Isaac Newton institute
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Polar Fluctuations Lead to Extensile Nematic Behaviour in Confluent Tissues

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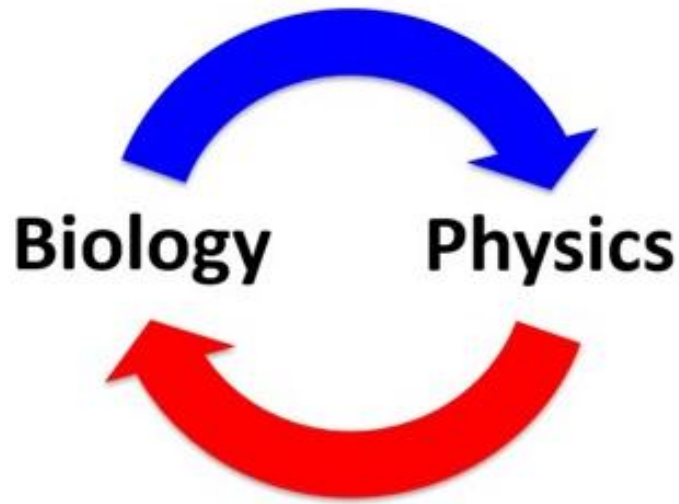
ICR The Institute of Cancer Research

