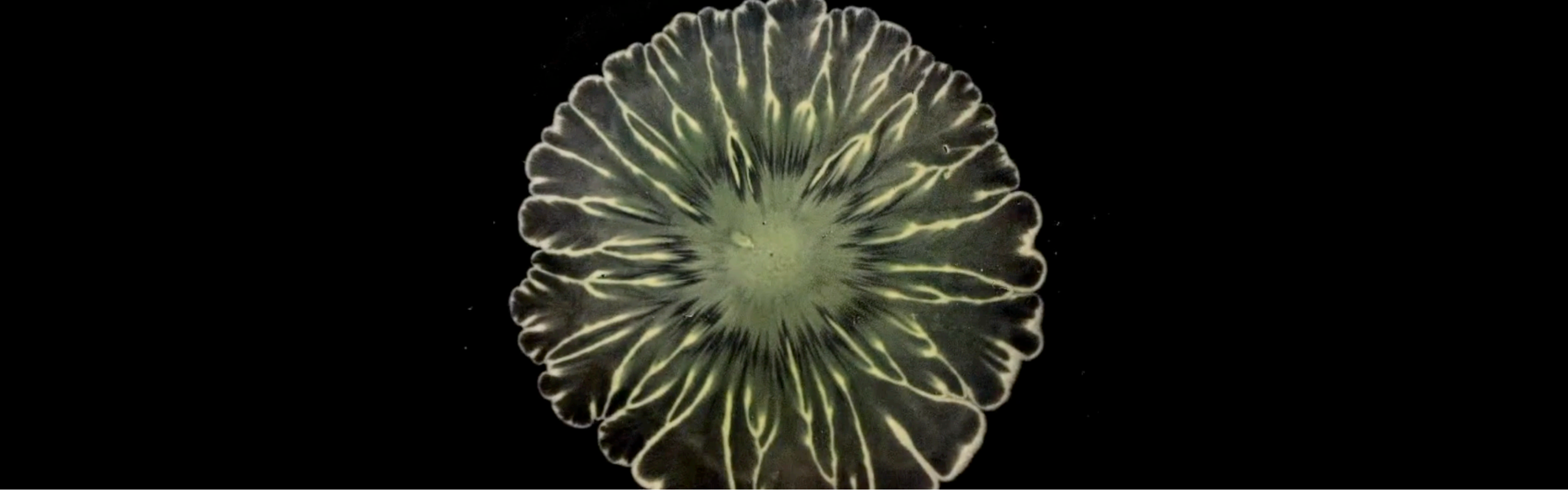


CROWDS IN MOTION:
HERDING, FLOCKING,
SWARMING

SOFT MACHINES:
COLLECTIVE MOTION AT THE MICRO-SCALE

Behaviour, Evolution & Emergence (BEE) 2026

Shakti N. Menon
IMSc Chennai

Video: BioCircuits Institute/UC San Diego https://www.youtube.com/watch?v=MUl1R_tho5g

“At the still point of the turning world. Neither flesh nor fleshless;

Neither from nor towards; at the still point, there the dance is”

— T. S. Eliot, *Four Quartets 1: Burnt Norton* (1936)

“It takes a motion to notion and it takes a notion to motion.”

— Sun Ra (1972)

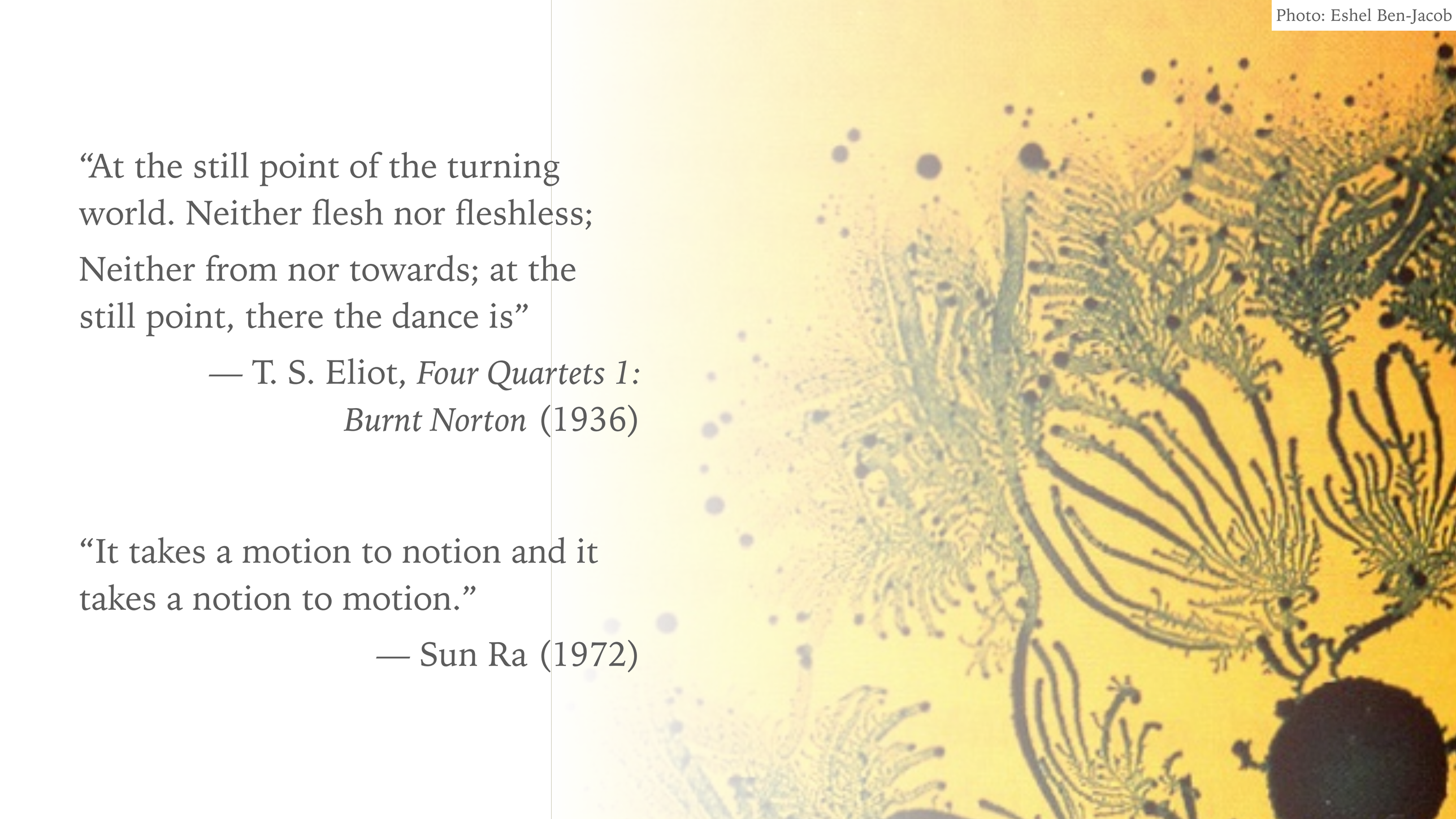
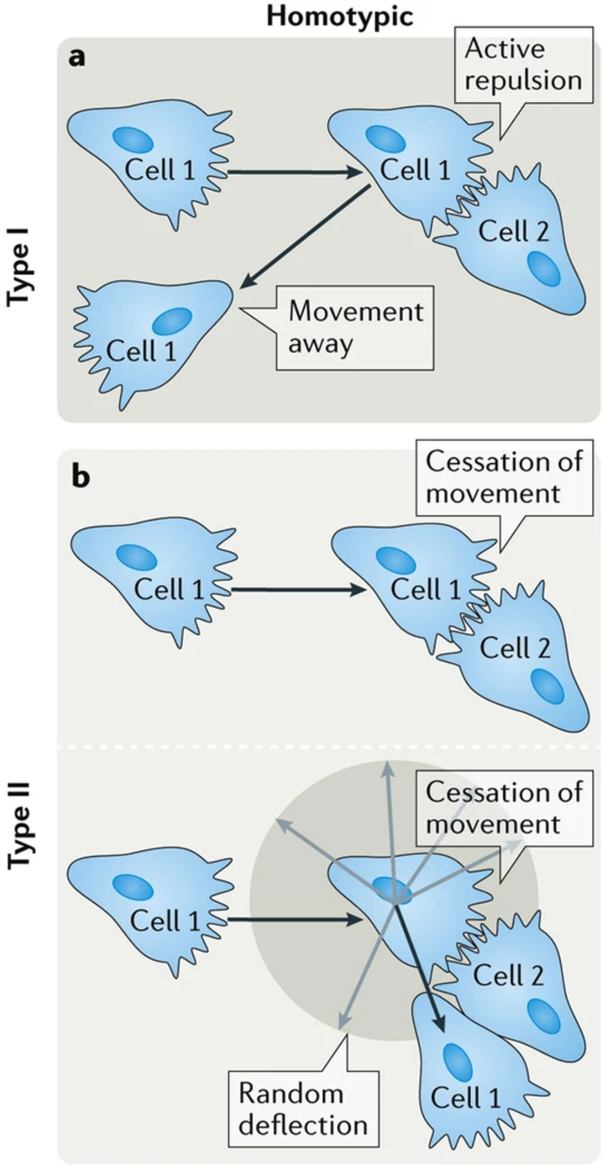
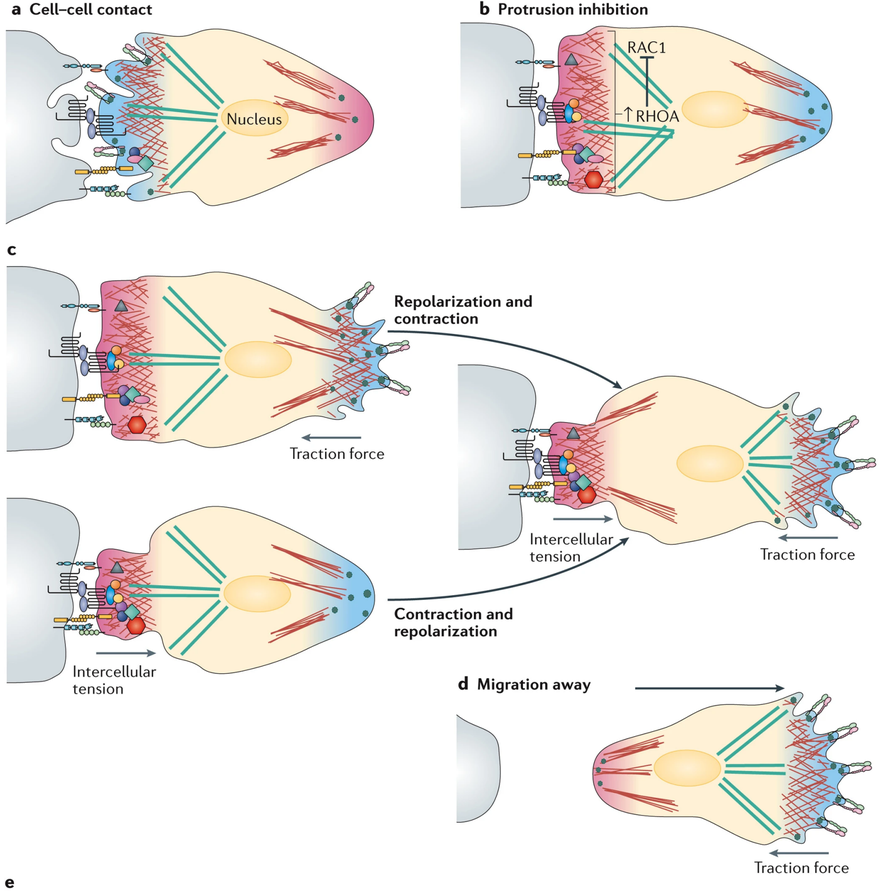


