t - t')$$

Active force is planar cell polarity like here. Role of presence/absence of substrate and driving from contracting edges.

- Collective motion
- Incorporate other drivers one by one
- Model large-scale epithelial layers

This is a hard problem!

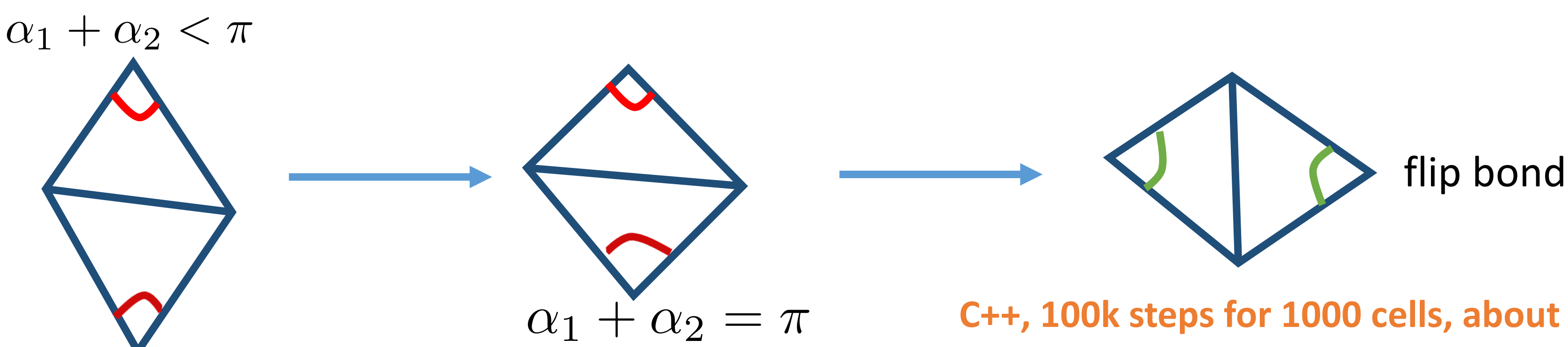
- For a hybrid model (SPV) to work, we need a one-to-one and **continuous mapping** between vertices and cell centres.



Otherwise, not a continuous energy function – no saddles, T1 events not resolved, does not equilibrate.

