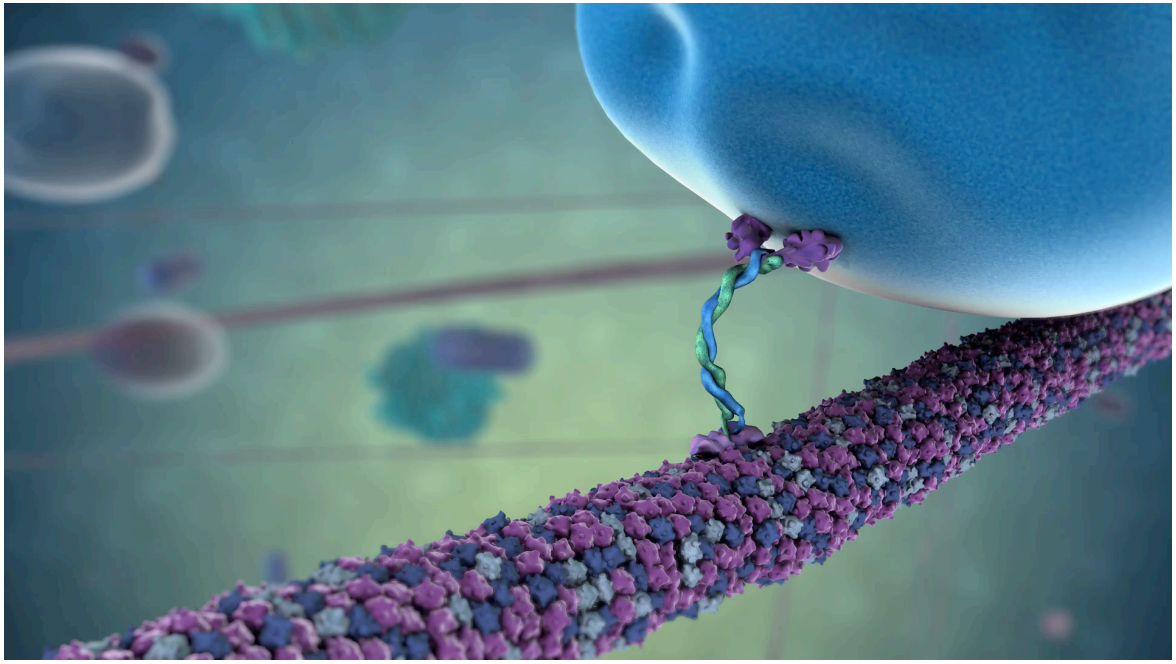
Niels Bohr Institutet

Active Matter: The Engines of Life

Amin Doostmohammadi



Funded by the Novo Nordisk Foundation

novo nordisk fonden

The Niels Bohr International Academy

Life is motion (Wallace Stevens)

'Hot Jazz' (image: glholtegaard.dk)

Outline

Part I. Cells: fundamental building blocks of life

The cell factory: molecular motors

Mechanics and cell motion

Cellular cooperation

- **Part II. Bacteria: self-propelled machines**

Bacterial collective motion

Micromachines

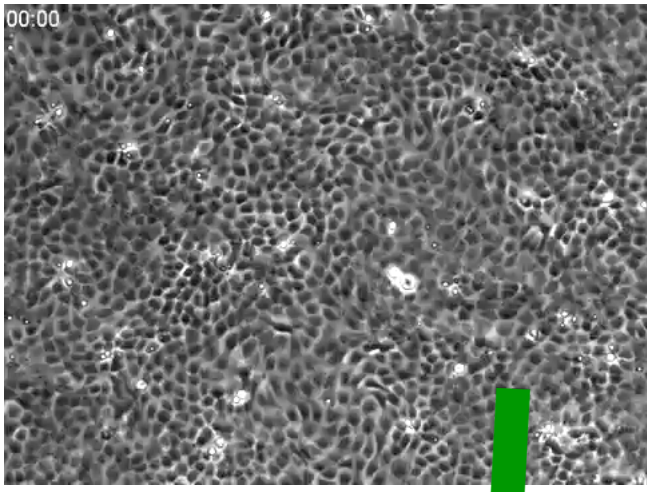
Bacterial competition

Active matter: nature's engines that power life

Each individual cell works as an engine:
consumes energy to create motion

https://www.youtube.com/watch?v=3nbjhpcZ9_g

Cellular tissue



Human cell

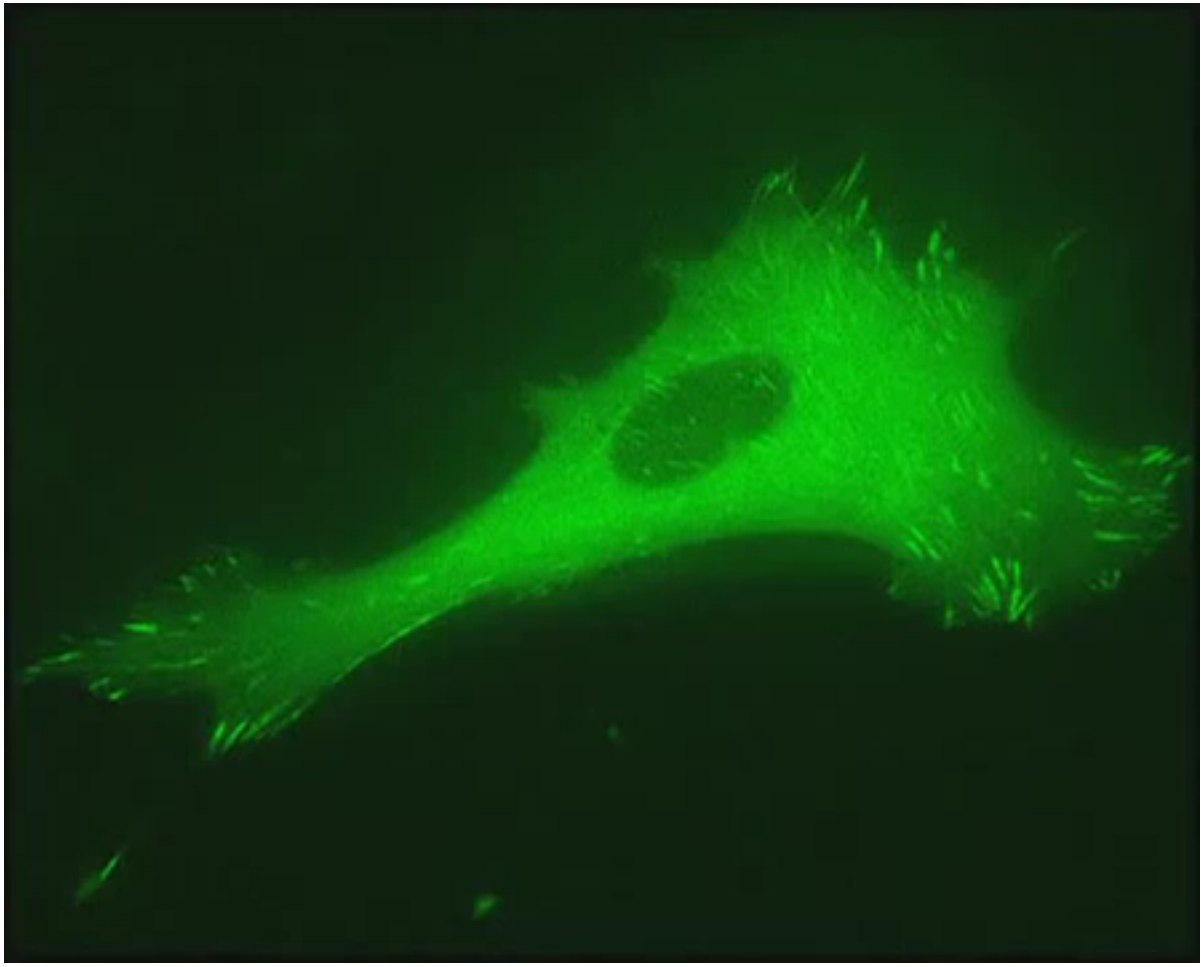
https://www.youtube.com/watch?v=T2MWEc_rrIA

Active matter: nature's engines that power life

Each individual cell works as an engine:
consumes energy to create motion

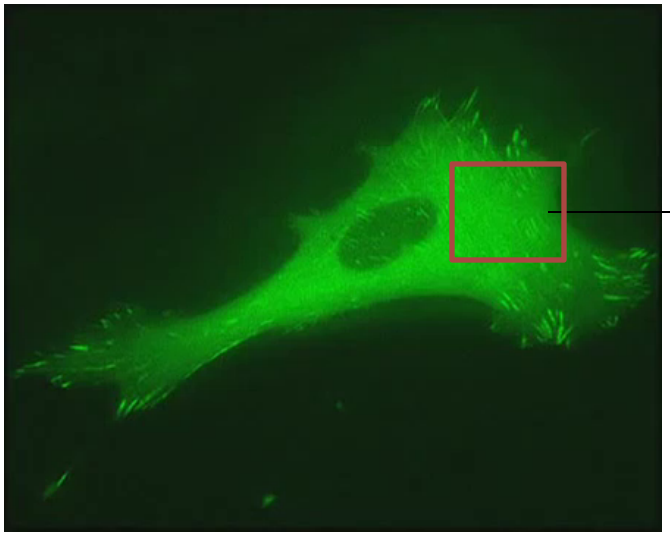
https://www.youtube.com/watch?v=hacbn_xcZdU

Materials inside the cell also move



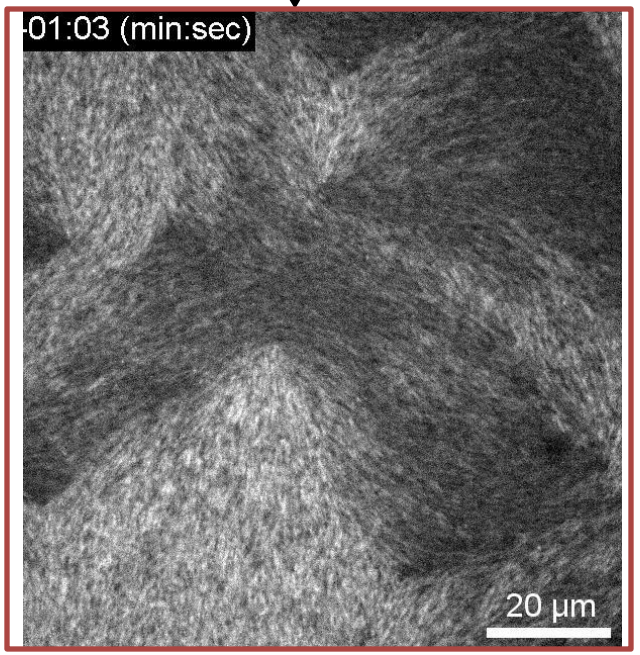
https://www.youtube.com/watch?v=sHFN48il9YY

Materials inside the cell also move



Take materials from inside the cell

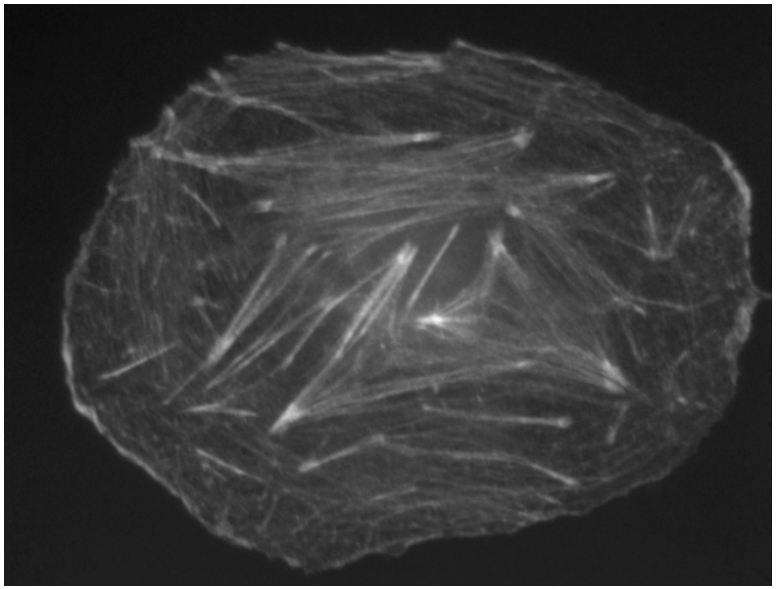
Put them in a dish !



Where does the motion inside the cell come from?

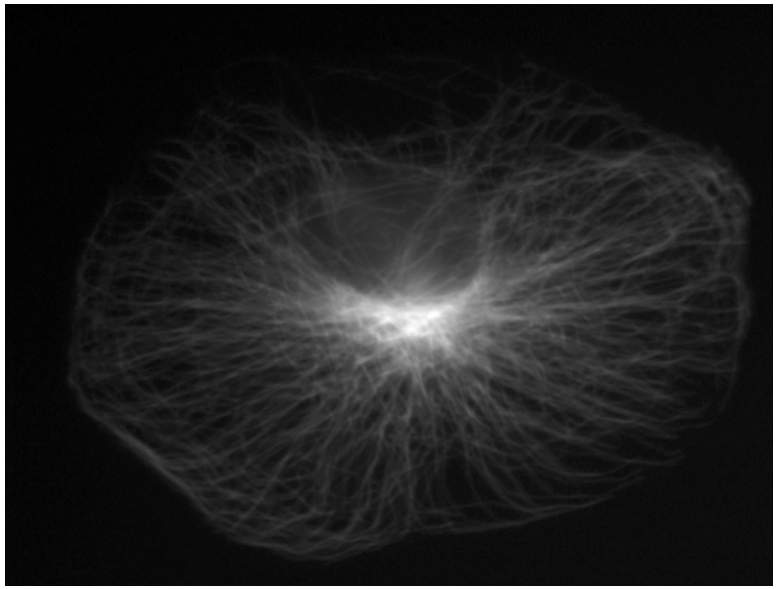
Kumar et al., Science Advances (2018)

A look into the skeleton of a cell

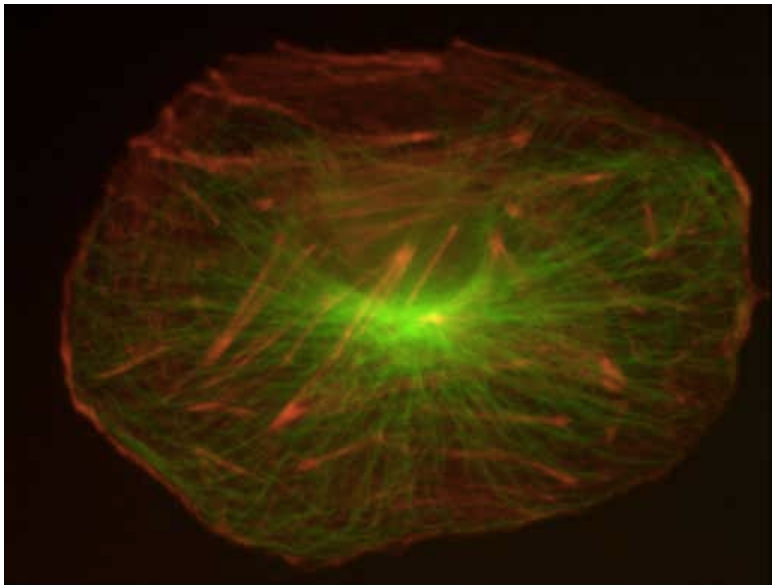


Actin filaments

+

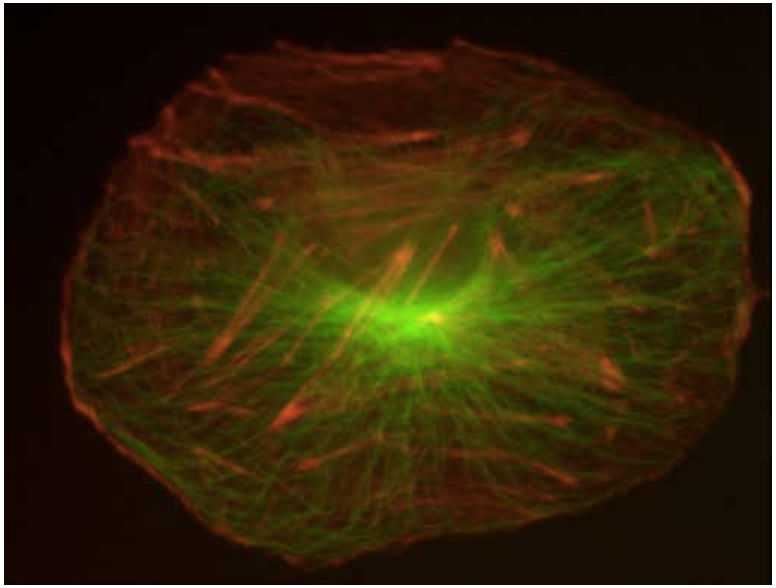


Microtubule filaments



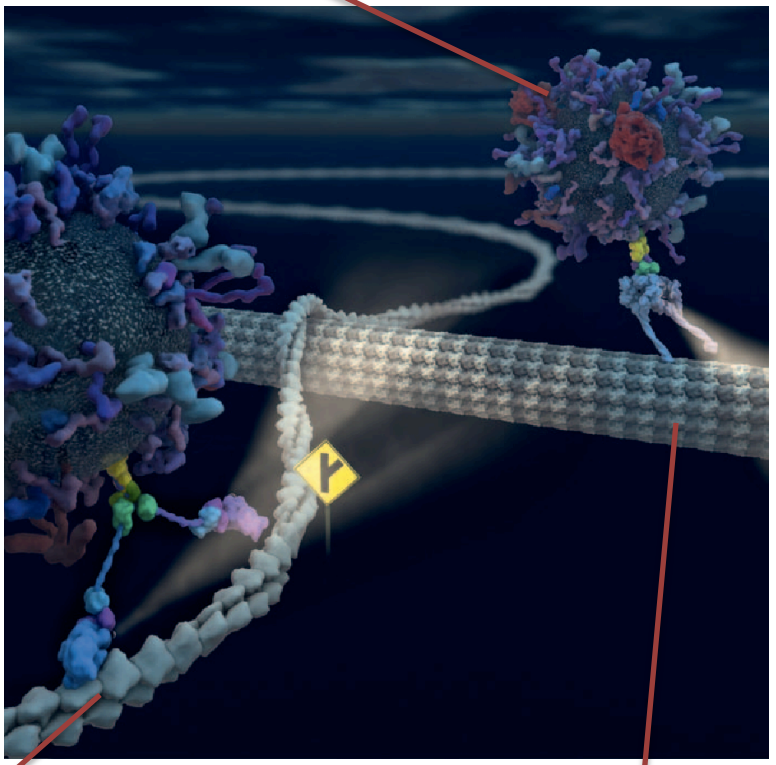
Credit: Imaging Technology Group, Beckman Institute for Advanced Science and Technology, U Illinois Urbana Champaign

A look into cell cytoskeleton



Credit: Imaging Technology Group, Beckman Institute for Advanced Science and Technology, U Illinois Urbana Champaign

???

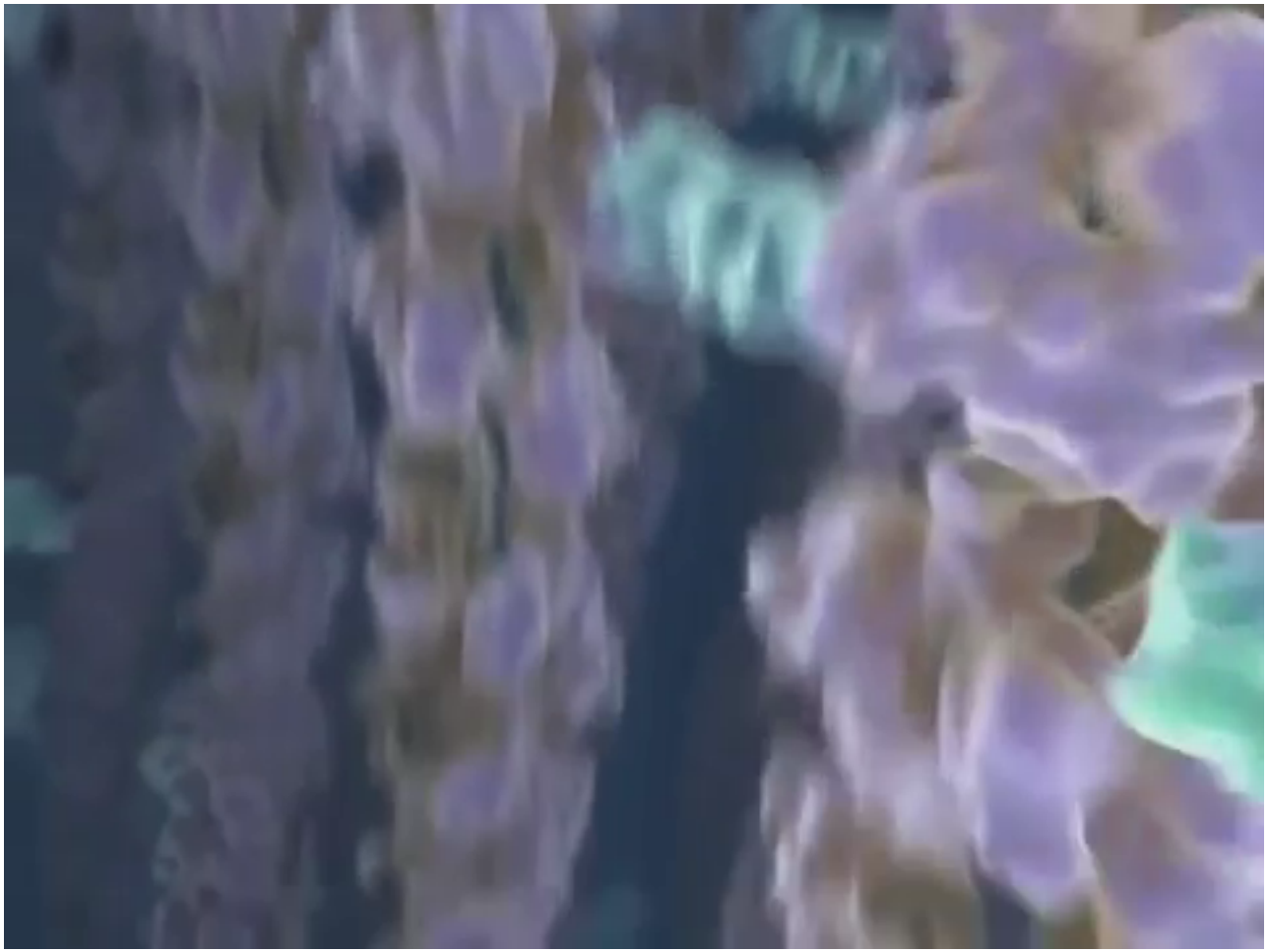


A. Rinaldi, EMBO Reports (2012)

Actin filaments

Microtubule filaments

Filaments are tracks for molecular motors



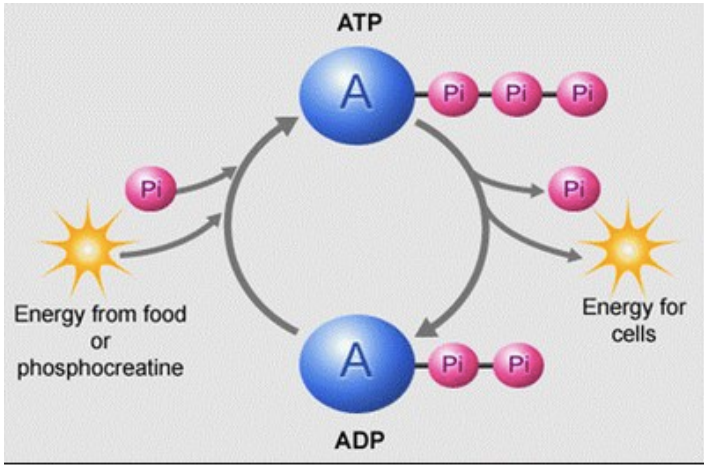
The inner life of a cell, BioVision, Harvard University

Molecular motors work as engines

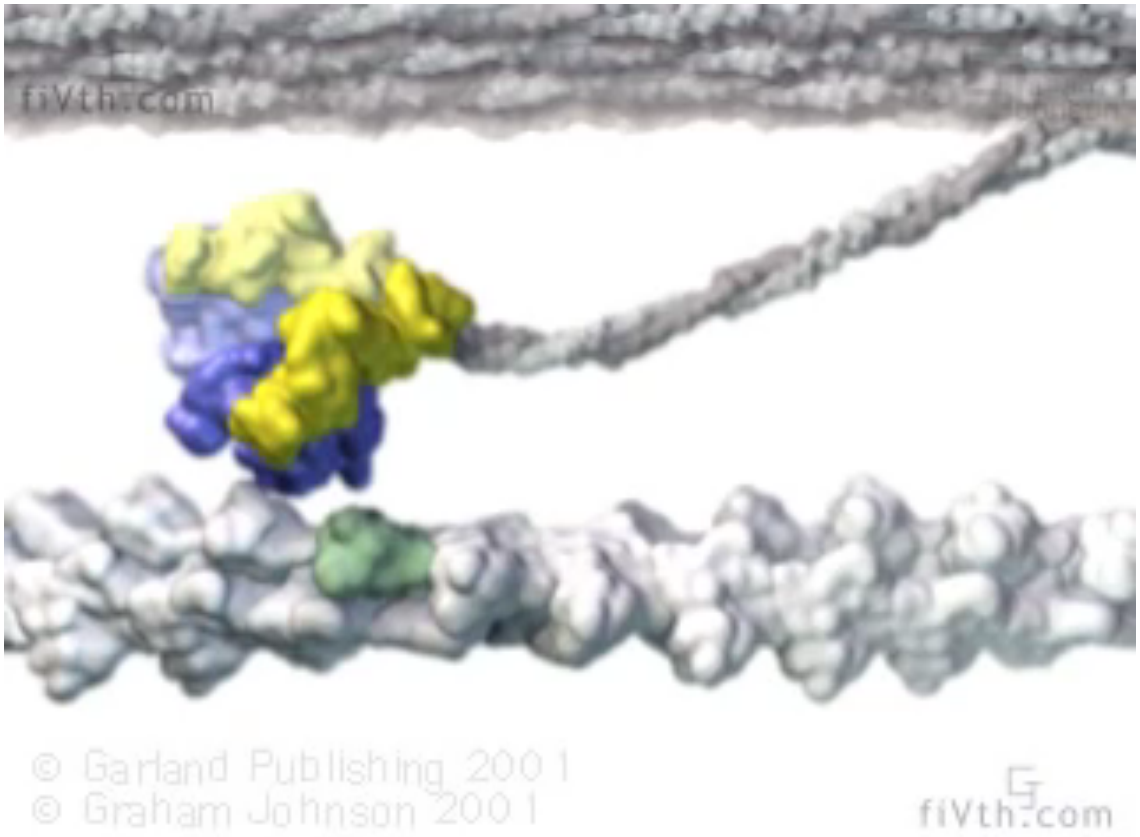
What is the fuel for a molecular motor?

