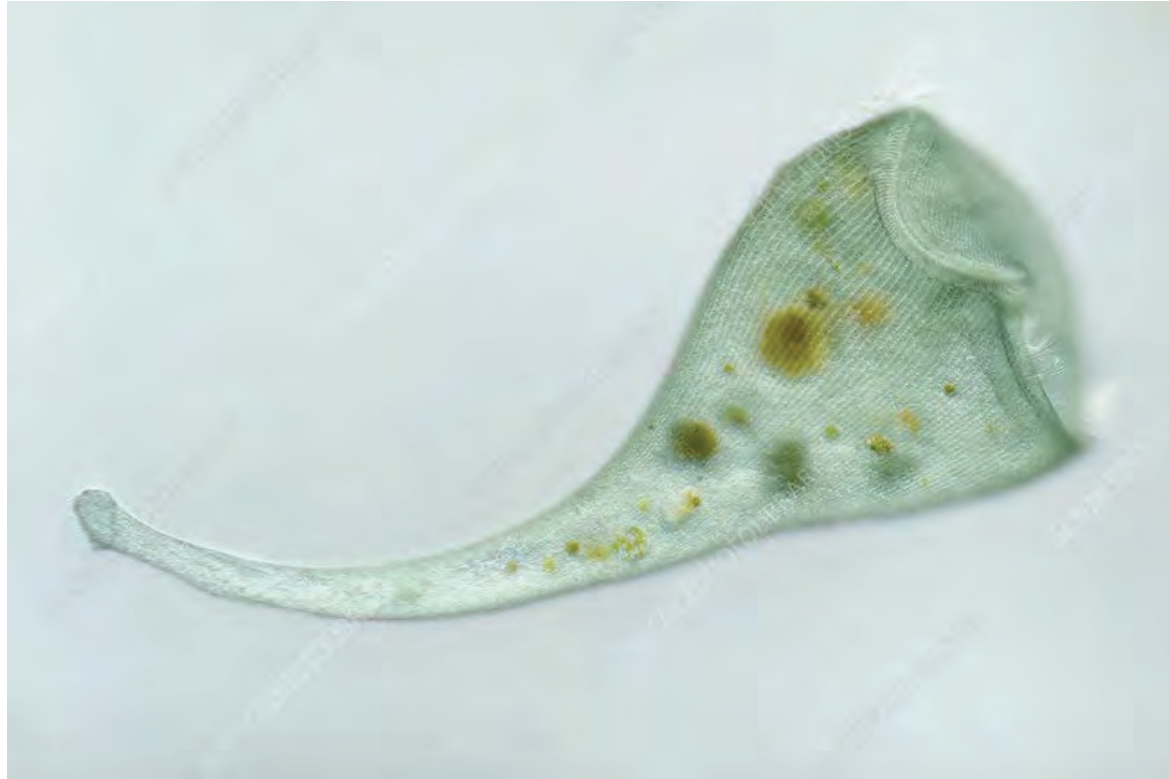


Cellular Growth and Form



Course 1: From tissues to cells: size and complexity

Thomas Lecuit

chaire: Dynamiques du vivant



COLLÈGE
DE FRANCE
—1530—

How to account for the extraordinary diversity of shapes?



PLANCTON Aux origines du vivant, Editions Ulmer, octobre 2013,

Christian Sardet



COLLÈGE
DE FRANCE
1530

Thomas LECUIT 2020-2021

In search of the principles of biological shapes...



Henri Poincaré (1854-1912)

« Le savant doit *ordonner*;
on fait la Science avec des faits comme une
maison avec des pierres ;
mais une accumulation de faits n'est pas plus
une science qu'un tas de pierres n'est une
maison. »

La science et l'hypothèse (1902)



Jean Perrin (1870-1946)

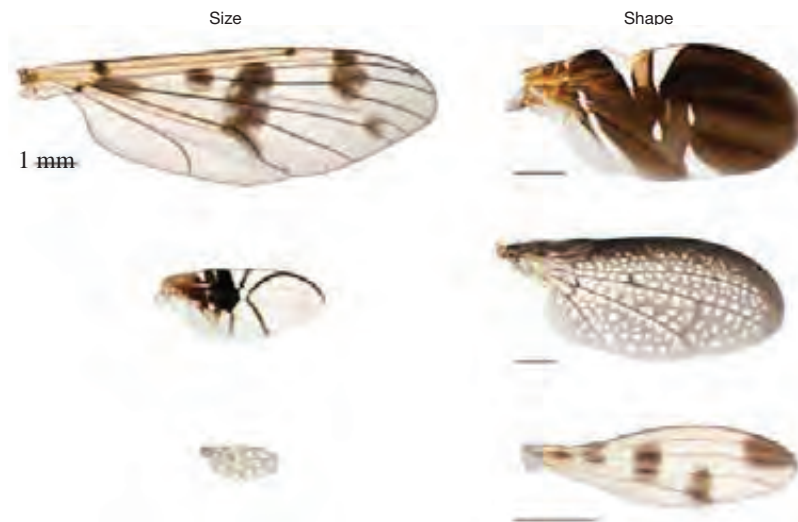
« La Science remplace du visible compliqué
par de l'*invisible simple*. »

Plasticity and constraints in morphogenesis

Tissue shape: 2017 and 2018

Tissue size: 2019

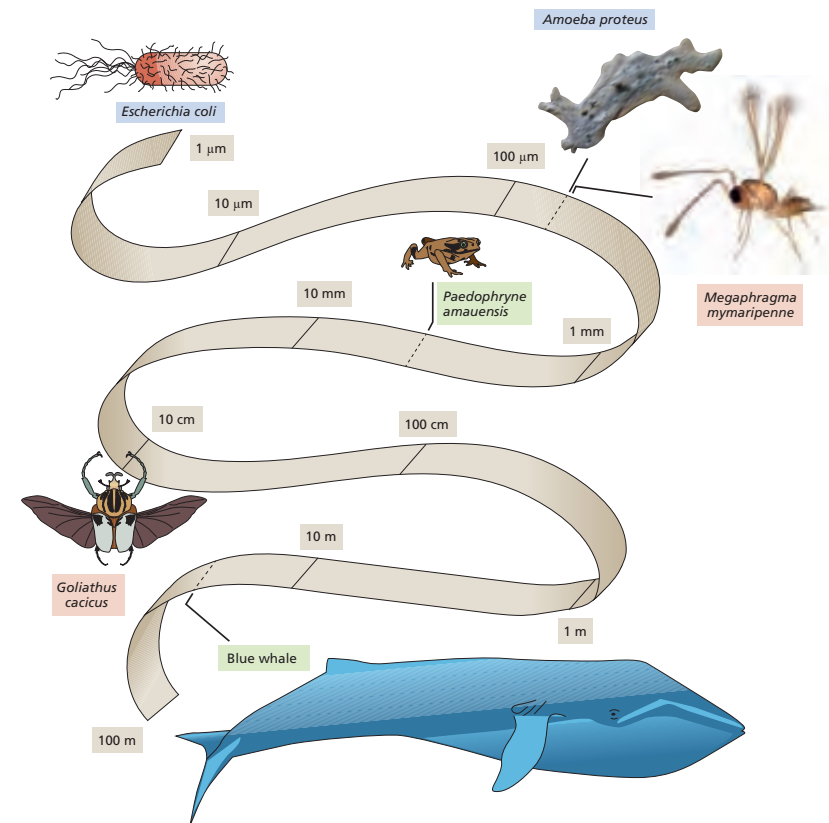
- Variation in shapes



Lecuit T. and Le Goff L. *Nature*. 2007 ;450(7167):189-92. doi: 10.1038/nature06304.

- Multicellularity: diversification of cell types, modularity of developing shapes.

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



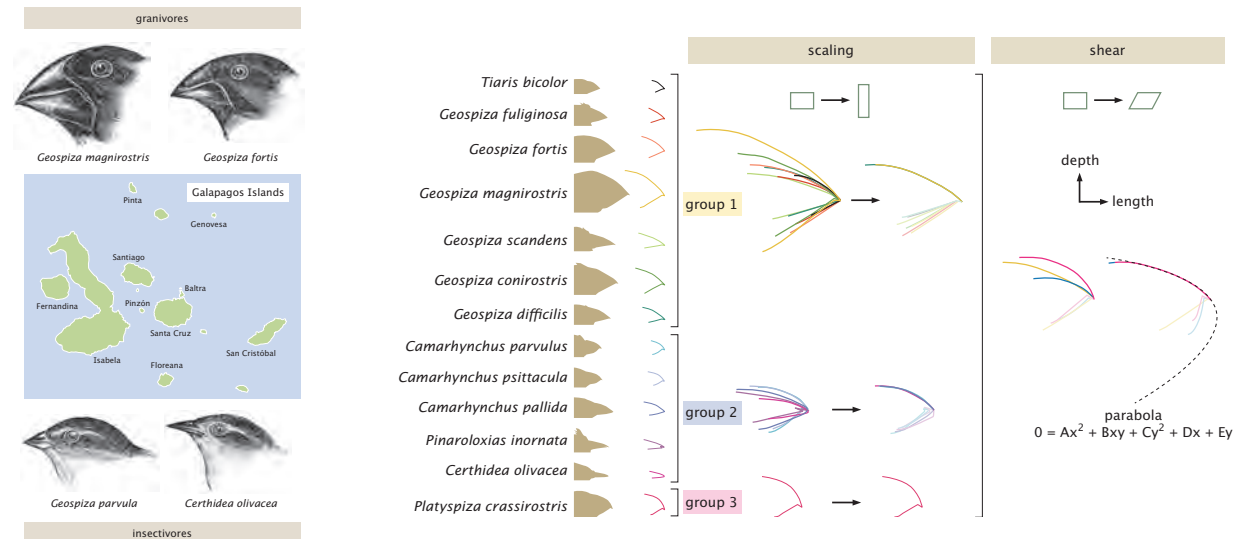
Plasticity and constraints in morphogenesis

- Evolutionary radiation with extensive or limited shape variation



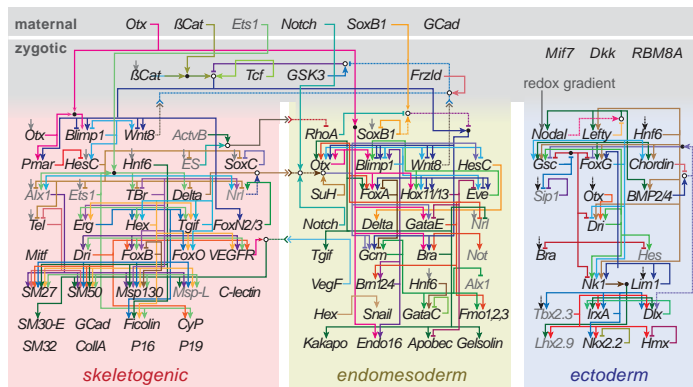
Nicolas Gompel (LMU Munich)

- Internal constraints:
 - historical, genetic (networks), functional and physical.



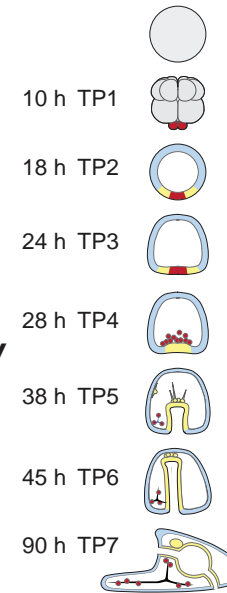
O. Campas et al. and A. Abzhanov, M. Brenner. *PNAS* (2010) | 107:3356–3360

Plasticity and constraints in morphogenesis

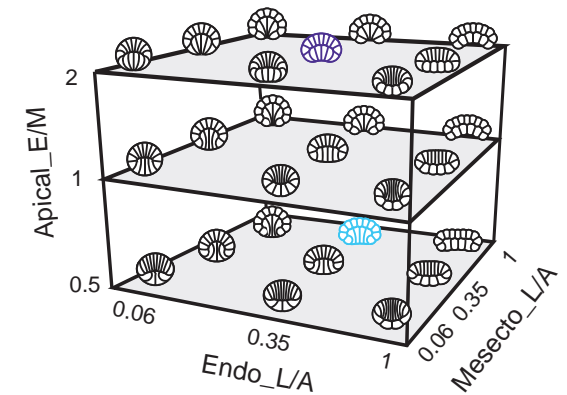


Garfield DA et al. *PLoS Biol* 11(10): e1001696. (2013) doi:10.1371/journal.pbio.1001696

dimensionality
reduction



development



Sherrard K et al *Current Biology* 20, 1499–1510

Genospace

> 15.000 genes

10 functional alleles per gene?

dimension: 10^{15000} !!!

Morphospace

much, much lower dimensional space

- viability/functional fitness
- constraints: historical, physical etc
- few effective parameters

See also, for a discussion: Ard A. Louis. *Studies in History and Philosophy of Biological and Biomedical Sciences* 58 (2016) Contingency, convergence and hyper-astronomical numbers in biological evolution

Colloque :

Constraints and plasticity in Development and Evolution

3-4 Juin 2021 – 9h-18h

Amphithéâtre Maurice Halbwachs

Organisateurs:

Denis Duboule (chaire: Evolution des génomes et développement)

Thomas Lecuit (chaire: Dynamiques du vivant)

Detlev Arendt (EMBL Heidelberg)
Virginie Courtier-Orgogozo (Paris)
Stanislas Dehaene (Collège de France)
Claude Desplan (NYU)
Caroline Dean (John Innes Center)
Liam Dolan (Oxford)
Hopi Hoekstra (Harvard)
Laurent Keller (Univ. Lausanne)
Natacha Kurpios (Cornell Ithaca)
Shigeru Kuratani (Kobe)
L. Mahadevan (Harvard)
Marie Manceau (Collège de France)
Nipam Patel (Woods Hole)
Olivier Pourquié (Harvard)
Luis Quitana-Murci (Pasteur & Collège de France)
Eric Siggia (Rockefeller University)
Vikas Tervidi (EMBL Barcelona)
Elly Tanaka (IMP Vienna)
Günter Wagner (Yale Univ.)



Plan

Course 1: From tissues to cells: size and complexity

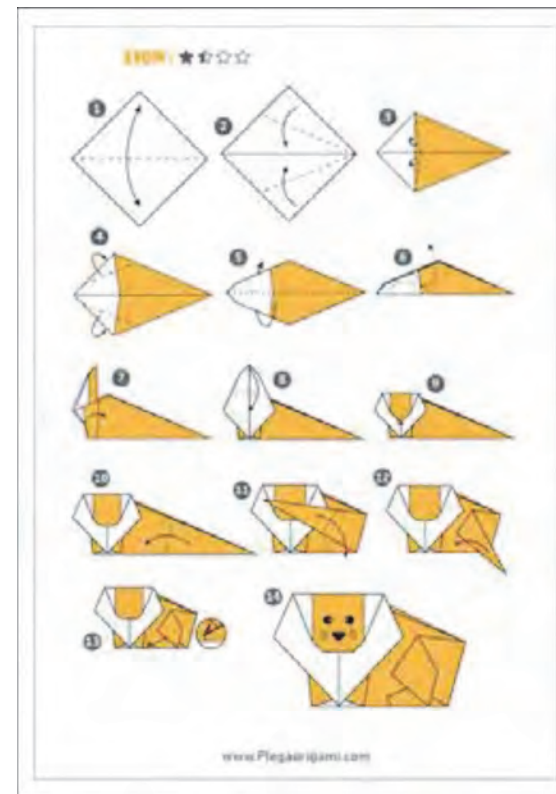
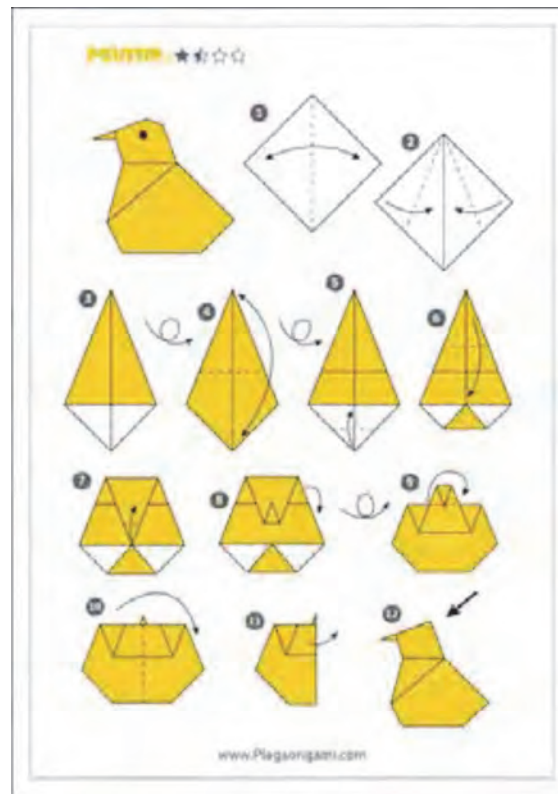
1. Universal classes of tissue shapes
2. Impact of multicellularity in shape space
 - Is multicellularity required for tissue shape?
3. Complexity of unicellular organisms
 - Large single cells can « behave » like multicellular organisms
 - From the most complex unicellulars to the most simple multicellulars

Universal classes of Shapes

All forms arise from few « elementary shape transitions »
operating across scales

Spatial and temporal combination of such operations

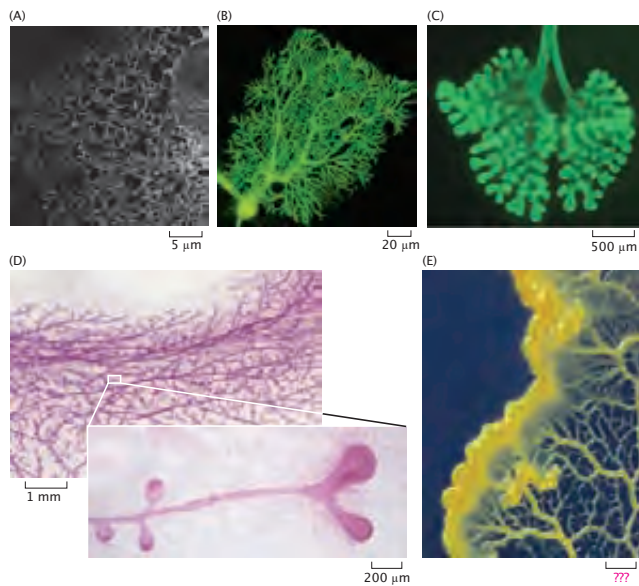
Folding



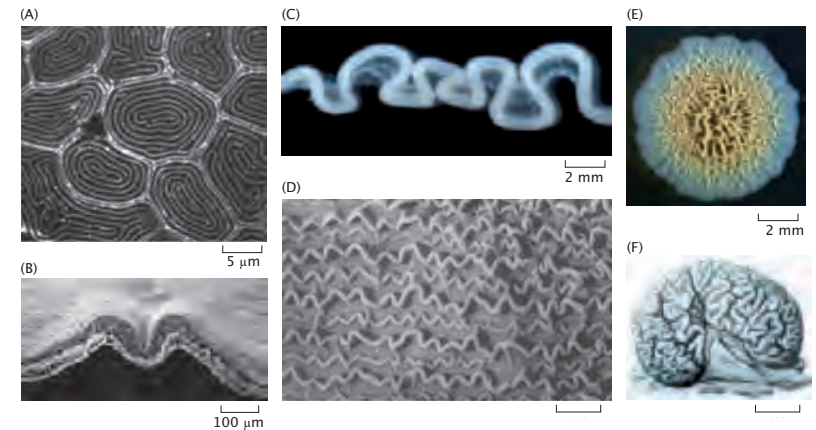
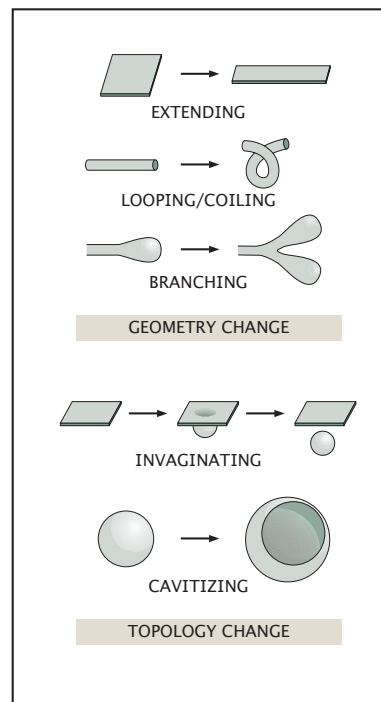
Universal classes of Shapes