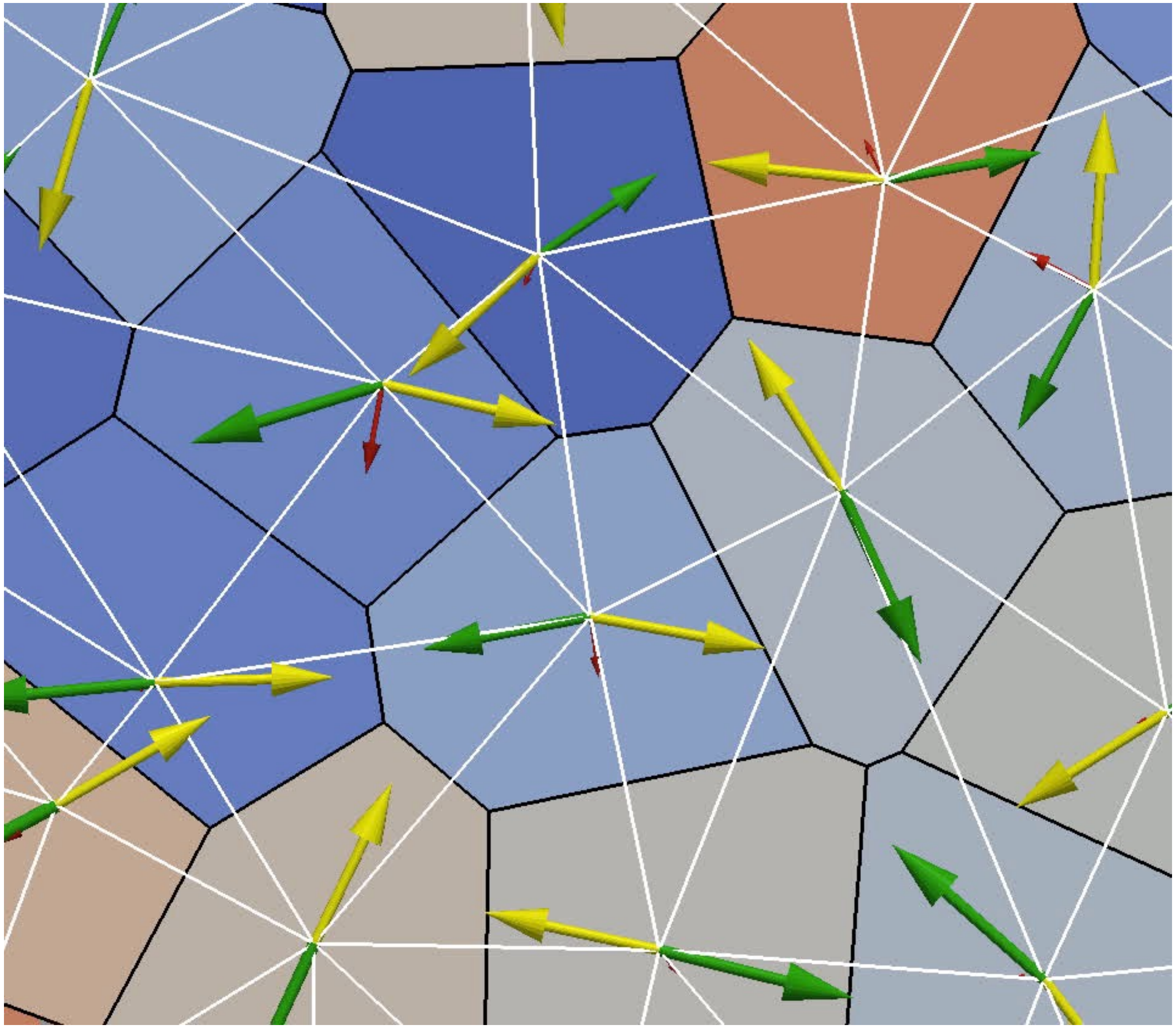
- The Delaunay triangulation / Voronoi tesselation is such a map (the only one?). However, it is **computationally expensive** to compute. Need to use tools from computational geometry to speed up.

- Final ingredients for an efficient algorithm:
  - Analytical computation of forces on cell centres through mapping between Delaunay circumcenters and Delaunay vertices
  - Edge flip to remain Delaunay triangulated at every step



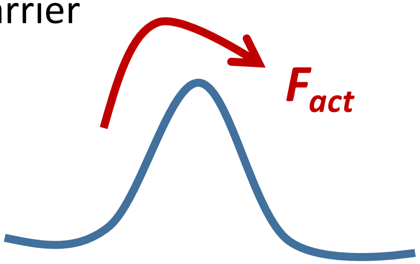
C++, 100k steps for 1000 cells, about 10 minutes