ATP (the molecule of energy – the energy currency of the cells)

- *Its energy comes from food (carbohydrates, fat, …)*
- *100 gram releases ~2 Kilo calorie*

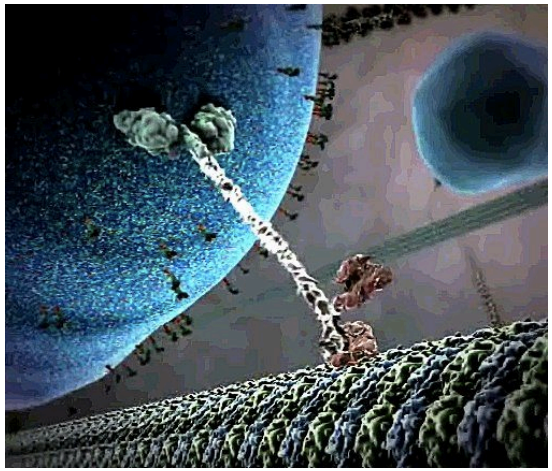


https://www.ptdirect.com



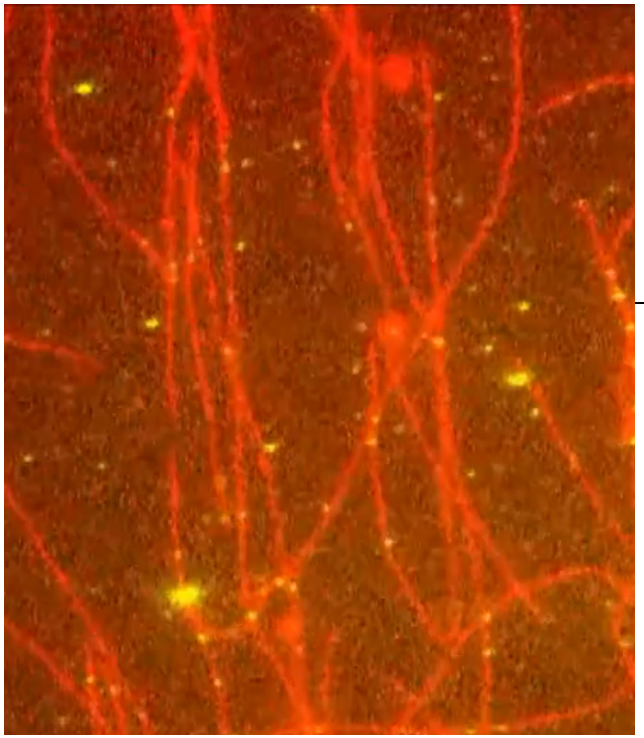
https://www.youtube.com/watch?v=oHDRIwRZRVI

Molecular motors work as engines



	Molecular motors	vs	cars
Velocity	10^{-6} Kilometer/hr		100 Kilometer/hr
Size	10^{-8} meter		2 meter
Movement/Size	10^{5} length/hr		10^{5} length/hr
Efficiency	60%		15%

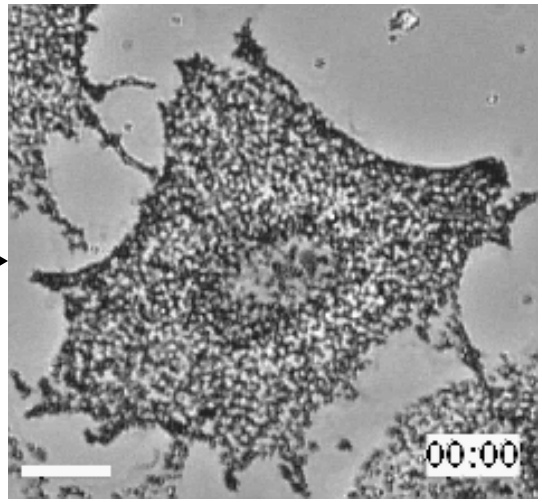
Motors transport materials in the cell

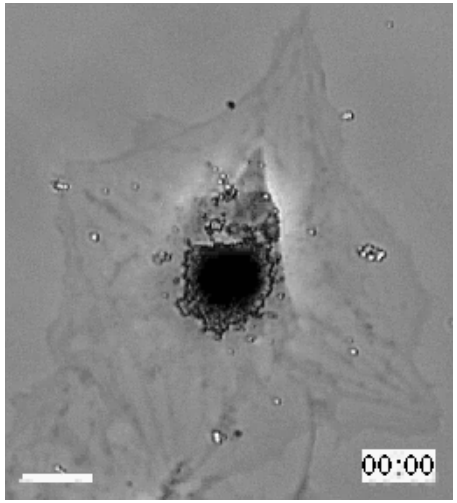


https://www.youtube.com/watch?v=-6g5icw1Zos

Example:

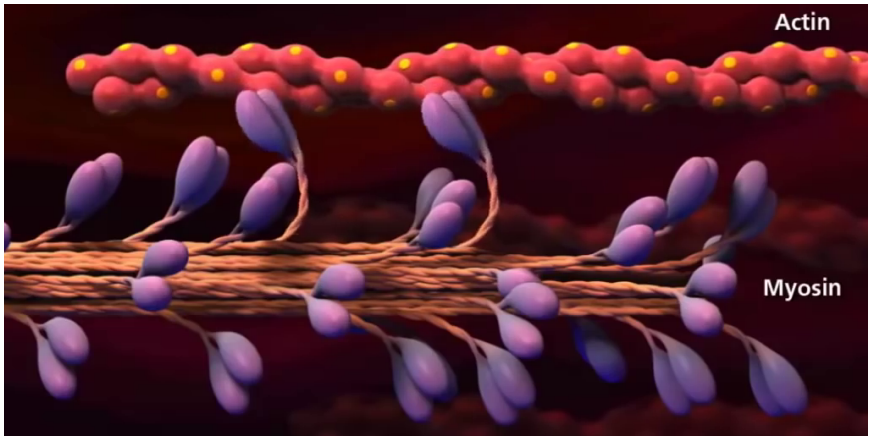
Transport of material for cell color



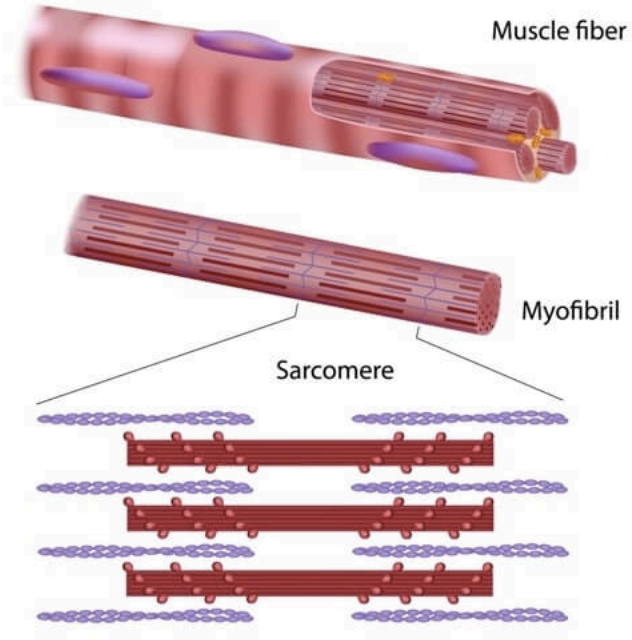


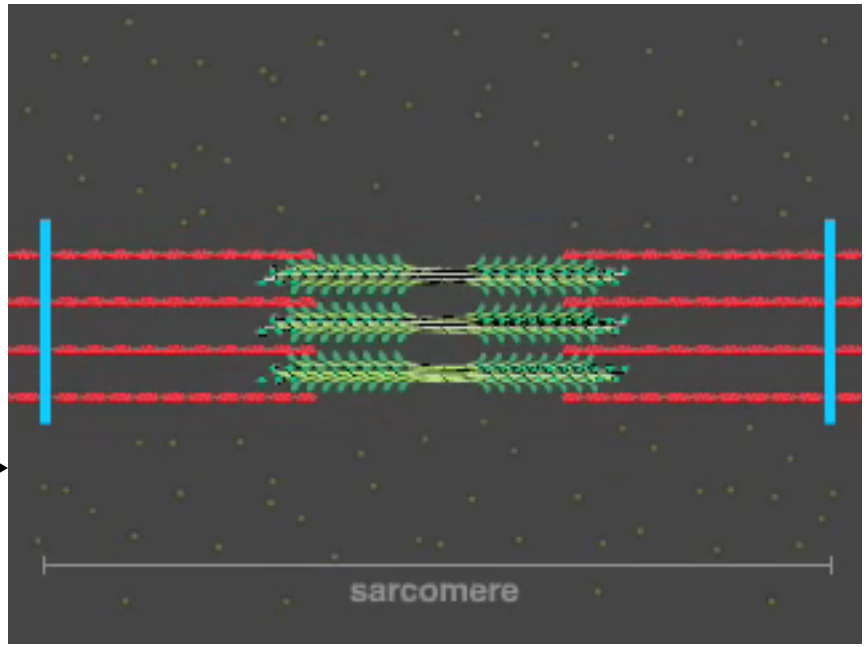
Semenova et al., Current Biology (2008)

Motors move filaments



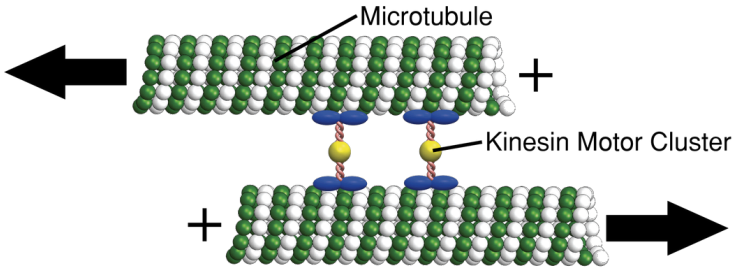
https://www.youtube.com/watch?v=ousflrOzQHc&t=188s



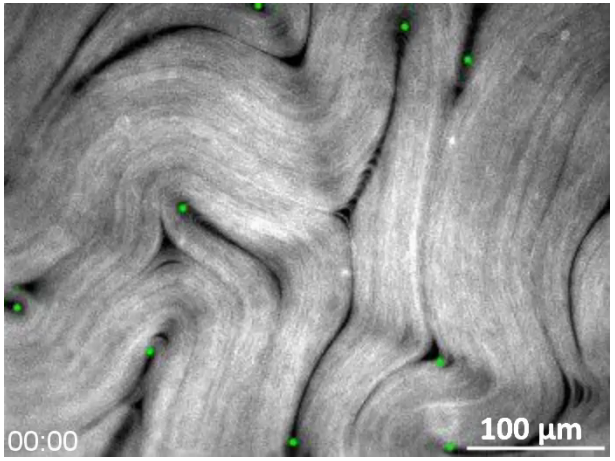


Making artificial cells

System made of subcellular filaments + motor protein

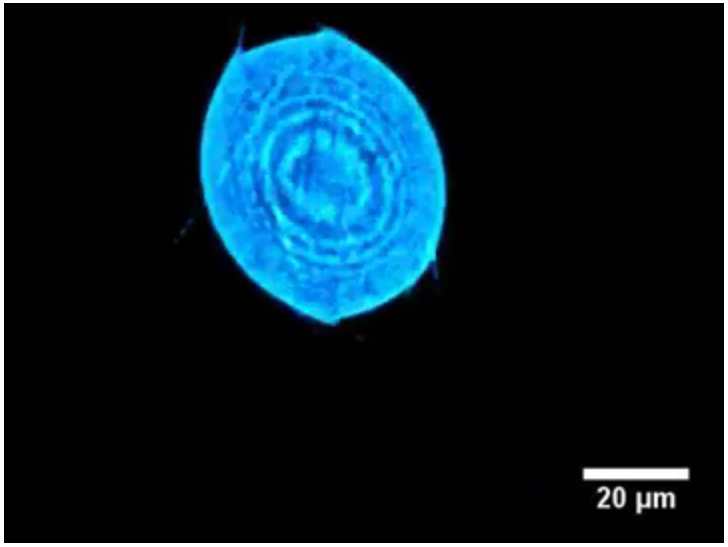


Sanchez et al., Nature 2012
Guillamat et al., PNAS 2016



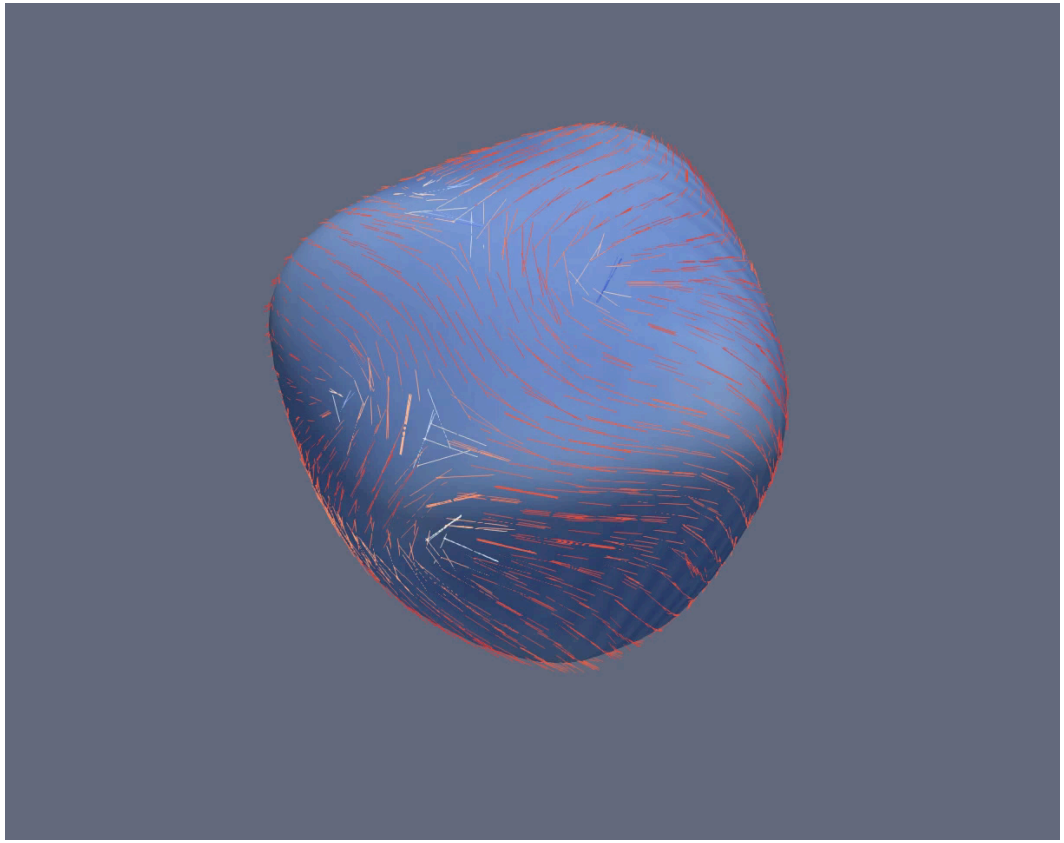
Doostmohammadi, Ignés, Yeomans, Sagués., "*Active nematics*", Nature comm, 2018

Self-deforming vesicles

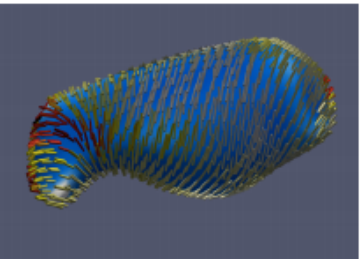


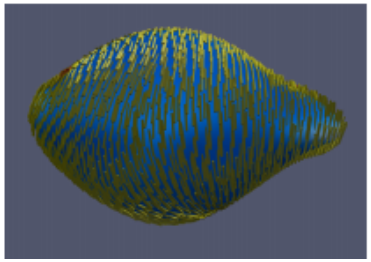
Keber et al., Science (2015)

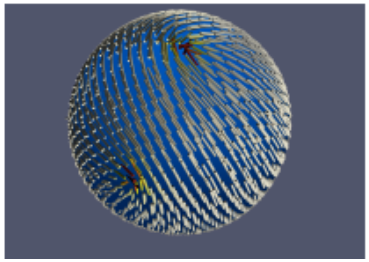
Modeling artificial cells

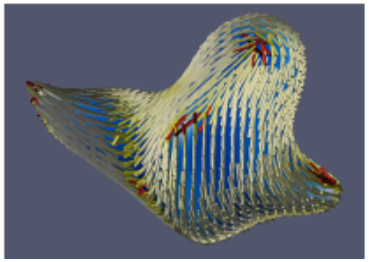


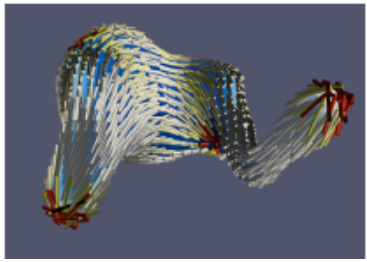
Luuk Metselaar
Oxford



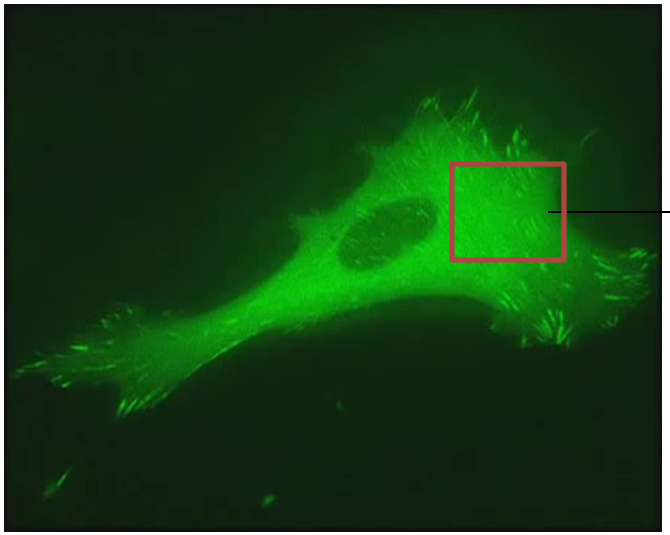






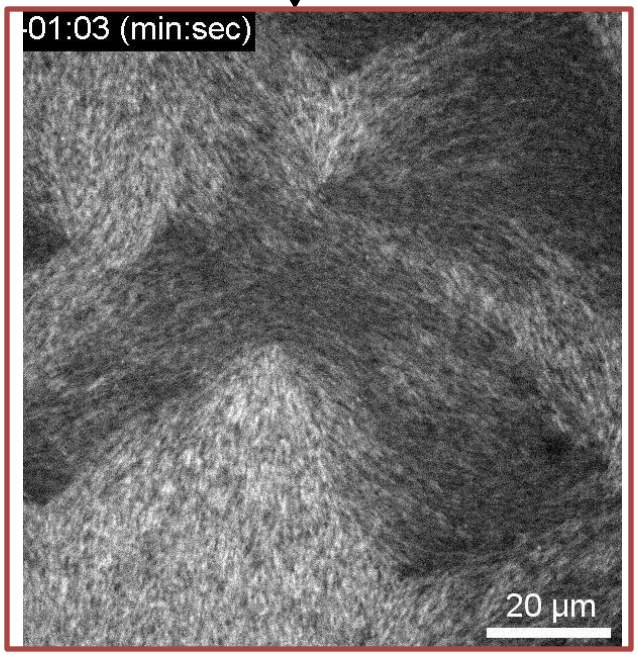


Materials inside the cell also move



Take materials from inside the cell

Put them in a dish !



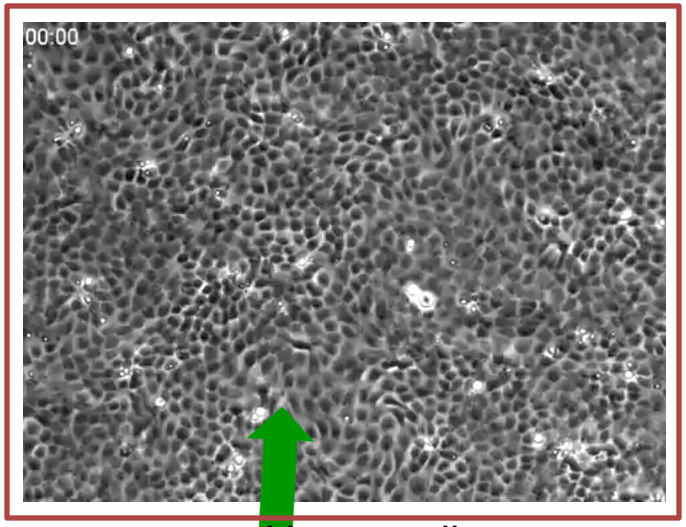
Where does the motion inside the cell come from?

Molecular engines moving filaments inside the cell

Kumar et al., Science Advances (2018)

Active matter: nature's engines that power life

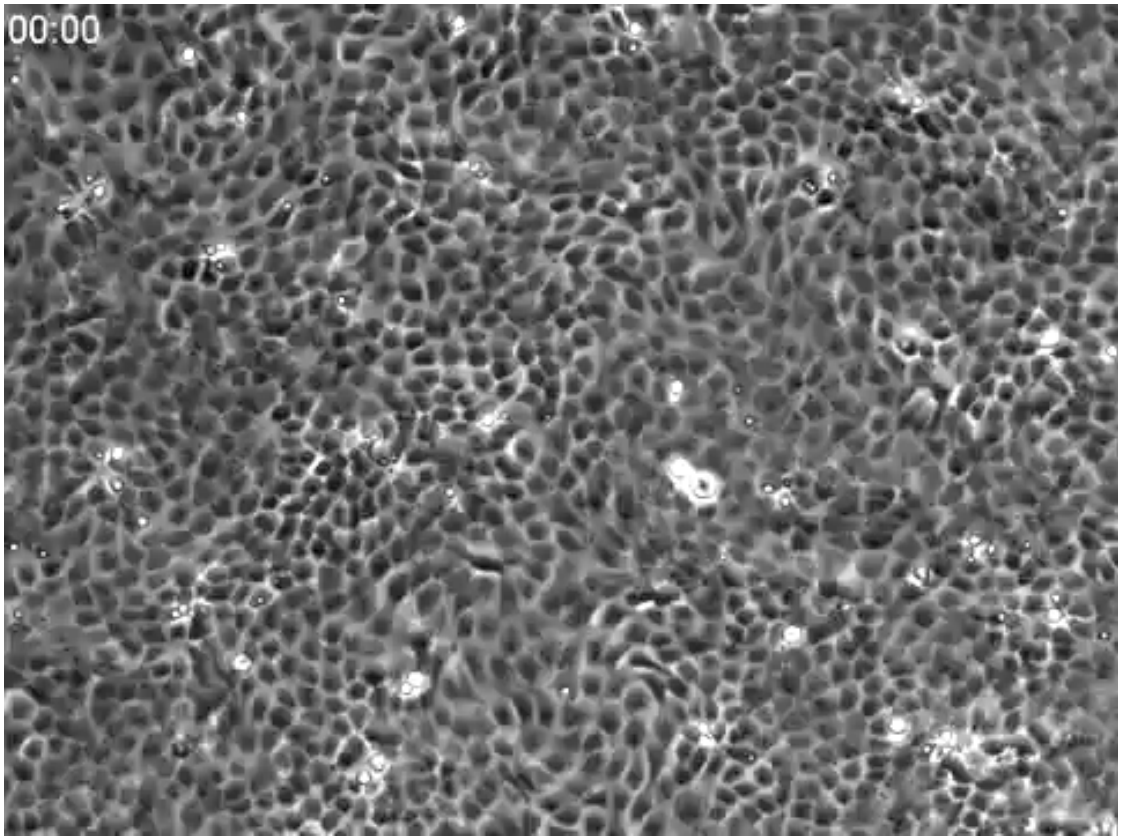
Cellular tissue



Human cell

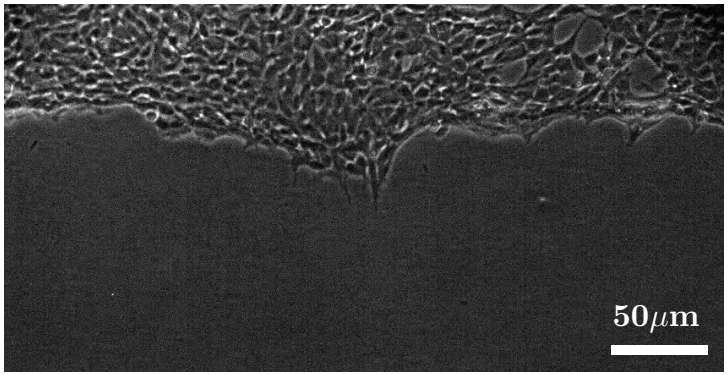
https://www.youtube.com/watch?v=T2MWEc_rrIA

How do cells work together?



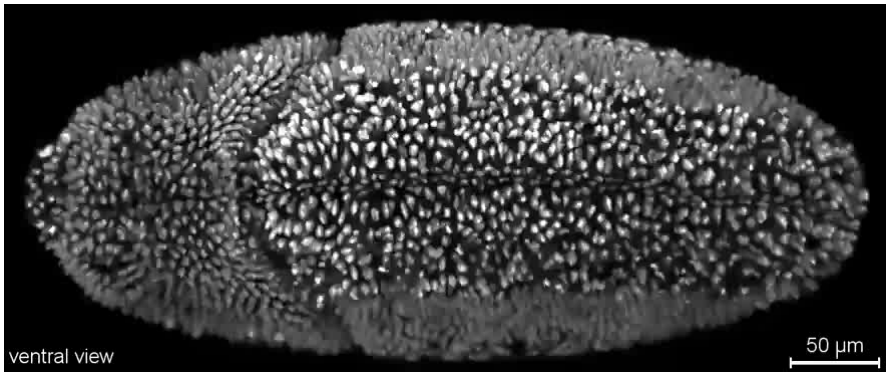
How do cells work together?