All forms arise from few « elementary shape changes » across scales

Spatial and temporal combination of shape changes



Branching

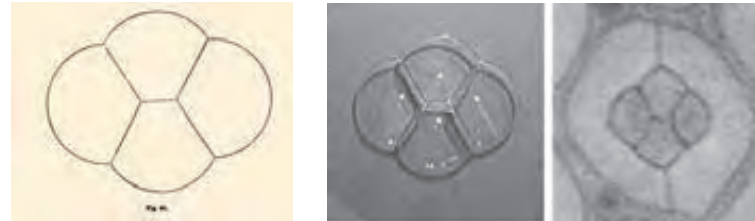


Bending, Folding, Looping

Universal classes of Shapes

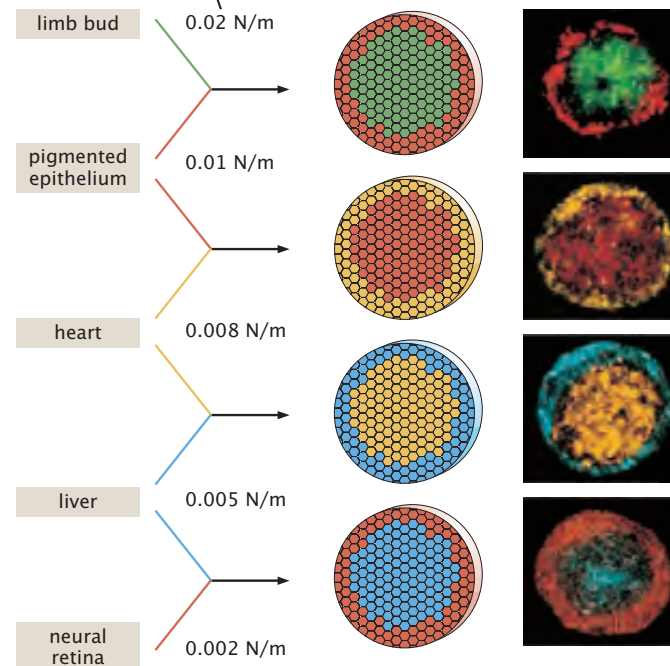
Arise from basic physical principles

- (near) Equilibrium shapes:
— surface tension: minimal surfaces



$$G_{\text{tot}} = \gamma \cdot A$$

$$\gamma = f(\text{cortical tension, adhesion})$$



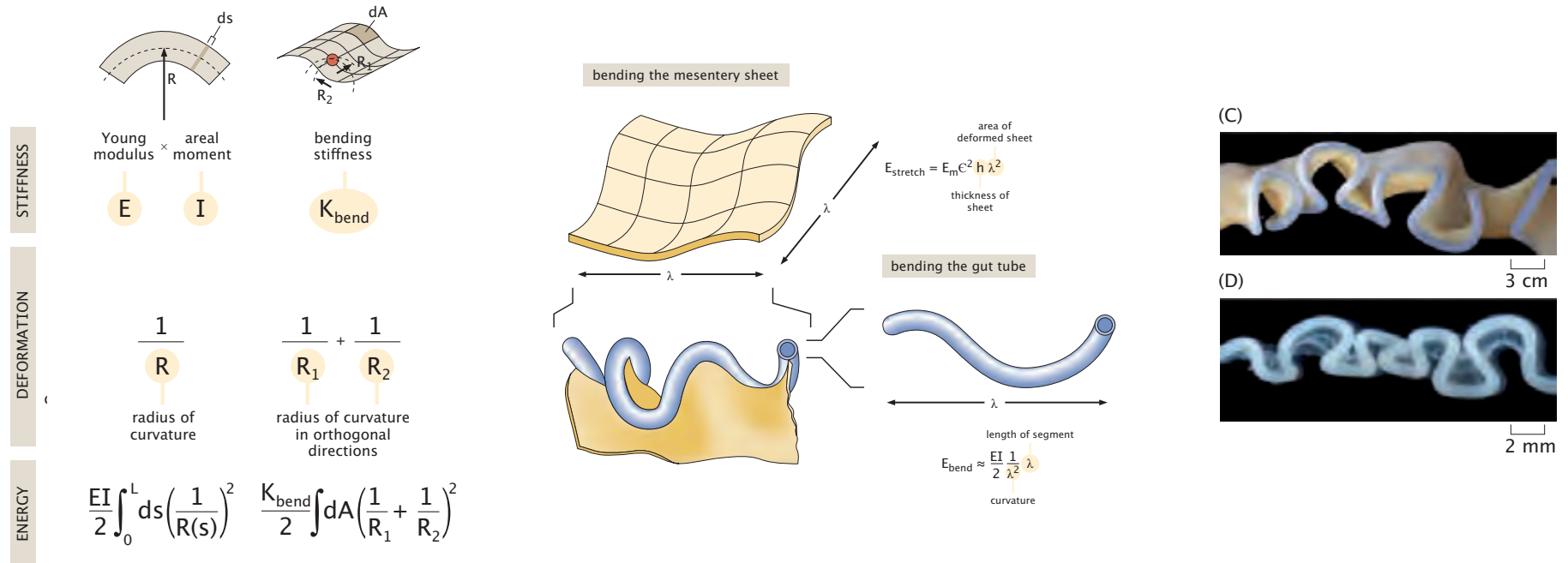
M. Steinberg et al

Universal classes of Shapes

Arise from basic physical principles

- (near) Equilibrium shapes:

— elasticity: buckling



from Rob Phillips (CalTech) and Christina Hueschen (Stanford Univ.)

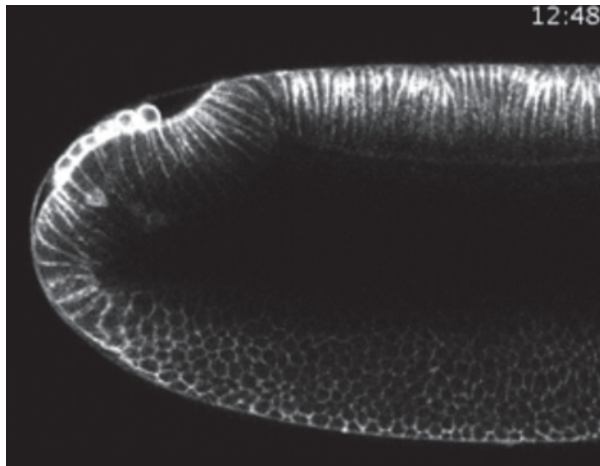
after Thierry Savin, et al, L. Mahadevan and Cliff Tabin. *Nature* (2011) 476:57-62.

Universal classes of Shapes

Arise from basic physical principles

- Dynamic steady-state shapes:
-activity driven self-organisation

—Flow, pulses, waves of contraction

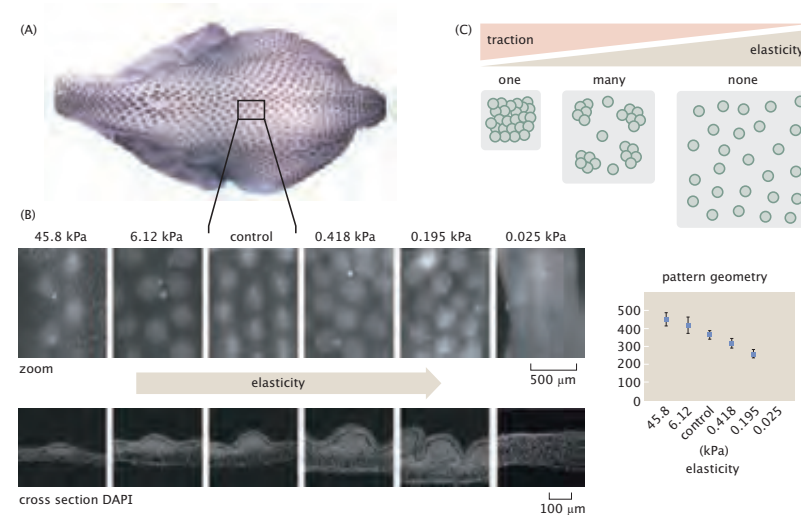


Wave of tissue folding (*Drosophila* embryo)

Bailles and Collinet et al. *Nature* 572, 467-473 (2019)

Thomas LECUIT 2020-2021

—Aggregation



force balance

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

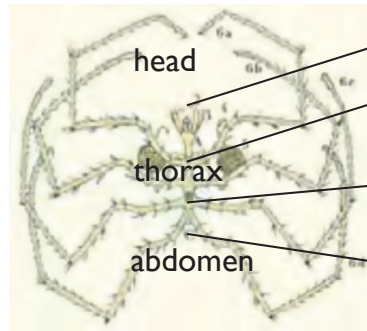
after Shyer et al. *Science* 357, 811-815 (2017)

Origin of tissue and organism shape diversity

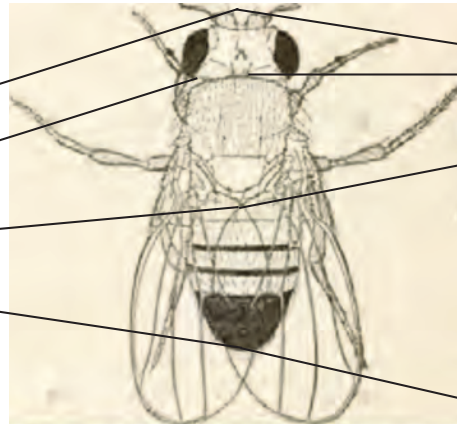
- **Developmental Modularity:** metamers (segments) and tagma
- Modular control of size and shape in each segment: morphological diversification



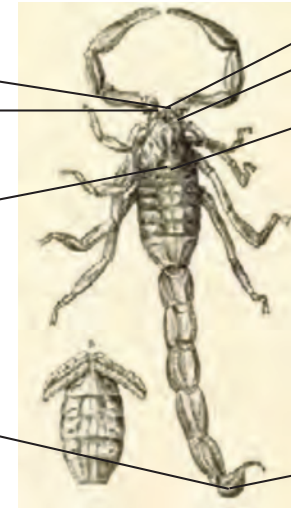
Marrella (Burgess Shale)
500 Mya



Pycnogonida



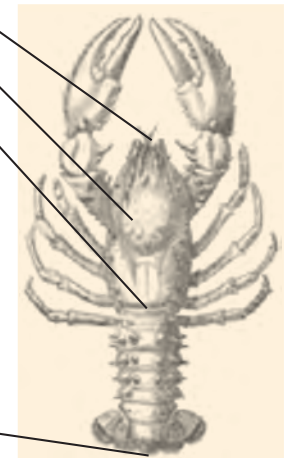
Drosophila melanogaster



Buthus occitanus



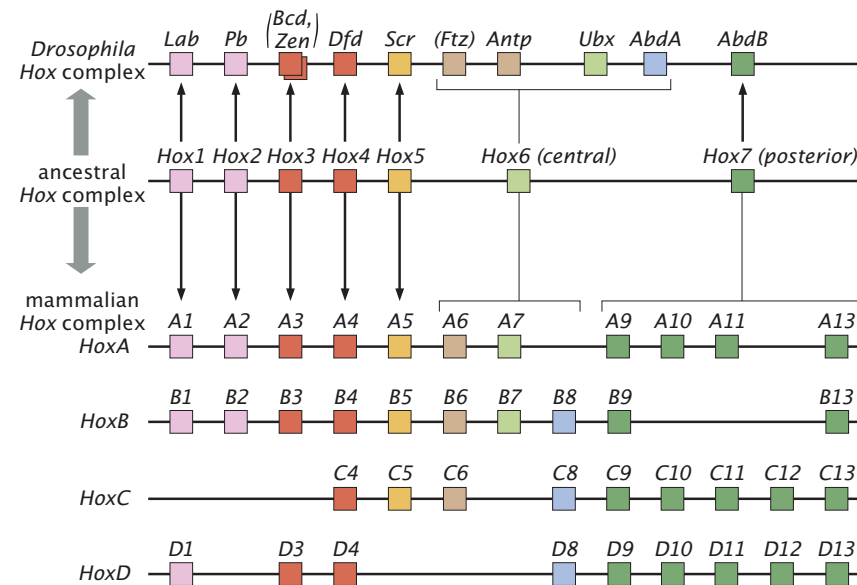
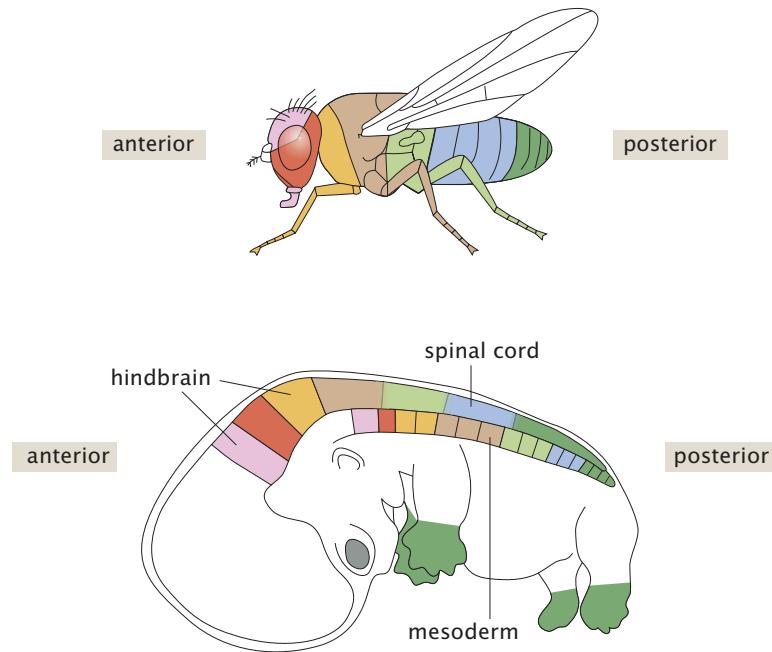
Scutigera forceps



Crayfish

Origin of tissue and organism shape diversity

- Modularity: metamers (segments) and tagma
- Modular genetic control of shape



Ed Lewis, C. Nüsslein-Volhard and E. Wieschaus (Nobel 1995)
 Denis Duboule and many other groups

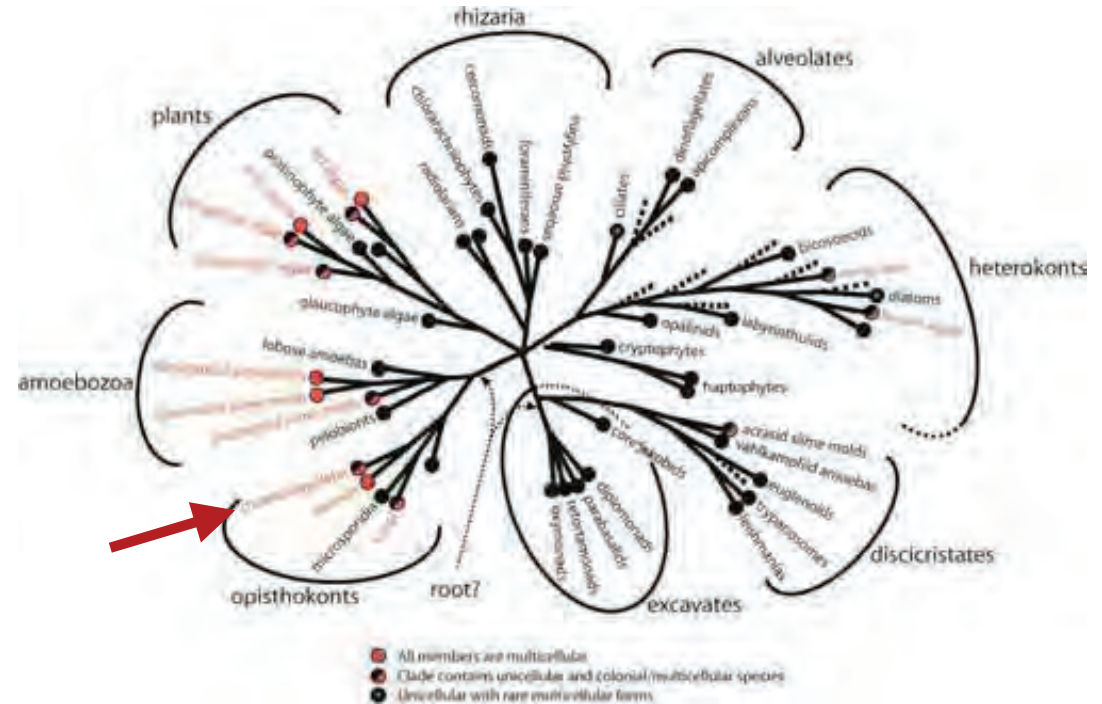
Plan

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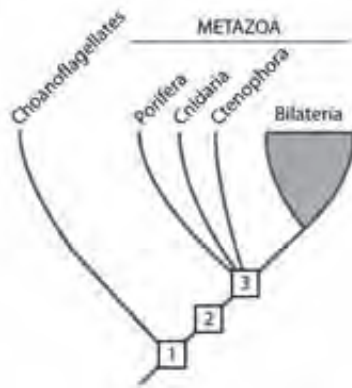
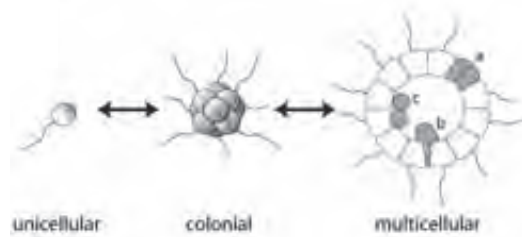
Impact of multicellularity on the morphospace

- Multicellularity occurred in at least 16 independent eukaryotic lineages
- Multicellularity allowed:
 - 1) escape from predation
 - 2) solution to motility/division antagonism (centriole required for both ciliogenesis and formation of mitotic spindle)
 - 3) exploration of new differentiated cell functions
- Molecular data support monophyletic origin of all Metazoa, including Porifera (sponges)

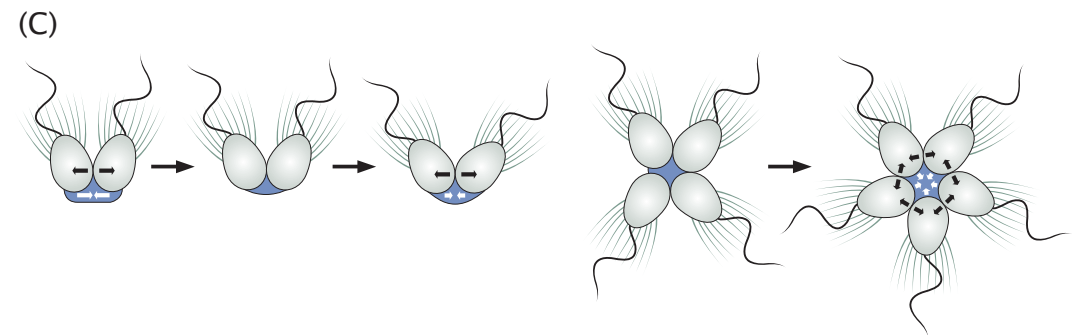
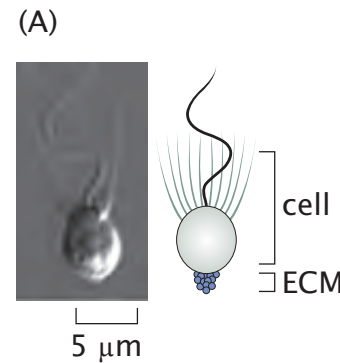