Dynamics of T1 transitions

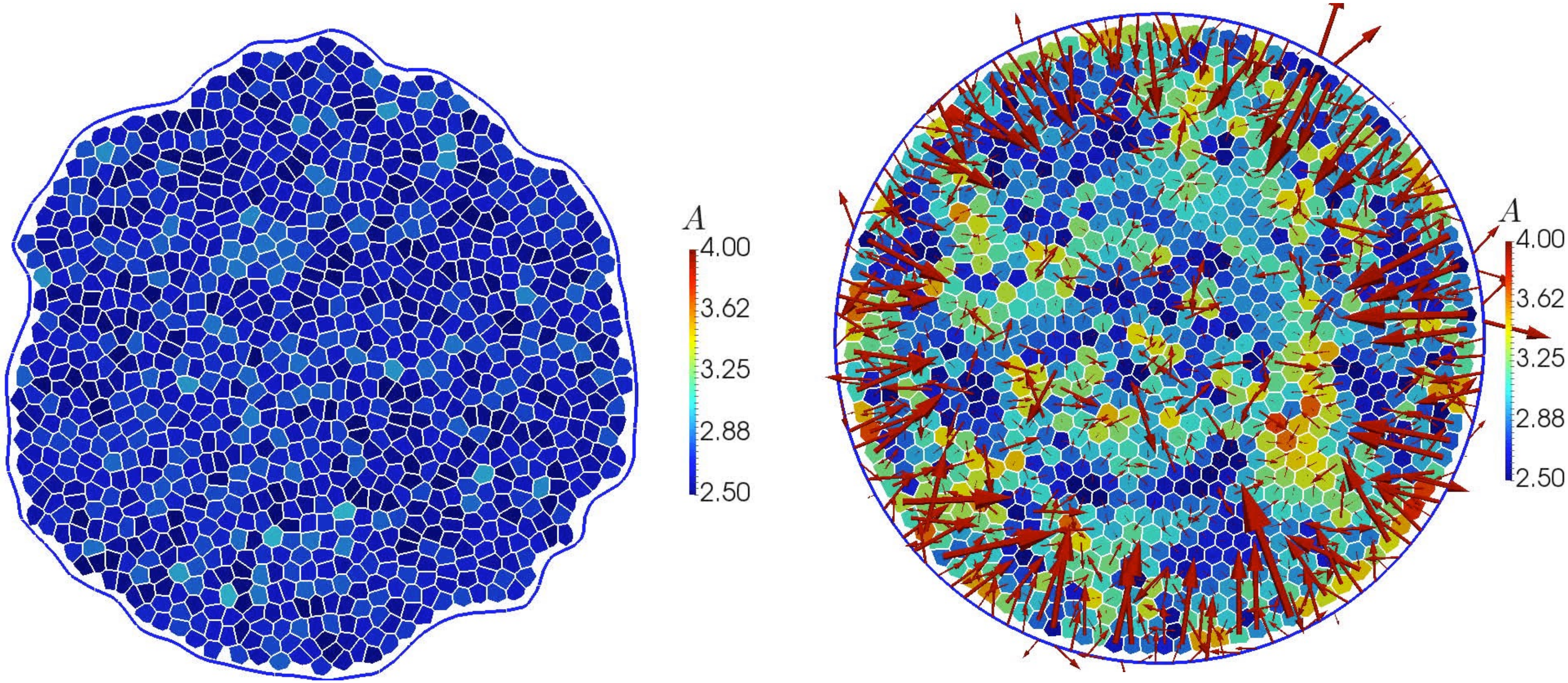


red: Cell centre velocity
green: active driving force
yellow: Conservative force from vertex model

Slow contraction followed by fast expansion. Consistent with being dragged over an energy barrier



Active glass transition

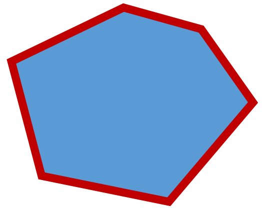


Liquid state: T1s and global flow

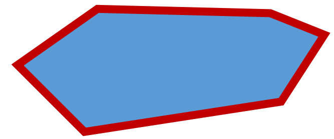
Glassy state: No T1s, no global flow of the tissue