Cell invasion



Breast cancer cells, Lene Oddershede, NBI

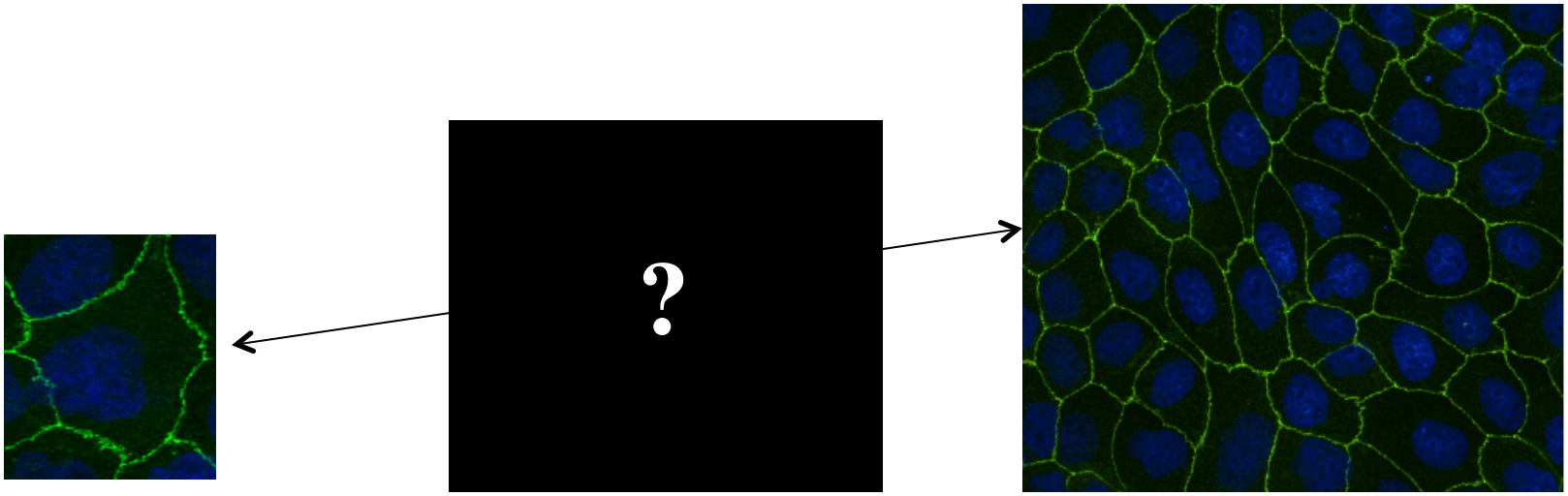
Organ development (morphogenesis)



Fly embryo, Tomer, et al., Nature. Meth.,2012

Wound healing

How do cells work together?



Single cell level

Tissue scale

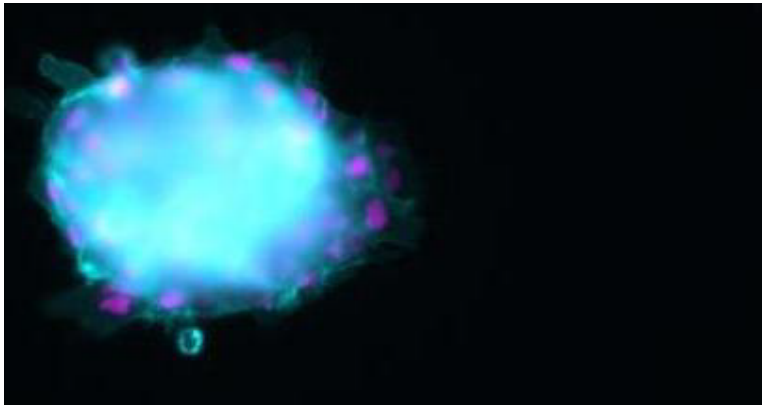
Cells sense mechanical forces

Renaissance in Biophysics

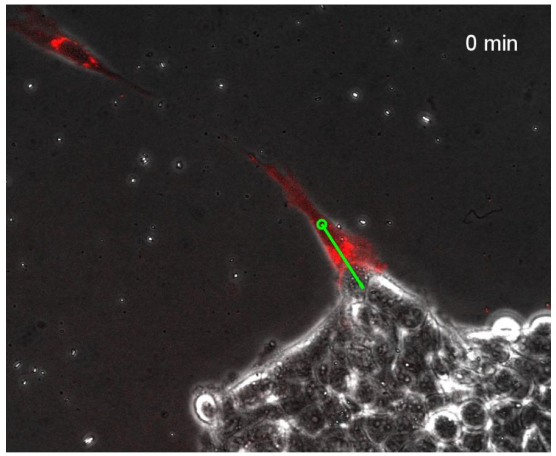
- Force measurement at single cell and at tissue level
- Mechanotransduction:

read mechanical cues ➔ translate into cell function (cell division/death, migration)

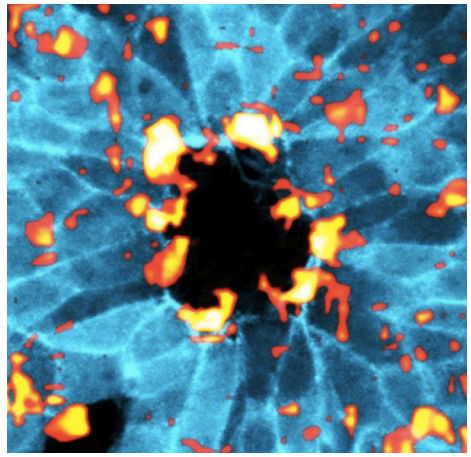
- Master regulator: YAP (yes-associated protein)



Tissue stiffening coordinates cell migration in organ development



Cell-level force guiding tumour mass

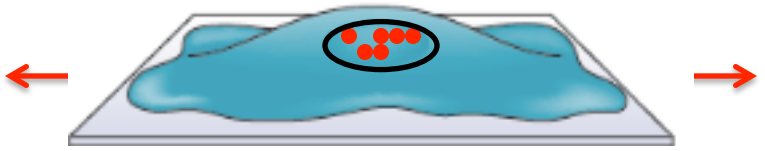


Tissue level forces driving wound healing

Mechanical forces determine cell response

- Reading forces by shuttling protein (YAP) between nucleus & cytoplasm:

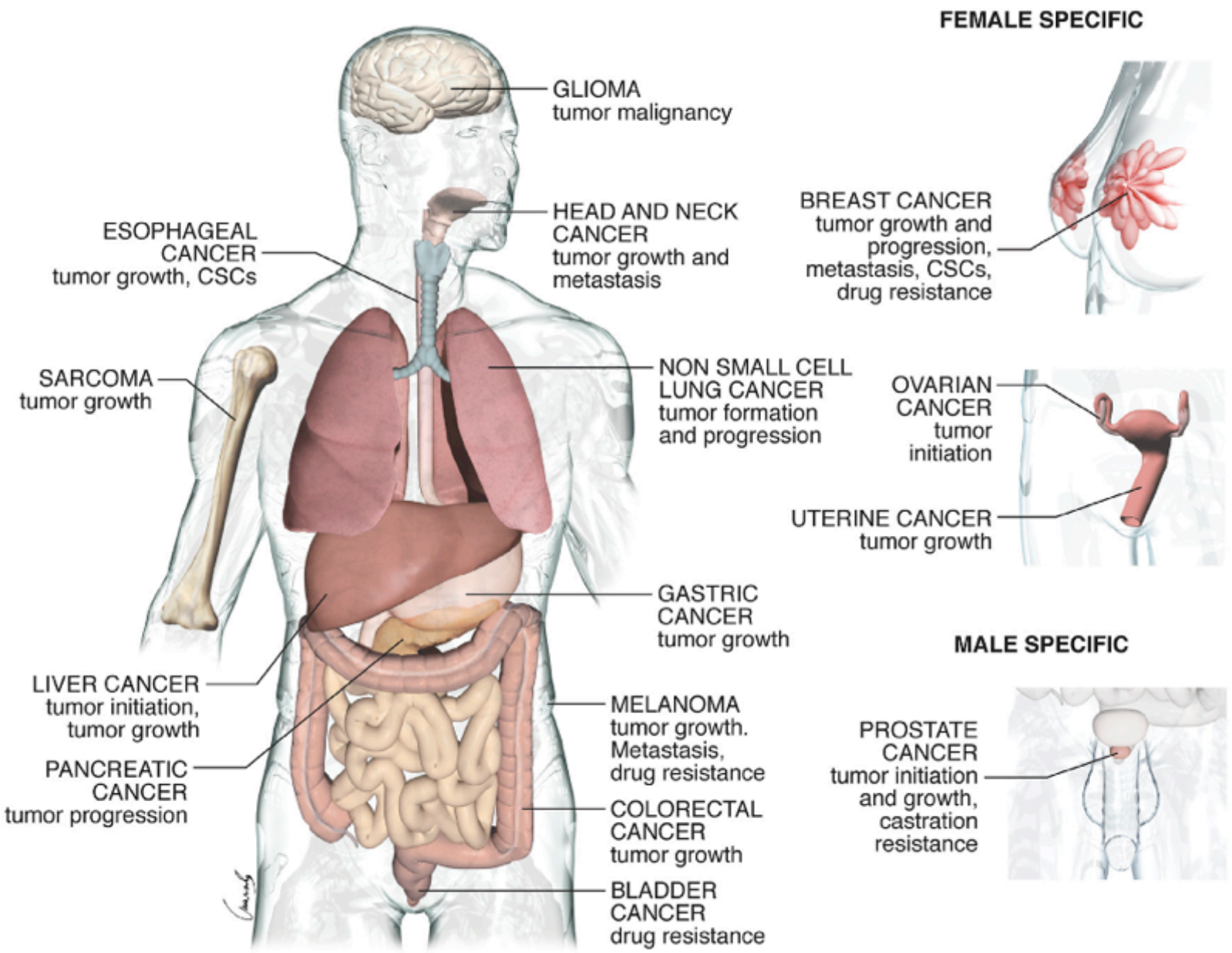
Physical deformation of cell

Stretching	compression
	
Protein in nucleus	Protein in cytoplasm
↓	↓
active (ON)	inactive (OFF)
↓	↓
cell division cell migration	cell death impaired motility

Regulation of signaling ➔ shapes organ during development

Deregulation of signaling ➔ leads to multiple diseases

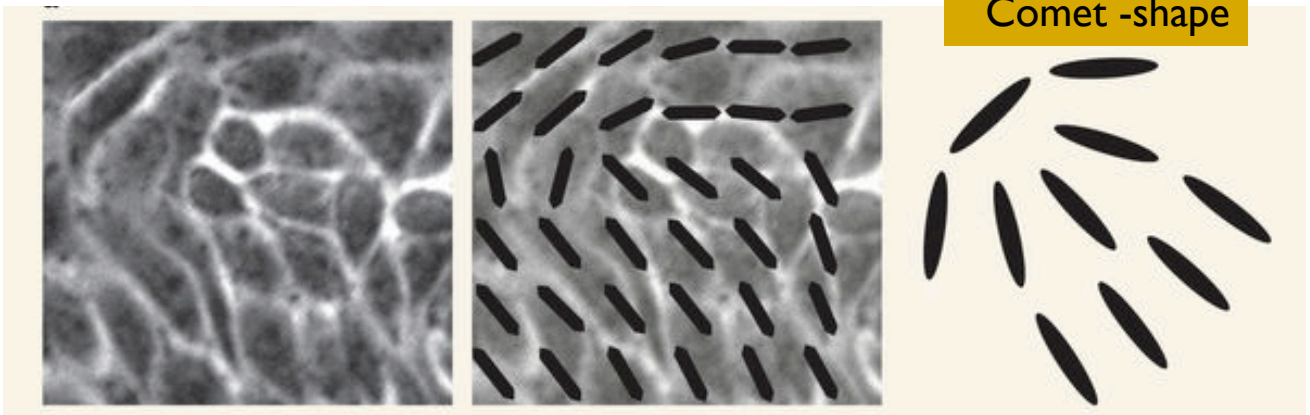
Excessive force ➔ signal overactivation ➔
- Unrestrained division
- Cancer development



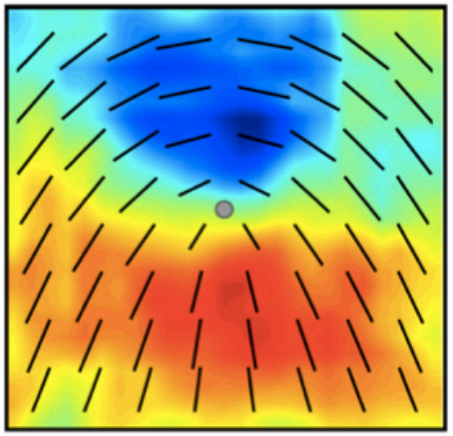
Tumor types for which epidemiological data and functional evidence of YAP activation have been reported.

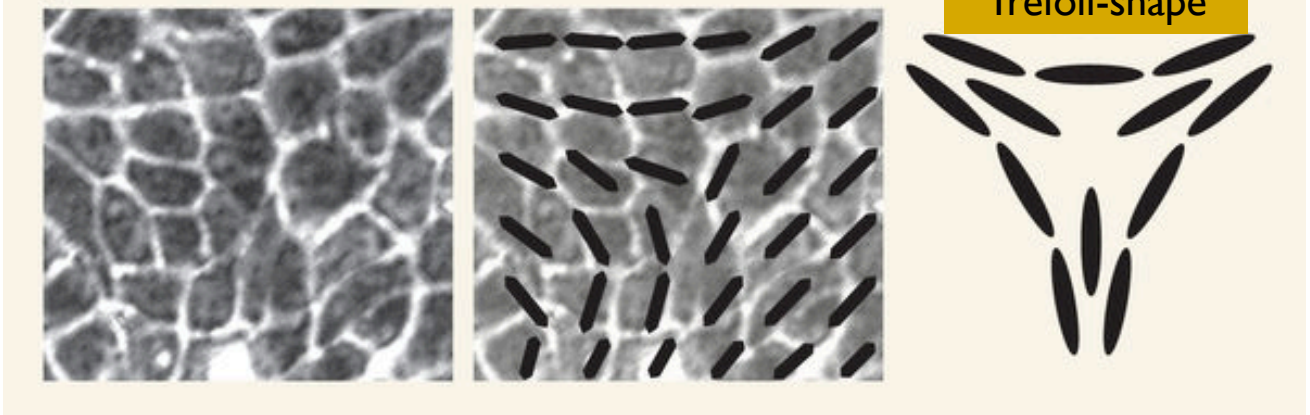
Zanconato et al., Cancer Cell, 2016

Special points for high mechanical forces

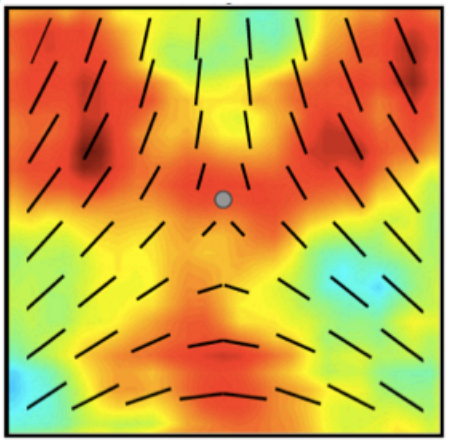


Comet -shape





Trefoil-shape



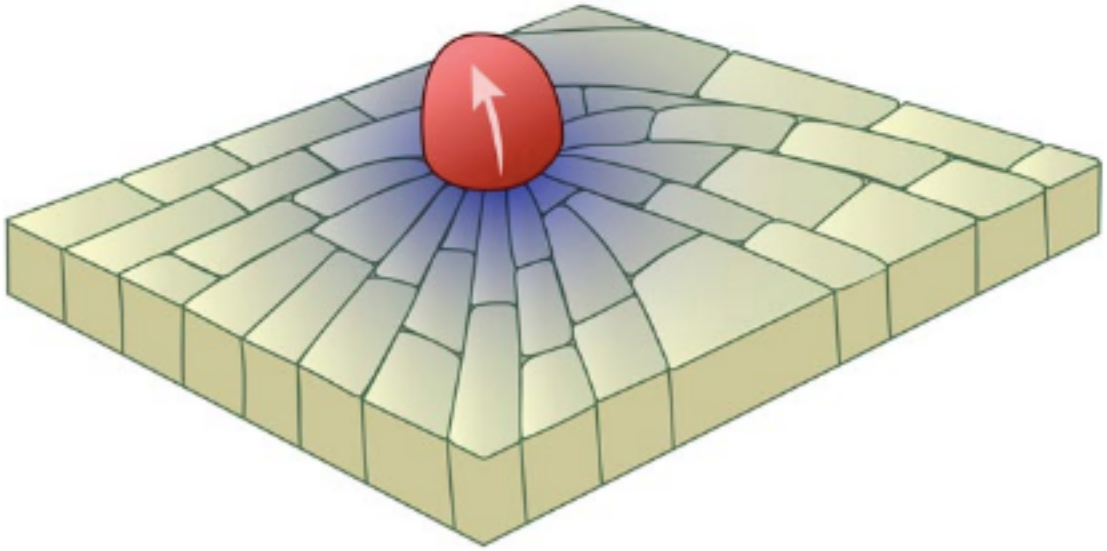
mechanical pressure

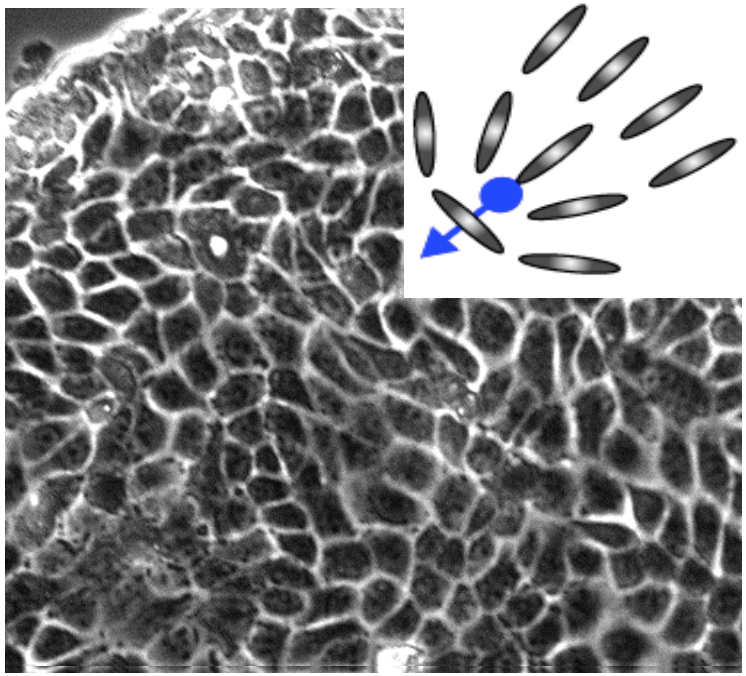
Blue: compressive – Red: tensile pressure

Thuan Beng Saw
National University of Singapore

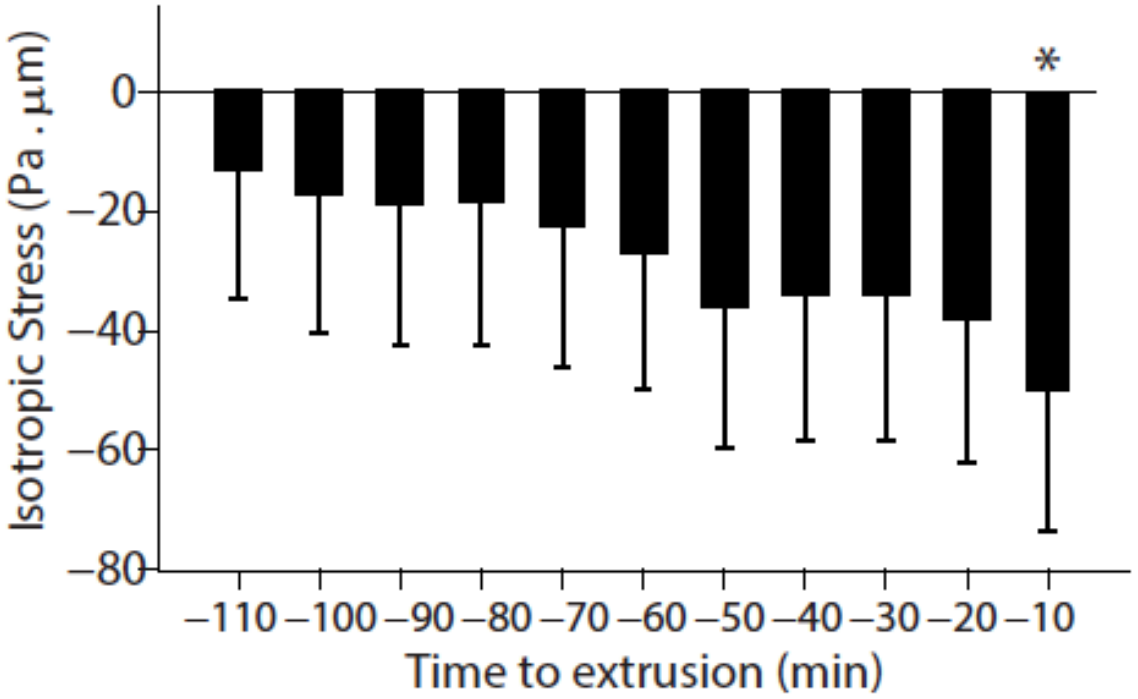
Saw, et al., Nature (2017)

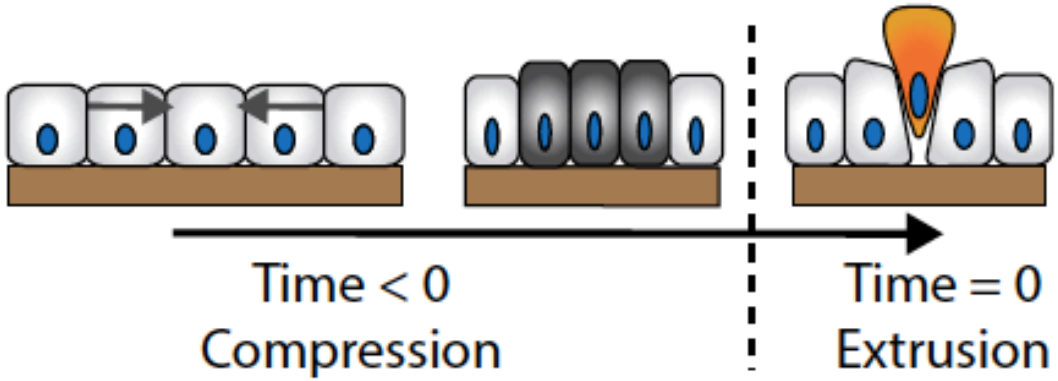
Cells die and get removed at comets



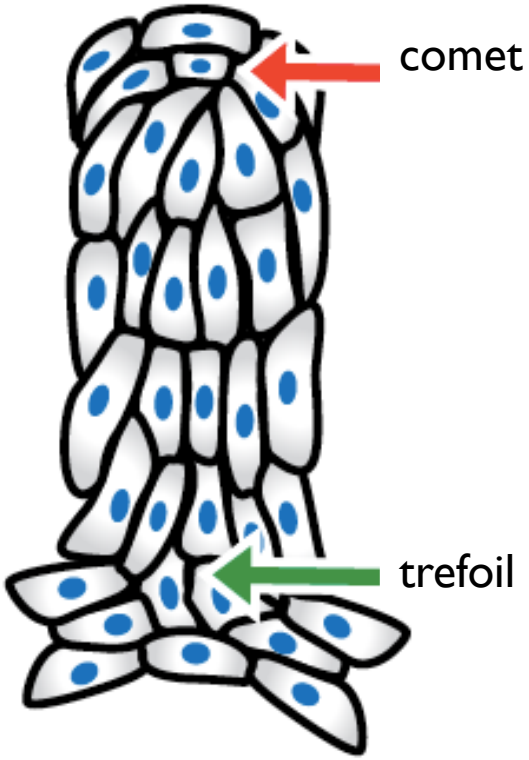


Compressive stress builds up before extrusion



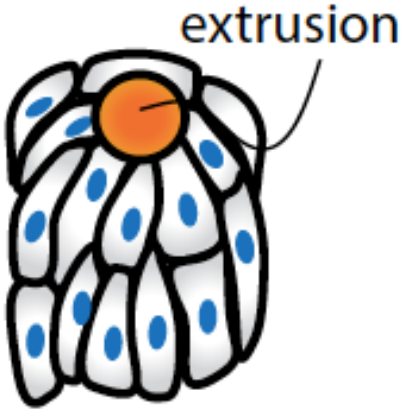


Cell death & extrusion



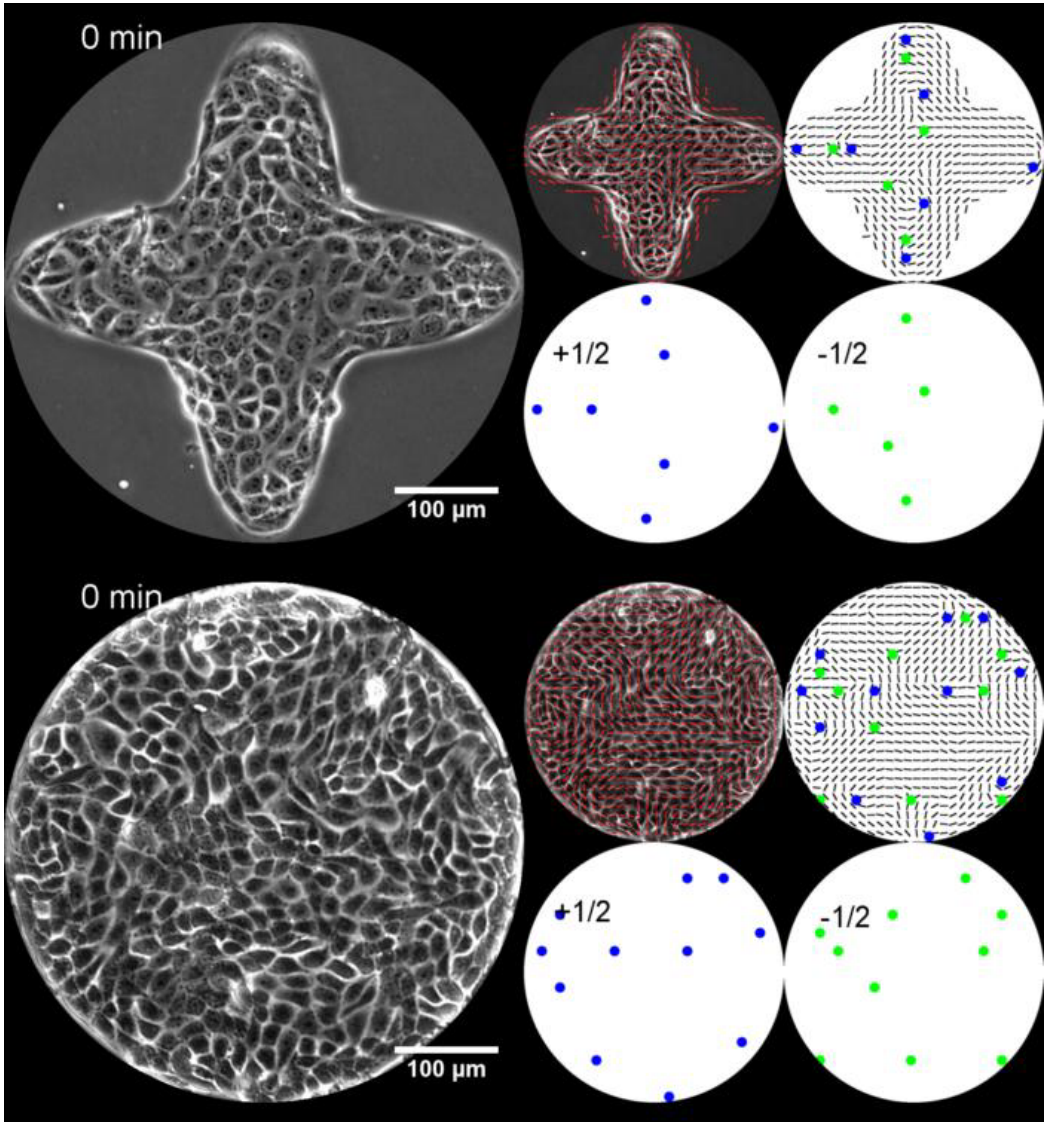
I. Collective motion of cells generates comets and trefoils