Imperial College London

Universality in Biology

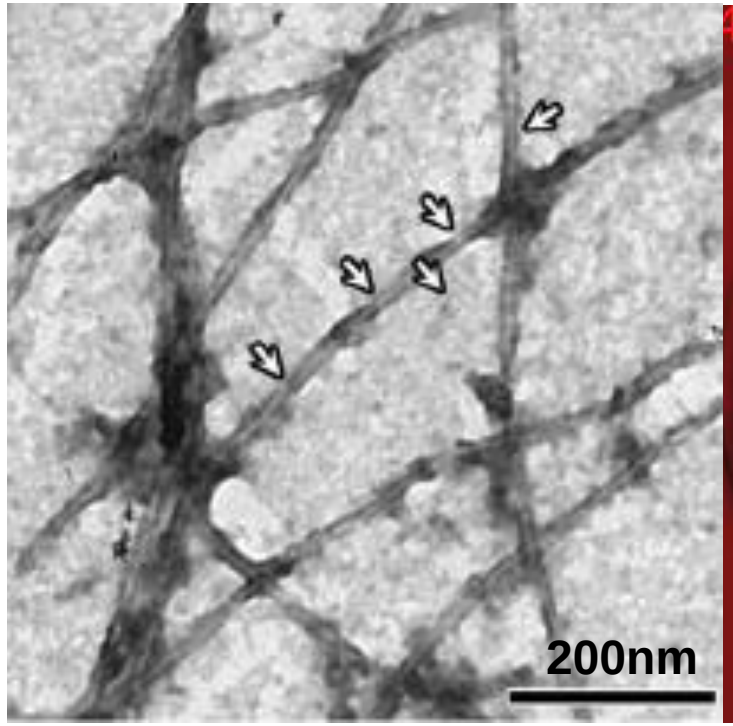
Biology inspires new physics



Physics leads to quantitative biology

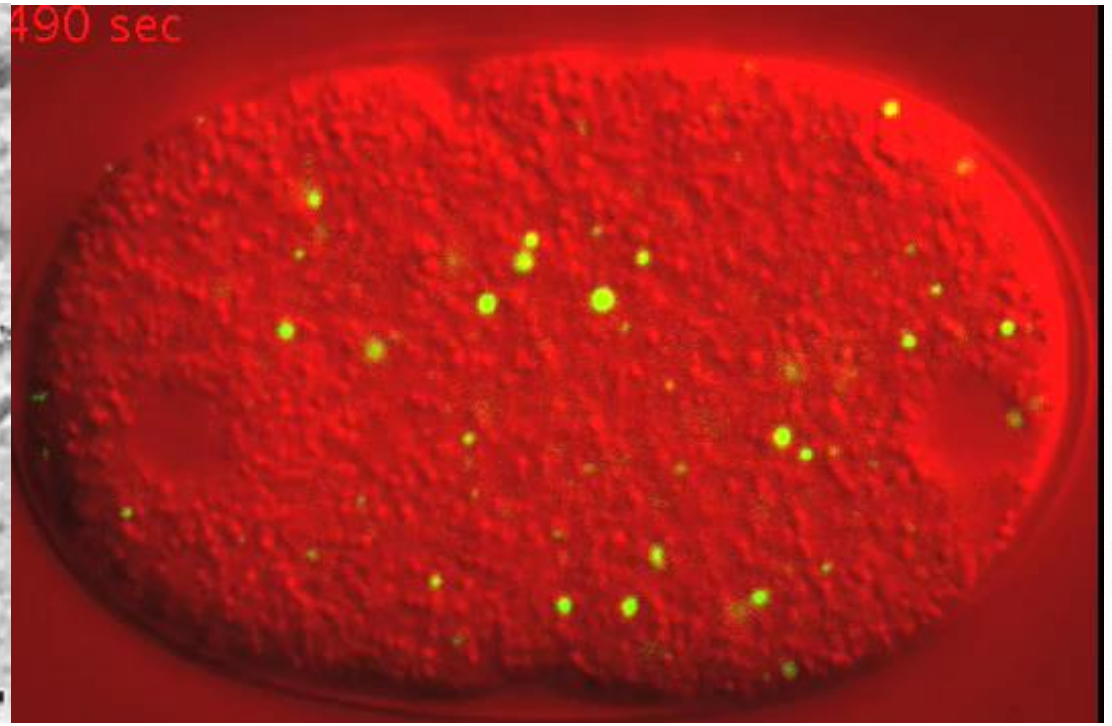
Universal physics in biology

Amyloid formation



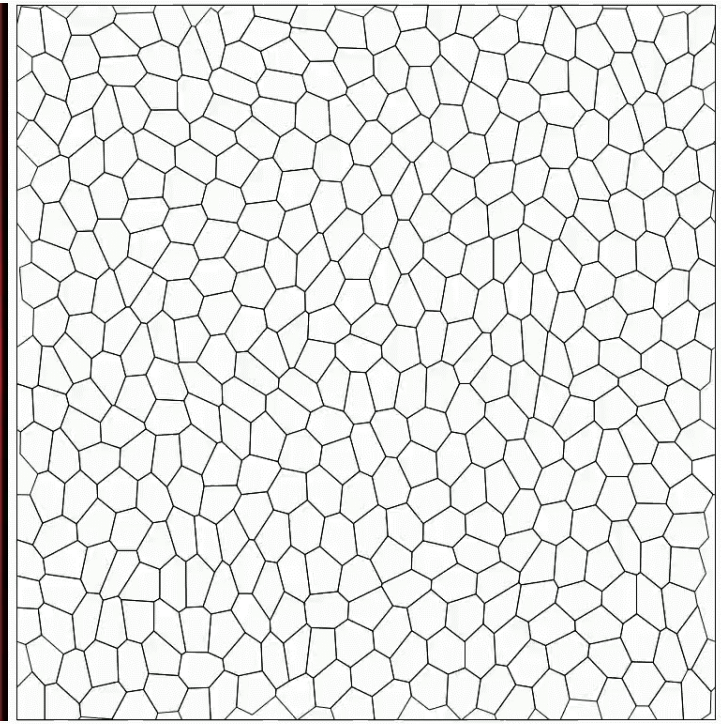
CF Lee et al (2012) J Biol Chem

Biomolecular condensates



C Brangwynne et al. (2009) Science

Active matter



Active vertex simulation by Andy Killeen

Newton Institute: 9-13 Oct 2023
Biological condensates: cellular mechanisms governed by phase transitions

Universality in Biology

Plan

1. Defining the problem
2. Universality of the tissue model
3. Resolving the problem using linear theory
4. Summary & outlook

Ref: Killeen, Bertrand & Lee (2022) Polar Fluctuations Lead to Extensile Nematic Behavior in Confluent Tissues Phys Rev Lett 128, 078001

Acknowledgement

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CANCER RESEARCH UK | IMPERIAL CENTRE
NIHR | Imperial Biomedical Research Centre

