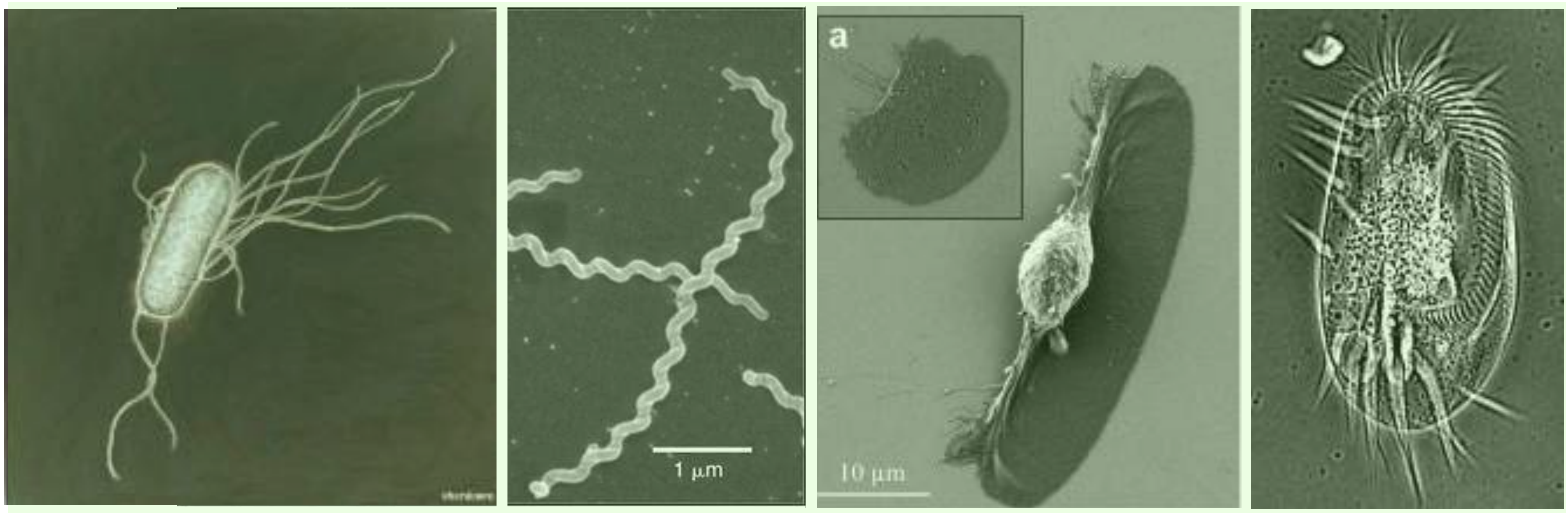
Cellular Motility



Course 1: Introduction – Principles of motility

Thomas Lecuit

chaire: Dynamiques du vivant

https://www.nies.go.jp/chiiki1/protoz/morpho/ciliopho/euplotes.htm

http://nikhil.superfacts.org/archives/2010/02/bacteria_dont_h.html

COLLÈGE
DE FRANCE
1530

Historical perspective

Movement is a defining feature of living organisms:

- movement of parts or of whole organism
- what is different between movement of living and inert matter?

Aristotle: 4 types of movement:

δύναμις (*Physics*, III, 1)

- quantitative: growth/shrinkage
- qualitative: aspect (shape, color etc)
- displacement: in geometrical space.
- genesis/corruption

μεταβολή,
κινήσεις
Υένεσις

XVIIth: Local movement only: Descartes, Galileo, Newton

Causes of movement:

- Mechanical view: Galileo, Descartes, etc.

  — Geometric representation. Organisms respond passively to external source of movement (eg. heat) as in a machine

- Leibniz:

  —Cause of movement is internal. Living matter is active

Organism and cell motility

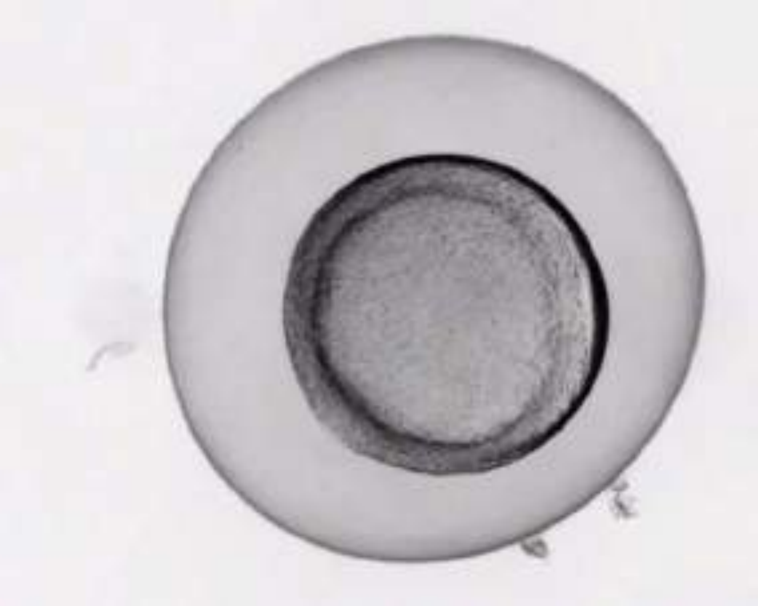
Ubiquity of cell movement:
Fonction

- source of energy/nutrition:

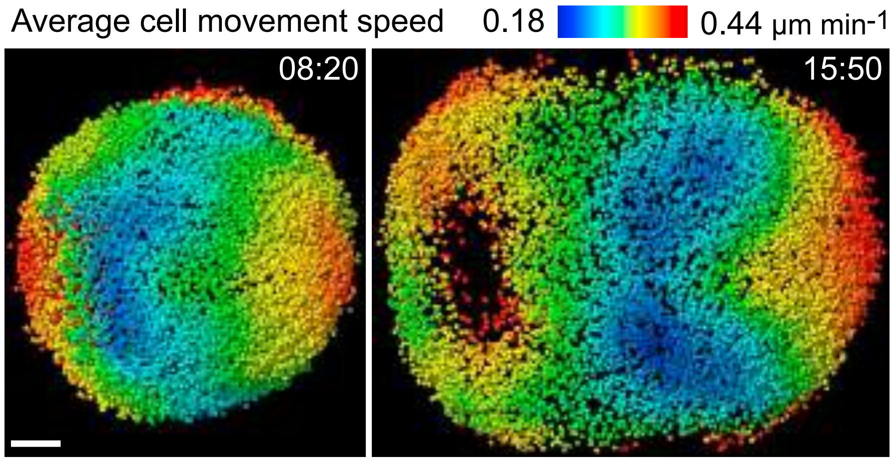
  phototaxis (eg. *Volvox, Euglena*), glucose (*E. coli*), anaerobic conditions (e.g. magnetotactic bacteria)
- reproduction: sperm cells
- escape from predators/toxins
- patrolling: immune defense (eg. dendritic cells)
- embryonic development
- regeneration-repair

PLoS ONE 11(10): e0162602. doi:10.1371/journal.pone.0162602

Tissue shape changes and cell movement

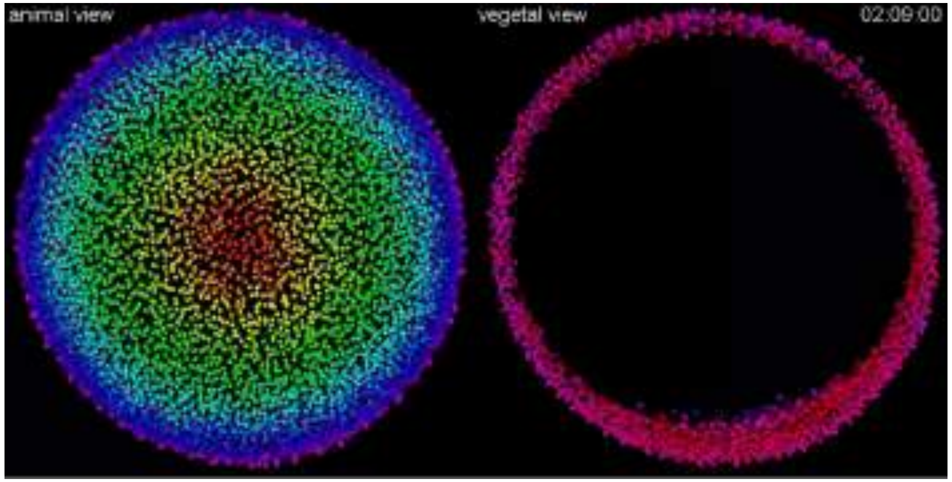


Zebrafish Embryo



Mouse cell embryo

McDoleK and Guignard L. et al., *Cell* 175, 859–876 (2018)



Cell tracking in Zebrafish

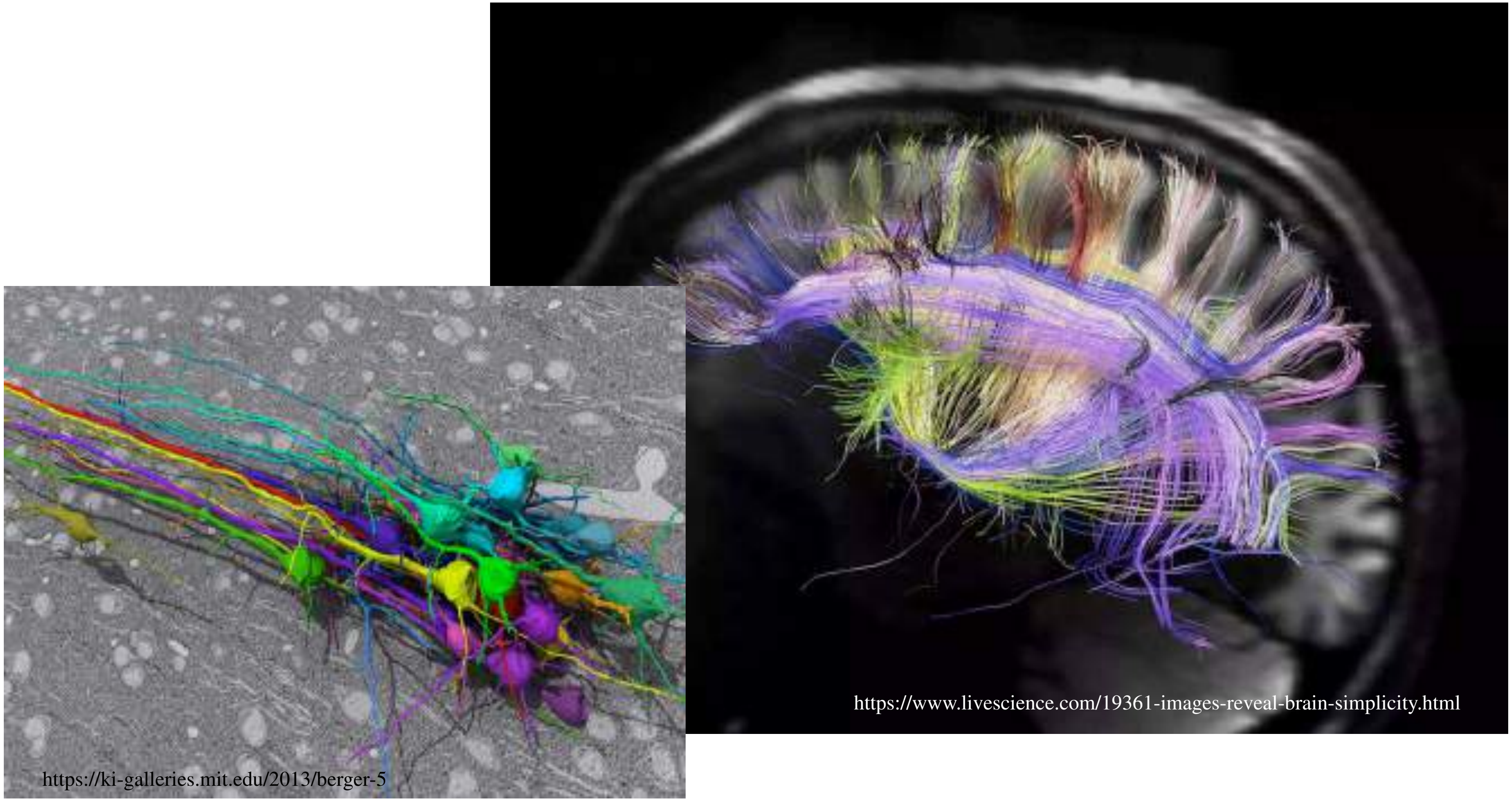
F; Amat et al . And P. Keller. Nat Methods. 11(9):951-8 (2014).

P. Keller et al. *Science* 322(5904):1065-9.(2008)

The nervous system illustrates the magnitude of cell motility

Wiring the human brain requires the laying down of about 1 million km of neurites, all proceeding through the crawling motility of growth cones.

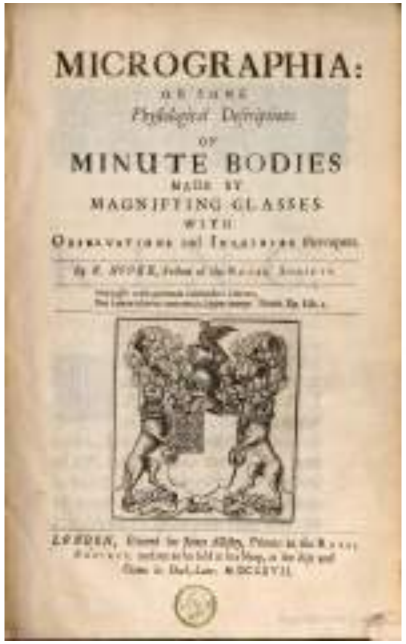
Pollard and Borisy *Cell*, Vol. 112, 453–465 (2003)



https://www.livescience.com/19361-images-reveal-brain-simplicity.html

https://ki-galleries.mit.edu/2013/berger-5

Discovery of cell motility



MICROGRAPHIA:
OR SOME
Physiological Descriptions
OF
MINUTE BODIES
MADE BY
MAGNIFYING GLASSES
WITH
OBSERVATIONS and INQUIRIES thereupon.

By R. HOOKE, Fellow of the ROYAL SOCIETY.

Robert Hooke (1635-1703)

Fig: 1.

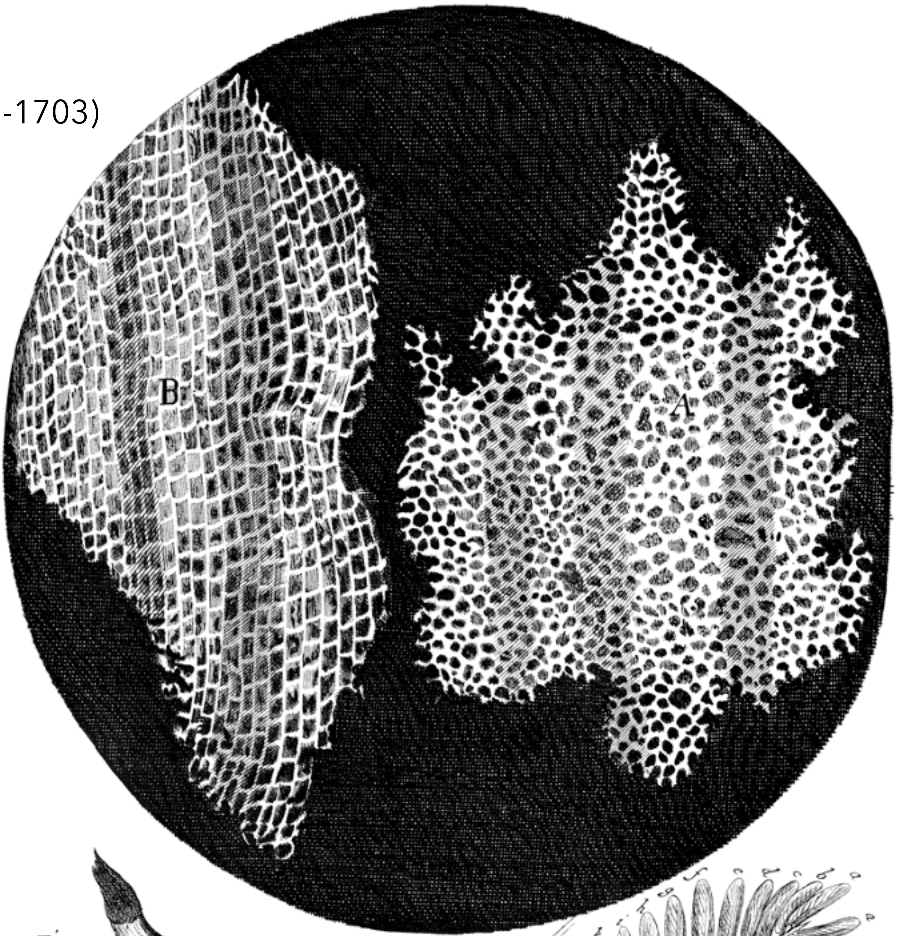
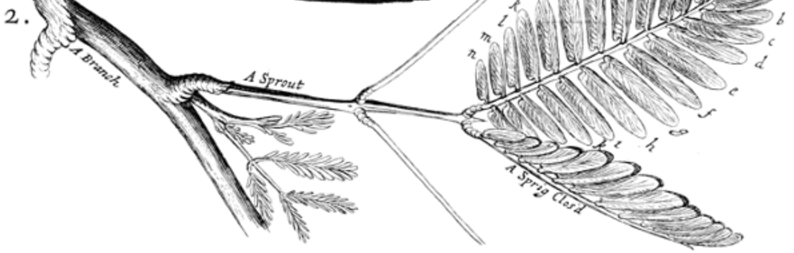


Fig: 2.



Discovery of cell motility

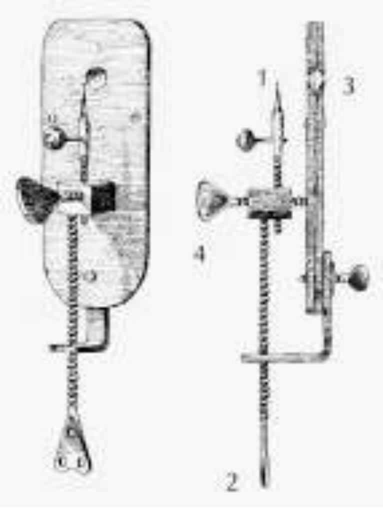
First observation of bacteria and movement

« I then most always saw, with great wonder, that in the said matter there were many very little living **animalcules**, very prettily a-moving. The biggest sort. . . had a **very strong and swift motion**, and shot through the water (or spittle) like a pike does through the water. The second sort. . . oft-times **spun round like a top**. . . and these were far more in number. »

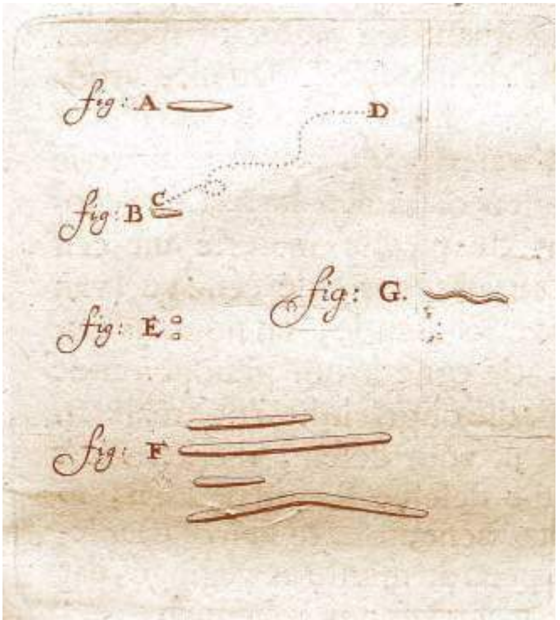
« The biggest sort. . . bent their body into curves in going forwards. . . Moreover, the other animalcules were in such enormous numbers, that all the water. . . seemed to be alive. »

September 17, 1683
Letter to Royal Society

Antoni van Leeuwenhoek (1632-1723)

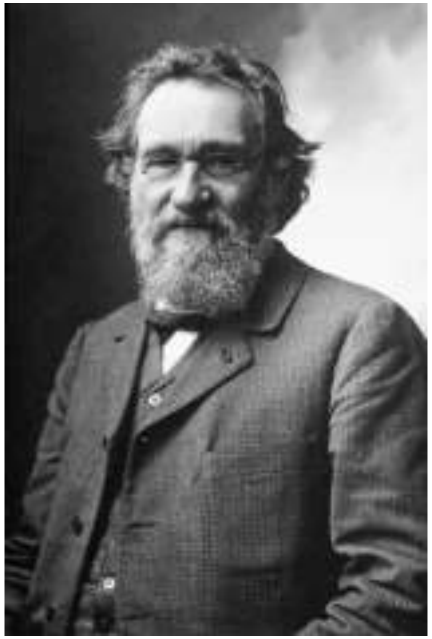


https://pixels.com/featured/leeuwenhoek-microscope-granger.html



A) is a motile *bacillus*. B) *Selenomonas buccalis* & the track of its movement (C to D). E) Micrococci. F) *Leptothrix buccalis*. G) A spirochaete,

Discovery of cell motility



Ilyia Metchnikoff (1845-1905)

Metchnikoff observed in Sicily (Messina) starfish larvae, noticed motile cells and hypothesized that this might underly response to external agents.

Used rose thorns under larval skin and observed leukocyte chemotaxis and phagocytosis

Metchnikoff's drawing of phagocytes at a site of inflammation (induced by silver nitrate) in the caudal fin of a Triton embryo.

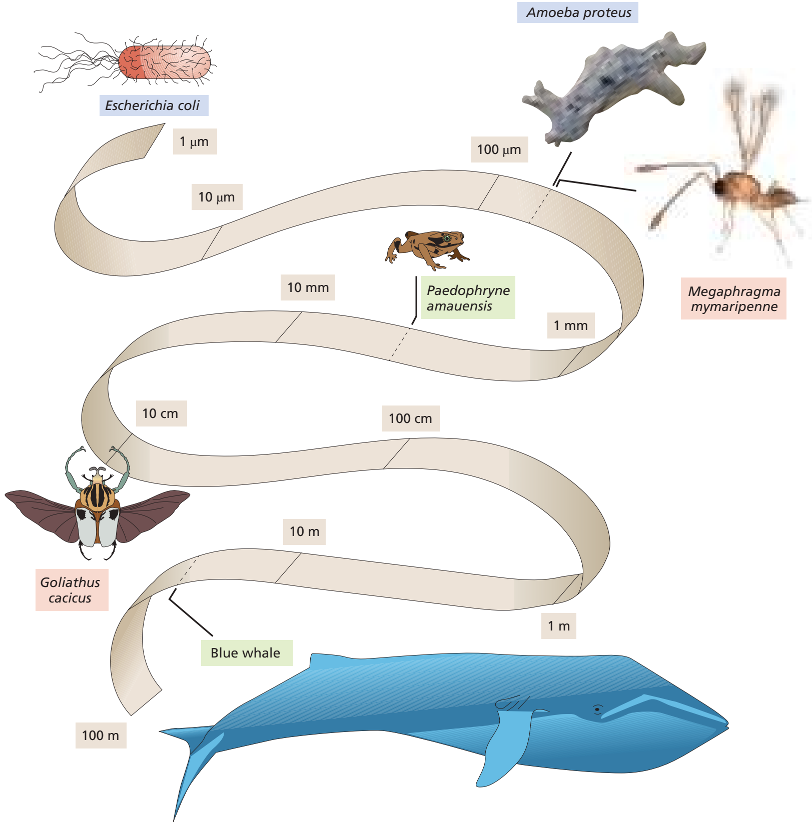
Metchnikoff, E. *Lectures on the Comparative Pathology of Inflammation*. (Reprinted by Dover, New York, 1968).

