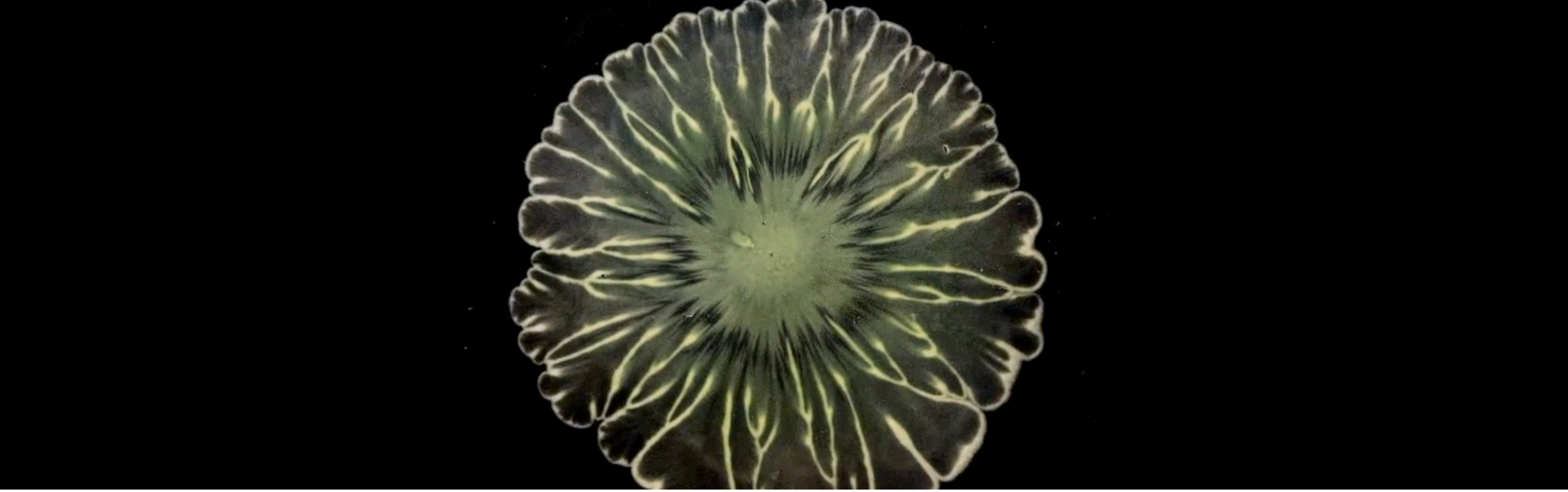


FROM SPINS TO FLOCKS:
AN INTRODUCTION TO DRY ACTIVE MATTER

SOFT MACHINES:
COLLECTIVE MOTION AT THE MICROSCALE

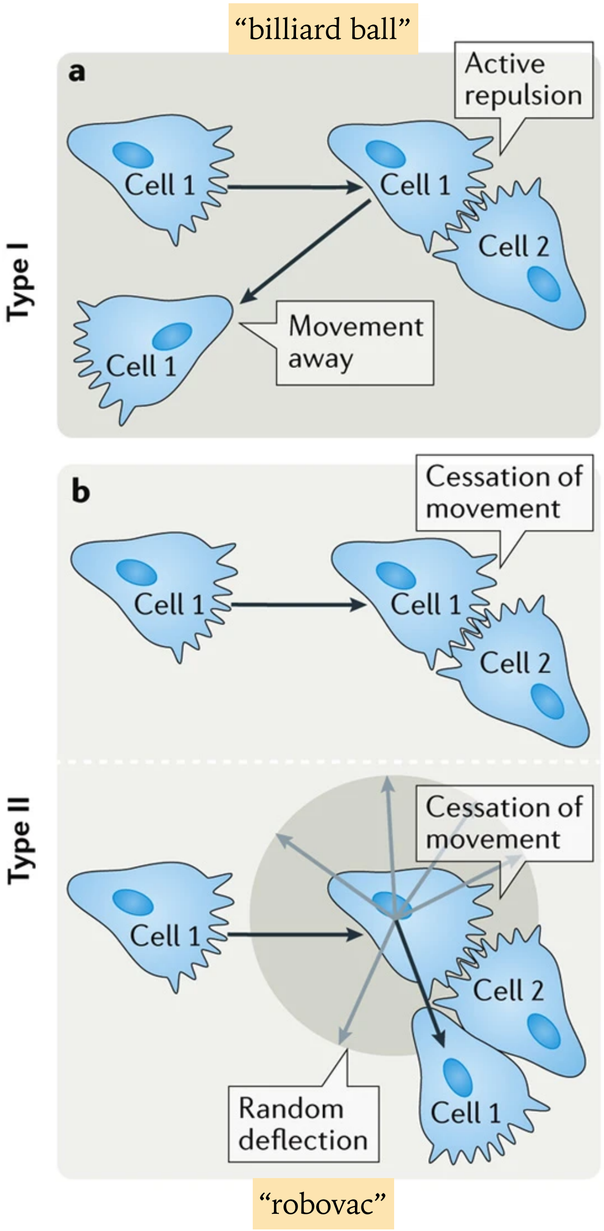
Spins, Games & Networks (SGN) 2026

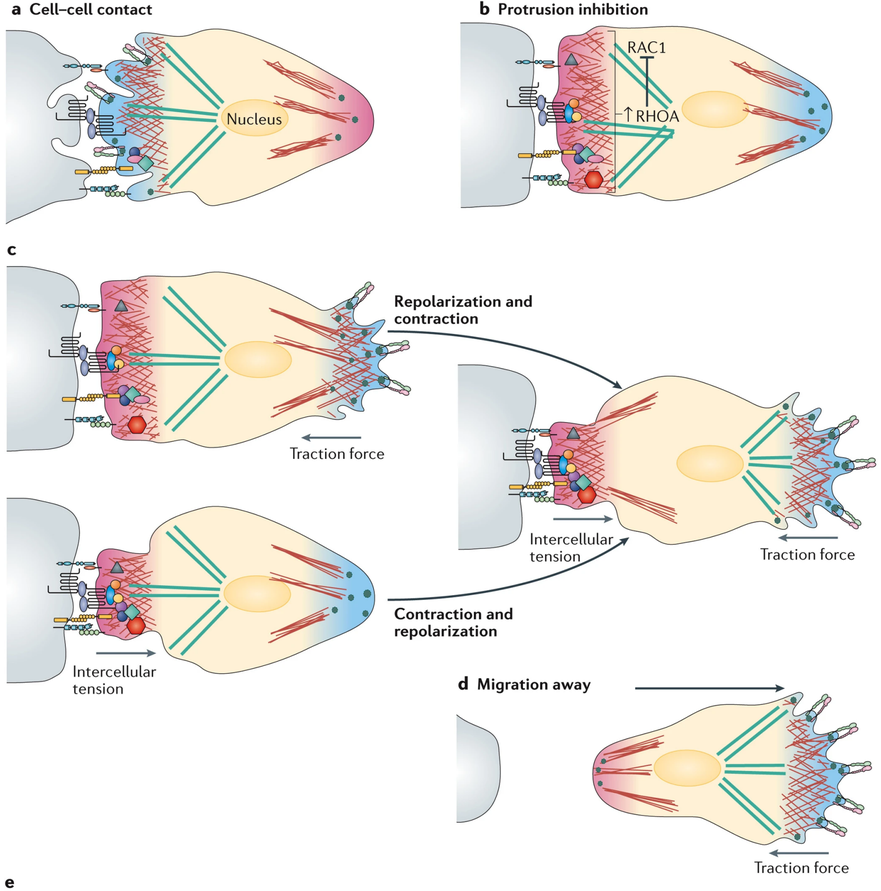
Shakti N. Menon
IMSc Chennai

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

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 or cease moving.
- 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).

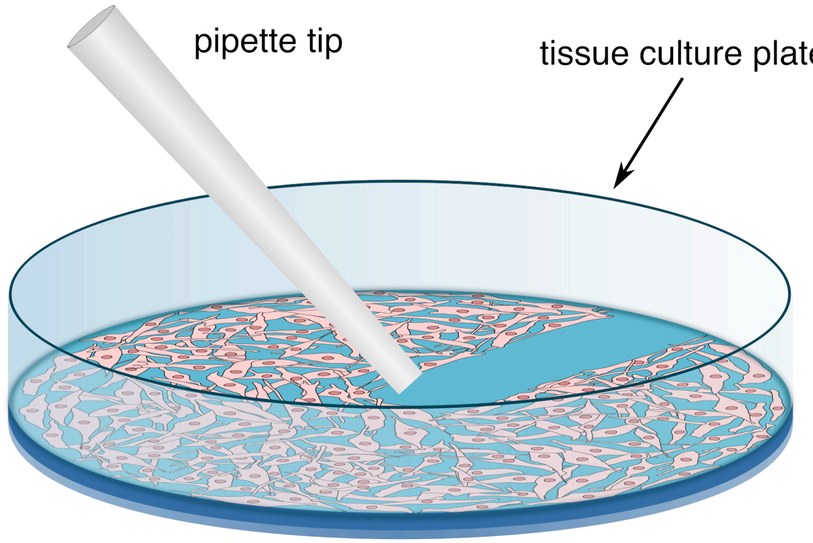
SN Menon & JA Flegg, Adv. Wound Care, **10**(6), 328-344 (2021)

CIL IN ACTION : 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



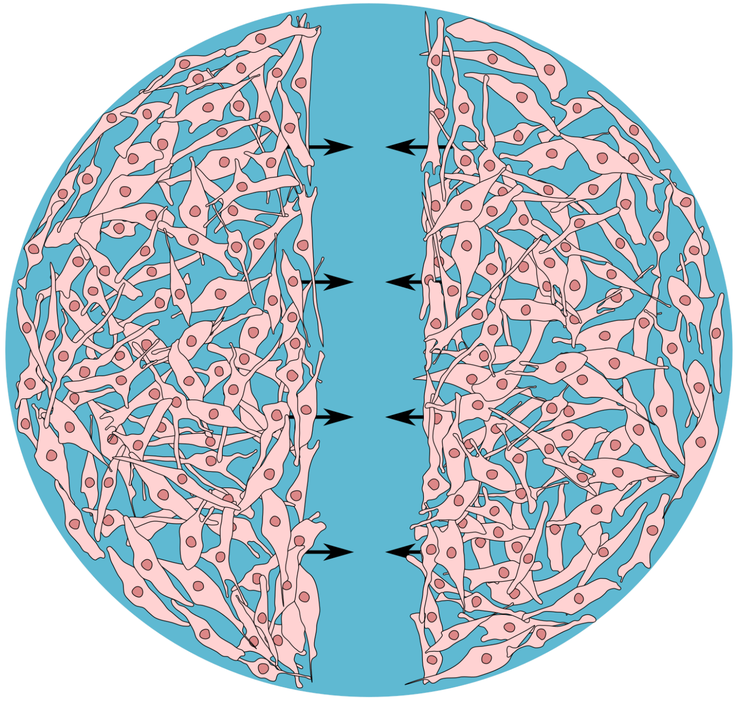
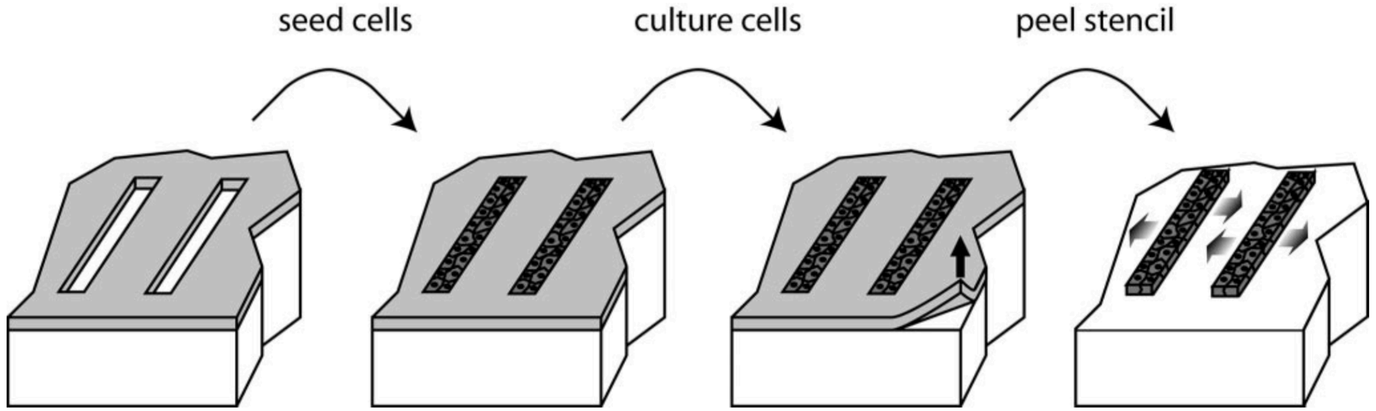


image: M Poujade (2007). Proc Natl Acad Sci USA, **104**(41), 15988-15993.