Impact of multicellularity on the morphospace

- Choanoflagellates are aquatic protozoans that share many features with animals, and thus are considered the closest unicellular relatives of animals
- Facultative multicellular (colonial) states in Choanoflagellates



King N. *Developmental Cell* 2004

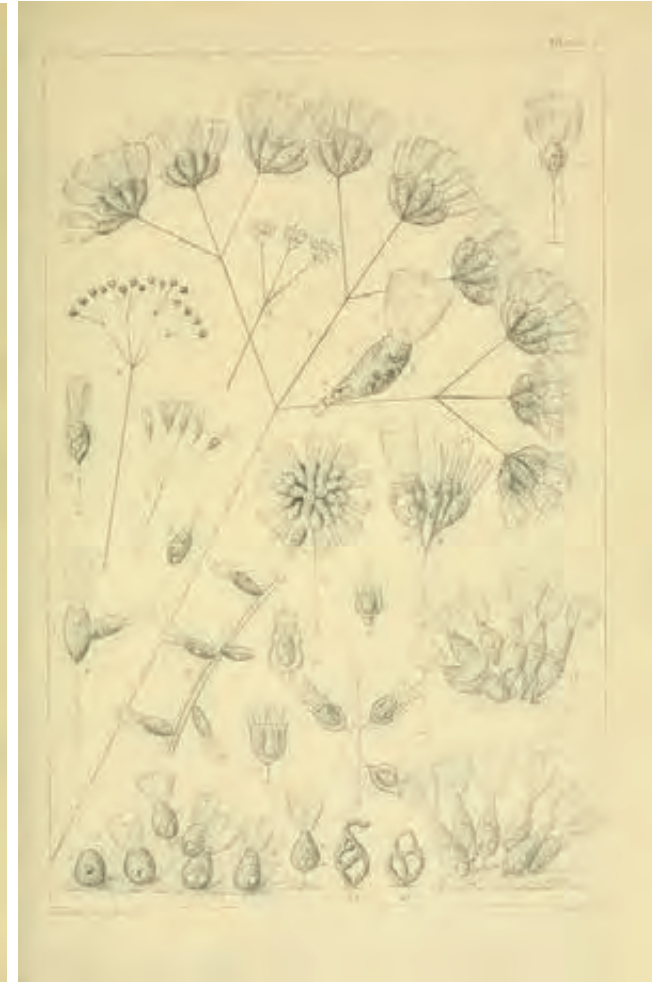


Impact of multicellularity on the morphospace

Saville-Kent explored the great diversity of Infusoria (Choanoflagelates)



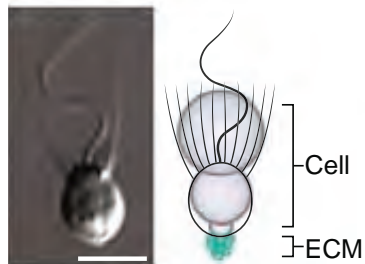
William Saville-Kent
(1865-1908)



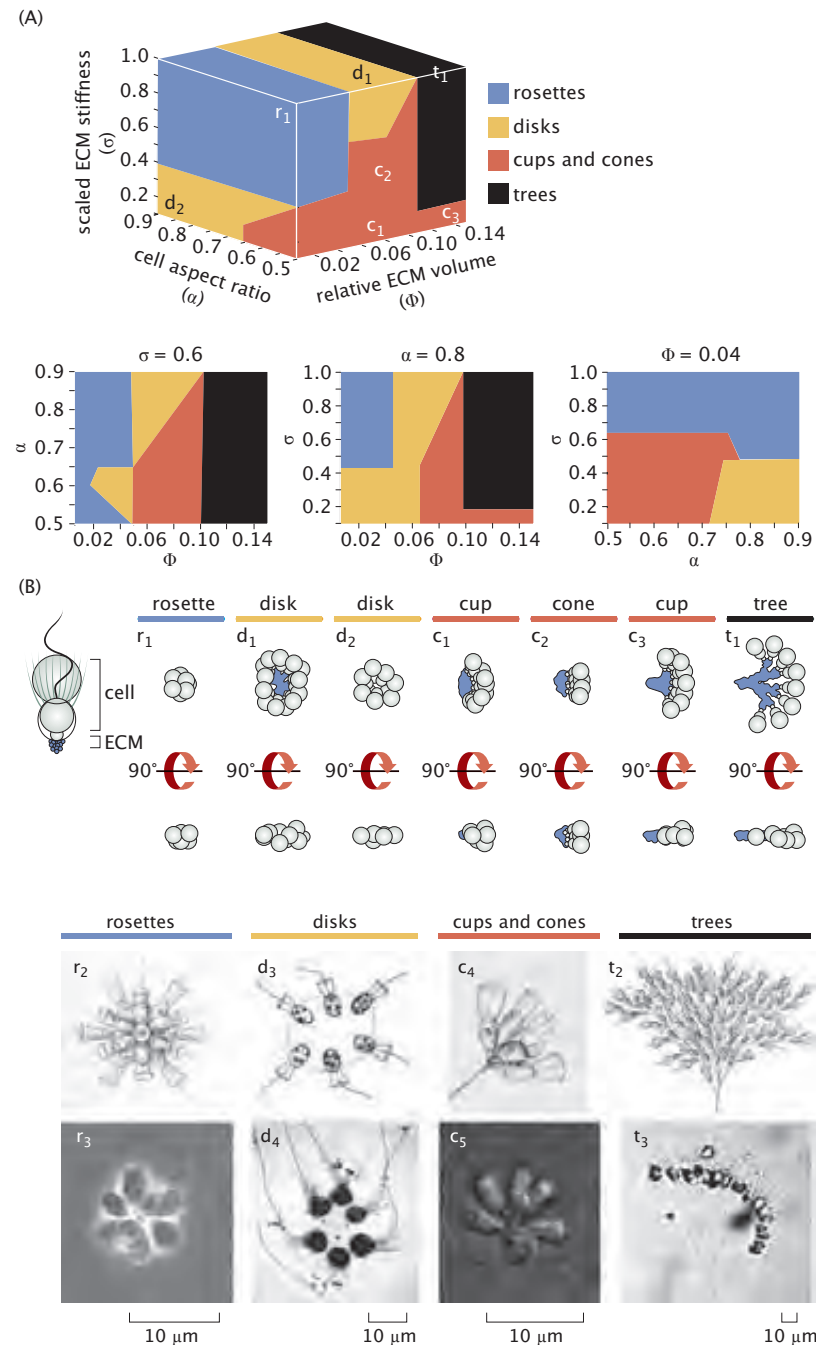
Manual of the Infusoria 1880-1882

Impact of multicellularity on the morphospace

- Morphogenesis of cell aggregates
- Mechanical model of self-assembly of cell aggregates.
- **3 effective parameters can change outcome of cell interactions and shape**
- Adhesion/cell coupling via the ECM
- Geometric parameter: aspect ratio

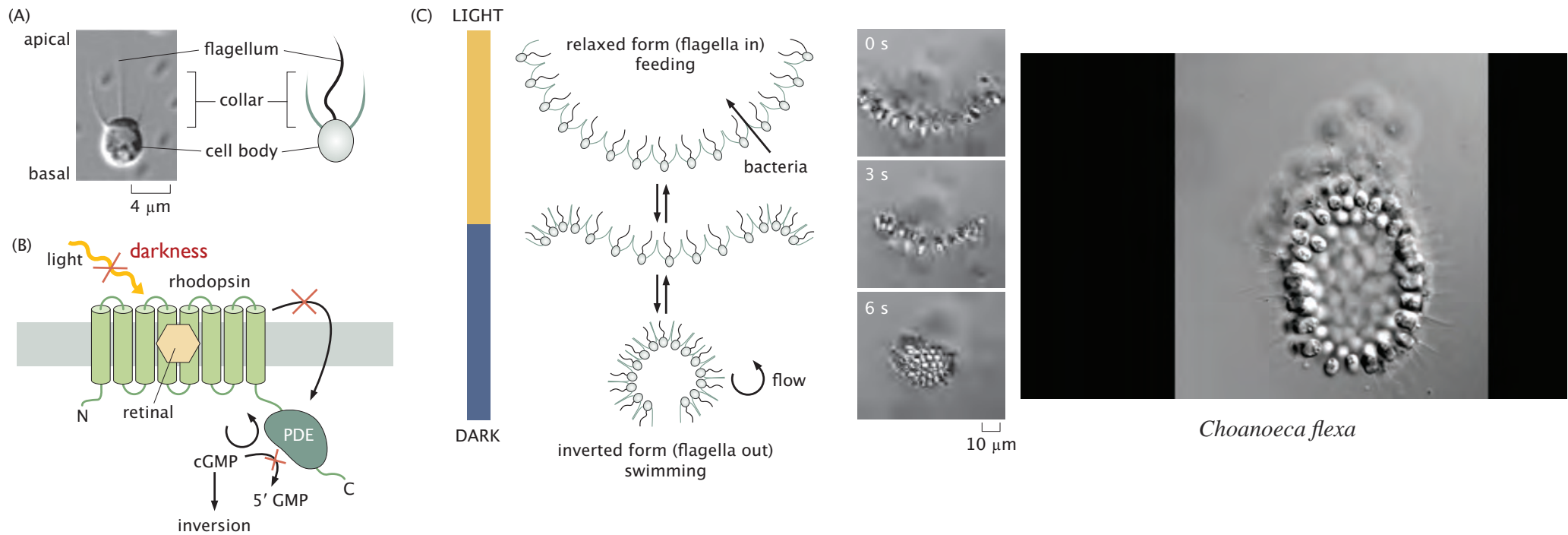


- Cell aggregates can (model) and do (experiments) form rosettes, disks, cups, cones or trees



Impact of multicellularity on the morphospace

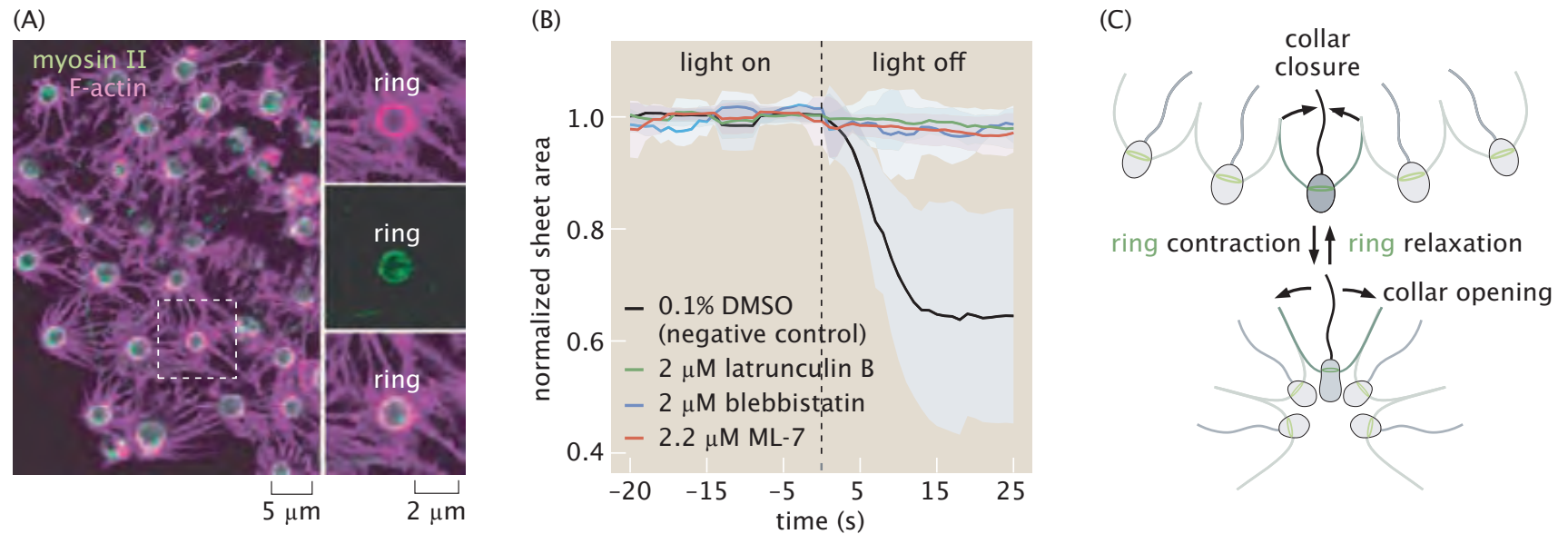
- Light induced morphological change in colony of Choanoflagellate (*Choanoeca flexa*)



T. Brunet et al., and N. King. *Science* 366, 326–334 (2019)

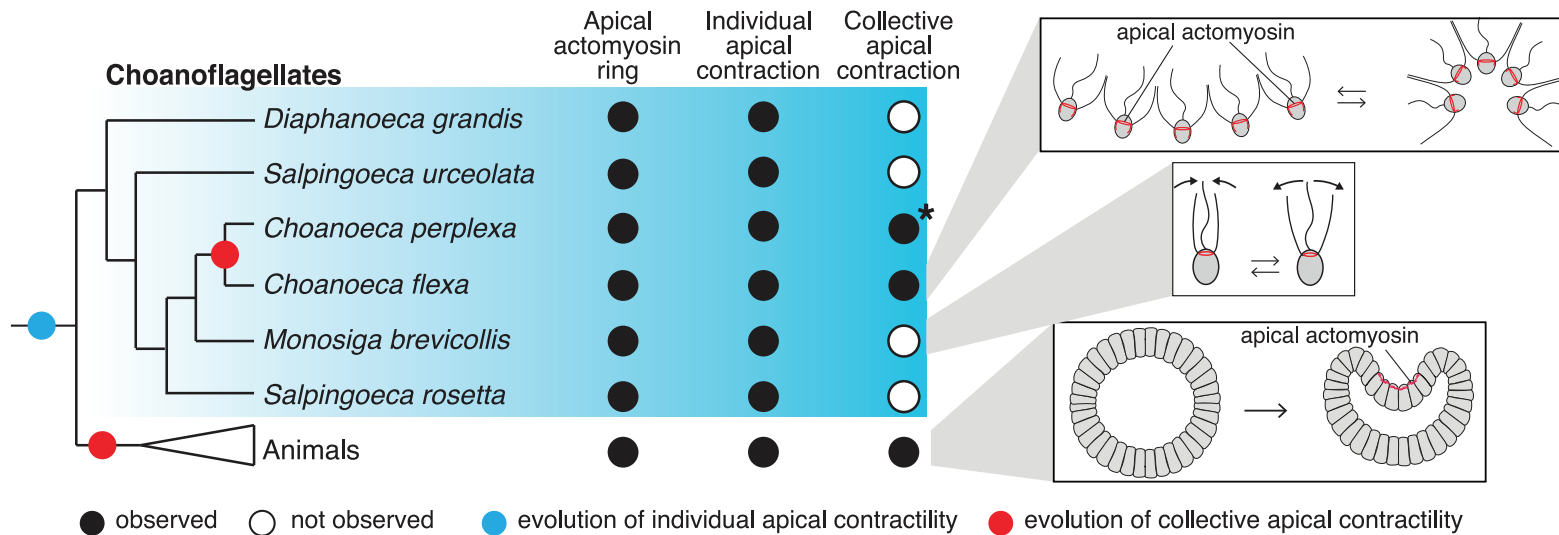
Impact of multicellularity on the morphospace

- Collective contractility drives colony shape changes



Impact of multicellularity on the morphospace

- Suggests that collective cell dynamics is required for emergence of complex shapes such as invagination.
- Such collective cell dynamics rests on a limited set of cellular processes such as contractility and cell-cell coupling



Tissue shape: is multicellularity required?

— *Drosophila* embryo gastrulation without cells

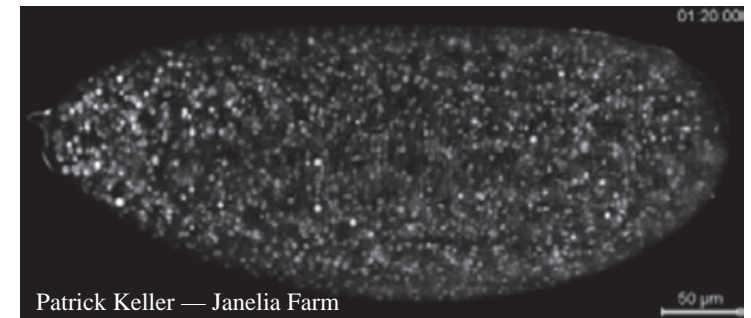
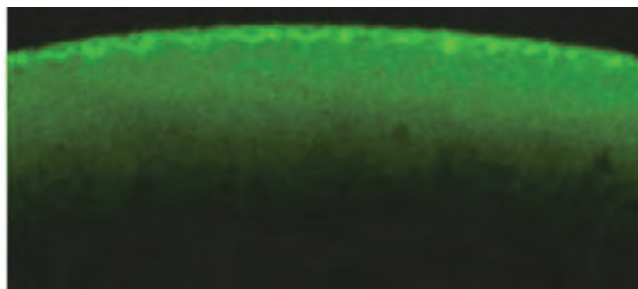
Syncytial divisions

1 cell : 1 nucleus

1 cell : 5000 nuclei

Cellularisation: 5000 cells

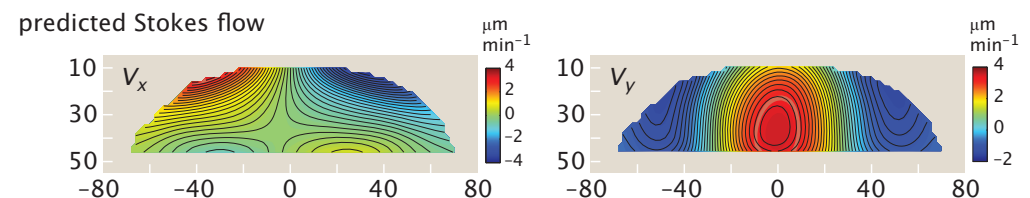
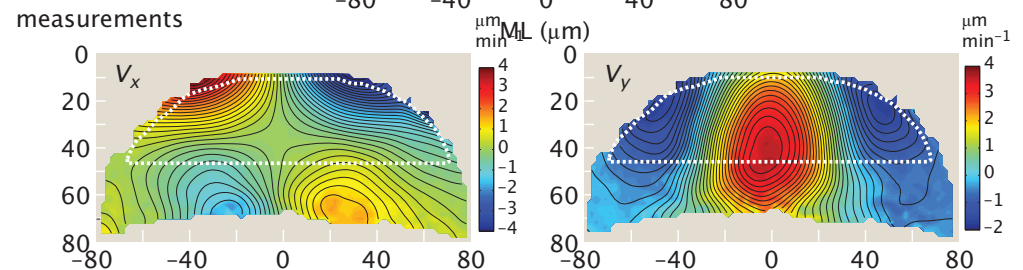
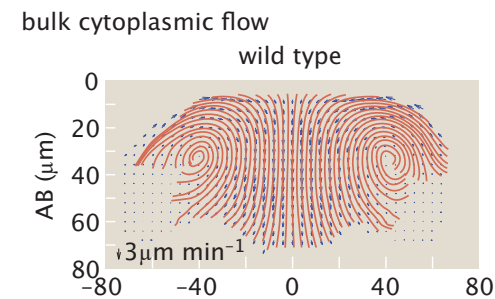
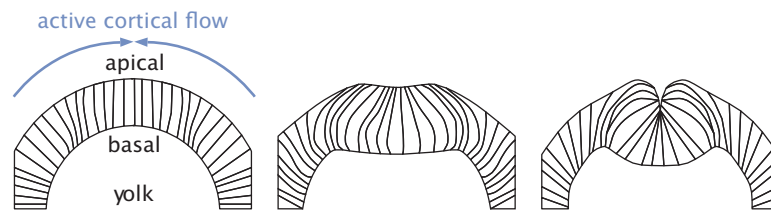
Membrane invagination leads to the formation of many cells at once



Tissue shape: is multicellularity required?