Cited in: G. A. Dunn and G. E. Jones *Nature Reviews Mol. Cell Biol.* 5:667-672 (2004)

Organism motility across scales

- All organisms except plants and fungi are motile: swimming, flying, walking, crawling, creeping etc m

    - Variation in size:
(6 orders of magnitude in Metazoa)



Bacillus subtilis

https://www.youtube.com/watch?v=n2nVrfgZ45s

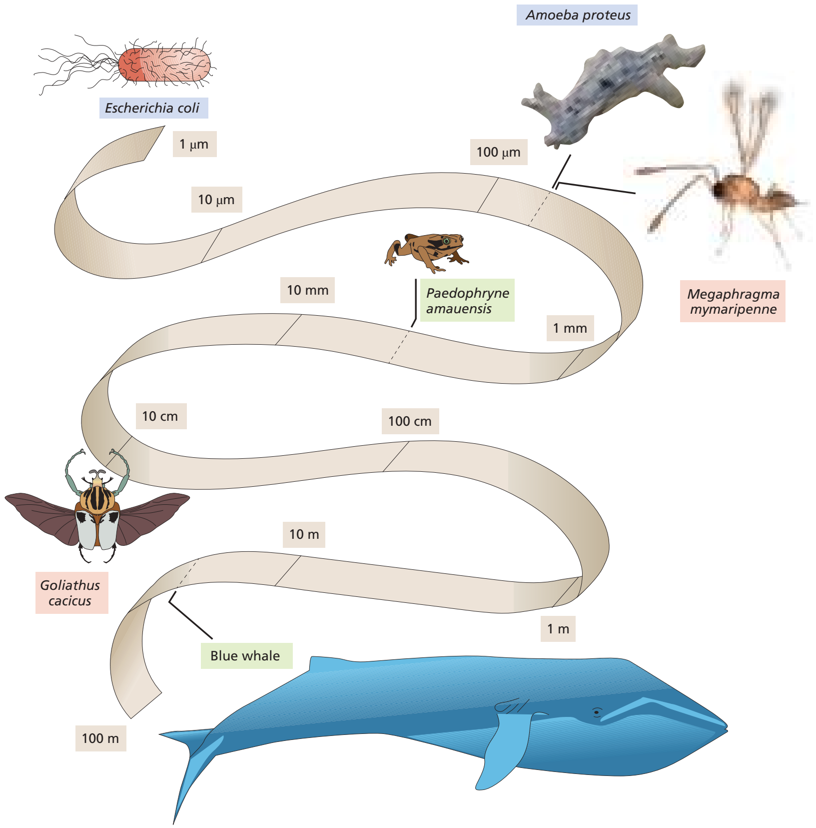
Sperm whale

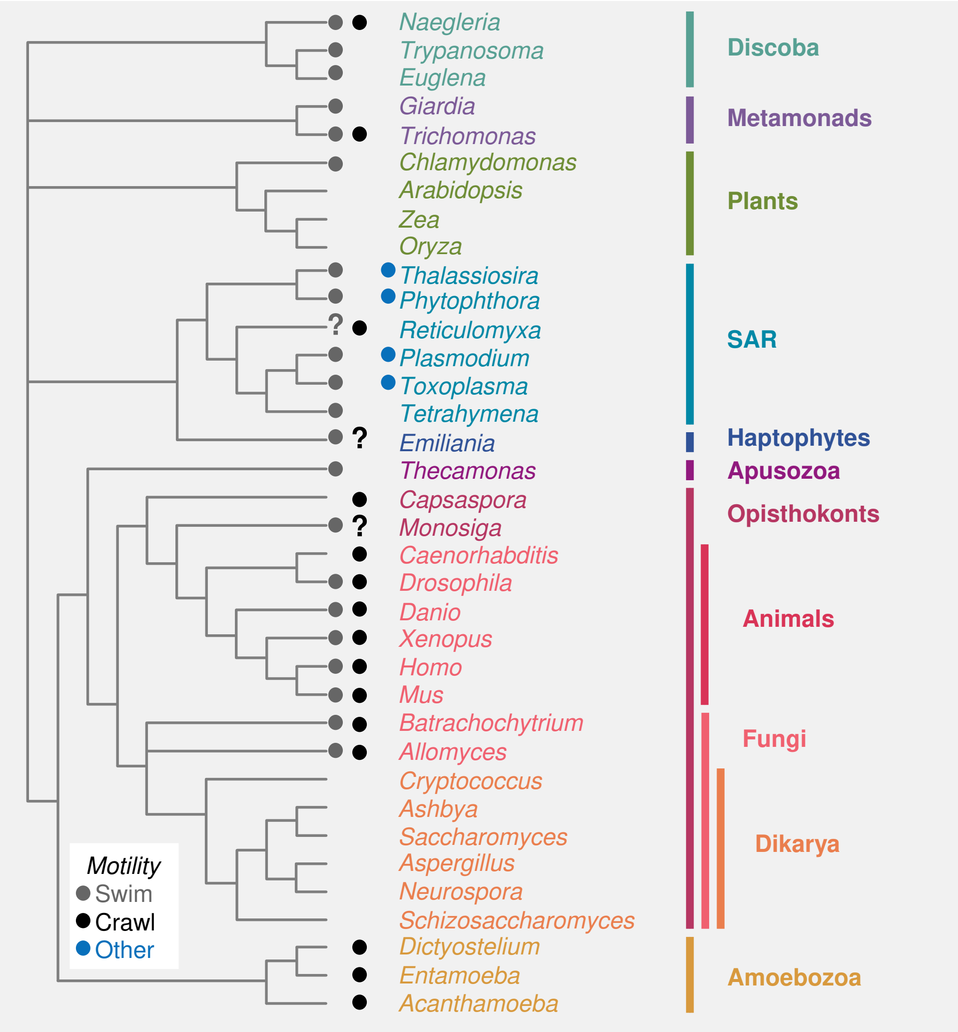
G. Néry. https://www.youtube.com/watch?v=OnvQggy3Ezw

Organism motility across scales

- All organisms except plants and fungi are motile: swimming, flying, walking, crawling and more

  - Variation in size:
    (6 orders of magnitude in Metazoa)



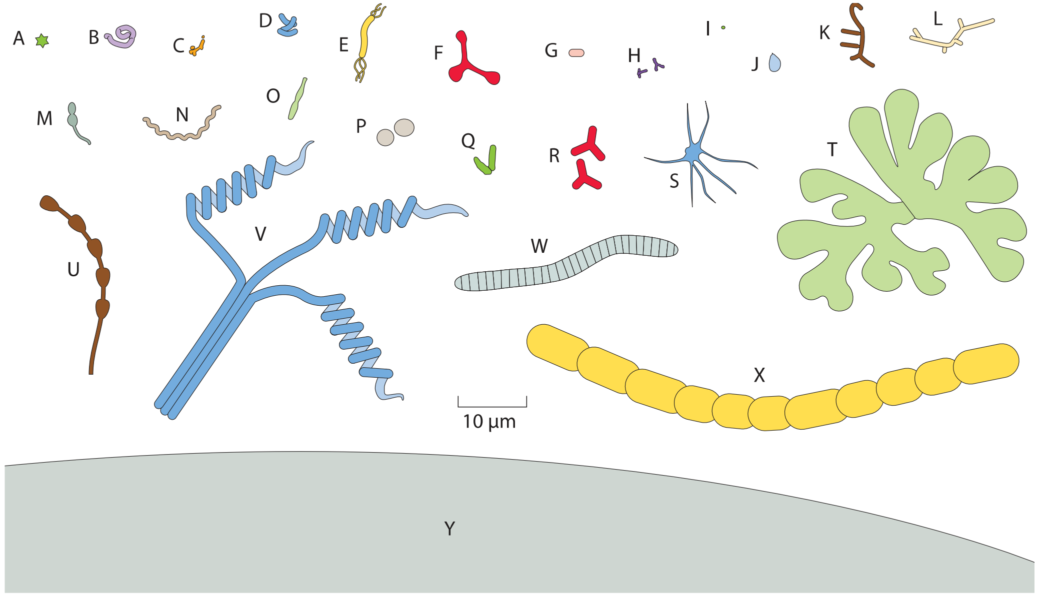


Current Biology

Cell motility across scales

- Motility in aequous (viscous) or visco-elastic environments (host, mud etc)

- Bacteria 1µm - few 10 of µm



(A) *Stella strain* IFAM1312 (380); (B) *Microcyclus* (a genus since renamed *Ancylobacter*) *flavus* (367); (C) *Bifidobacterium bifidum*; (D) *Clostridium cocleatum*; (E) *Aquaspirillum autotrophicum*; (F) *Pyroditium abyssi* (380); (G) *Escherichia coli*; (H) *Bifidobacterium* sp.; (I) transverse section of ratoon stunt-associated bacterium; (J) *Planctomyces* sp. (133); (K) *Nocardia opaca*; (L) Chain of ratoon stunt-associated bacteria; (M) *Caulobacter* sp. (380); (N) *Spirochaeta halophila*; (O) *Prosthecobacter fusiformis*; (P) *Methanogenium cariaci*; (Q) *Arthrobacter globiformis* growth cycle; (R) gram-negative *Alphaproteobacteria* from marine sponges (240); (S) *Ancalomicrobium* sp. (380); (T) *Nevskia ramosa* (133); (U) *Rhodomicrobium vannielii*; (V) *Streptomyces* sp.; (W) *Caryophanon latum*; (X) *Calothrix* sp. (Y) A schematic of part of the giant bacterium *Thiomargarita namibiensis* (290). All images are drawn to the same scale. (Adapted from K. D. Young, Microbiology & Molecular Bio. Rev., 70:660, 2006.)

- Protozoans 0.2 - 2 mm long

Bland J. Finlay
Science 296, 1061 (2002);
DOI: 10.1126/science.
1070710

Scale range among motile single cells: X 2000

Cell Biology by the numbers. Ron Milo, Rob Phillips, *illustrated* by Nigel Orme. *Garland Science* 2012

Cell motility across scales

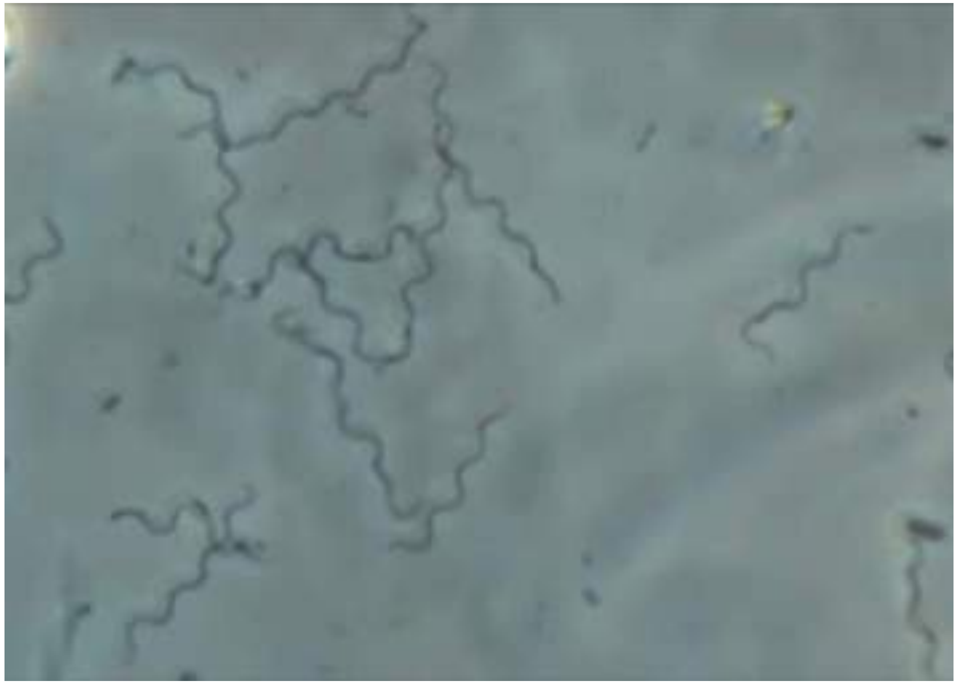
Prokaryotes

Escherichia coli motility

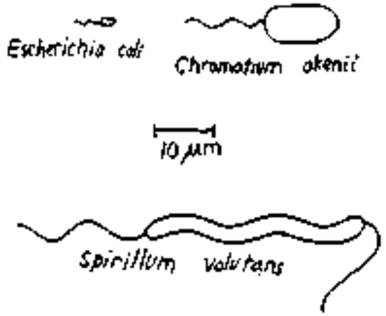
http://www.rowland.harvard.edu/labs/bacteria/movies/ecoli.php

Howard Berg

Spirochetes motility (Lyme, disease, siphylis, leptospirosis etc)



https://www.youtube.com/watch?v=cXYfT5hSLoQ



Cell motility across scales

Eukaryotes

- Giant cell motility >1mm

Amoeba proteus (phylum: Amoebozoa)

https://www.youtube.com/watch?v=rAkzrXxS2tI

http://www.edu.upmc.fr/biomedia/

Spirostomum a

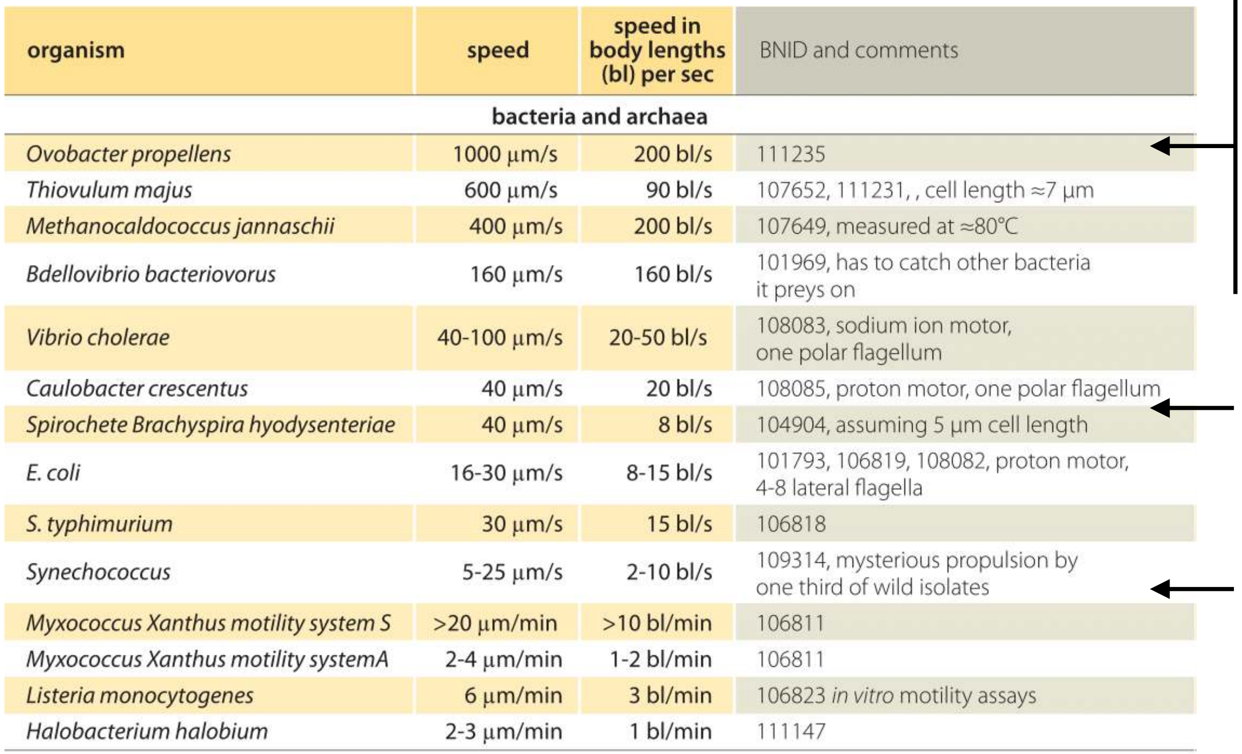
https://www.youtube.com/watch?v=hN9YUwKa9aE

Ferry Siemensma

Cell motility across scales

Velocities

Prokaryotes

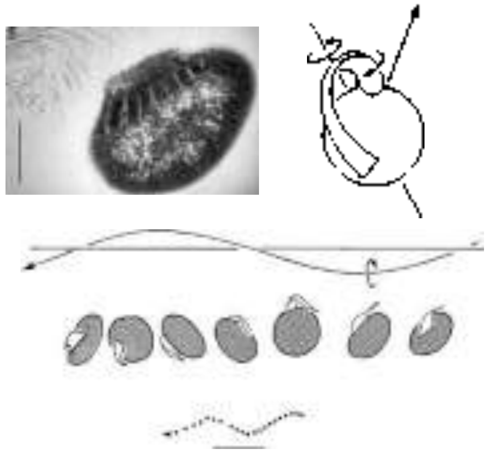


organism	speed	speed in body lengths (bl) per sec	BNID and comments
bacteria and archaea			
Ovobacter propellens	1000 µm/s	200 bl/s	111235
Thiovulum majus	600 µm/s	90 bl/s	107652, 111231, , cell length ≈7 µm
Methanocaldococcus jannaschii	400 µm/s	200 bl/s	107649, measured at ≈80°C
Bdellovibrio bacteriovorus	160 µm/s	160 bl/s	101969, has to catch other bacteria it preys on
Vibrio cholerae	40-100 µm/s	20-50 bl/s	108083, sodium ion motor, one polar flagellum
Caulobacter crescentus	40 µm/s	20 bl/s	108085, proton motor, one polar flagellum
Spirochete Brachyspira hyodysenteriae	40 µm/s	8 bl/s	104904, assuming 5 µm cell length
E. coli	16-30 µm/s	8-15 bl/s	101793, 106819, 108082, proton motor, 4-8 lateral flagella
S. typhimurium	30 µm/s	15 bl/s	106818
Synechococcus	5-25 µm/s	2-10 bl/s	109314, mysterious propulsion by one third of wild isolates
Myxococcus Xanthus motility system S	>20 µm/min	>10 bl/min	106811
Myxococcus Xanthus motility systemA	2-4 µm/min	1-2 bl/min	106811
Listeria monocytogenes	6 µm/min	3 bl/min	106823 *in vitro* motility assays
Halobacterium halobium	2-3 µm/min	1 bl/min	111147

swim

glide

twitch



T; Fenchel *FEMS Microb. Ecol.* 48:231–238 (2004)

Sailfish *Istiophorus platypterus:* 30 m/s, 15 bl/sec, like *E.coli*

Michael Phelps: 100m in 50s, 1 bl/sec (for 1 min)

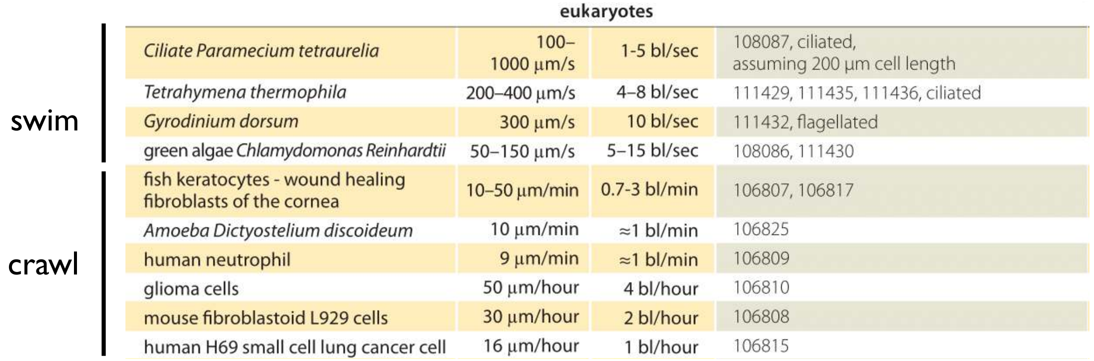
- swimming speed ranges from 5-1000µm/s (200 fold range)
- gliding/twitching speed ranges from 2-20µm/min (10 fold range)
- swimming about 1000 fold faster than gliding/twitching

Cell Biology by the numbers. Ron Milo, Rob Phillips, *illustrated* by Nigel Orme. *Garland Science* 2012

Cell motility across scales

Velocities

Eukaryotes

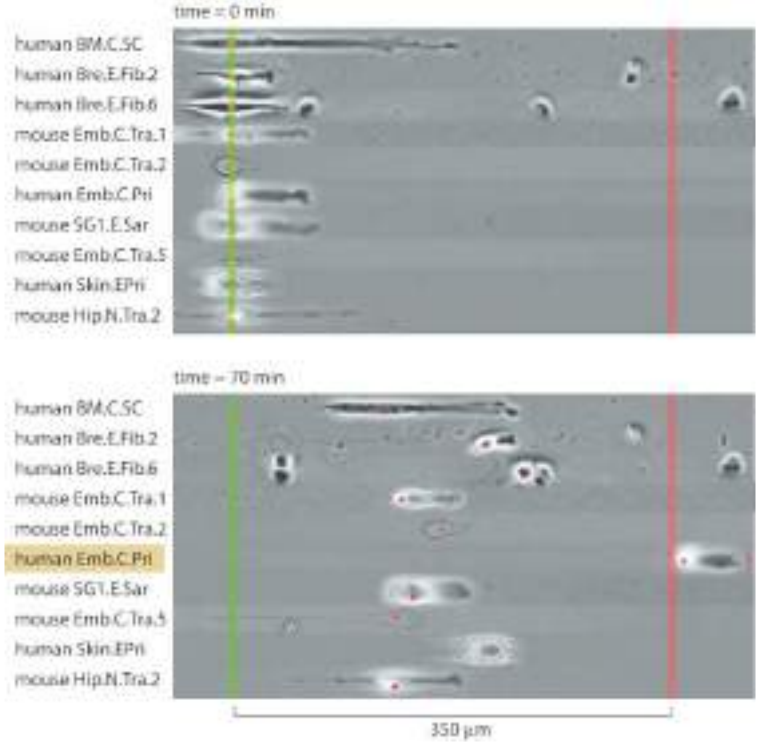


eukaryotes

swim	*Ciliate Paramecium tetraurelia*	100–1000 µm/s	1-5 bl/sec	108087, ciliated, assuming 200 µm cell length
	Tetrahymena thermophila	200–400 µm/s	4–8 bl/sec	111429, 111435, 111436, ciliated
	Gyrodinium dorsum	300 µm/s	10 bl/sec	111432, flagellated
	green algae *Chlamydomonas Reinhardtii*	50–150 µm/s	5–15 bl/sec	108086, 111430
crawl	fish keratocytes - wound healing fibroblasts of the cornea	10–50 µm/min	0.7-3 bl/min	106807, 106817
	Amoeba Dictyostelium discoideum	10 µm/min	≈1 bl/min	106825
	human neutrophil	9 µm/min	≈1 bl/min	106809
	glioma cells	50 µm/hour	4 bl/hour	106810
	mouse fibroblastoid L929 cells	30 µm/hour	2 bl/hour	106808
	human H69 small cell lung cancer cell	16 µm/hour	1 bl/hour	106815

Cell Biology by the numbers. Ron Milo, Rob Phillips, *illustrated* by Nigel Orme. *Garland Science* 2012

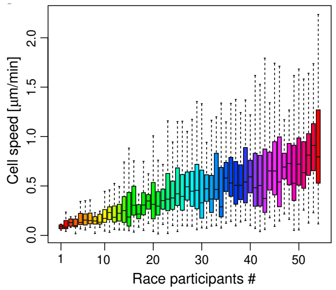
Finals of the World Cell Race (Théry & Piel et al)



Race track:4 µm- and 12 µm-wide fibronectin lines

- swimming speed ranges from 50-1000µm/s (20 fold range)
- crawling speed ranges from 16-3000µm/hour (200 fold range)

- swimming about 1000 fold faster than crawling



Maiuri, P., et al. (2012). The first world cell race. *Curr. Biol. 22*, R673–R675.