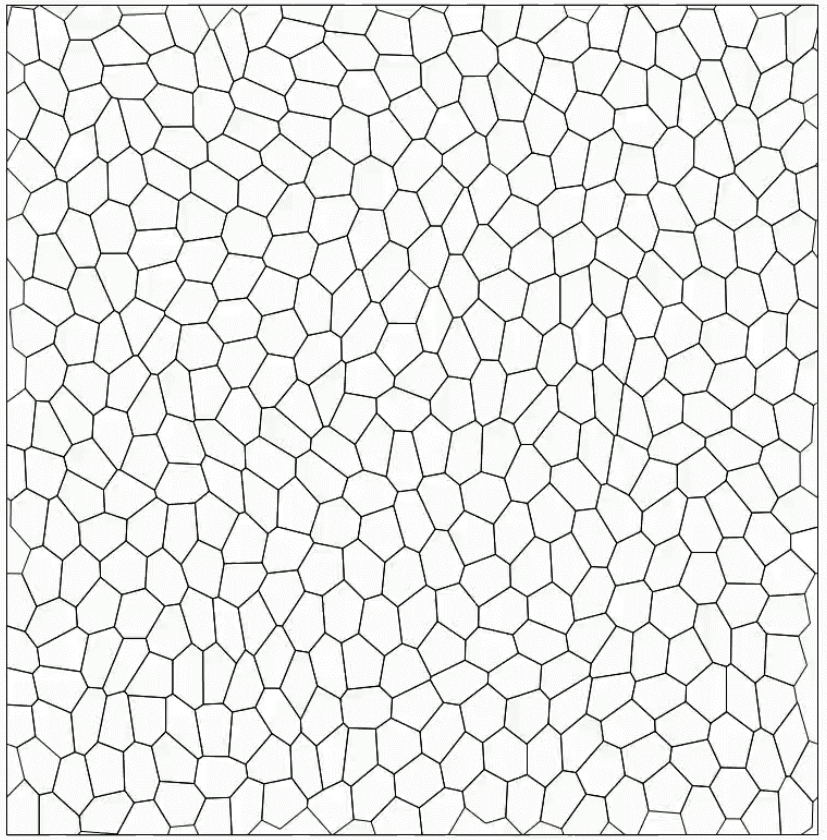
1. Defining the problem

Polar fluctuations
lead to
extensile nematic behaviour
in
confluent tissues

Confluent Tissues

A dense, gapless collection of cells

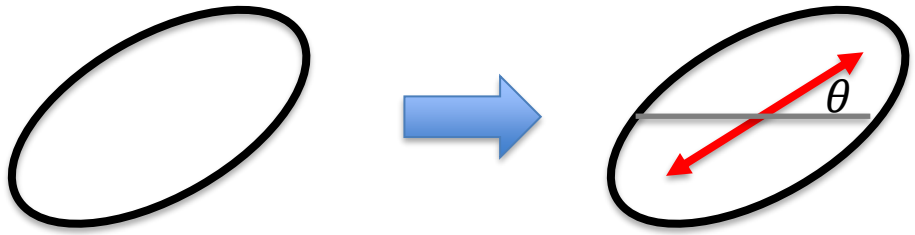
E.g., Madin-Darby canine kidney (MDCK) epithelial cell tissue



For the real experiments, see Saw, T., Doostmohammadi, A., Nier, V. *et al.* Topological defects in epithelia govern cell death and extrusion. *Nature* **544**, 212–216 (2017)

Nematic behaviour in confluent tissues

Cell shape (cell elongation) → nematic director



Nematic director $\vec{n} = (\cos\theta\,, \sin\theta)$

Nematic behaviour in confluent tissues

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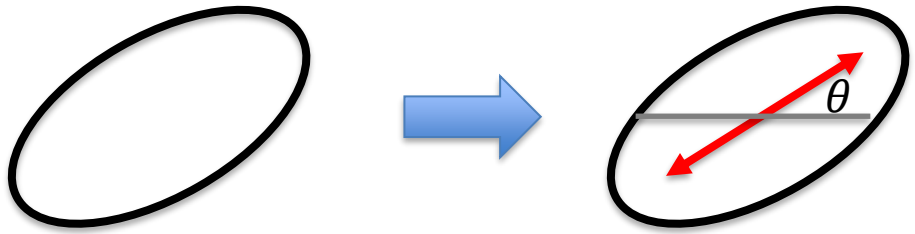

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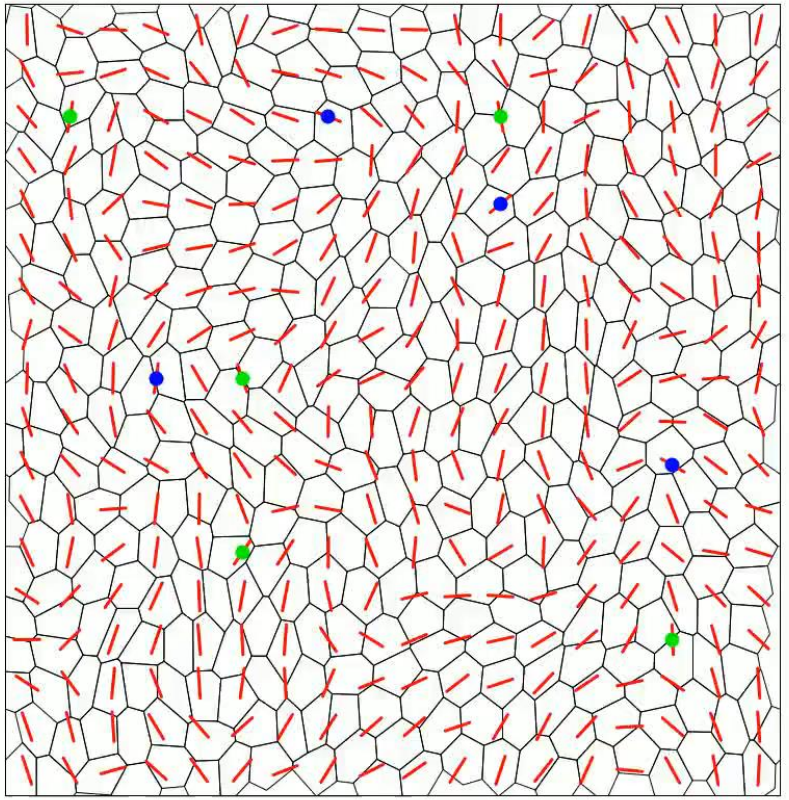

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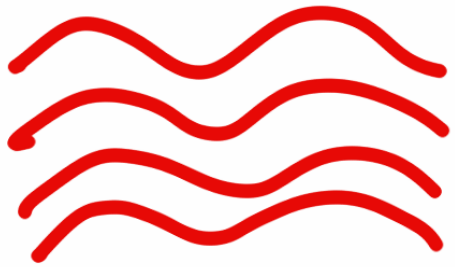
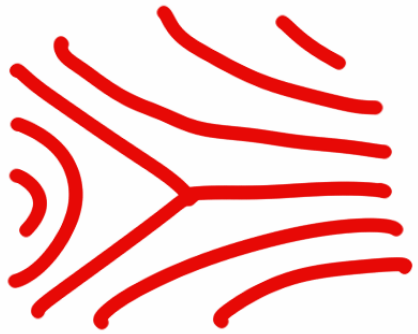
Nematic behaviour in confluent tissues