— *Drosophila* embryo gastrulation without cells

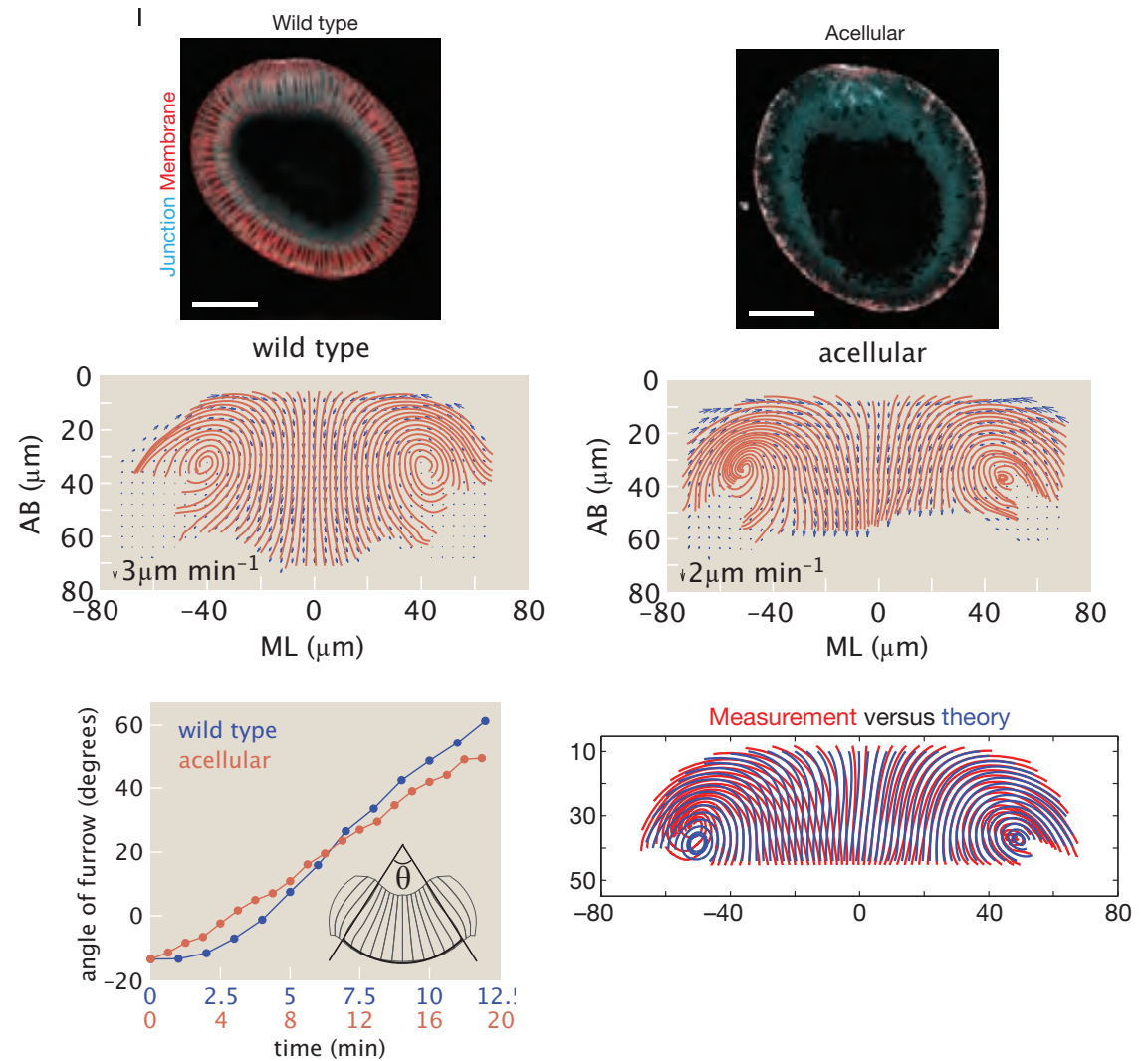
- Bulk cytoplasmic flow in the ventral mesoderm is associated with tissue invagination
- Bulk flow is similar to predicted Stokes flow given known boundary conditions (active cortical flow driven by actomyosin contractility)
- Suggests that tissue behaves as a homogenous fluid (cytoplasm)



Tissue shape: is multicellularity required?

— *Drosophila* embryo gastrulation without cells

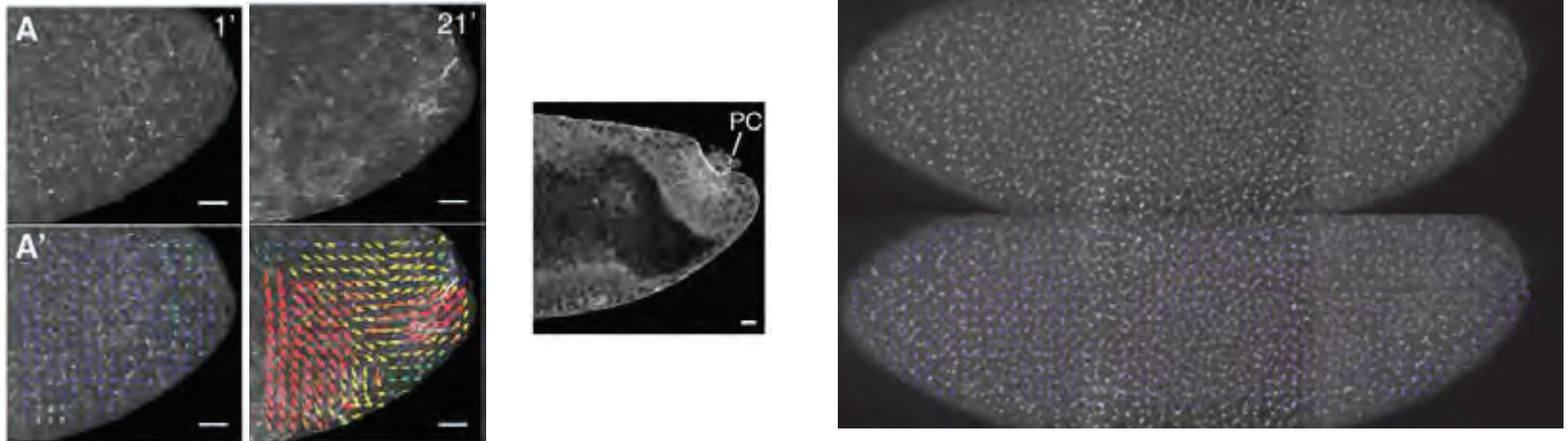
- In an acellular embryo (syncytium) bulk cytoplasmic flow still occurs
- Acellular flow is similar to predicted Stokes flow, and also similar to flow in cellularized tissue
- « tissue » furrowing occurs (albeit more slowly) in acellular embryo.



Tissue shape: is multicellularity required?

— *Drosophila* embryo gastrulation without cells

- Cortical flow can be predicted from pattern of MyosinII and geometry.
- Flow still occurs in *acellular* embryo



Lye CM, et al, and B. Sanson. (2015) *PLoS Biol* 13(11): e1002292. doi:10.1371/journal.pbio.1002292

See also:

Dicko M, Saramito P, Blanchard GB, Lye CM, Sanson B, Étienne J. *PLoS Comput Biol*. 2017 Mar 27;13(3):e1005443.
Streichan S. et al *eLife*. 2017

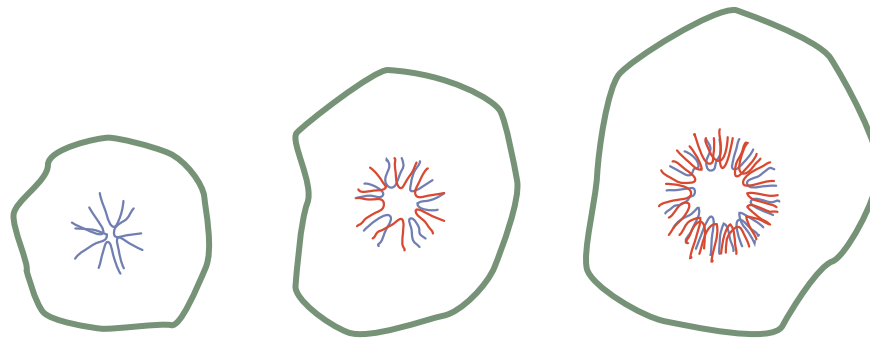
Tissue shape: is multicellularity required?

— Tubulogenesis in Salamanders:

Morphogenesis is independent of cell size and cell number.

- Cell size compensates for change in cell number
- A single cell forms a lumen

(A)

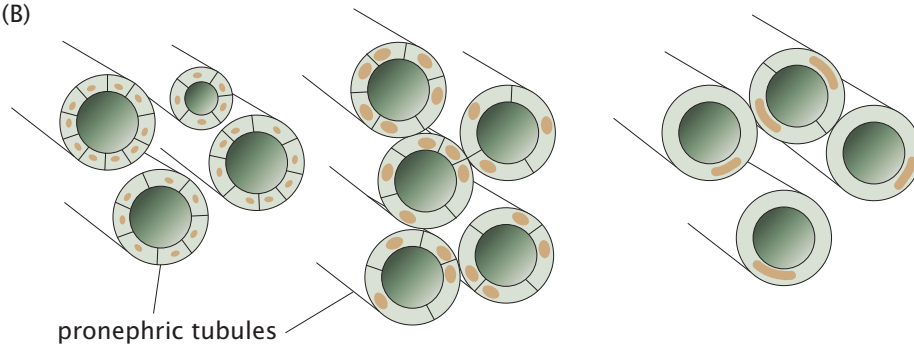


haploid (n)

diploid (2n)

pentaploid (5n)

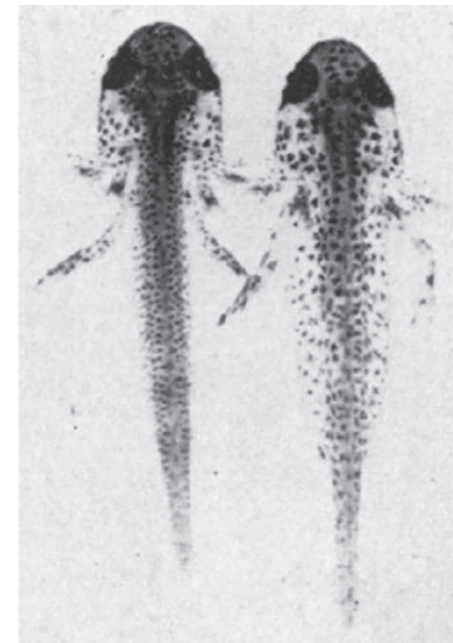
(B)



pronephric tubules

(C)

larvae



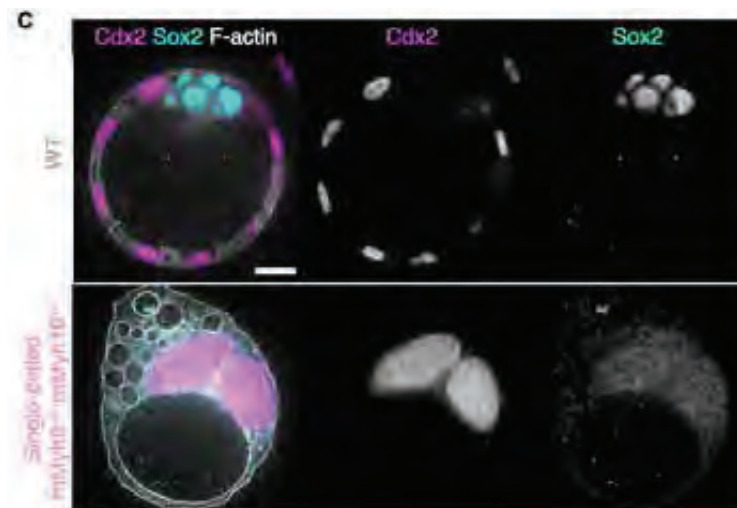
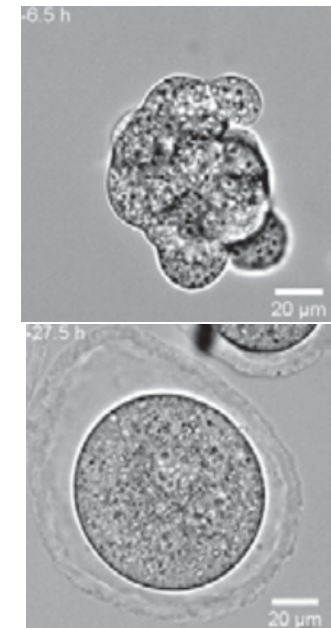
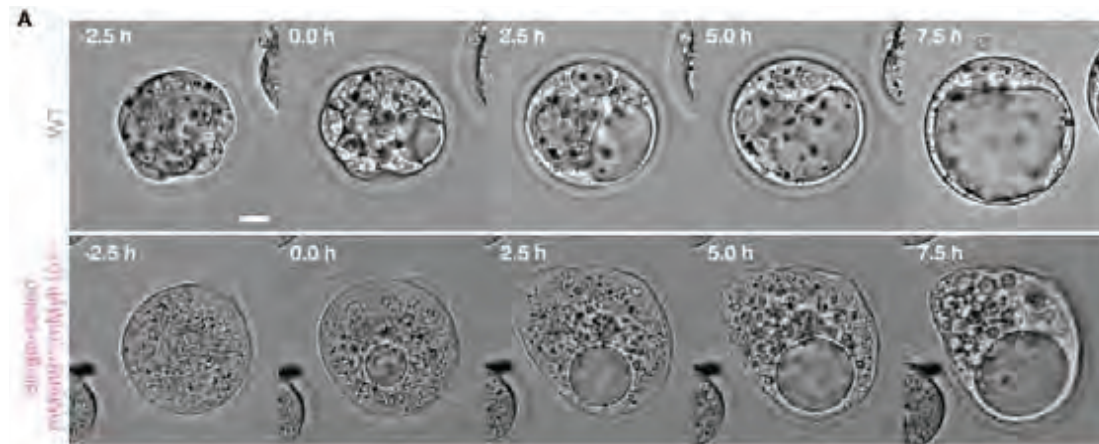
diploid (2n)

pentaploid (5n)

Fankhauser G. 1945. *J Exp Zool* 100: 445–455.

Tissue shape: is multicellularity required?

- Mouse embryo lumenisation without cells?
 - Formation of the blastocoel in mouse embryos occurs in non-muscle Myosin-II heavy chain mutants that block cytokinesis
 - This leads to the formation of intracellular lumenisation and growth of a vacuole

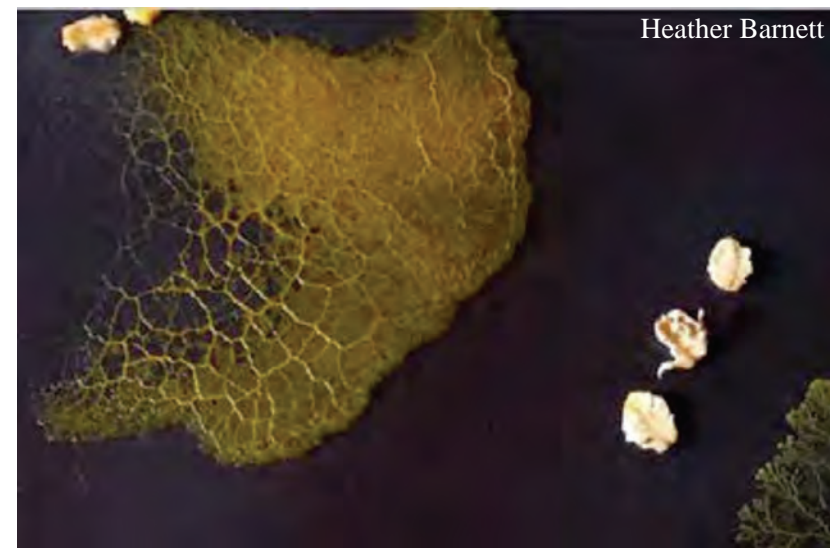
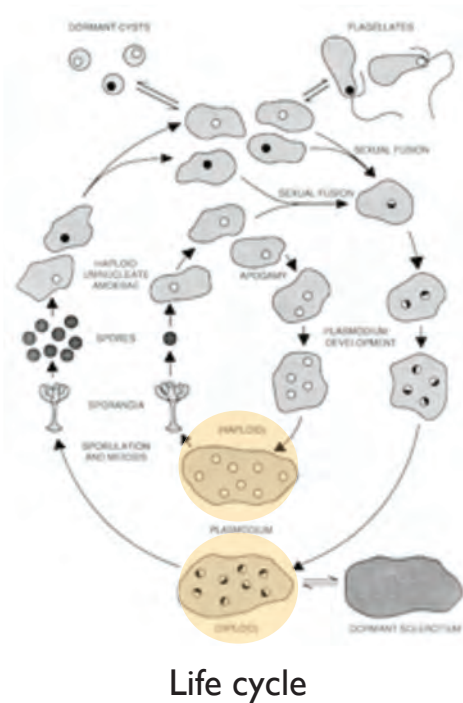


M.F. Schliffka et al, and J-L. Maître.
bioRxiv <https://doi.org/10.1101/2020.09.10.291997>

mzMyh9^{-/-}; mzMyh10^{+/-} embryo

Tissue shape: is multicellularity required?

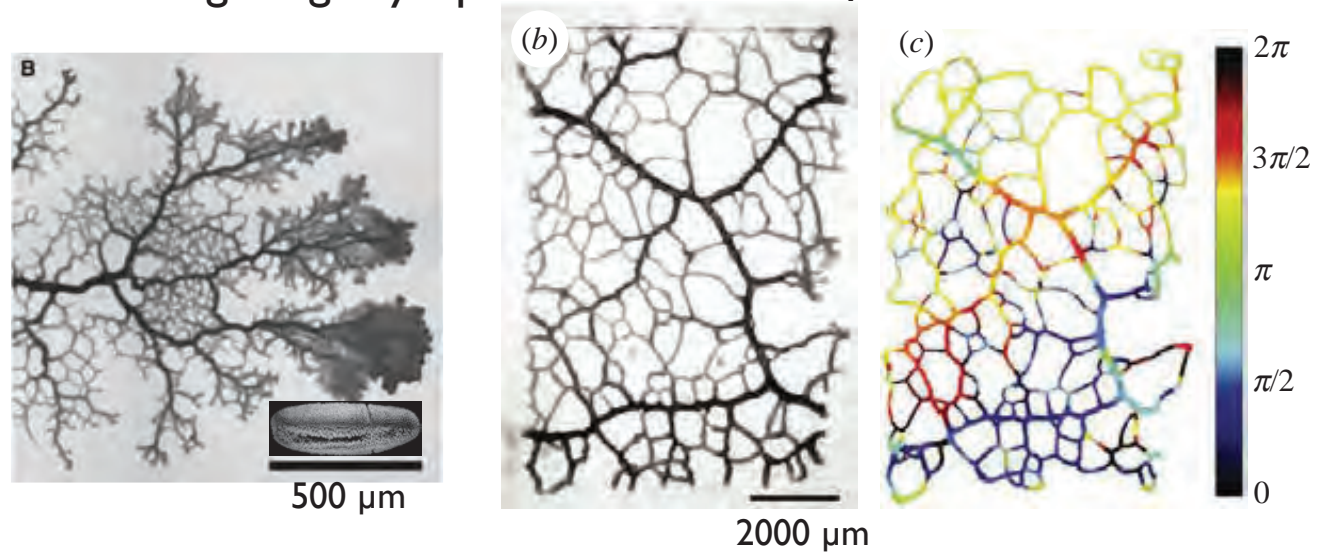
- *Physarum polycephalum*: an acellular self-organized optimal transport system
- A plasmodial myxomycete (Protist, Amoebozoa)
 - Contains 1000s to millions of nuclei in a syncytium called plasmodium
 - Grows towards food source
 - Self-organizes a hydrodynamic network to distribute food to the entire cell/organism



Tissue shape: is multicellularity required?