II. High compression At comet heads kills the cells

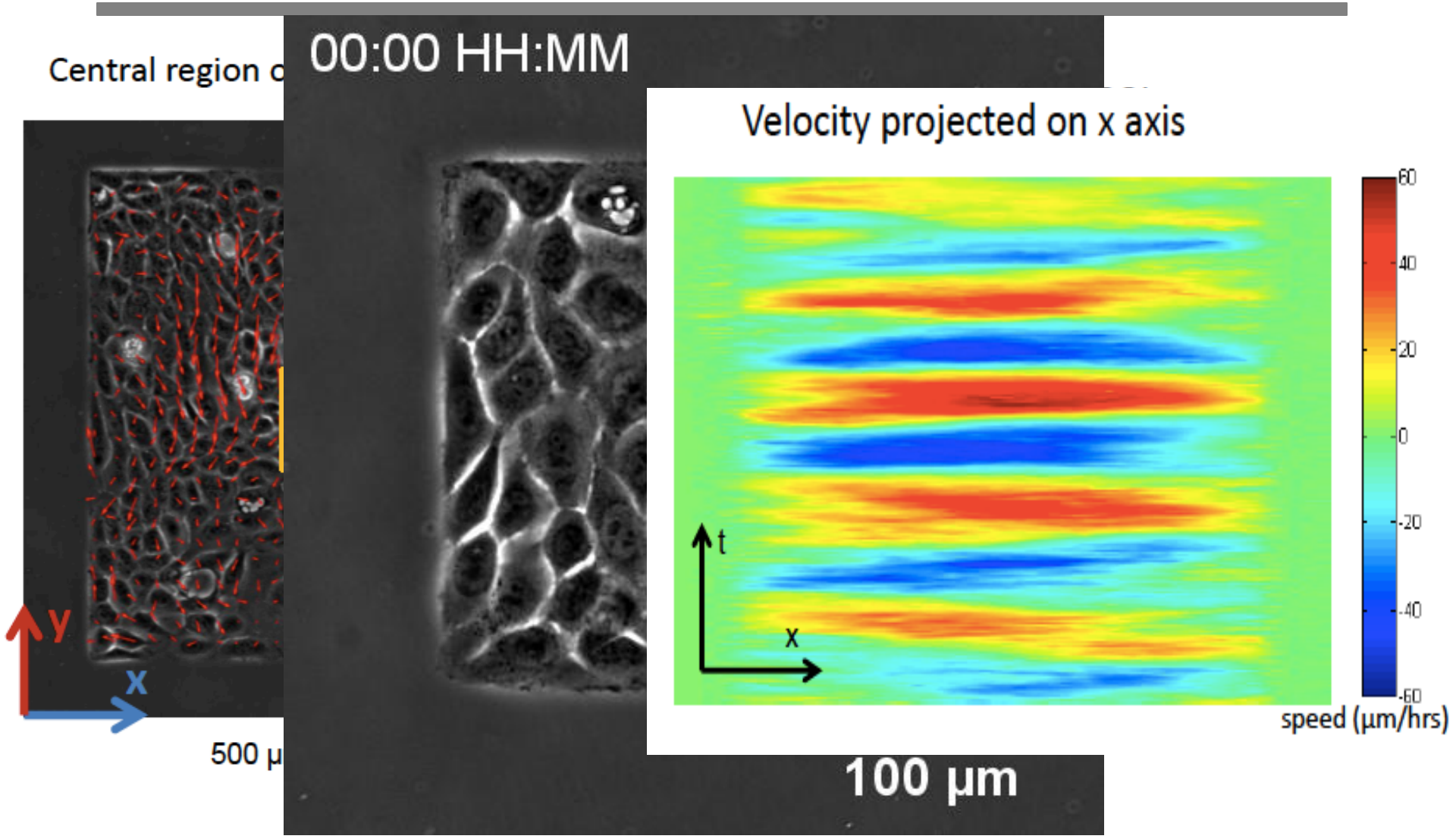


III. Dead cells are pushed out of the layer

Can we control cell death?



Cells oscillate together when they are confined

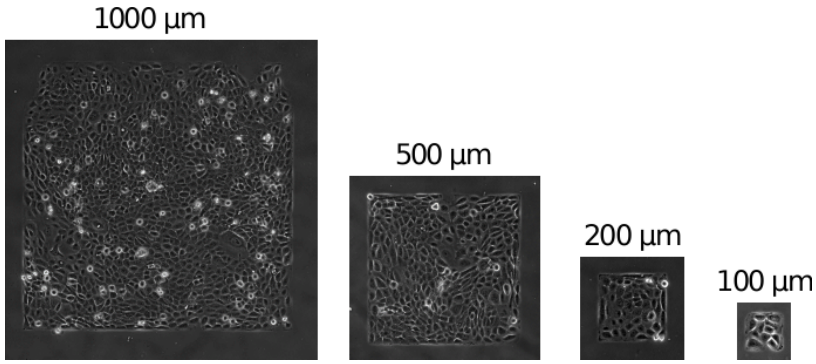


HaCaT cells in a square confinement

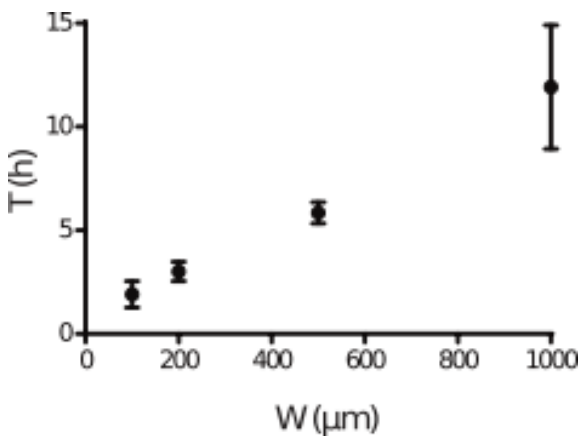
Benoit Ladoux's Lab, Paris Diderot

Oscillations depend on the size of the box

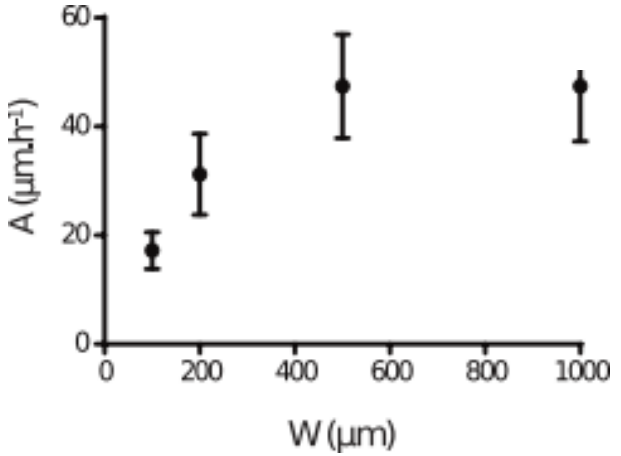
Size of confinement controls the properties of the oscillations:



Period



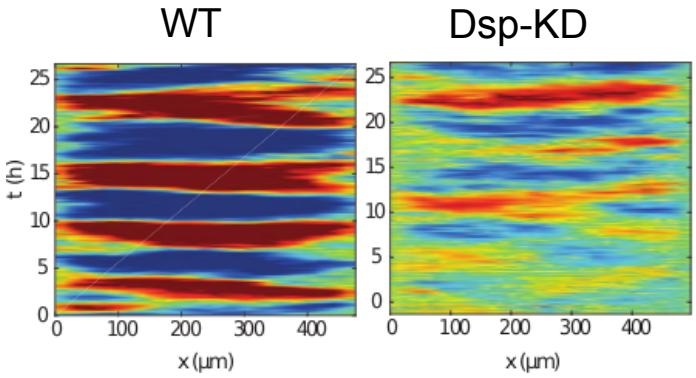
Amplitude



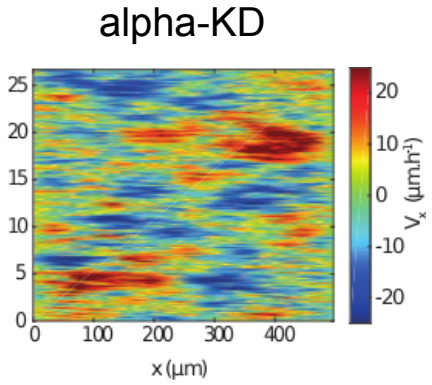
Genetic & molecular perturbations

- Cell motion: Inhibition of molecular motors

→ cell speed decreases rapidly
→ weaker oscillations still visible



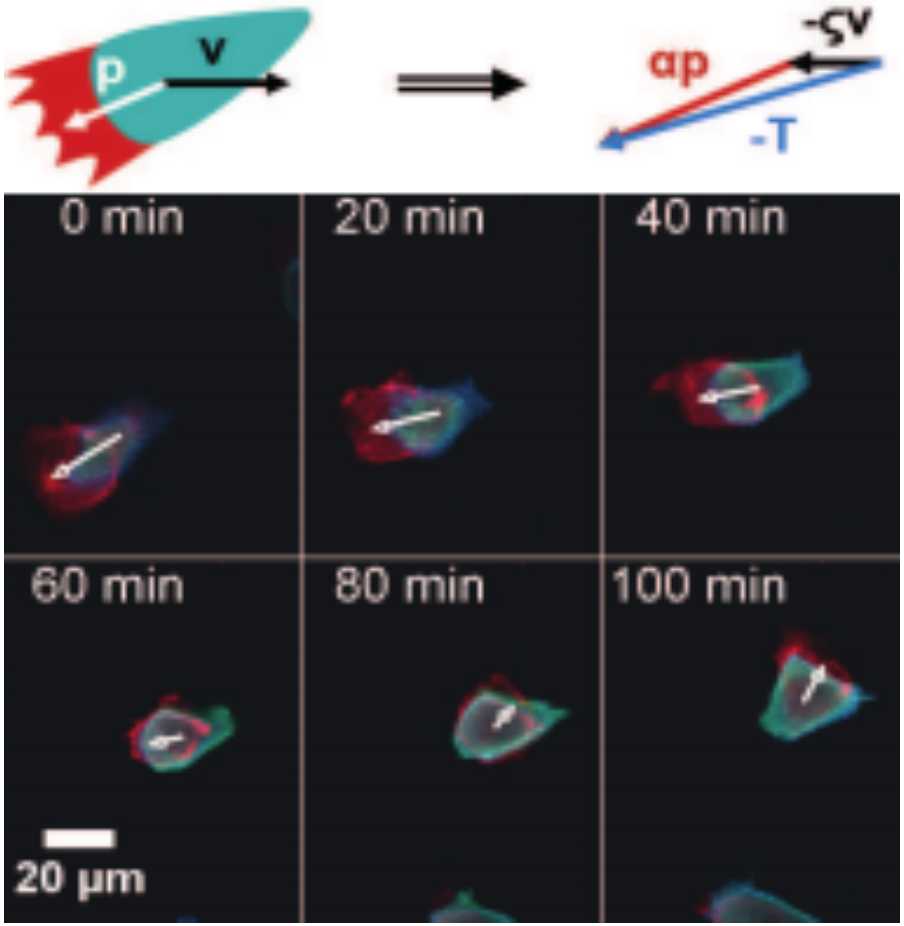
- Cell-cell contacts: Inhibition of the cell-cell force transmission
  → (dsp) oscillations are much weaker
  → (alpha-cat) oscillations completely disappear



Only force transmission at cell-cell junctions seems to be crucial

Mechanism of cell reorientation

- The direction of the motion of cell follows the force direction with a delay



Needed: model of many cells working together

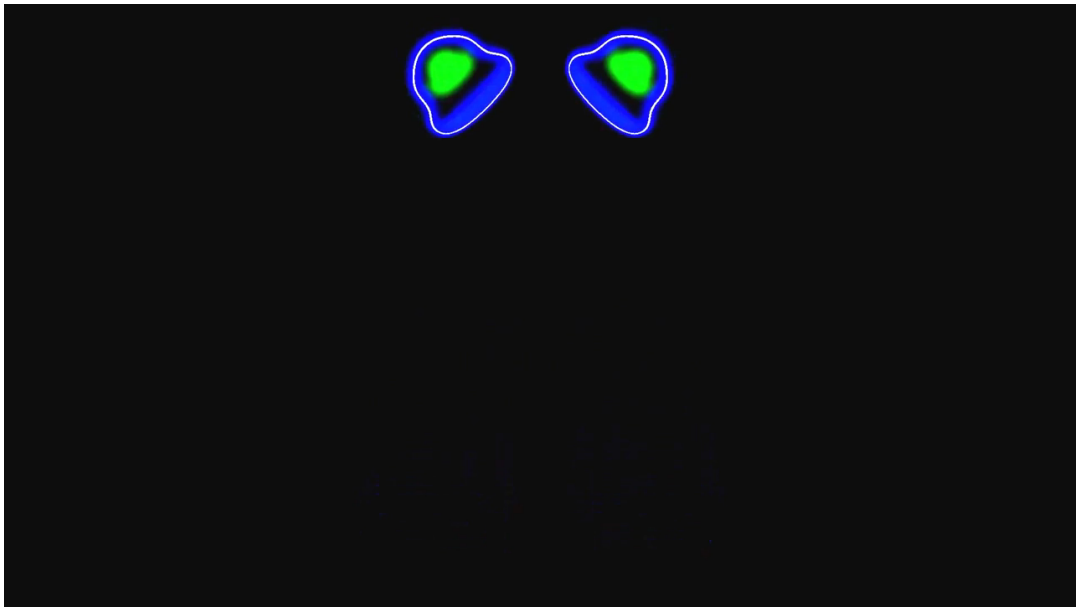
Cells as moving deformable droplets

Each cell is moving

Cells bump into each other

Cells can deform

Romain Mueller
Oxford



Löber et al., Scientific Reports (2015)

Alignment dynamics

- From experiments: velocity follows force with delay

- Hence we set

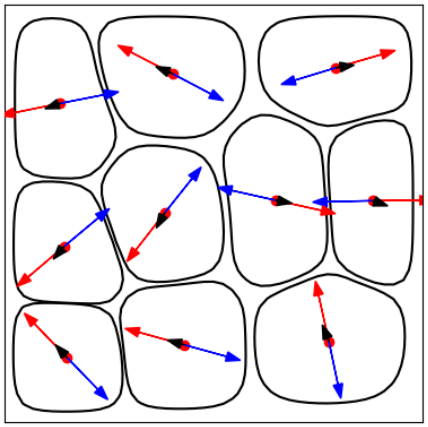
$$\mathbf{p}_i = (\cos\theta_i, \sin\theta_i)$$

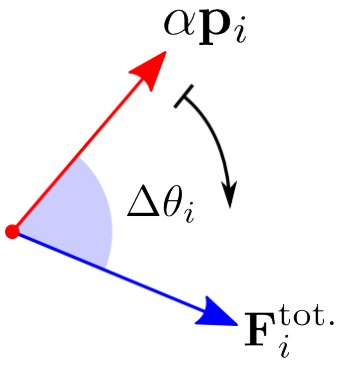
$$\partial_t \theta_i = -J\,|\mathbf{F}_i^{\text{tot.}}|\,\Delta\theta_i$$

Direction of cell motion

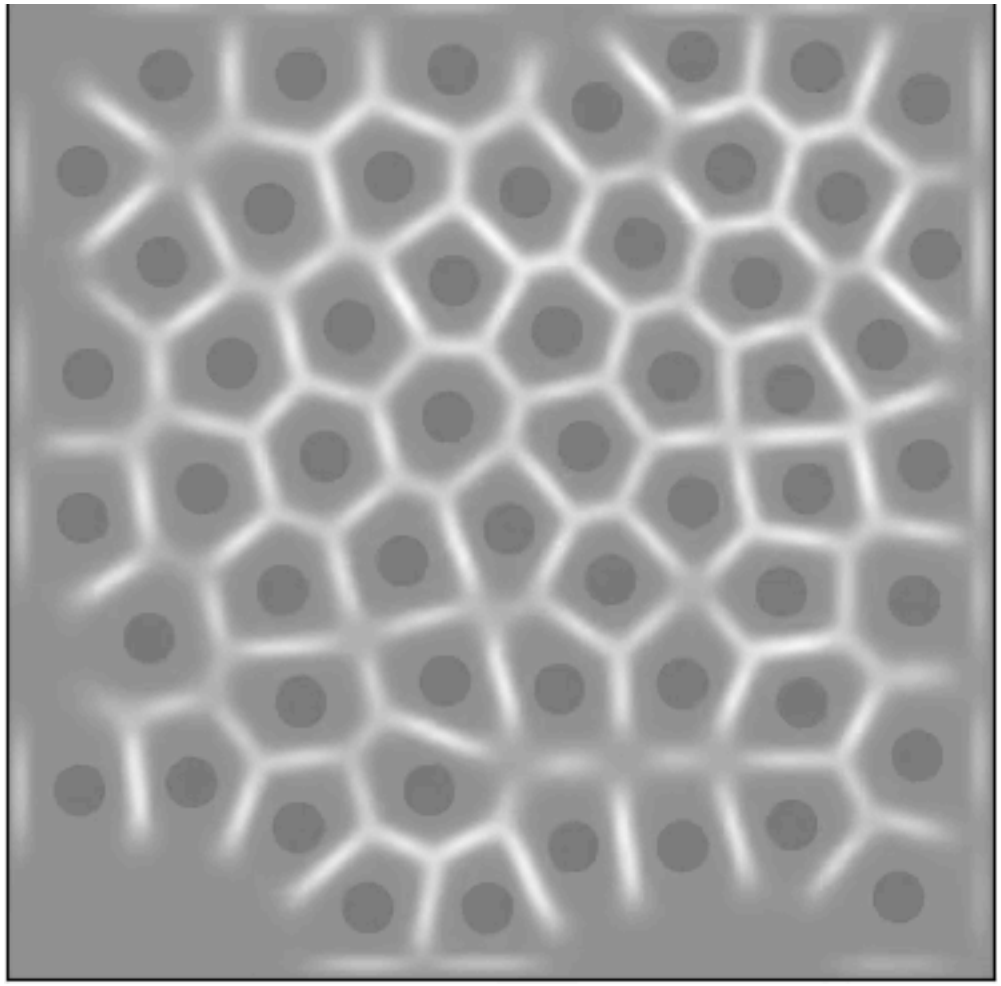
Delay time

Total force on the cell from its neighbors

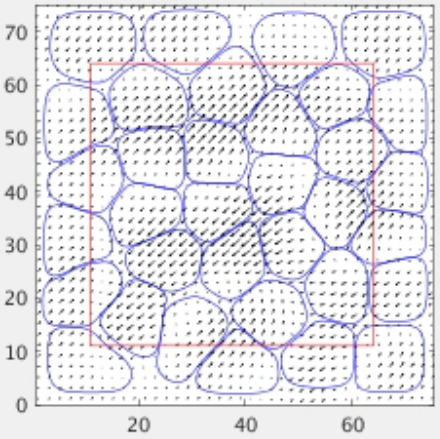


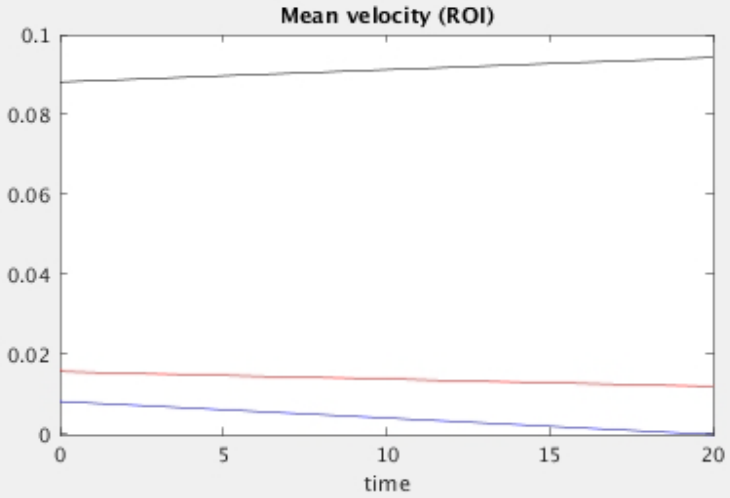


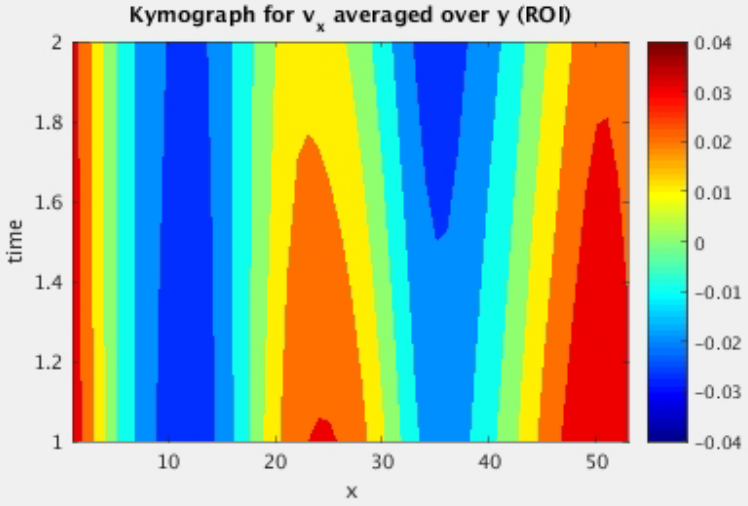
Simulations: cells in a box

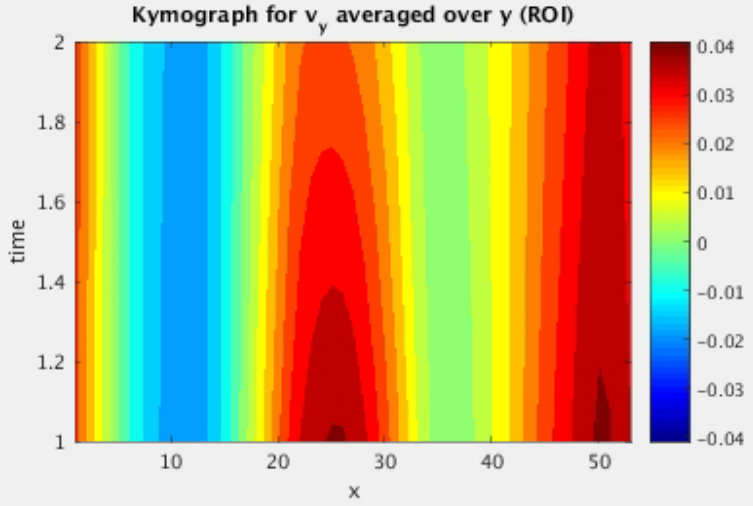


Simulations: Cell-based approach



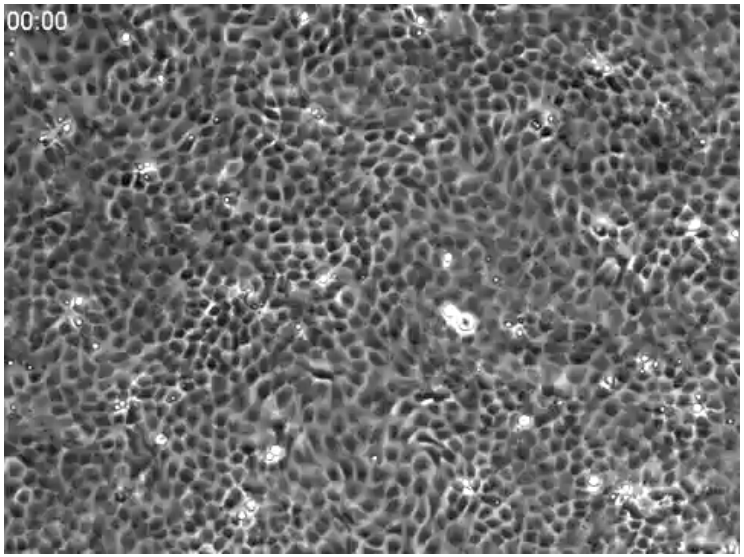


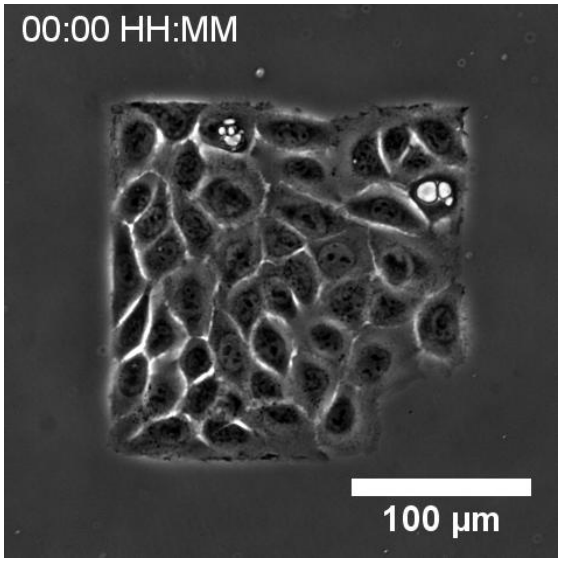


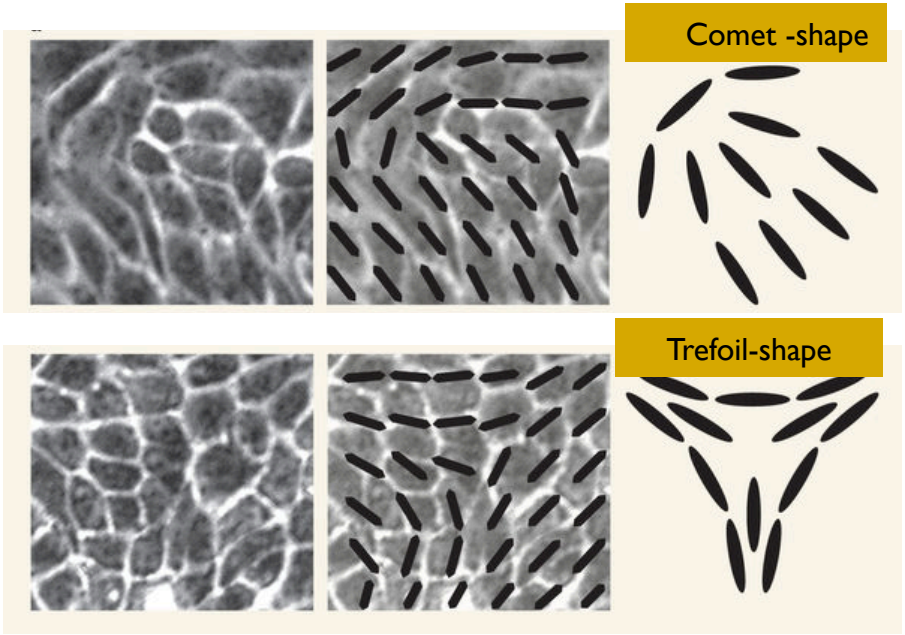


Peyret, et al., Biophysical Journal (2019)

