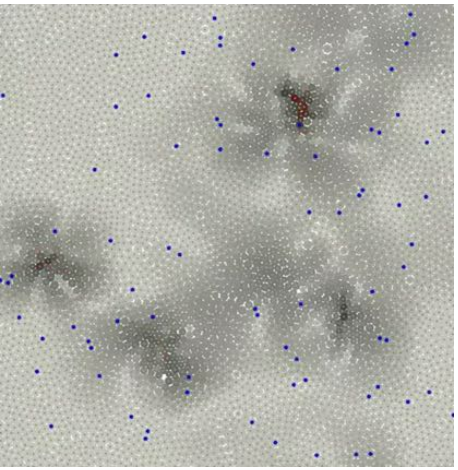
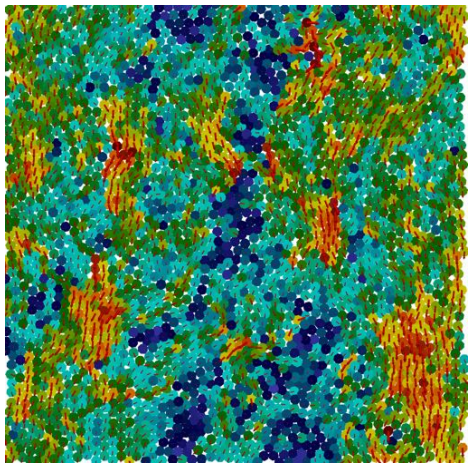
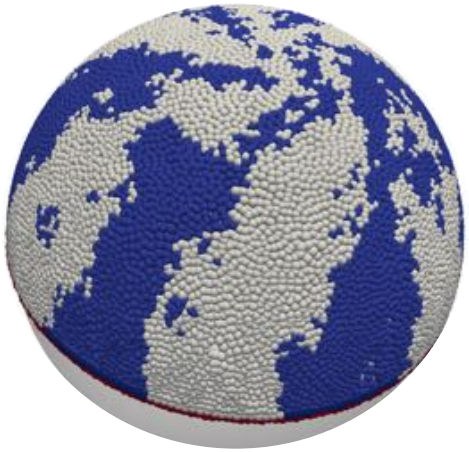
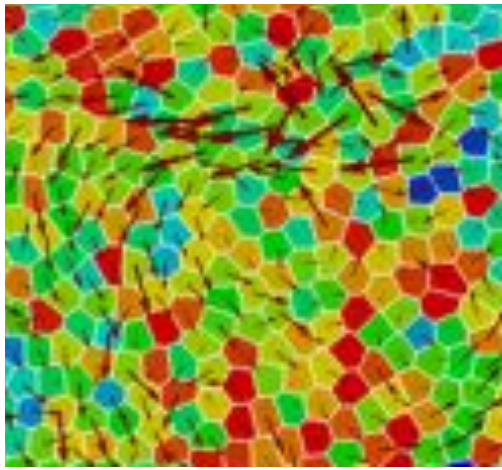
Modelling epithelial cell sheets as active matter

https://github.com/sknepneklab/SAMoS

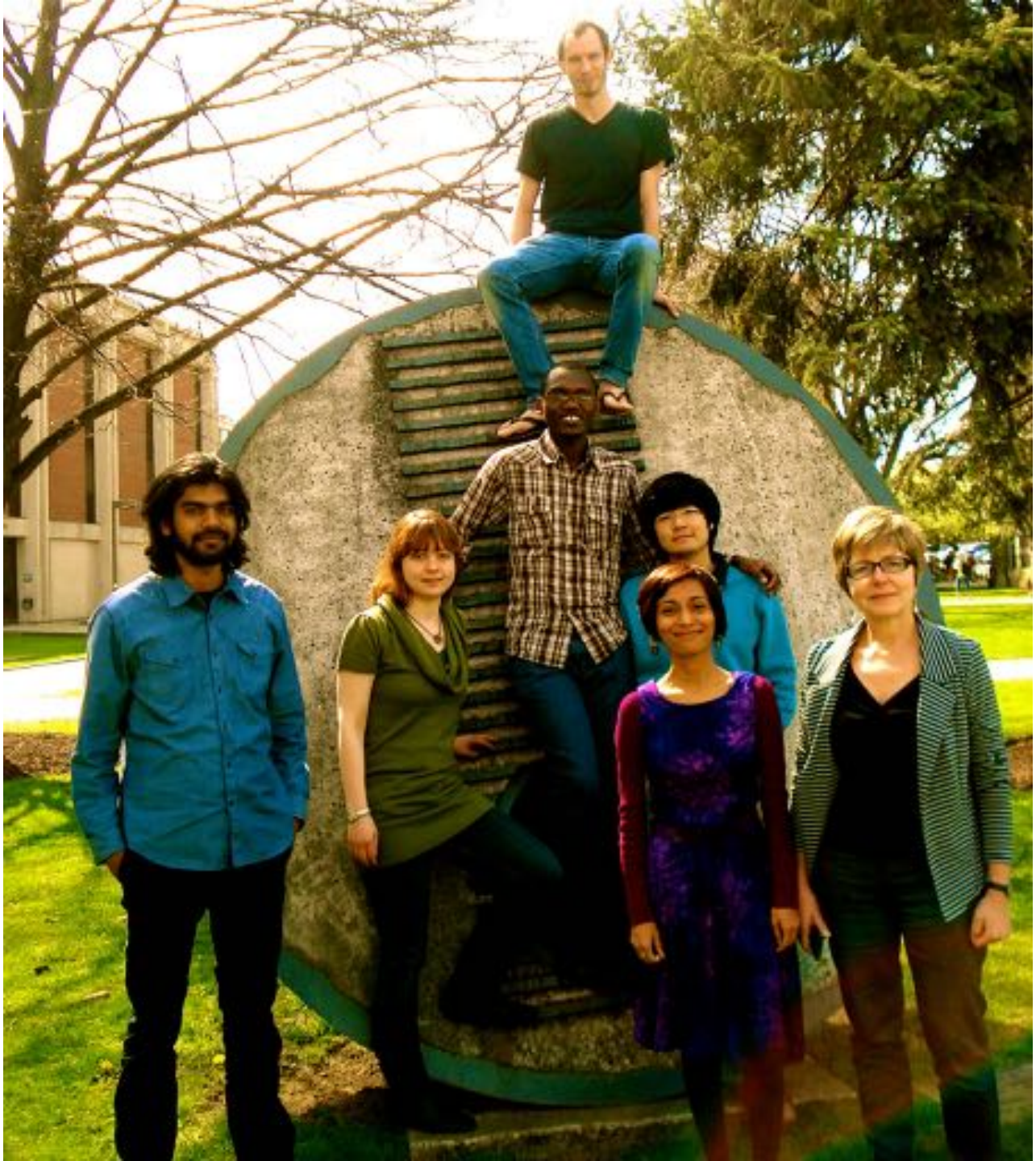
Silke Henkes

Institute for Complex Systems and Mathematical Biology,

University of Aberdeen, Scotland, UK

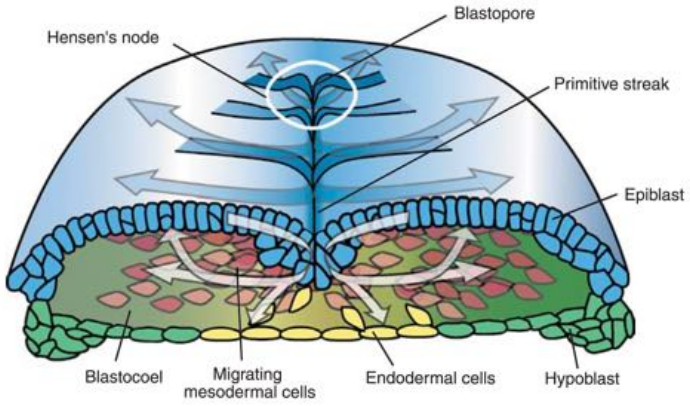





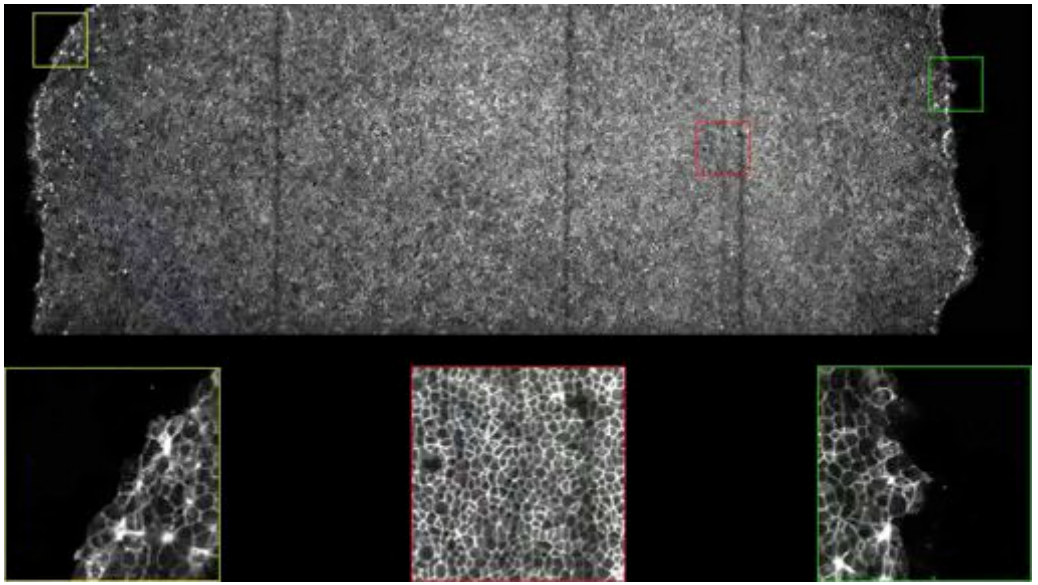
Congratulations to Guenter Ahlers, Shelly Goldstein, and Cristina Marchetti!