CIL IN ACTION : STENCILED ASSAYS

- In a scratch assay it is unclear as to what extent the observed behaviours are the 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.
- This provides direct proof of the CIL hypothesis - they are quiescent in dense neighbourhoods and only experience collisions from behind at the free edge, causing them to move to the empty space.

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

PHASE TRANSITION IN THE COLLECTIVE MIGRATION OF TISSUE CELLS

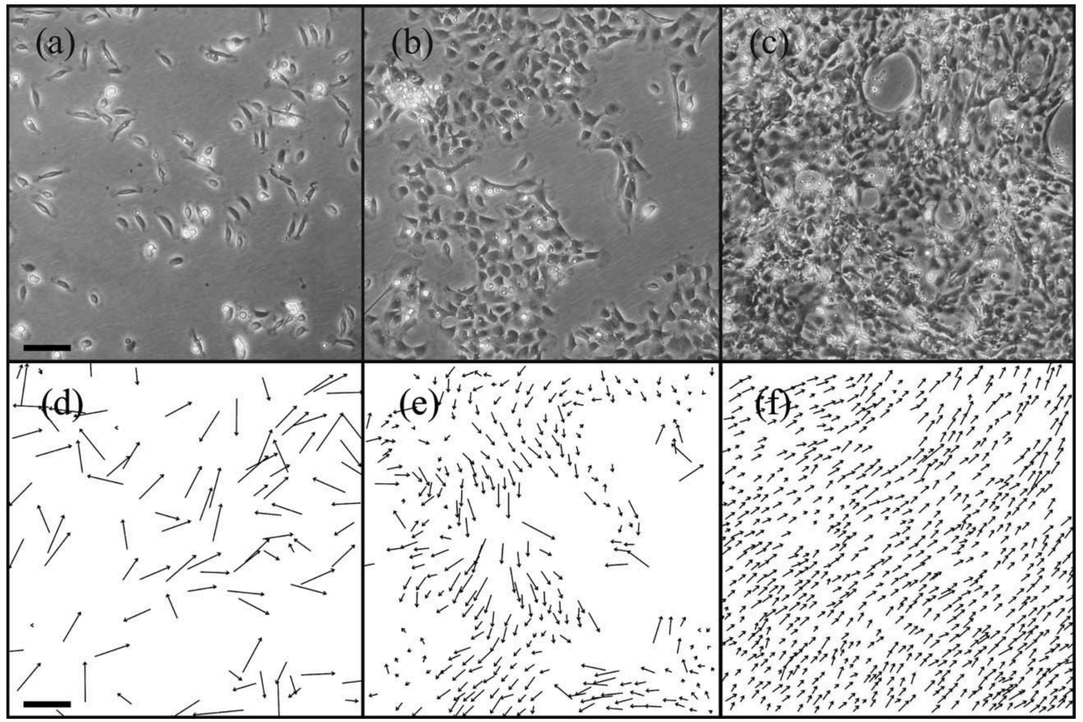
- Keratinocytes are found in epithelial tissue and play a significant role in wound closure.
- As the density of cells is increased one sees a sharp transition from disordered to ordered motion.
- To model this, Szabó et al (2006) described the cell velocity as:

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

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:

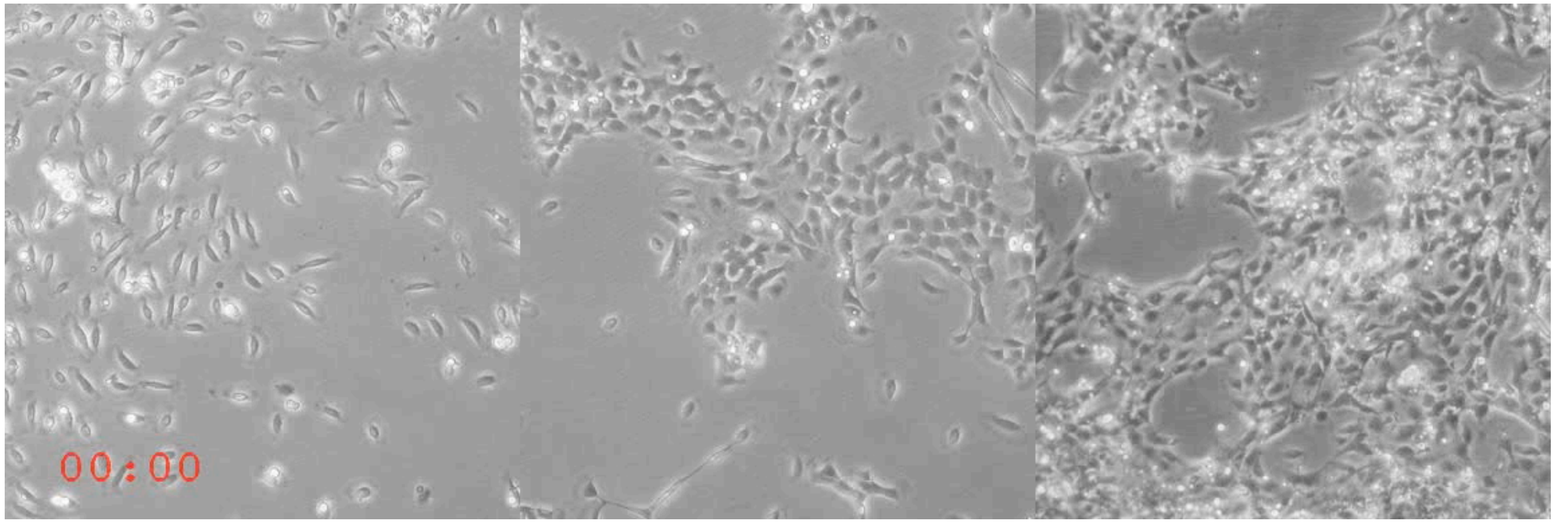


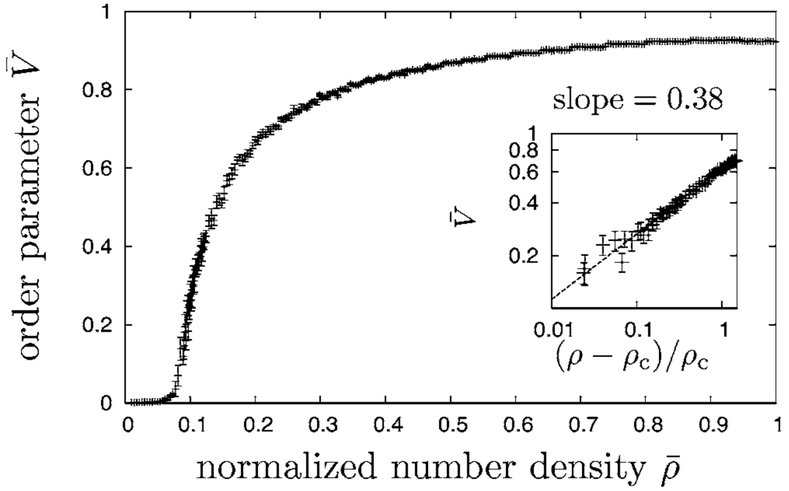
$$\mathbf{F}(\mathbf{r}_i, \mathbf{r}_j) = \frac{\mathbf{r}_j - \mathbf{r}_i}{|\mathbf{r}_i - \mathbf{r}_j|} \begin{cases} F_{rep} \dfrac{d_{ij} - R_{eq}}{R_{eq}}, & \text{if } d_{ij} < R_{eq}, \\ F_{adh} \dfrac{d_{ij} - R_{eq}}{R_0 - R_{eq}}, & \text{if } R_{eq} \le d_{ij} \le R_0, \\ 0, & \text{if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

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.





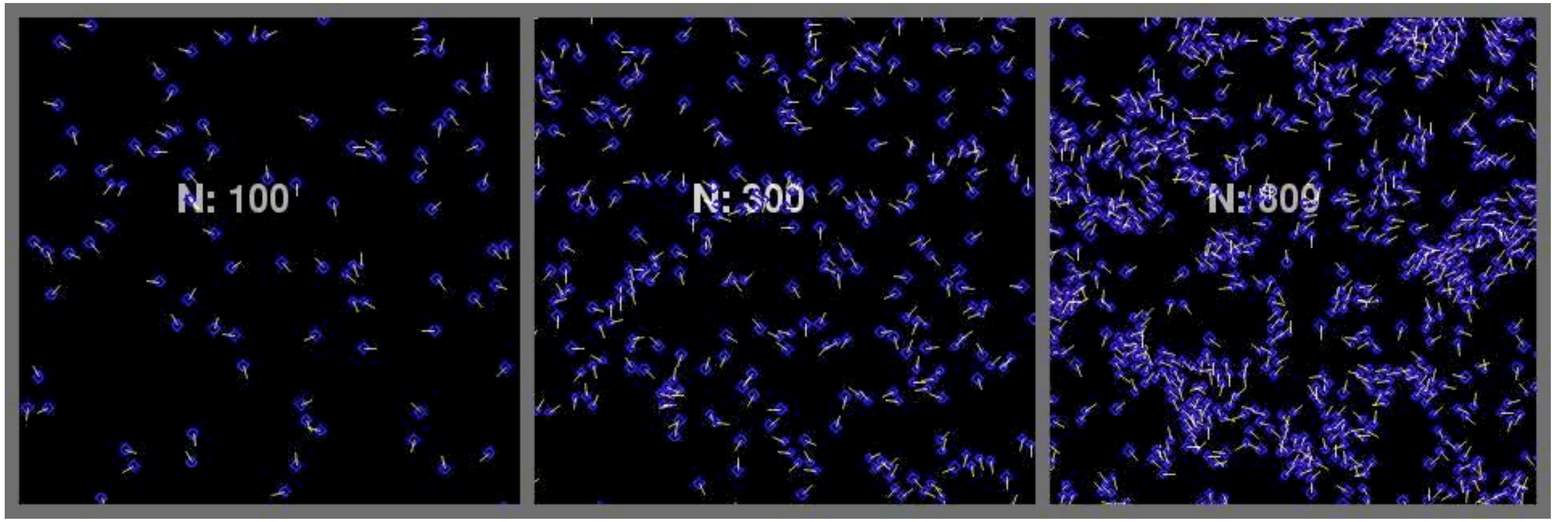
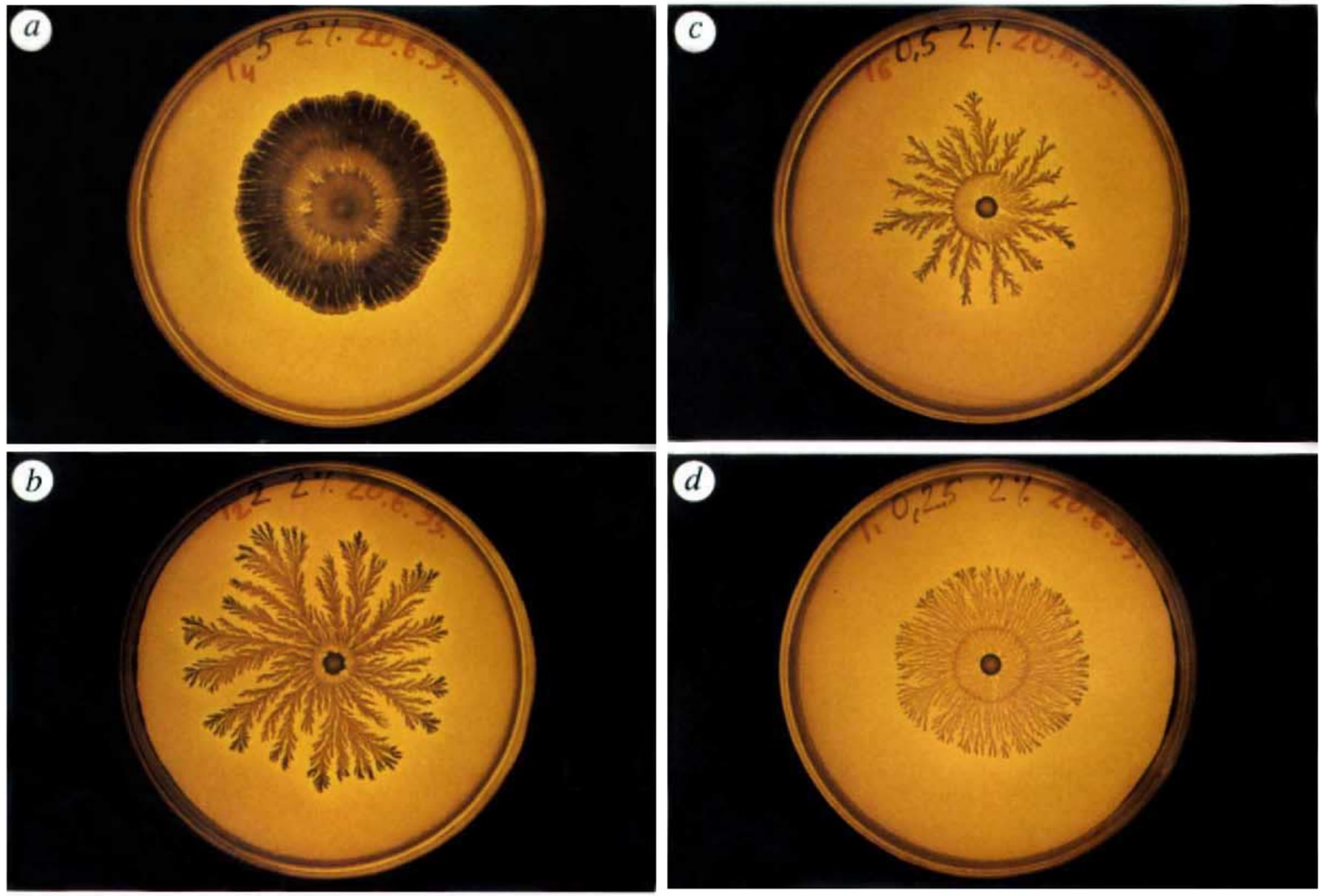