Photo: Eshel Ben-Jacob

CELLS AS ACTIVE PARTICLES

- Migratory cells (fibroblasts, keratinocytes, etc) move through a sequence of protrusion, adhesion and contraction.
- They are “polarized” and have a preferred direction of motion.
- Upon colliding with other cells a cell-cell contact (via cadherins and other receptors) is generated.
- This leads to a “repolarization” of the cell due to reorientation of its microtubules. Consequently they migrate away from the cell they were in contact with.
- This process, known as “contact inhibition of locomotion” (CIL), has been implicated in many vital physiological processes.
- Thus the active matter framework is well suited to describe such behaviour.





e

Component	Cell type
Cell–cell adhesion	
Cadherin	Neural crest cells[27,30,31], fibroblasts[33,35], epithelial cells[32,35] and myoblasts[34]
Additional, undefined adhesion complexes	*Drosophila melanogaster* macrophages[26] and fibroblasts[28,29]
Adhesion regulator	
α-Catenin and β-catenin	Epithelial cells[32], fibroblasts[36] and neural crest cells[27]
p120	Neural crest[27] and pancreatic carcinoma cells[38]
Cell–matrix adhesion	
Integrin	*D. melanogaster* macrophages[61] and myoblasts[34]
Focal adhesion remodelling	Neural crest cells[27,63]
Cytoskeletal components and their regulators	
Actomyosin contraction	Fibroblasts[54] and *D. melanogaster* macrophages[26]
Microtubule remodelling	Neural crest cells[48], *D. melanogaster* macrophages[26,59,93] and fibroblasts[60]
Diaphanous	*D. melanogaster* macrophages[26]
Clasp	*D. melanogaster* macrophages[93]

Component	Cell type
Signalling receptors	
Eph–ephrin	Prostate cancer cells[41,42] and Cajal–Retzius cells[40]
Slit–Robo	Fibroblasts[50]
Frizzled–WNT11	Neural crest cells[25]
Polarity modulators	
PAR3	Neural crest cells[48]
DSH	Neural crest cells[25]
PCK	Neural crest cells[25]
STBM	Neural crest cells[25]
Small GTPases and their regulators	
RAC1, CDC42	Fibroblasts[51] and prostate cancer cells[41]
RHOA and ROCK	Prostate cancer cells[42], fibroblasts[51,54] and neural crest cells[25]
TRIO	Neural crest cells[48]
SRGAP2	Fibroblasts[50]
VAV2	Prostate cancer cells[42]
NM23-H1	Glia[53]

Nature Reviews | Molecular Cell Biology

images: B. Stramer & R. Mayor, Nat. Rev. Mol. Cell Biol., **18**(1), 43-55 (2017).

B Szabó et al, Phys Rev E, **74**(6), 061908 (2006).

PHASE TRANSITION IN THE COLLECTIVE MIGRATION OF TISSUE CELLS

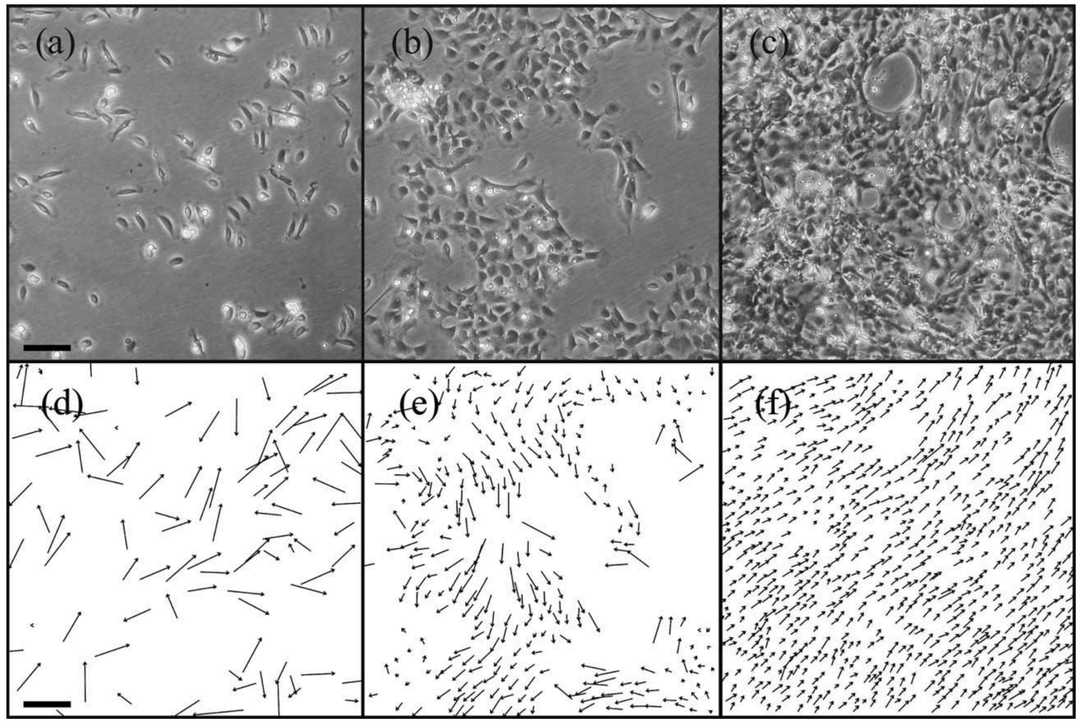
- Keratinocytes are found in epithelial tissue and play a significant role in wound closure.
- As the density of cells is increased one sees a sharp transition from disordered to ordered motion.
- To model this, Szabó et al (2006) described the cell velocity as:

$$\mathbf{v}_i(t) = \frac{d\mathbf{r}_i(t)}{dt} = v_0 \mathbf{n}_i(t) + \mu \sum_{j=1}^{N} \mathbf{F}(\mathbf{r}_i, \mathbf{r}_j)$$

where the direction of the self propelling velocity, described by the angle $\theta_i^{\mathbf{n}}(t)$, attempts to relax to $\mathbf{v}_i(t)$ with a relaxation timescale τ:

$$\frac{d\theta_i^{\mathbf{n}}}{dt} = \frac{\theta_i^{\mathbf{v}} - \theta_i^{\mathbf{n}}}{\tau} + \xi$$

and defining $d_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$, the intercellular forces acting on each cell from its neighbours are given by:

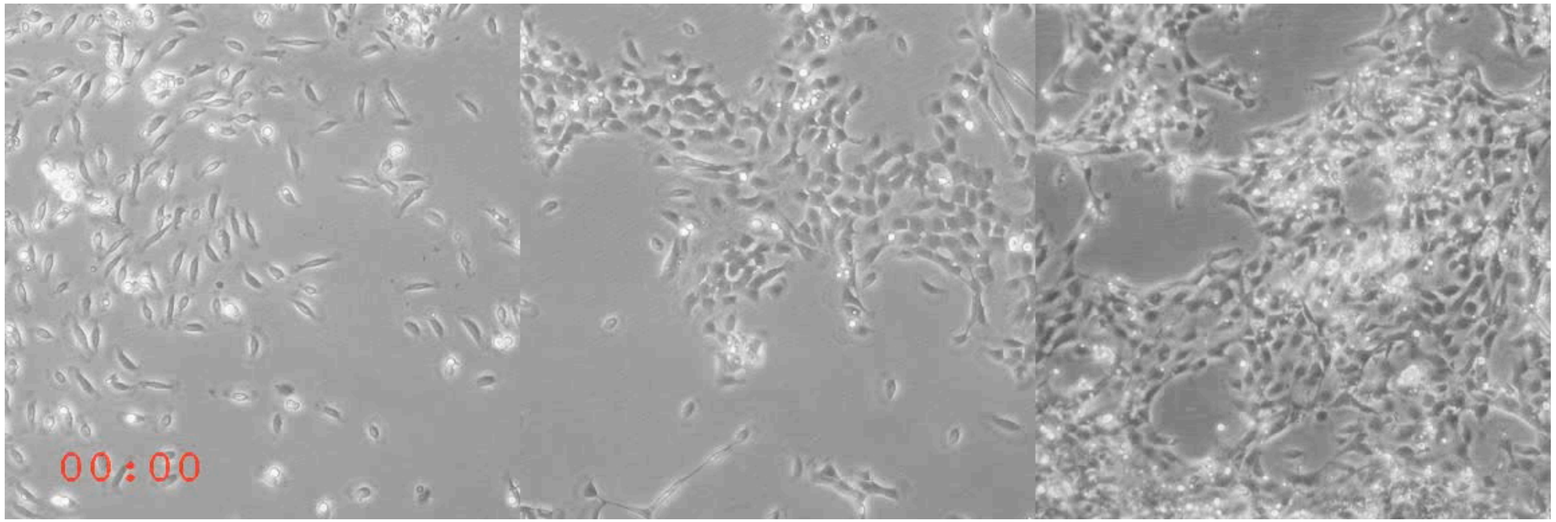


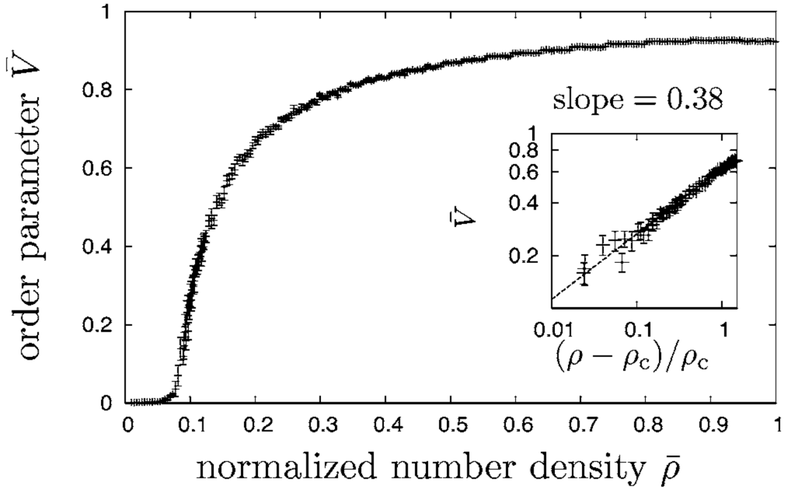
$$\mathbf{F}(\mathbf{r}_i, \mathbf{r}_j) = \frac{\mathbf{r}_j - \mathbf{r}_i}{|\mathbf{r}_i - \mathbf{r}_j|} \begin{cases} F_{rep} \dfrac{d_{ij} - R_{eq}}{R_{eq}}, & \text{if } d_{ij} < R_{eq}, \\ F_{adh} \dfrac{d_{ij} - R_{eq}}{R_0 - R_{eq}}, & \text{if } R_{eq} \le d_{ij} \le R_0, \\ 0, & \text{if } R_0 < d_{ij}, \end{cases}$$

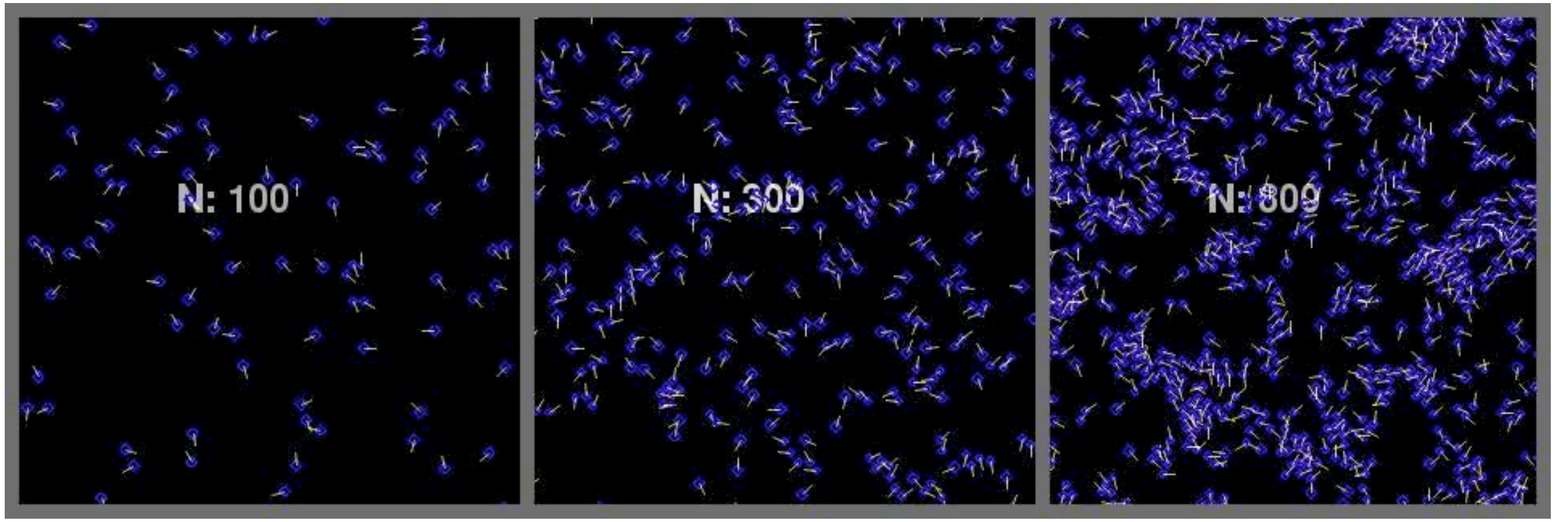
B Szabó et al, Phys Rev E, **74**(6), 061908 (2006).