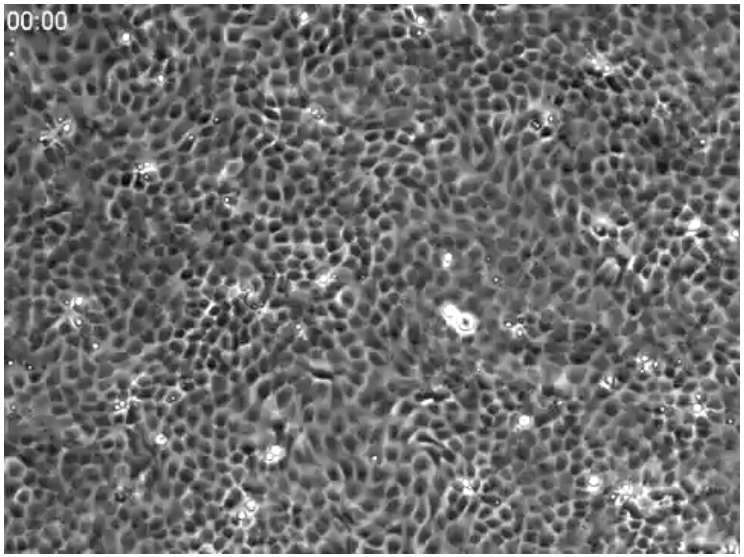
Cells move collectively

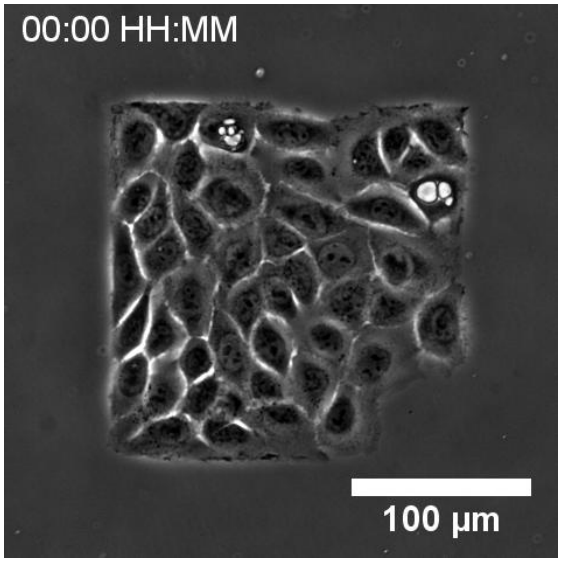


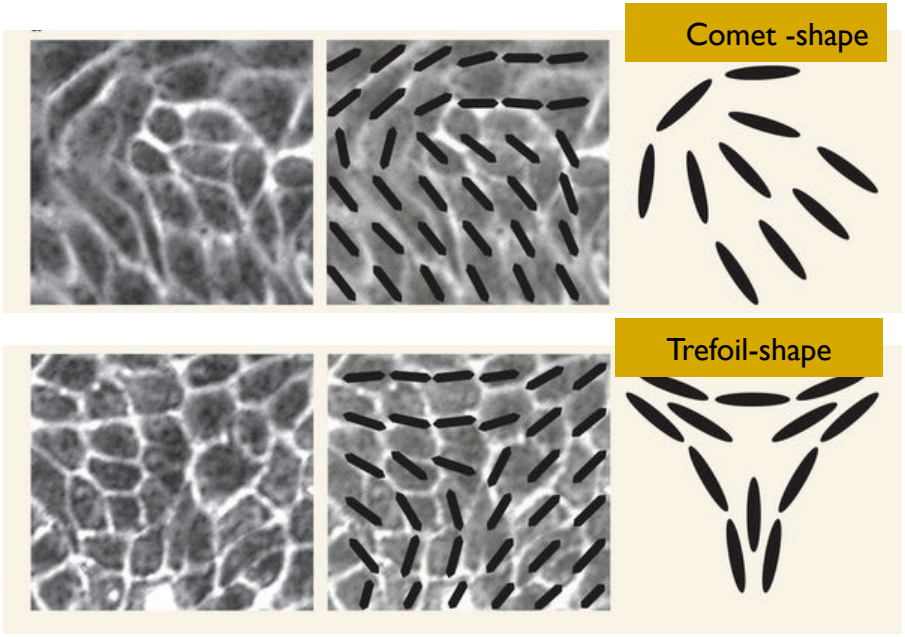




From Part A: Cells move collectively







Collective motion is common in living systems

Surfing with a starling murmuration

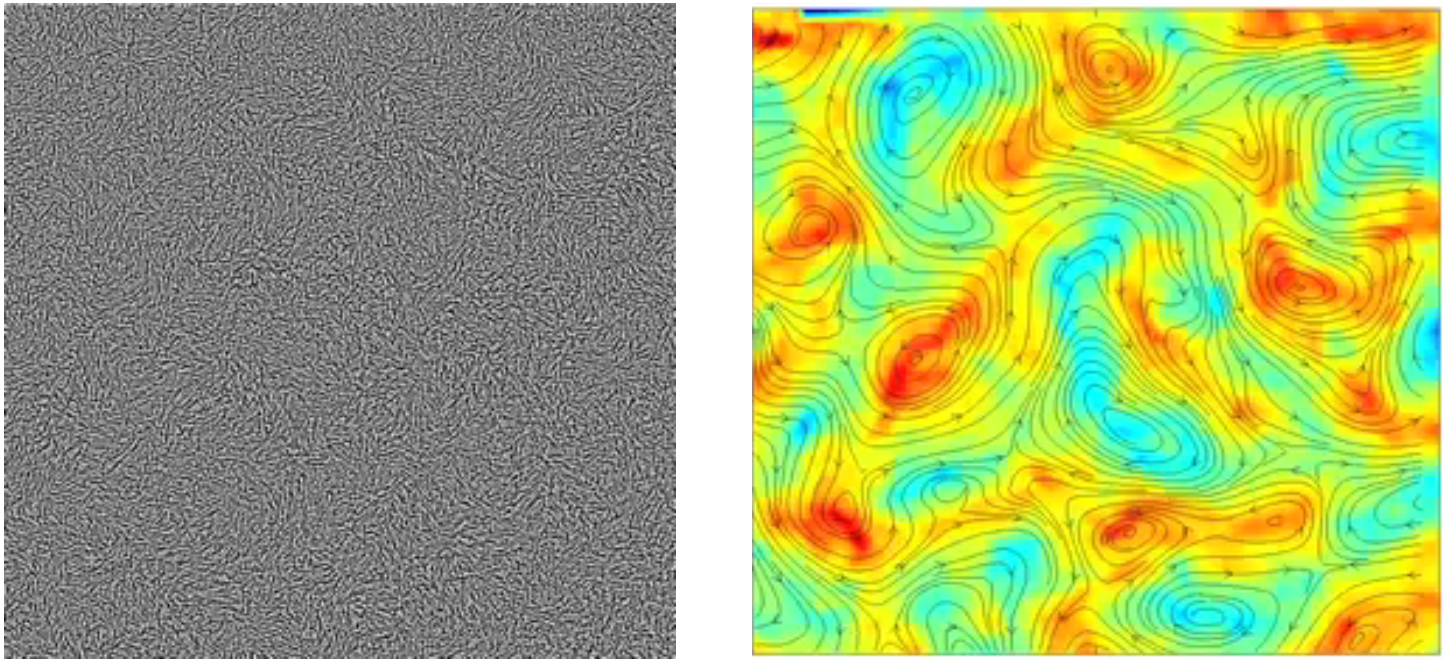
Starling murmuration: a school of fish

https://www.youtube.com

Collective motion in micro-scale

Active Fluid:
Fluid is constantly driven by motion of individual organisms that form the fluid

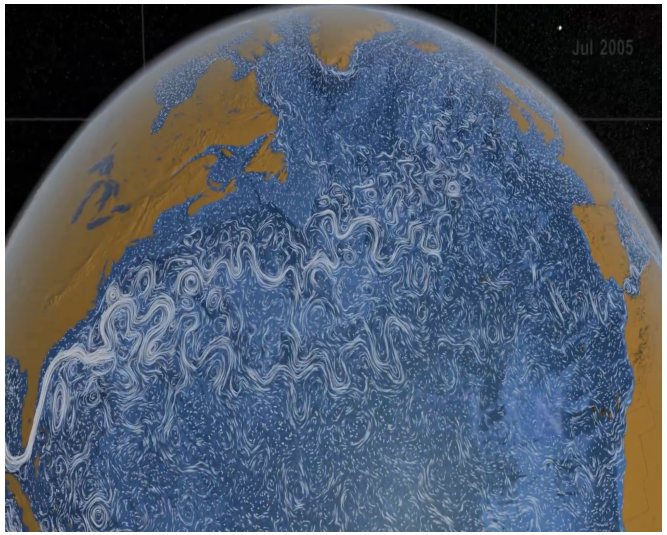
Bacterial colony

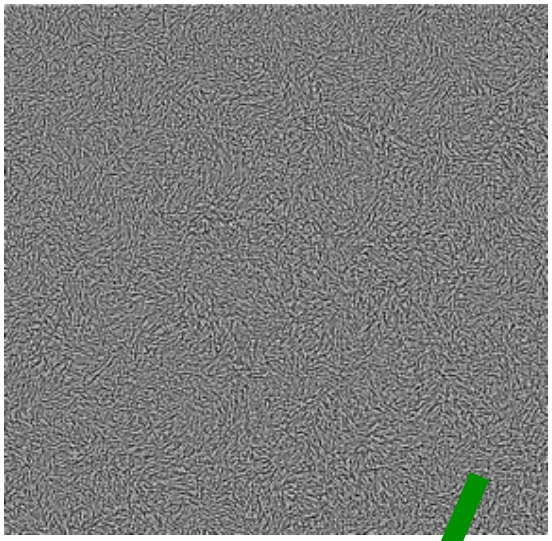


Wensink et al., PNAS (2012)

Why active fluids are different?

Why active fluids are different?





$O(km)$

$O(m)$

$O(\mu m)$

Flow length scale

Moving at micro-meter scales is different

$$Re\left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u}\cdot\nabla\mathbf{u}\right) = \nabla\cdot\mathbf{\Pi} \qquad Re = \frac{UL}{\nu} = \frac{\text{inertial force}}{\text{viscous force}} \ll 1$$

$$L \approx 10^{-6}m \quad U \approx 10^{-6}m/s \quad \nu \approx 10^{-6}m^2/s$$

There is no inertial effect

There is no time dependence !

https://www.youtube.com/watch?v=1wNmtle6qkE

Moving at micro-meter scales is difficult !

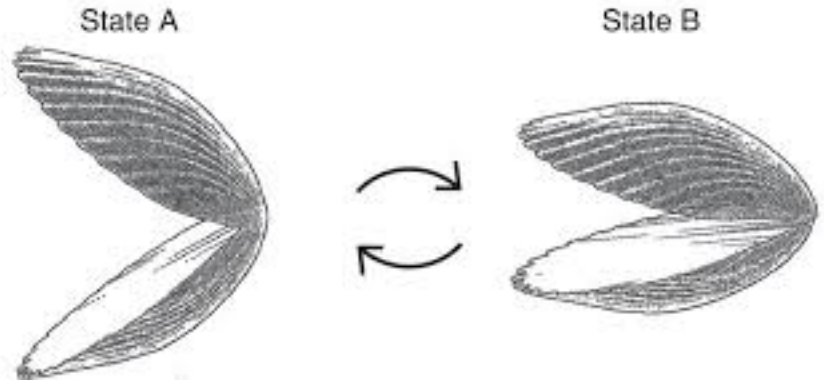
$$Re\left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u}\cdot\nabla\mathbf{u}\right) = \nabla\cdot\mathbf{\Pi} \qquad Re = \frac{UL}{\nu} = \frac{\text{inertial force}}{\text{viscous force}} \ll 1$$

$$L \approx 10^{-6}m \quad U \approx 10^{-6}m/s \quad \nu \approx 10^{-6}m^2/s$$

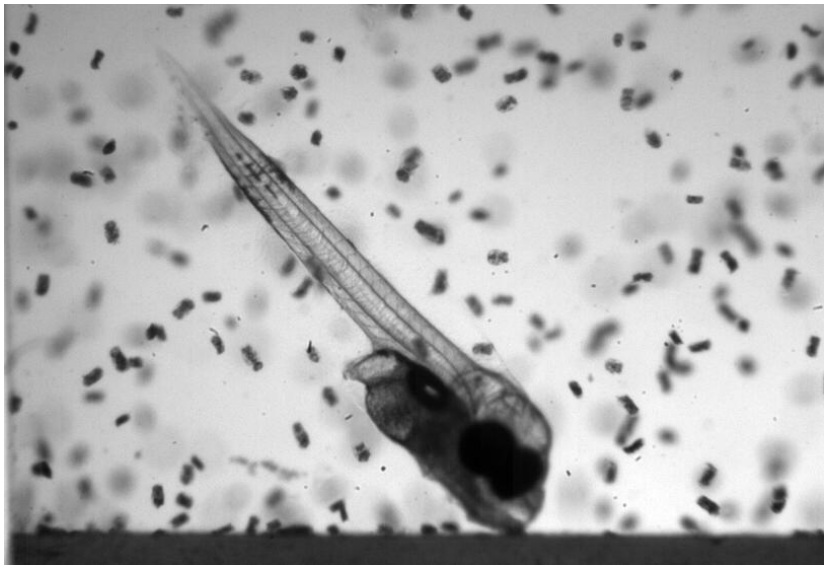
There is no inertial effect

There is no time dependence !

Purcell's scallop theorem: No net displacement for reciprocal motion



Fish larvae failing to capture food at low Re



China & Holzman., PNAS, 2014

Moving at micro-meter scales is difficult !

$$Re\left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u}\cdot\nabla\mathbf{u}\right) = \nabla\cdot\mathbf{\Pi} \qquad Re = \frac{UL}{\nu} = \frac{\text{inertial force}}{\text{viscous force}} \ll 1$$

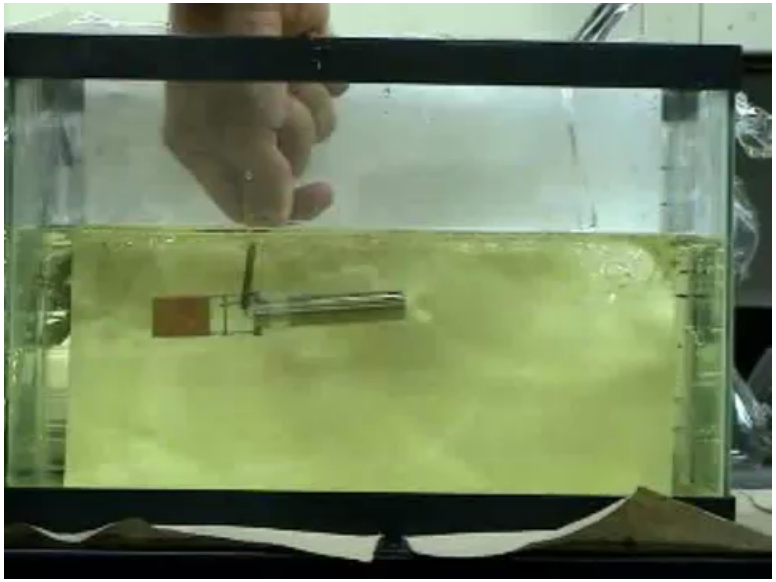
$$L \approx 10^{-6}m \quad U \approx 10^{-6}m/s \quad \nu \approx 10^{-6}m^2/s$$

There is no inertial effect

There is no time dependence !

Purcell's scallop theorem: No net displacement for reciprocal motion

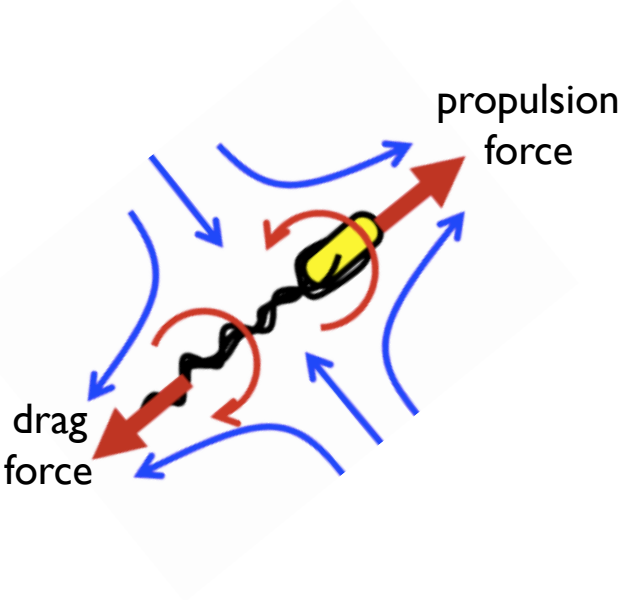
No net motion for reciprocal movement



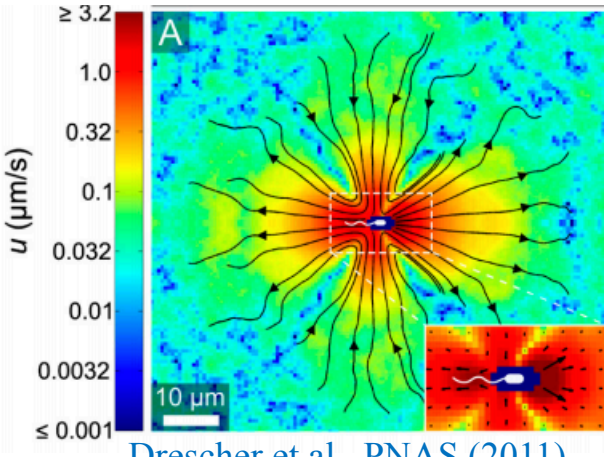
Successful motion for rotating helix

Cells' strategies to move at zero Reynolds number

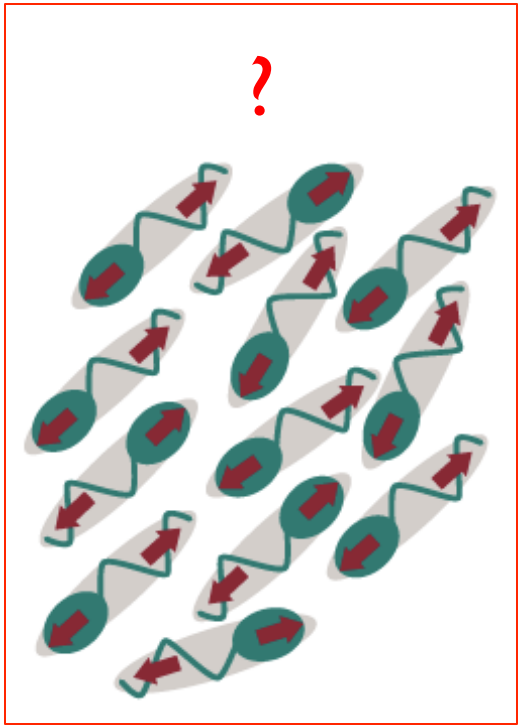
$$Re\left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u}\cdot\nabla\mathbf{u}\right) = \nabla\cdot\mathbf{\Pi} \qquad Re = \frac{UL}{\nu} = \frac{\text{inertial force}}{\text{viscous force}} \ll 1$$



Experimentally measured flow field around *E coli* bacteria



Drescher et al., PNAS (2011)

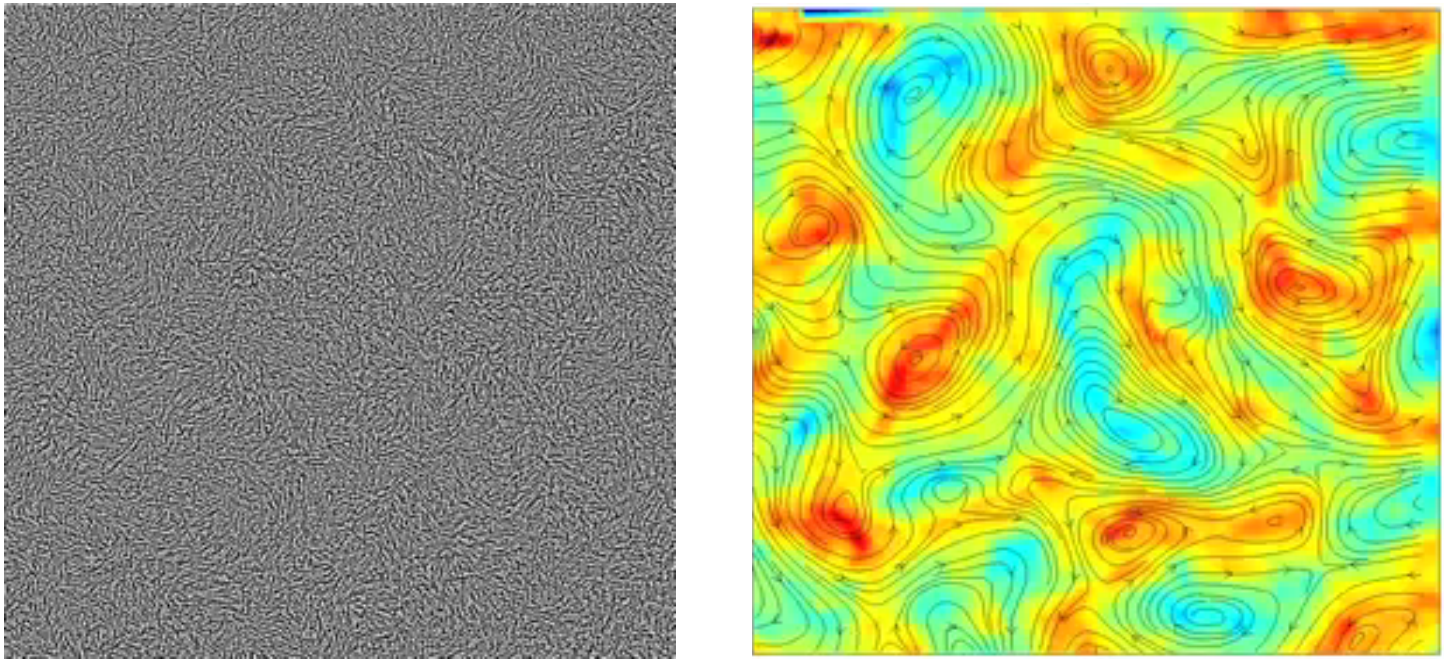


Each particle creates a dipole flow field

Collective motion in micro-scale

Active Fluid:
Fluid is constantly driven by motion of individual organisms that form the fluid

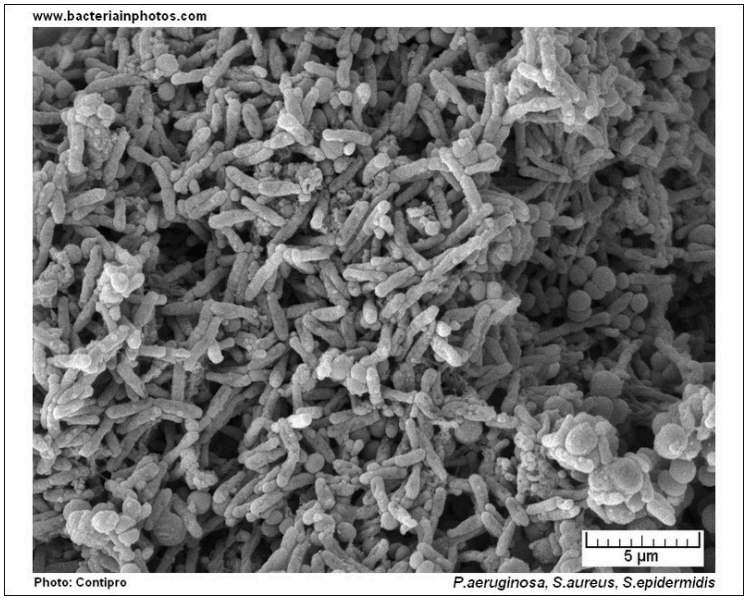
Bacterial colony



Wensink et al., PNAS (2012)

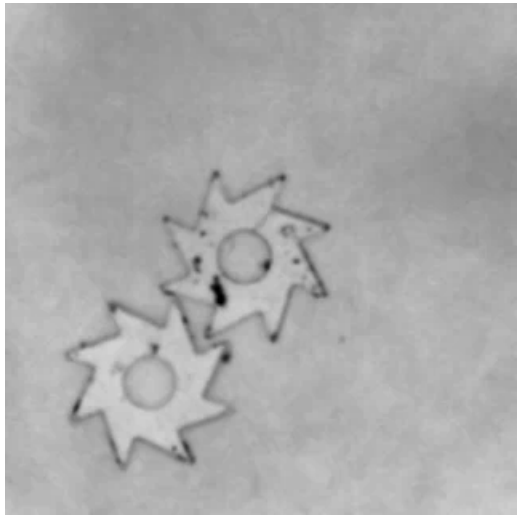
Why studying bacteria?

- There are more bacteria in our body (~40 trillion) than our own cells (~30 trillion) !
- The total amount of bacteria on earth is much larger than plants + animals together
- Bacteria generate their own motion (self-propulsion)



Can we use bacteria to do work?