image: Ben-Jacob et al, Nature, **368**, 46-49 (1994)

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.

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

COOPERATIVE GROWTH PATTERNS IN BACTERIAL COLONIES

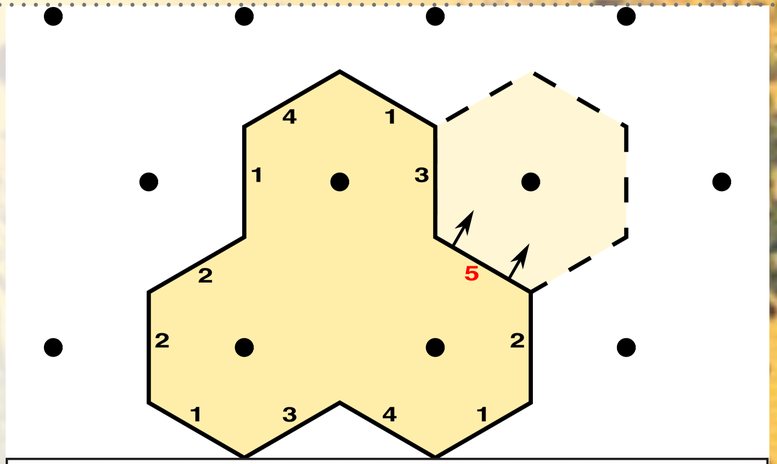
- The model consists of N walkers i that move via an off-lattice random walk on a triangular lattice via $\mathbf{r}_i' = \mathbf{r}_i + d(\cos\Theta, \sin\Theta), \Theta \in [0, 2\pi]$, where if $\mathbf{r}_i'$ crosses the envelope defined on this lattice, the step is rejected and instead a counter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

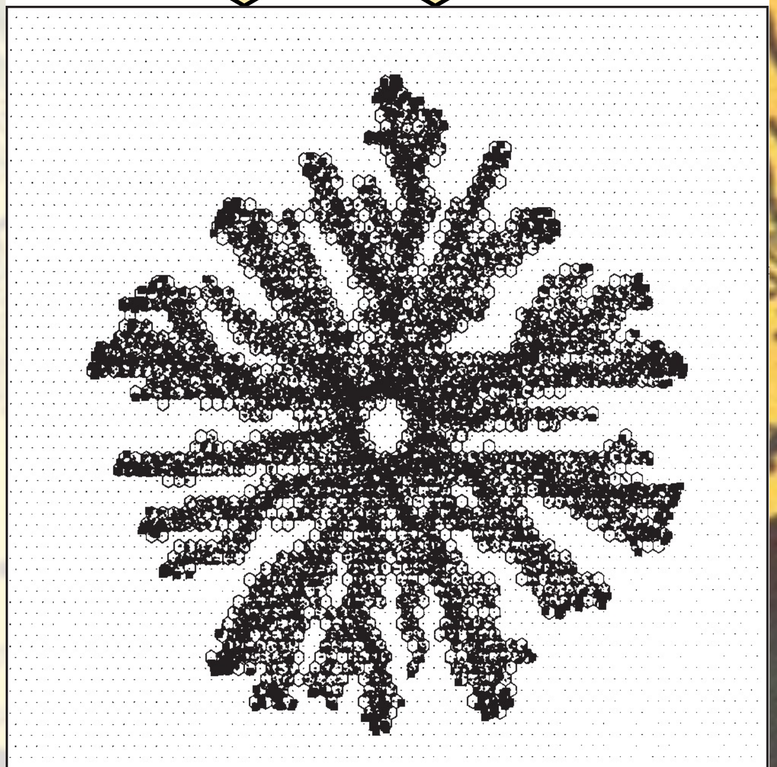
- The walkers have a finite energy store W_i that is lost at a fixed rate e as they move, and is replenished by consuming the underlying nutrient $c(\mathbf{r}, t)$ at a rate c_r (or, if in a low nutrient environment, the full underlying amount): $\dfrac{dW_i}{dt} = \min(c_r, c(\mathbf{r}, t)) - e$

- 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 $c(\mathbf{r}, t)$ is consumed by active walkers ($awlk$), and diffuses at a rate D_c

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





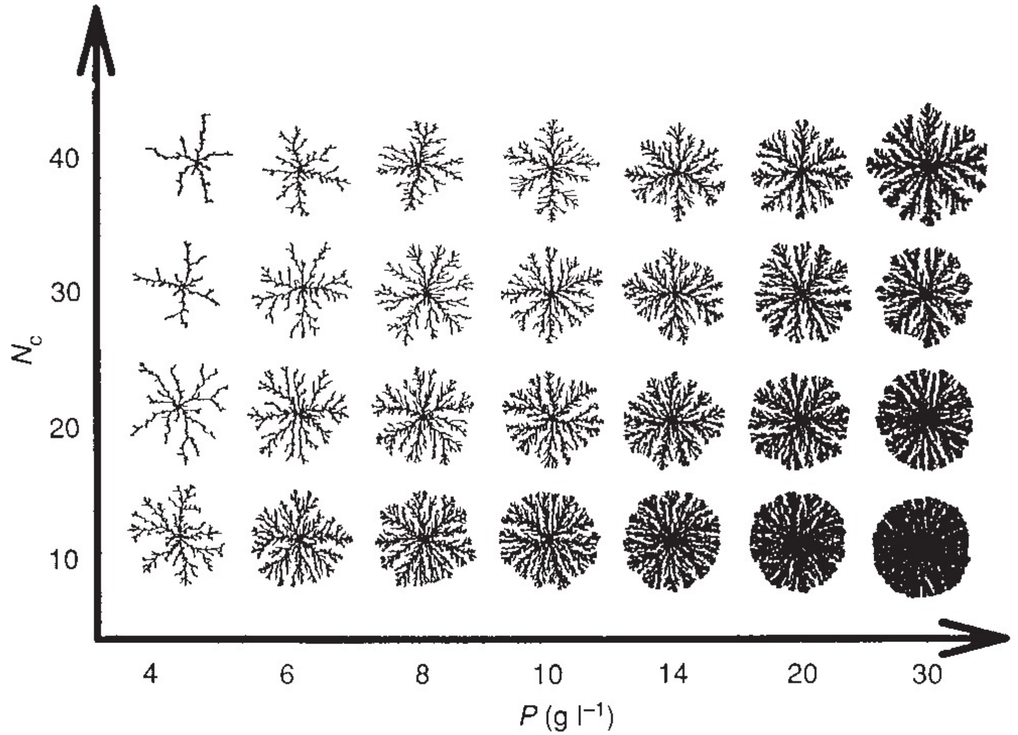
Source: Ben-Jacob et al, Nature, **368**, 46-49 (1994)

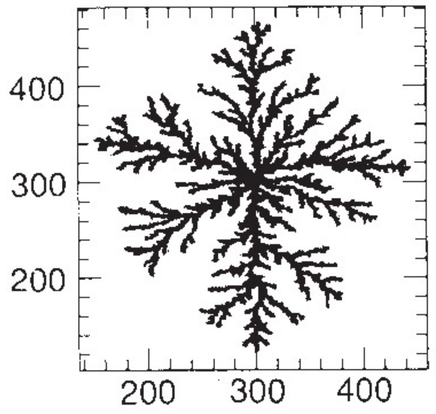
COOPERATIVE GROWTH PATTERNS IN BACTERIAL COLONIES

- Simulations were performed for different initial values $c(\mathbf{r},0) = P$, i.e. the peptone level, and agar concentration N_c . The system size is 600×600 with $\sim 10^4$ walkers (each walker represents 10^5 bacteria).
- 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 (*swlk*) to produce a chemical $s(\mathbf{r}, t)$ at rate s_r (for example as a distress signal), which is consumed by active walkers at rate c_c :

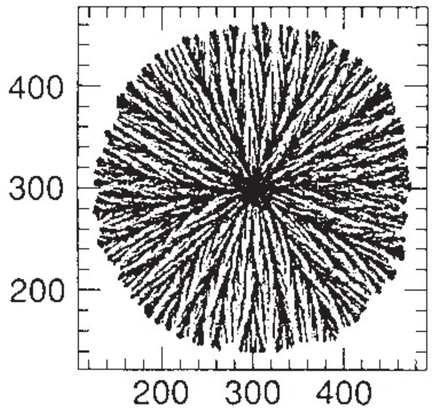
$$\frac{\partial s(\mathbf{r}, t)}{\partial t} = D_s \nabla^2 s(\mathbf{r}, t) + \sum_{swlk} \delta(\mathbf{r} - \mathbf{r}_i) s_r - \sum_{awlk} \delta(\mathbf{r} - \mathbf{r}_i) \min(c_c , s(\mathbf{r}, t))$$