PHASE TRANSITION IN THE COLLECTIVE MIGRATION OF TISSUE CELLS

- Simulations were consistent with experimental observations and a continuous transition to the ordered phase was observed.



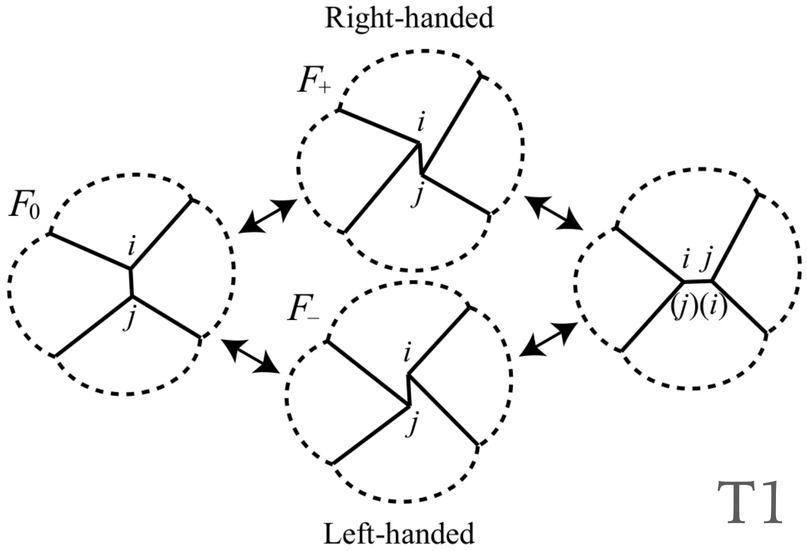




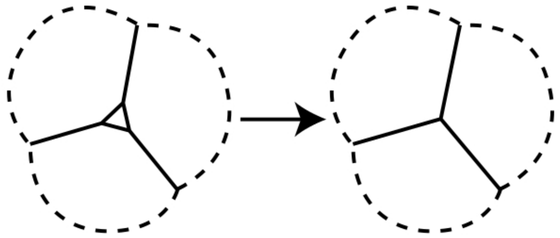
Farhadifar et al., Curr. Biol. **17**, 2095–2104 (2007).

MODELLING CELL MOVEMENT IN CONFLUENT TISSUE

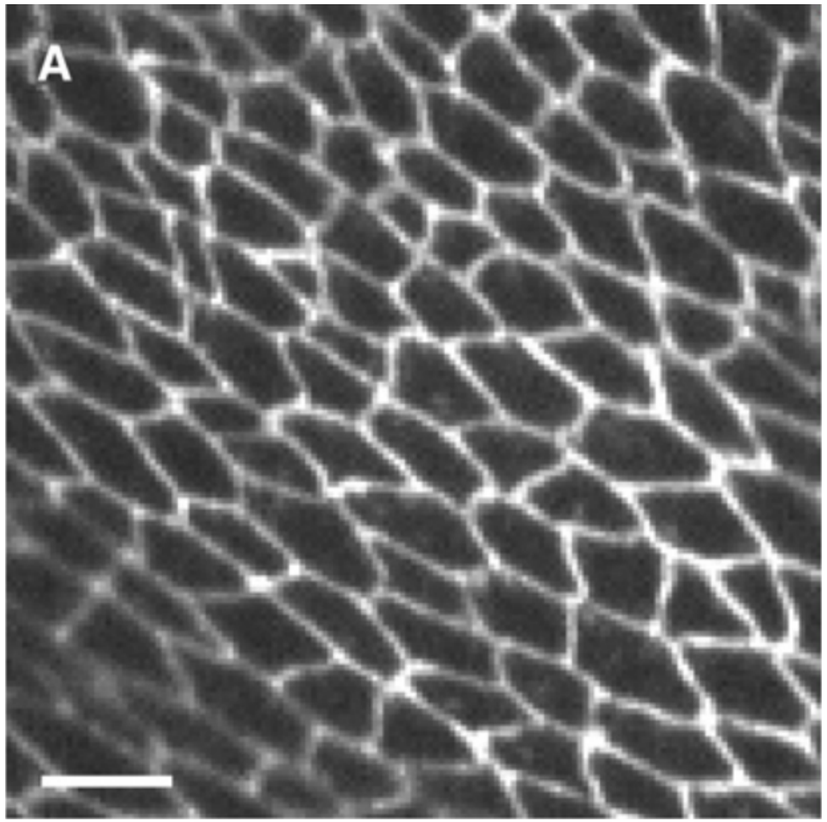
- Confluent tissues are continuous cellular sheets that have no gaps. The significant reduction in cell surface area and increased compression trigger cell cycle arrest.
- Although contact inhibition of proliferation is also triggered, the cells cannot “move away”, so they glide past each other in an attempt to reduce the overall mechanical energy.



T1



T2



epithelial cells from wing
of Drosophila melanogaster

Farhadifar et al., Curr. Biol. **17**, 2095–2104 (2007).