Migration patterns in epithelial tissues

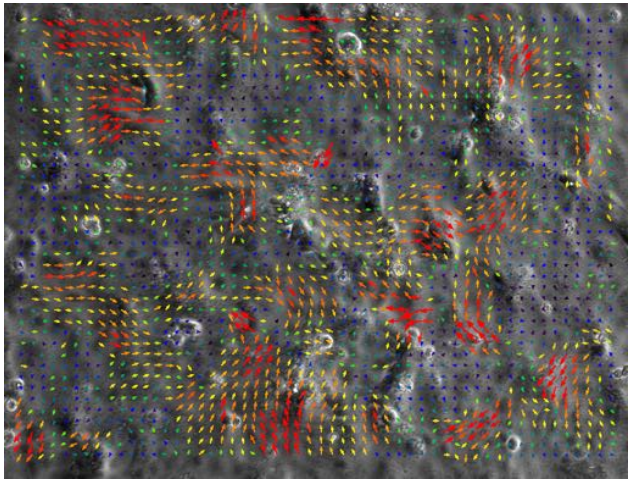
The chick embryo:
large-scale flow

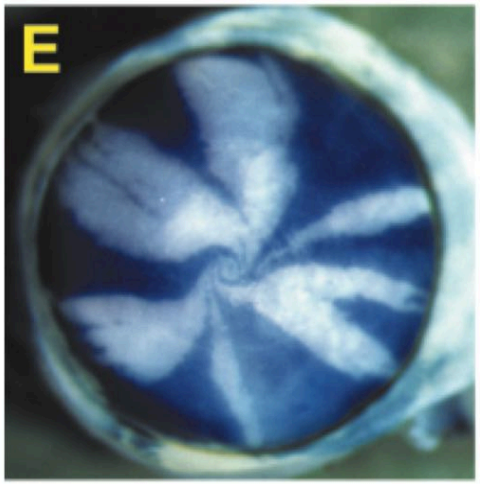




E. Rozbicki et al, Nature Cell Biology 17, 397–408 (2015)

The corneal epithelium: cells migrating on a hemisphere

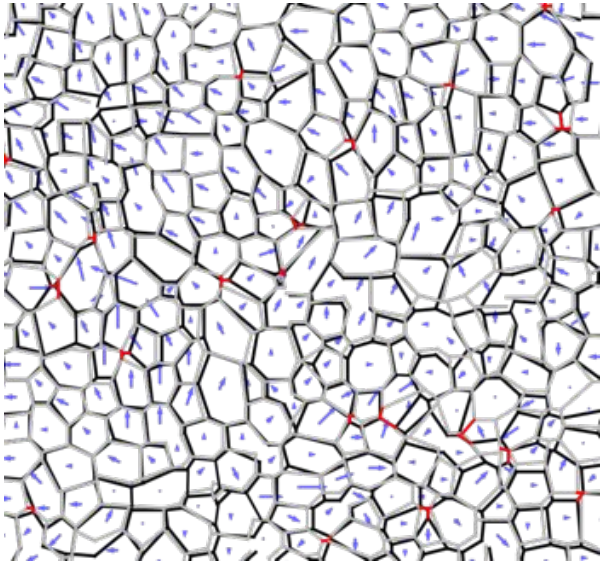




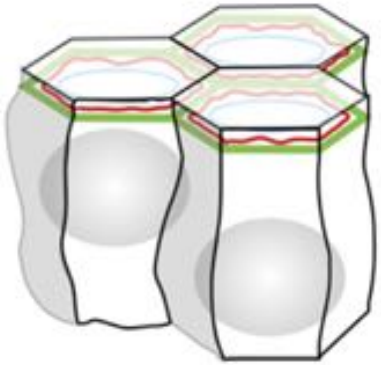
J. M. Collinson et al., Dev. Dyn. 224, 432 (2002)

Left: in-vitro corneal epithelial cells, Kaja Kostanjevec

Active drivers in epithelial tissues

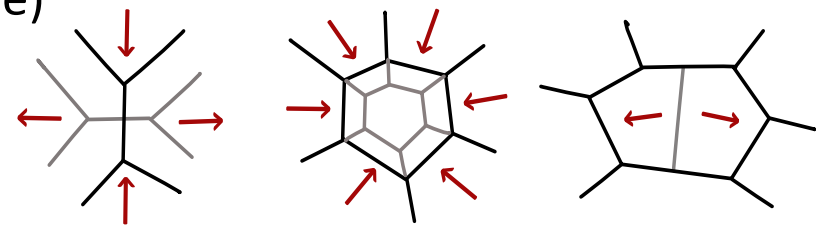


Migration and T1s in same chick embryo



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

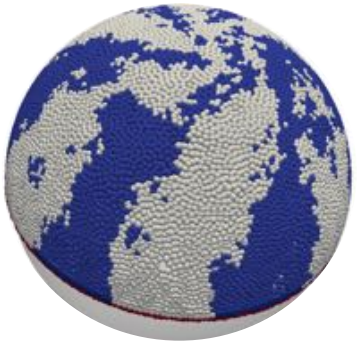


Microscopic nonaffine processes – cell intercalation (T1 event), ingression or apoptosis and division

Building models: What tools do we need?

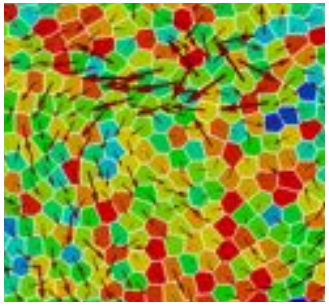
Particle based models:

- Large scale flow properties
- Link to rheology, granular and glass physics literature



Active vertex models:

- Cell junction properties
- Stresses



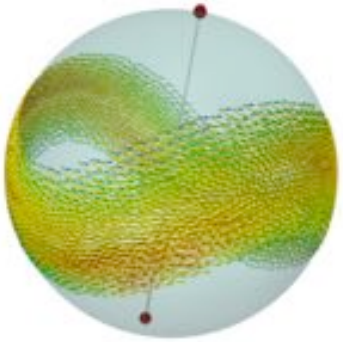
Additionally:

- Complex developmental environments with many cell types, chemical migration cues
- Incorporating curvature of sheets, e.g. cornea or in the gut epithelium

Need efficient, flexible simulation tool that can incorporate all of these effects. Build on success of e.g. CHASTE, COMPUCELL

All simulation results shown here are created with SAMoS.

Soft
Active
Matter
on
Surfaces



https://github.com/sknepneklab/SAMoS

Lead developer: **Rastko Sknepnek**

- Arbitrary surfaces
- All types of driving
- Multiple cell types
- Particle based or active vertex

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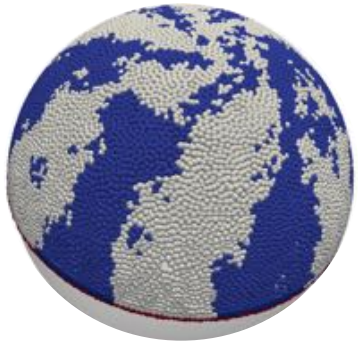

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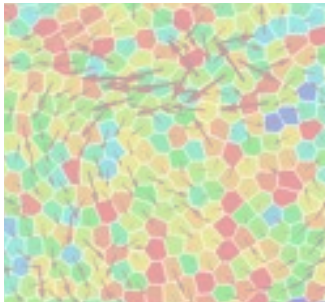

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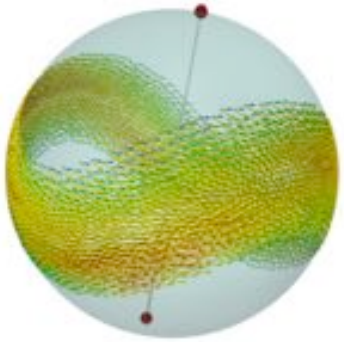

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In collaboration with:

University of Dundee

Rastko Sknepnek

Kees Weijer

Dan Barton

UJF Grenoble

Daniel Matoz-Fernandez

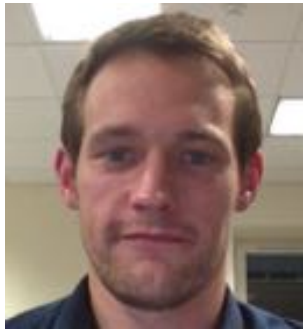
Kirsten Martens

Eric Bertin

University of Aberdeen

Kaja Kostanjevec

Martin Collinson



Luke Coburn

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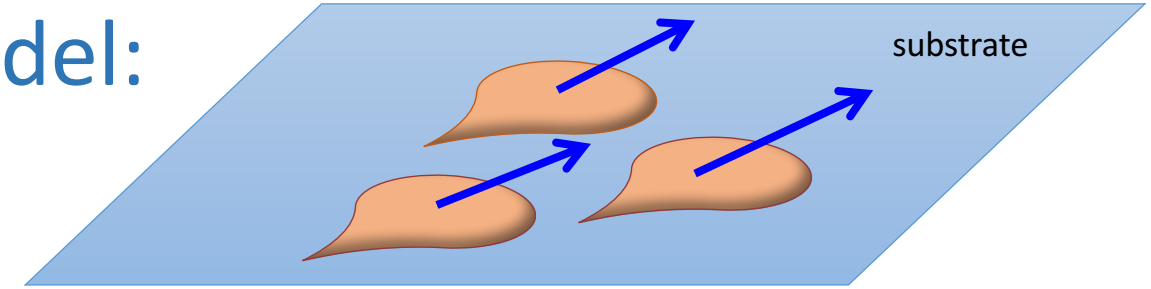
CPTGA visiting scientist program