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



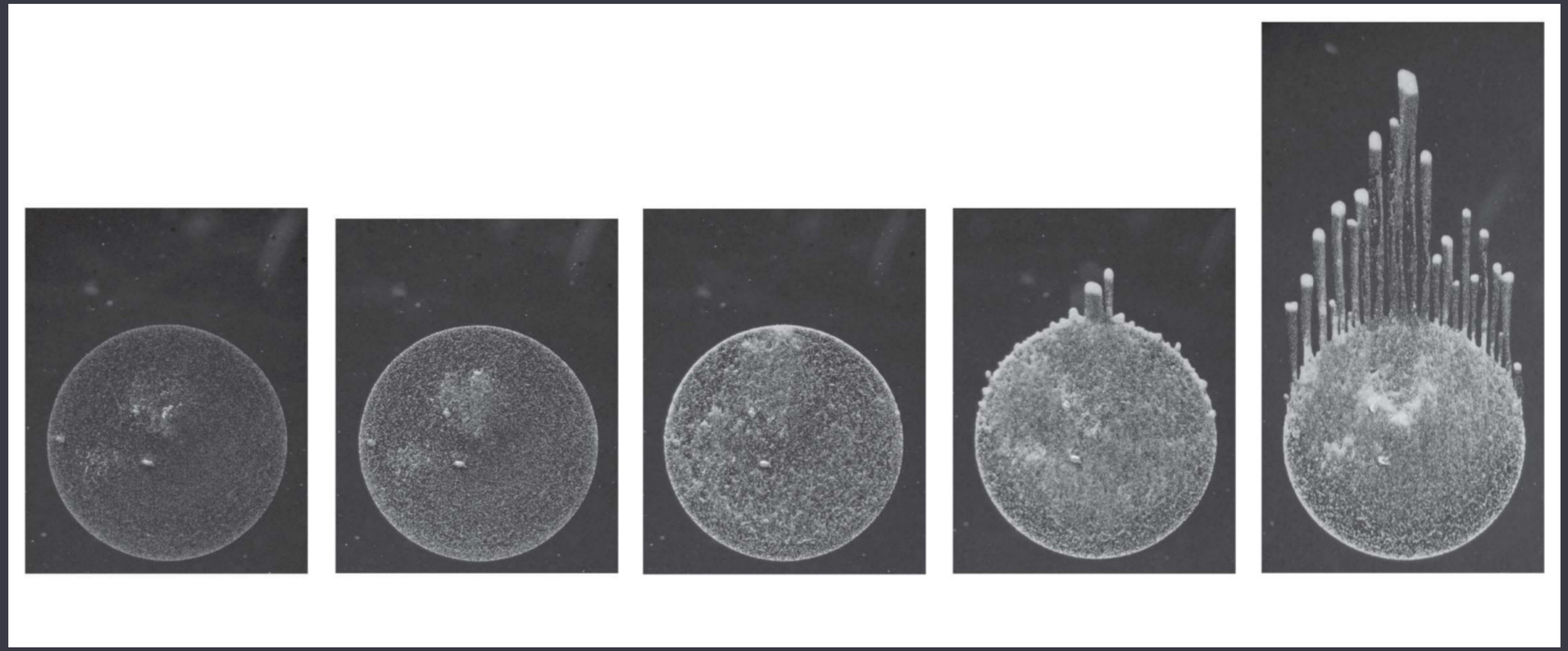


without chemotaxis



with chemotaxis

PHOTOTAXIS IN CYANOBACTERIA



Cells in a colony of Synechocystis move towards a source of light, aggregate at the colony boundary and emerge from the colony in the form of “fingers”

image: Ursell et al, PLoS Comp Biol, 9(9):e1003205 (2013)

videos: https://dpb.carnegiescience.edu/labs/bhaya-lab/social-motility/videos

PHOTOTAXIS IN CYANOBACTERIA

Directional Light perception in SynechoCystis Sp.

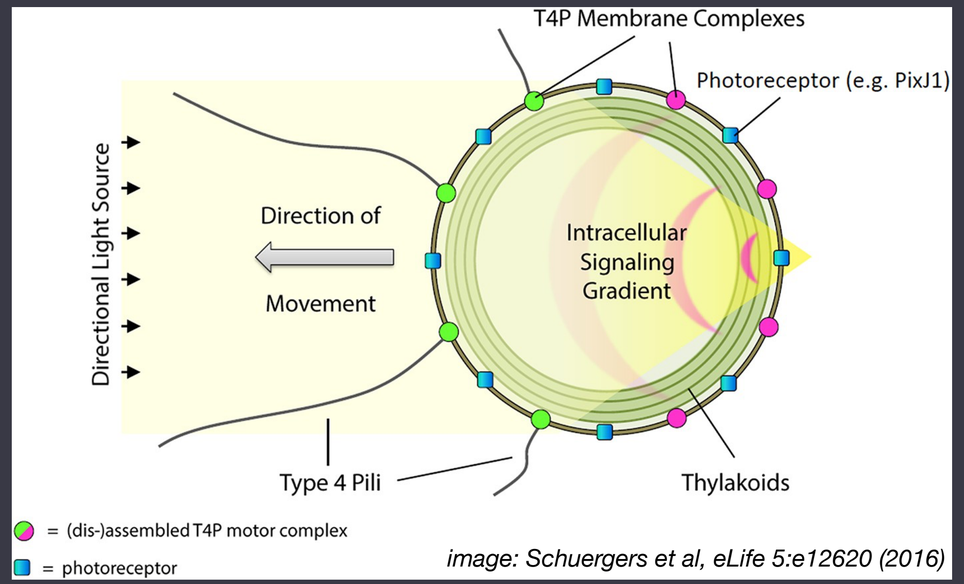
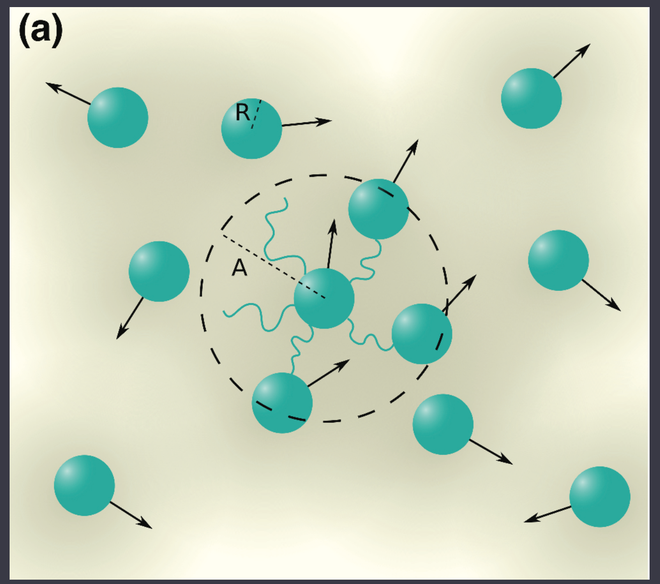
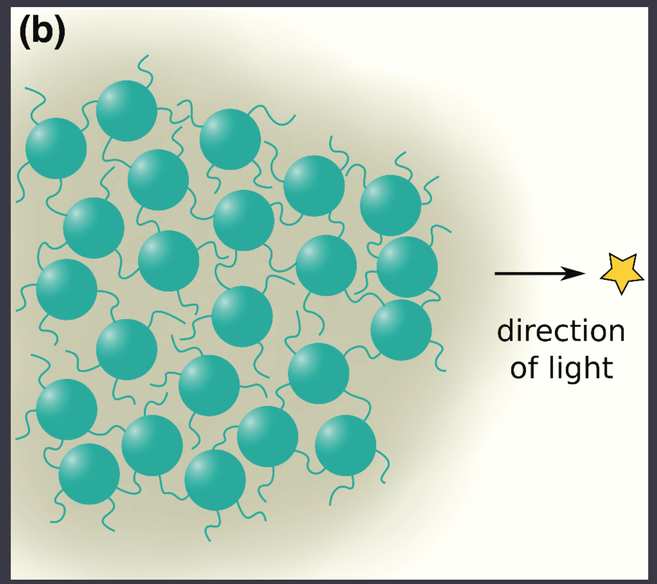


image: Schuergers et al, eLife 5:e12620 (2016)

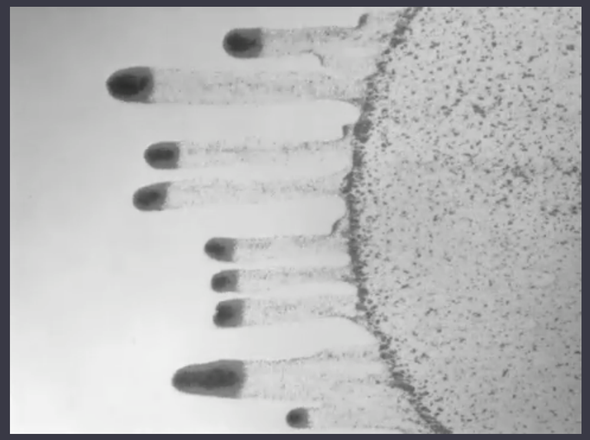
Cells exert forces on their neighbours through type 4 pili (T4P).



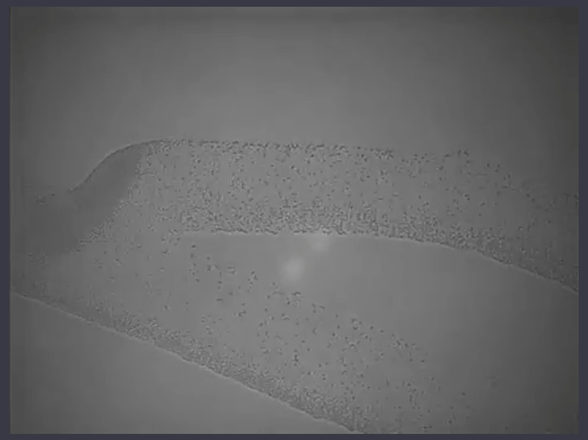
Cells lay down slime and move as a group towards light