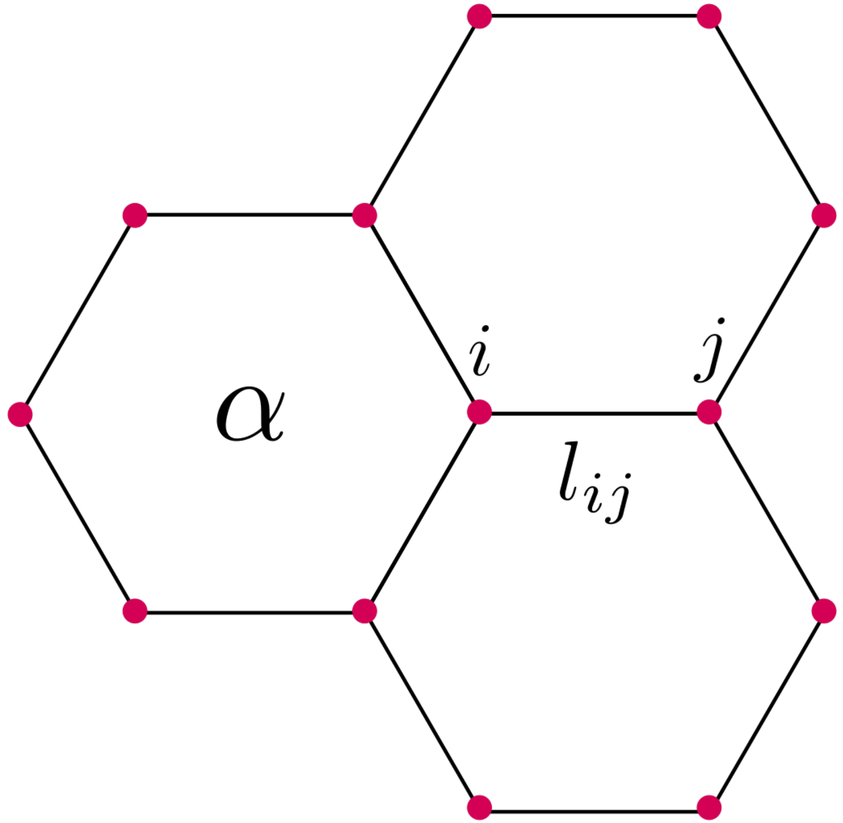
VERTEX MODEL

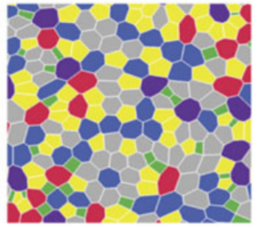
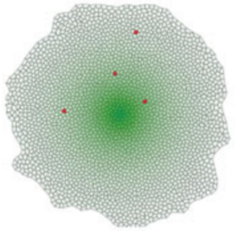
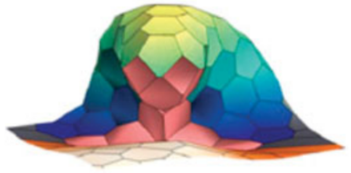
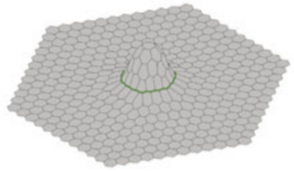
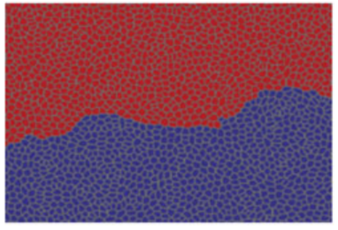
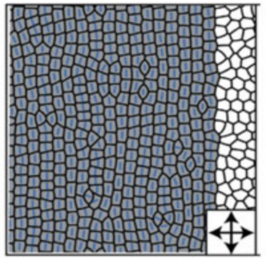
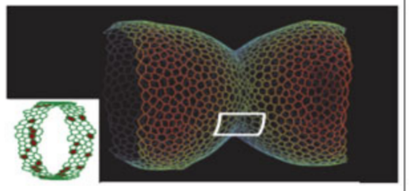
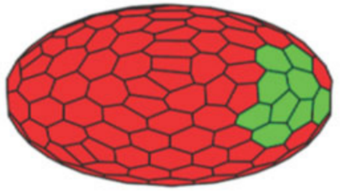
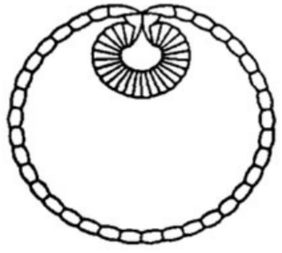
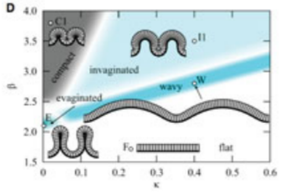
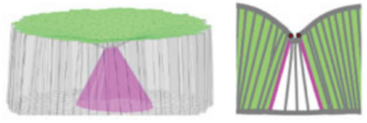
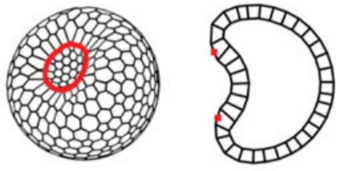
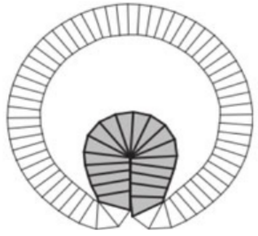
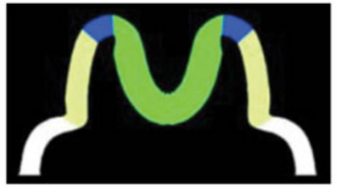
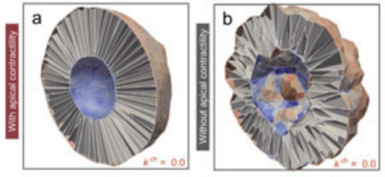
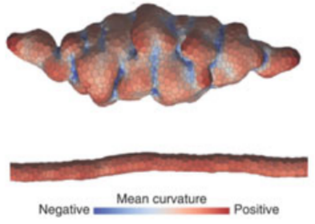
The mechanical state of the lattice can be expressed in terms of the following potential or work function:

$$\mathscr{E} = \underbrace{\sum_{\alpha} \frac{K_\alpha}{2}(A_\alpha - A_\alpha^{(0)})^2}_{\text{elasticity}} + \underbrace{\sum_{<i,j>} \Lambda_{ij} l_{ij}}_{\text{adhesion}} + \underbrace{\sum_{\alpha} \frac{\Gamma_\alpha}{2} L_\alpha^2}_{\text{contraction}}$$

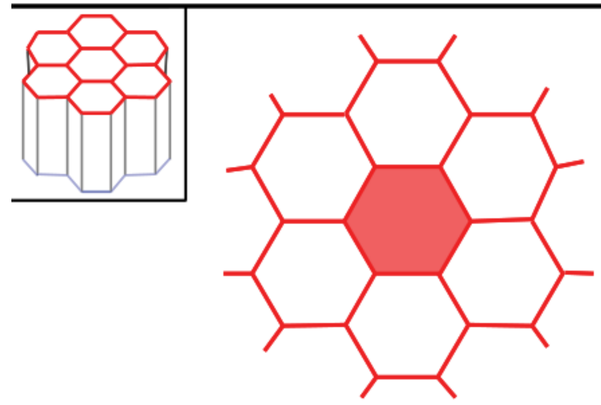
where A_α and L_α are the area and perimeter of cell α, l_{ij} is the length of the bond connecting vertices i and j, $A_\alpha^{(0)}$ is the "preferred" area of cell α, K_α is the area elastic modulus (which relates to cell stiffness), Λ_{ij} is the bond tension and Γ_α is the perimeter elasticity coefficient, which accounts for changes in bond tension due to changes in perimeter.

The bond tension arises from the contractility of the actomyosin ring that underlies the adherens junctional network, as well as the mechanics of cell adhesion.



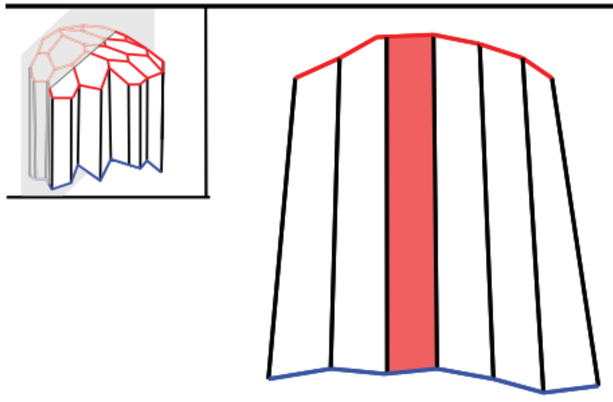
	2D		3D	
apical	(*a*) cell shape distribution 	tissue size control 	(*b*) appendage formation 	epithelial buckling 
	interface morphology 	cell arrangement 	epithelial folding 	cell migration 
lateral	(*c*) neural tube formation 	epithelial folding 	(*d*) cyst formation 	shape changes of spheres 
	gastrulation 	optical cup formation 	surface smoothness 	vesicle growth 