Particle based model: Active brownian particles



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

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

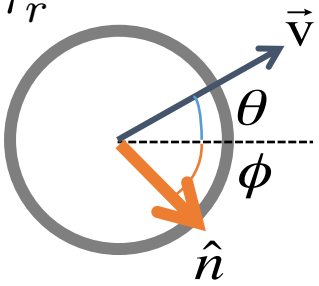
Fully overdamped

Self-propulsion

Short-range repulsion/attraction forces

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

Diffusive angular dynamics



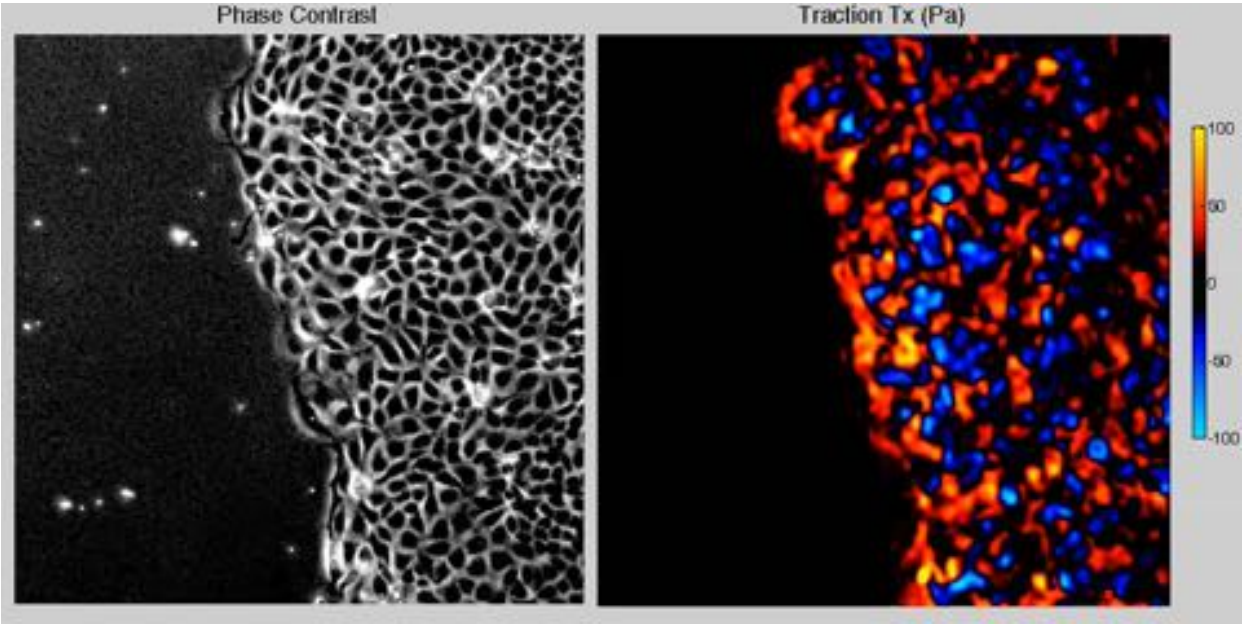
Related cell models without division/death:
B. Szabo et. al., PRE 74 (2006)
SH et al., PRE 84 (2011)
M. Basan et al., PNAS 110 (2013)
N. Sepulveda et al., PLOS Comp. Biol. 9 (2013)

And also active glasses:
R. Ni et al., Nature Comm. (2013)
L. Berthier, PRL (2014)
Y. Fily et al., Soft Matter (2014)

SH, Y.Fily and M. C. Marchetti, PRE 84, 040301(R) (2011)
Y. Fily, SH and M. C. Marchetti, Soft Matter 10, 2132 (2014)

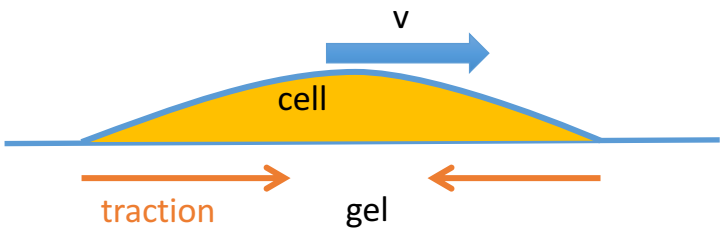
Migration patterns in confluent cell layers

Experimental stresses via force traction microscopy

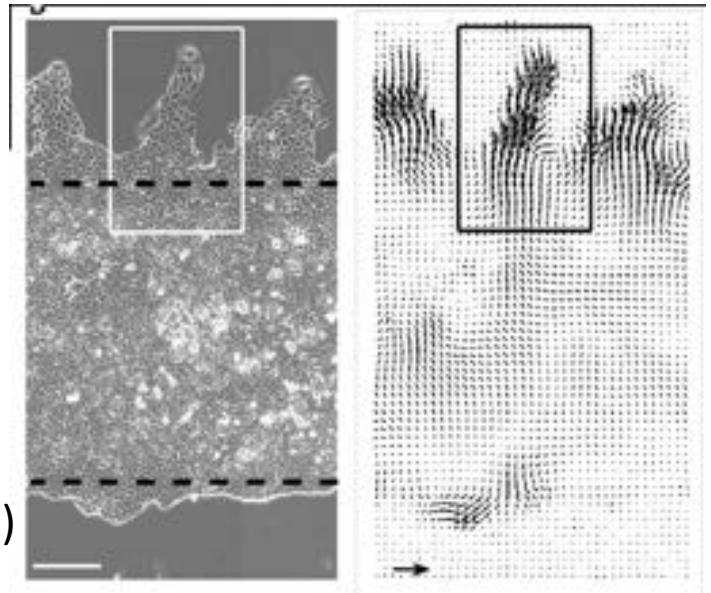


X. Trepat et al., Nature Physics, 5, 426 (2009)

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



"Cell on a gel" setup



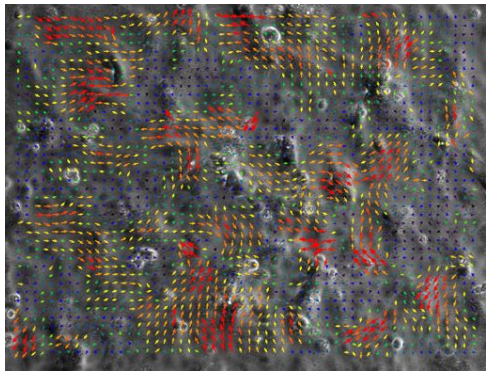
Fingering instability at the edges of the cell layer
L. Petitjean et al., Biophys. J., 98 1790–1800 (2010)

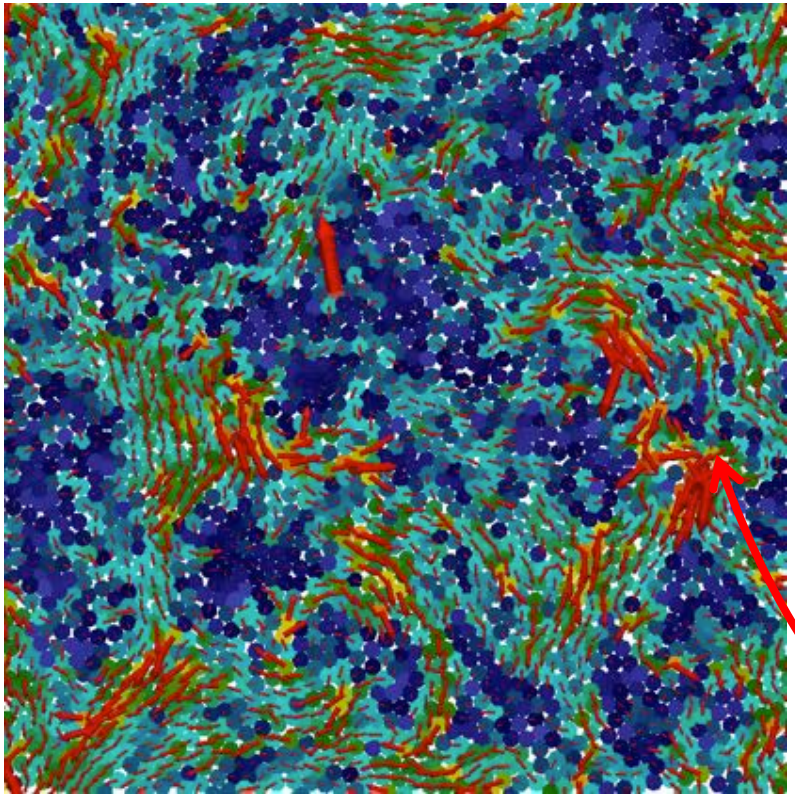
1. Velocity fluctuations in cell sheets

Self-propulsion with correlation time τ

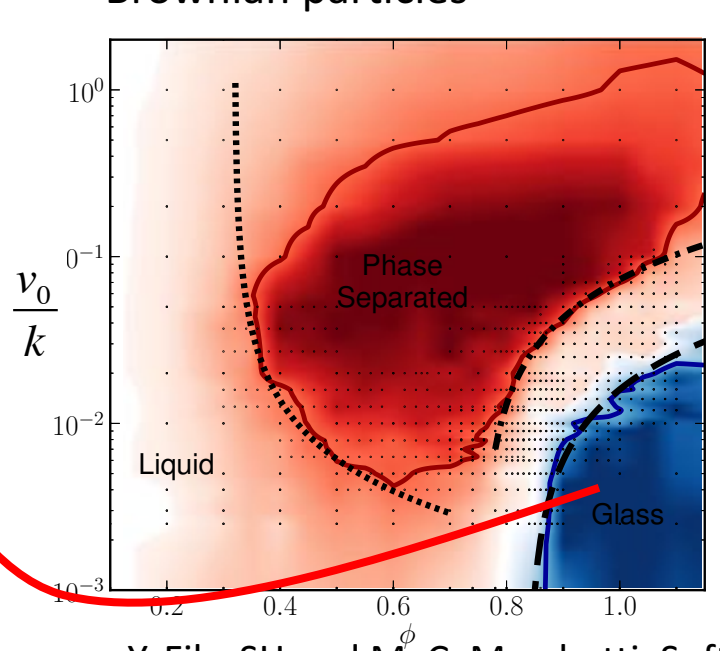
$$\dot{\phi} = \eta, \quad \langle \eta(t)\eta(t') \rangle = \frac{1}{\tau_r}\delta(t-t')$$

$$V_{ij} = \frac{k}{2}\left(R_i + R_j - |\mathbf{r}_{ij}|\right)^2$$ soft elastic repulsion