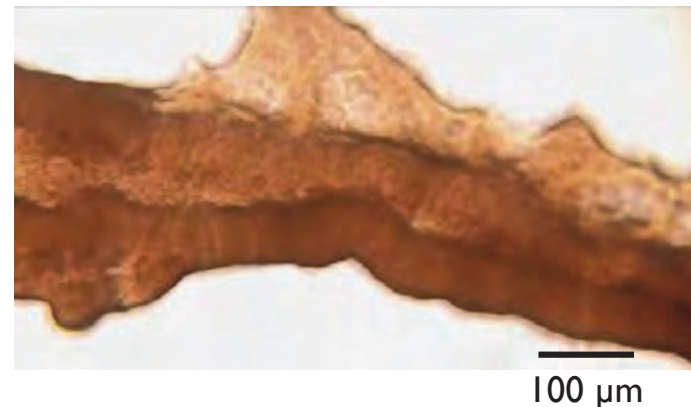
— *Physarum polycephalum*: an acellular self-organised optimal transport system

- Self-organisation of network morphology
- Phase gradient of contraction across network
- Peristaltic wave drives long-range cytoplasmic flow in the plasmodium



Alim K. 2018 Fluid flows shaping organism morphology.

Phil. Trans. R. Soc. B 373: 20170112. <http://dx.doi.org/10.1098/rstb.2017.0112>



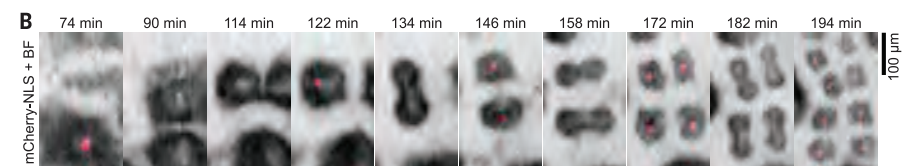
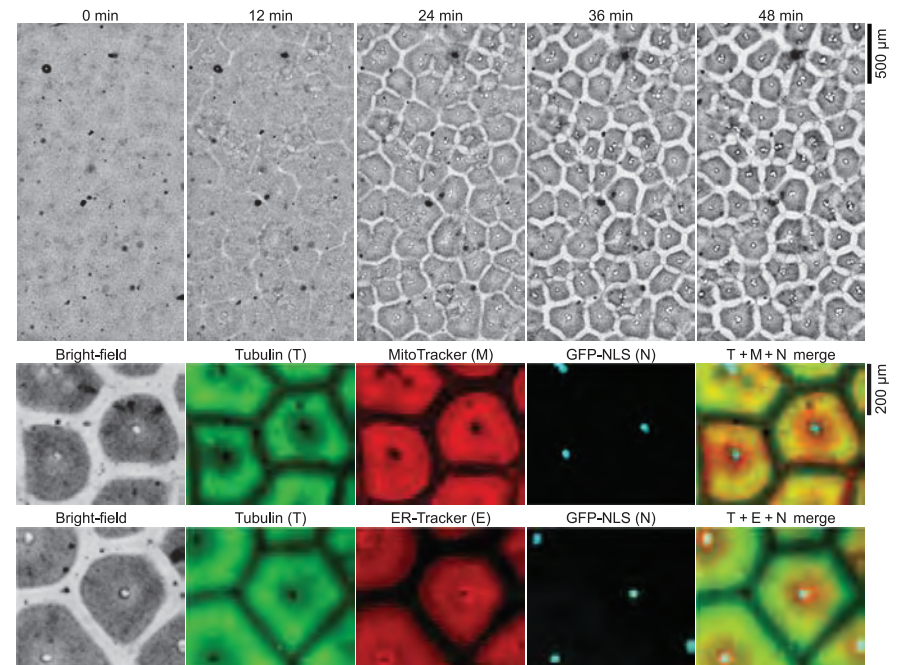
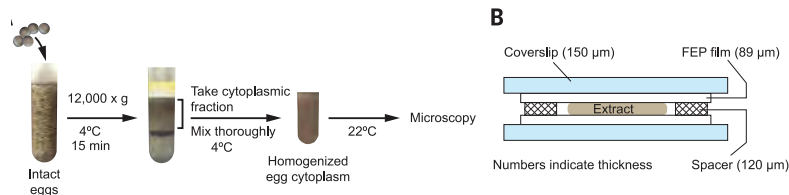
Tissue shape: is multicellularity required?

- Obviously yes, **But:**
- **No, to a certain extent:**
- It reflects the amazing self-organising properties of intracellular material (non genetic, non deterministic information).

- Compartmentation in absence of membranes
- Cell-like units can divide (a sperm-supplemented cycling *X. laevis* egg extract)

Spontaneous emergence of cell-like organization in *Xenopus* egg extracts

Xianrui Cheng^{1*} and James E. Ferrell Jr.^{1,2*}



Tissue shape: is multicellularity required?

- Obviously yes, **But:**
- **No, to a certain extent:**
- It reflects the self-organising properties of intracellular material (non genetic, non deterministic information).
- The **efficacy of continuum physical models** is consistent with this: In such coarsened-grained descriptions, cell individuality is lost and tissues are described as a continuous medium driven by active mechano-chemical processes.
Elasticity theory, Active matter theory etc.
- Especially in large cells (or acellular tissues).
- **Large single cells can behave like multicellular organisms**

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Size and complexity

- Large single cells can behave like multicellular organisms

Megaphragma mymaripenne
7500 cells in brain

Motility
Feeding
Environment sensing



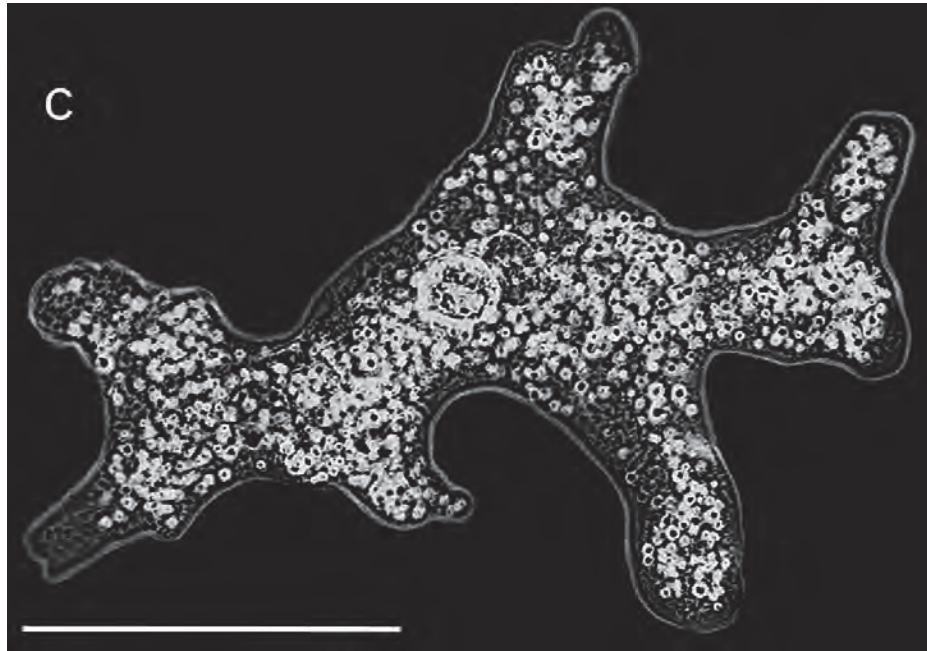
200 μ m

Paramecium caudatum

Amoeba proteus

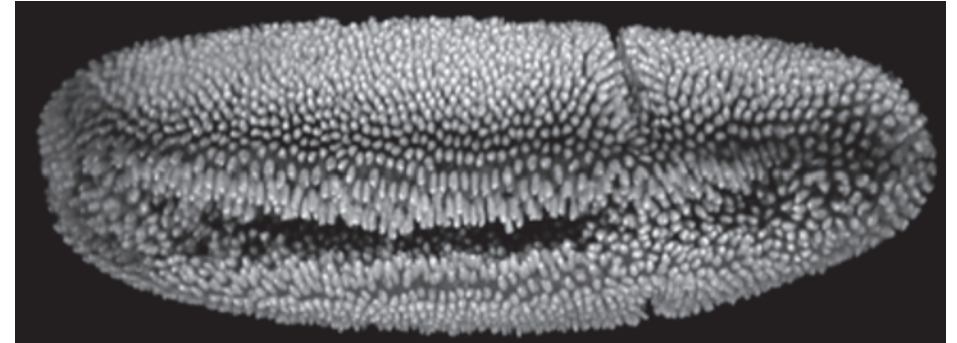
Size and complexity: « single cell organisms »

- Pure self-organisation of single cell



I cell I fate

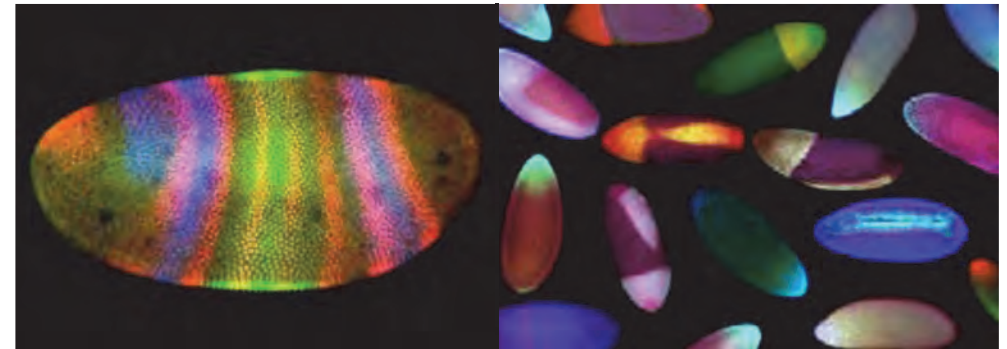
- Genetic determination of 5000 cells



<https://sguenther.eu/data/life-in-perspective/fruit-fly-embryo/>

5000 cells

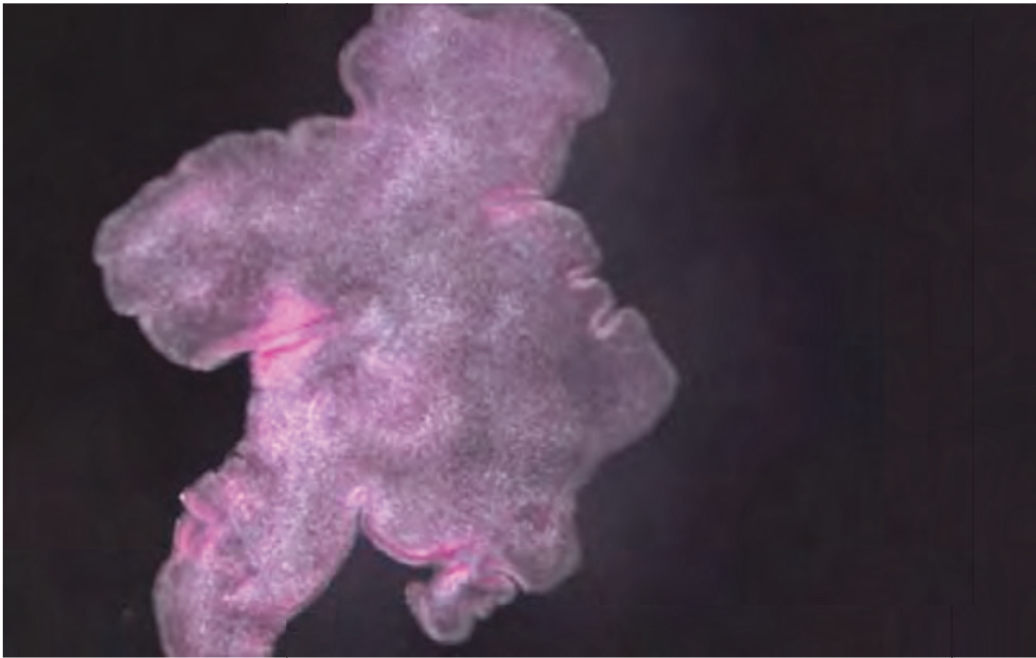
10-100 fates



Size and complexity: single cell organisms

- Multicellular tissue dynamics

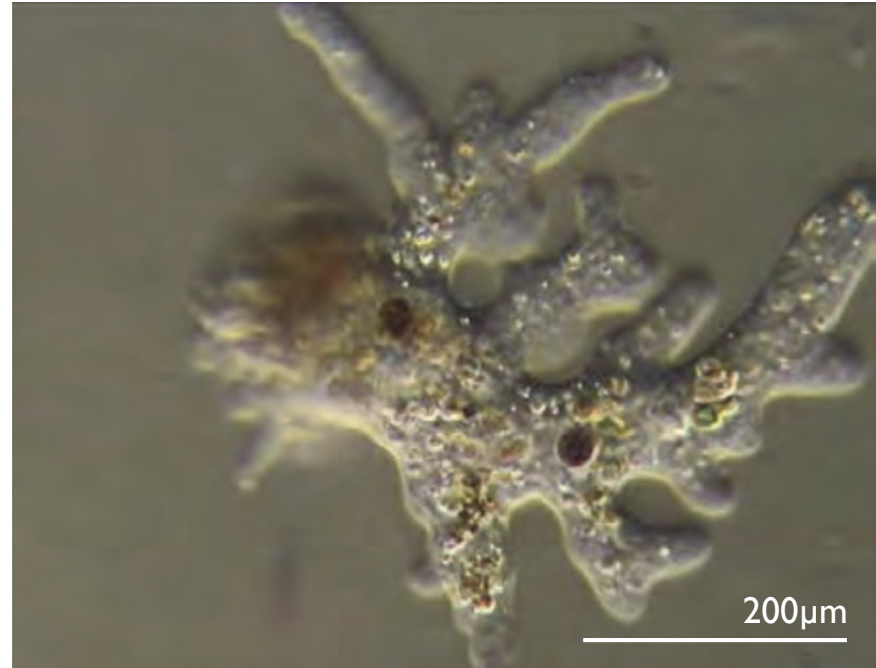
Trichoplax adhaerens motility



Several 1000 cells

- Giant cell dynamics

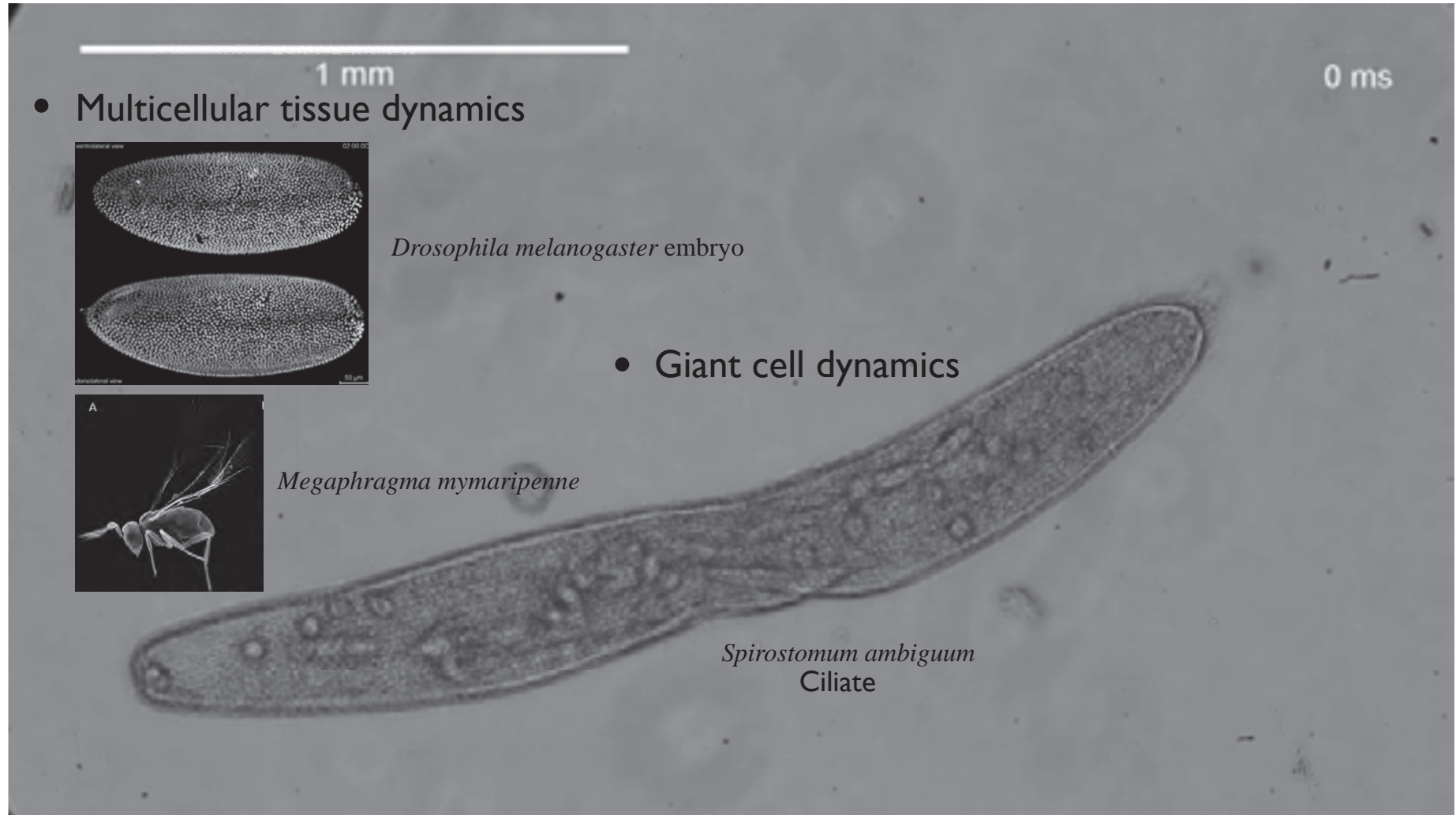
Amoeba proteus motility



1 cell

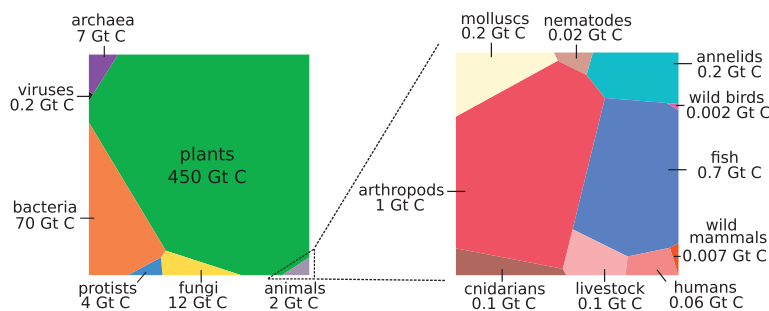
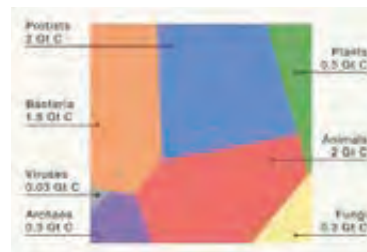
(from Manu Prakash, Stanford Univ.)

Size and complexity: « single cell organisms »



Unicellulars versus Multicellulars

- Unicellular organisms contribute approximately $\frac{2}{3}$ of the total biomass of marine organisms (protists and bacteria) and 10% of land organisms.
- Protists (non animals/plants/fungi, 30% of biomass), are mostly unicellular non-photosynthetic eukaryotes, and photosynthetic algae.
- Biomass of marine and land protists is 3 times the biomass of all land animals!