2D apical vertex model



flat apical surface

2D lateral vertex model

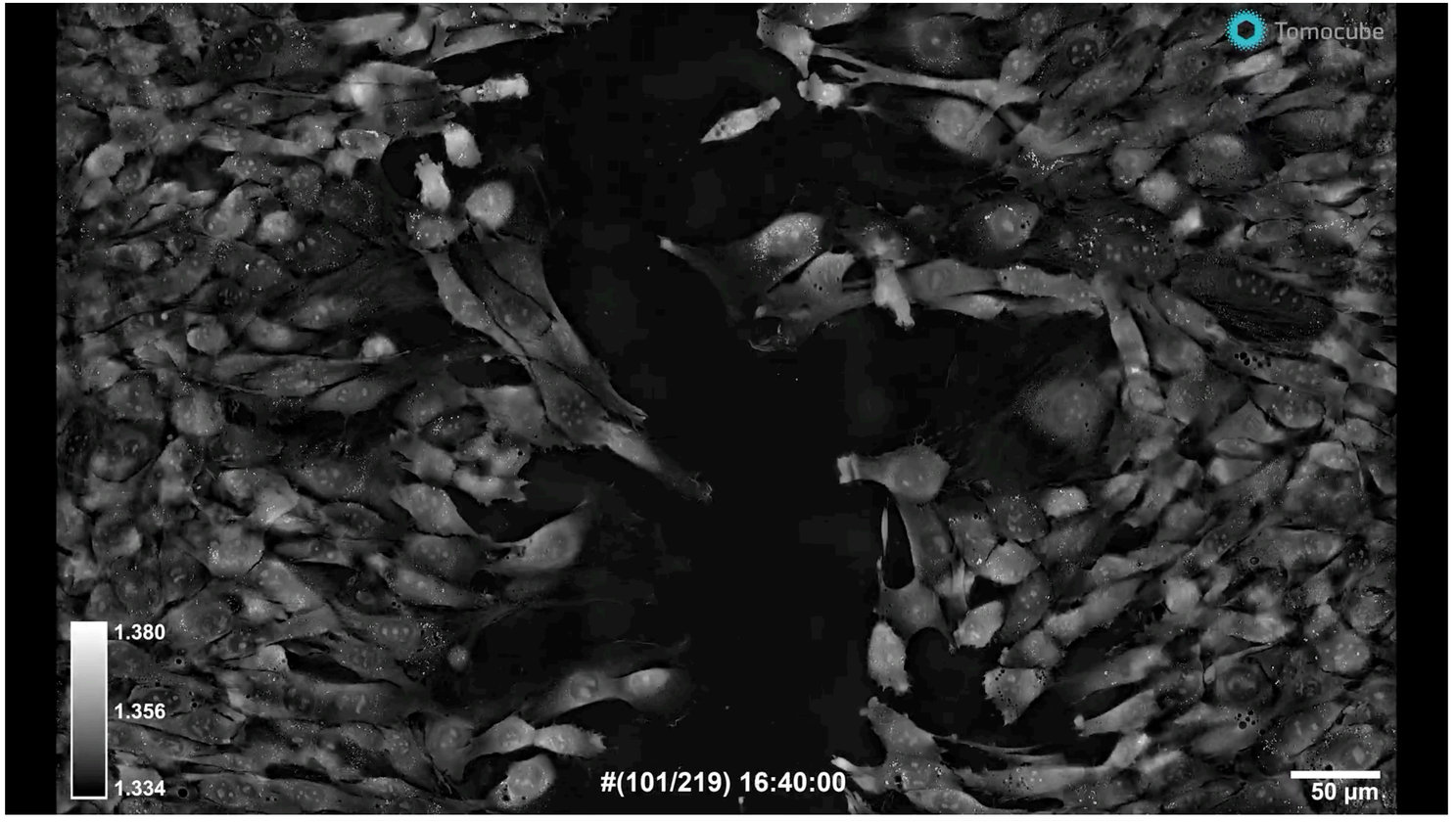


lateral cross section

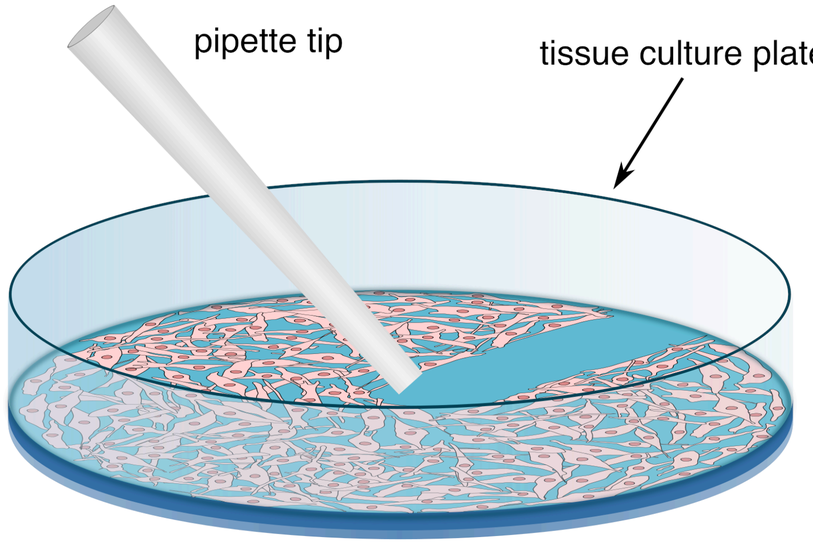
SN Menon & JA Flegg, Adv. Wound Care, **10**(6), 328-344 (2021)

SCRATCH ASSAYS

- Scratch assays are commonly used to study wound healing and other phenomena.
- Cells receive mechanical cues that trigger motility.



video: Tomocube Inc. https://www.youtube.com/watch?v=_yCe76CIDm0



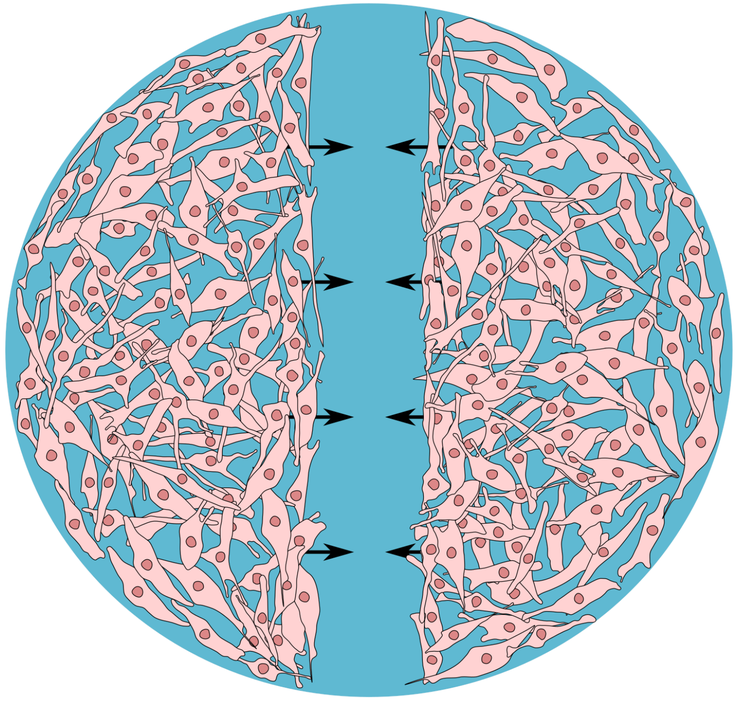
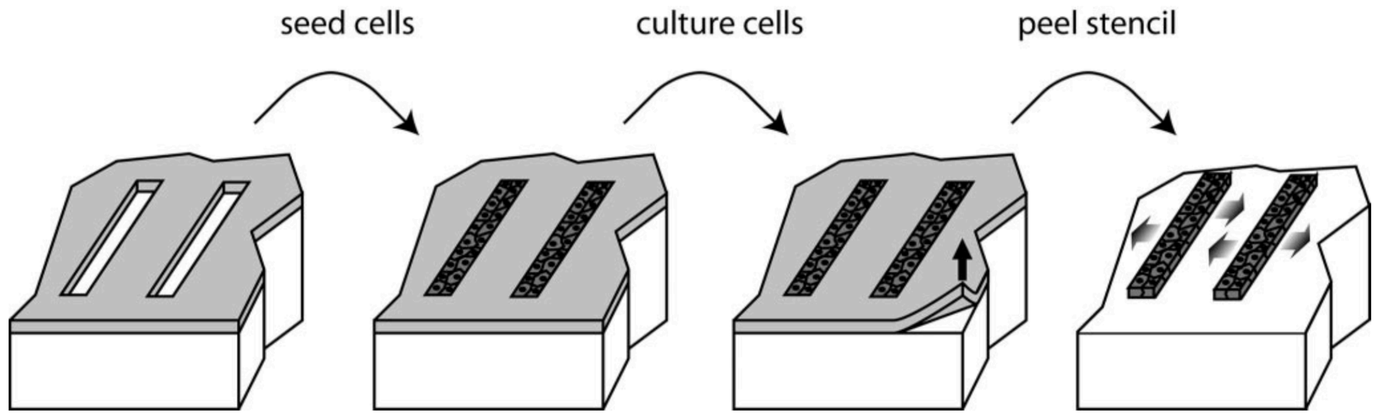


image: M Poujade (2007). Proc Natl Acad Sci USA, **104**(41), 15988-15993.

STENCILED ASSAYS

- One issue with scratch assays is that it is unclear as to what extent the observed behaviors are due result of some cells being injured during scratching.
- For this purpose Poujade et al (2007) developed an alternative assay approach using a microstencil.