Phase diagram of Active Brownian particles



Y. Fily, SH and M. C. Marchetti, Soft Matter 10, 2132 (2014)

SH, Eric Bertin & collaborators, to be submitted

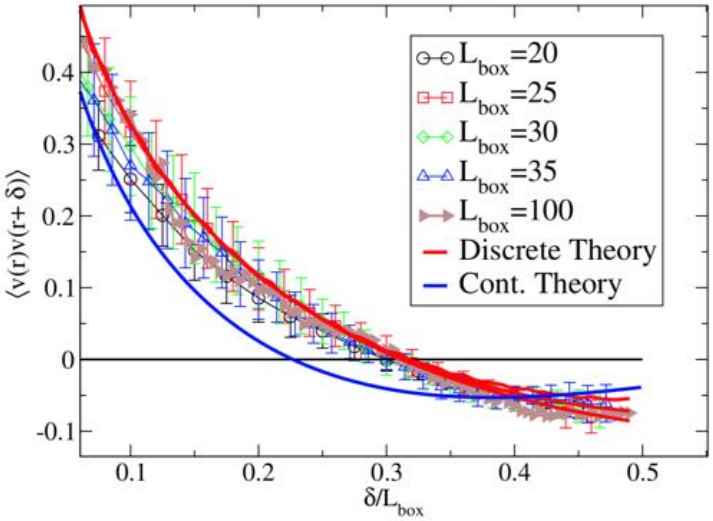
Origin: persistent forces

C. Maloney, PRL 2006, and later with A. Lemaitre:

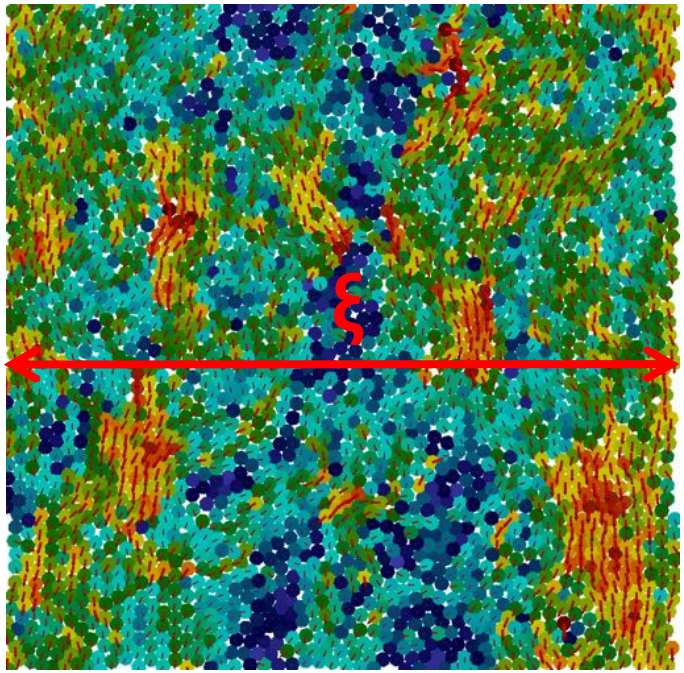
Model forces in a sheared (granular) system as a set of random, persistent forces

$$\Xi_{i\alpha} = \sum_j H_{i\alpha j\beta} \frac{d\mathring{r}_{j\beta}}{d\gamma}$$

Extract nonaffine part of motion through the Hessian matrix and compute velocity correlation functions



Result: correlation length = system size



Active systems in linear response:

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

Active forces are randomly oriented, time-correlated forces applied at every particle level. Adapt method, for finite correlation time, and extract finite correlation length.

Universal velocity correlation function

In normal modes formalism, equations decouple, and noise becomes Ornstein-Uhlenbeck

$$\dot{a}_\mu = -\lambda_\mu a_\mu + \eta_\mu$$

$$\langle \eta_\mu(t)\eta_{\mu'}(t')\rangle = \frac{v_0^2}{2} e^{-|t-t'|/\tau}\delta_{\mu,\mu'}$$

Energy spectrum is very far from equipartition:

$$E_\mu = \frac{1}{2}\lambda_\mu \langle a_\mu^2\rangle = \frac{v_0^2\tau}{4(1+\lambda_\mu\tau)}$$

Short persistence time: thermal with $T_{\text{eff}} = \frac{1}{2}v_0^2\tau$

Long persistence time: Amplifications of low modes, same as sheared system of Maloney.

Velocity correlation function expressed in normal modes:

$$\hat{G}(\mathbf{q}) = \sum_{\mu,\mu'} \langle \dot{a}_\mu \dot{a}_{\mu'}\rangle \, \boldsymbol{\xi}_\mu(\mathbf{q}) \cdot \boldsymbol{\xi}_{\mu'}(\mathbf{q})^*$$

Can be computed exactly, with modes evaluated numerically:

$$\hat{G}(\mathbf{q}) = \sum_\mu \frac{v_0^2}{2(1+\lambda_\mu\tau)} ||\boldsymbol{\xi}_\mu(\mathbf{q})||^2 \qquad \textbf{A}$$

Using the Dispersion relation into longitudinal and transverse speeds of sound:

$$\lambda = \omega^2,$$
$$\omega_L = v_L q$$
$$\omega_T = v_T q$$

$$\hat{G}(\mathbf{q}) = \frac{v_0^2}{2}\left[\frac{D_L(q)}{1+v_L^2q^2\tau} + \frac{D_T(q)}{1+v_T^2q^2\tau}\right] \qquad \textbf{B}$$

Correlation length scale:

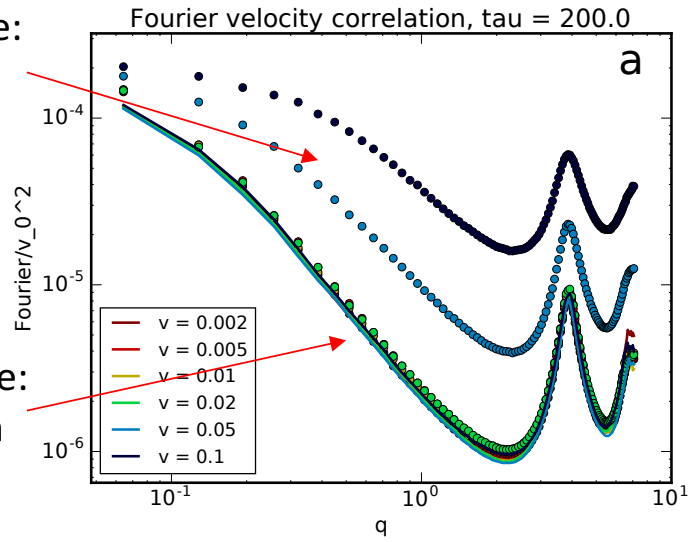
$$\xi_L = v_L\sqrt{\tau}, \quad \xi_T = v_T\sqrt{\tau}$$

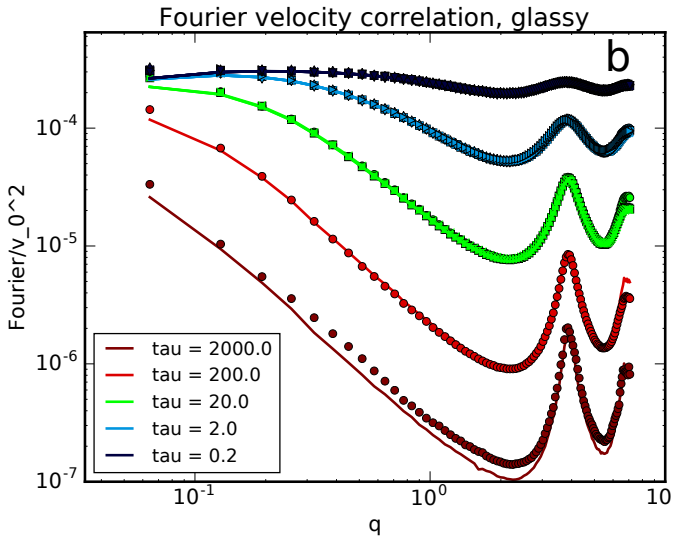
Based on ideas of active jamming in
SH, Y.Fily and M. C. Marchetti, PRE 84, 040301(R) (2011)