Y. Bar-On and Ron Milo *Cell* 179:1451

Y Bar-On, Rob Phillips and Ron Milo *PNAS* 115: 6506–6511

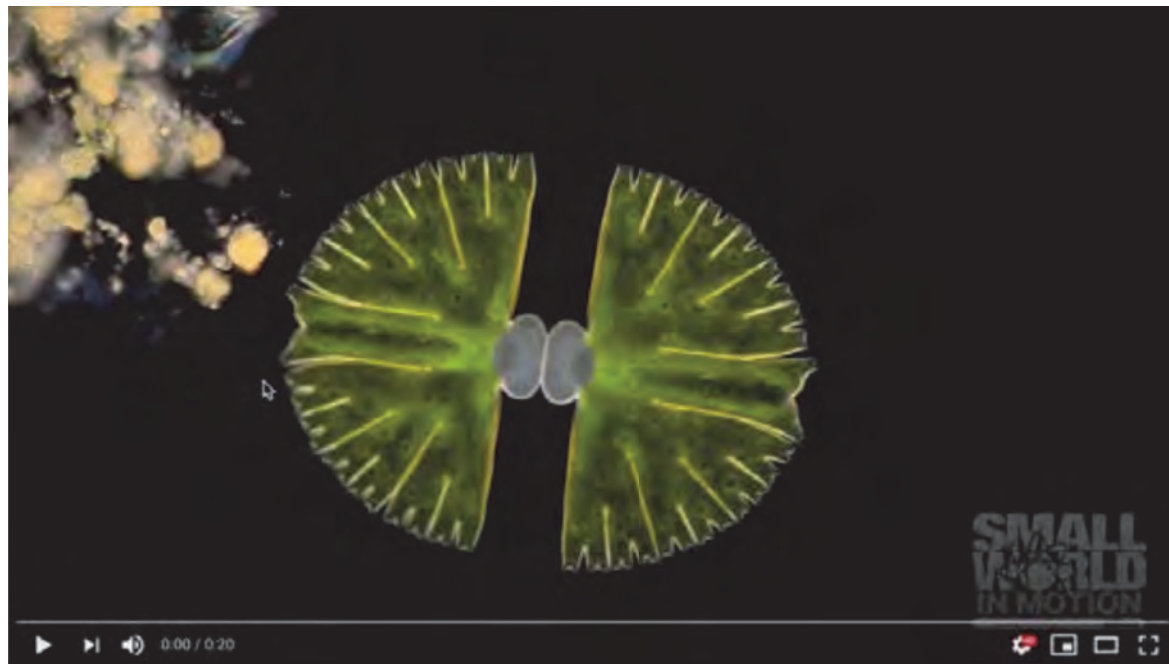
Unicellulars versus Multicellulars

- Complex Organisation (ie. differentiated cell)
- Division
- Regeneration
- Motility
- Behaviour: food uptake, attack/killing
- Cooperative behaviours (in some cases)

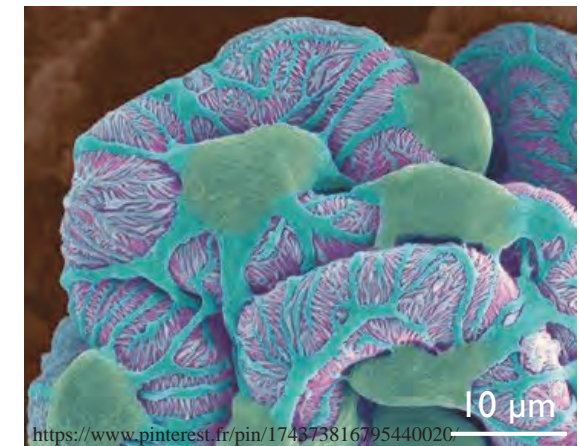
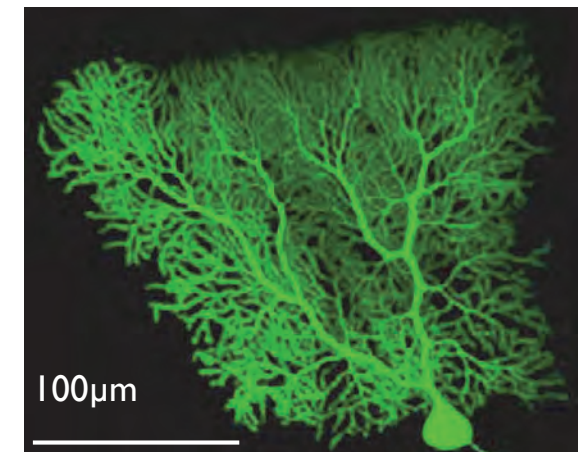


Complexity of unicellulars

- Division of cells in spite of complex organisation
- In multicellular organisms, complex cells (ie. differentiated cells) are non mitotic (the absence of cell division relaxed a constraint on cell complexity and allowed increase in cell size with complex shapes)



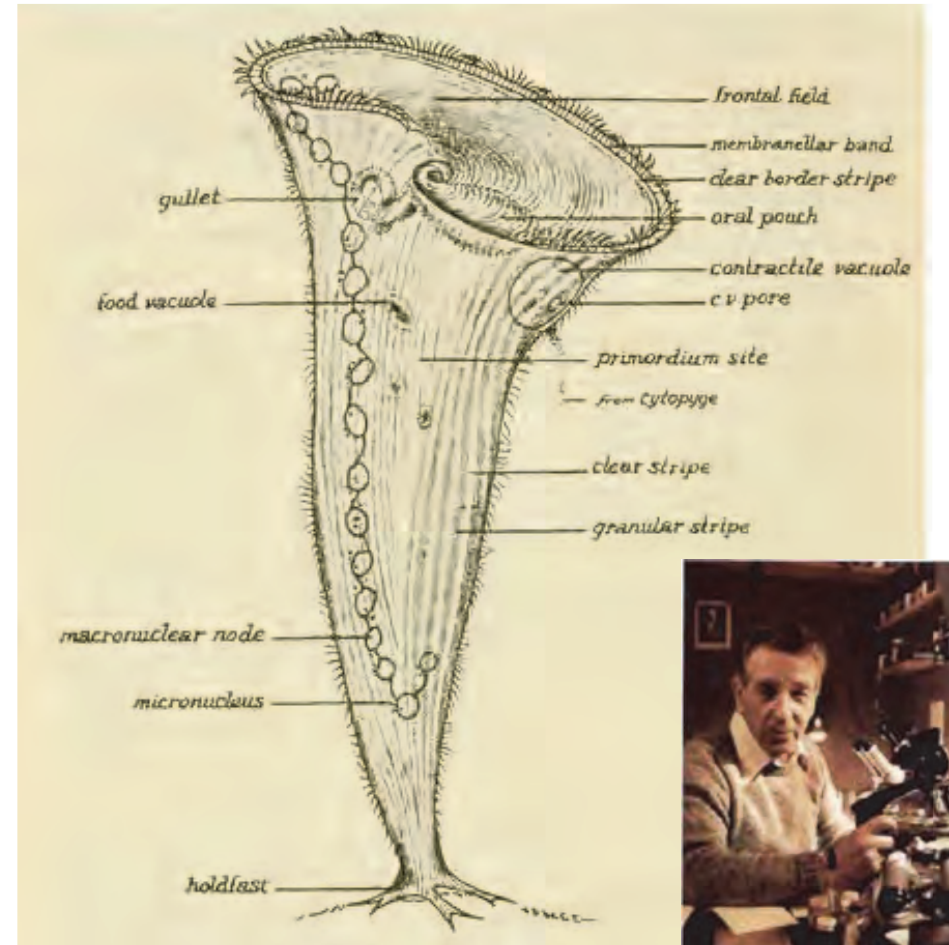
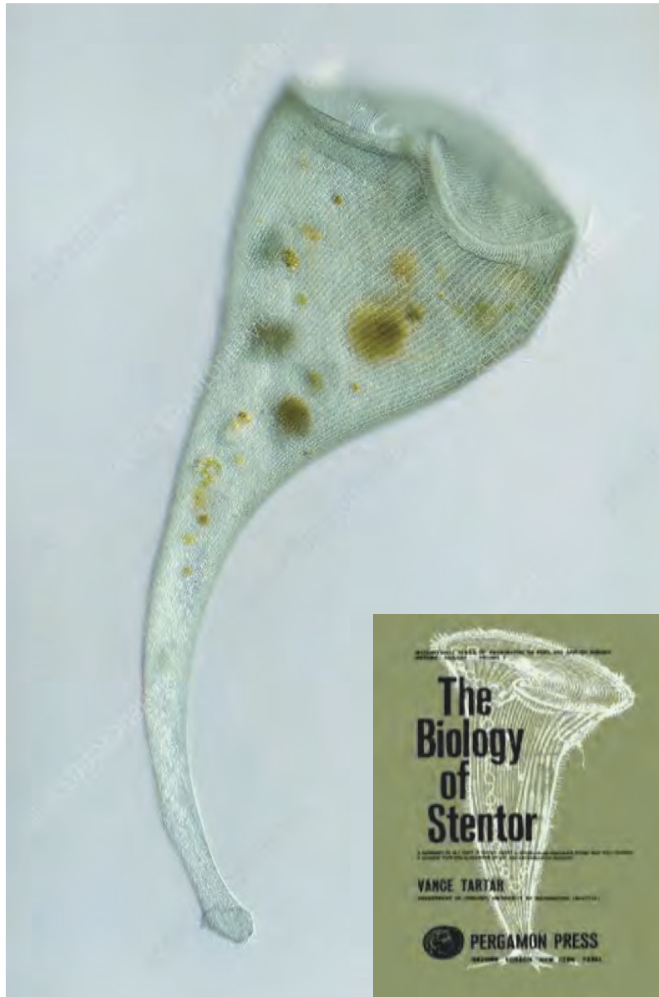
Green alga – *Micrasterias rotata*



Podocyte

Complexity of unicellulars

- *Stentor coeruleus*: Complex organisation of a Ciliate



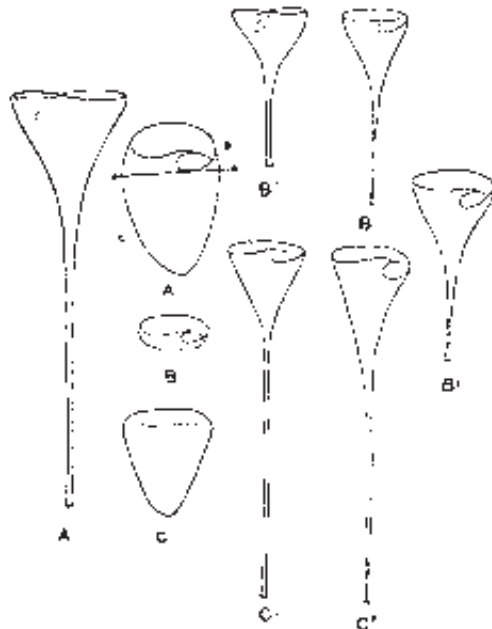
Vance Tartar 1911-1991

Complexity of unicellulars

- Regeneration: *Stentor coeruleus* (Ciliate)

REGENERATION OF PROPORTIONATE STRUCTURES IN STENTOR.

F. H. MORGAN 1901



Thomas H. Morgan
1866-1945

Biological Bulletin, Jun., 1901, Vol. 2, No. 6 (Jun., 1901), pp. 311-328

Reconstitution of Minced *Stentor coeruleus*'

YANKE TARTAR 1960

Department of Zoology, University of Wisconsin, Seattle

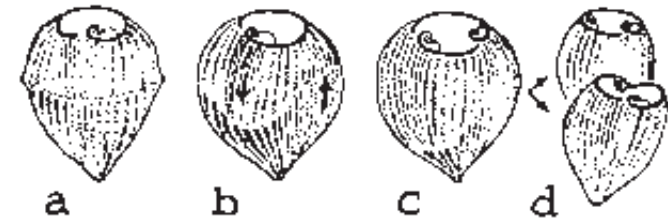
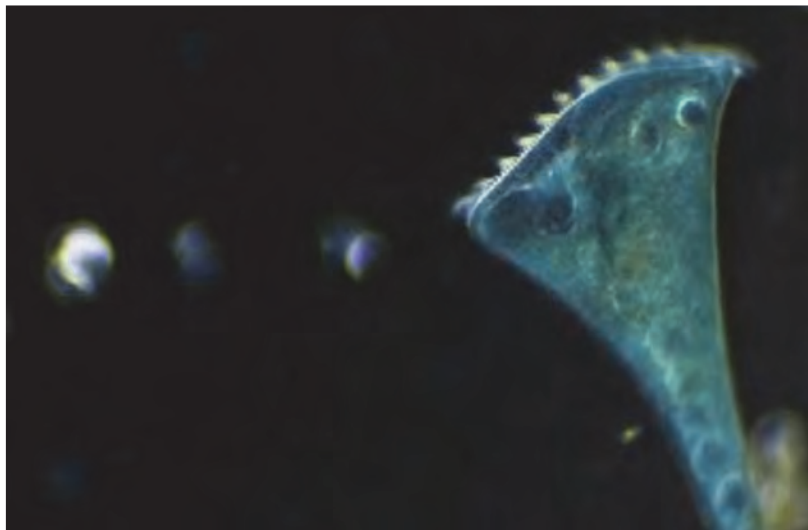
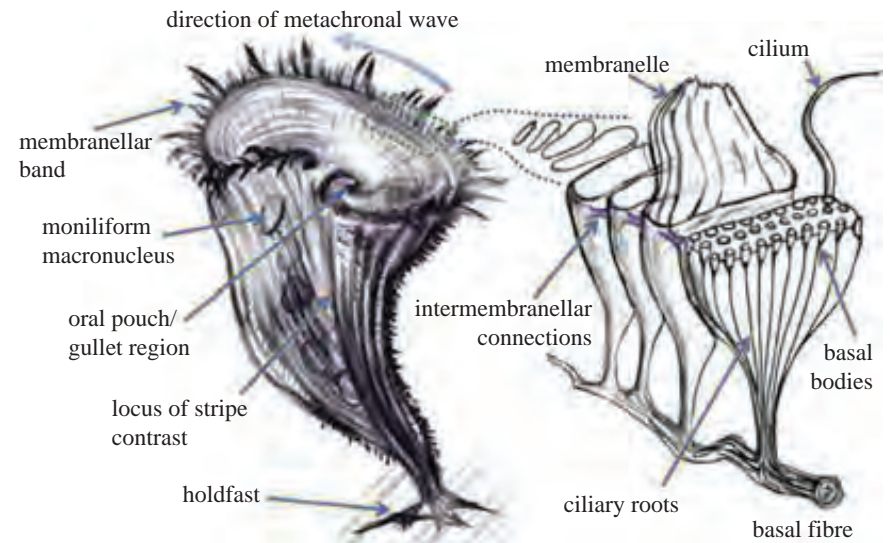


Fig. 6. Conversion of single stentor to doublet. a. Anterior half rotated 180° on posterior. Stripes generally do not match up and join. b. Four-hour zones of each half interpenetrate and re-align with stripe areas of the other, forming two peristaltic waves resulting in reorganization as a doublet (c) which persists, reproducing the doublet biotype (d).

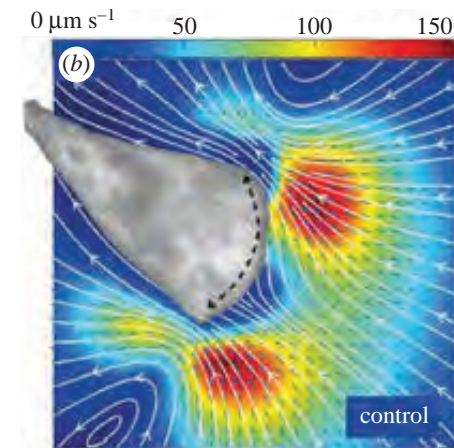
1. Minced stentors cut into about 40 adherent pieces show normal survival and regenerate missing parts as well as reconstituting the normal form.

Complexity of unicellulars

- Behaviour - Predation: *Stentor coeruleus* (Ciliate)



<https://www.youtube.com/watch?v=PZoaKzEXzi8&t=86s>

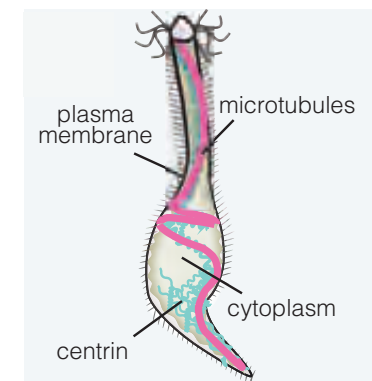
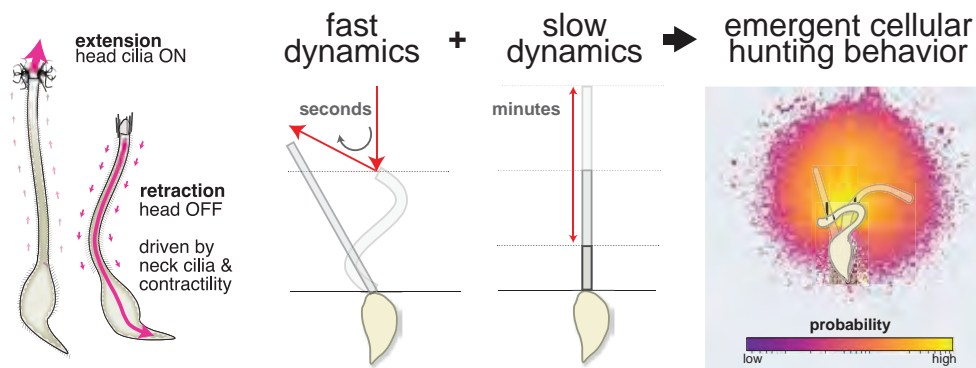
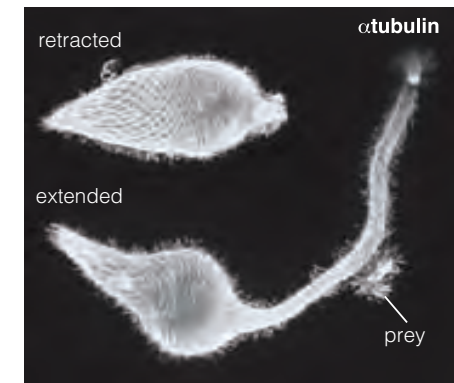
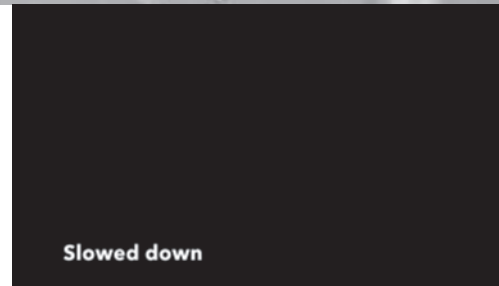
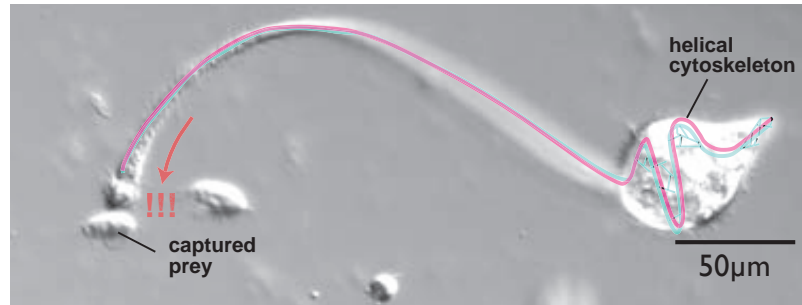


K. Wan et al, and W. Marshall
Philos Trans R Soc Lond B Biol Sci
. 2020 Feb 17;375(1792):20190167.

Complexity of unicellulars

- Behaviour - Predation: *Lacrymaria olor* (Ciliate)