Physical constraints on cell motility

— Newton’s second Law: $F = m.a$

- inertia: movement at constant speed ($a=0$) without applied force (e.g. force is not necessary at all time: eg. swimming)
- This is not true for cells and small objects: force needs to be constantly applied for motion.
- Life operates at so called low Reynolds number

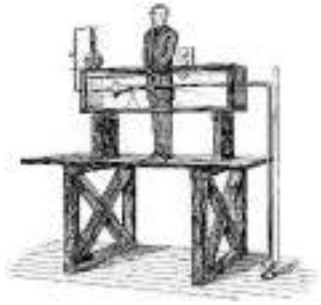
Osborne Reynolds
(1842-1912)

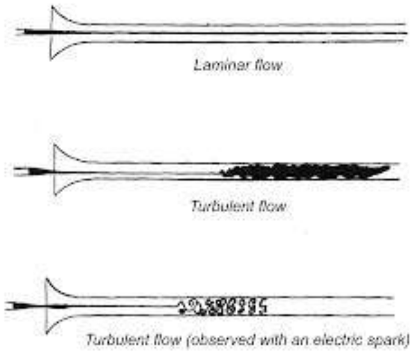
- Fluid mechanics: studied the impact of flow speed on nature of flow and conditions in which flow remains laminar
- This depends on ratio of inertial forces and viscous forces.
- Reynolds the number is a dimensionless parameter that compares the effect of inertial and viscous forces

$$\boxed{\mathrm{Re} = \frac{UL\rho}{\eta}}$$

U length scale of system
L velocity scale of system
ρ density
η viscosity

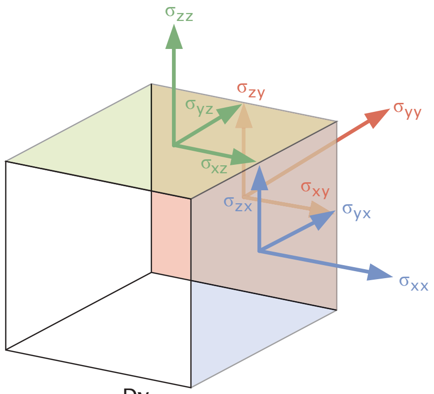
${}^{\eta}/_{\rho}$ kinematic viscosity





Low Reynolds number world

FORCE BALANCE



$$\underbrace{\rho \frac{D\mathbf{v}}{Dt}}_{\text{mass density} \times \text{acceleration}} = \underbrace{\nabla \cdot \boldsymbol{\sigma}}_{\text{divergence of stress}}$$

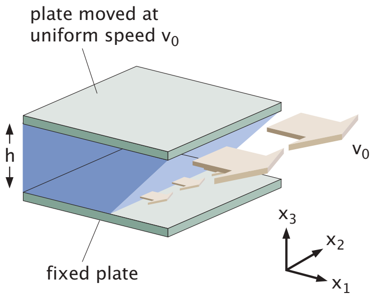
$$\boldsymbol{\sigma} = -p\mathbf{I} + 2\eta\mathbf{D}$$

NAVIER-STOKES EQUATIONS

$$\rho \frac{D\mathbf{v}}{Dt} = -\nabla \mathbf{p} + \eta \nabla^2 \mathbf{v}$$

CONSTITUTIVE LAW FOR NEWTONIAN FLUID

relates shear stress and strain in fluid



strain rate tensor:

$$D_{ij} = \frac{1}{2}\left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i}\right).$$

Navier stokes equation

$$\underbrace{\rho\left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v}\cdot\nabla\mathbf{v}\right)}_{\text{inertial term}} = -\nabla p + \underbrace{\eta\nabla^2\mathbf{v}}_{\text{viscous term}},$$

Dimensionless version:

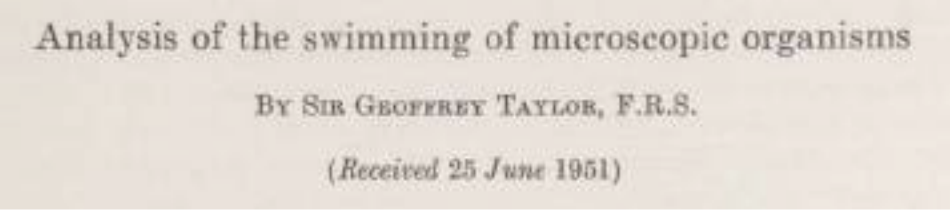
$$\left(\frac{\partial \mathbf{v}^*}{\partial t^*} + \mathbf{v}^*\cdot\nabla_*\mathbf{v}^*\right) = -\frac{1}{Re}\nabla_* p^* + \frac{1}{Re}\nabla_*^2\mathbf{v}^*.$$

$$v^* = \frac{v}{U} \qquad x_i^* = \frac{x_i}{L}, \qquad p^* = \frac{p}{(\eta U/L)} \qquad t^* = \frac{t}{(L/U)}.$$

When Re <<1, the right hand term dominates the inertial term on the left

R. Phillips and C. Hueschen, *in prep.*

Low Reynolds number world

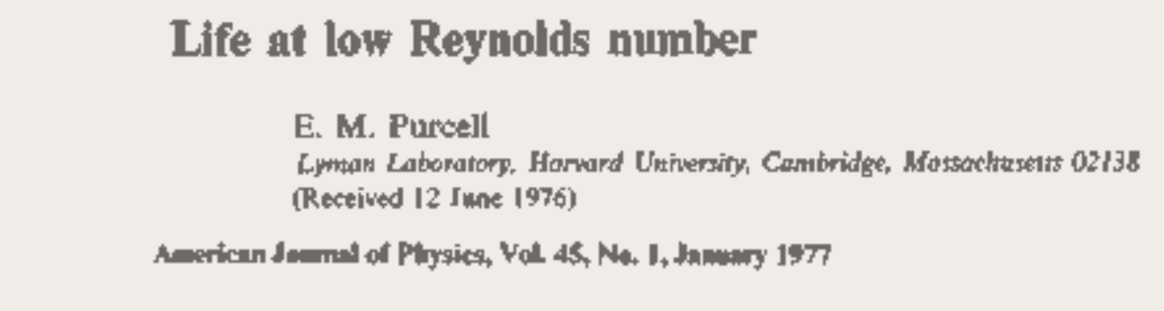


Analysis of the swimming of microscopic organisms

By Sir Geoffrey Taylor, F.R.S.

(*Received 25 June 1951*)

Proc. R. Soc. Lond. A 209:447-461 (1951) doi: 10.1098/rspa.1951.0218



Life at low Reynolds number

E. M. Purcell
Lyman Laboratory, Harvard University, Cambridge, Massachusetts 02138
(Received 12 June 1976)

American Journal of Physics, Vol. 45, No. 1, January 1977

American Journal of Physics 45, 3 (1977); http://doi.org/10.1119/1.10903

G.I. Taylor
(1886-1975)

Edward Purcell
(1912-1997)

$$\mathrm{Re} = \frac{UL\rho}{\eta}$$

water: density ρ 1g/cm3
viscosity η 10^{-2} g/cm. s (=1mPa.s or 1cP)

Fish: 1 cm and: U=10 cm/s $\mathrm{Re} = 10^{3}$

Human (max): 2m, 2m/s. $\mathrm{Re} = 4.\ 10^{6}$

Whale: up to 30 m and max 45km/h (12.5 m/s) $\mathrm{Re} = 3.\ 10^{8}$

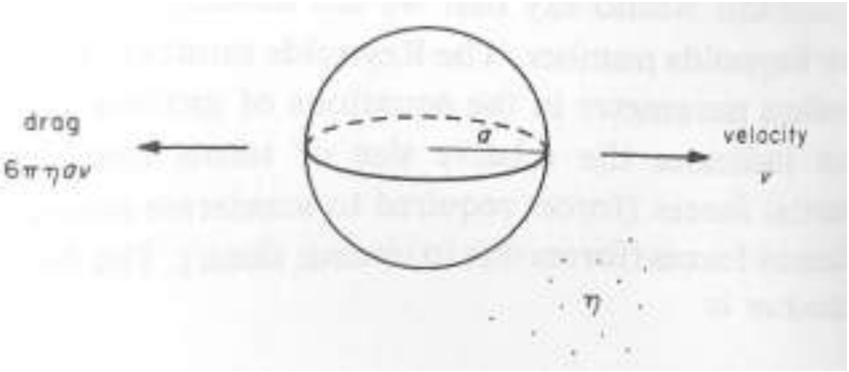
dominated by inertia

but for a Bacterium: 1µm and 10µm/s $\mathrm{Re} = 10^{-5}$

dominated by viscosity

Low Reynolds number world

Stokes law:

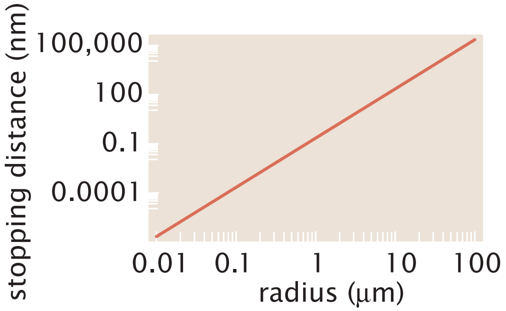


http://www.rowland.harvard.edu/labs/bacteria/movies/ecoli.php

Motion of a bacterium (modeled as a sphere): $m(-dv/dt) = 6\pi\eta av$

$v(t) = v(0)e^{-t/\tau}$, and $\tau = \dfrac{m}{6\pi\eta a} = \dfrac{2a^2\rho_s}{9\eta}$.

With a= 1μm, this is 0.2 μs. So a bacterium stops in about 1μs
Starting at 20μm/s, a bacterium coasts 0.004 nm



E. Purcell. *American Journal of Physics* 45, 3 (1977)
Howard C. Berg. Random walk in biology. *Princeton Univ. press* (1993)

Physical constraints on cell motility

- Consequences of Low Reynolds number (no inertia) for motion in a fluid:

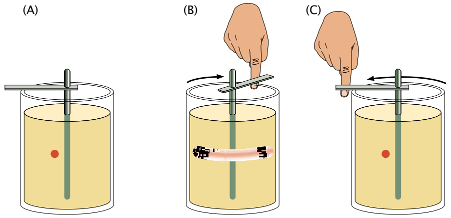
$$\nabla p - \eta \nabla^2 \mathbf{v} = \mathbf{F},$$

Body force

The Scallop Theorem

There is no explicit consideration of time:

E.M. Purcell *American Journal of Physics* 45, 3 (1977)



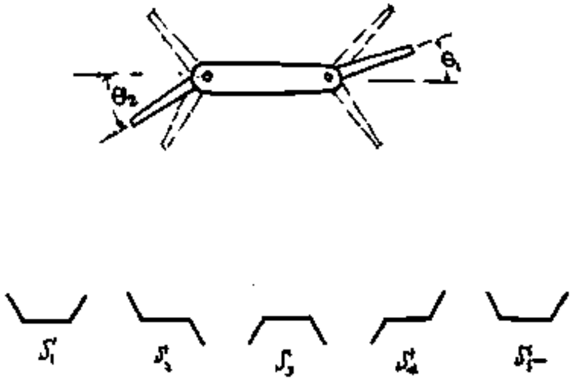
- **Reciprocal movement is time symmetric.**
  Corresponds to 1 degree of freedom in configuration space

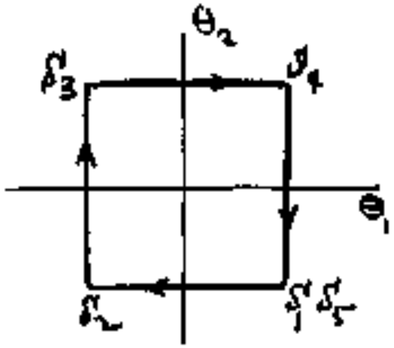
National Committee for Fluid Mechanics: G.I. Taylor

https://www.youtube.com/watch?v=51-6QCJTAjU&list=PL0EC6527BE871ABA3&index=9

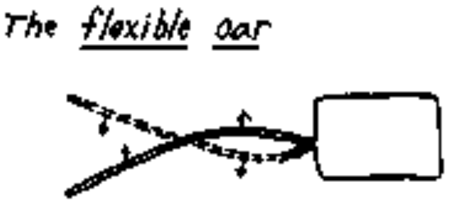
Physical constraints on cell motility

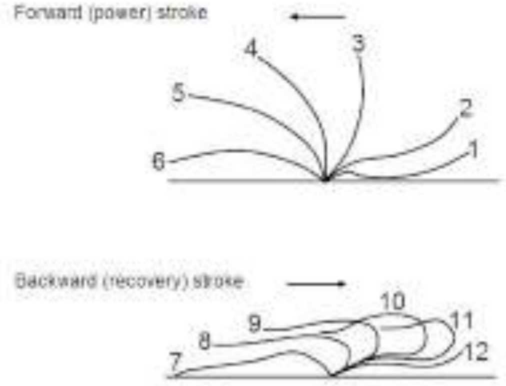
- However: **Non-reciproqual** movement leads to net forward movement at low Reynolds number





- **Beating** of *flexible* filament (e.g. cilia)

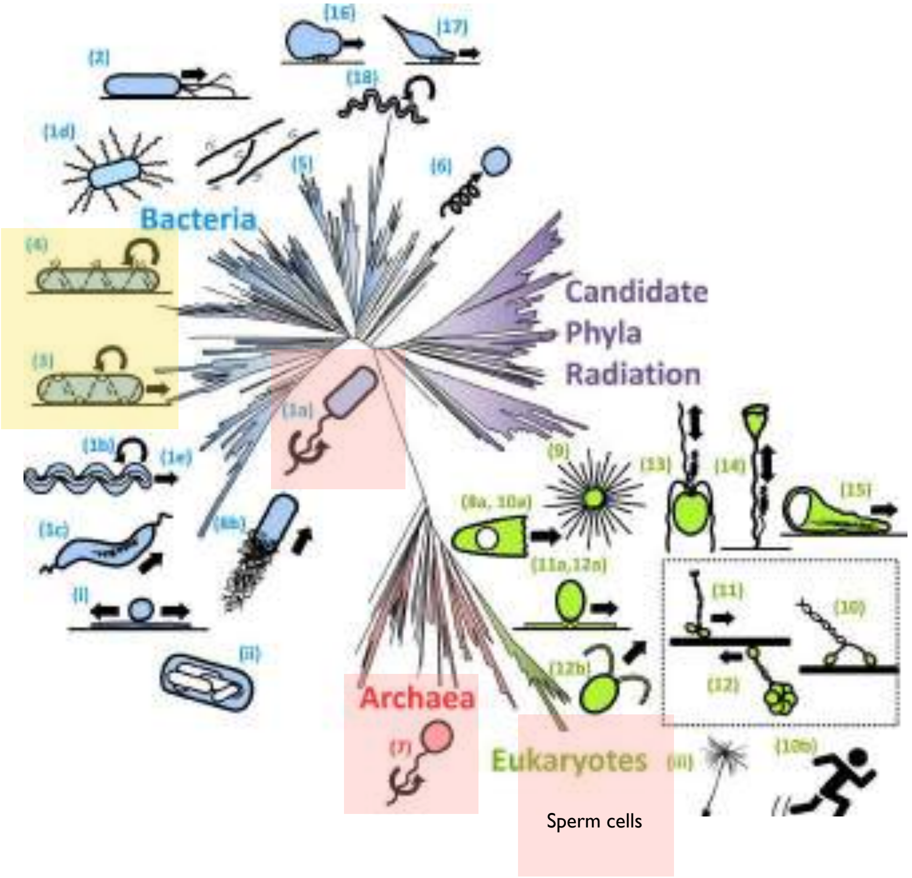




- **Rotation** of *helical* structure (e.g. flagellum)

E. Purcell. *American Journal of Physics* 45, 3 (1977)

The Tree of cell motility



- 5 Systems based on motor system:
  Bacterial flagella, Actin polymerization and
  Motor proteins (Myosin, Kinesin, Dynein)
- 18 classes based on force/movement-producing protein architectures

- Movement requires coupling between motor output and the cell envelope to propel the cell via interactions with environment.

- Evidence of **widespread evolution of motility mechanisms**: extensive in Bacteria (envelope), not in Archea (no envelope)

- **Evidence of convergent evolution**:
  — flagella in Bacteria (1a) and archaella in Archea (7), flagella in Eukarya sperm

  — helix rotation at cell periphery (3, 4) *Myxococcus xanthus* (ProteoB), and *Flavobacterium johnsoniae* (Bacteroidetes)

Miyata M, Robinson RC, Uyeda TQP, et al. Tree of motility – A proposed history of motility systems in the tree of life. *Genes Cells*. 2020;25:6–21. https://doi.org/10.1111/ gtc.12737

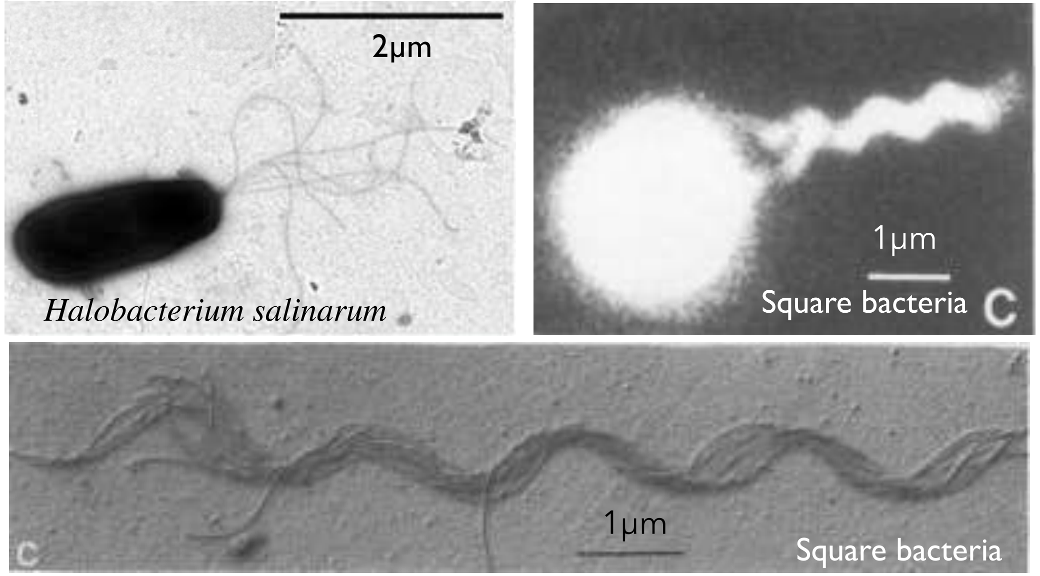
Convergent evolution

Case study 1: swimming

— flagella in Bacteria and archaella in Archea

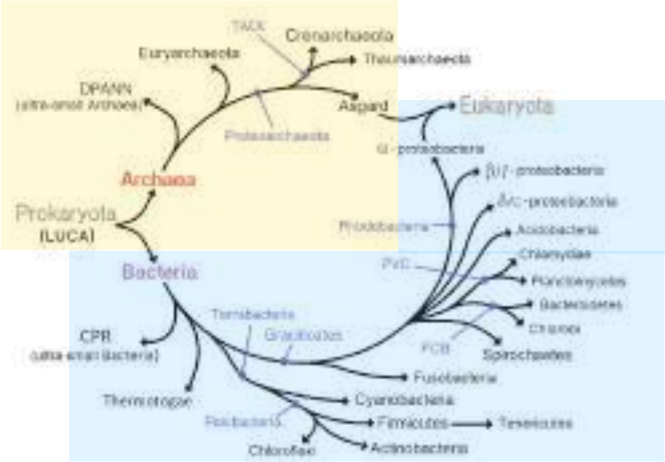
Propeller: helical structure powered by a rotary motor anchored to cell periphery

Archaea — Halobacteriaceae



Alam *et al. EMBO Journal*, 1984, 3:2899-2903

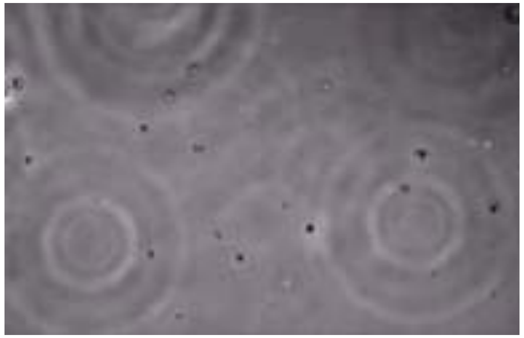
Rotates clockwise and counterclockwise



https://en.wikipedia.org/wiki/Bacteria
after: Zhu et al *Nat. Com.* 2019
doi:10.1038/s41467-019-13443-4

Archaea — Sulfolobaceae

Sulfolobus acidocaldarius



https://www.youtube.com/watch?v=PDRJA1yB5Jo

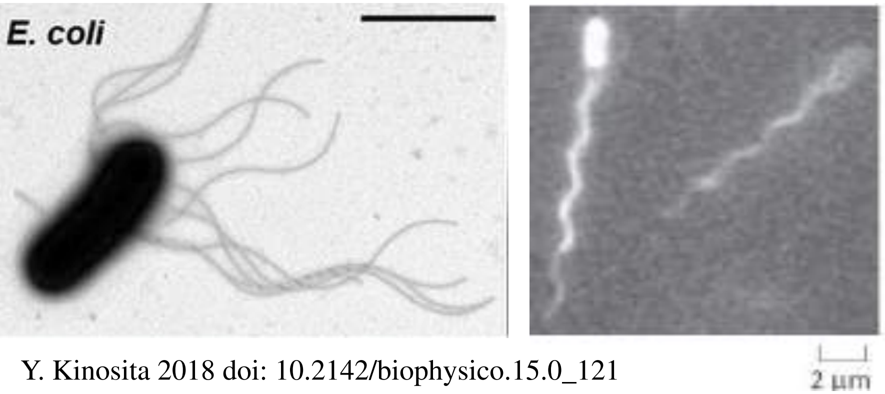
Convergent evolution

Case study 1: swimming

— flagella in Bacteria and archaella in Archea

Propeller: helical structure powered by a rotary motor anchored to cell periphery

Bacteria —Gammaproteobacteria (Gram -)

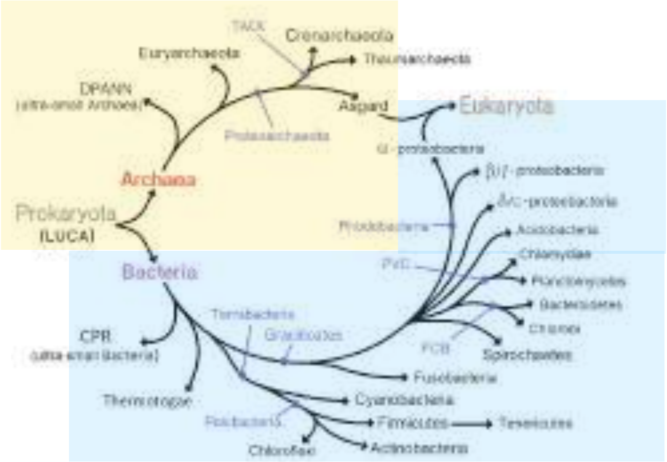


Y. Kinosita 2018 doi: 10.2142/biophysico.15.0_121

Howard Berg

http://www.rowland.harvard.edu/labs/bacteria/movies/ecoli.php

Rotates clockwise and counterclockwise



https://en.wikipedia.org/wiki/Bacteria
after: Zhu et al *Nat. Com.* 2019
doi:10.1038/s41467-019-13443-4

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Convergent evolution

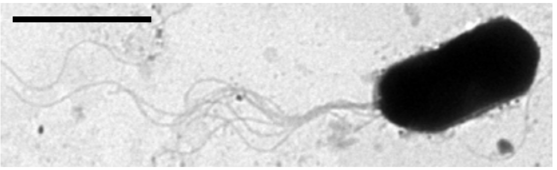
Case study 1: swimming

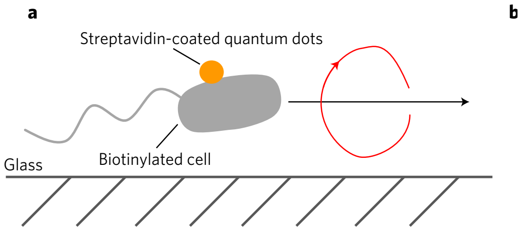
— flagella in Bacteria and archaella in Archea

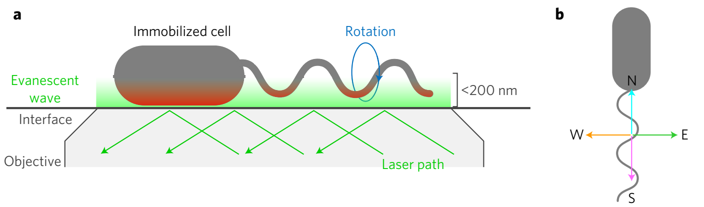
Propeller: helical structure powered by a rotary motor anchored to cell periphery

archaella use the free energy of ATP to rotate.