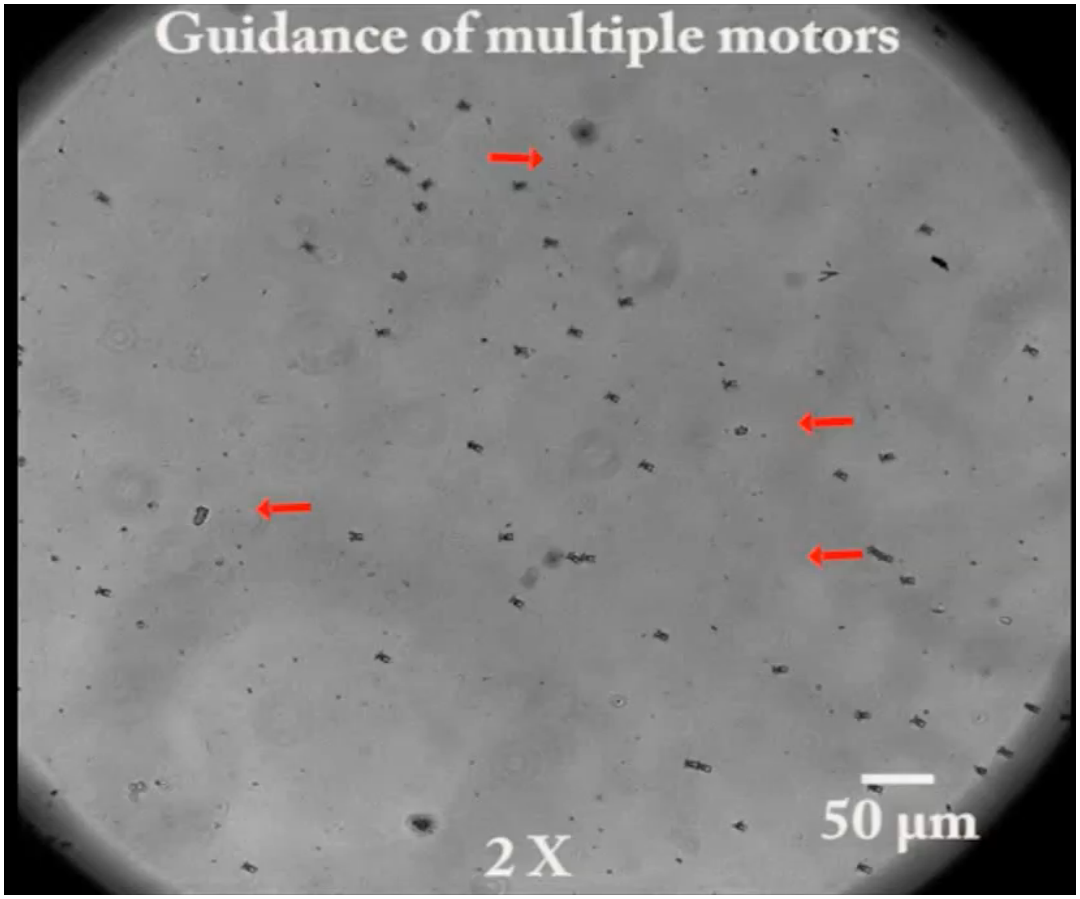
Can we domesticate bacteria?



Microgears in bacterial bath, Sokolov et al., PNAS, 2010

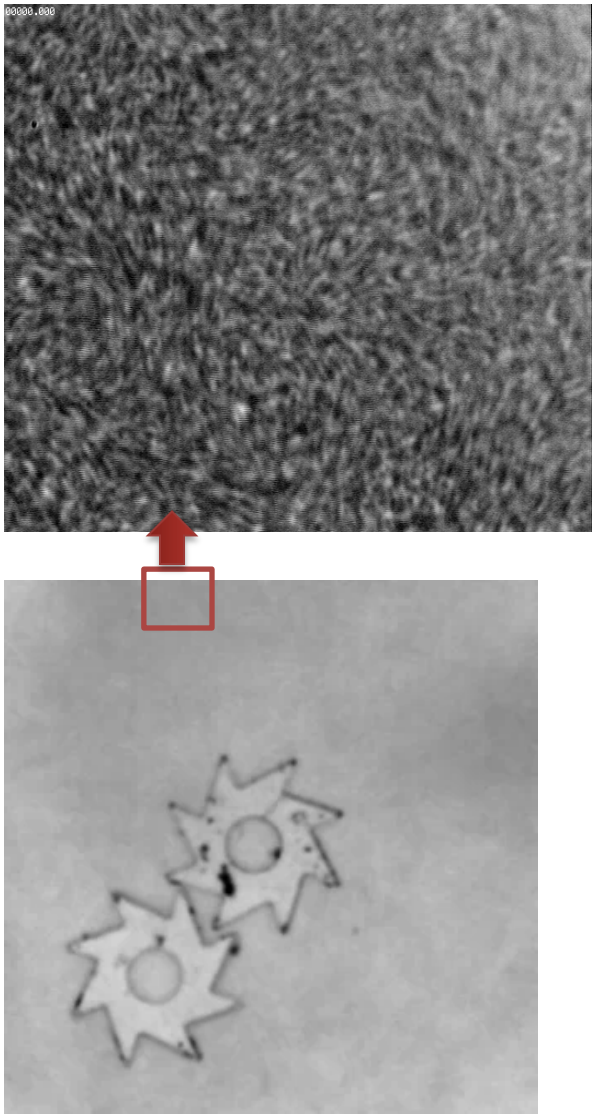
Can we use self-propulsion?

Targeted drug delivery



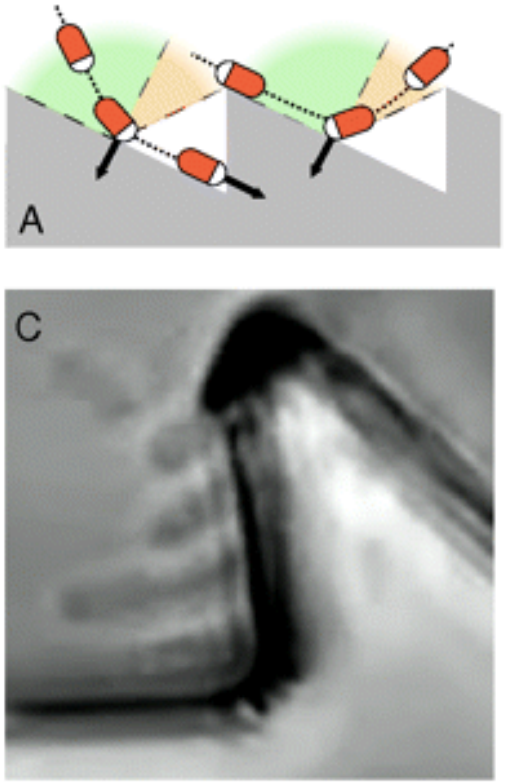
Xu et al., ASC Nano, 2017

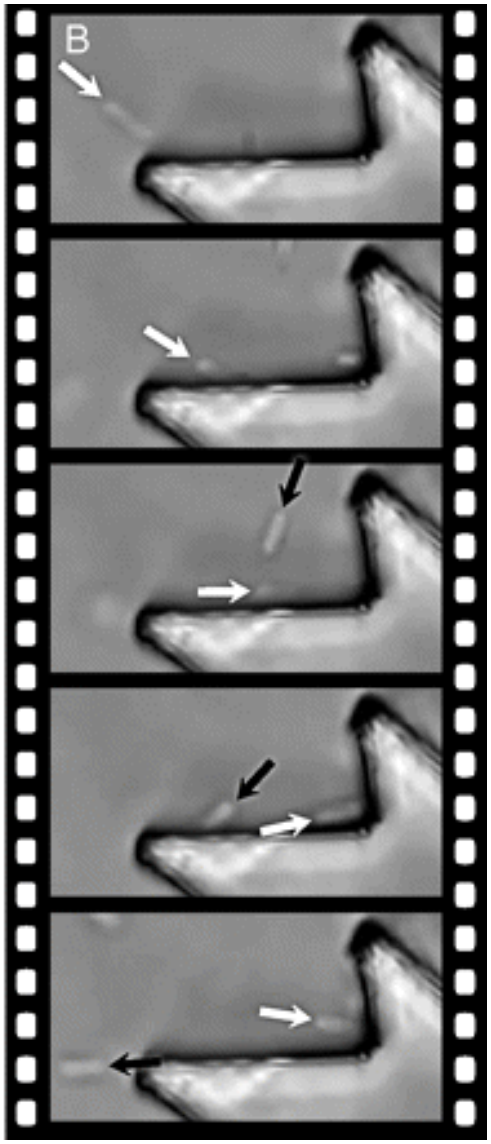
Can we use bacterial collective motion?



Microscopic gears in a bacterial bath

Sokolov et al., PNAS (2010)

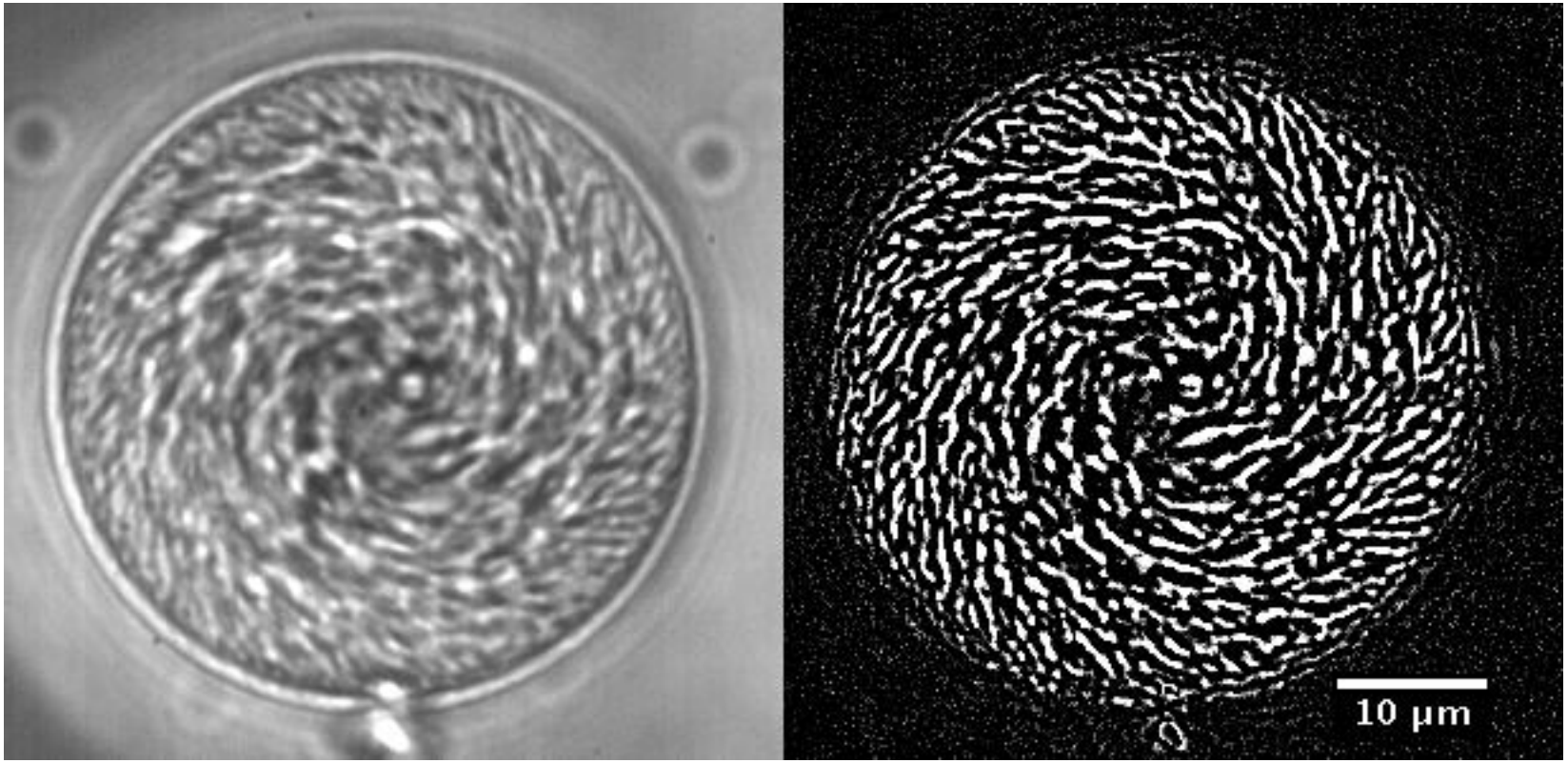




DiLeonardo et al., PNAS (2010)

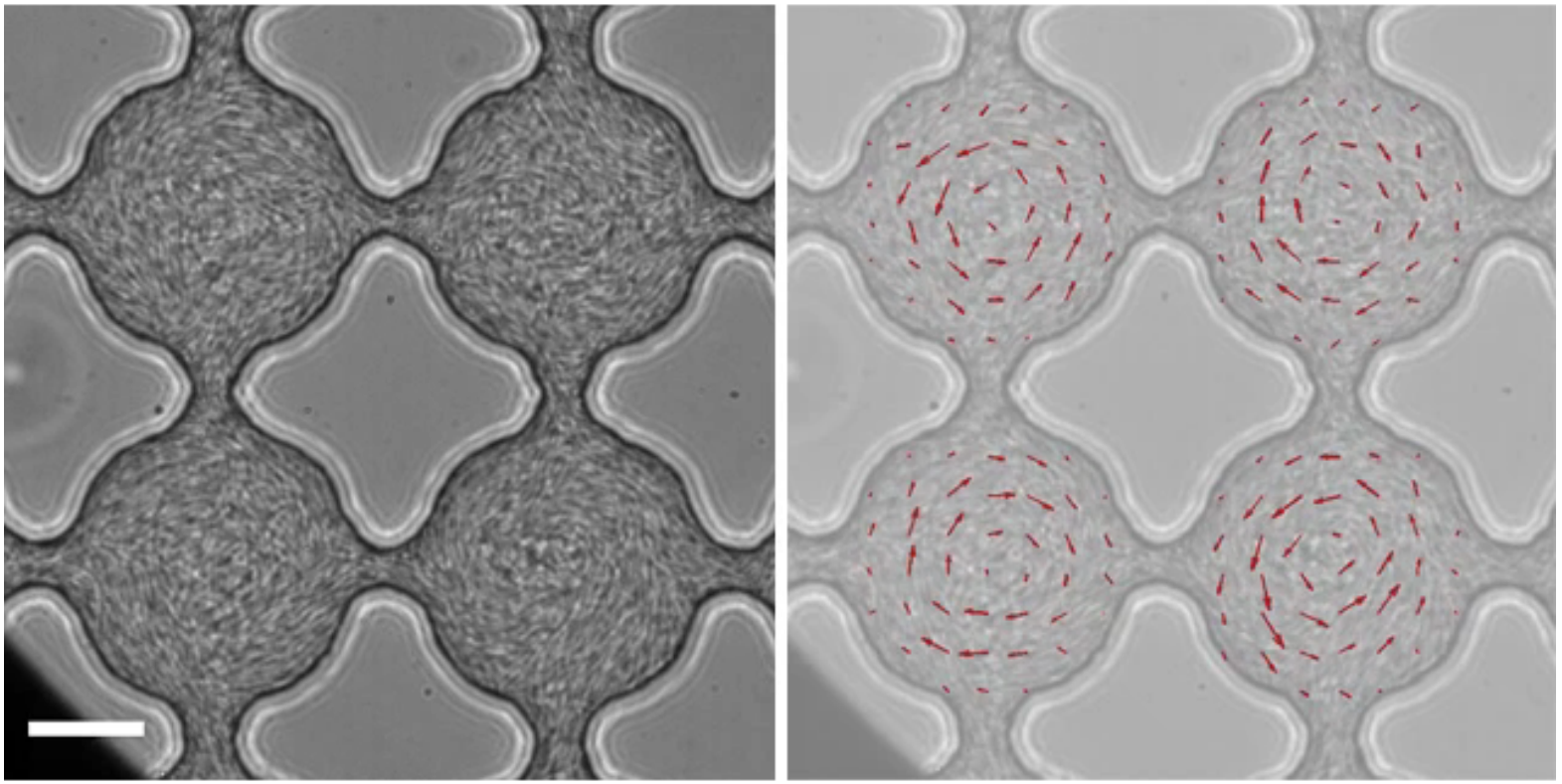
Can we control collective bacterial motion?

Confinement forces bacteria to rotate



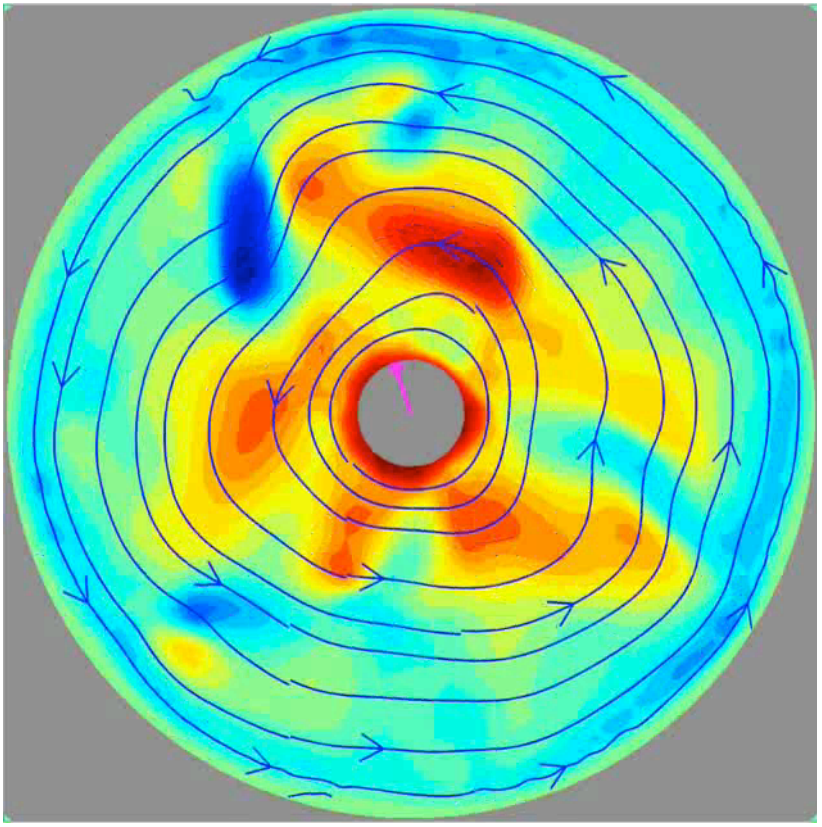
Wioland et al., PRL, 2013

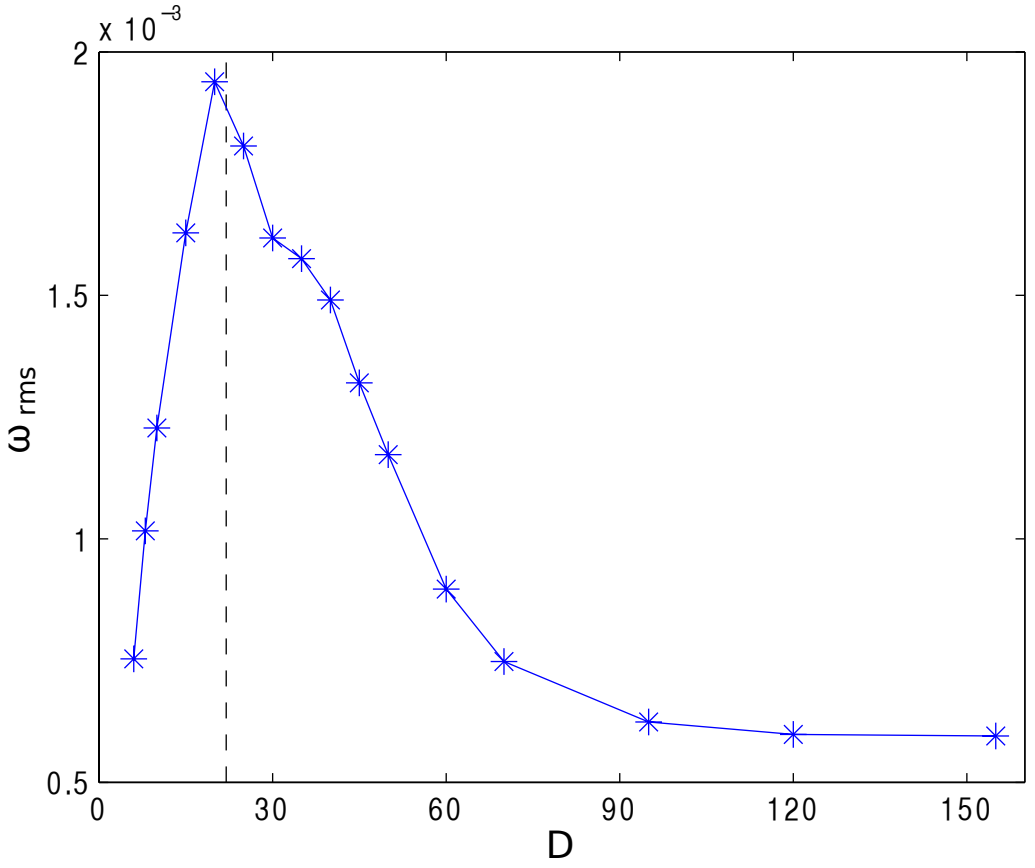
Can we control collective bacterial motion?



Wioland et al., Nature Physics (2016)

Can we use collective bacterial motion?

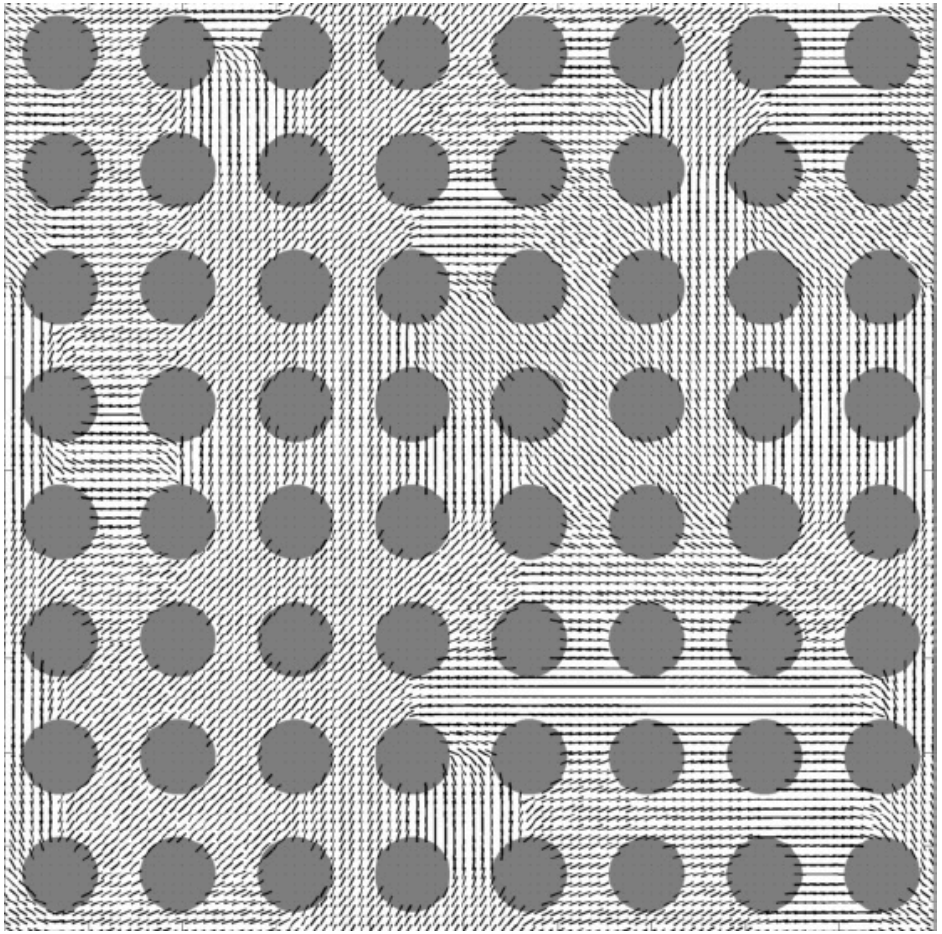




Single rotor in a confined flow

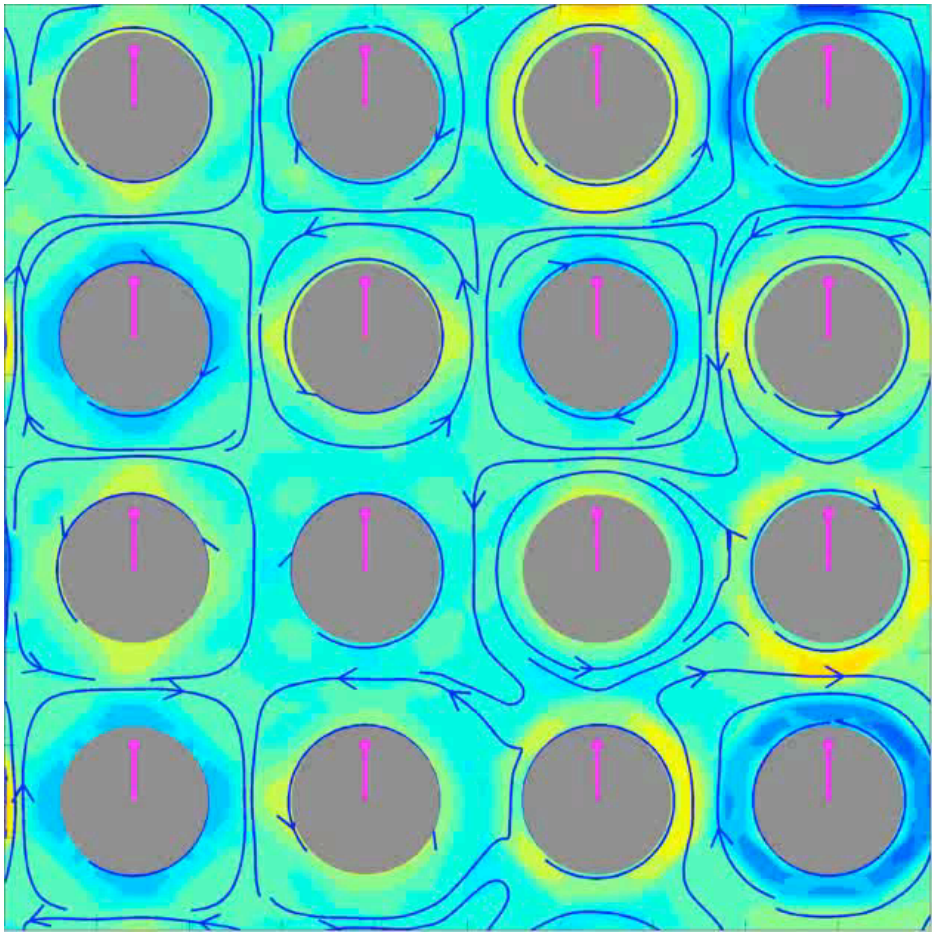
Can we use collective bacterial motion?

Active micro-machines



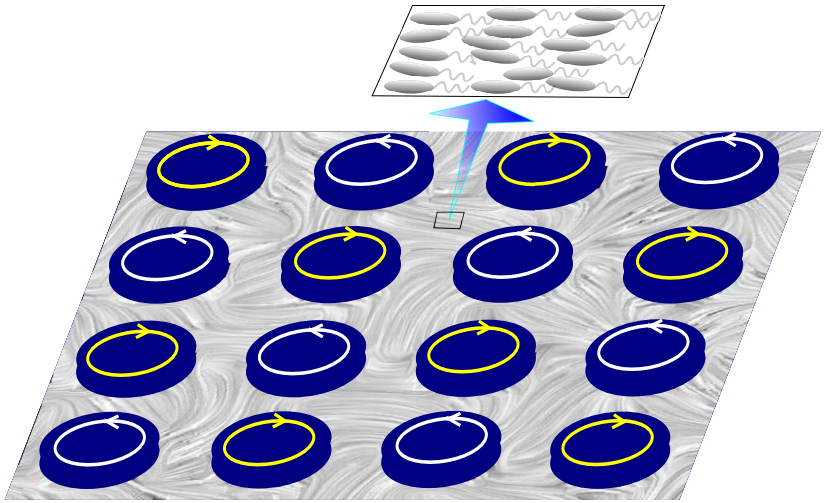
Static array of freely rotating disks suspended in active flow

Active micro-machines



Neighbouring rotors turn in opposite directions

Can we use collective bacterial motion?