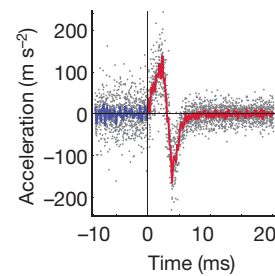
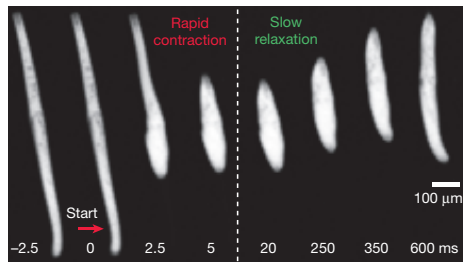
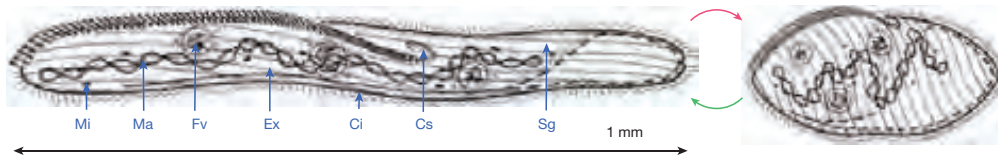
- *Lacrymaria* is a unicellular predator that hunts using extreme morphology dynamics
- Morphology dynamics result in dense stochastic sampling of the local environment
- Behavior emerges from fast and slow response of helical cytoskeleton to cyclic stress



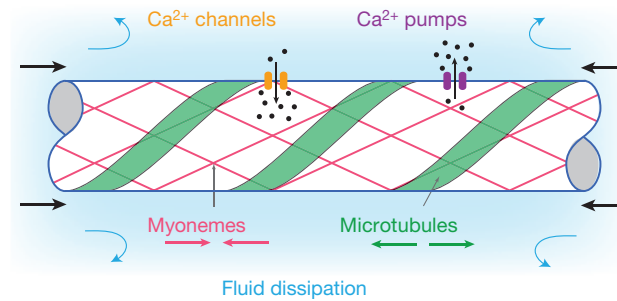
Complexity of unicellulars

- Behaviour - Collective protection: *Spirostomum*

- One of the largest Ciliates (up to 2 mm long) undergoes ultra fast contraction



Spirostomum ambiguum

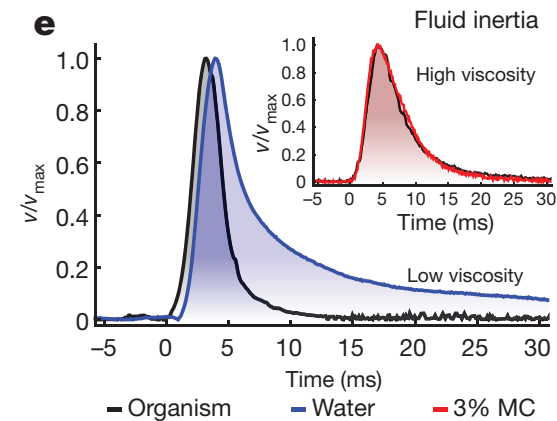
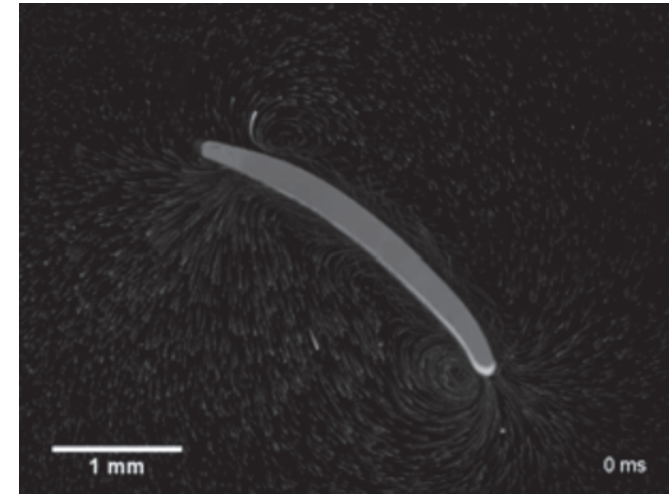
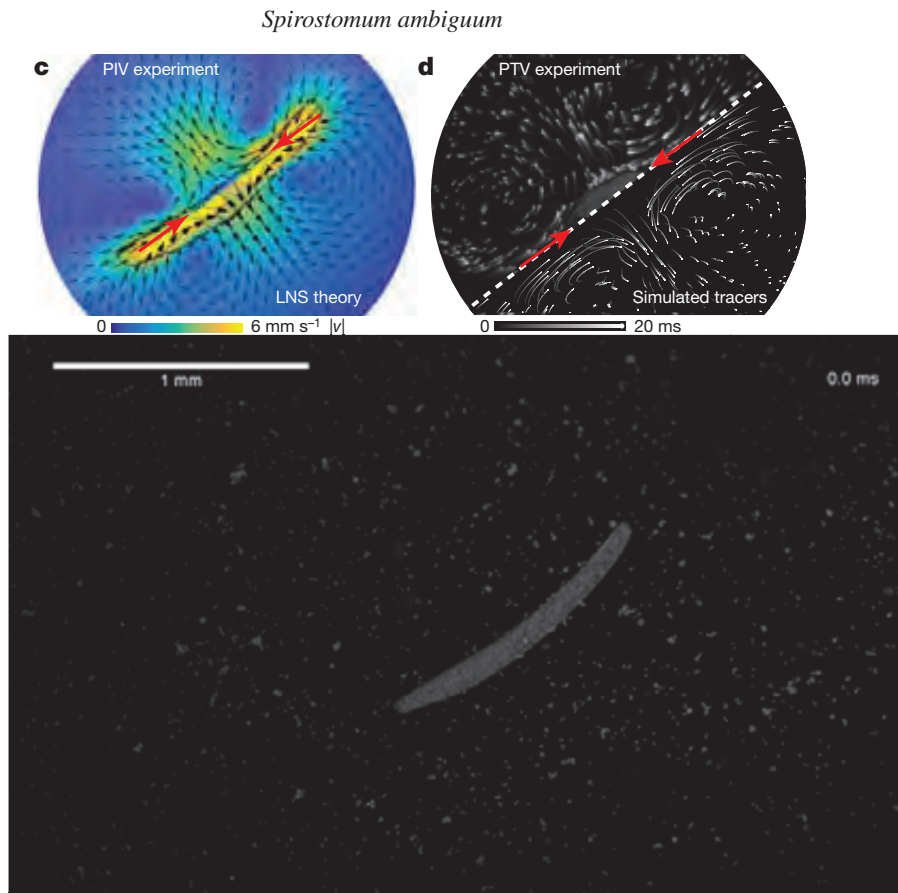


Complexity of unicellulars

- Behaviour - Collective protection: *Spirostomum*

— At rest, metachronal waves of cilia cause fluid flow

— Ultrafast contraction causes inertial flow



A. JTM, Mathijssen et al. and M. Prakash. *Nature*. 2019 Jul;571(7766):560-564.
doi: 10.1038/s41586-019-1387-9

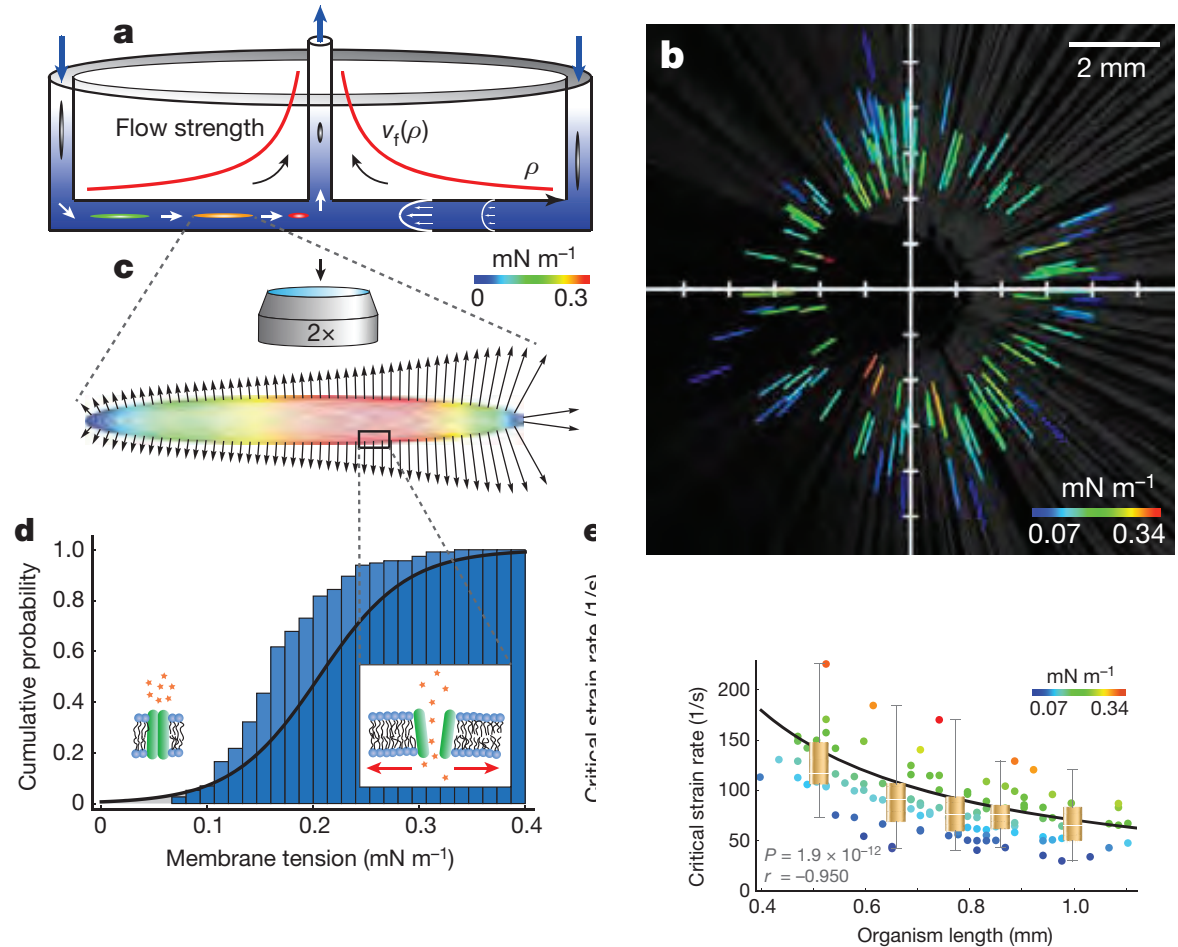
Complexity of unicellulars

- Behaviour - Collective protection: *Spirostomum*

— A gradient of flow causes a gradient of membrane tension at the cell surface

— This elicits opening of gated mechanosensitive calcium channels and cell contraction

— The critical strain rate decreases with cell size: large cells are more mechanosensitive

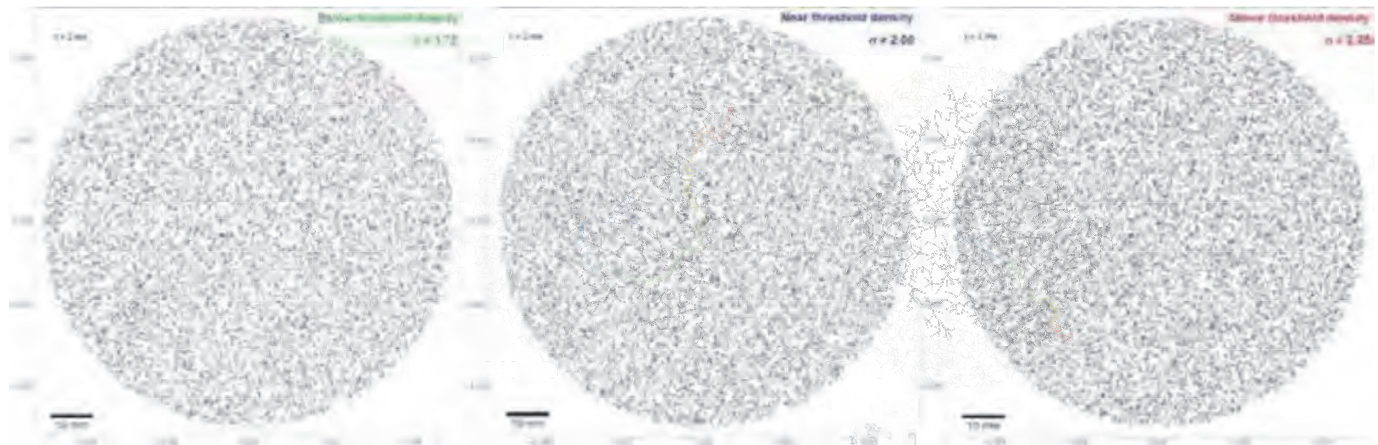
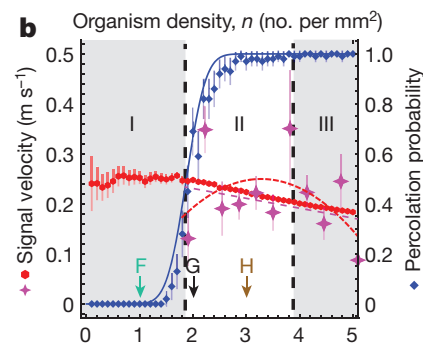
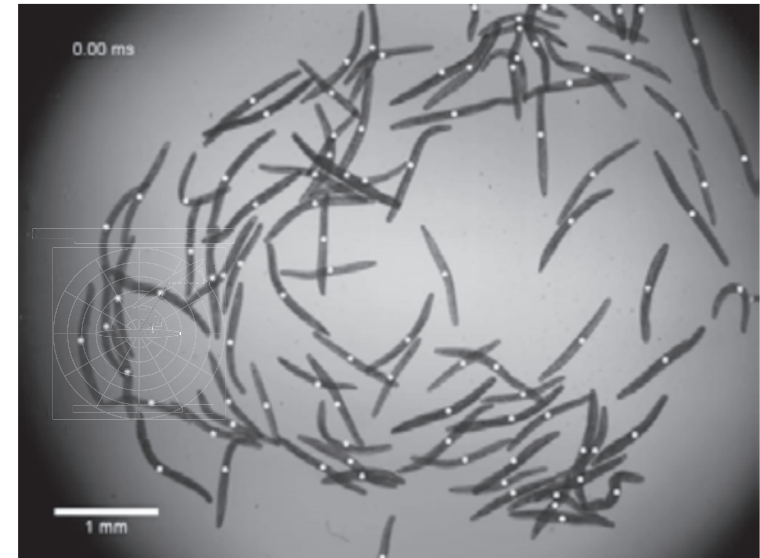
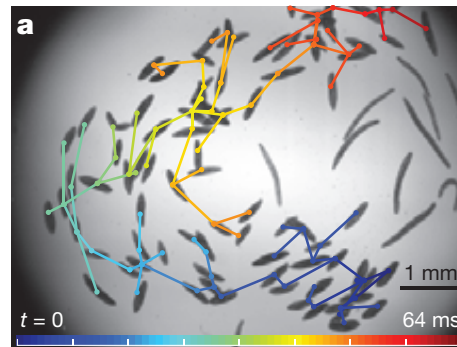


Complexity of unicellulars

- Behaviour - Collective protection: *Spirostomum*

—A hydrodynamic « trigger wave » propagate cell contraction in a population of *Spirostomum*.

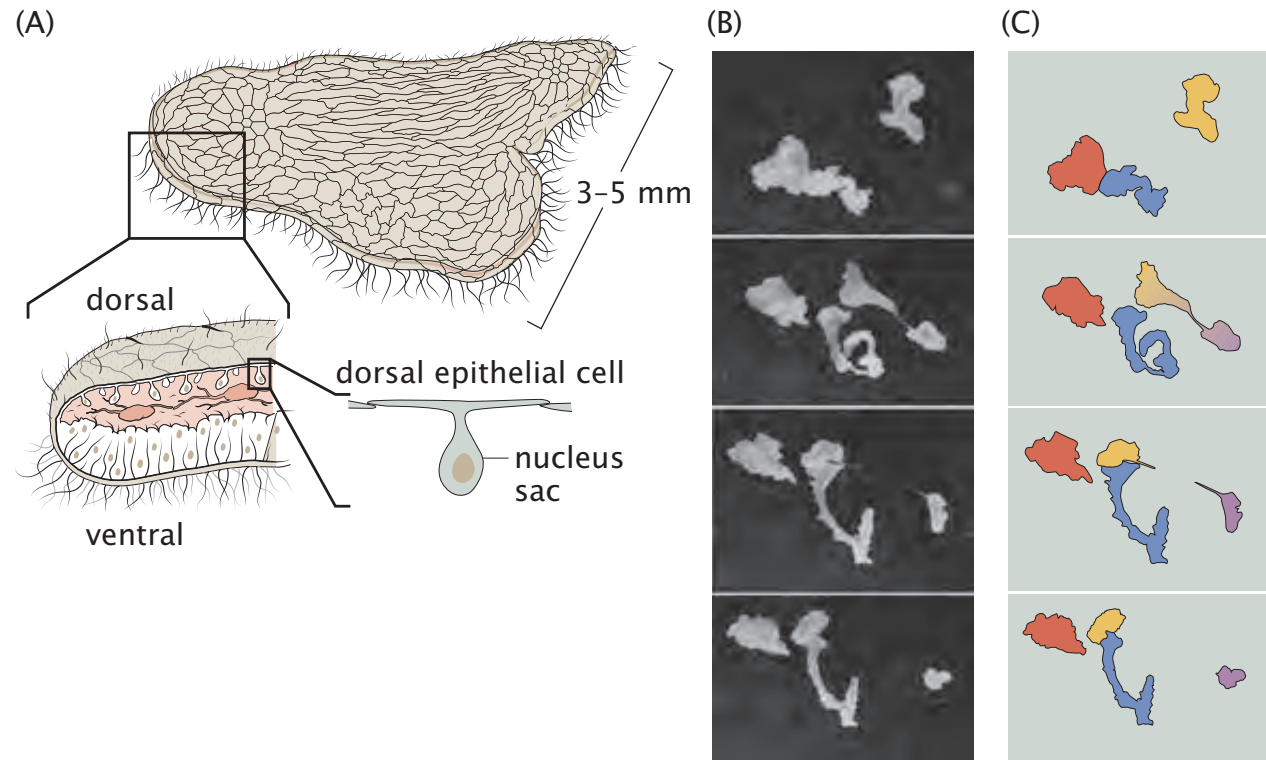
—The percolation probability depends on cell density.



The most simple multicellular

Placozoa: *Trichoplax adhaerans*

- The most simple animal, a marine organism without distinct shape
- Forms a thin sheet, contains 6 cell types only, without muscle and nerve cell.
- *Trichoplax* move and change shape constantly and split.—What is the difference between large single cell and small sheet of cell?