Halobacterium salinarum

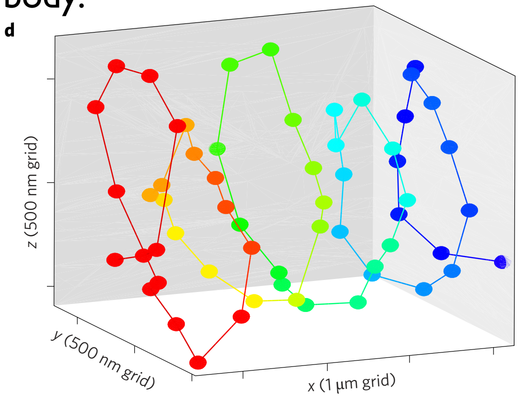




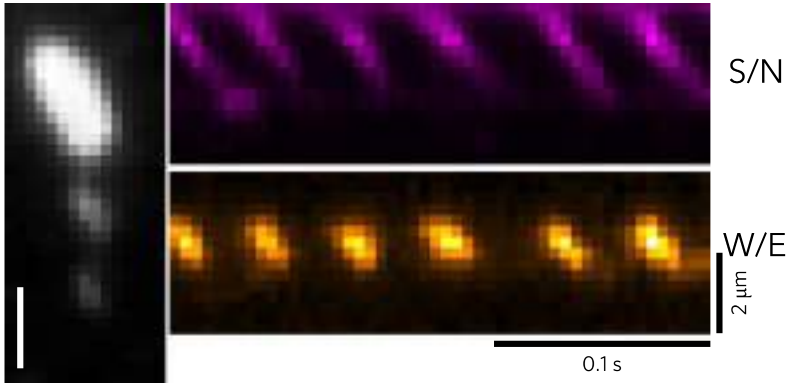


Right-handed helical structure of archaella with a rotation speed of 23 ± 5 Hz
Estimated torque of 50 pN.nm

Rotation of cell body:



Direct observation of rotation



Y. Kinosita *et* al. *Nat Microbiol* 26;1(11):16148. (2016)
doi: 10.1038/nmicrobiol.2016.148.

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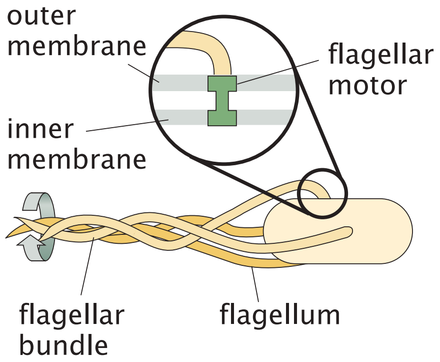
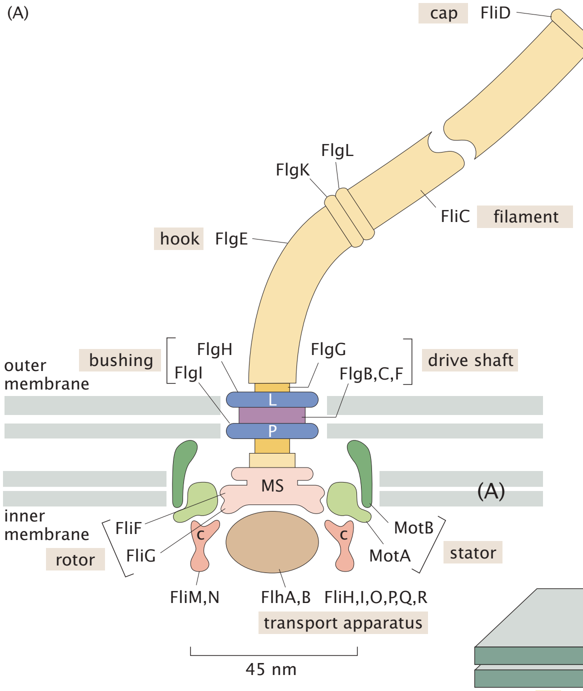
Convergent evolution

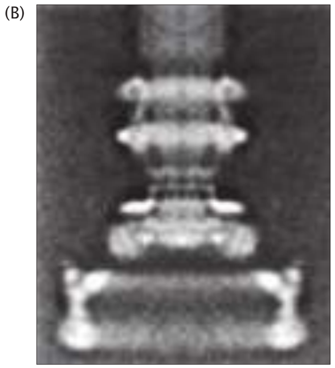
Case study 1: swimming

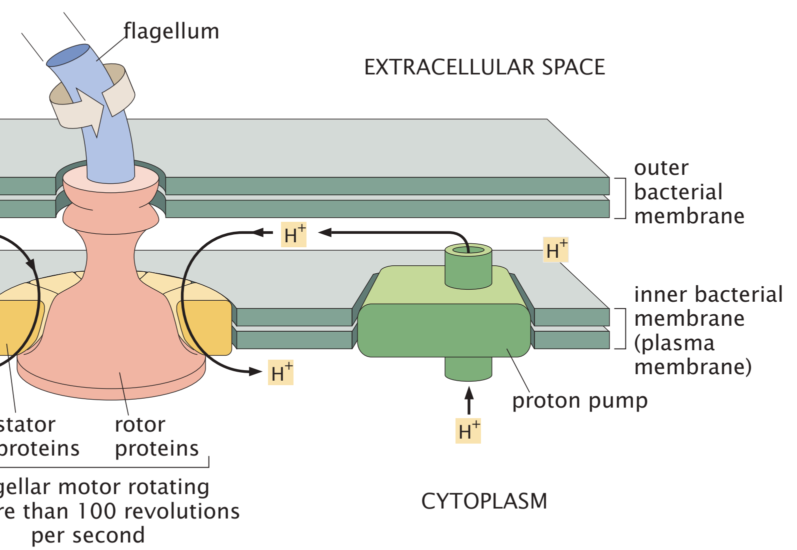
— flagella in Bacteria and archaella in Archea

Propeller: helical structure powered by a rotary motor anchored to cell periphery
Flagella use the free energy of H+ gradient to rotate
Rotation speed: 100Hz or more









R. Phillips, J. Kondev, J. Thériot & H. Garcia. *Physical Biology of the Cell (Garland Science)* 2012

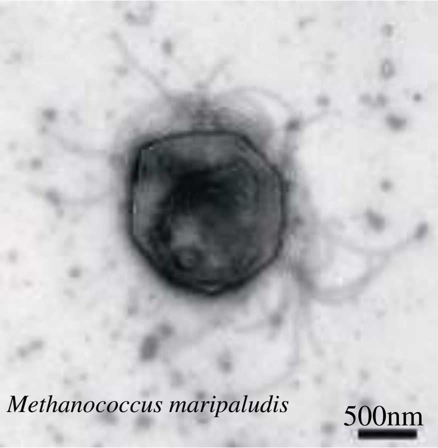
Convergent evolution

Case study 1: swimming

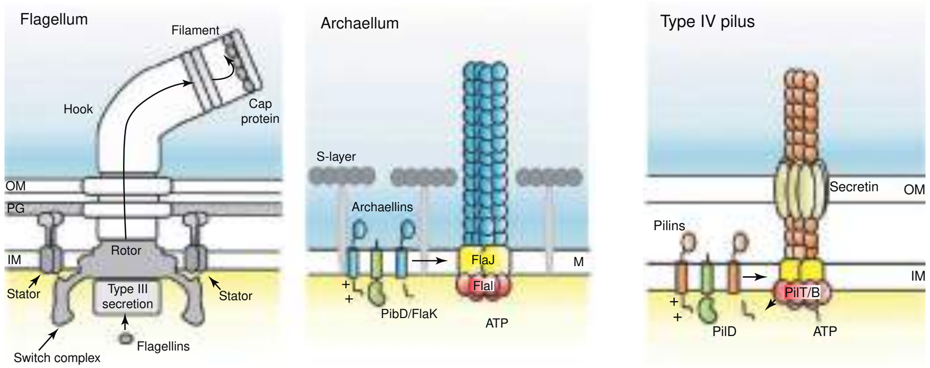
— flagella in Bacteria and archaella in Archea

Propeller: helical structure powered by a rotary motor anchored to cell periphery

- The **archaellum** comprises a rigid helical filament that is attached to the cell membrane by a molecular motor
- Archaea do not code for any of the proteins that are part of the flagellum
- Archaella are evolutionarily and structurally related to type IV filament systems (TFF)
- TFF diversified into archaella, Type IV Pili etc.



K. Jarrell and S-V. Albers. *Frontiers in Microbiology,* 2015, 6:23.



18-22 nm
10-14nm
5-9nm

Type III secretion
Type IV secretion

H+ or Na+ flux
ATP hydrolysis

rotation
rotation

K. Jarrell and S-V. Albers. *Trends in Microbiology,* 2012, 20: 307-312

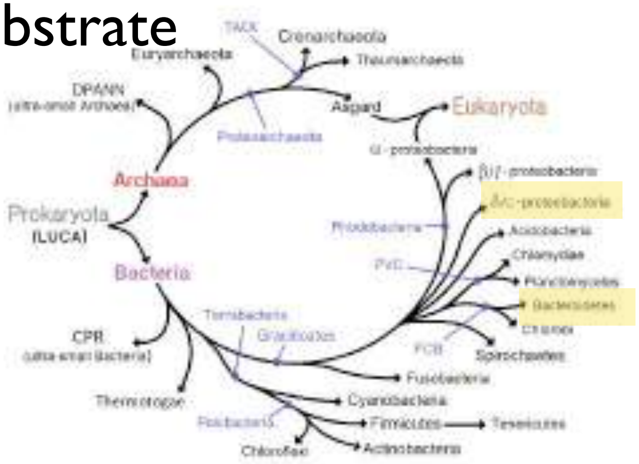
http://dx.doi.org/10.1016/j.tim.2012.04.007

Convergent evolution

Case study 2: Rotary gliding on a substrate

— helix rotation at periphery of cell resisted by adhesion on cell surface

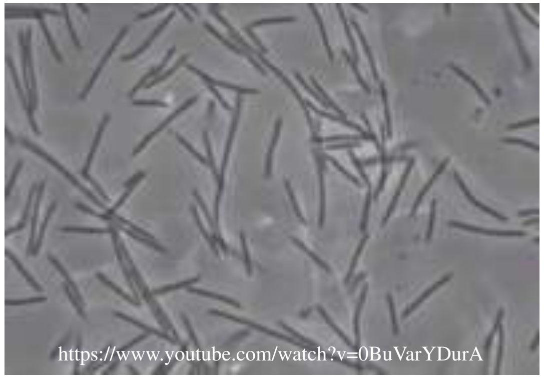
Myxococcus xanthus (ProteoB), and *Flavobacterium johnsoniae* (Bacteroidetes),



https://en.wikipedia.org/wiki/Bacteria
after: Zhu et al *Nat. Com.* 2019
doi:10.1038/s41467-019-13443-4

Flavobacterium johnsoniae (Bacteroidetes)

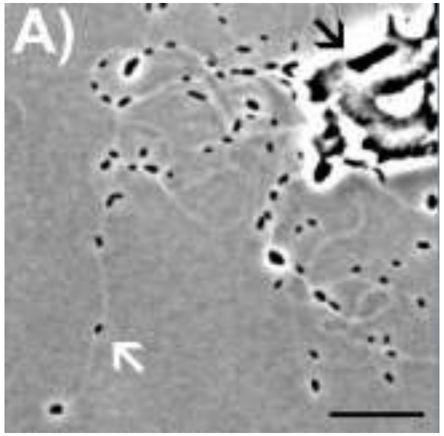
Moves at 2µm/s


https://www.youtube.com/watch?v=0BuVarYDurA

Myxococcus xanthus (ProteoB),

Moves at 2-4 µm/min


https://www.youtube.com/watch?v=iHg15E414lk



cells secrete components that enhance adhesion: stigmergy

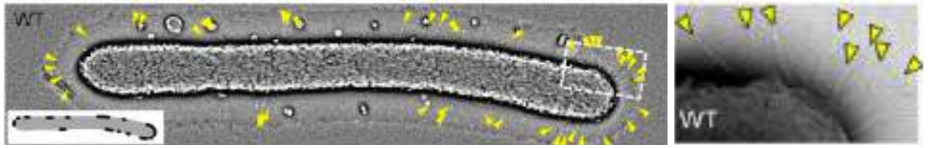
S.T. Islam, T. Mignot / *Seminars in Cell & Developmental Biology* 46 (2015) 143–154

Convergent evolution

Case study 2: Rotary gliding on a substrate

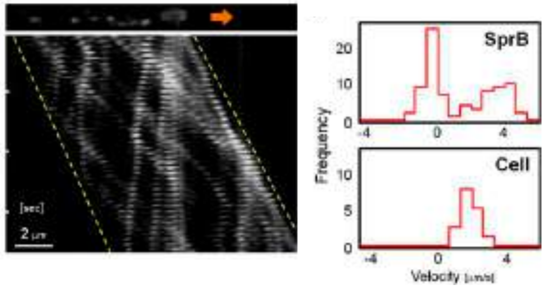
— *Flavobacterium johnsoniae* (*Fj*, Bacteroidetes)

Fj is covered with 150nm SprB filaments at the cell surface.



SprB moves along helical path on cell surface in both directions

In substrate referential, movement of SprB is asymmetric if the cell moves (at 2µm/s):
Forward movement in substrate referential at average 4µm/s or 0µm/s:
Retrograde movement in cell is immobile in substrate referential



BUT: In immobile cells, SprB movement is symmetric in substrate referential

D. Nakane et al, and K. Nakayama. 2013 *PNAS*, 110: 11145–11150

Convergent evolution

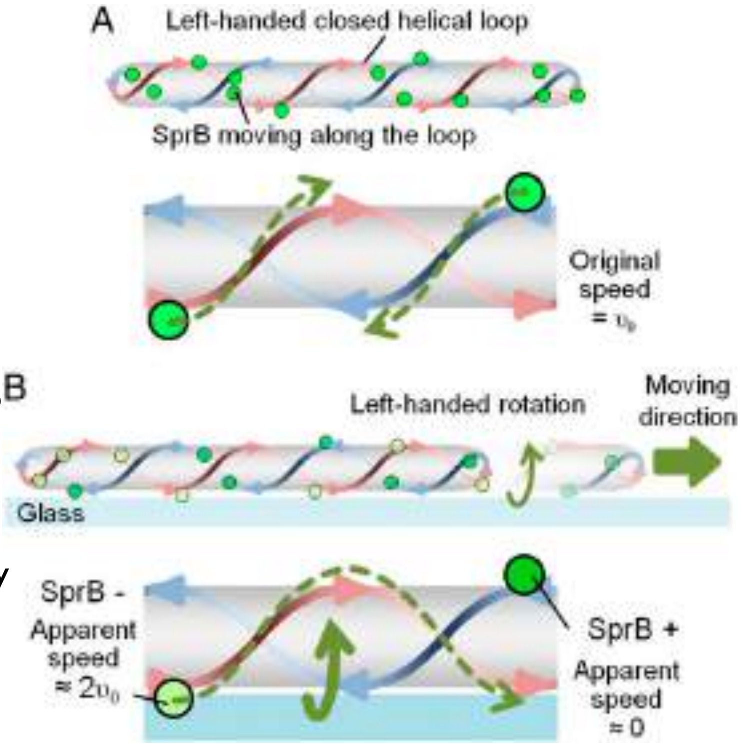
Case study 2: Rotary gliding on a substrate

— *Flavobacterium johnsoniae* (*Fj*, Bacteroidetes)

Model: screw-like mechanism

A nontranslocating cell. Adhesin SprB moves along the left-handed helical loop with a speed of υ_0.

In a translocating cell, SprB moving toward the rear of the cell adheres to the surface, generating left-handed rotation and right-directed translocation of the cell. SprB moving toward the front of the cell apparently runs twice as fast with respect to the glass surface than SprB on a nontranslocating cell.



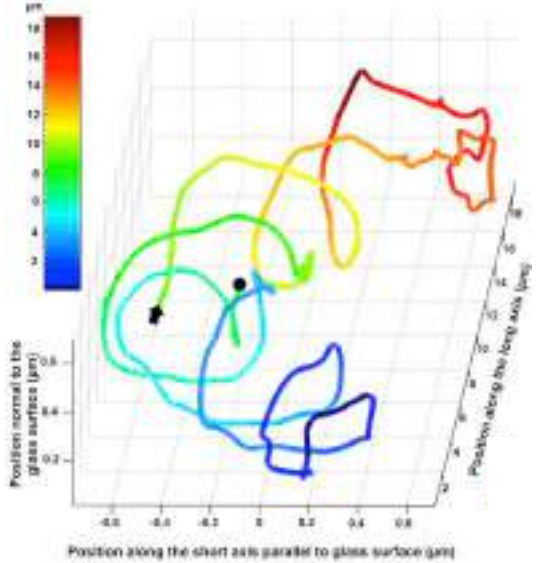
D. Nakane et al, and K. Nakayama. 2013 *PNAS*, 110: 11145–11150

Experimental test:

Cells roll on substrate

Gold nanoparticles coated with SprB antibody rotate right-handedly on cell surface

So if cell adhered to substrate instead of nanoparticle, it would rotate in opposite direction as particle



Shrivastava et al. and H. Berg, 2016 *Biophysical Journal* 111, 1008–1013

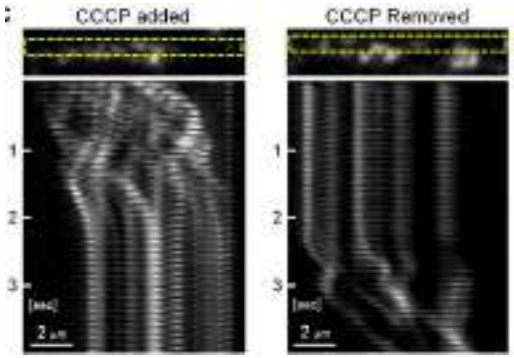
Convergent evolution

Case study 2: Rotary gliding on a substrate

— *Flavobacterium johnsoniae* (*Fj,* Bacteroidetes)

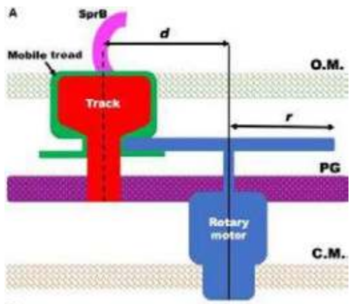
Energy source: Surface helicoidal movement of SprB requires proton gradient

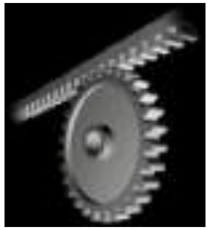
D. Nakane et al, and K. Nakayama. 2013 *PNAS*, 110: 11145–11150



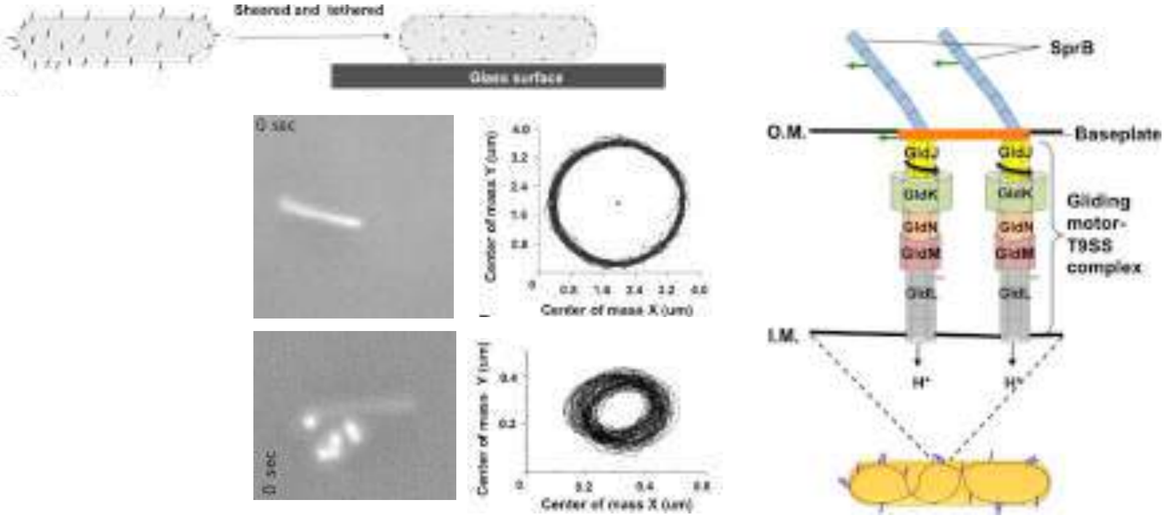
Model: Rack and pinion

Motor and track are fixed. The motor works as a pinion engaged in mobile tread on fixed track

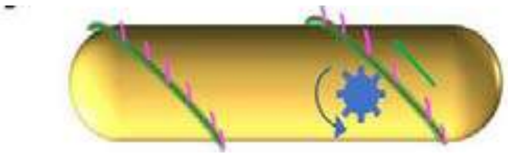




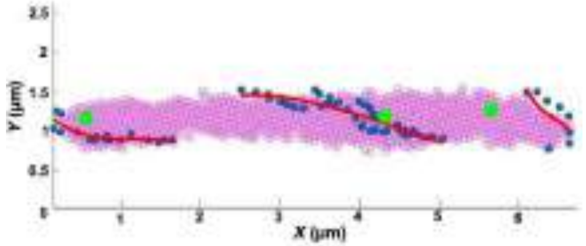
Motor: A cell attached to a single motor GldL rotates and exerts torque



Shrivastava et al. and H. Berg, 2015, *Current Biology* 25, 338–341



GldL localizes within 90nm of SprB helicoidal tracks



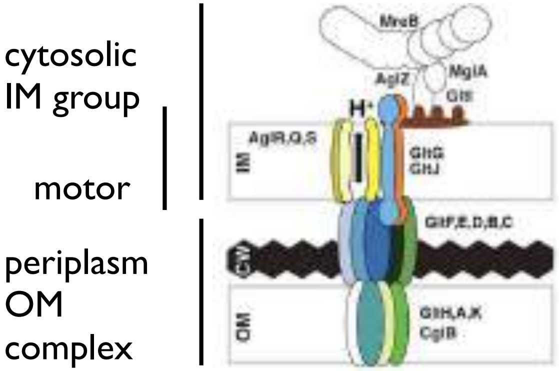
Shrivastava et al. and H. Berg, 2019 *Science Advanced* 111, 1008–1013

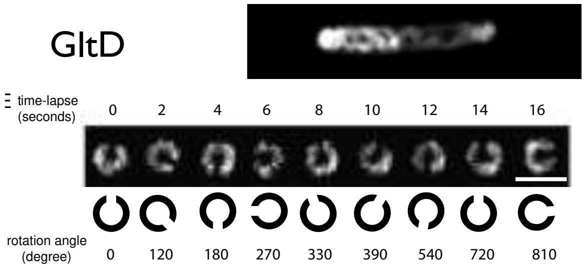
Convergent evolution

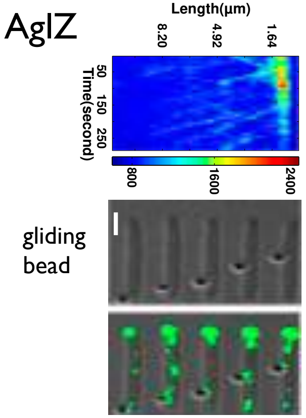
Case study 2: Rotary gliding on a substrate

— *Myxococcus xanthus* (*Mx*, Deltaproteobacteria)

- Existence of Motility complex
- Components of Motility Complex move along right-handed helical tracks on cell
- Movement of the complex requires a proton gradient



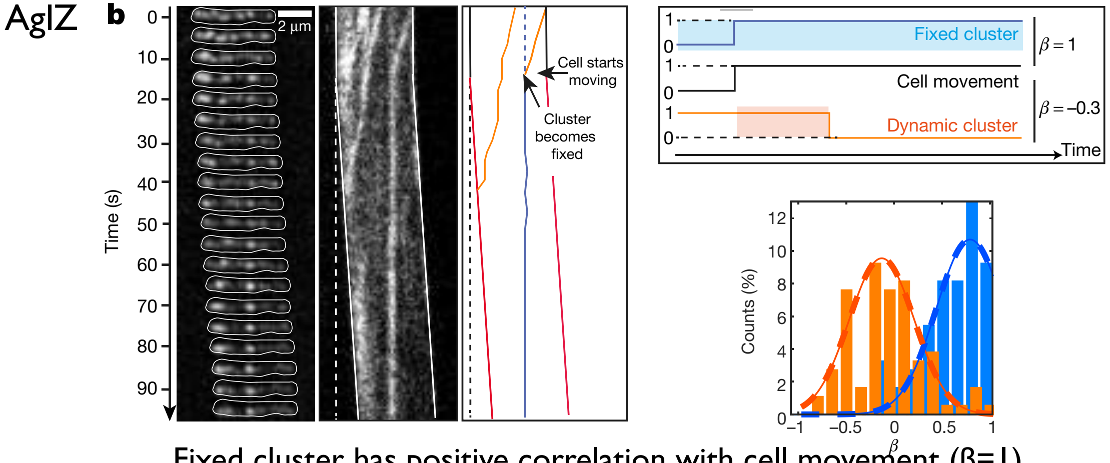




B. Nan et al. and G. Oster and D. Zusman. 2011. *PNAS* 108:2498-2503

M. Sun et al and T. Mignot 2011. *PNAS* 108: 7559-7564

- Motile complex is immobile in substrate referential when the cell is moving
- Formation or Focal adhesion sites are required for cell movement



Fixed cluster has positive correlation with cell movement (ß=1)
Dynamic cluster is weakly negatively correlated