Simulation results

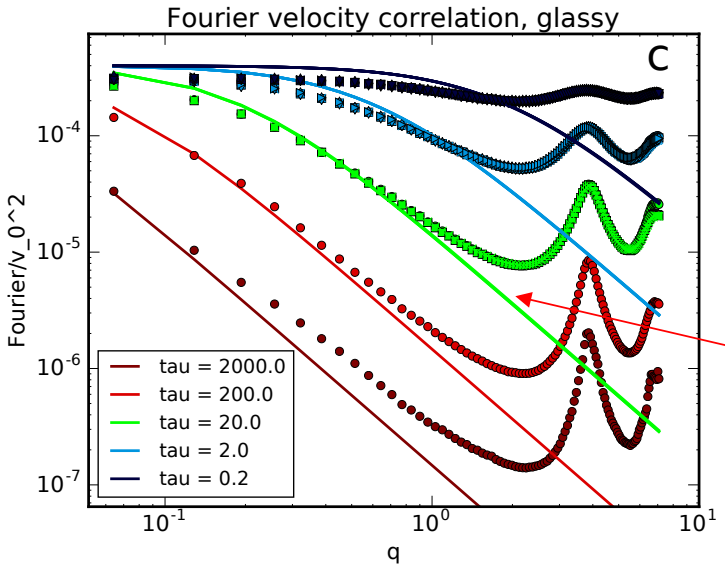
Liquid phase: strong correlation persists

Glassy phase: exact match





Emergence of length scale that reaches system size with increasing τ

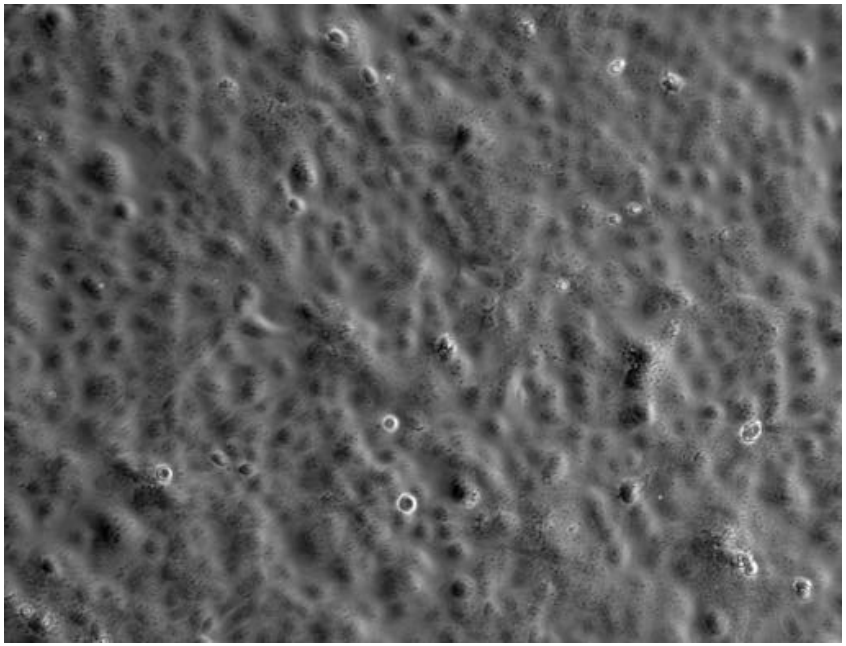


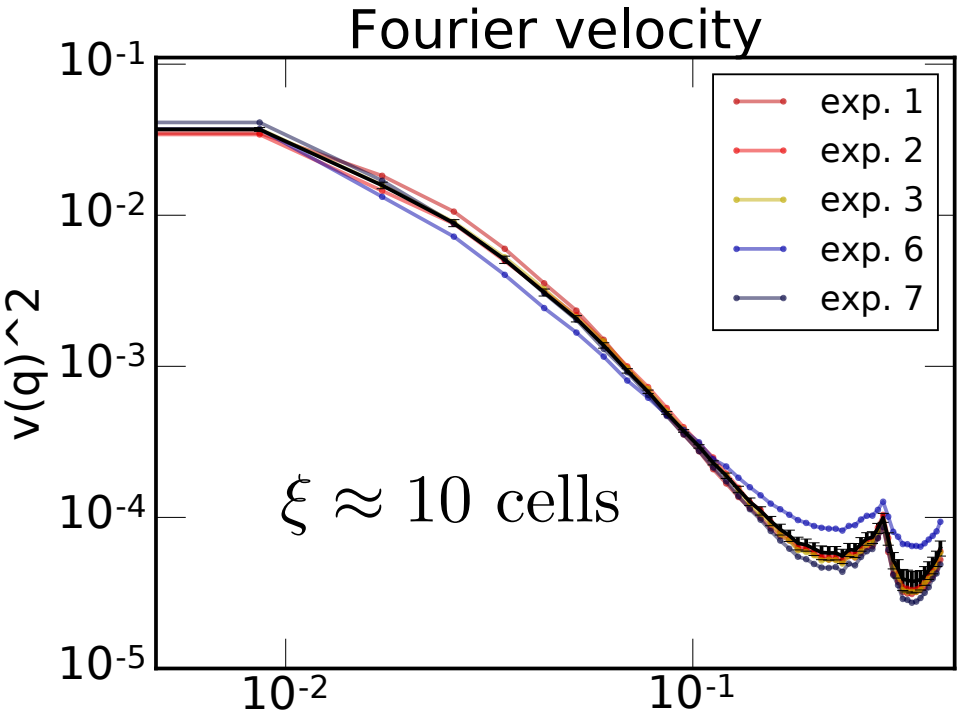
Dots are velocity correlations evaluated numerically

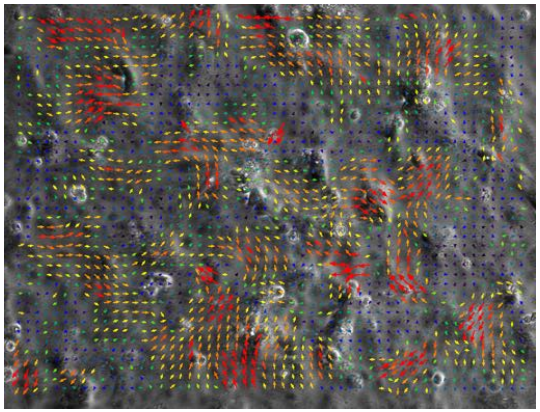
Top: Lines are exact evaluation of **A**

Bottom: Lines are scaling relation **B**, using numerically obtained speed of sound.

Experimental cell dynamics







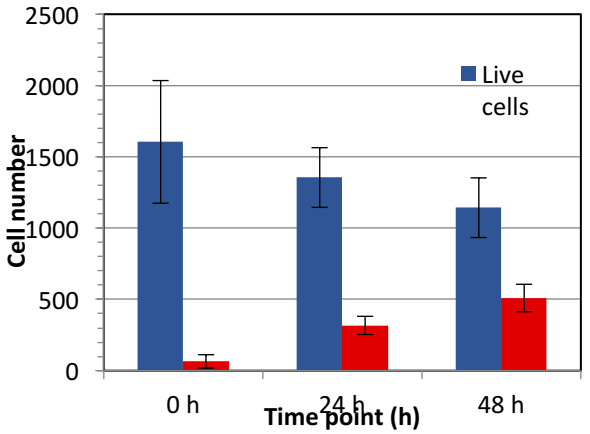
PIV

Kaja Kostanjevec

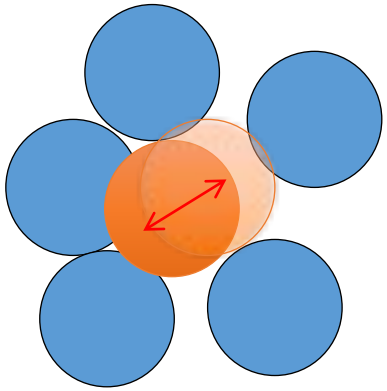
In vitro HCE (human corneal epithelial) cells on a glass substrate. Measure

- Cell velocities and correlations
- Division and death rate

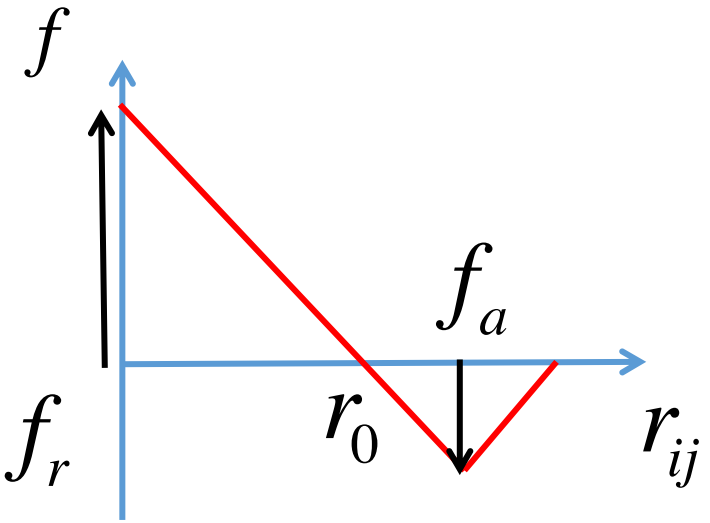
Migration patterns similar to other epithelial cell lines, e.g. in vitro MDCK