Cell shape (cell elongation) → nematic director → Nematic field at tissue level

no fluctuations



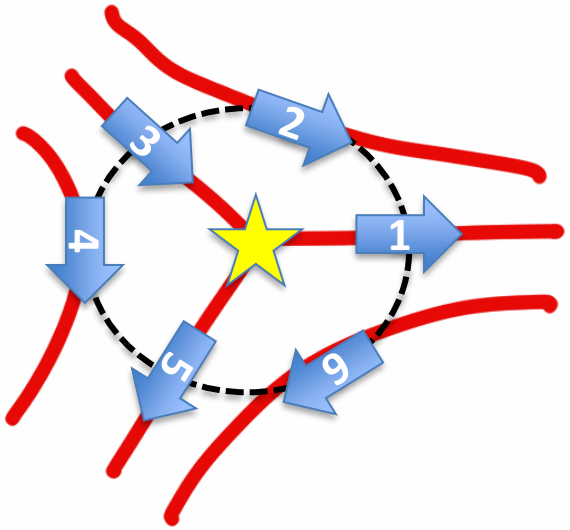
more fluctuations



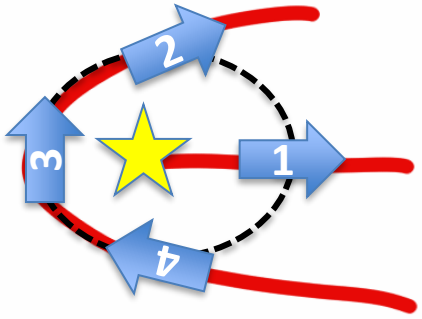
even more fluctuations → defects

Nematic behaviour in confluent tissues

Half integral defects in nematic fields



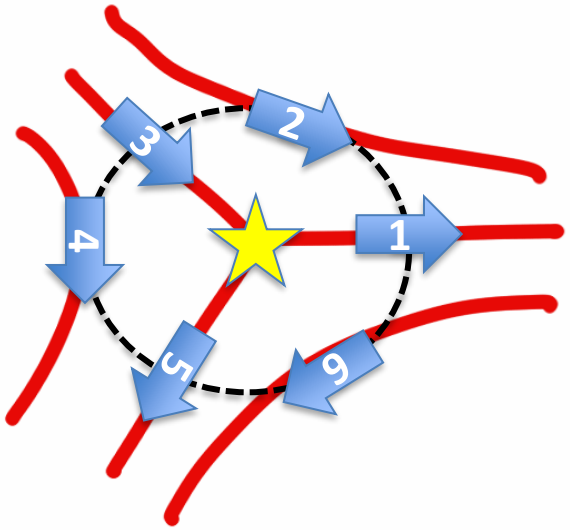
Winding by -180° : -1/2 defect



Winding by 180° : +1/2 defect

Nematic behaviour in confluent tissues

Half integral defects in nematic fields



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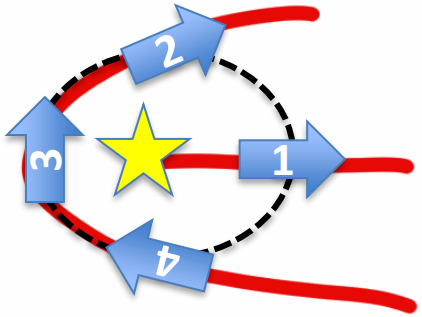
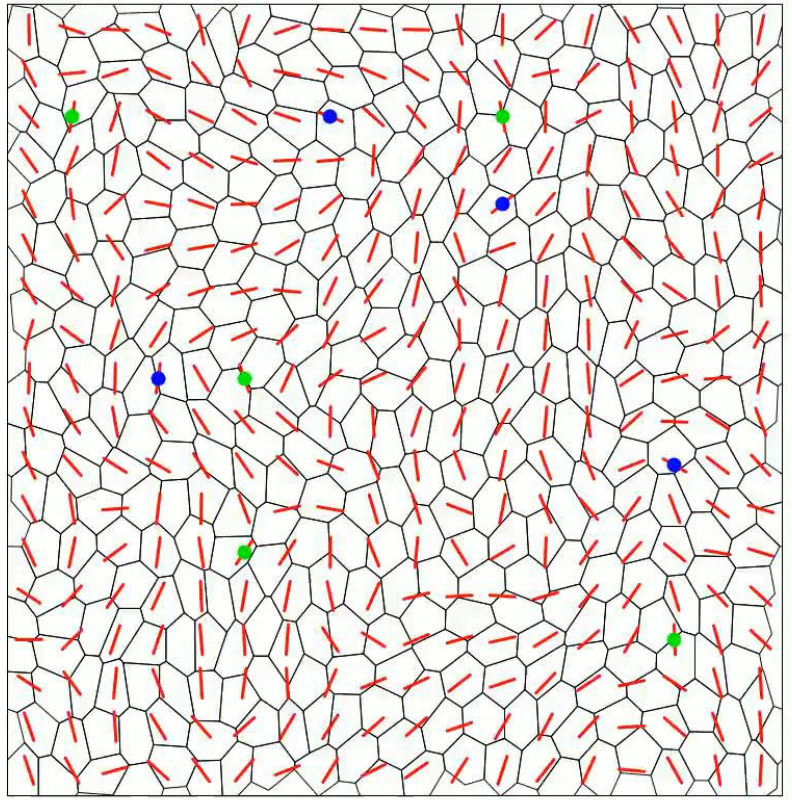