L. Faure et al, and T. Mignot *Nature* 2016, 539:530-535

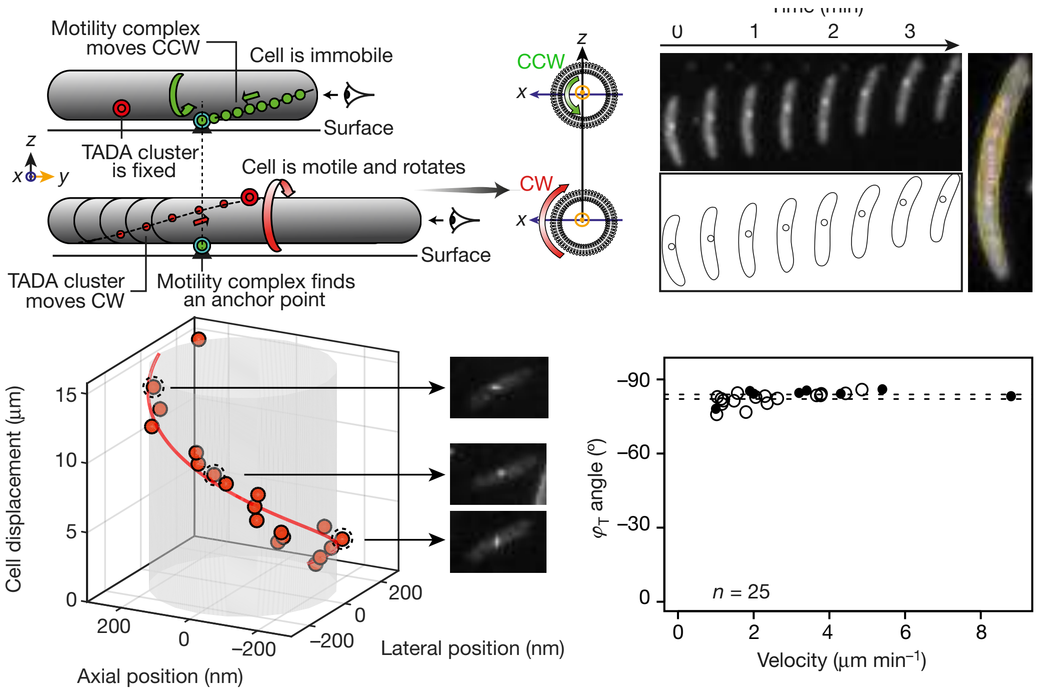
Convergent evolution

Case study 2: Rotary gliding on a substrate

— *Myxococcus xanthus* (*Mx*, Deltaproteobacteria)

- Cells rotate and cell rotation is coupled to cell motility

Propulsion is linked to the counterclockwise movement of the motility complex (AglZ–YFP), because a fiducial marker at the cell surface rotates along a helical path of opposite handedness to cells



L. Faure et al, and T. Mignot *Nature* 2016, 539:530-535

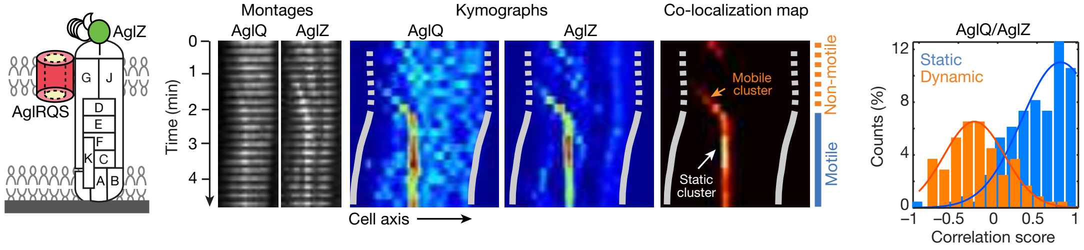
Convergent evolution

Case study 2: Rotary gliding on a substrate

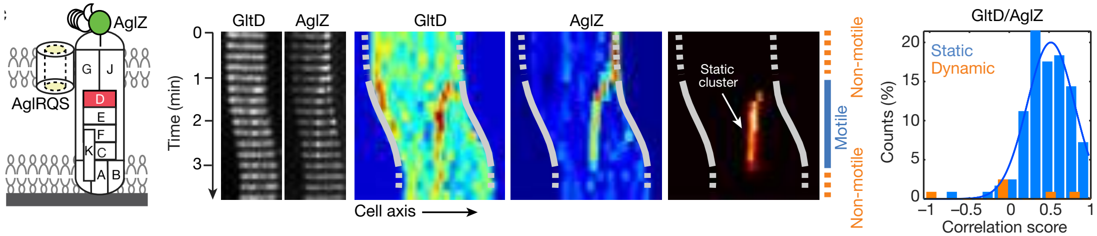
— *Myxococcus xanthus* (*Mx*, Deltaproteobacteria)

- Inner membrane components of motility complex and Motor co-localize in dynamic and static clusters

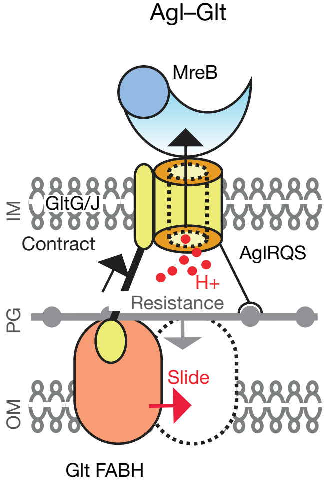
  Only static such clusters correlate with cell movement

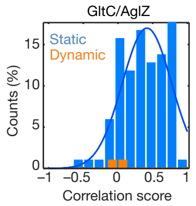


- Periplasmic and Outer membrane components co-localize with Motor in static clusters only, and this correlates with cell movement



- **Model**: Contact and Mechanical coupling between inner and outer-membrane components is required for cell propulsion





L. Faure et al, and T. Mignot *Nature* 2016, 539:530-535

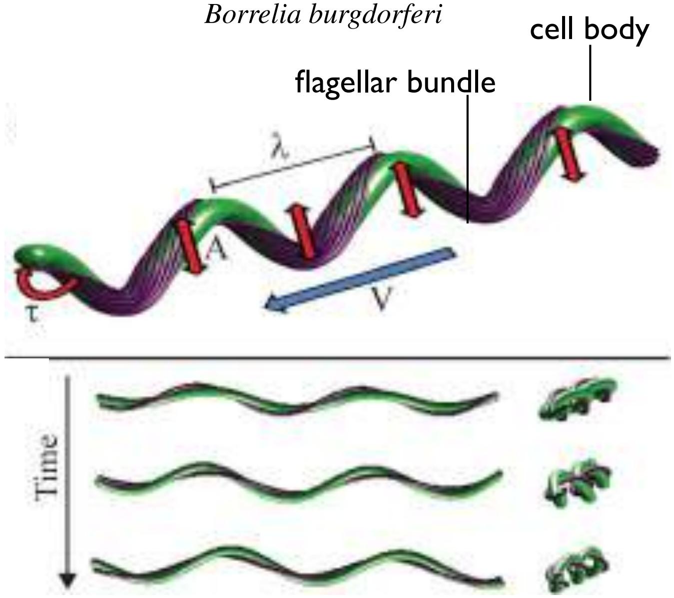
Convergent evolution

Case study 2: More on « screwing motility »

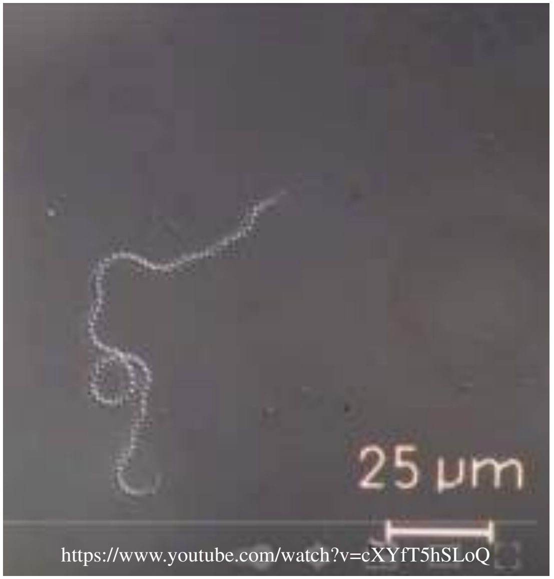
Trypanosoma vs Spirochetes: corkscrew spiraling motility

Bacteria: *Spirochetes* motility: Syphilis, Lyme disease, etc
Motility on viscous substrates in vivo and in vitro

Borrelia burgdorferi



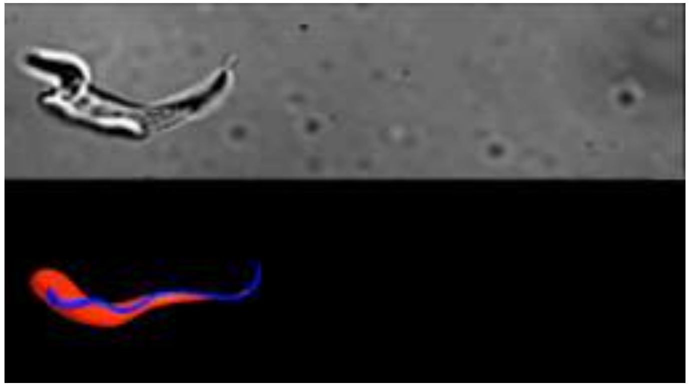
Spirocheta plicatilis



https://www.youtube.com/watch?v=cXYfT5hSLoQ

Trypanosoma brucei

Gull Lab courtesy of Sue Vaughan, Wellcome Images



https://www.youtube.com/watch?v=my58lrHqGWY

Intracellular bundle of flagella form a helical bundle that applies torque to cell body

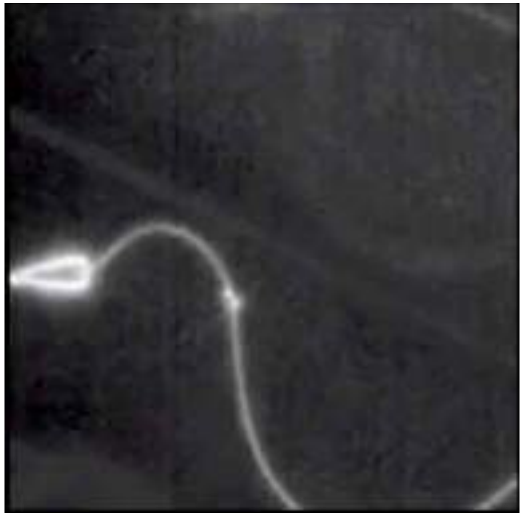
Cell body stiffness exerts opposite torque

This gives rise to planar wave of cell body that rotates

M. Harman et al. C. Wolgemuth. (2013) *Biophysical Journal* 105(10) 2273–2280

Eukaryotic cilia and flagella bending and beating

- Flagella — Sperm cell (sea Urchin)



https://www.youtube.com/watch?v=4vsYNPwSZks

Brokaw CJ. 1989. *Science* 243:1593–1596. doi: 10.1126/science.2928796

Brokaw CJ. *J Cell Biol*. 114 (6): 1201–1215. (1991)

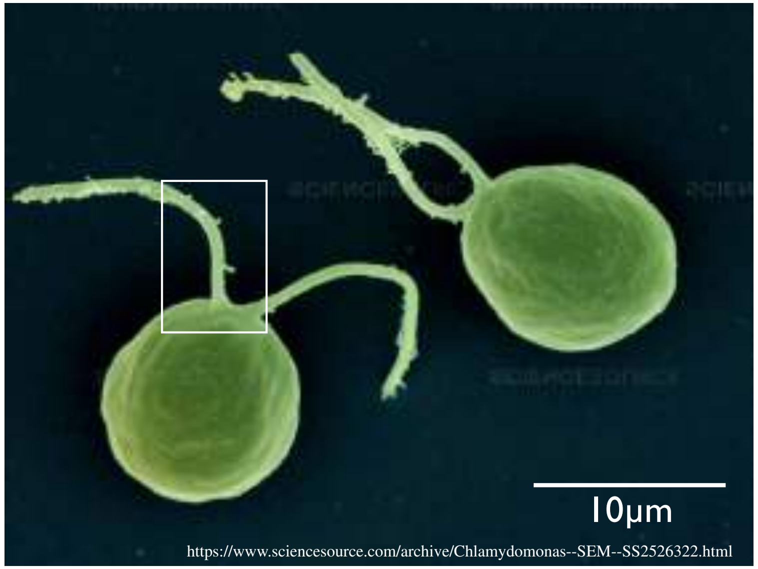
- Cilia - swimming protists

Pharyngomonas kirbyi

Protist, 162, 691–709 (2011)

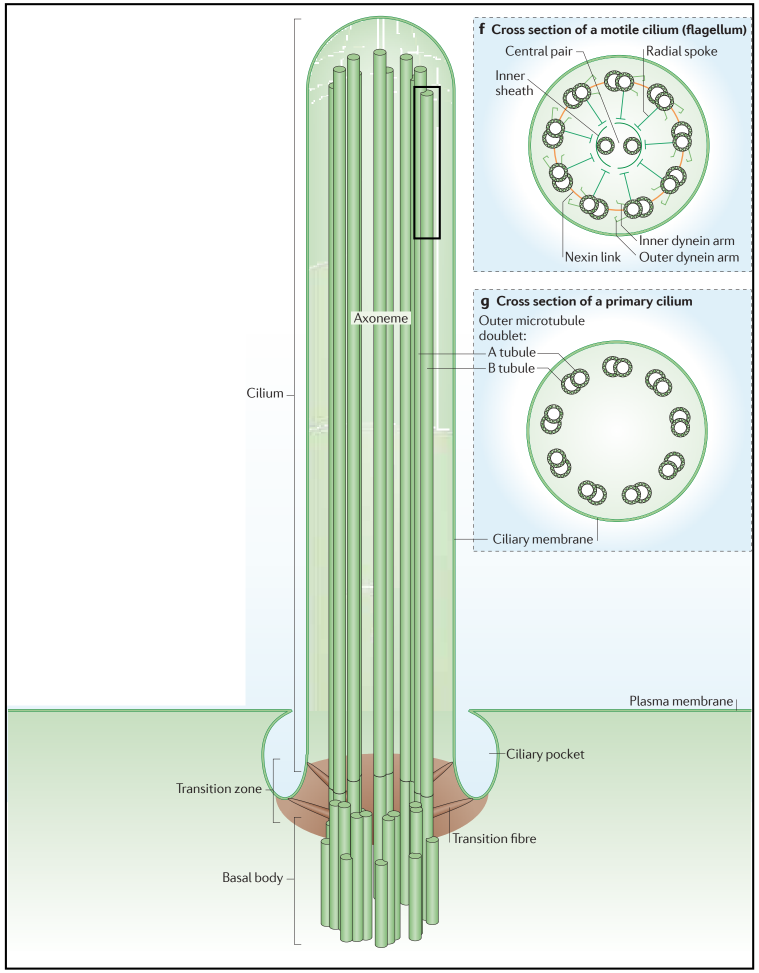
Eukaryotic cilia and flagella bending and beating

— Ultrastructure



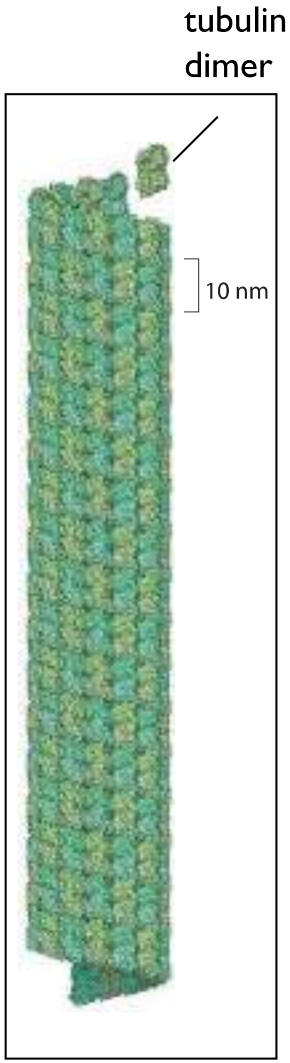
https://www.sciencesource.com/archive/Chlamydomonas--SEM--SS2526322.html

Chlamydomonas reinhardtii
Green algae



cilium

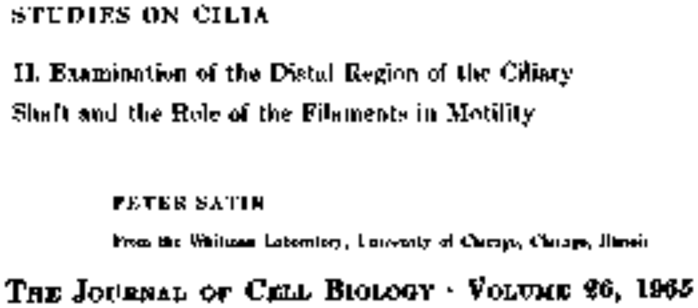
H Ishikawa and WF Marshall *Nature Reviews Mol Cell Biol* 12: 222-234 (2011)



microtubule

Eukaryotic cilia and flagella bending and beating

— Bending models



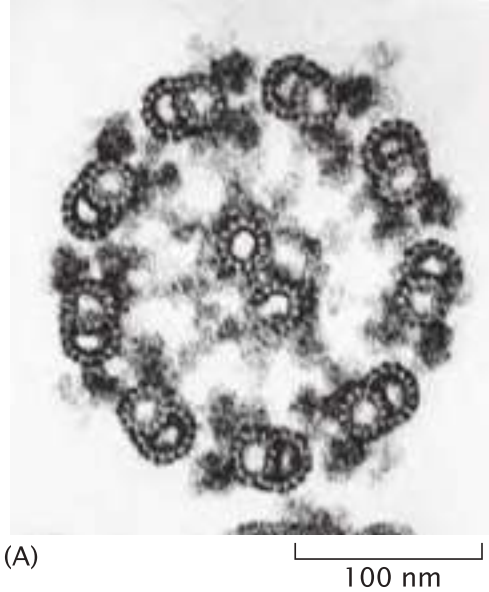
STUDIES ON CILIA

II. Examination of the Distal Region of the Ciliary Shaft and the Role of the Filaments in Motility

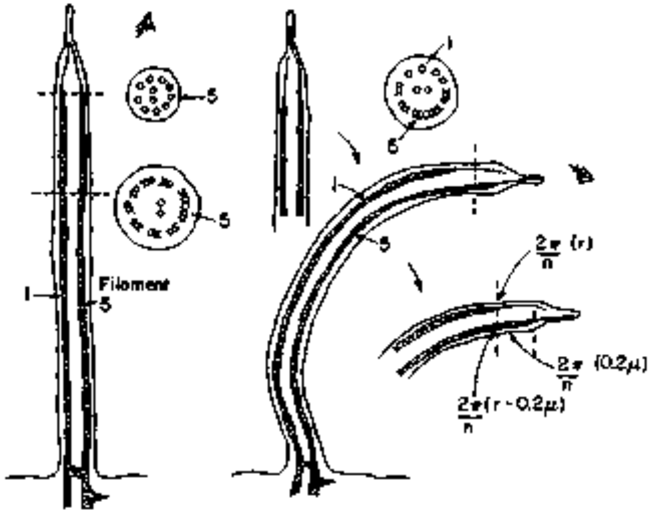
PETER SATIR

From the Whitman Laboratory, University of Chicago, Chicago, Illinois

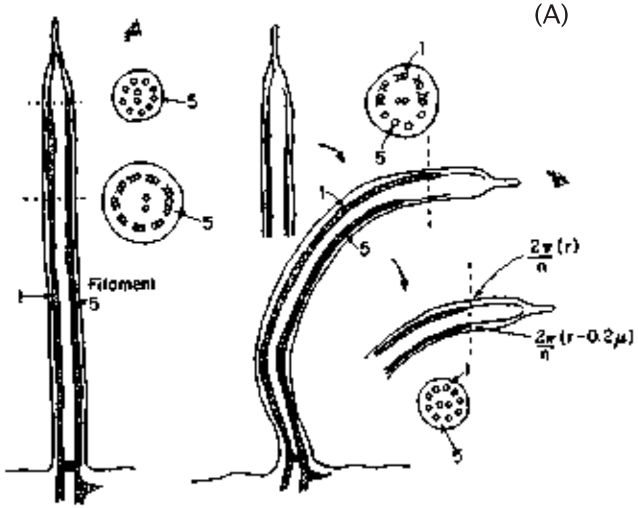
THE JOURNAL OF CELL BIOLOGY · VOLUME 26, 1965



Axoneme



- Sliding model



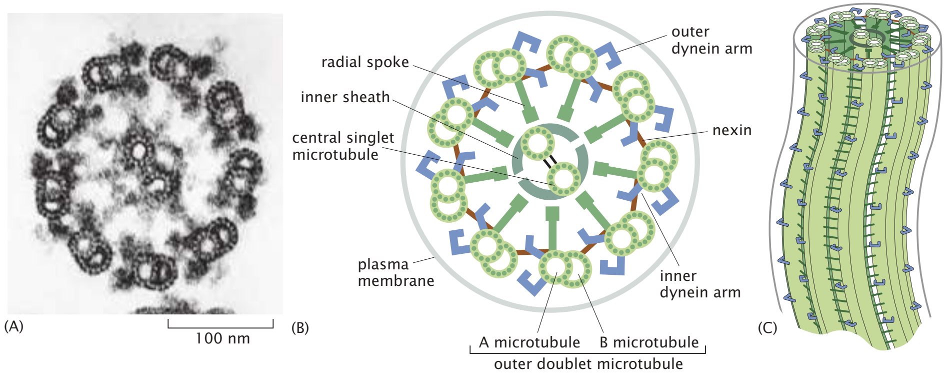
- Contraction model
  Filaments shorten on one side to bend cilium

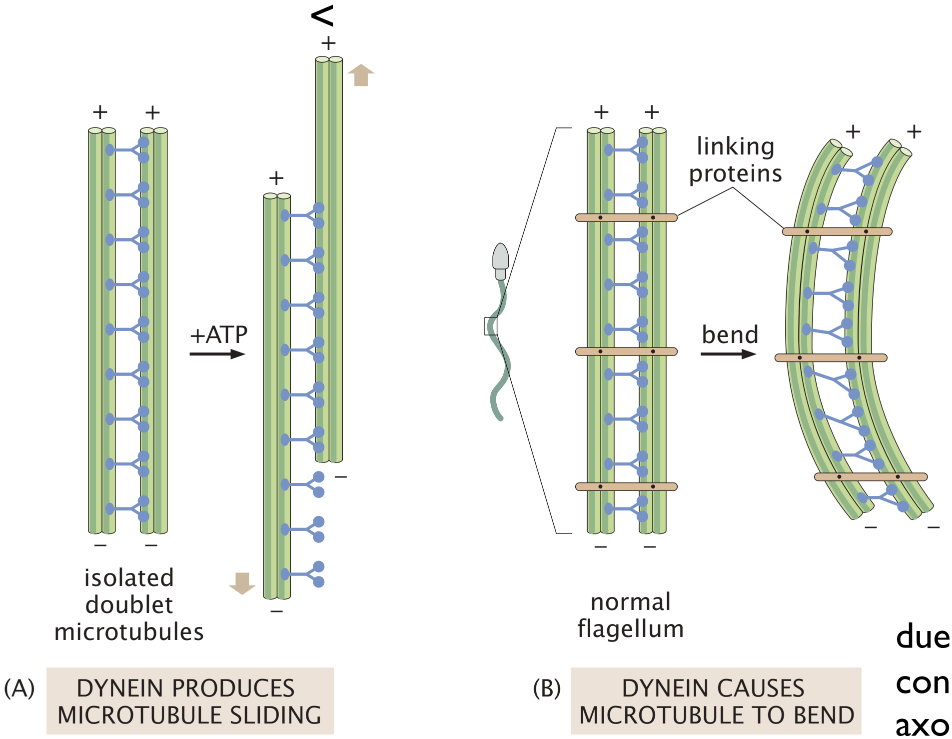
Eukaryotic cilia and flagella bending and beating

— Motor driven sliding forces

- Cilia bend in response to Dynein motor activity
- Dynein induce sliding forces at doublets interfaces

Dynein motors convert the chemical energy of ~10^5 ATP per beat into a relative sliding motion among the nine microtubule doublets of the axonemal sheath. This causes a tension of ~10 nN to build up between neighbouring doublets.