ScienceNews

NEWS BIOPHYSICS

Mini 'wind farm' could capture energy from microbes in motion

Chaotic swirling becomes synchronized swimming to rotate turbines, simulation shows

BY EMILY CONOVER 2:00PM, JULY 8, 2016

PINT-SIZED POWER Computer simulations show how the motion of swimming bacteria could be harnessed to generate power using a device like the wind farm shown above — but on a microscopic scale.

Thampi, et al., Science Advances (2016)

Can we command bacterial motion?

Painting with photokinetic bacteria

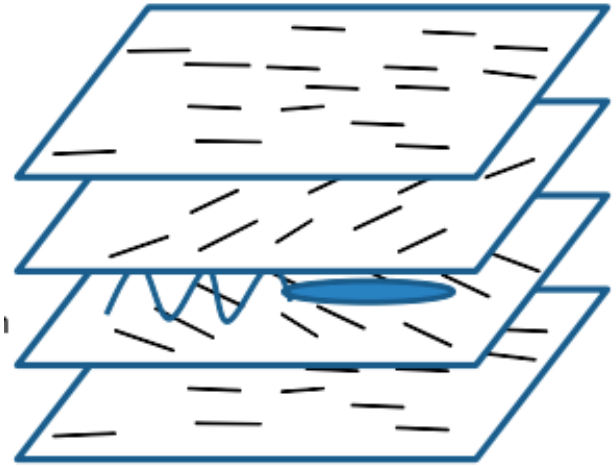
Light intensity map

Frangipane et al., eLife, 2018

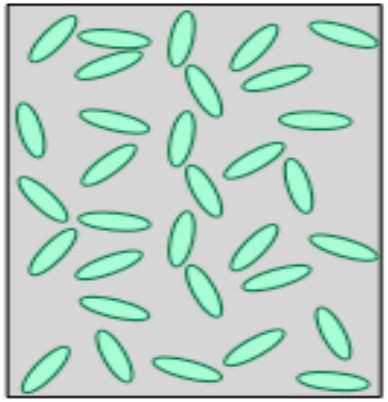
Can we command bacterial motion?

Disperse bacteria in liquid crystal

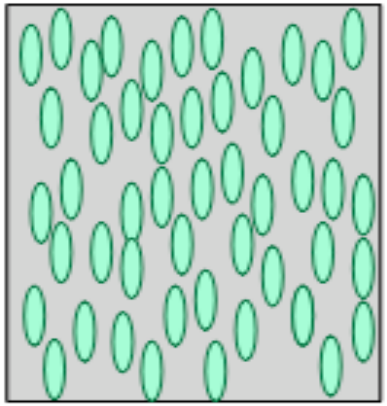
Orientation of liquid crystal molecules can be controlled by rubbing the surface



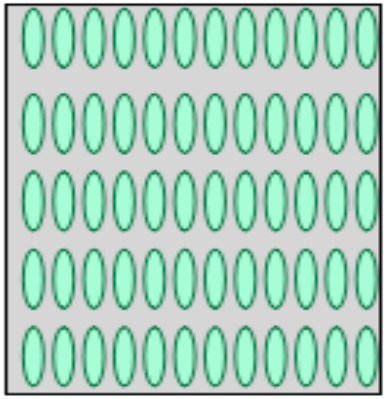
Sokolov et al., PNAS, 2014



liquid phase
no positional order
no orientational order



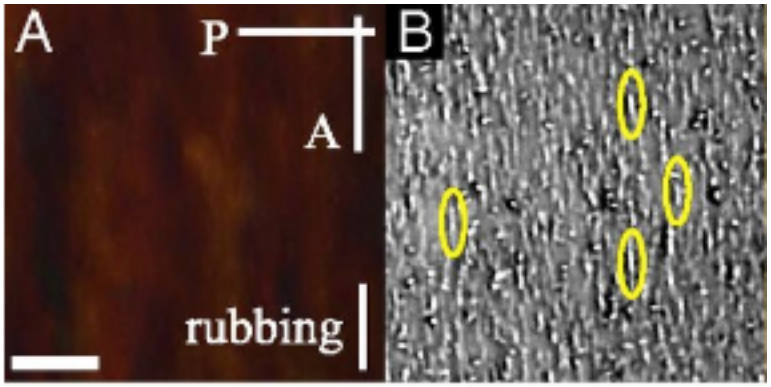
liquid crystal phase
no positional order
orientational order

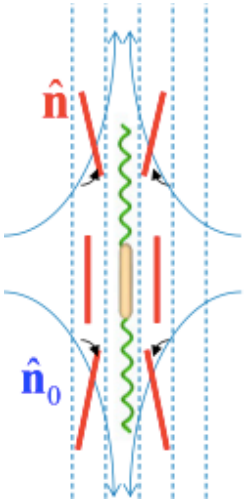


crystal phase
positional order
orientational order

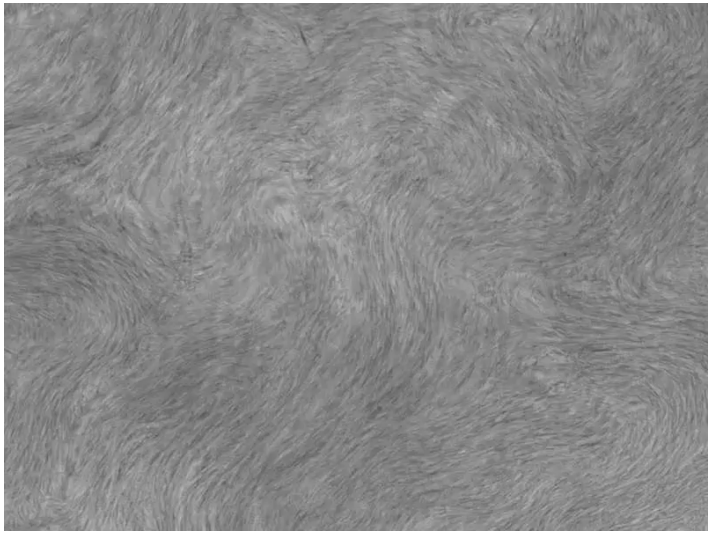
Can we command bacterial motion?

Bacteria at low concentration





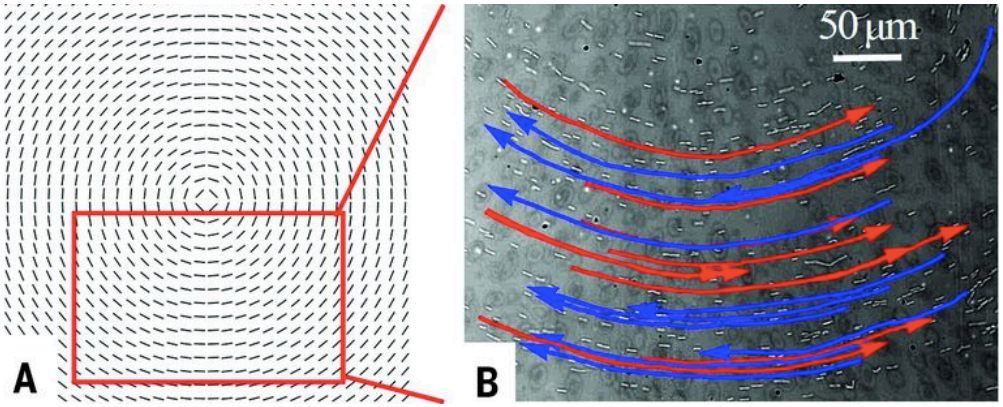
Bacteria at high concentration



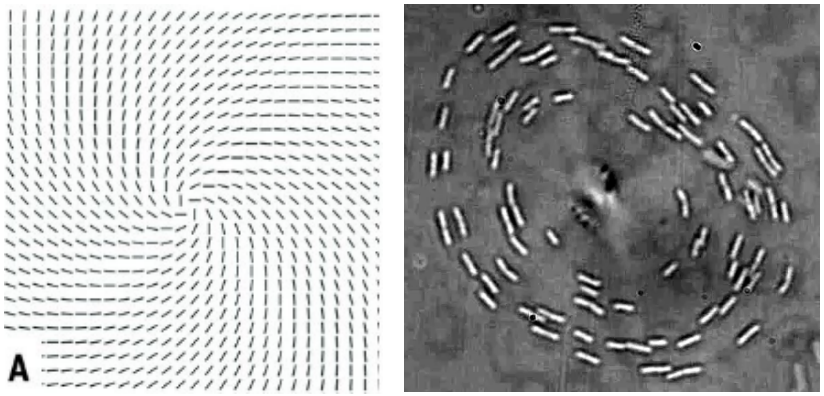
Sokolov et al., PNAS, 2014

Can we command bacterial motion?

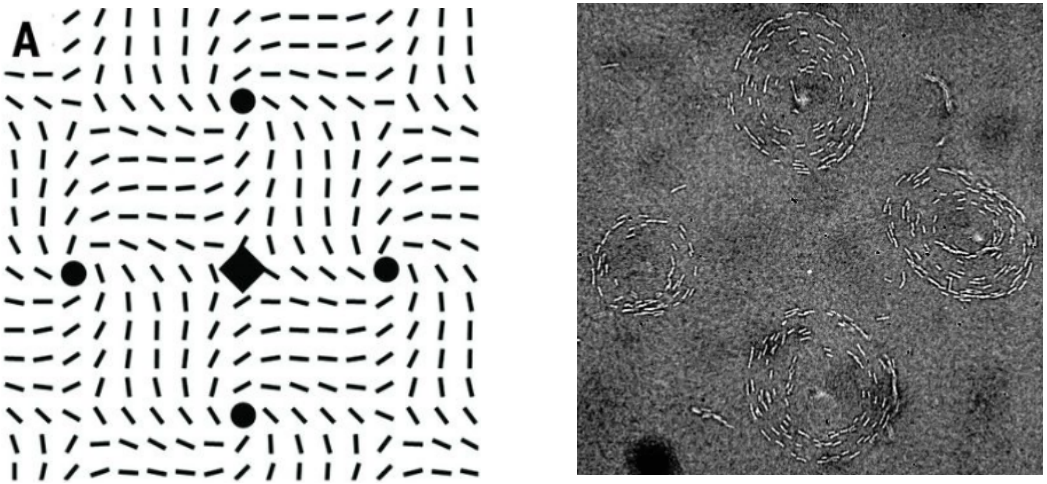
Bacteria in a vortex



Bacteria in a spiral



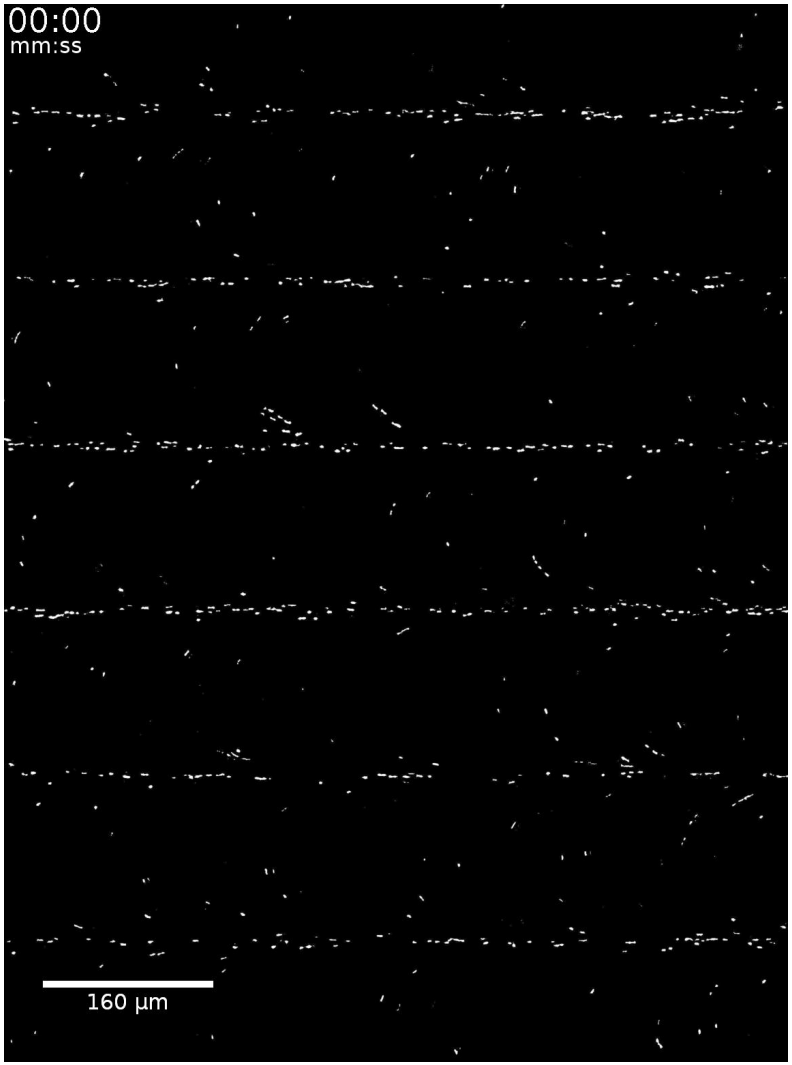
Multiple spirals



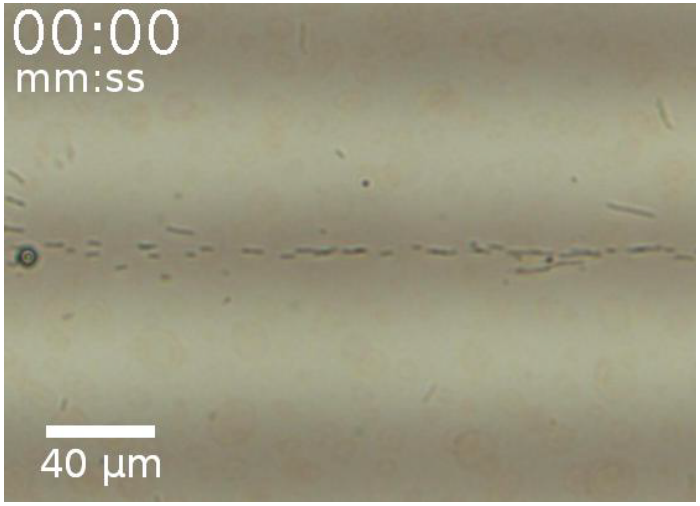
Peng et al., Science, 2016

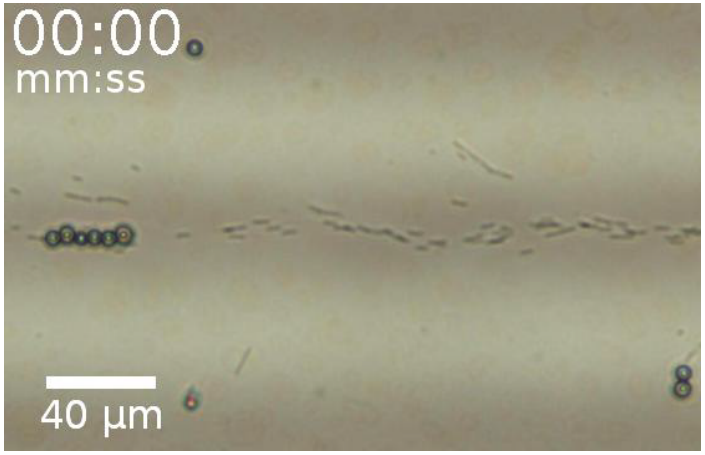
Can we command bacterial motion?

Bacteria form jets in a C-shaped pattern



Using bacterial jets for cargo transport





Videos courtesy of O. Lavrentovich, Kent State Universty

Why studying bacteria?

- There are more bacteria in our body (~40 trillion) than our own cells (~30 trillion) !
- The total amount of bacteria on earth is much larger than plants + animals together
- Bacteria generate their own motion (self-propulsion)

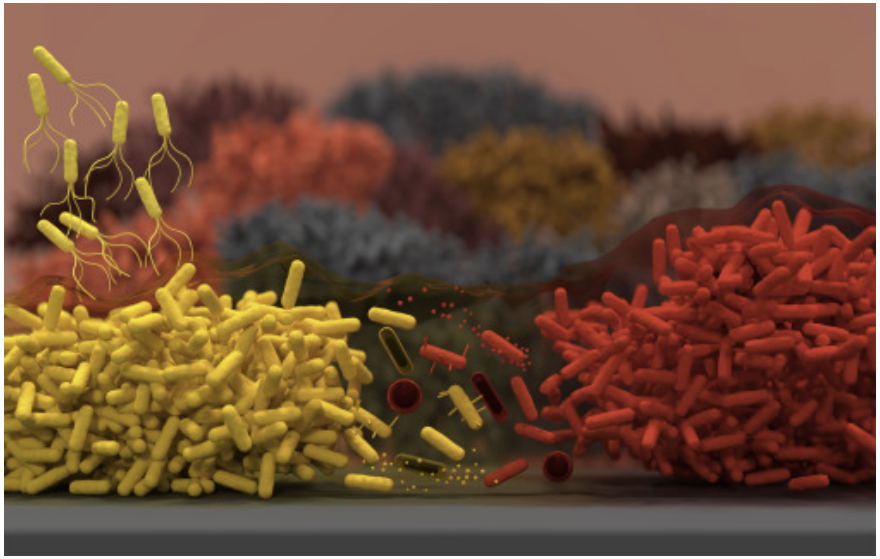
- Bacterial collective are very efficient in invading space
- ~700,000 people die of microbial infection every year
- By 2050, antibiotic resistant bacteria can cause ~10 million death per year

Why studying bacteria?

- Bacteria live in dense communities
- They have developed various strategies to compete and to win

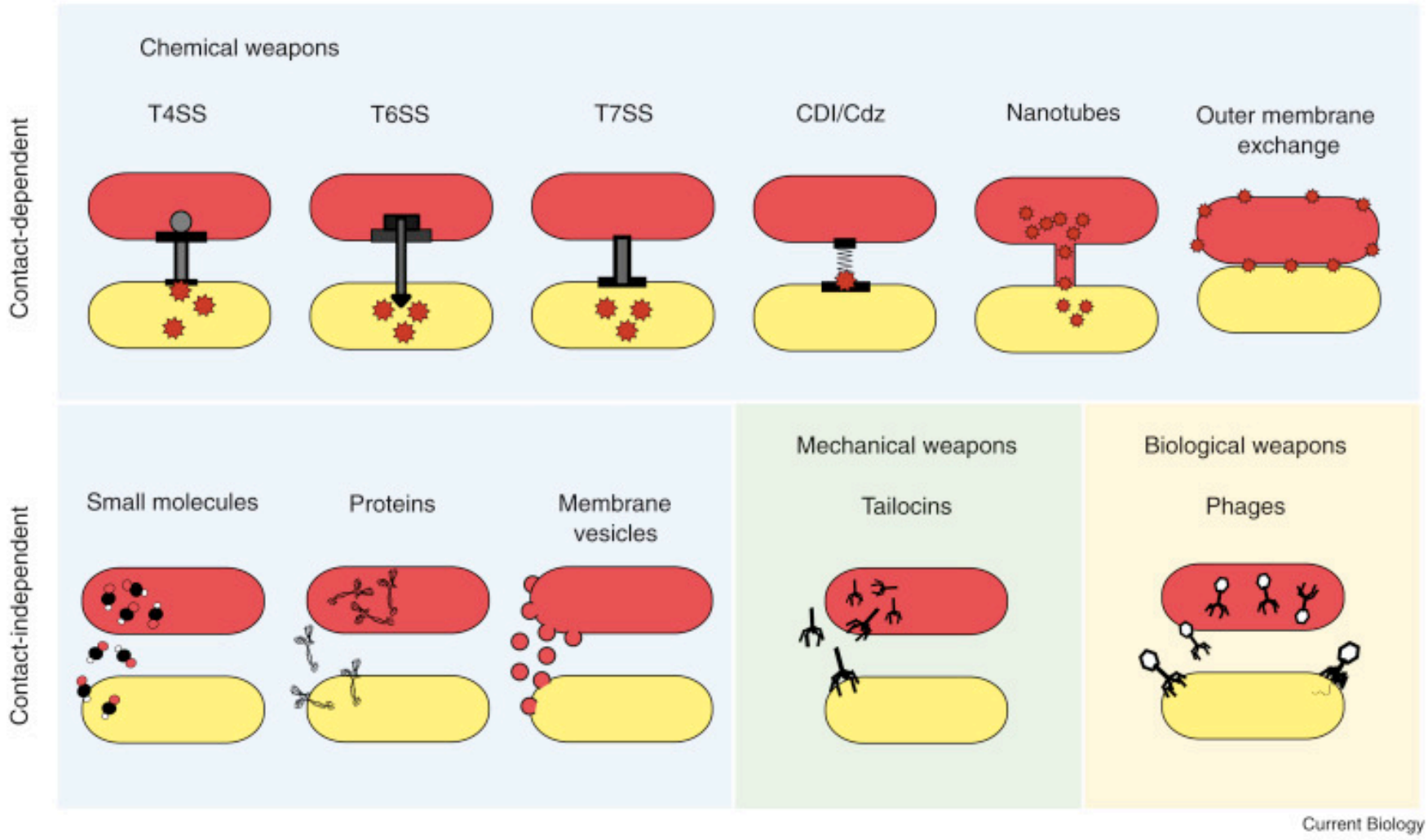
Zusman Lab at UC Berkely

Can we suppress bacterial invasion by understanding bacterial competition?



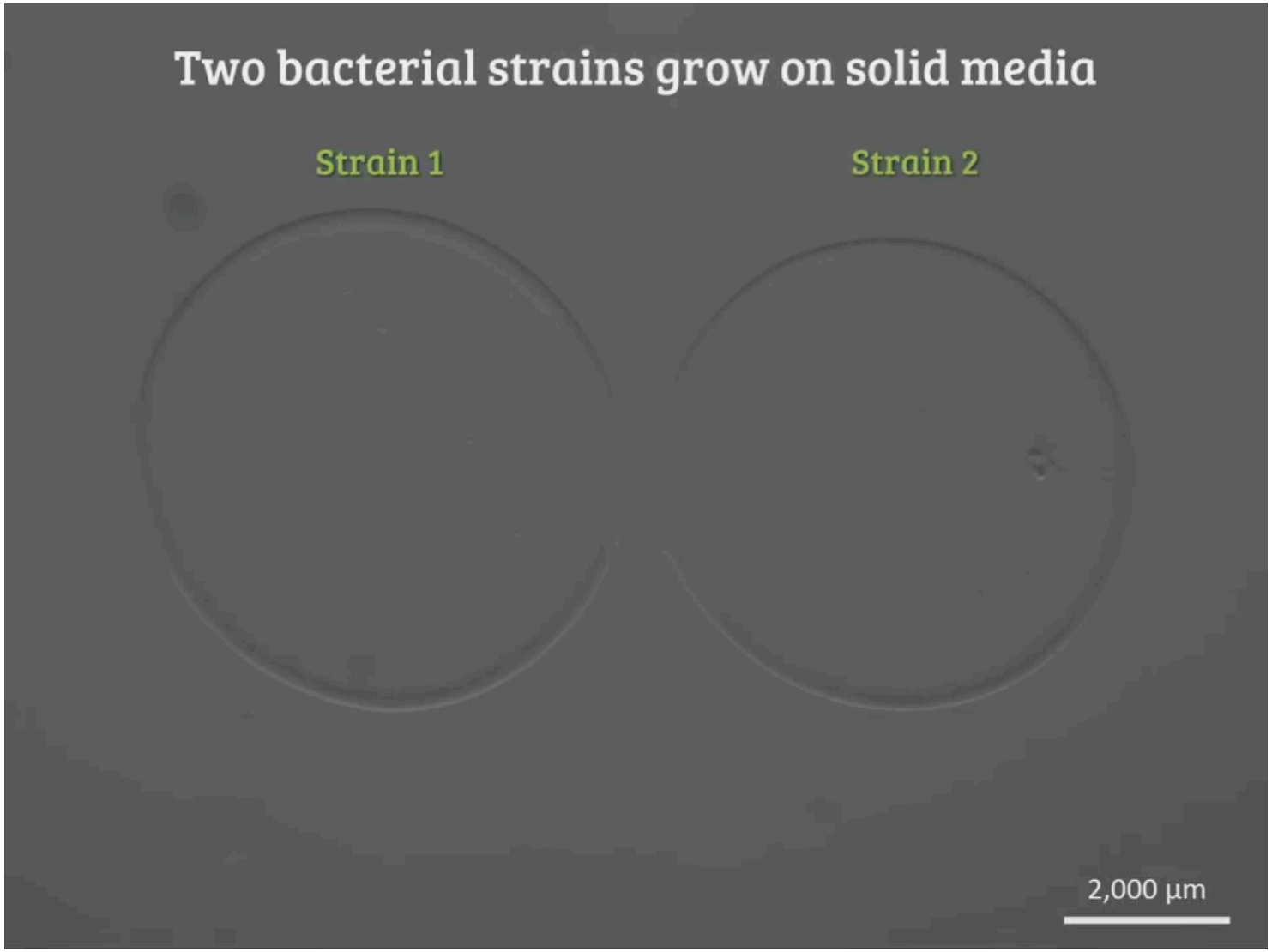
Granato, Legrand, Foster, Curr. Biol. (2019)

Bacterial warfare



Granato, Legrand, Foster, Curr. Biol. (2019)

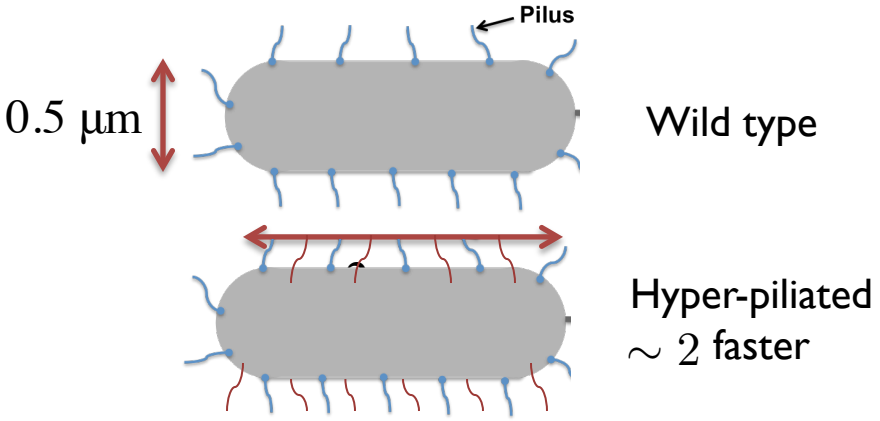
Bacterial game of thrones



Mavridou, et al., *Bacteria Use Collective Behavior to Generate Diverse Combat Strategies*, Current Biology, 2018