Shape parameter and phase diagram

$$p_0 = \frac{-\Lambda}{\Gamma\sqrt{A_0}}$$



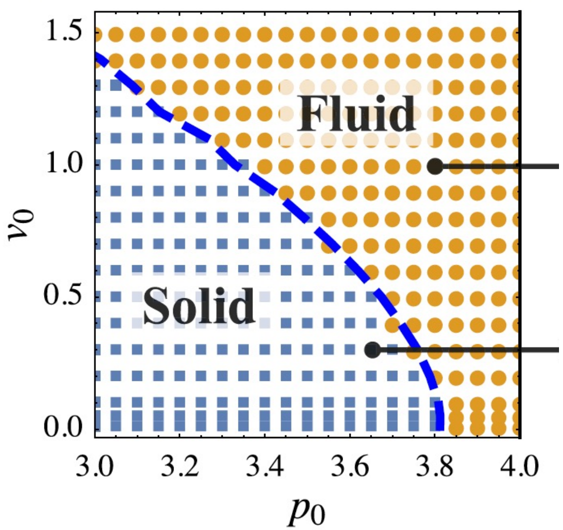
Small p_0: rounded shapes, hexagons

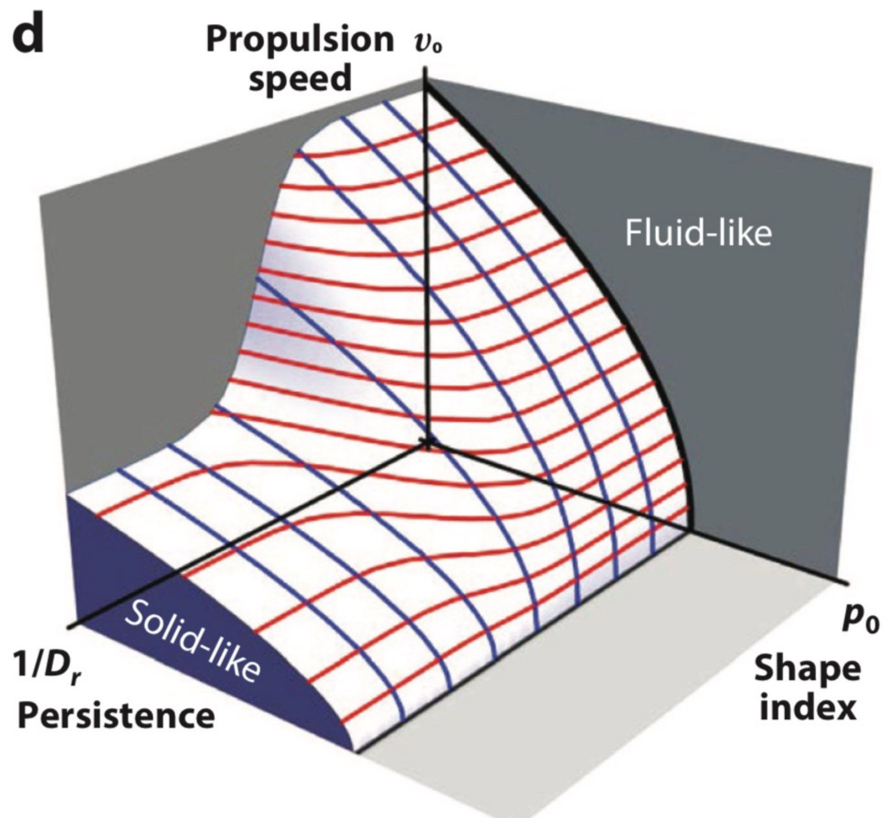


Large p_0: elongated cells, disorders, broader neighbour number distribution

(a)

(b)



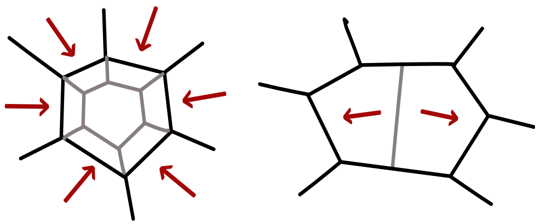


Fluid/solid transition as a function of p0 and v0:
D. Bi et al., PRX 6, 021011 (2016):
Transition point at p_0=3.81