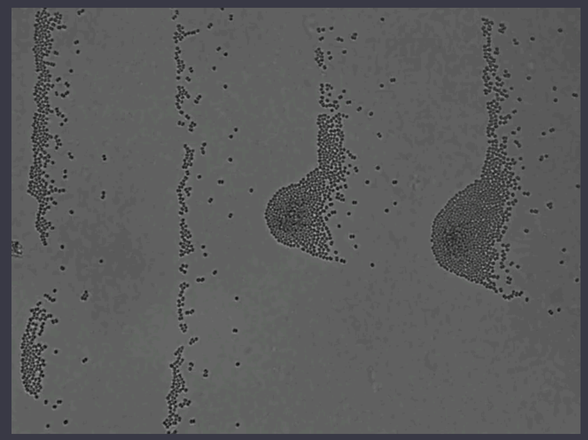
First 24 hrs of finger formation



A finger meets a slime trail

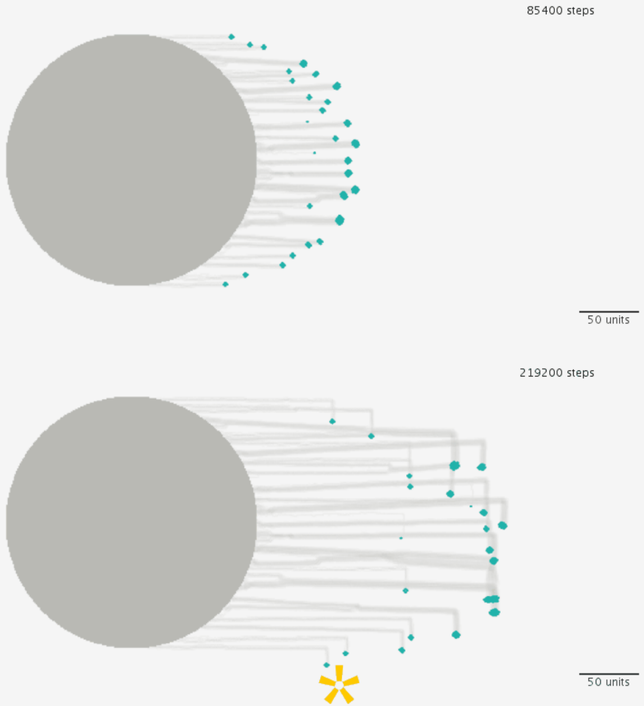


Moving the location of the light source

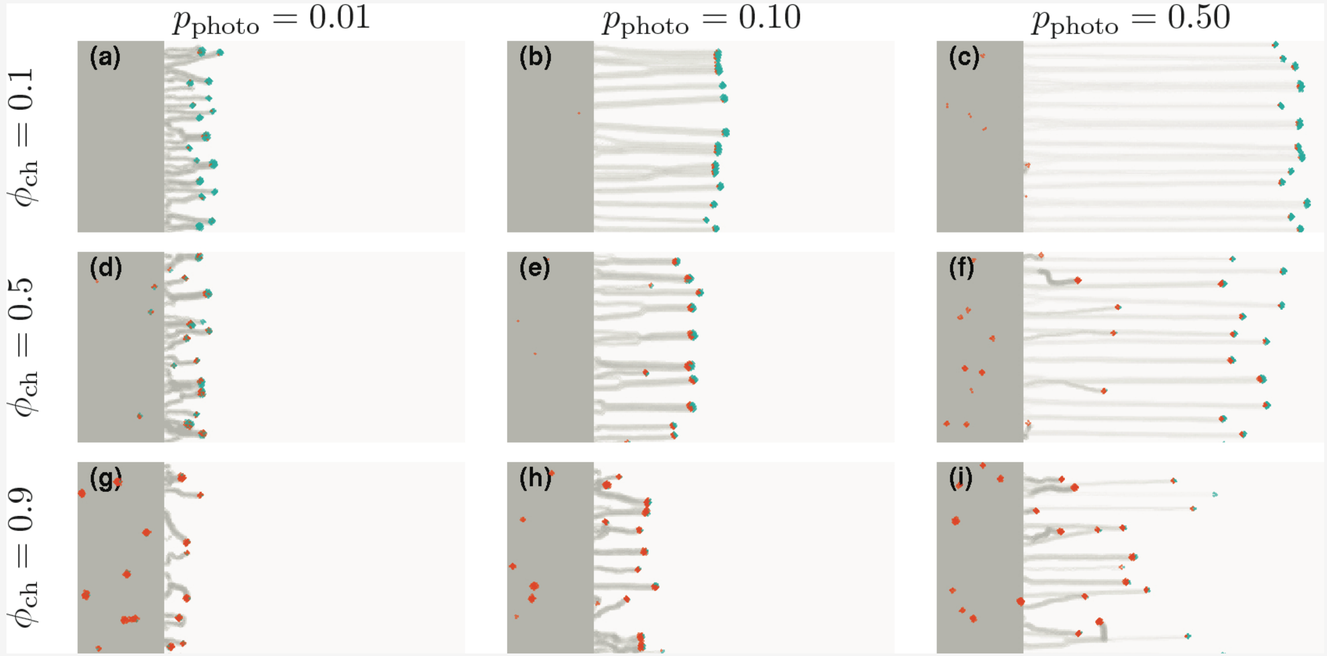


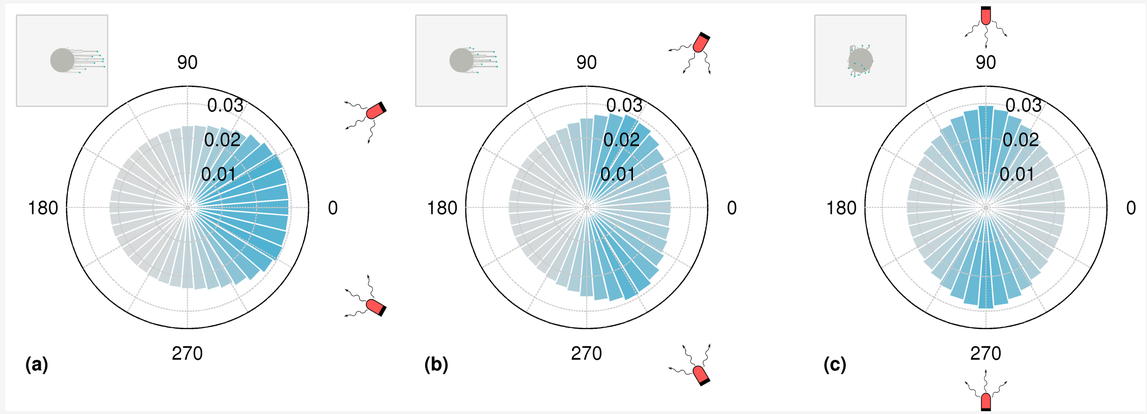
PHOTOTAXIS IN CYANOBACTERIA

P Varuni, SN Menon & GI Menon, *Sci. Rep.* **7**(1):17799 (2017)
P Varuni, SN Menon & GI Menon, *Plos Comp. Biol.* **16**(4):e1007807 (2020)

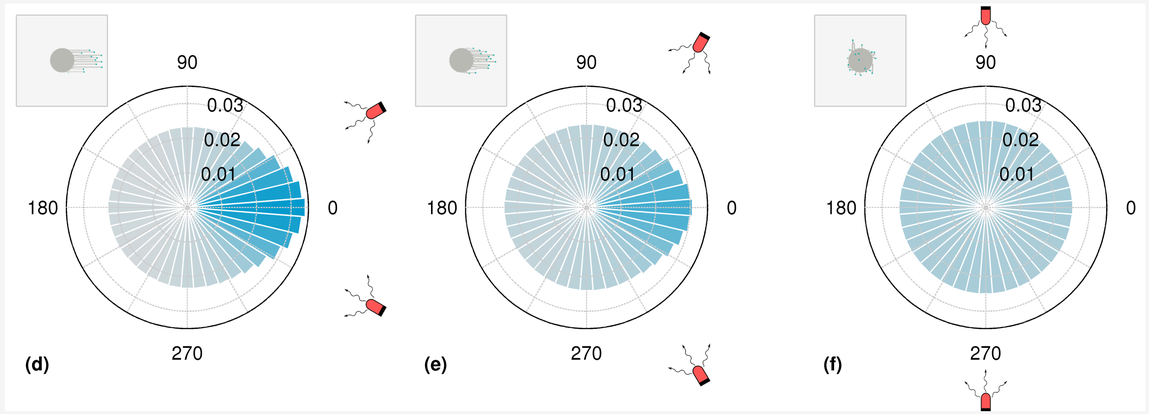


effect of "freeloaders"





stochastic switching

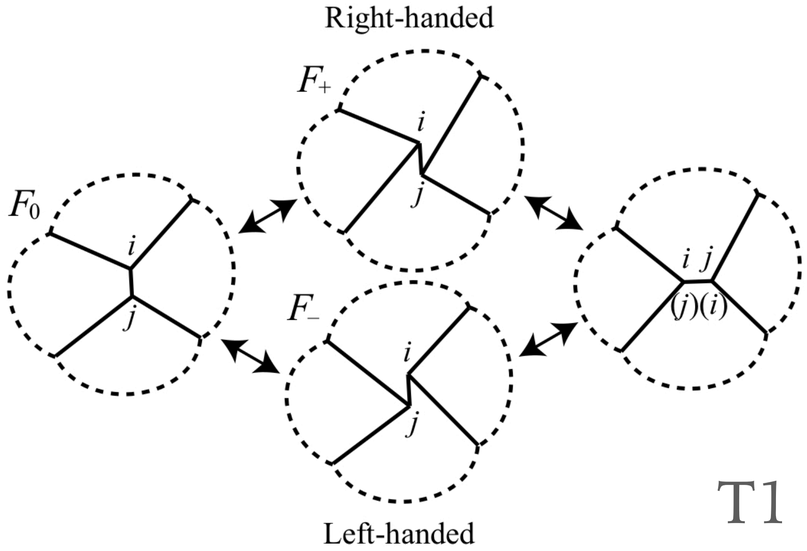


vector integration

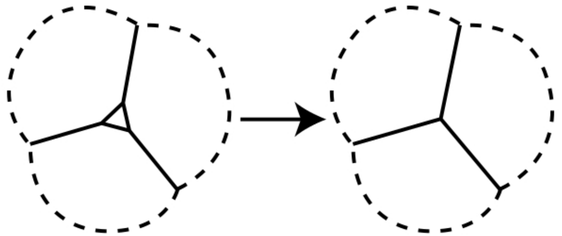
Farhadifar et al., Curr. Biol. **17**, 2095–2104 (2007).

CELL MOVEMENT IN CONFLUENT TISSUE

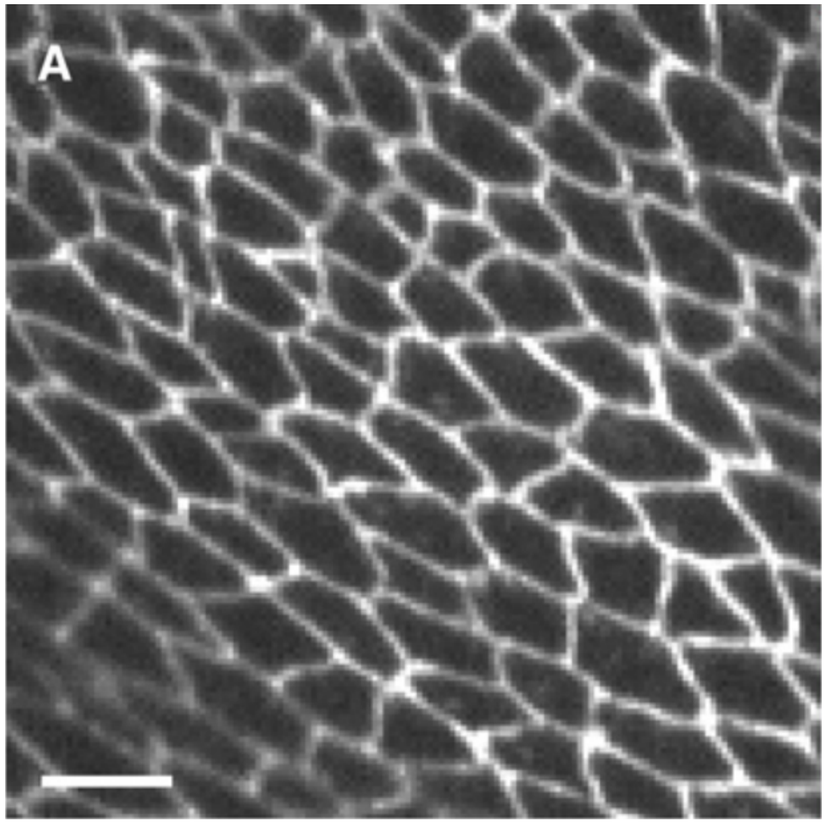
- Confluent tissues are continuous cellular sheets that have no gaps. The significant reduction in cell surface area and increased compression trigger cell cycle arrest.
- Although CIL is also triggered, the cells cannot “move away”, so they glide past each other in an attempt to reduce the overall mechanical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