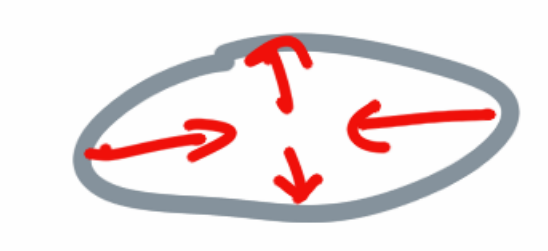
Winding by 180° : +1/2 defect



+1/2 defect

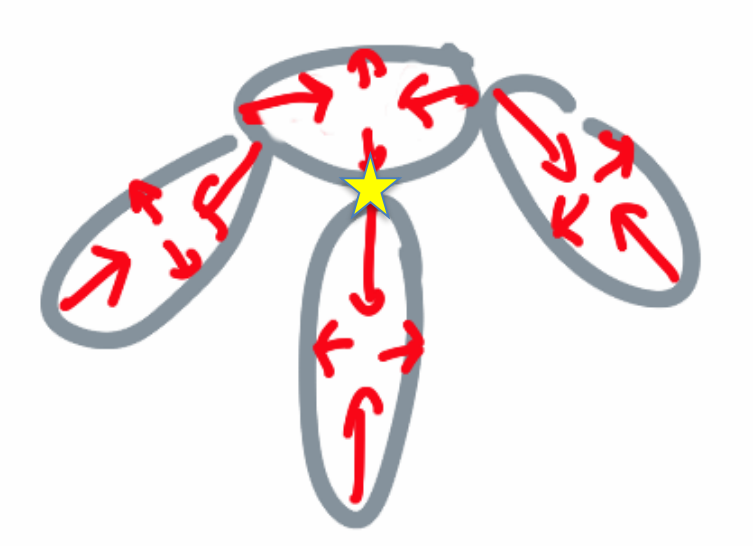
- 1/2 defect

Cellular contractile stresses → contractile nematics



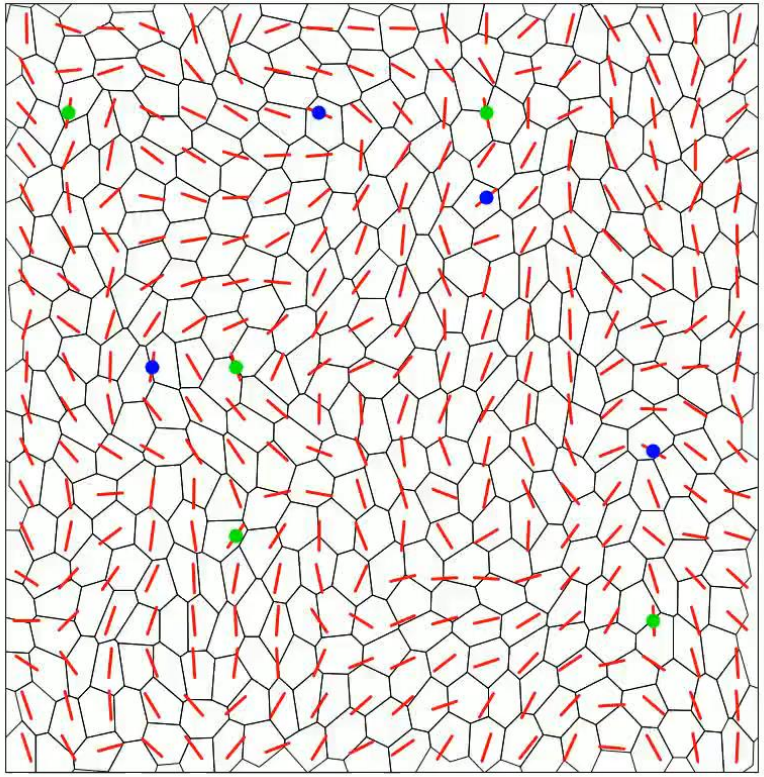
Cell is contractile

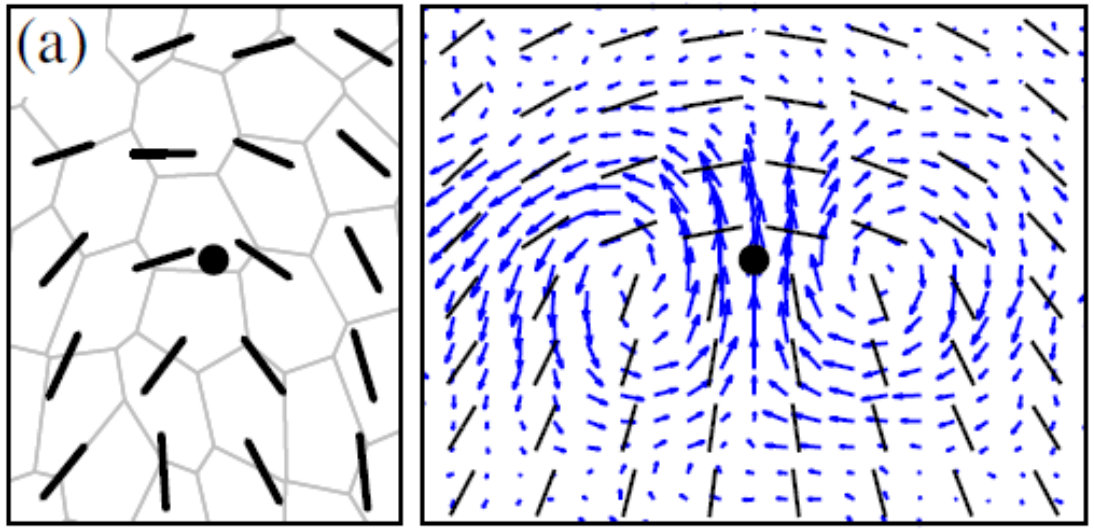
For the real experiment, see Balasubramaniam, L., Doostmohammadi, A., Saw, T.B. *et al.* Investigating the nature of active forces in tissues reveals how contractile cells can form extensile monolayers. *Nat. Mater.* **20**, 1156–1166 (2021).



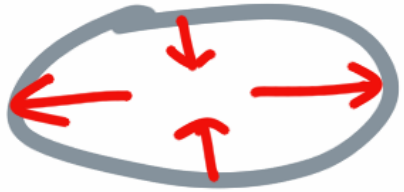
Expects +1/2 defect to move down