2. A (very) simple cell division model



division through fading-in new particles



- Implement constant death rate *a*, but density-dependent division rate

$$d = d_0\left[1 - \frac{z}{z_{\max}}\right]$$

Model with only **three** scaled parameters, becomes tractable

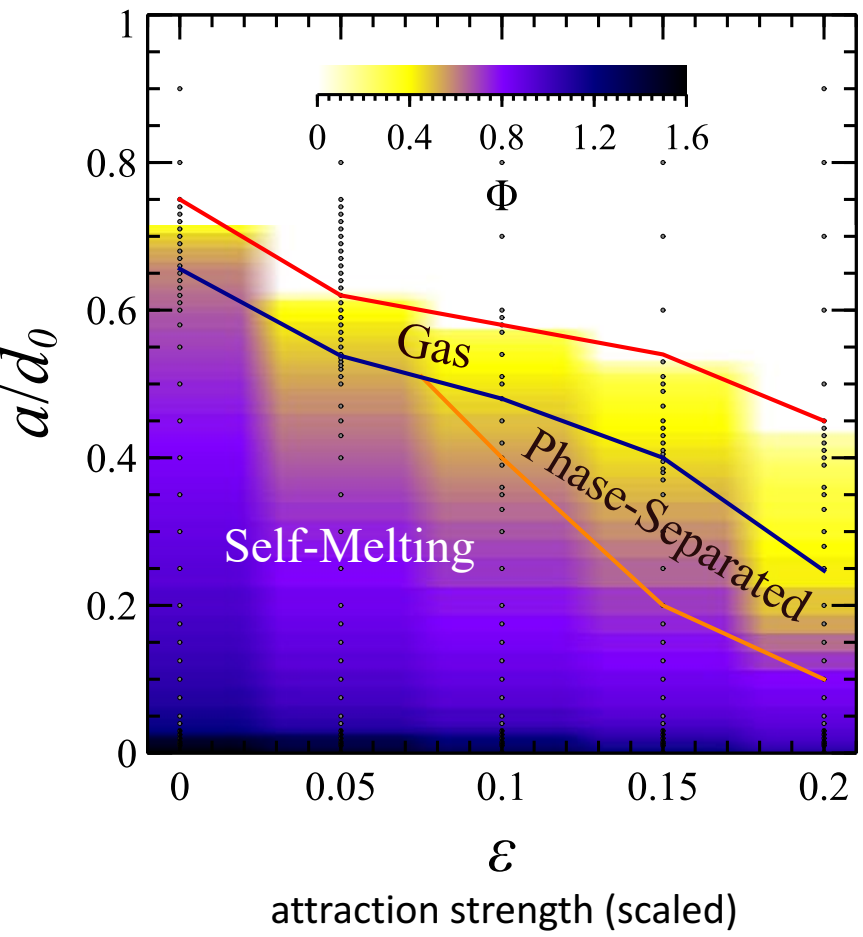
d_0 bare division rate

$\frac{a}{d_0}$ ratio of death to division

$\frac{f_a}{f_r}$ ratio of attraction to repulsion

D. A. Matoz-Fernandez, K. Martens, R. Sknepnek, J. L. Barrat and SH, Soft Matter 13, 3205-3212 (2017)

Phase diagram

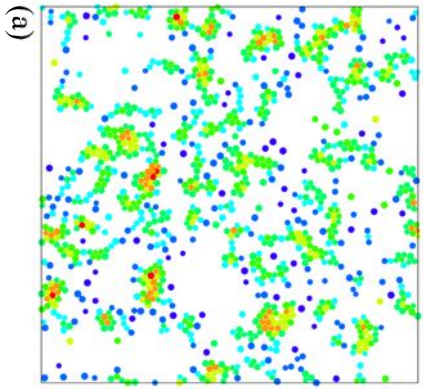


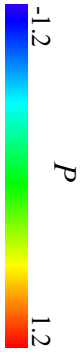
attraction strength (scaled)