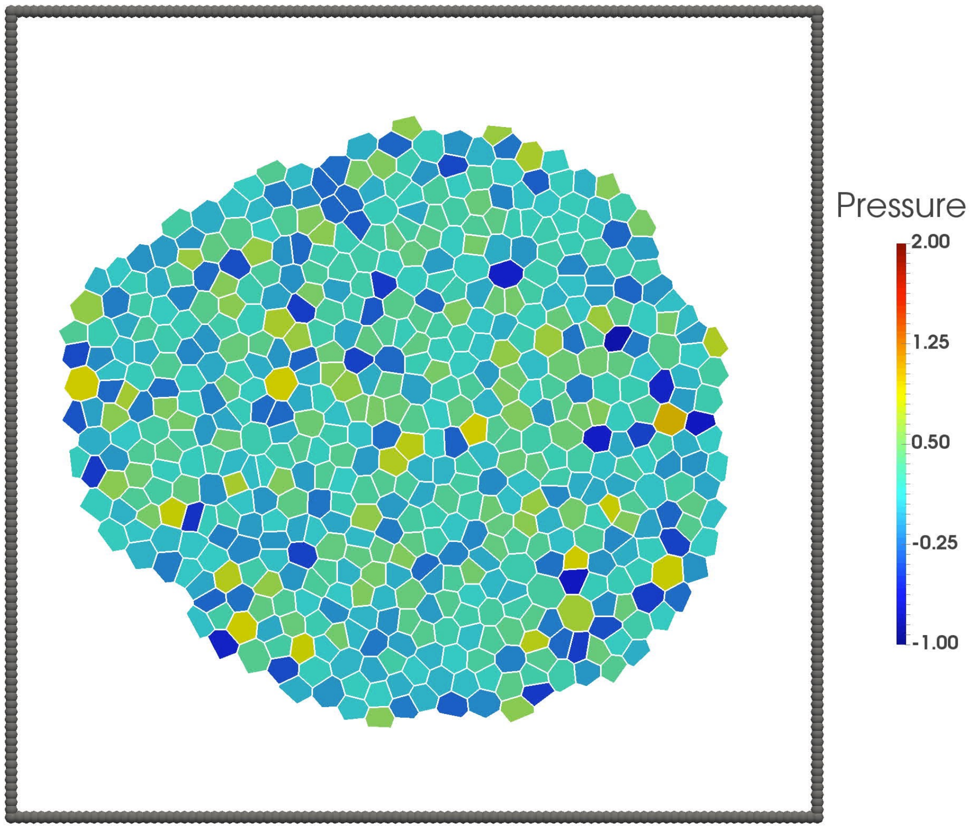
Cell Division and death

$$A_0 = A_{\min} e^{r_g t}$$

Divide when cell size doubles



Cells die after a characteristic age

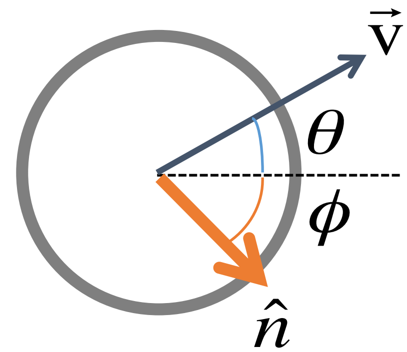


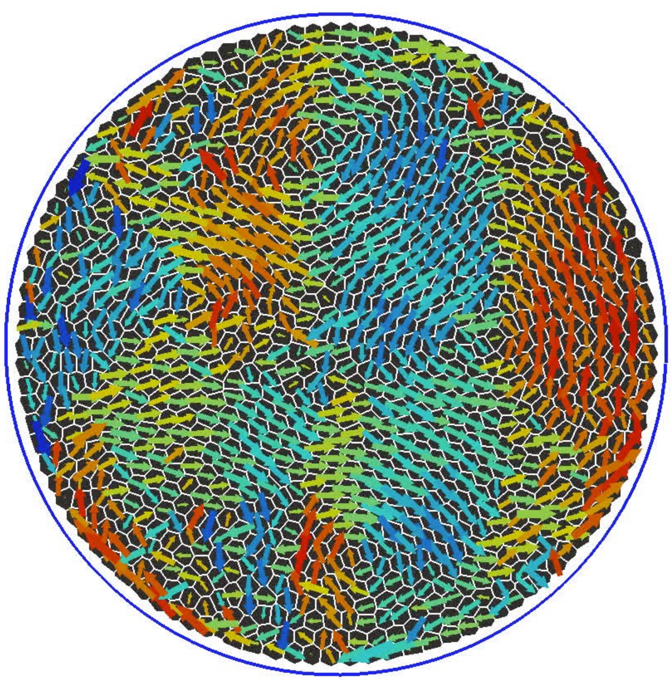
Compute stresses between cells using Hardy stress decomposition:
Not pair forces, careful procedure necessary.