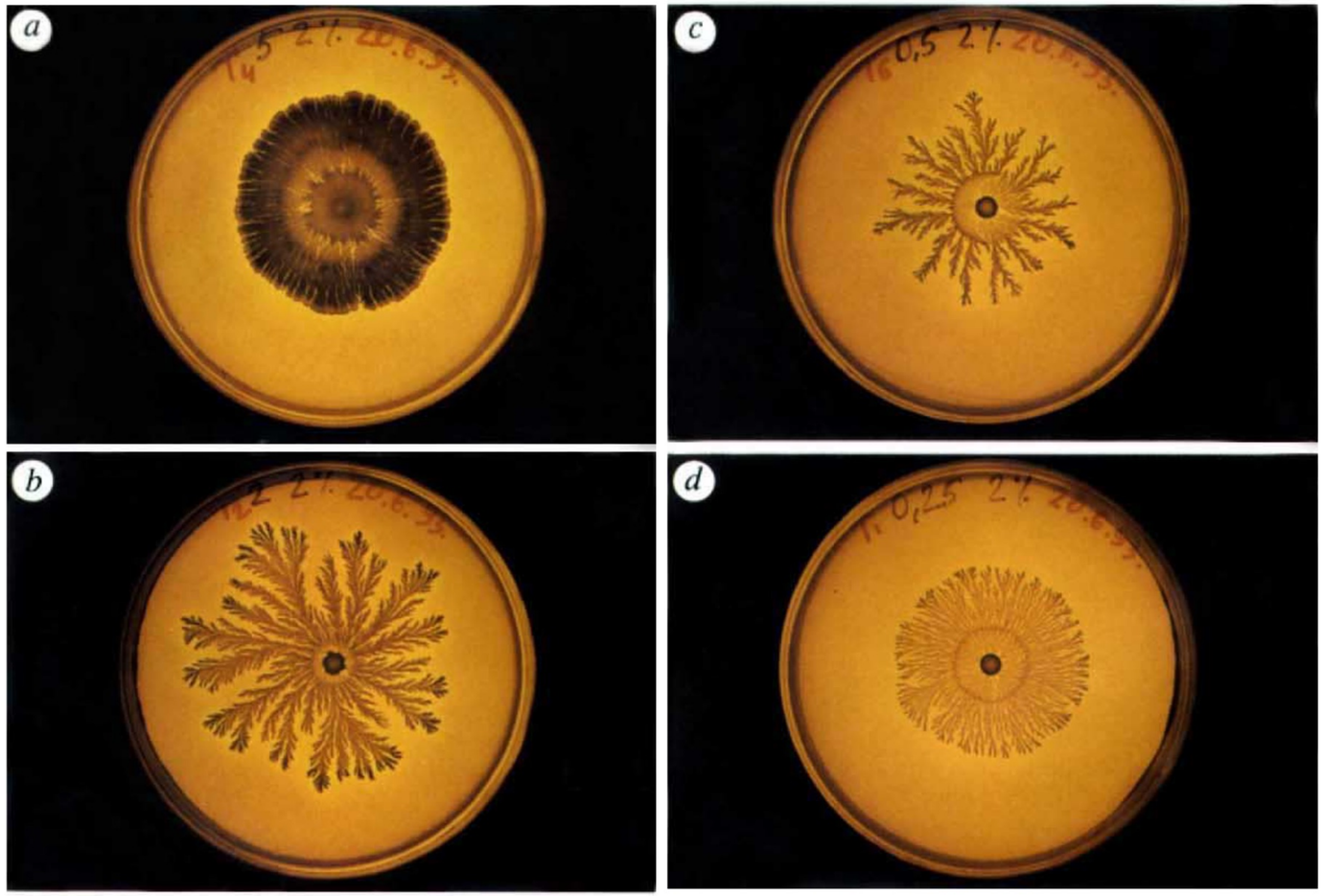


- Experiments with this setup confirmed that a sudden increase in available space is sufficient to trigger collective motility.
- They observed that there were clear leaders/followers, characterized by different morphologies.

Source: Ben-Jacob et al, Nature, **368**, 46-49 (1994)

COOPERATIVE GROWTH PATTERNS IN BACTERIAL COLONIES

- In bacterial colonies, individual bacteria push through agar
- To cope with poor nutrient conditions bacterial colonies can exhibit complex growth patterns that arise from cooperative behaviour.
- Here, bacteria communicate indirectly by means of chemotactic feedback. That is, cells secrete a signalling chemical that other cells respond to.
- Ben-Jacob et al (1994) proposed a model for explaining the dependence of colony morphology on nutrient (peptone) level and agar concentration.

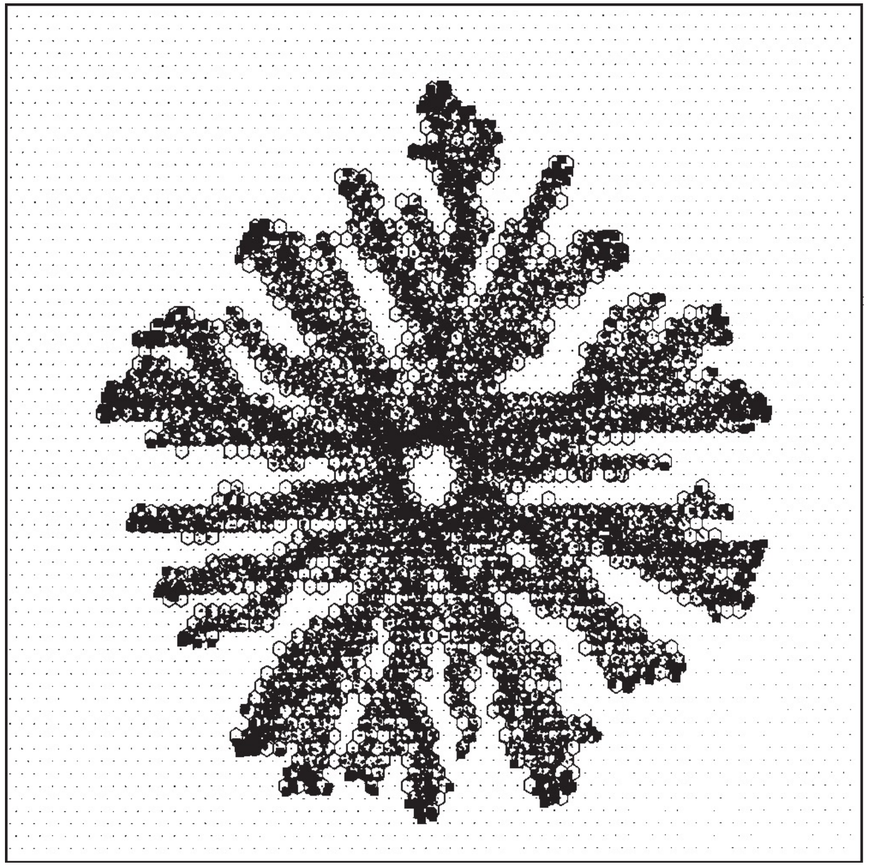


Patterns in *Bacillus subtilis* at different levels of peptones.

Source: Ben-Jacob et al, Nature, **368**, 46-49 (1994)

COOPERATIVE GROWTH PATTERNS IN BACTERIAL COLONIES

- The model consists of N walkers i that move via an off-lattice random walk on a triangular lattice via $\mathbf{r}_i' = \mathbf{r}_i + d(\cos\Theta, \sin\Theta), \Theta \in [0,2\pi]$, where if $\mathbf{r}_i'$ crosses the envelope defined on this lattice, the step is rejected and instead a counter on that line segment is updated. If the counter reaches N_c that segment of the envelope is shifted one lattice step - this represents the "pushing" of the agar.



- The walkers have a finite energy store W_i and lose energy at a fixed rate e as they move. They replenish W_i by consuming the underlying nutrient $c(\mathbf{r}, t)$ at a rate c_r (or, if in a low nutrient environment, the full underlying amount): $\dfrac{dW_i}{dt} = \min(c_r, c(\mathbf{r}, t)) - e$
- If W_i drops to zero, the walker becomes stationary, while if it crosses a threshold t_r the walker reproduces, i.e. divides into two walkers.
- The nutrient is consumed by active walkers, and diffuses at a rate D_c:

$$\frac{\partial c(\mathbf{r}, t)}{\partial t} = D_c \nabla^2 c(\mathbf{r}, t) - \sum_{awlk} \delta(\mathbf{r} - \mathbf{r}_i) \min(c_r c(\mathbf{r}, t))$$