Problem: +1/2 moves in opposite direction as expected





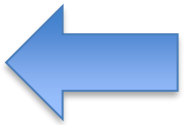
Expt: +1/2 defects behave as if the cells are extensile:



Q: Why the contractile (cellular level) → extensile (tissue level) transition?

Resolution: cell-substrate interactions

Cell tissues can crawl on a substrate



For the real experiments, see, e.g., Petitjean, L. et al. Velocity Fields in a Collectively Migrating Epithelium Biophysical Journal, Volume 98, Issue 9, 1790 - 1800

Resolution: cell-substrate interactions

Cell tissues can crawl on a substrate

↓

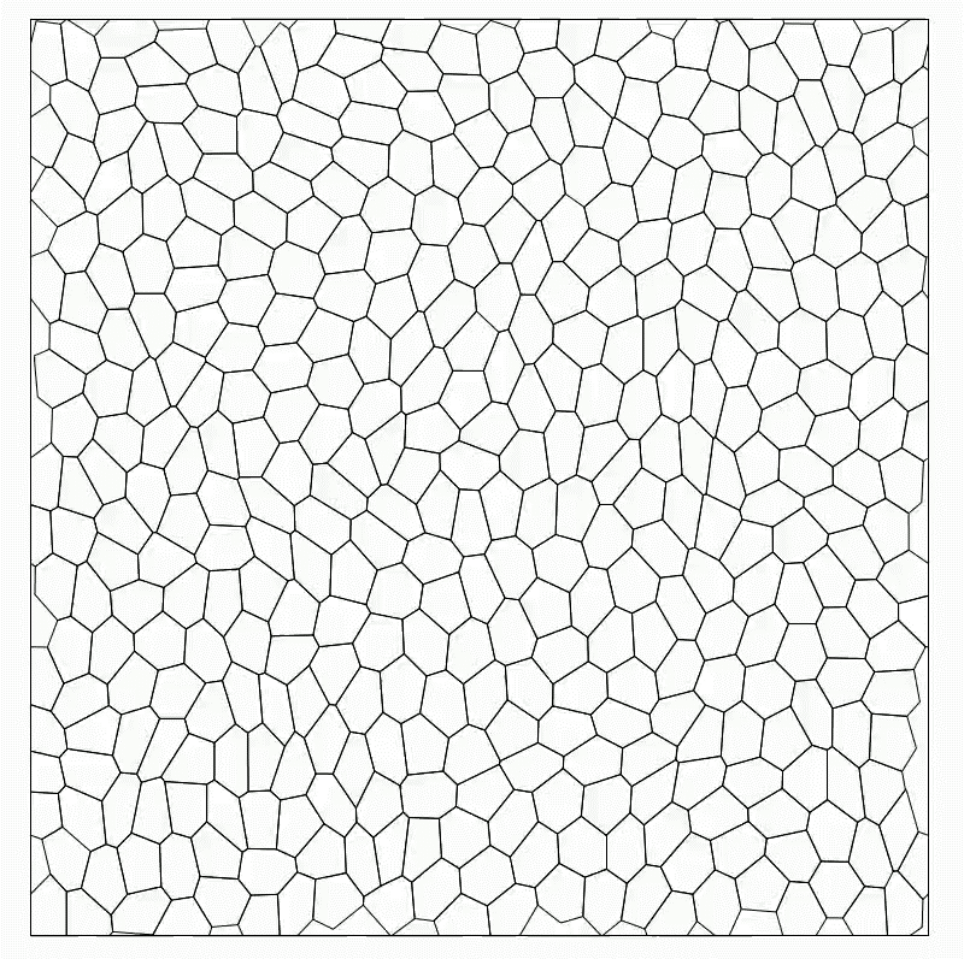
Polar (directional) fluctuations at cellular level