Alignment of migration direction with total force on cell

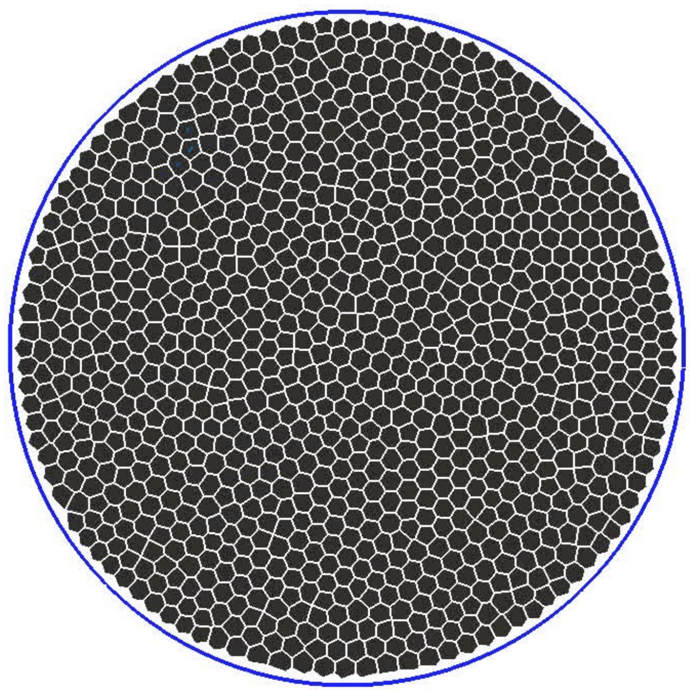
$$\mathbf{F}_{\mathrm{act}} = v_0 \mathbf{n}_i$$