due to crosslinks and constraints at the base of axoneme

R. Phillips, J. Kondev, J. Thériot & H. Garcia.
Physical Biology of the Cell (Garland Science) 2012

Eukaryotic cilia and flagella beating

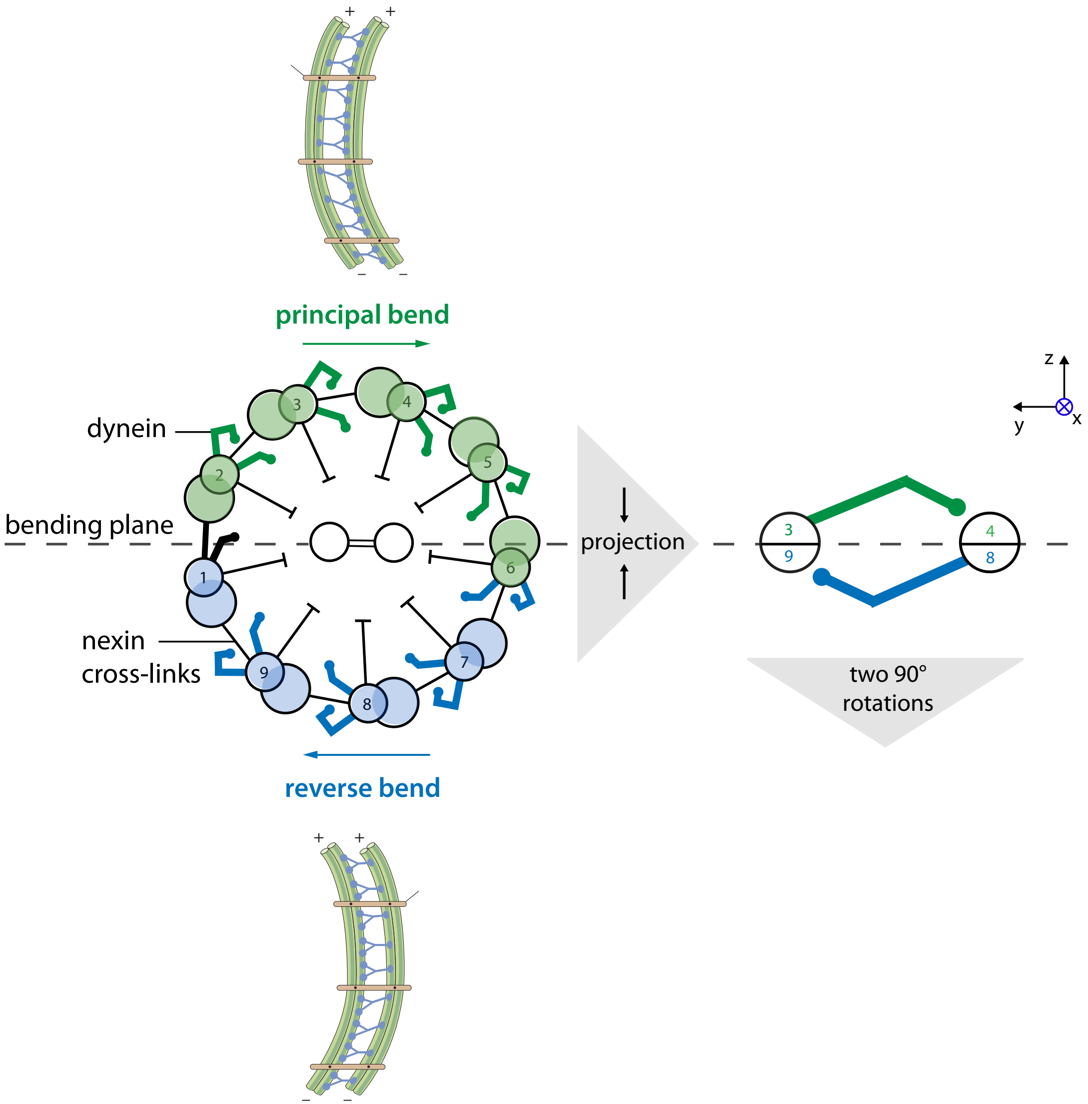
— Beating models: Mechanical Feedbacks

- Bending and beating require spatial and temporal coordination of motor activity on both sides of axoneme
- Bending induces stresses that feedback on and regulate motor activity

- Dynein motor activity needs to alternate between the 2 sides of axoneme. If forces are equal, then they cancel each other and no bending occurs

- Motor switching is rapid (2x per cycle @ 100Hz in *Chlamydomonas*) :

- **Mechanical feedback model**

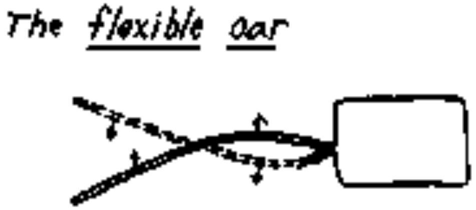


P. Sartori et al. F. Jülicher and J. Howard. *eLife* 2016;5:e13258. DOI: 10.7554/eLife.13258

Physical constraints on cell motility

Convergent evolution

- Consequences of Low Reynolds number (no inertia) for motion in a fluid or visco-elastic medium



Motility: 3 general problems

1. Decoding the environment: What is the nature of cues?
    - Cells don’t move randomly but sense an external cue
    - What is the nature of external cues? Diversity of cues (chemical, mechanical, electric, light)
    - Temporal vs spatial decoding

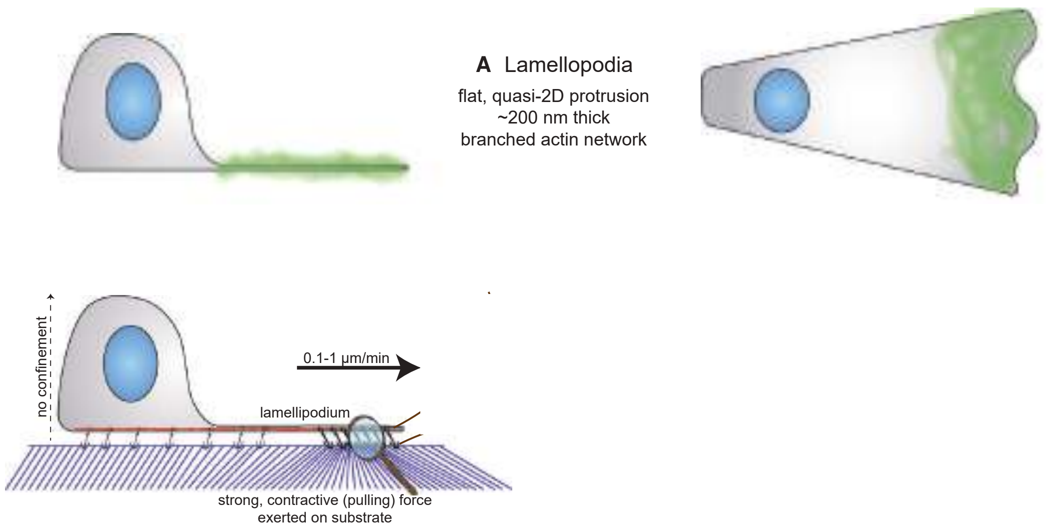
2. Processing the cue: Cell polarisation
    - Symmetry breaking: converting external gradient into vectorial cell organisation
    - Deterministic vs Stochastic processing
    - Polarisation of a cell or a trajectory

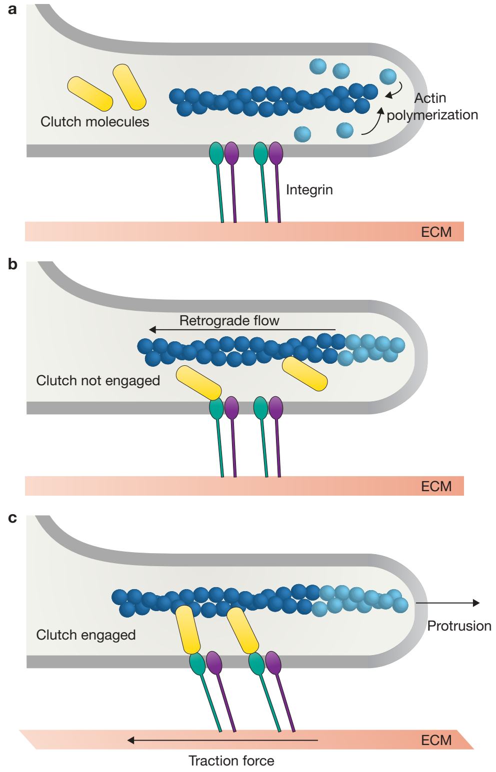
3. Mechanical response: Principles of movement
    - Depends on environment
    - **Force generation:** Active processes: actin pushing forces, actin flow, actomyosin contractility
    - **Force transmission:** Passive resistance: friction/adhesion, viscous resistance of medium.

Mechanics of cell motility

- Adhesion dependent motility: on 2D substrates

–Force generation: actin polymerization (front), contractility (rear)
–Force transmission: adhesion



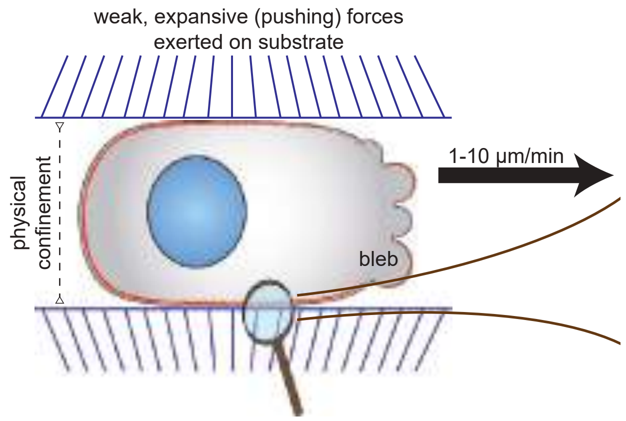


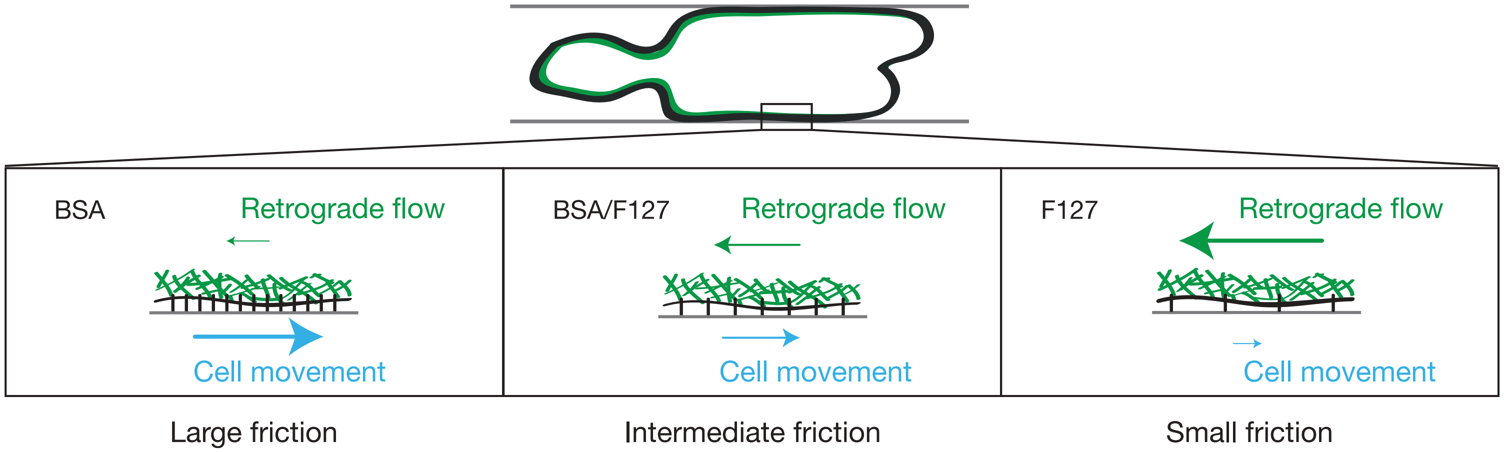
Lindsay B Case and Clare Waterman *Nat Cell Biol*. 2015 Apr;17(4):955-963

Bodor et al. and E. Paluch. *Developmental Cell*. 52: 550-562 (2020)

Mechanics of cell motility

- Adhesion independent motility: induced by 3D confinement
  - –Force generation: actin retrograde flow (induced by contractility)
  - –Force transmission: friction and/or topography of environment



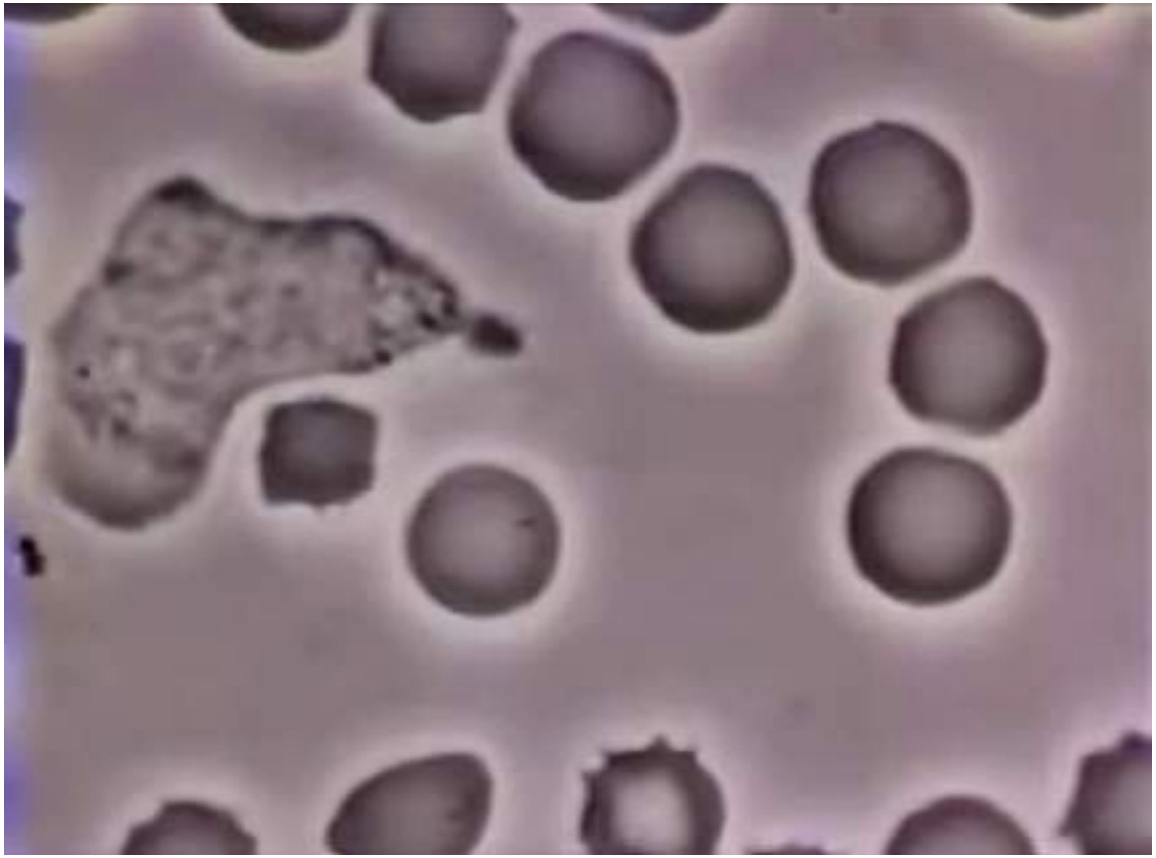


Bergert et al, G. Salbreux and E. Paluch. *Nat Cell Biol*. 17(4):524-9 (2015)

Bodor et al. and E. Paluch. *Developmental Cell*. 52: 550-562 (2020)

Guidance of cell motility

- Neutrophile chasing a bacterium (*Staphilococcus aureus*)



David Rogers at Vanderbilt University. https://www.youtube.com/watch?v=I_xh-bkiv_c

Deterministic vs Stochastic Guidance

Deterministic:

- Spatial mechanism: comparison of chemoattractant concentration along cell length

- Temporal mechanism: comparison of chemoattractant at different positions

Stochastic:

- Statistical mechanism: biased random walk.

– probability of changing direction is a function of chemoattractant concentration: Asymmetric runs up and down a gradient of chemoattractant (temporal comparison)

Stochastic Guidance

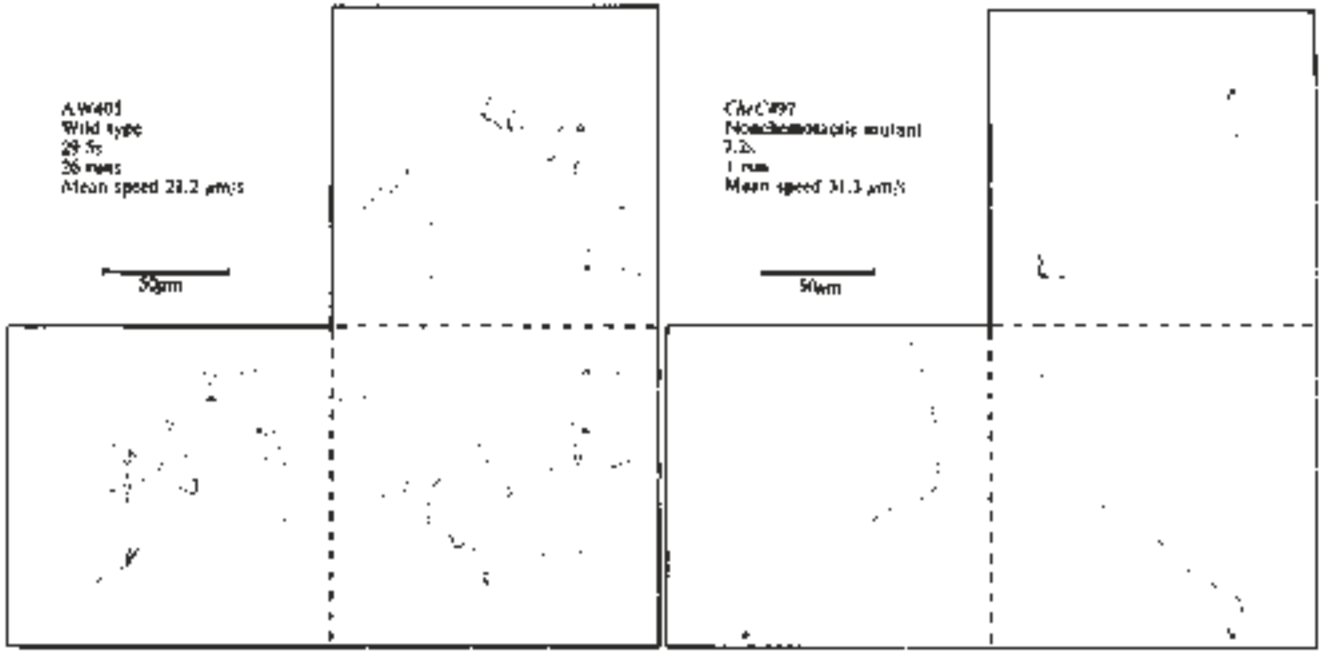
–runs and tumbles: biased random walk in *Bacteria*

Chemotaxis in *Escherichia coli* analysed by Three-dimensional Tracking

HOWARD C. BERG & DOUGLAS A. BROWN

Department of Molecular, Cellular and Developmental Biology, University of Colorado, Boulder, Colorado 80302

Chemotaxis toward amino-acids results from the suppression of directional changes which occur spontaneously in isotropic solutions.



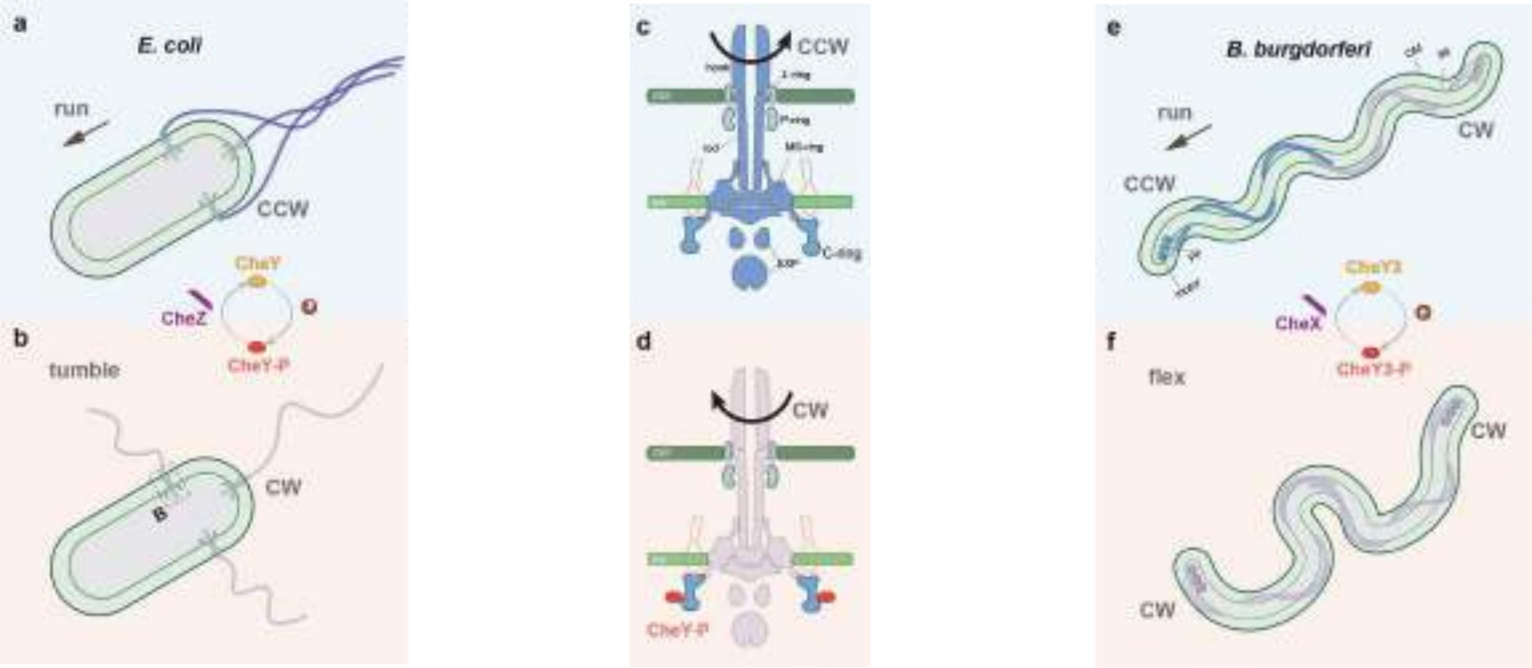
Howard Berg and Douglas Brown. 1972, *Nature* 239, 500-504

Stochastic Guidance

–runs and tumbles and polarity switches

- orientation of motor rotation

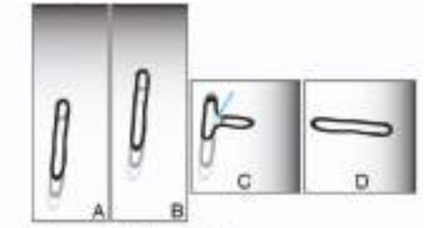
- run
- tumble



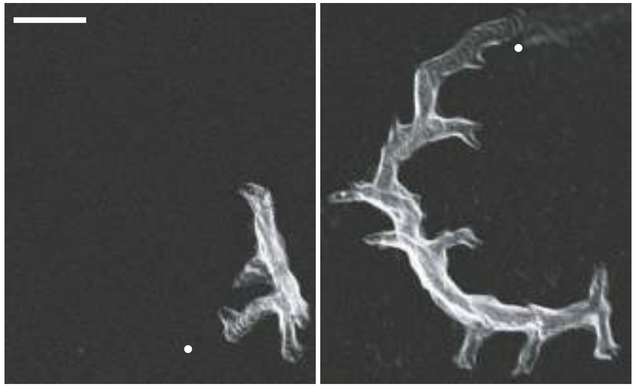
Y. Chang et al … and J Liu. *Nature Structural & Molecular Biology* 27, 1041–1047 (2020)

Deterministic vs Stochastic Guidance

–Informed choice model



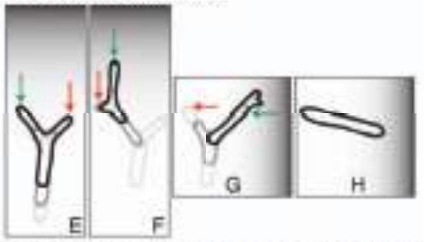
compass choice model



Dictyostelium discoideum

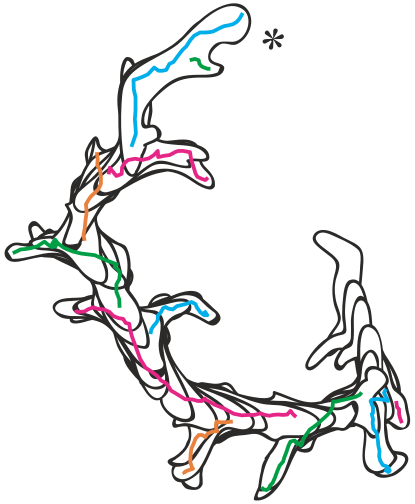
- Cells make many pseudopods are regular intervals and select the better ones up the gradient