T1



T2



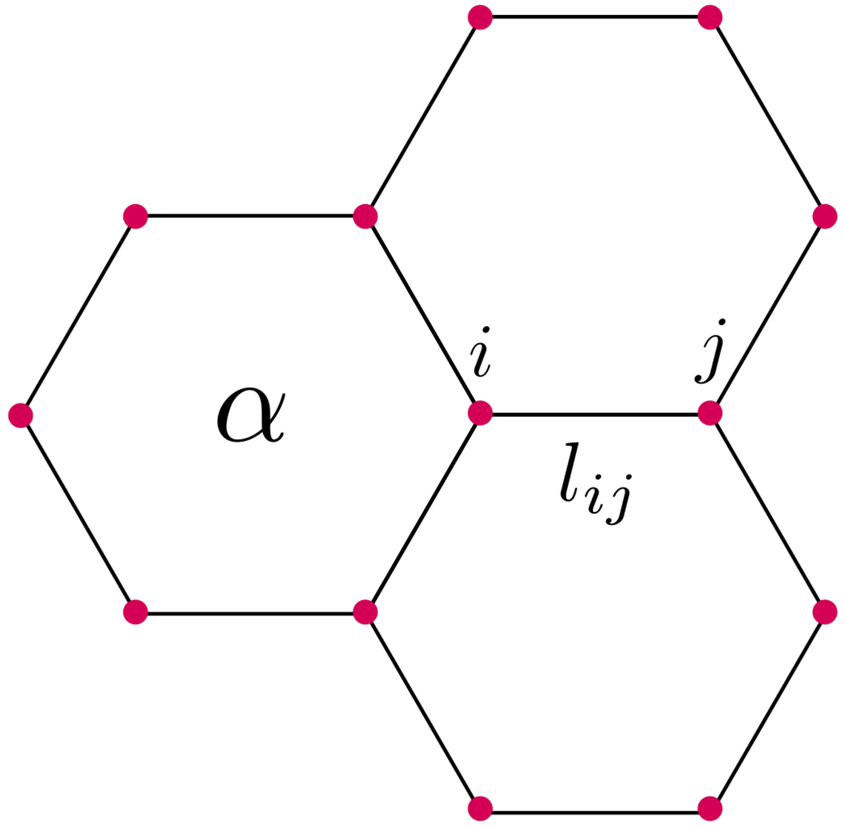
epithelial cells from wing
of Drosophila melanogaster

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

MODELLING CELLS IN CONFLUENT TISSUE : THE VERTEX MODEL

Farhadifar et al (2007) proposed that the mechanical state of the lattice can be expressed in terms of the potential energy:

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

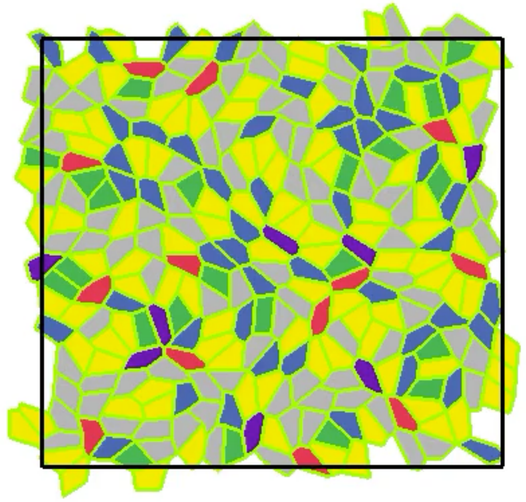


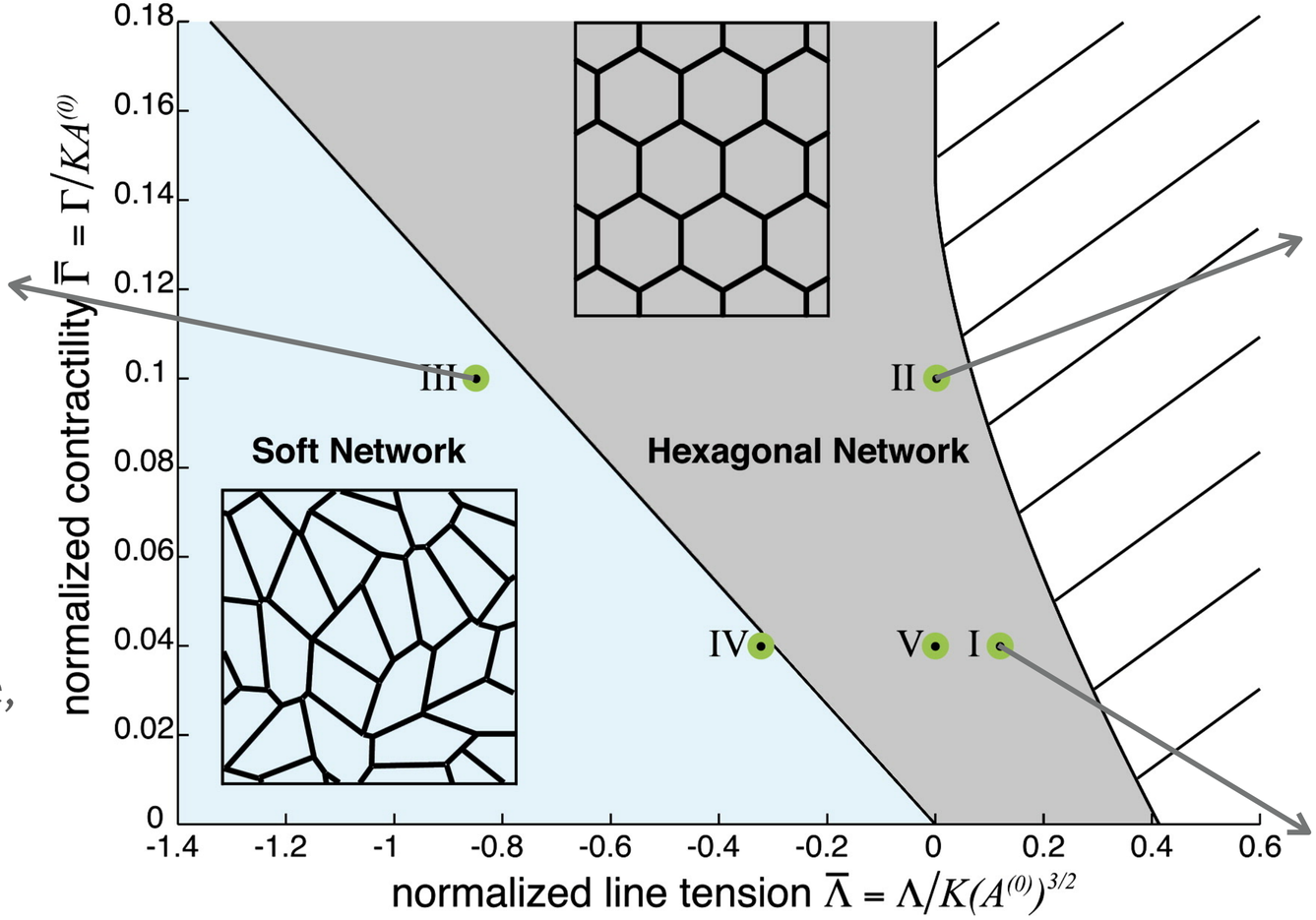
where A_α and L_α are the area and perimeter of cell α, l_{ij} is the length of the bond connecting vertices i and j, $A_\alpha^{(0)}$ is the "preferred" area of cell α, K_α is the area elastic modulus (which relates to cell stiffness), Λ_{ij} is the bond/line tension and Γ_α is the perimeter elasticity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

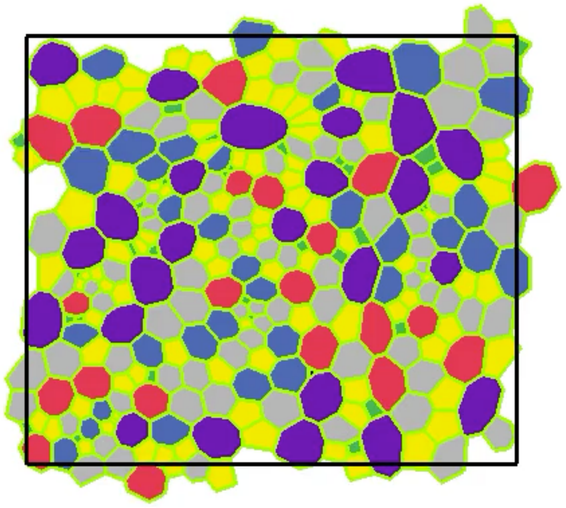
Line tension Λ_{ij} is dependent on cell-cell adhesion as well as the contractility of the actomyosin ring.

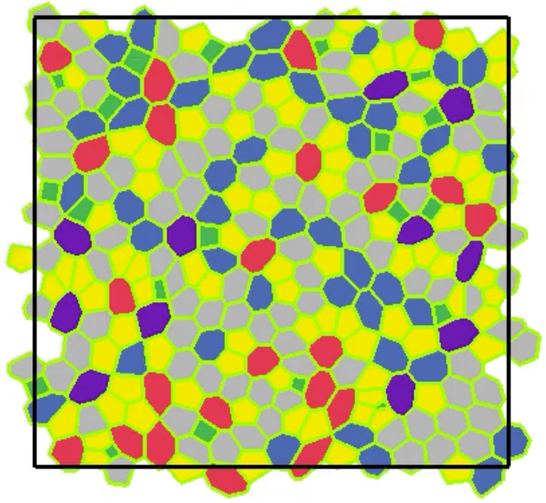
Farhadifar et al., Curr. Biol. **17**, 2095–2104 (2007).

PHASE TRANSITION BETWEEN SOFT AND SOLID STATES







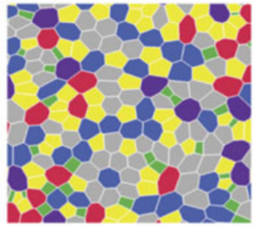
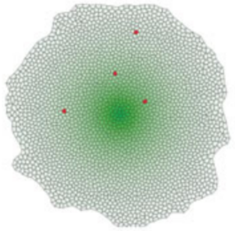
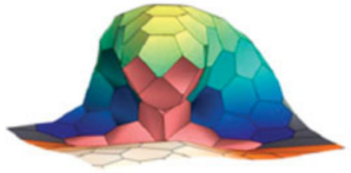
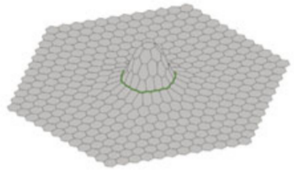
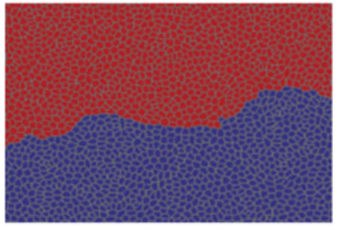
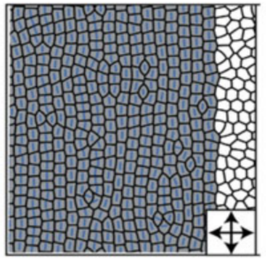
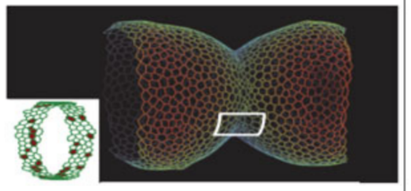
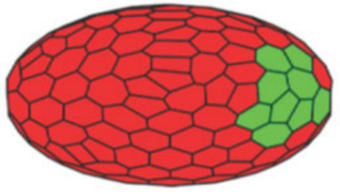
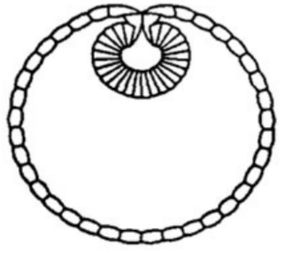
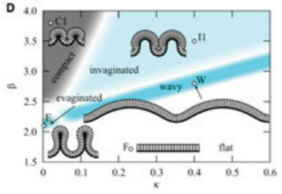
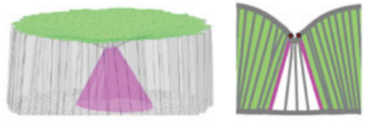
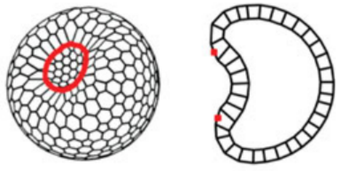
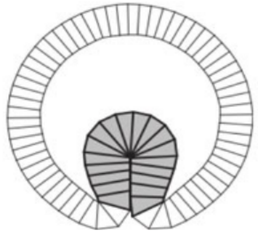
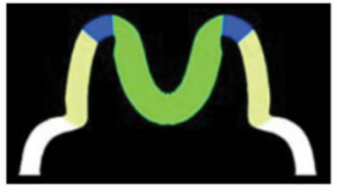
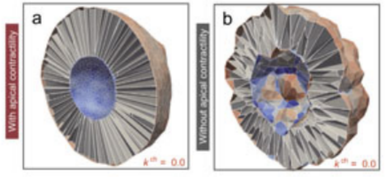
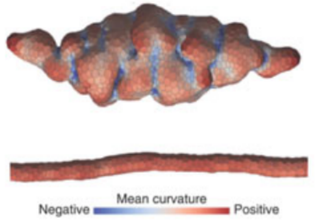


The soft network is irregular and liquid-like, allowing it to be easily remodelled.