↓

Generic extensile nematic behaviour at tissue level,
even for contractile cells

[Killeen, Bertrand & Lee (2022) Phys Rev Lett;
See also Vafa, Bowick, Shraiman & Marchetti (2021) Soft Matt for a related perspective]

2. Universality of the tissue model



Q: Given how complicated biological systems are (e.g., cell tissues), how is meaningful modelling ever possible?

A: Even if the microscopic dynamics is complicated, the underlying symmetry & conservation law may be simple

→ universal hydrodynamic equations of motion

Example: Navier-Stokes eqns for thermal fluids

- Incompressible limit for simplicity
- Hydrodynamic variable: velocity $\vec{v}$
- Equation of motion (EOM):

$$\partial_t \vec{v} = \rho^{-1} \vec{F} \text{ , with constraint } \nabla \cdot \vec{v} = 0$$

- What is the force field $\vec{F}$?

Symmetries

EOM: $\partial_t \vec{v} = \rho^{-1}\vec{F}$

- Temporal invariance: **F** does not depend on time
- Translational invariance: **F** does not depend on position **r**
- Rotational invariance: **F** does not depend on a particular direction
- Chiral (parity) invariance: **F** is not right-handed or left-handed
- Galilean invariance: EOM invariant under a boost

- To order $O(v^2, \partial^2)$ [hydrodynamics], incompressible NS EOM:

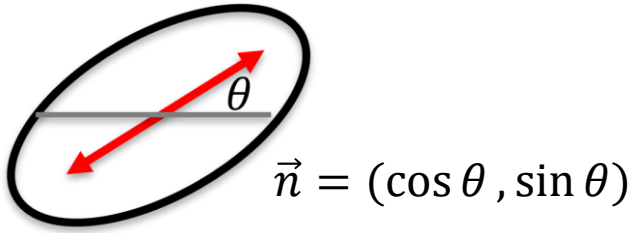
$$\partial_t v_i + v_j \partial_j v_i = \nu \nabla^2 v_i + \rho^{-1} \partial_i p$$

Lagrange multiplier to enforce the incomp. condition

Modelling confluent tissues

- Hydrodynamic variables
  - velocity $\vec{v}$ + nematic field $Q = S(2\vec{n} \otimes \vec{n} - \mathrm{I})$
  - Q is a symmetric, traceless, 2×2 matrix

S: strength of nematic alignment



- Equations of motion (EOM):

$$\partial_t \vec{v} = A, \text{ with constraint } \nabla \cdot \vec{v} = 0$$

$$\partial_t Q = B, \text{ such that } B \text{ is symmetric \& traceless}$$

Symmetries & constraints → universal EOM

- Same symmetries as in Navier-Stokes, except no Galilean invariance

- For small $\vec{v}, Q$, linear theory suffices:

$$0 = \mu\nabla^2\mathbf{v} - \nabla P + \alpha\nabla\cdot\mathbf{Q} - \Gamma\mathbf{v} + \boldsymbol{\xi}$$
$$0 = \lambda\left[\boldsymbol{\nabla}\mathbf{v} + (\boldsymbol{\nabla}\mathbf{v})^{\mathsf{T}}\right] + D\nabla^2\mathbf{Q} - \eta\mathbf{Q} + \boldsymbol{\Omega}$$

Cell stresses on substrate → Polar fluctuations:

$$\langle\xi_i(t,\mathbf{r})\rangle = 0,$$
$$\langle\xi_i(t,\mathbf{r})\xi_j(t',\mathbf{r}')\rangle = 2\Delta\delta_{ij}\delta(t-t')\delta^2(\mathbf{r}-\mathbf{r}').$$

Cell-cell interactions → Nematic fluctuations:

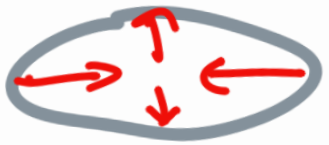
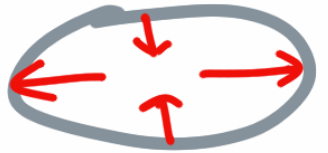
$$\langle\Omega_{ij}(t,\mathbf{r})\Omega_{kl}(t,\mathbf{r}')\rangle = 2\Delta_Q\delta(t-t')\delta^2(\mathbf{r}-\mathbf{r}')\epsilon_{ijkl}$$
$$\epsilon_{ijkl} = \frac{1}{2}\left(\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk} - \delta_{ij}\delta_{kl}\right)$$

Generic linear theory

$$0 = \mu\nabla^2\mathbf{v} - \nabla P + \alpha\nabla\cdot\mathbf{Q} - \Gamma\mathbf{v} + \boldsymbol{\xi}$$
$$0 = \lambda\left[\boldsymbol{\nabla}\mathbf{v} + (\boldsymbol{\nabla}\mathbf{v})^{\mathsf{T}}\right] + D\nabla^2\mathbf{Q} - \eta\mathbf{Q} + \boldsymbol{\Omega}$$