$$\dot{\phi} = \frac{1}{\tau}(\theta - \phi) + \eta$$



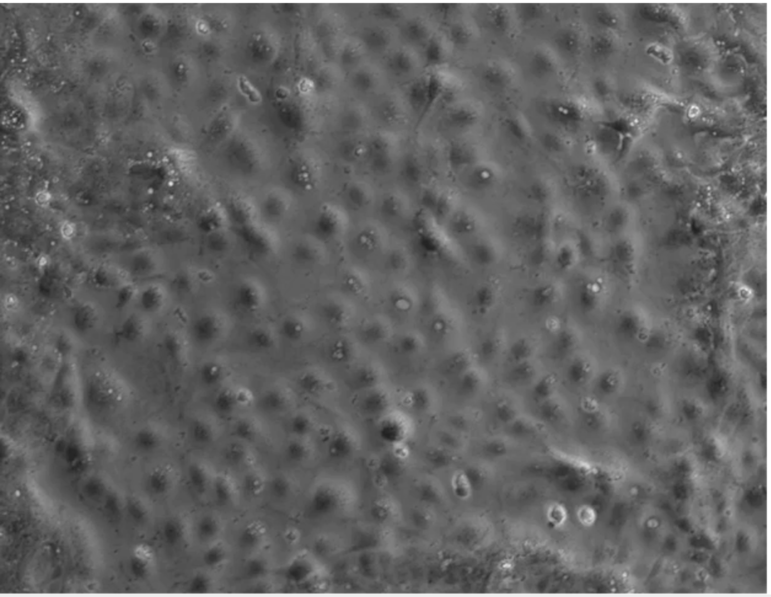


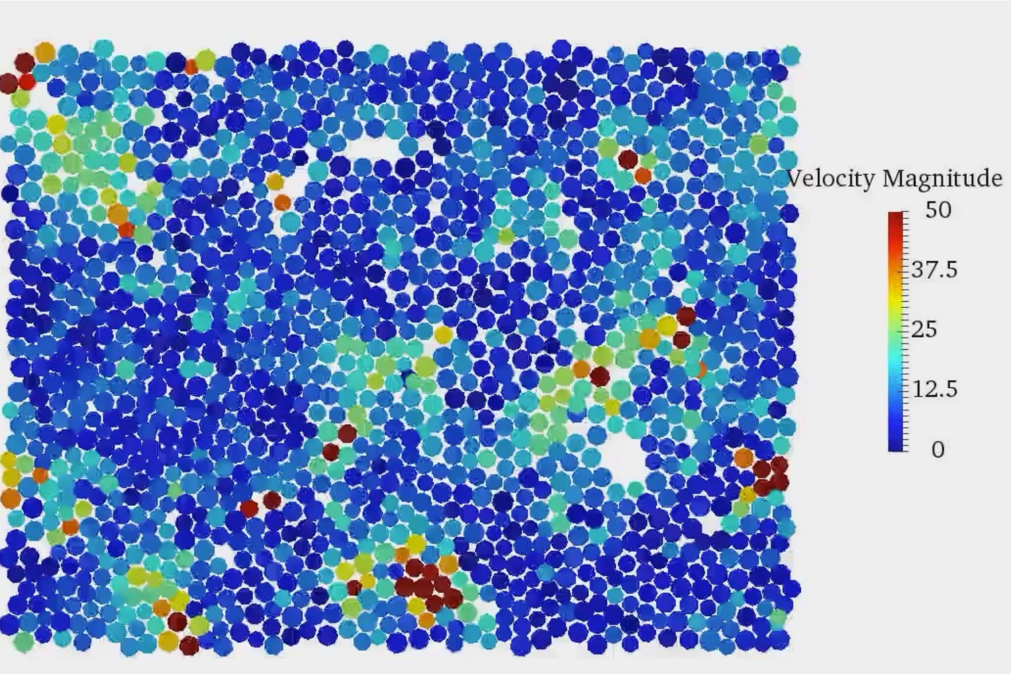
Confinement: oscillations, wave propagation



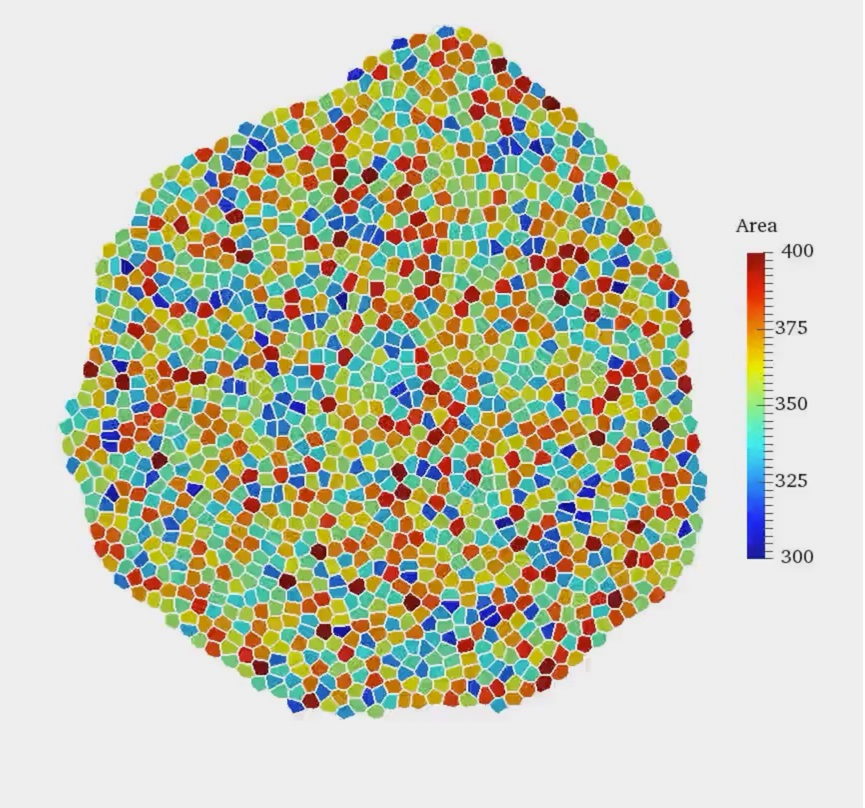
Open boundaries: flock migration

Fully parametrised simulations of corneal epithelium





Active vertex model



Thank you!

The physics of Living Matter