Two competing bacterial types

- Make fast moving and slow moving bacteria, which one spreads faster?
- Pseudomonas. aeruginosa: infectious, antibiotic resistant bacteria



Nasty picture of Pseudomonas infection

Two competing bacterial types

- Individual $\Delta pilH$ cells are ~ 2 times faster than individual WT cells

Oliver Meacock
Oxford

Reminder: Tortoise vs hare competition (skildpadden og haren)

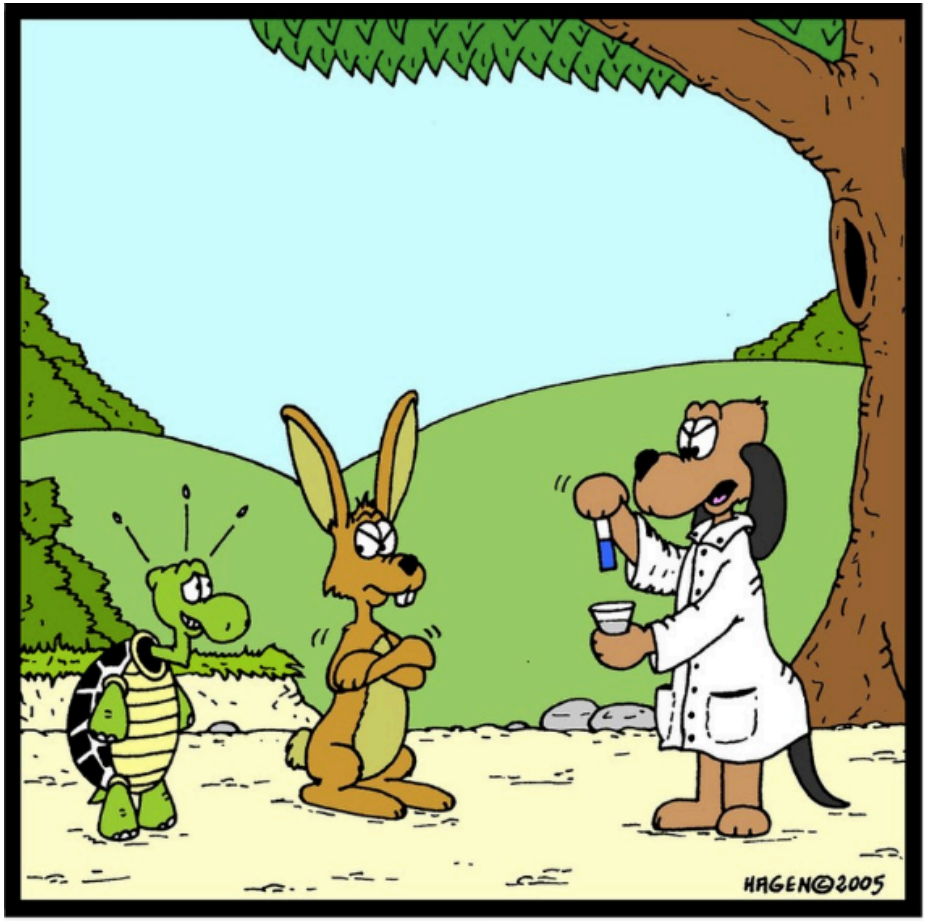
The moment story came true …

"It does not matter how slowly you go, as long as you don't stop." – Confucius

Tortoise & hare in bacterial competition

- Individual $\Delta pilH$ cells are ~ 2 times faster than individual WT cells

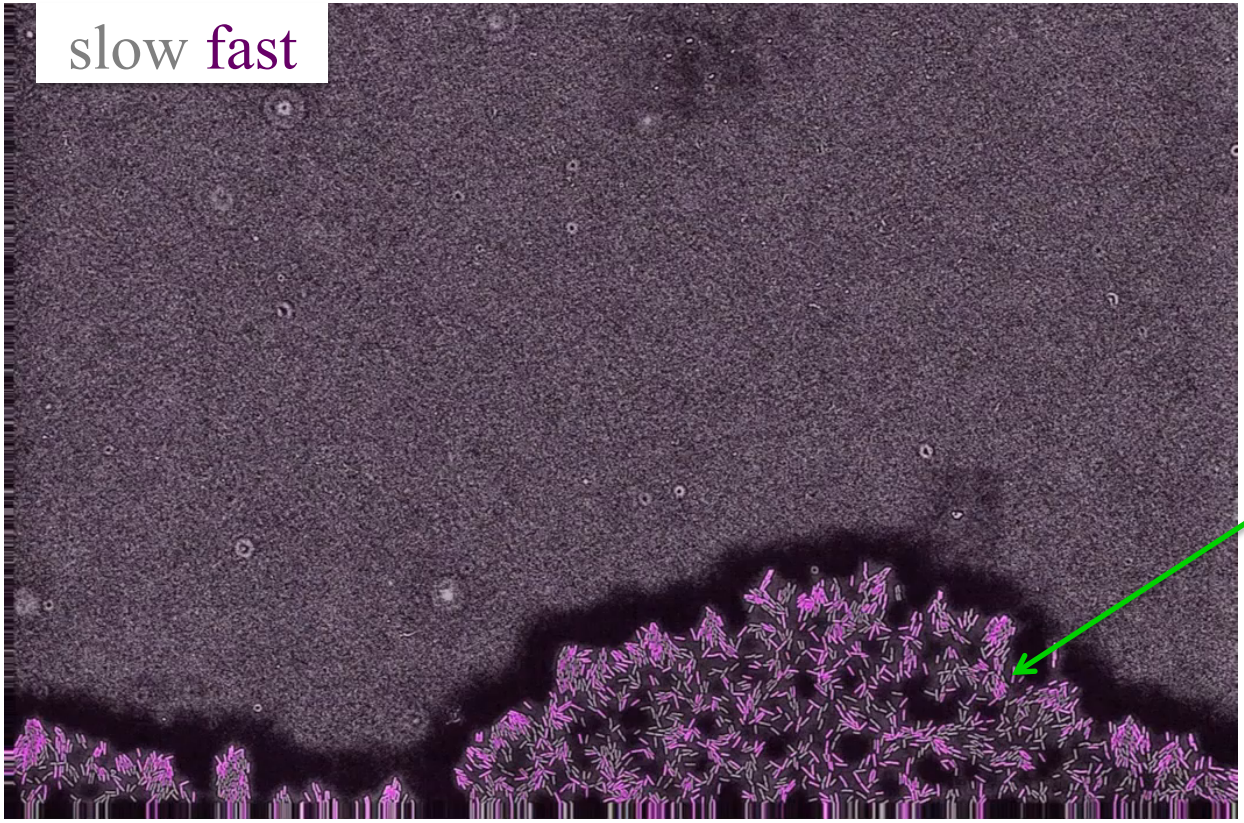
Conspiracy Theorems



Yes Mr Hare, you were right: He IS on steroids!

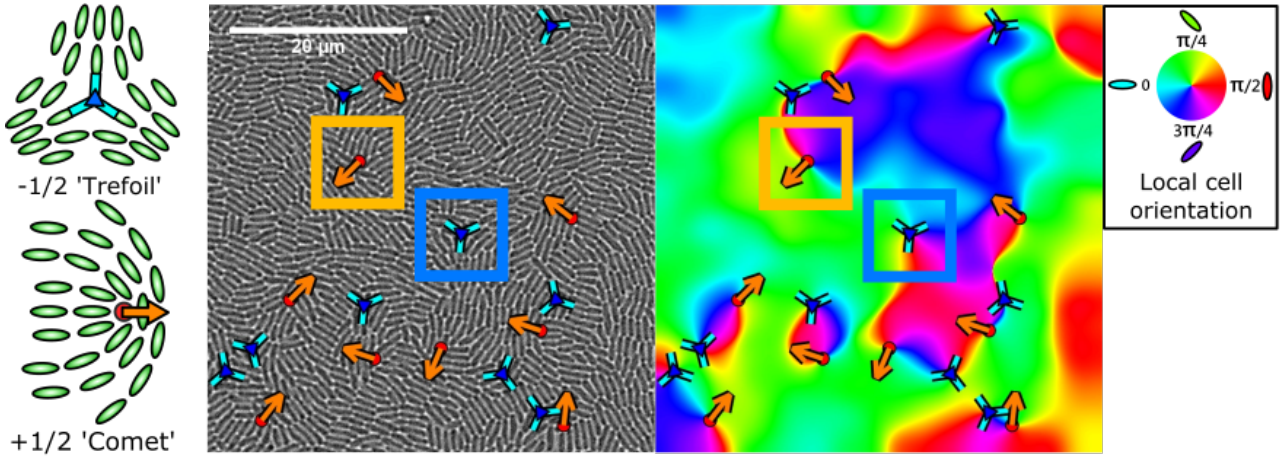
Rosette formation

- Mixing fast moving and slow moving bacteria, which one spreads faster?

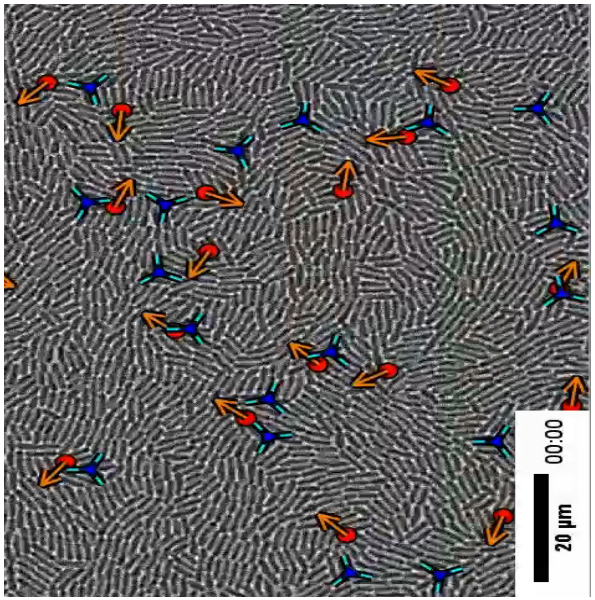


Slow moving bacteria (normal) outcompetes the fast (hyper-mutated) one !

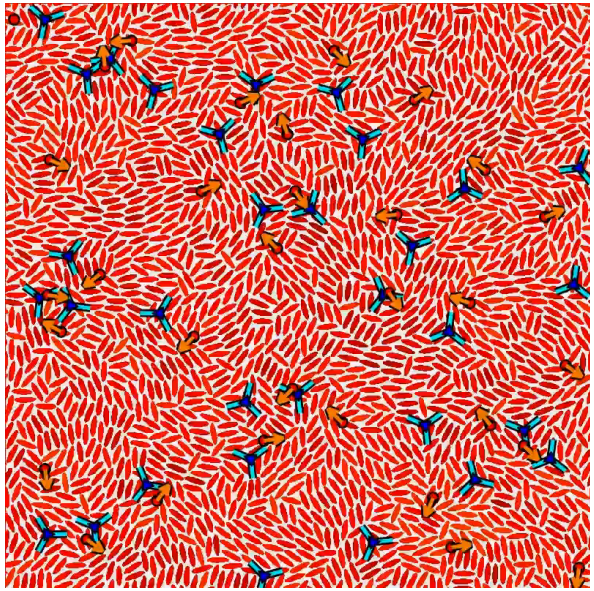
Bacteria show physics of liquid crystals



Experiment



Discrete Model



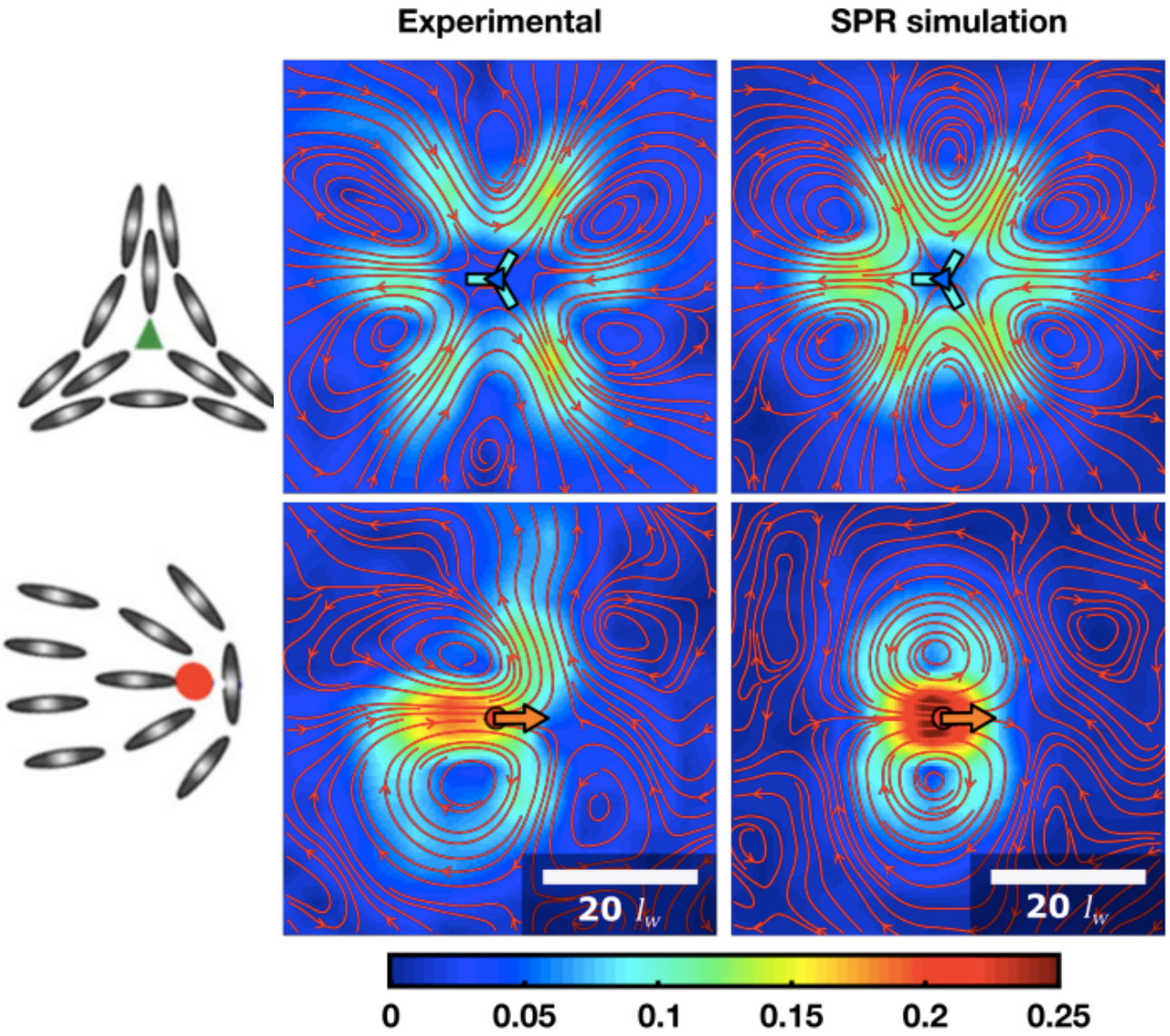
Self-propelled Rods (SPR):

- Hard rods interacting via volume exclusion
- Each rod subject to a driving force

$$f_r \frac{\partial \underline{r}}{\partial t} = -\frac{\partial U}{\partial \underline{r}} + F^{\text{active}}$$

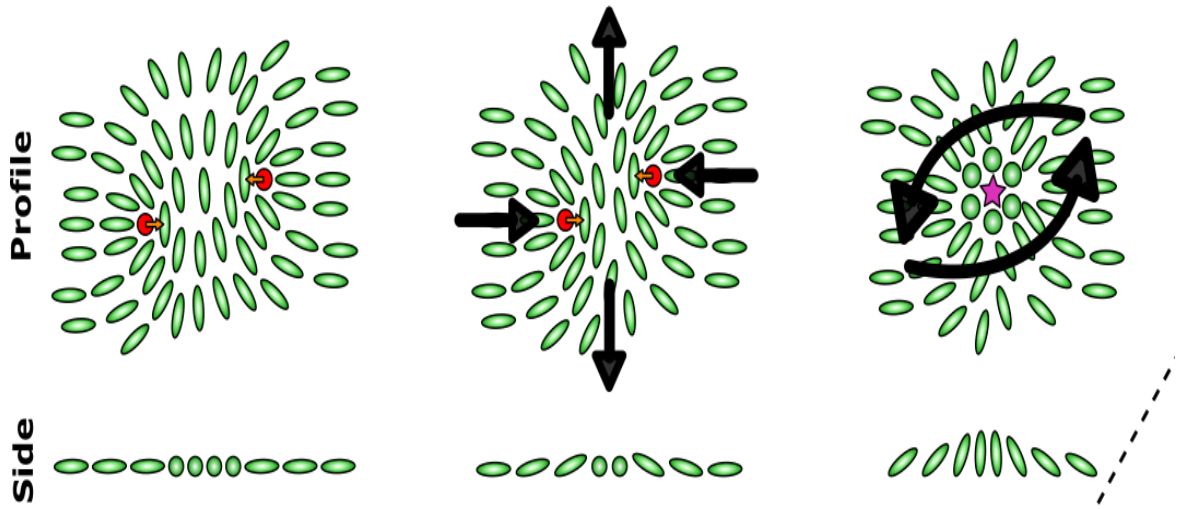
$$f_\theta \frac{\partial \theta}{\partial t} = -\frac{\partial U}{\partial \theta}$$

Topological defects in bacterial colonies



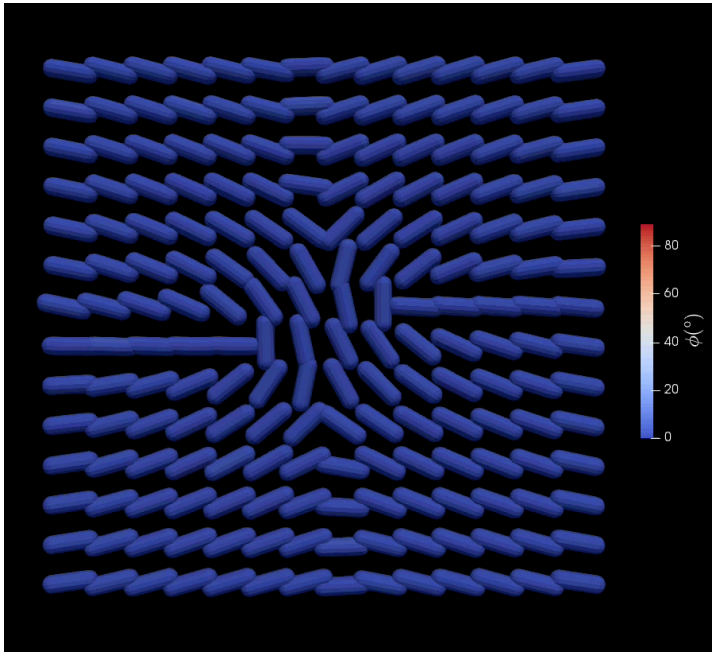
Rosettes (hypothesis)

- Rosettes form when fast comets collide

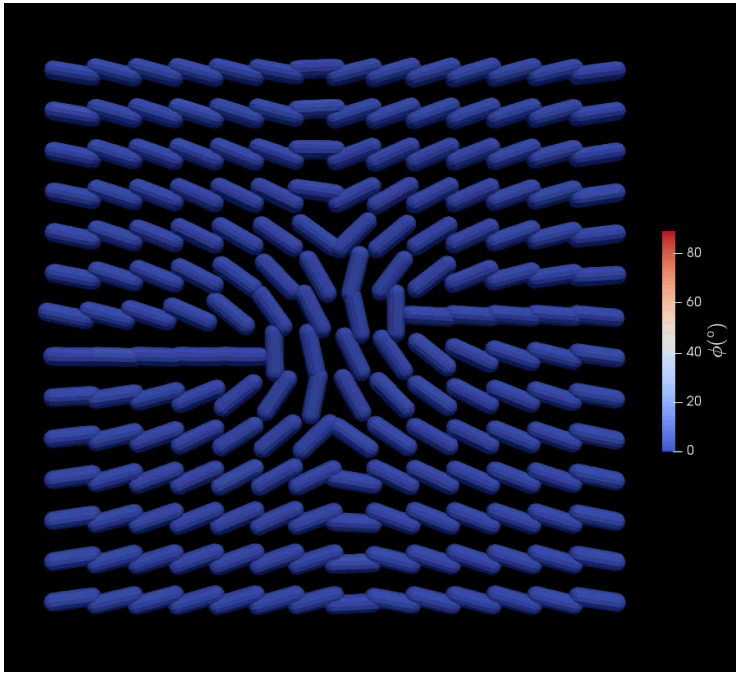


Two comets approach

Rosettes form when fast +1/2 defects collide



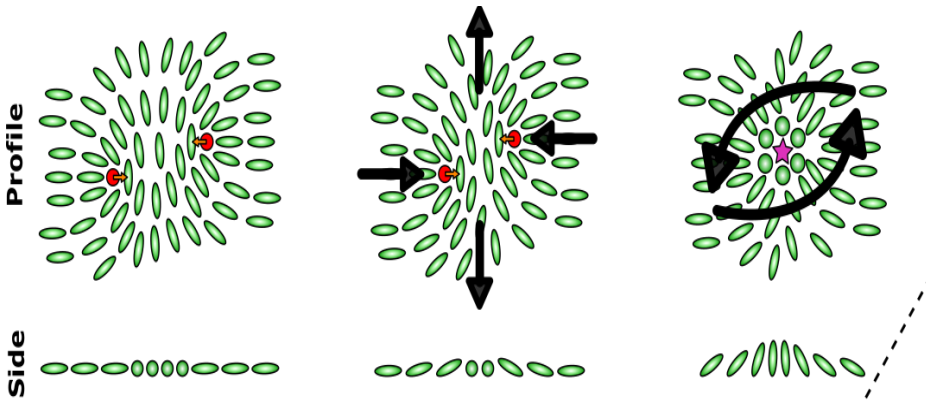
Slow moving

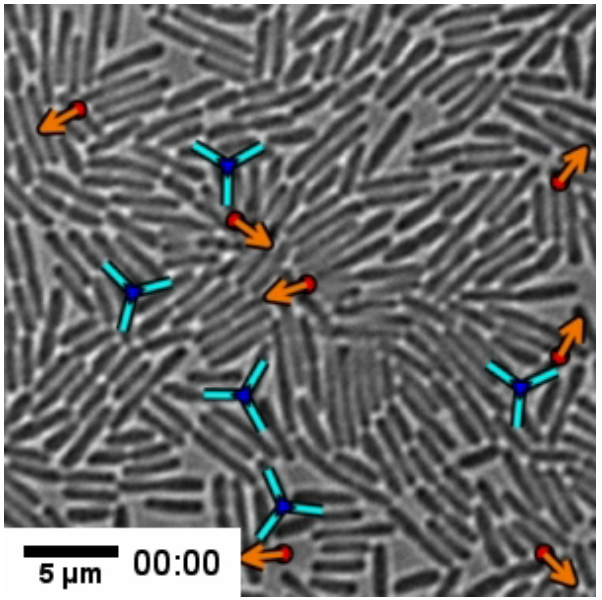


Fast Moving

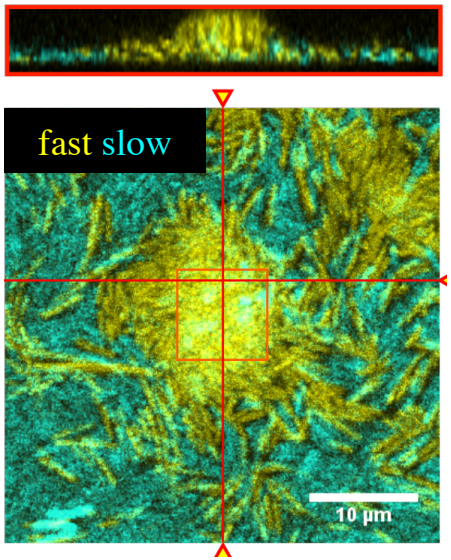
Rosette formation (experiments)

two comets approach





fast moving bacteria (yellow)
stand up when two +1/2 defects
approach and can not spread



Outlook

What is New

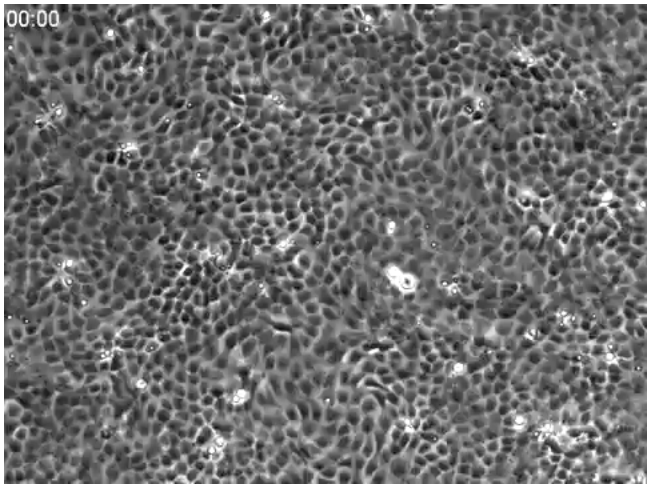
- A physics understanding of fundamental biological processes
- Designing new ways of controlling living materials

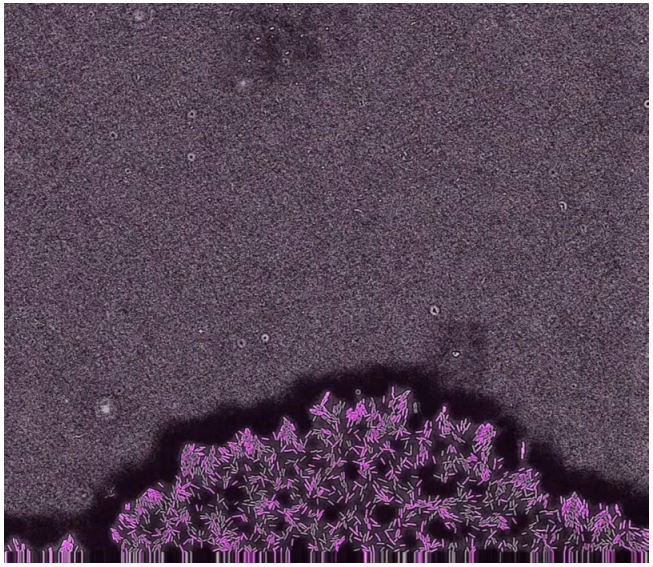
What is Exciting

- To predict cell fate based on its mechanical features
- To program materials that are capable of self-propulsion

What is Important

- Physics is only one part of the complexity of living organisms





Thank You