While we don't know what the parameters are, we expect:

- For stability reason: $\mu, \Gamma, D, \eta > 0$
- $\lambda > 0$ because, e.g., $\partial_x v_x > 0$ should lead to an increasing Q_{xx}
- Finally, what is α?
  - Remember NS, $\partial_t \vec{v} =$ … $+ \nabla\cdot\sigma + \cdots$, where σ is the stress tensor. Hence $\sigma \sim \alpha Q$
  - Consider  where $Q = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}$

→ the system is contractile when α>0  ; extensile when α<0 

Therefore, for MDCK cells, we expect that $\alpha > 0$

So, why do we see extensile behaviour at the tissue level?

$$0 = \mu\nabla^2\mathbf{v} - \nabla P + \alpha\nabla\cdot\mathbf{Q} - \Gamma\mathbf{v} + \boldsymbol{\xi}$$
$$0 = \lambda\left[\boldsymbol{\nabla}\mathbf{v} + (\boldsymbol{\nabla}\mathbf{v})^{\mathsf{T}}\right] + D\nabla^2\mathbf{Q} - \eta\mathbf{Q} + \boldsymbol{\Omega}$$

Ans: the effective α is 'renormalised' by other parameters in the system.

Specifically, if we focus only on how the defects move by ignoring other dynamical features, we are effectively assuming that

$$\Gamma\vec{v} \approx \alpha_{\text{eff}}\nabla\cdot Q$$

Since $\alpha_{\text{eff}} \propto \langle\vec{v}\cdot(\nabla\cdot Q)\rangle$, we can calculate the sign of α_{eff} :

$$\langle\mathbf{v}\cdot(\boldsymbol{\nabla}\cdot\mathbf{Q})\rangle = \int \frac{d^2\mathbf{k}}{(2\pi)^2(Dk^2+\eta)}\left\{-2\lambda\Delta k^2 G(k)^2 + \alpha\Delta_Q k^2\left[\frac{G(k)}{Dk^2+\eta} - \frac{\alpha\lambda k^2 G(k)^2}{(Dk^2+\eta)^2}\right]\right\}$$

where $\quad G(k) = \{\mu k^2 + \Gamma + [\lambda\alpha k^2/(Dk^2+\eta)]\}^{-1}$

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Cell-substrate noise strength

Cell contractility noise strength

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Always –

Always +

where $\quad G(k) = \{\mu k^2 + \Gamma + [\lambda\alpha k^2/(Dk^2+\eta)]\}^{-1}$

Compressible tissues

- Hydrodynamic variables
  - Density ρ + velocity $\vec{v}$ + nematic field Q

- Equations of motion (EOM) from symmetry consideration

$$\partial_t \rho = -\rho_0 (\boldsymbol{\nabla} \cdot \mathbf{v})$$
$$\partial_t \mathbf{v} = \mu_1 \nabla^2 \mathbf{v} + \mu_2 \boldsymbol{\nabla} (\boldsymbol{\nabla} \cdot \mathbf{v}) - c^2 \boldsymbol{\nabla} \rho - \Gamma \mathbf{v} + \boldsymbol{\xi}$$
$$\partial_t \mathbf{Q} = \lambda (\boldsymbol{\nabla} \mathbf{v} + \boldsymbol{\nabla} \mathbf{v}^T) + D \nabla^2 \mathbf{Q} - \eta \mathbf{Q} \ ,$$

- Same analysis → same conclusion

Tissues as active solids

- Hydrodynamic variables
  - Displacement field $\vec{u}$ + nematic field Q

- Equations of motion (EOM) from symmetry consideration

$$\Gamma \mathbf{v} = A\nabla^2 \mathbf{u} + B\nabla(\nabla \cdot \mathbf{u}) + \boldsymbol{\xi}$$

$$\eta \mathbf{Q} = C\left[\boldsymbol{\nabla}\mathbf{u} + (\boldsymbol{\nabla}\mathbf{u})^{\mathsf{T}}\right] + \lambda\left[\boldsymbol{\nabla}\mathbf{v} + (\boldsymbol{\nabla}\mathbf{v})^{\mathsf{T}}\right] + D\nabla^2 \mathbf{Q}$$

- Same analysis → same conclusion

Summary

Q: How come contractile cells can exhibit extensile active nematic behaviour at the tissue level?

A: Extensile dynamics comes from cell-substrate fluctuations

Demonstration using universal linear theory for confluent tissues

Similar conclusion applies for

- Compressible confluent tissues
- Confluent tissues in the solid state

Ref: Killeen, Bertrand & Lee (2022) Polar Fluctuations Lead to Extensile Nematic Behavior in Confluent Tissues Phys Rev Lett 128, 078001

A broader perspective

1. Identify variables (fields) of interest
2. Symmetry consideration → universal model equations
3. Hydrodynamics → dramatic reduction in model parameters
   → tractable model
4. Biophysical inputs → meaningful conclusions