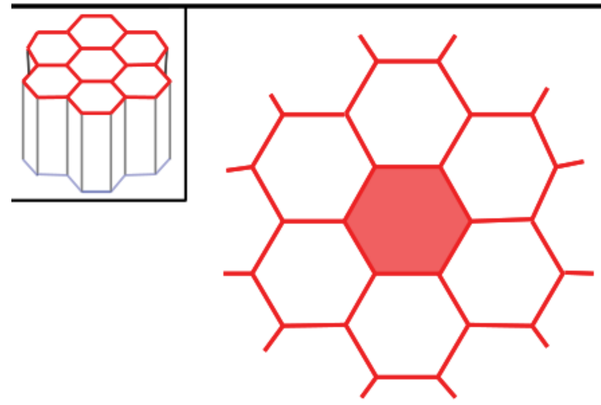
So, increased adhesion (leading to $\Lambda < 0$) can facilitate rearrangement.

Legend:



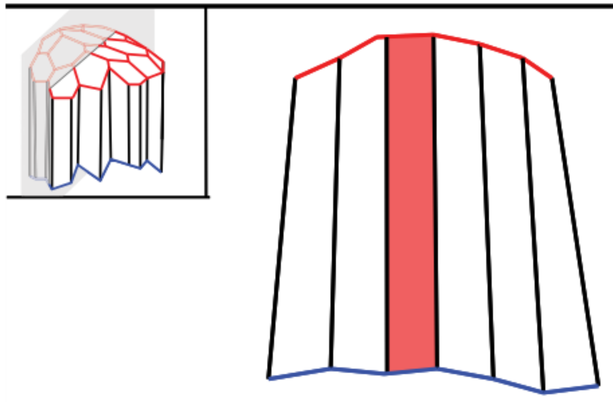
	2D		3D	
apical	(*a*) cell shape distribution 	tissue size control 	(*b*) appendage formation 	epithelial buckling 
	interface morphology 	cell arrangement 	epithelial folding 	cell migration 
lateral	(*c*) neural tube formation 	epithelial folding 	(*d*) cyst formation 	shape changes of spheres 
	gastrulation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

2D apical vertex model



flat apical surface

2D lateral vertex model



lateral cross section

Bi et al, Phys. Rev. X, **6**(2), 021011 (2016).

MODELLING CELLS IN CONFLUENT TISSUE : SELF-PROPELLED VORONOI MODEL

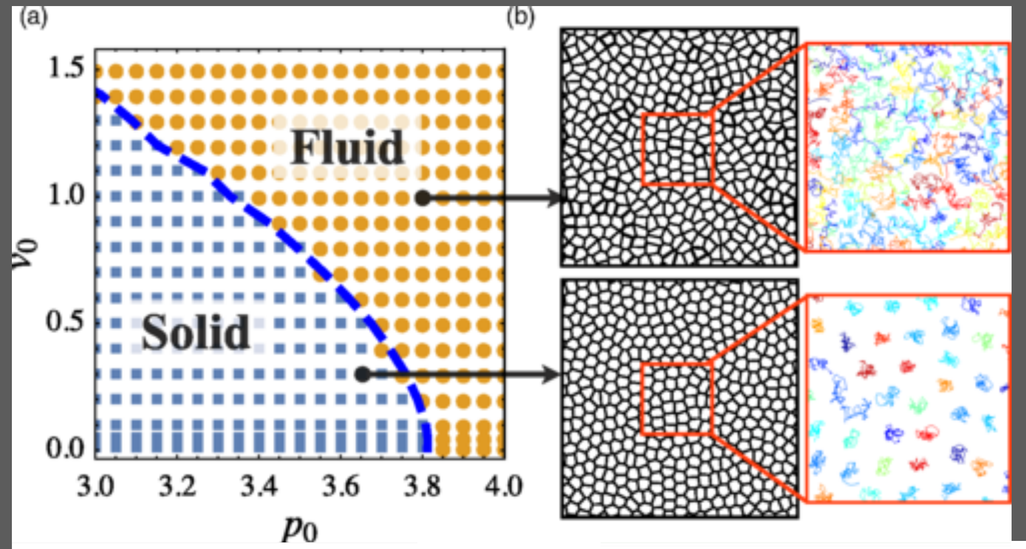
- The Self-propelled Voronoi (SPV) model, proposed by Bi, Manning and others, combines active self-propulsion with geometric cell mechanics.
- Rather than track the individual cell shapes, the model follows the center $\mathbf{r}_i$ of each cell i. The shapes are then computed via Voronoi tessellations to obtain the area $A(\mathbf{r}_i)$ and perimeter $P(\mathbf{r}_i)$.
- The the total tissue mechanical energy is

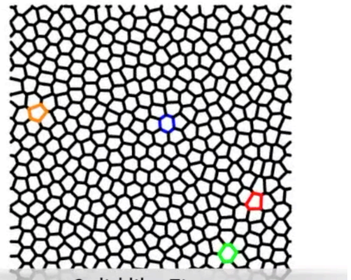
$$E = \sum_{i=1}^{N} \left[K_A \left(A(\mathbf{r}_i) - A_0 \right)^2 + K_P \left(P(\mathbf{r}_i) - P_0 \right)^2 \right]$$

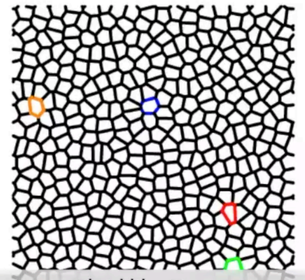
where K_A and K_P are the area and perimeter moduli and one can introduce an effective target shape index $p_0 = P_0/\sqrt{A_0}$.

- The effective mechanical interaction force experienced by cell i is $\mathbf{F}_i = -\nabla_i E$ and the cells exhibit a self-propulsion force along their polarity vector $\hat{\mathbf{n}}_i = (\cos\theta_i, \sin\theta_i)$. These forces in turn control the overdamped equation of motion of the cell centers $d\mathbf{r}_i/dt = \mu \mathbf{F}_i + v_0 \hat{\mathbf{n}}_i$ and the orientation is assumed to randomly diffuse: $\dot{\theta}_i = \eta_i(t)$.

There is an unjamming transition (from solid-like to fluid-like tissue) when the shape index p_0 crosses a critical threshold







MODELLING CELLS IN TISSUES: CELLULAR POTTS MODEL

- This model was proposed in 1992 by James Glazier and François Graner, and subsequently popularised by Paulien Hogeweg.
- Here a "cell" is a contiguous cluster of lattice sites with a unique "cell ID" σ, volume $v(\sigma)$ and "type" τ.
- If $V_{\tau(\sigma)}$ is the target volume for cell σ of type τ one can write the Hamiltonian:

$$\mathscr{H} = \sum_{\langle i,j \rangle} J(\tau(\sigma_i), \tau(\sigma_i))\left(1 - \delta_{\sigma_i, \sigma_j}\right) + \lambda \sum_{\sigma} [v(\sigma) - V_{\tau(\sigma)}]^2$$

  where λ is a Lagrange multiplier.
- Depending on the problem under consideration, one sets the values of the surface energy $J(\tau(\sigma_i), \tau(\sigma_i))$.
- In addition, one can add terms related to chemotaxis and/or other cell behaviours.


James Glazier


François Graner


Paulien Hogeweg

source: Voß-Böhme et al, Cellular Potts Model. In: Encyclopedia of Systems Biology (2013).

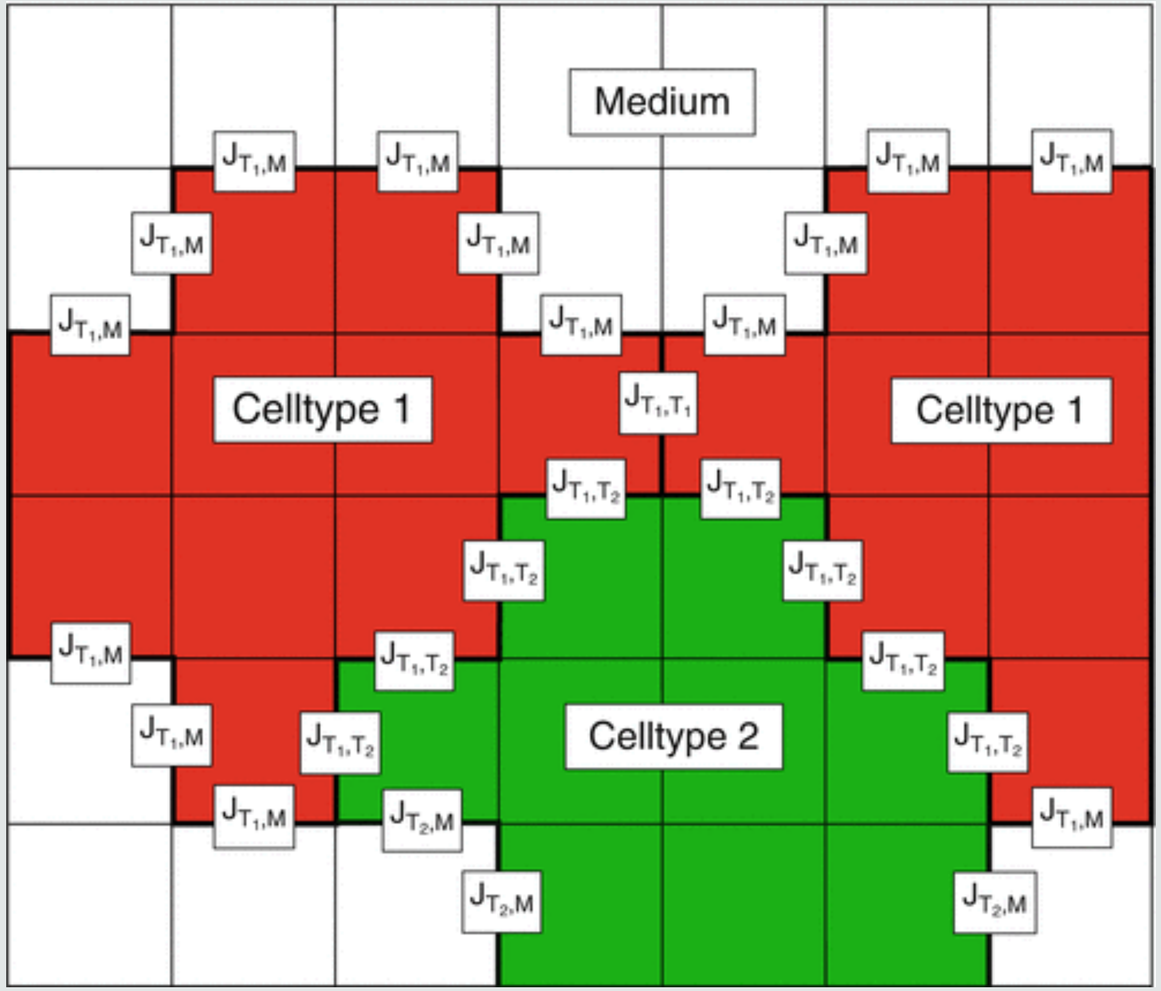
MODELLING CELLS IN TISSUES: CELLULAR POTTS MODEL

- In their original work (Graner & Glazier, 1992) they studied cell sorting in a medium ($\tau = M$) with a mixture comprising two cell types ($\tau = T_1, T_2$) Then they set $J(T_1, T_2)$, $J(M, T_2)$, $J(T_1, M)$ etc.