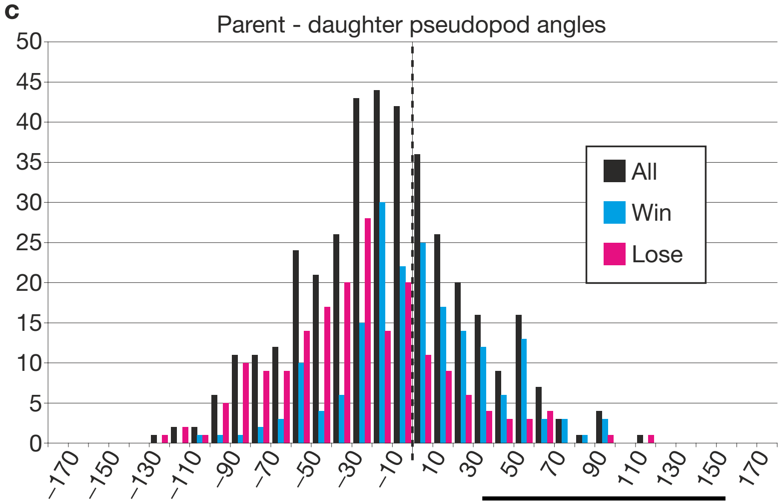
- The pseudopod that are better aligned with gradient have an increased survival (bias for survival)



Informed choice model

Reinforcement of most up gradient protrusion





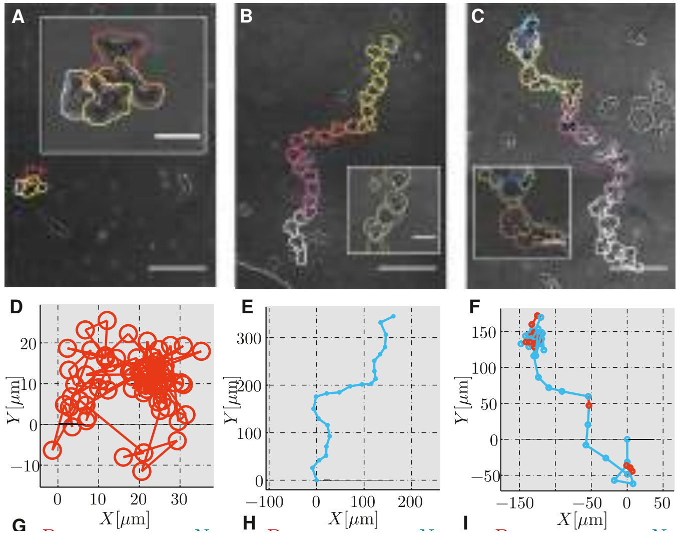
improves alignement with gradient

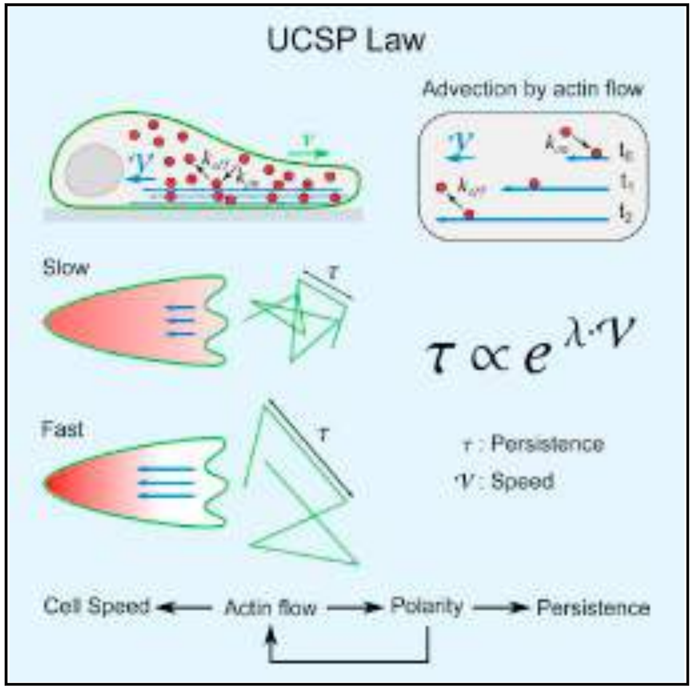
N. Andrew and R. Insall. *Nature Cell Biol.*.2: 193-200 (2007)

Stochastic Guidance

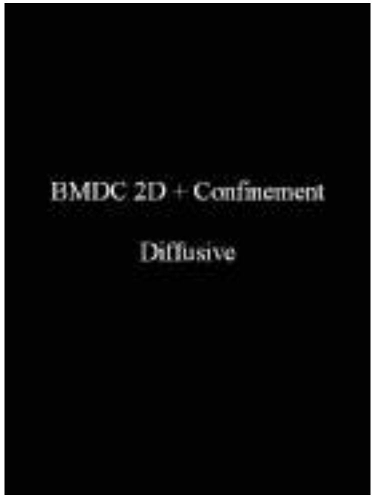
–runs and tumbles: biased random walk in Eukaryotes

- Cells exhibit different persistence during motility
- Faster cells are more persistent
- **Universal coupling between speed and persistence**
- This stems from feedback between polarity and retrograde actin flow





$$\tau \propto e^{\lambda \cdot V}$$



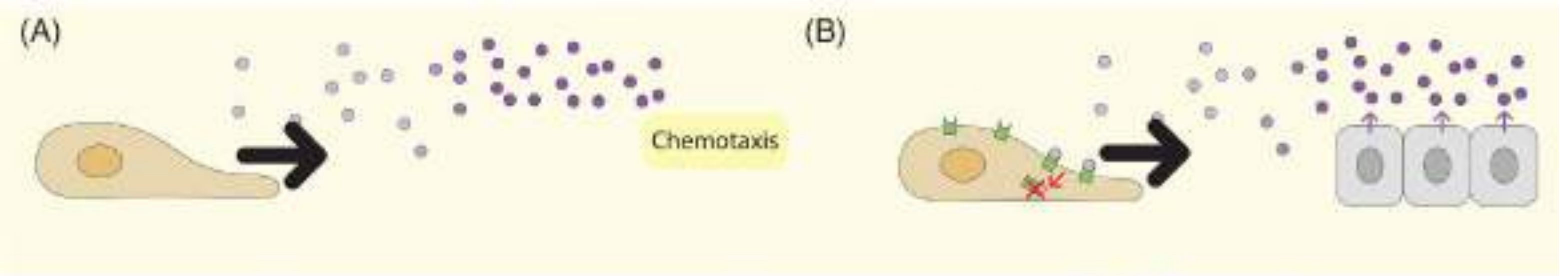
BMDC 2D + Confinement

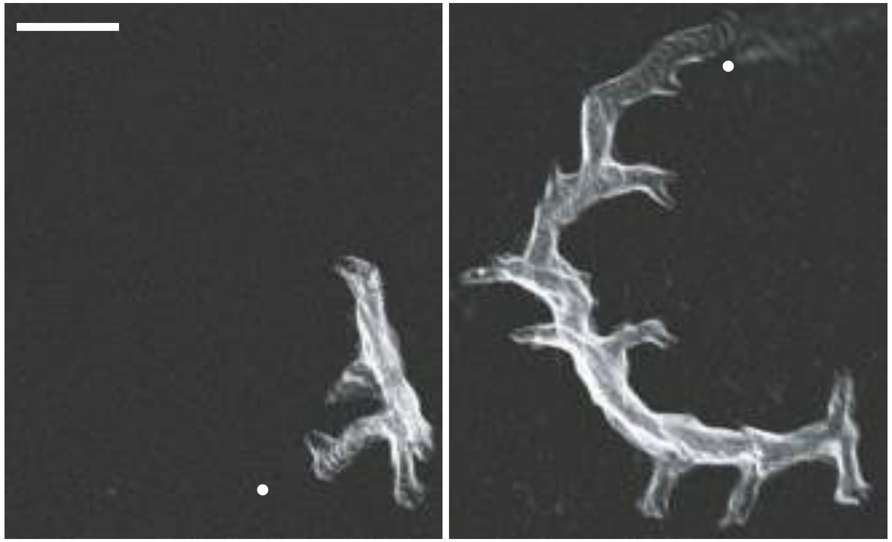
Diffusive

P. Maiuri, JF. Rupprecht, ..., M. Sixt, R. Voituriez 2015. *Cell 161*, 374–386

Nature of guidance cues

– Chemotaxis





Dictyostelium discoideum

Migration mode	Cue	Signal generation
Chemotaxis	Diffusible chemical released from cells or deposited extracellular vesicles	Simple diffusion Regulated removal by degradation of the chemoattractant or decoy receptors Release of extracellular vesicles

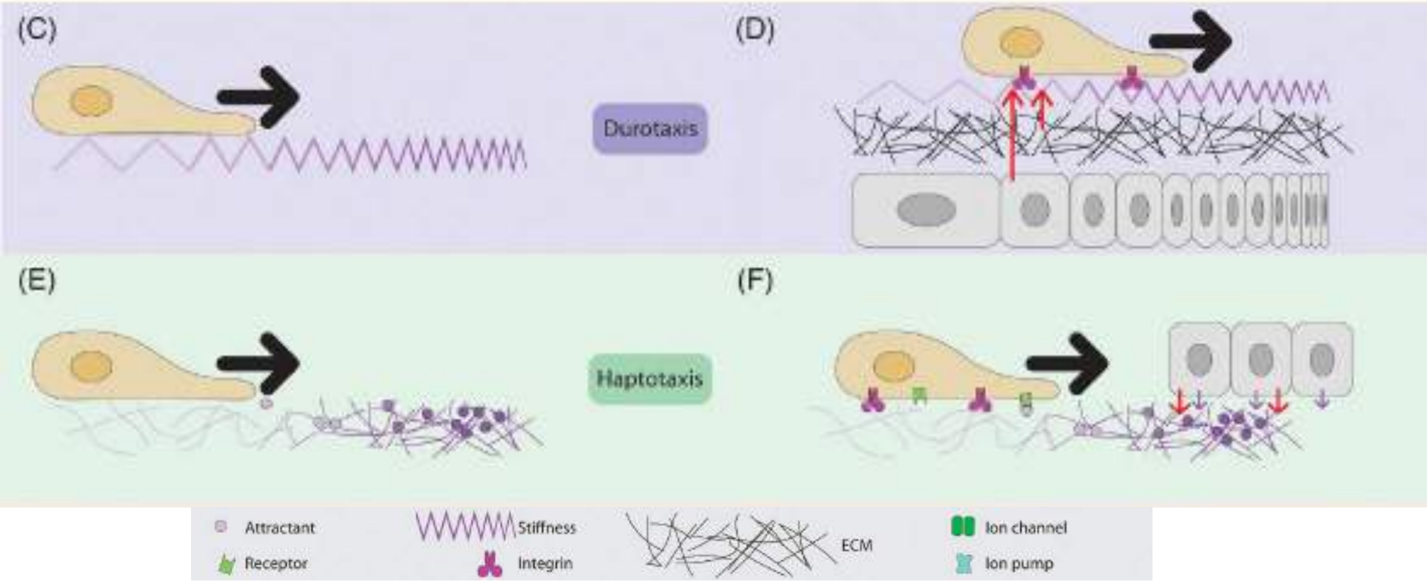
S. SenGupta, C. A. Parent and J. E. Bear, *Nature Rev Mol. Cell Biol.* 2021
https://doi.org/10.1038/ s41580-021-00366-6

Nature of guidance cues

– Mechanical guidance:

- Substrate stiffness gradient
  — Durotaxis

- Adhesion gradient
  — Haptotaxis



Migration mode	Cue	Signal generation
Haptotaxis	Substrate-bound chemical cues such as an immobilized chemokine or ECM	ECM secretion and deposition Binding of soluble factors to a substrate (mostly ECM) Exposing new sites on the substrate through enzymatic action
Durotaxis	Differential substrate compliance	Passive: creating a stiff substrate by crosslinking of ECM components or ECM deposition Active: cells or tissues exerting a force on the substrate that is sensed by other cells

S. SenGupta, C. A. Parent and J. E. Bear, *Nature Rev Mol. Cell Biol.* 2021
https://doi.org/10.1038/ s41580-021-00366-6

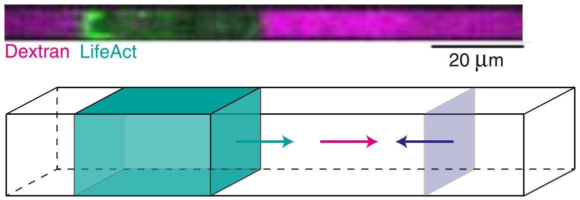
Nature of guidance cues

– Mechanical guidance:

— Barotaxis

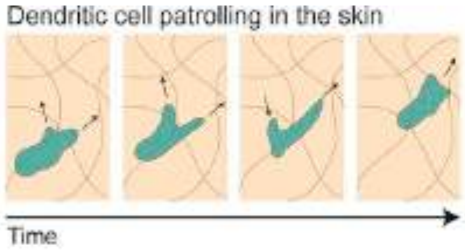
- Cell migration is resisted by the pressure associated with fluid in front of a cell in a confined environment
- Guidance by hydraulic resistance arises from small force imbalance which is amplified by actomyosin contractility

Confined impermeable cell

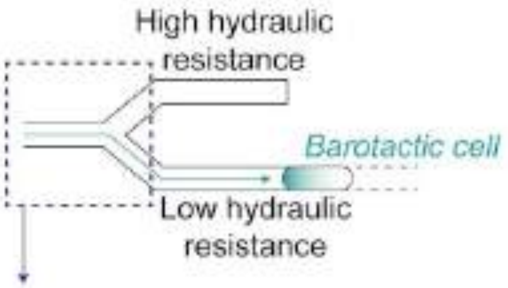


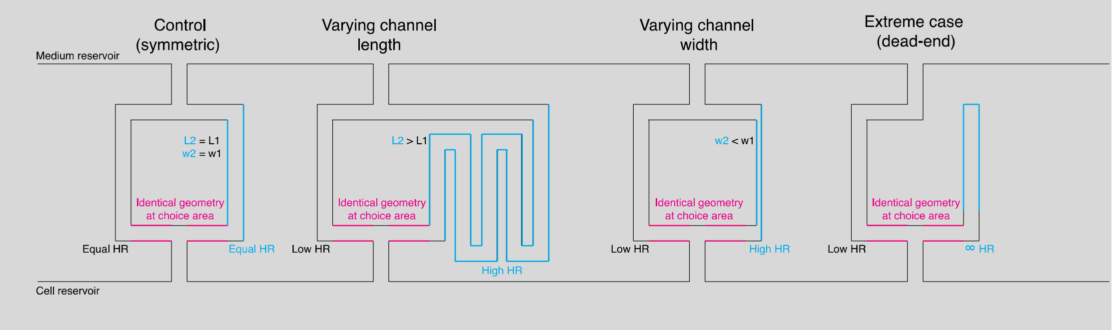
1. Cell migrates
2. Fluid is being pushed
3. HR is generated

Hélène Moreau and Ana-Maria Lennon-Duménil. *Current Opinion in Cell Biology* 2021, 72:131–136



- Cells « read » their environment ahead of time and take the path of least hydraulic resistance: shortest path and avoidance of dead-end



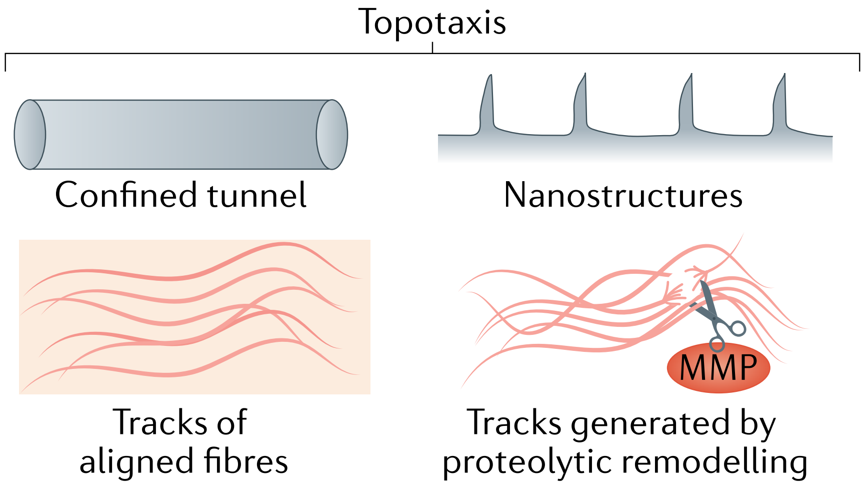


H. Moreau et al. and Raphael Voituriez, Matthieu Piel,
Ana-Maria Lennon-Duménil, 2019, *Developmental Cell* 49, 171–188

Nature of guidance cues

– Mechanical guidance:

— Topotaxis

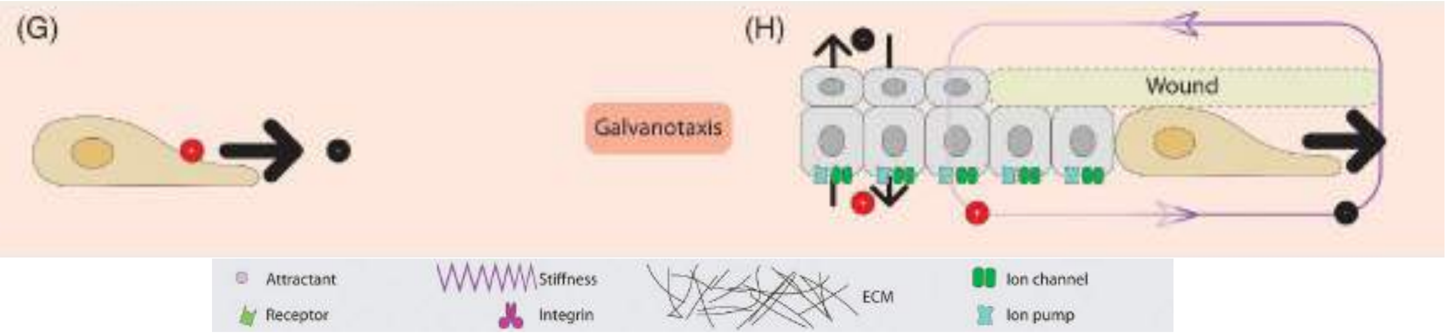


Migration mode	Cue	Signal generation
Topotaxis	Geometric properties of the migration substrate irrespective of mechanical or chemical properties	Preformed tunnels created by other cells Trails created by proteolytic ECM remodelling Topological features created by non-lytic ECM deformation 1D fibrils such as bundles of collagen Topology of natural tissue elements

S. SenGupta, C. A. Parent and J. E. Bear, *Nature Rev Mol. Cell Biol.* 2021
https://doi.org/10.1038/ s41580-021-00366-6

Nature of guidance cues

— Galvanotaxis

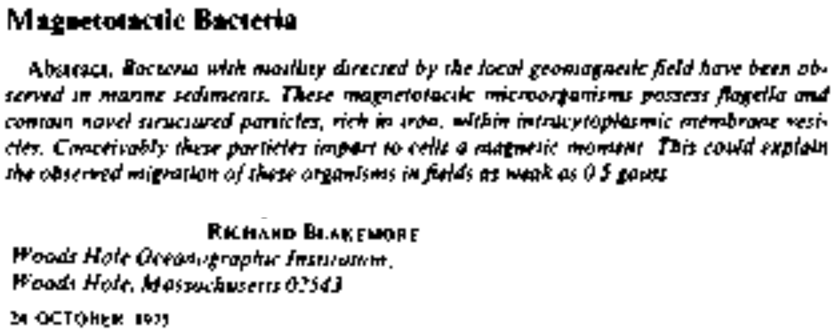


Migration mode	Cue	Signal generation
Galvanotaxis	Electric fields	Ionic differences generated by transepithelial barriers such as in the skin, disrupted by wounding

S. SenGupta, C. A. Parent and J. E. Bear, *Nature Rev Mol. Cell Biol.* 2021
https://doi.org/10.1038/ s41580-021-00366-6

Nature of guidance cues

— Magneto-aerotaxis



Magnetotactic Bacteria

Abstract. *Bacteria with motility directed by the local geomagnetic field have been observed in marine sediments. These magnetotactic microorganisms possess flagella and contain novel structured particles, rich in iron, within intracytoplasmic membrane vesicles. Conceivably these particles impart to cells a magnetic moment. This could explain the observed migration of these organisms in fields as weak as 0.5 gauss.*

RICHARD BLAKEMORE
Woods Hole Oceanographic Institution,
Woods Hole, Massachusetts 02543

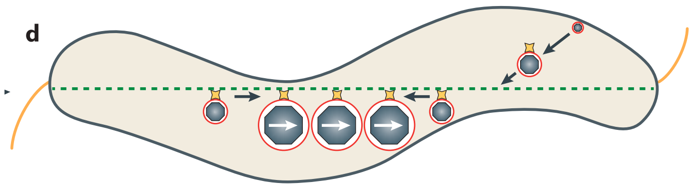
24 OCTOBER 1975

Geomagnetic pole (N)
Reverse magnetic field

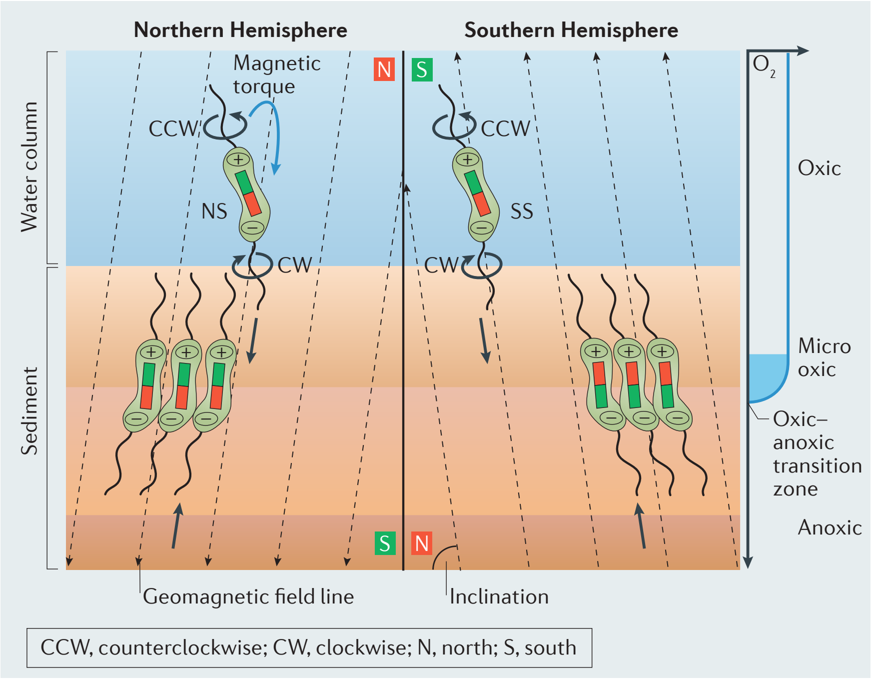
10μm

Magnetosome

R. Blackmore. *Science* 190:377-379 (1975)



Magnetosome: curboctahedral magnetite crystals
Magnetospirillum gryphiswaldense



R. Uebe and D. Schüler. *Nature Rev MicroBiology* 14, 621-637 (2016)

Deterministic vs Self-organised Guidance

How do cells navigate over long range in situ (development, immune system, cancer)?