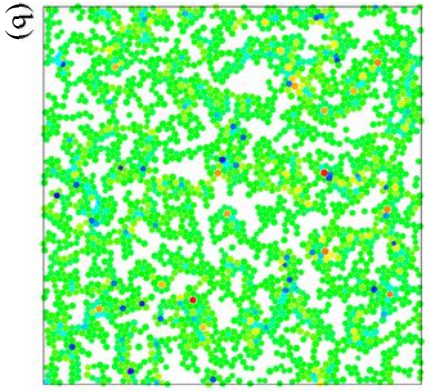
Non-percolated gas phase

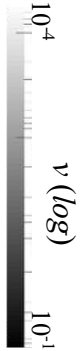
Phase separation: remodeling gel phase

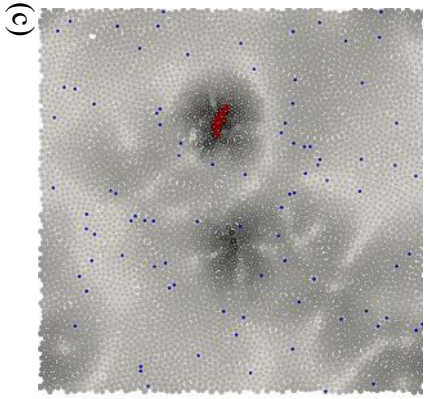
Confluent self-melting phase



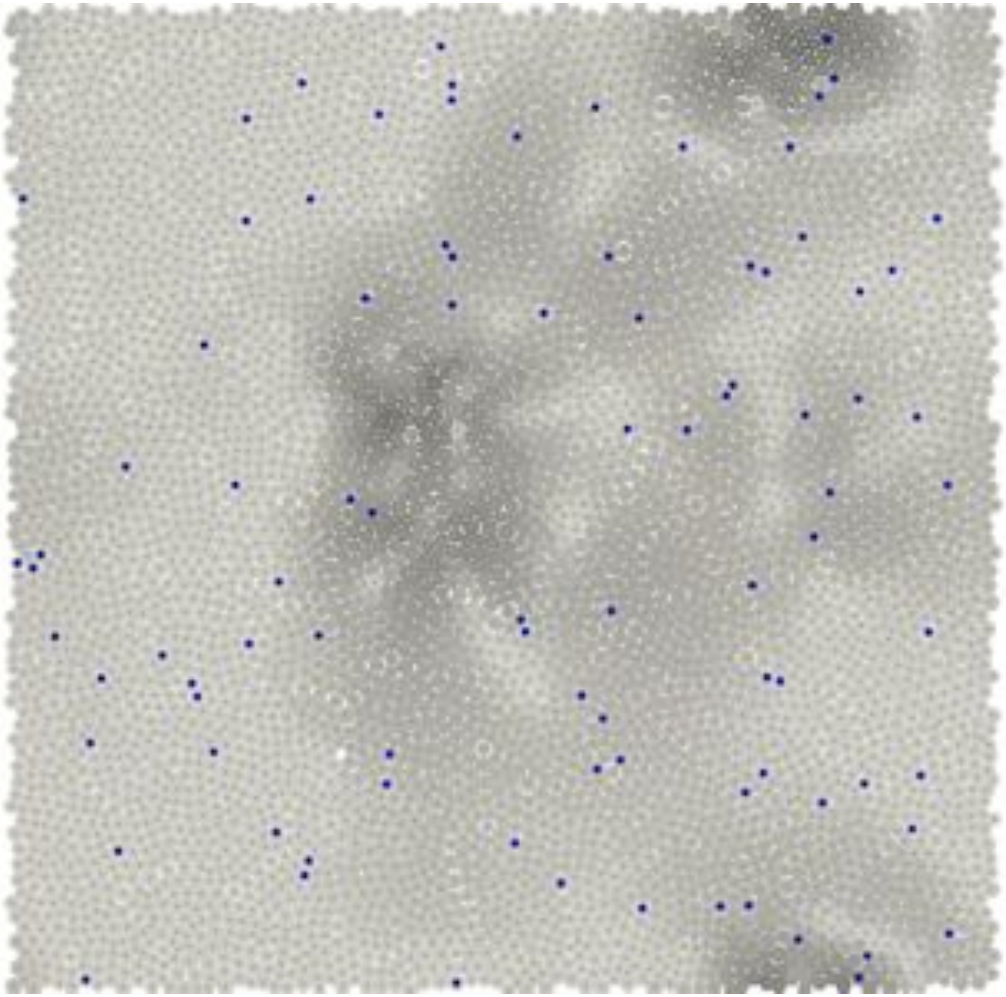






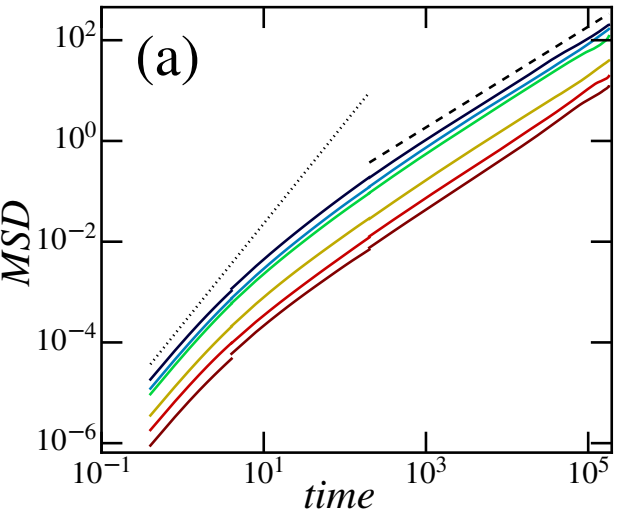


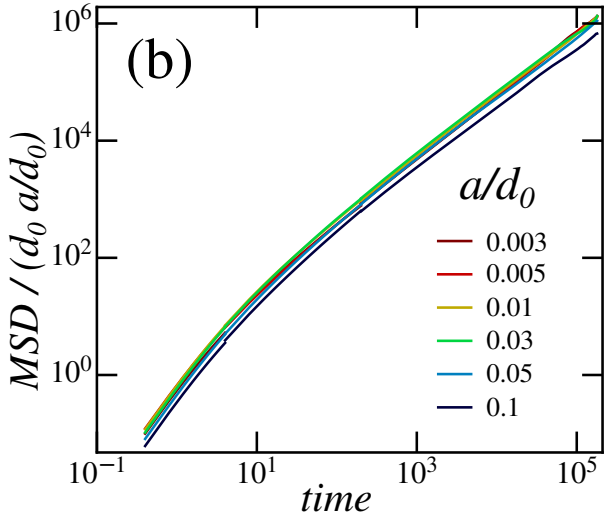
Steady-state dense self-melting phase

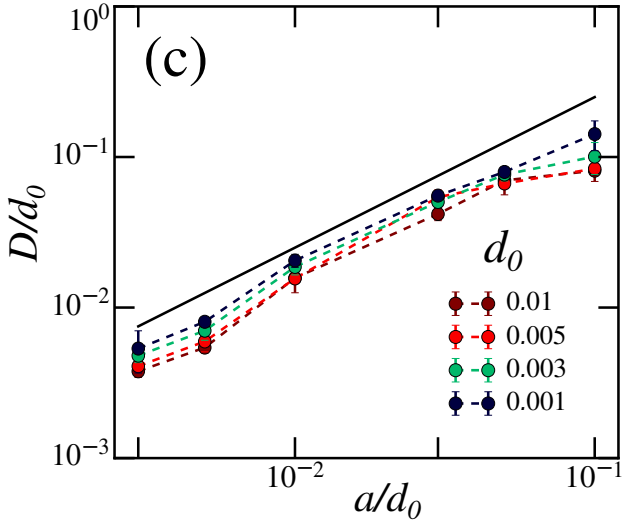


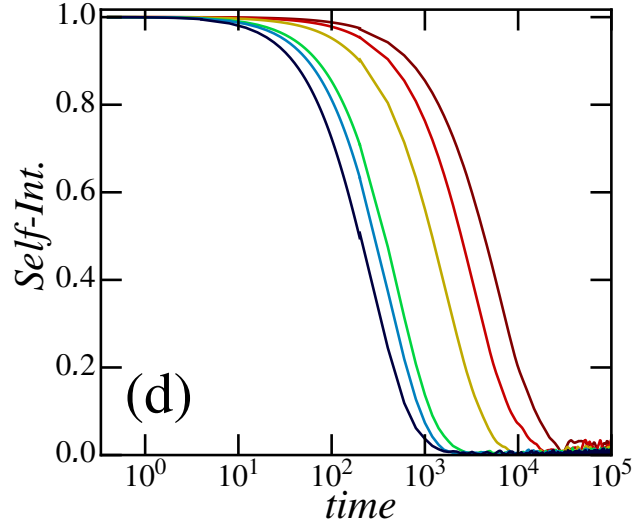
$\frac{f_a}{f_r} = 0.15$ $\quad d_0 = 0.005$ $\quad z_{\max} = 6$

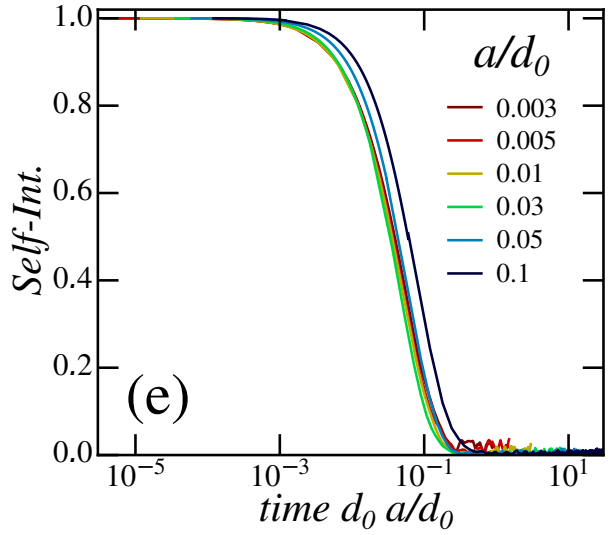
Not a glass! Single time scale fluid

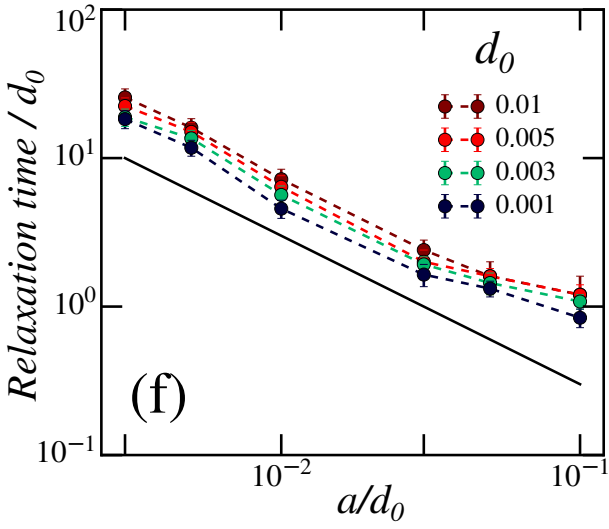












$\tau = 1/a$ death rate = effective division rate in steady state

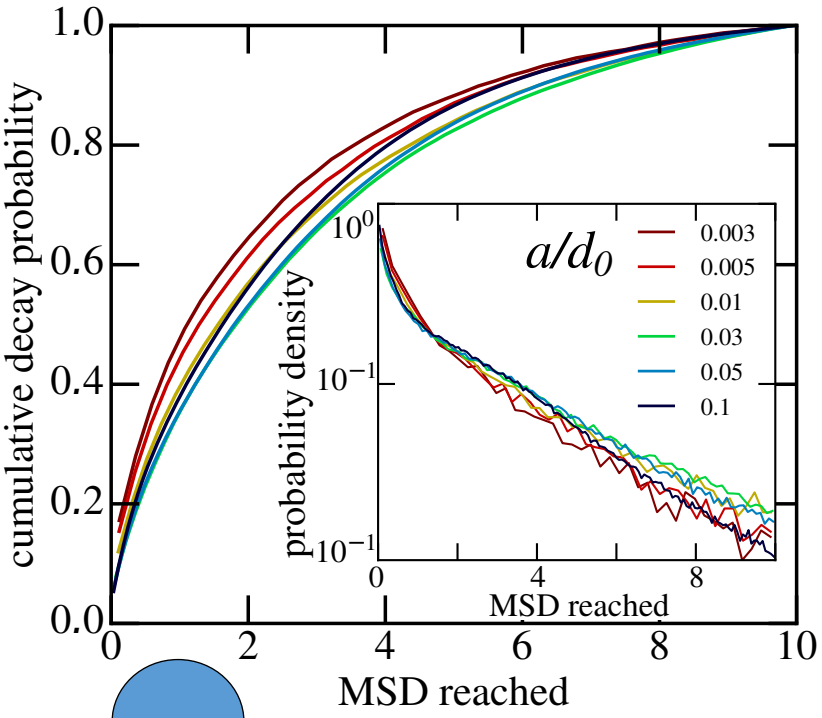
Should this be surprising?

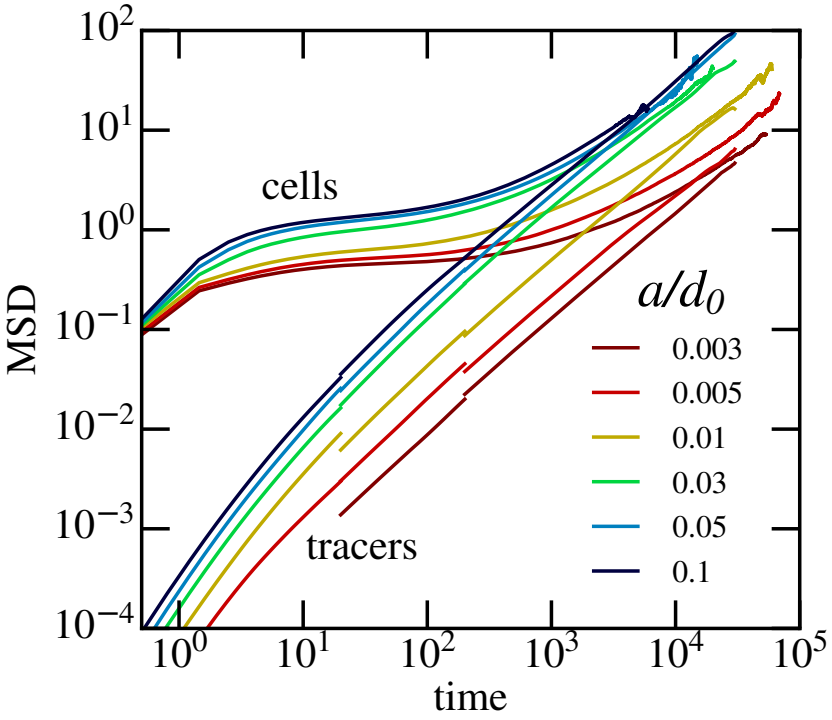
$$\partial_t \rho + \nabla \cdot (\rho \mathbf{v}) = -\nabla \cdot \mathbf{J} + \sigma$$

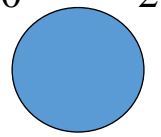
Continuity equation: When a growth (or fluctuation) term is added, density is not conserved any more