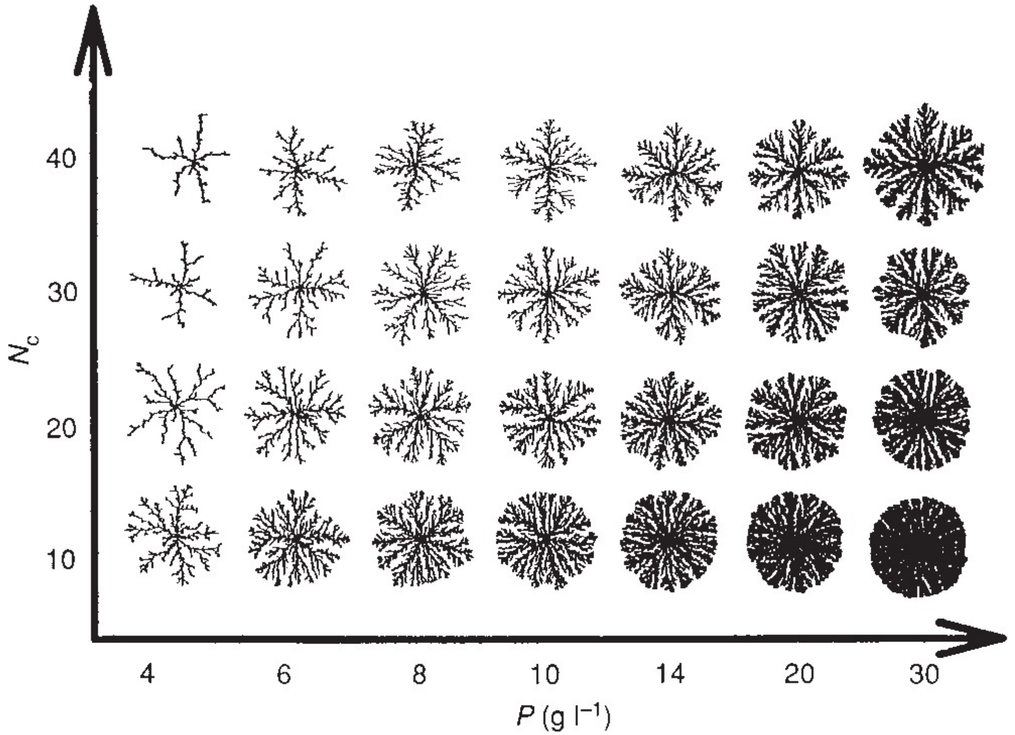
Source: Ben-Jacob et al, Nature, **368**, 46-49 (1994)

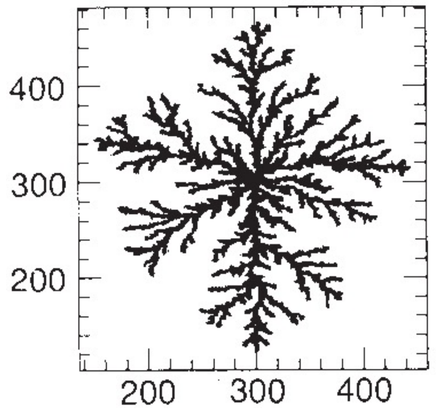
COOPERATIVE GROWTH PATTERNS IN BACTERIAL COLONIES

- Simulations were performed for different initial values of $c(\mathbf{r}, t)$, i.e. the peptone level P and agar concentration N_c. The system size is 600×600 with $\sim 10^4$ walkers (each walker represents 10^5bacteria).
- The patterns are compact/fractal at high/low peptone levels, and are more ramified at higher agar concentrations.
- Chemotactic communication is added to the model by allowing stationary walkers to produce a chemical $s(\mathbf{r}, t)$ at rate s_r (for example as a distress signal). In addition, active walkers consume this chemical at rate c_c. Thus,

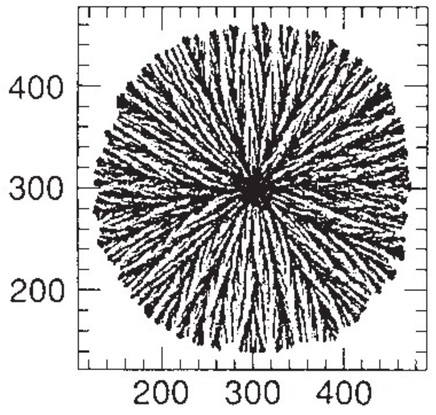
$$\frac{\partial s(\mathbf{r}, t)}{\partial t} = D_s \nabla^2 s(\mathbf{r}, t) + \sum_{swlk} \delta(\mathbf{r} - \mathbf{r}_i) s_r - \sum_{awlk} \delta(\mathbf{r} - \mathbf{r}_i) \min(c_c, s(\mathbf{r}, t))$$

- If one now introduces a bias in active walkers for moving towards higher chemical density, aggregation is enhanced.





without chemotaxis



with chemotaxis

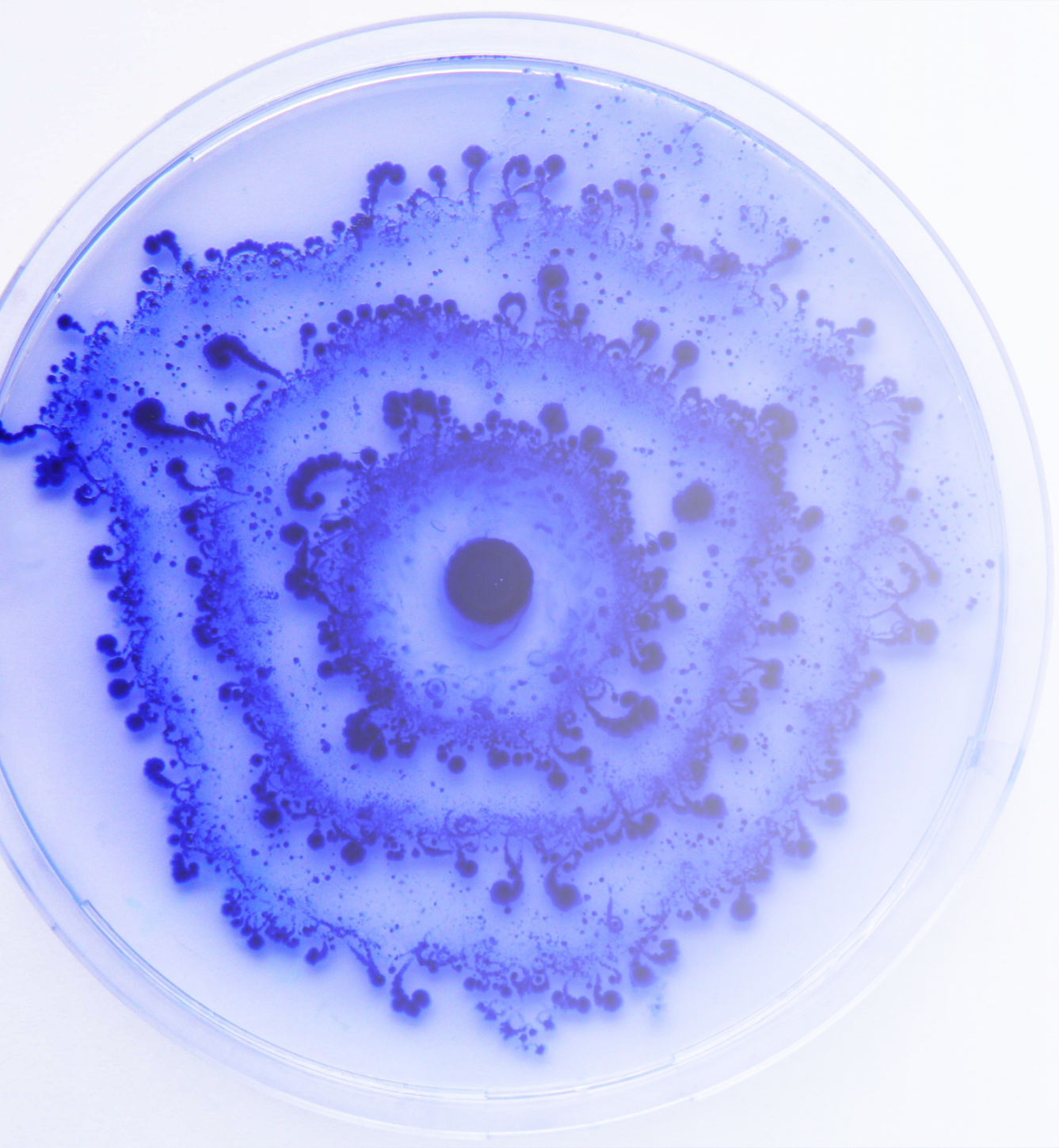


image: G Book et al, PLoS ONE 12(12): e0190037 (2017).

FURTHER READING

Articles/Reviews

- B Szabó et al, *Phase transition in the collective migration of tissue cells: experiment and model*, Phys Rev E, **74**(6), 061908 (2006).
- E. Ben-Jacob et al, *Generic modelling of cooperative growth patterns in bacterial colonies*, Nature **368**, 46–50 (1994).
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- R. Mayor & S. Etienne-Manneville, *The front and rear of collective cell migration*, Nat. Rev. Mol. Cell Biol., **17**(2), 97-109 (2016).

THANK

YOU!

source: https://www.youtube.com/watch?v=CmixnzZdSOk