- Here, analogous to spin models, the system evolves via a random neighbour of a randomly picked site attempting to "flip" to its ID at each step. The new configuration is accepted based on the change in overall energy (**lower**: accept, **higher**: accept with probability $\exp(-\Delta\mathscr{H}/T)$).

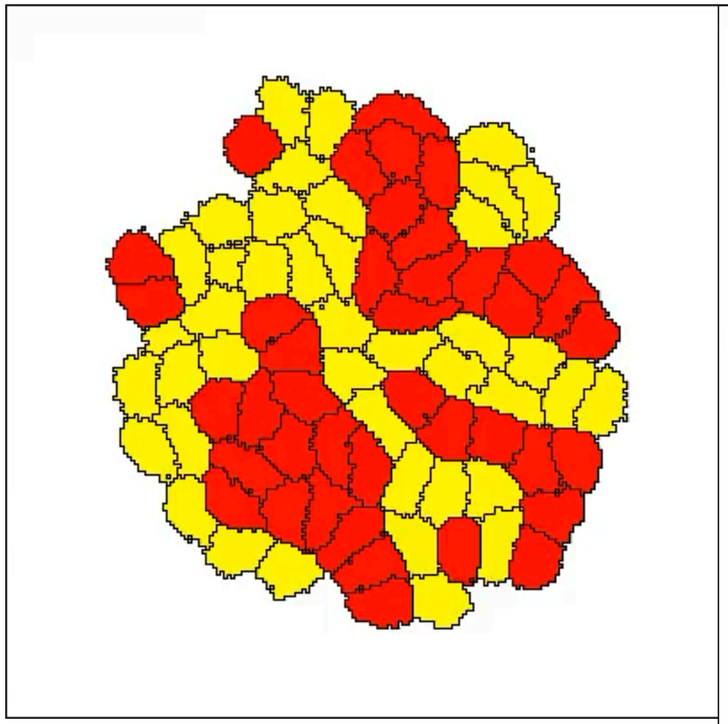
- Processes such as cell division can easily be incorporated, for instance by checking if the cell volume exceeds a target value, and assigning new unique cell IDs for lattice sites on either side of the long axis (or a random axis).

- Similarly other processes such as apoptosis and differentiation can be incorporated with suitable flags.

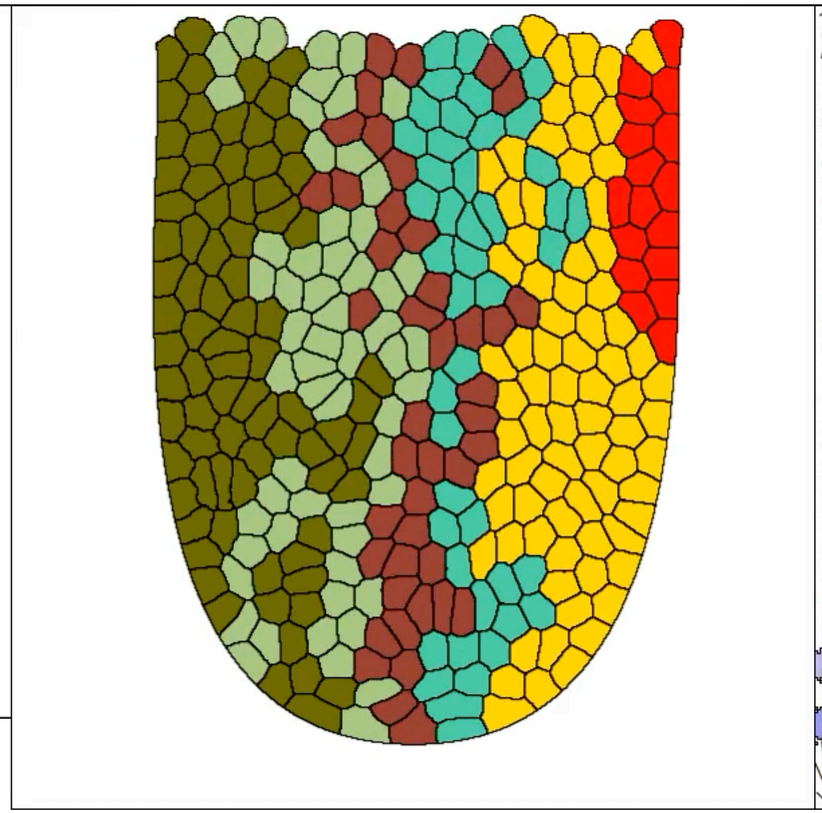


EXAMPLES OF CELLULAR POTTS MODEL SIMULATIONS

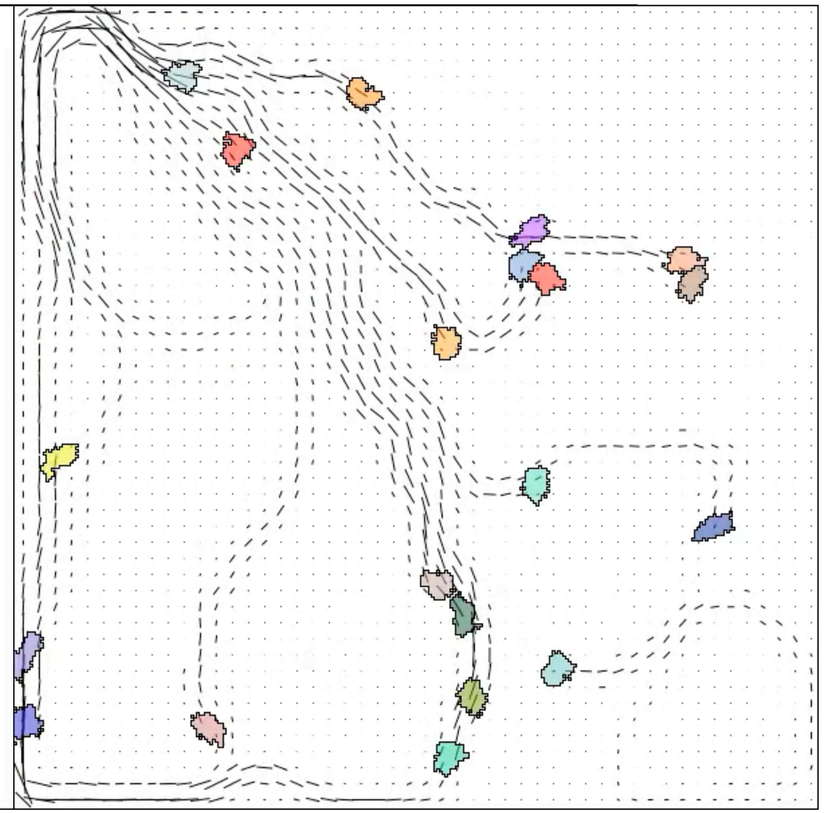
cell sorting based on the differential adhesion hypothesis



emergence of clonal populations from stem cells in an intestinal crypt



cells move in a persistent manner, modify their environment and tend to follow this orientational information



Simulated using Morpheus: https://morpheus.gitlab.io

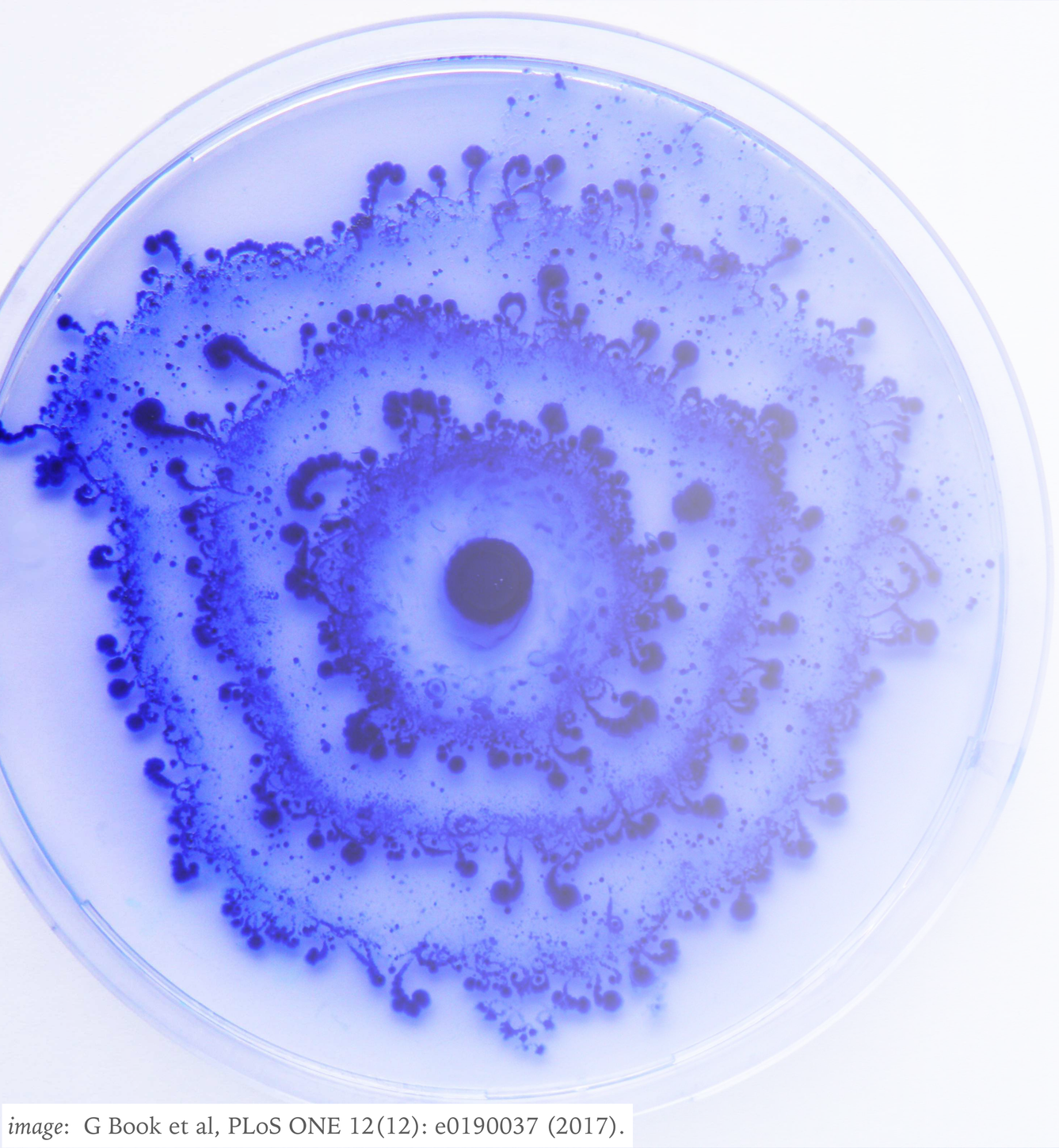


image: G Book et al, PLoS ONE 12(12): e0190037 (2017).

FURTHER READING

Articles

- 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).
- P Varuni, SN Menon & GI Menon, *Phototaxis as a collective phenomenon in cyanobacterial colonies*, Sci. Rep. **7**(1):17799 (2017).
- F Graner & J Glazier, *Simulation of biological cell sorting using a two-dimensional extended Potts model*, Phys. Rev. Lett. **69**(13): 2013–74 (1992).
- Farhadifar et al., *The influence of cell mechanics, cell-cell interactions, and proliferation on epithelial packing*, Curr. Biol. **17**, 2095–2104 (2007).

Reviews

- R. Mayor & S. Etienne-Manneville, *The front and rear of collective cell migration*, Nat. Rev. Mol. Cell Biol., **17**(2), 97-109 (2016).

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

— Sun Ra (1972)

THANK YOU!



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