J. Ranft, M. Basan, J. Elgeti, J.-F. Joanny, J. Prost and F. Jülicher, PNAS, 107 (2010): **Fluidization of tissues by cell division and apoptosis**

Continuum treatment shows the long-time diffusive behaviour with same time scale as ours







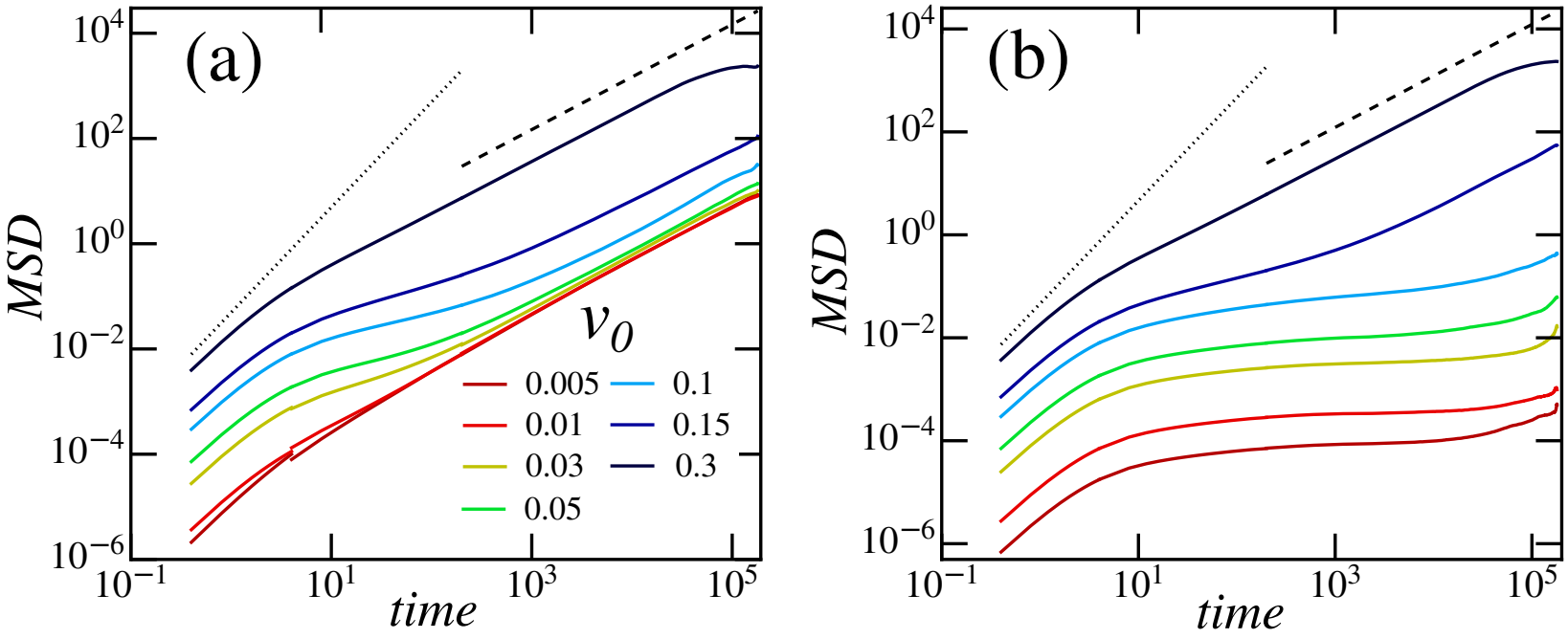
Cell size

There is no caging: Cell centres displace at birth, and then slowly diffuse away. Tracers are necessary to see the overall, purely diffusive behaviour of the tissue.

Any level of division results in fluid state

Active with a little bit of division/death (death rate 10^{-5}):
Always fluid, at any active driving speed

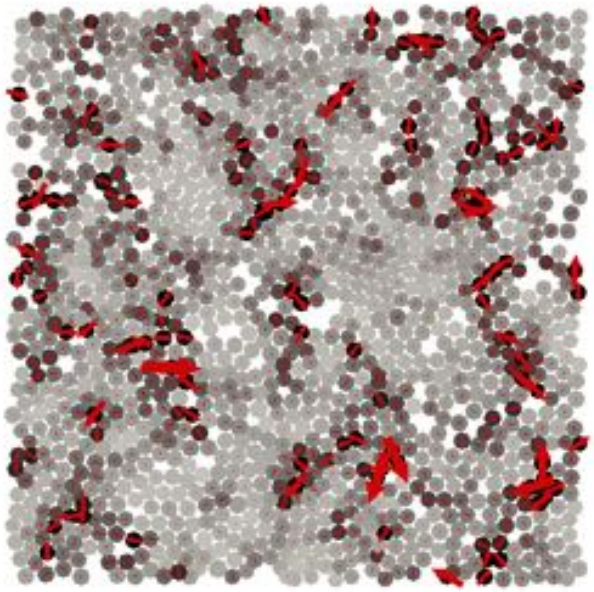
Active driving only:
Glassy phase which melts at high driving.



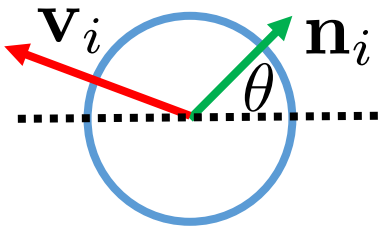
Shear rheology of the same system: The division also destroys glassy features in the rheology, D. A. Matoz-Fernandez, E. Agoritsas, J.-L. Barrat, E. Bertin, and K. Martens PRL **118**, 158105 (2017)

Application: Coarse-grained model for corneal epithelium

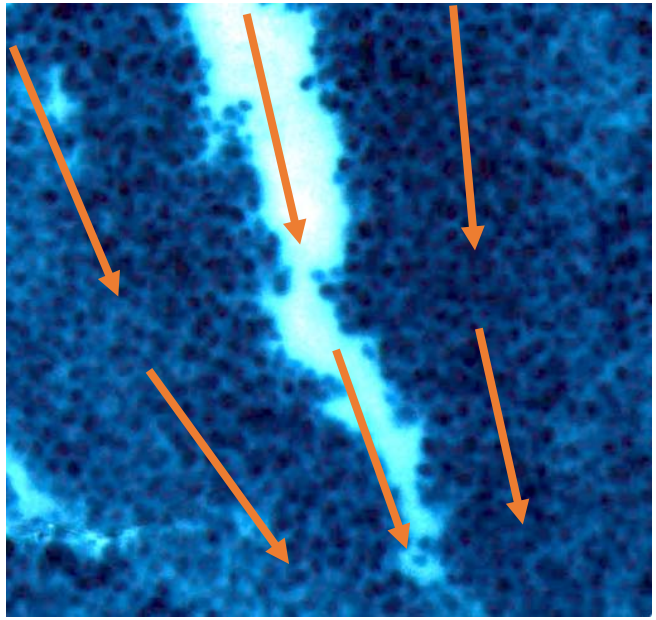
Use results to (approximately) calibrate our model with self-propulsion and model the behaviour of TA cells on the corneal surface.



Alignment or PCP: Add polar neighbour and velocity alignment



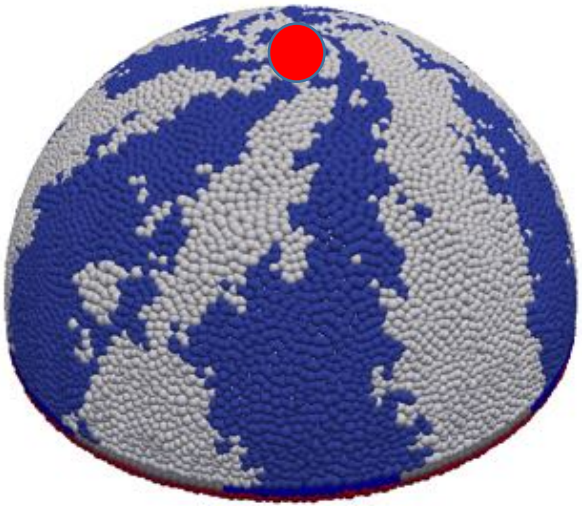
$$\dot{\theta}_i = -J\,\mathbf{n}_i \times [\sum_{j=1}^{z_i} \mathbf{n}_j + \mathbf{v}_i] \cdot \mathbf{N}_i + \eta_i$$



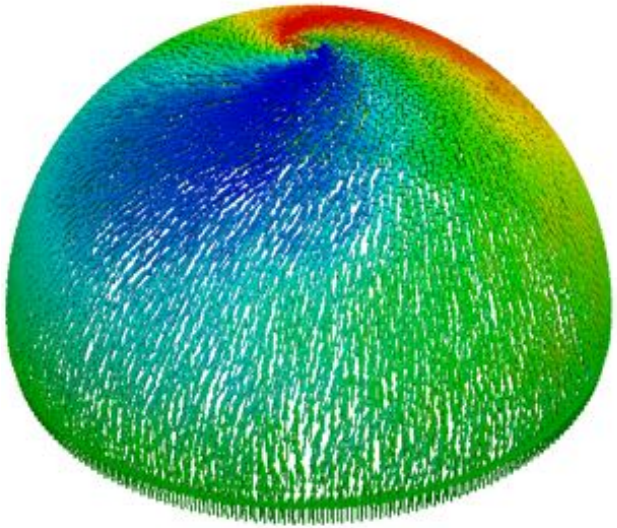
- Captures homeostasis of tissue
- Captures velocity correlations, large scale flow properties
- Does not capture cell-scale motion patterns

Obtain central vortex flow

+ 1 topological defect



Director field



Thank you!