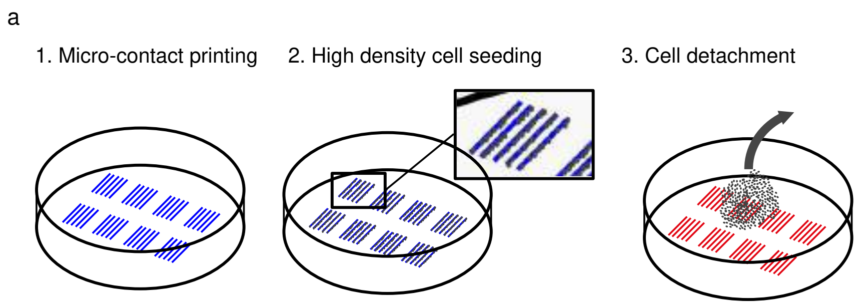
>>Interaction between cells and environment:

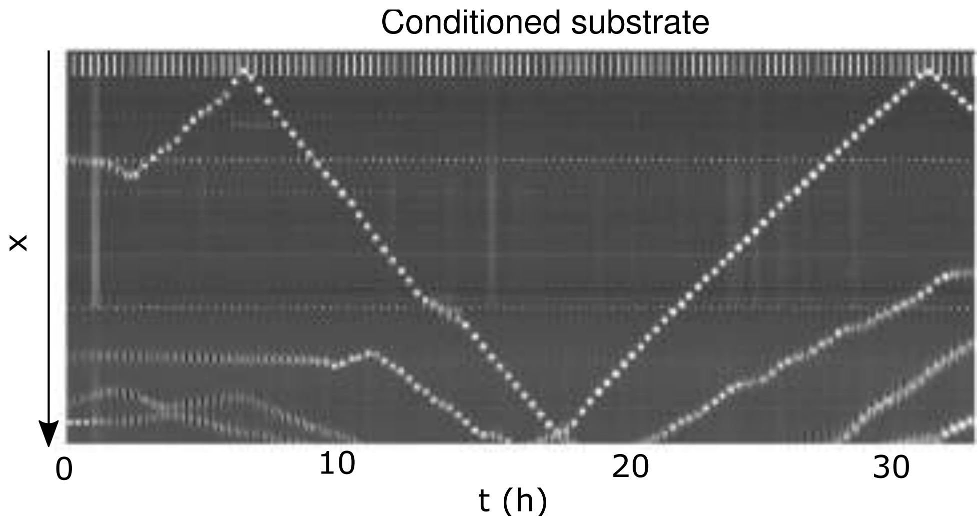
cells generate/modify their own guidance cue through such interactions

The structure of the environment matters (eg. confinement)

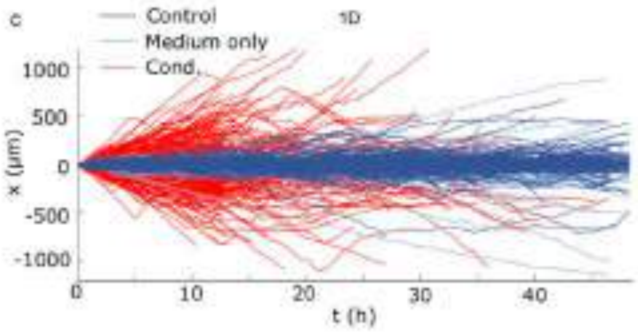
Self-organised guidance

Reinforcement of guidance landscape by cells: spatial memory akin to stigmergia





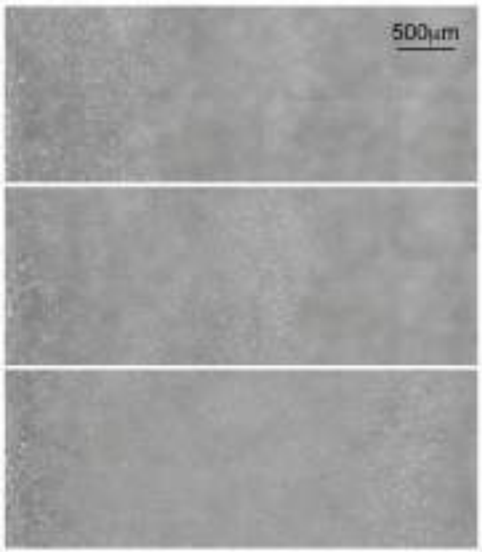
- Conditioned substrate enhances cell motility
- Oscillatory migration in 1D channels

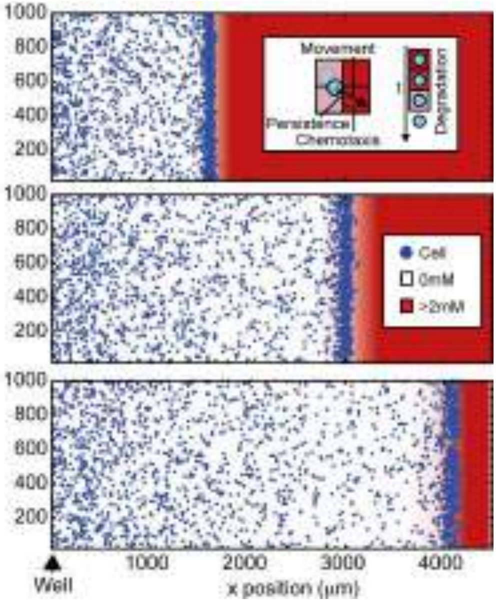


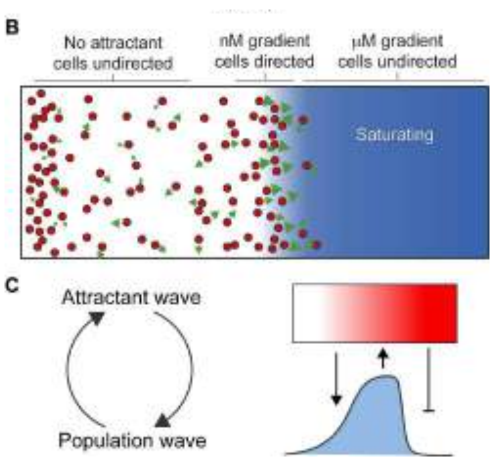
d’Alessandro et al. RM Mège R. Voituriez and B. Ladoux *Nature Communications* 12:4118 (2021)
https://doi.org/10.1038/s41467-021-24249-8

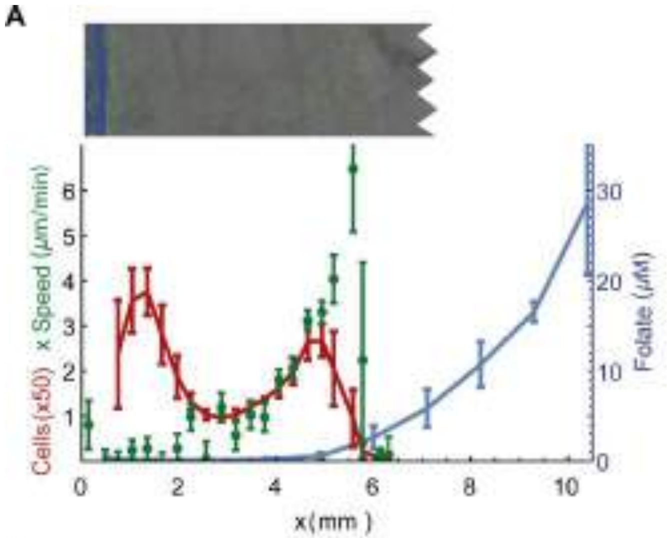
Self-organised chemotaxis

- Cells produce an activity that degrades the chemoattractant
- A **gradient of attractant is formed at the edge of cell cluster**, that steers cells forward leaving behind no attractant where cells have random motility.
- A front wave emerges that self-propagates
- Self-reinforcing process: if a few cells go pass the front, they will adopt random motility because they can't produce a new gradient of chemoattractant. If attractant diffuses behind the front, it will attract more cells



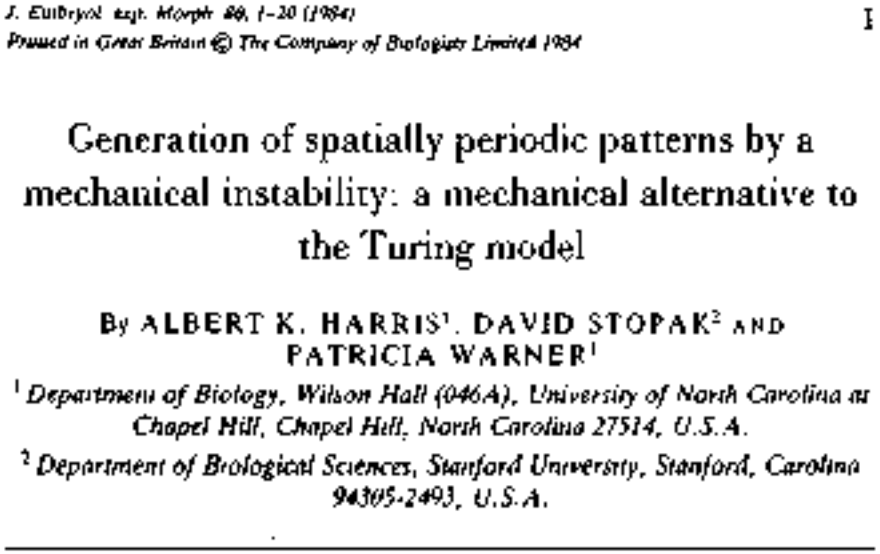






Tweedy L, Knecht DA, Mackay GM, Insall RH (2016) *PLOS Biology* | DOI:10.1371/journal.pbio.1002404

Self-organised mechanical guidance



J. Embryol. exp. Morph. 80, 1–20 (1984)
Printed in Great Britain © The Company of Biologists Limited 1984

1

Generation of spatially periodic patterns by a mechanical instability: a mechanical alternative to the Turing model

By ALBERT K. HARRIS[1], DAVID STOPAK[2] AND
PATRICIA WARNER[1]
[1] *Department of Biology, Wilson Hall (046A), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514, U.S.A.*
[2] *Department of Biological Sciences, Stanford University, Stanford, Carolina 94305-2493, U.S.A.*

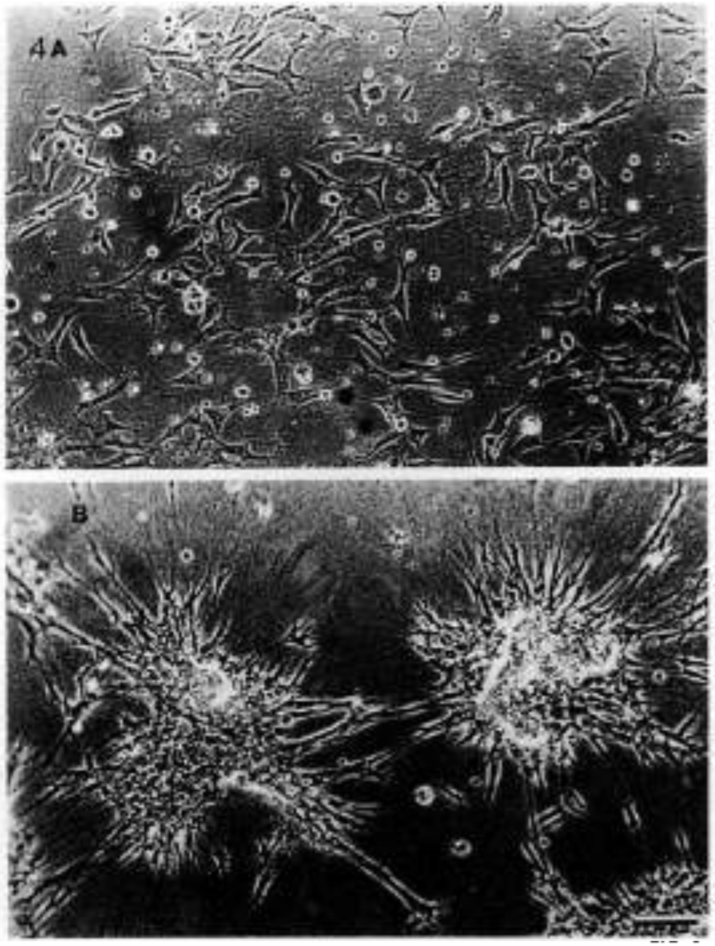
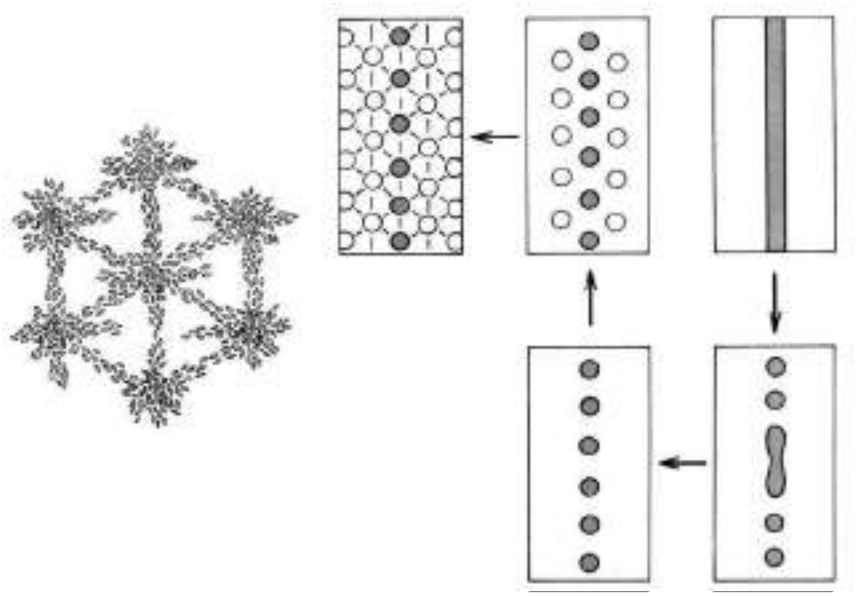


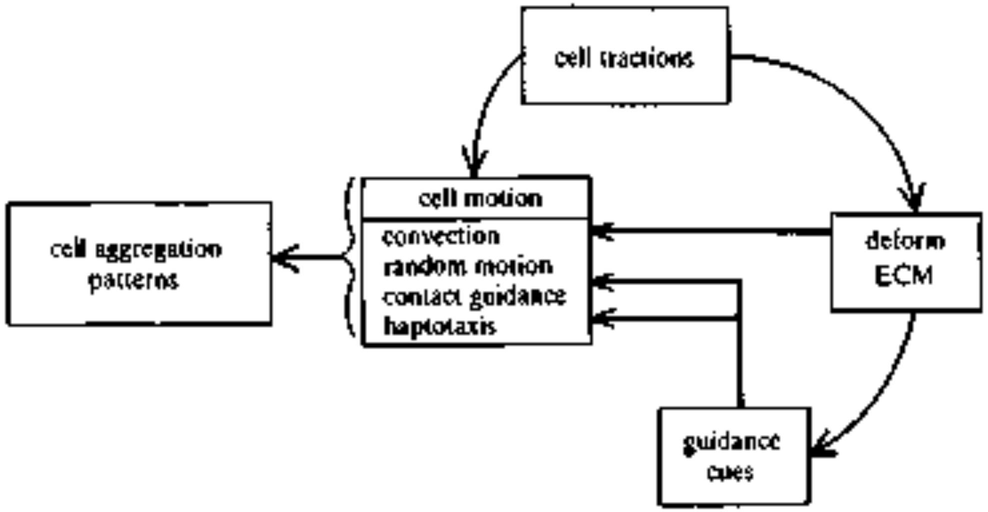
Fig. 4. Time sequence of pattern development. A. 24 h after plating, fibroblasts are still evenly distributed. B. After 6 days, the formation of periodic condensations is complete. The scale bar equals 100 μm.

A.K Harris, D. Stopak and P. Warner. *J. Embryol exp. Morph.* 1984. 80:1-20

Self-organised mechanical guidance

- Feedback mechanism between cells and the matrix: traction forces due to cell motility causes matrix deformation which steers cell motility





cell tractions

cell motion
convection
random motion
contact guidance
haptotaxis

cell aggregation patterns

deform ECM

guidance cues

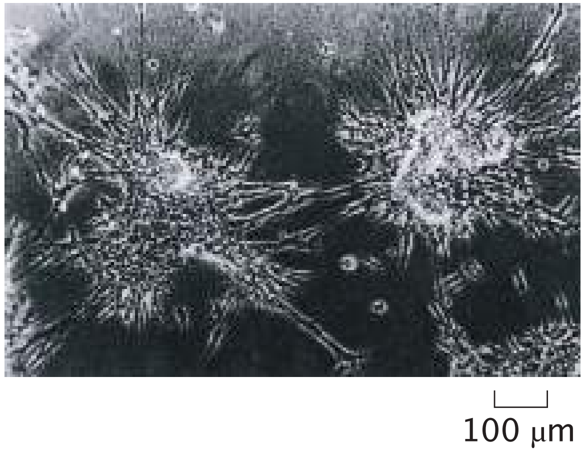
See lecture 27 Nov 2018
Mechanochemical instabilities
https://www.college-de-france.fr/site/thomas-lecuit/course-2018-11-27-10h00.htm

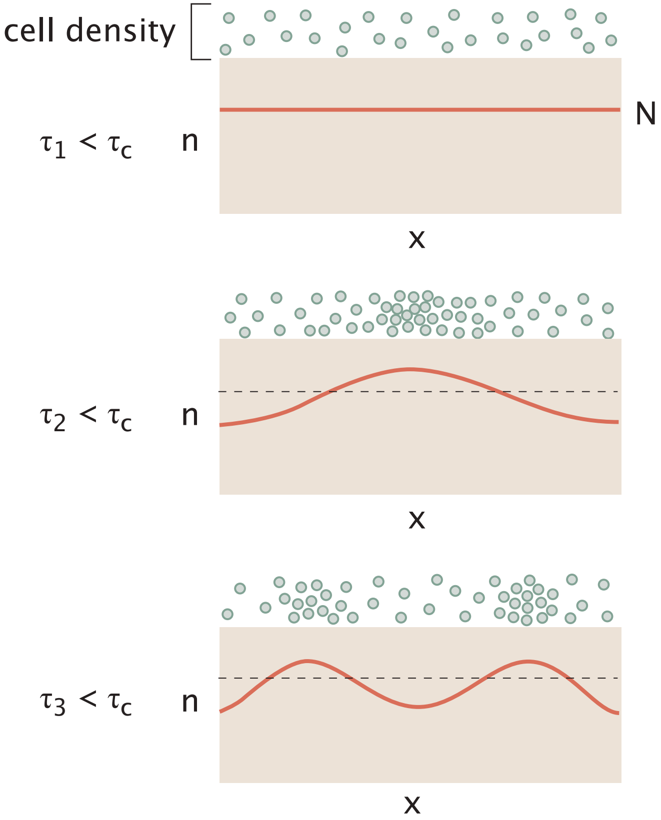
G.F. Oster, J.D. Murray, and A.K. Harris. *J. Embryol. esp. Morph.* 1983. 78:83-125
J.D. Murray, G.F. Oster and A.K. Harris. *J. Math. Biology* 1983. 17:125-129

Self-organised mechanical guidance

time = 0

time = 5 days





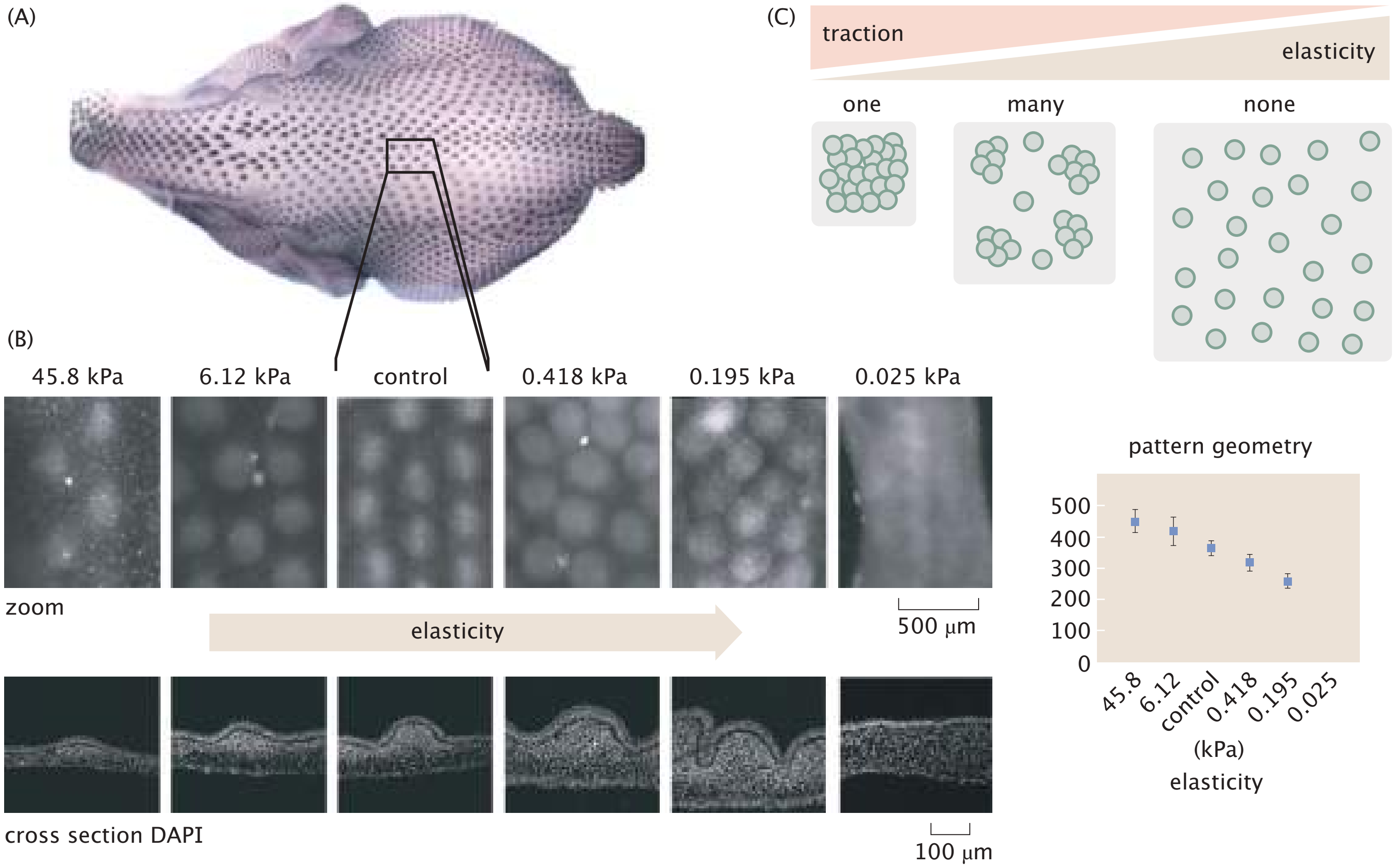
τ = traction force

force balance

$$\nabla \cdot \left[\sigma_{\text{viscous}} + \sigma_{\text{elastic}} + \sigma_{\text{traction}}\right] = 0$$

Self-organised mechanical guidance

- Emergence of cellular patterns during development



Shyer *et al.*, *Science* **357**, 811–815 (2017) 25 August 2017

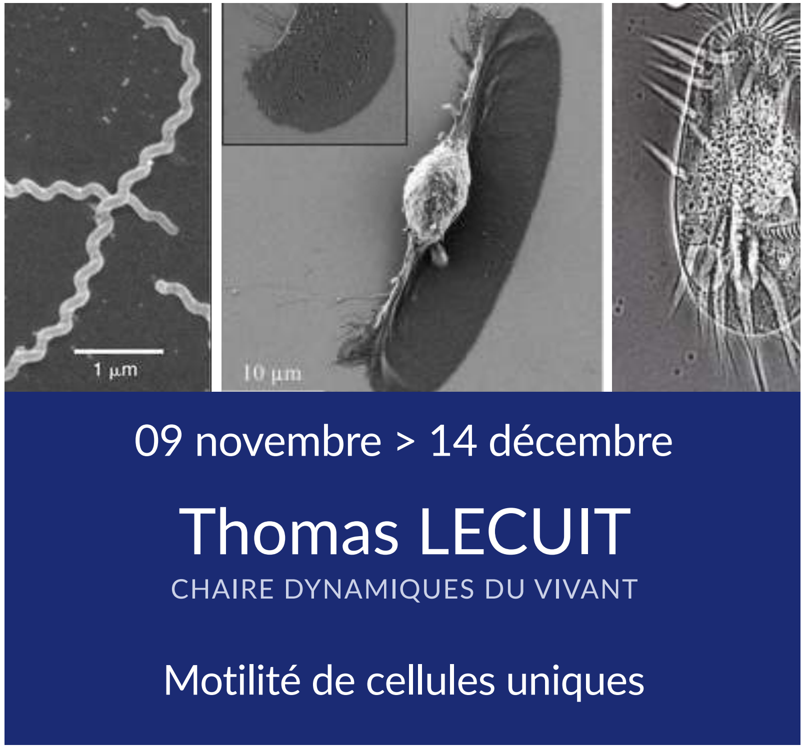
Conclusions

1. Phenomenology across scales: diversity and convergence

2. Mechanics
   - Physical constraints
   - Invariant modalities

3. Guidance
   - Deterministic and
   - self-organised

Plan du cours



09 novembre > 14 décembre

Thomas LECUIT

CHAIRE DYNAMIQUES DU VIVANT

Motilité de cellules uniques

Cours

Les mardis, de 10h à 11h30
Amphithéâtre Guillaume Budé

Conformément aux consignes gouvernementales, l'accès au Collège de France est soumis au contrôle d'un passe sanitaire ainsi qu'au respect des gestes barrières.
Le port du masque est obligatoire dans les amphithéâtres.

09 novembre 2021
Introduction : principes généraux de la motilité cellulaire

16 novembre 2021
Mécanique de la motilité I - (sur substrats)

23 novembre 2021
Mécanique de la motilité II - (confinement)

30 novembre 2021
Mécanique de la motilité III - (nage)

07 décembre 2021
Guidage chimique

14 décembre 2021
Guidage mécanique