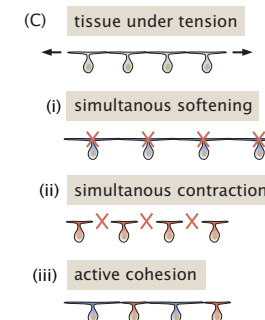
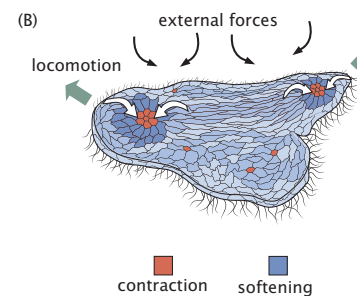
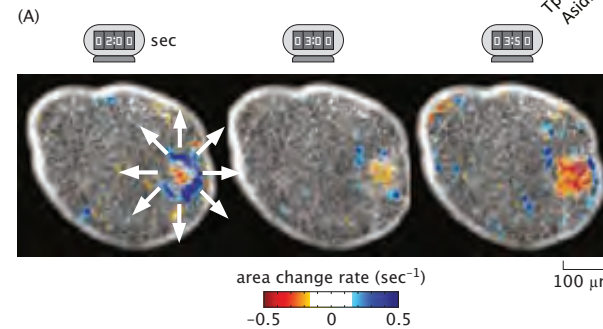
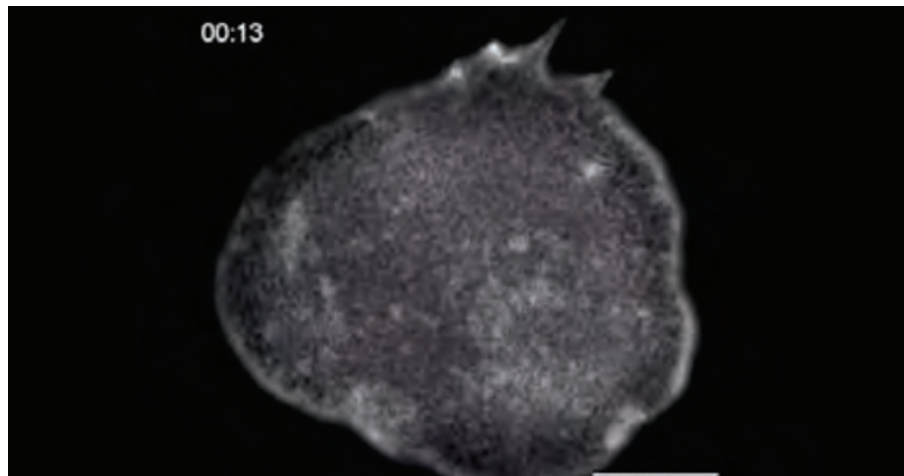
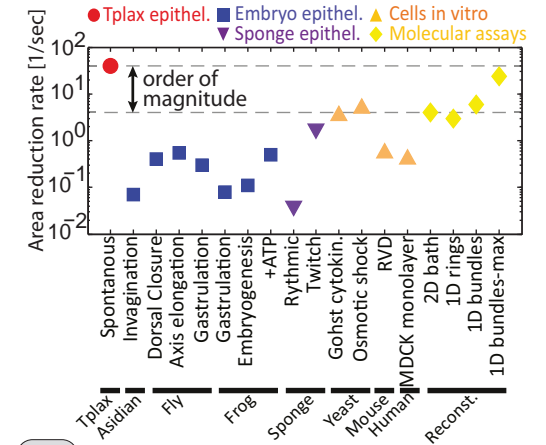
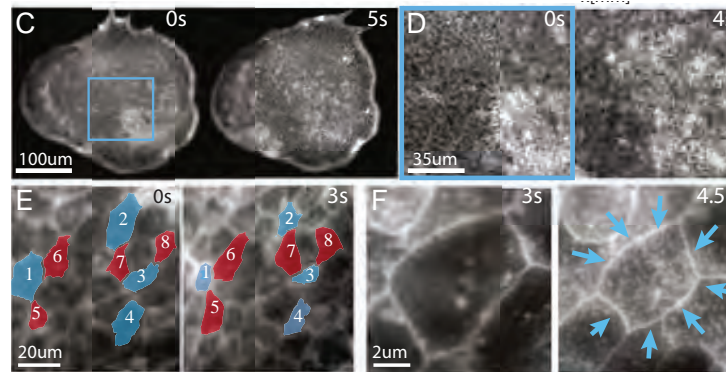


The most simple multicellular

Placozoa: *Trichoplax adhaerans*

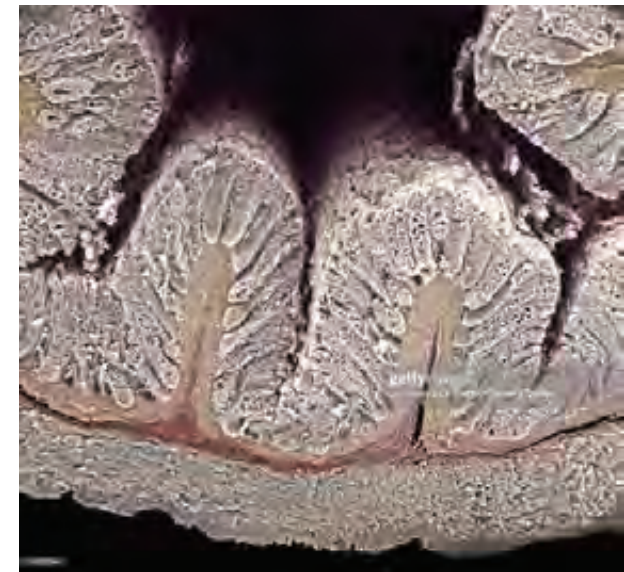
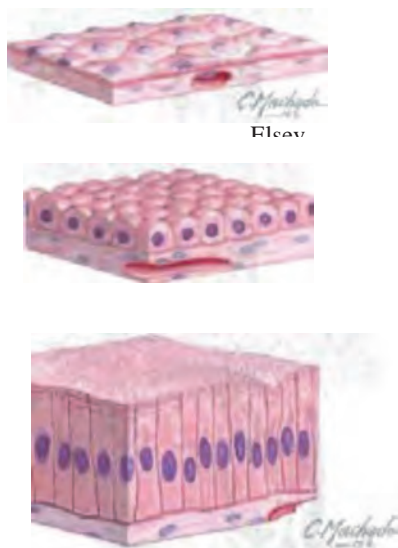
—Ultrafast cell contraction depends on MyosinIII contractility

—Active cohesion mechanism ensures tissue integrity



Size and complexity: comparing cells and tissues

- Metazoan cells during development: simple shapes and small size
 - Are cells simple building blocks with a limited diversity of shapes and size?
 - In animals and plants, most cells exhibit simple morphology.
 - Simple cell shapes underly complex tissue shapes: epithelial cells, mesenchymal cells.
 - **Tissue multicellular complexity requires collective properties of large number of simply shaped cells**
 - **Single cell complexity emerges from self-organising properties of cellular material**



Summary

Complexity tends to increase with size

- Many small cells in large tissue
- Or single large cells

Stems from self-organising properties of living matter:

- Emergence of macroscopic order from homogenous disordered/stochastic lower scale state
- Fluctuations amplified through feedbacks

The cell as a complex organism

The cell in 1665: simple and static

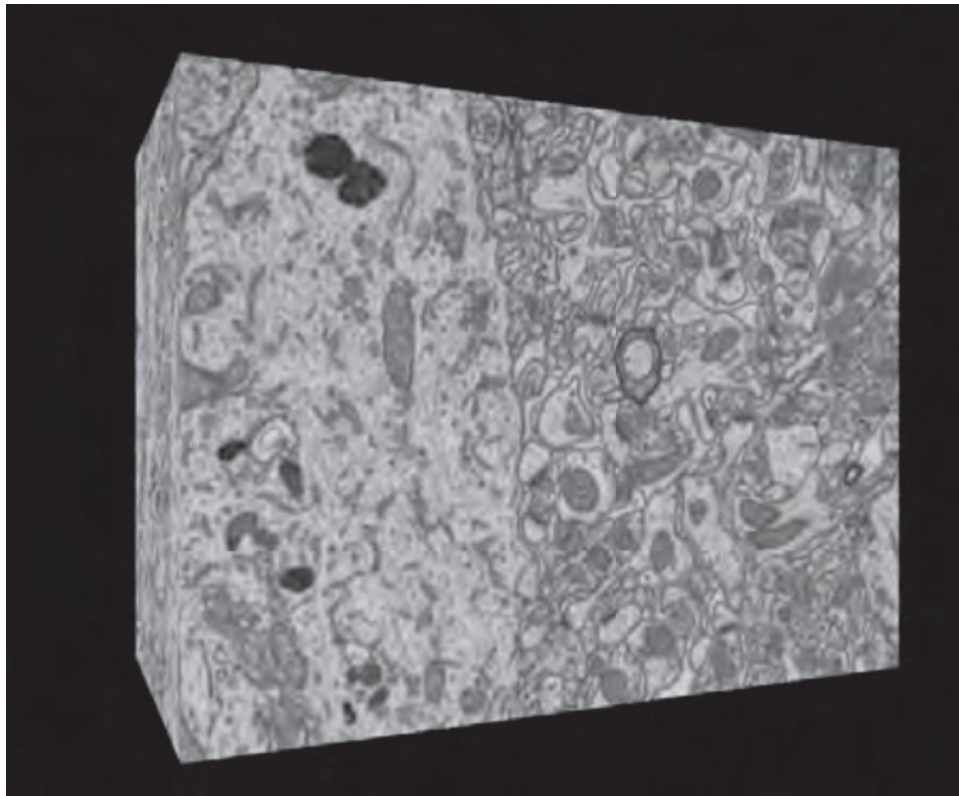


Robert Hooke
(1635-1703)

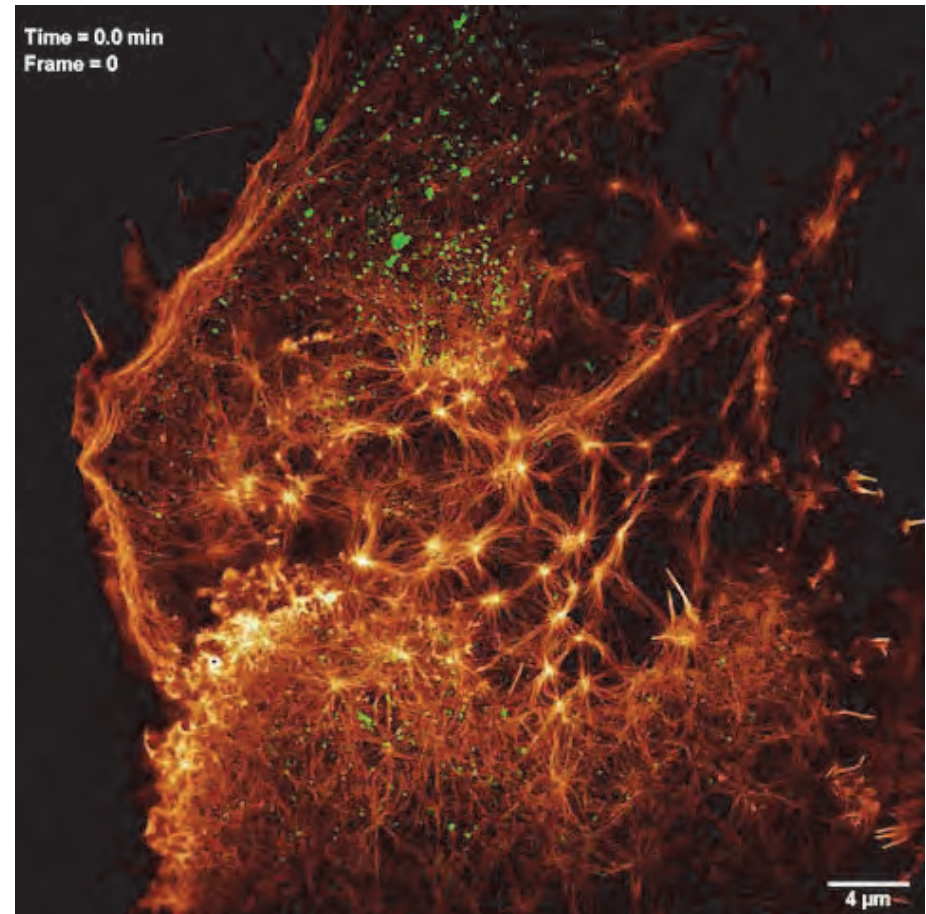


Micrographia (1665)

The cell in 2020: complex and dynamic



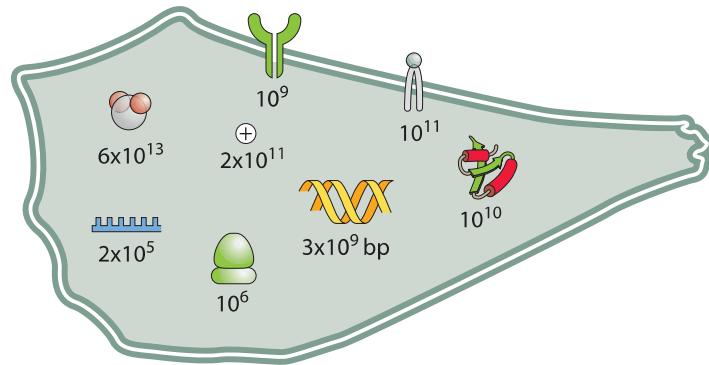
T. Falk et al. *Nature Methods* volume 16, 67–70 (2019)



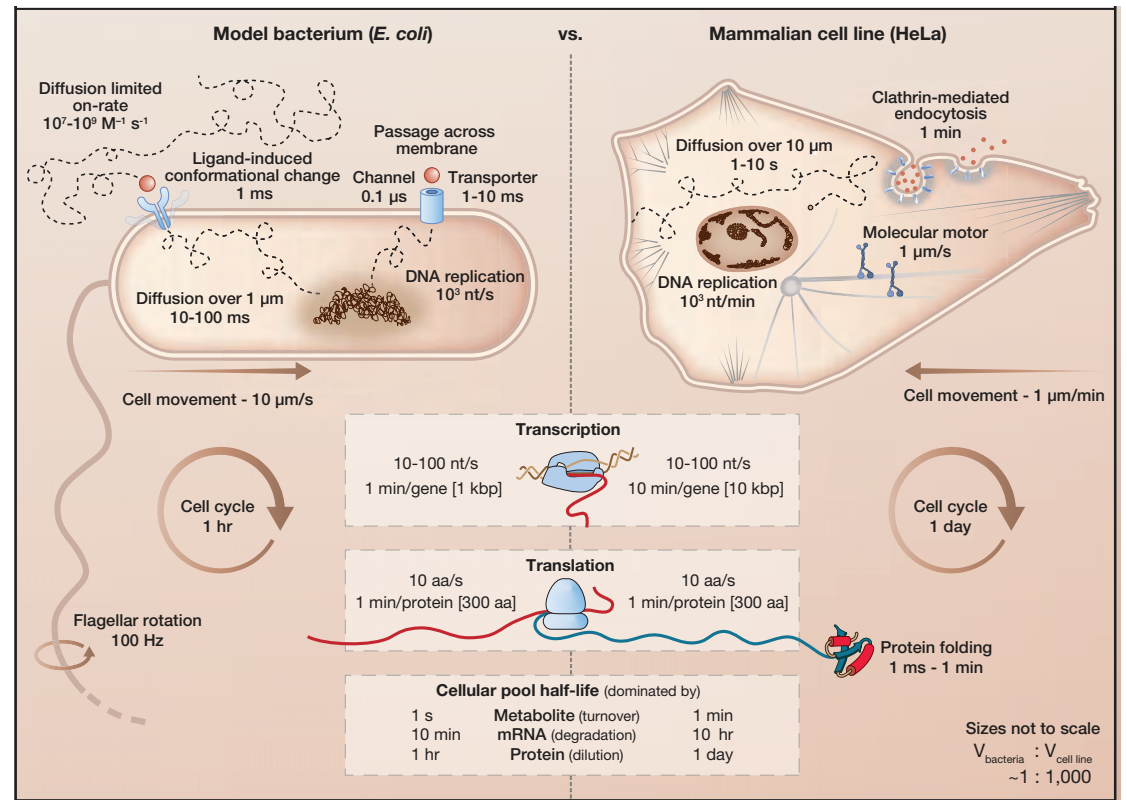
Dong Li et al. and E. Betzig; *Science* 28 Aug 2015:
Vol. 349, Issue 6251, aab3500
DOI: 10.1126/science.aab3500

The cell in 2020: numbers!

(C) mammalian cell (specifically, HeLa: $V \approx 3000 \mu\text{m}^3$; $L \approx 20 \mu\text{m}$; $\tau \approx 1$ day)



H. sapiens (HeLa cell line)

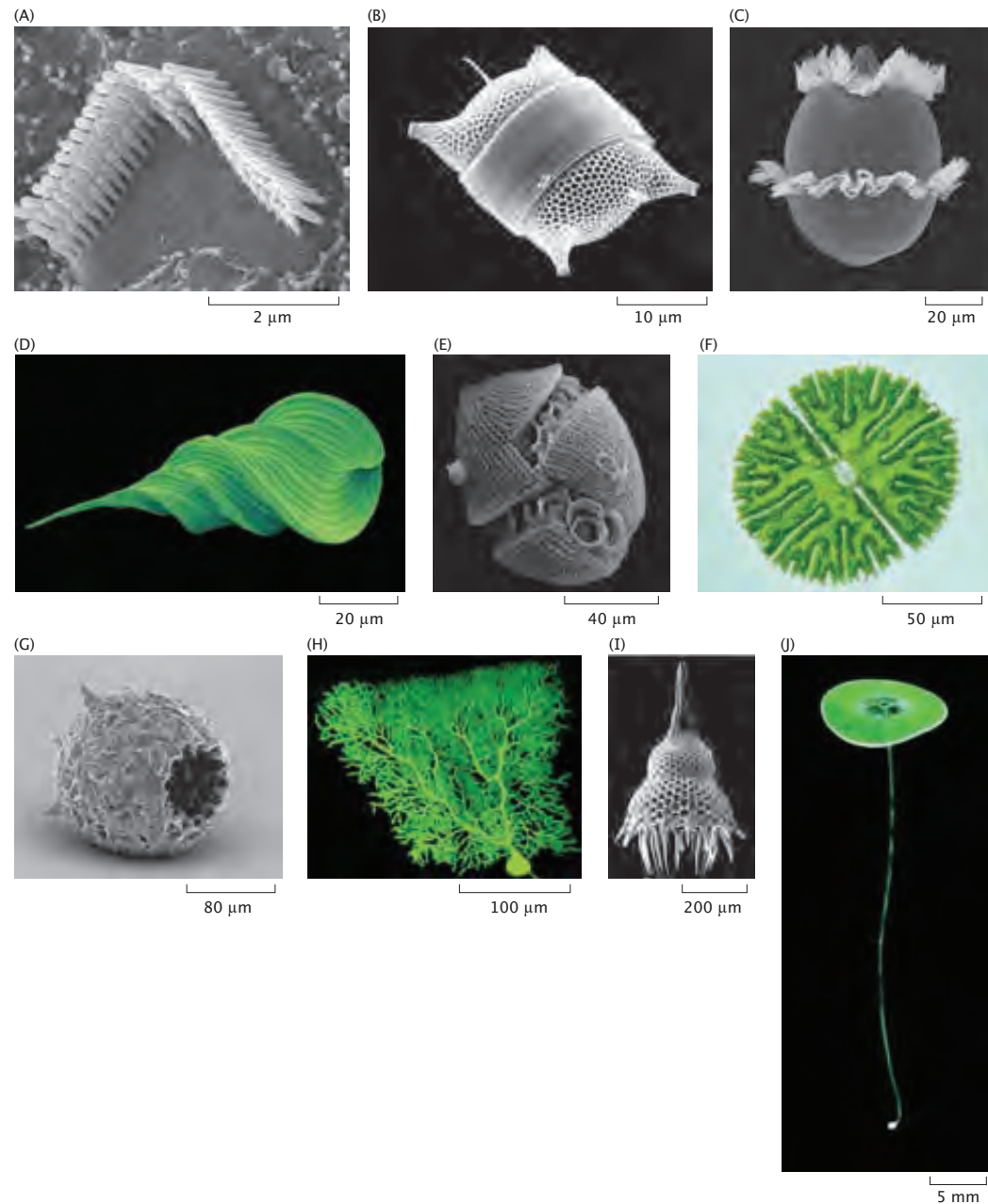


Maya Shamir,¹ Yinon Bar-On,¹ Rob Phillips,² and Ron Milo¹

Cell 164, 2016 DOI <http://dx.doi.org/10.1016/j.cell.2016.02.058>

The shape space of single cells

- Extensive variety of shapes
- Extensive variety of size

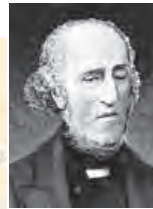
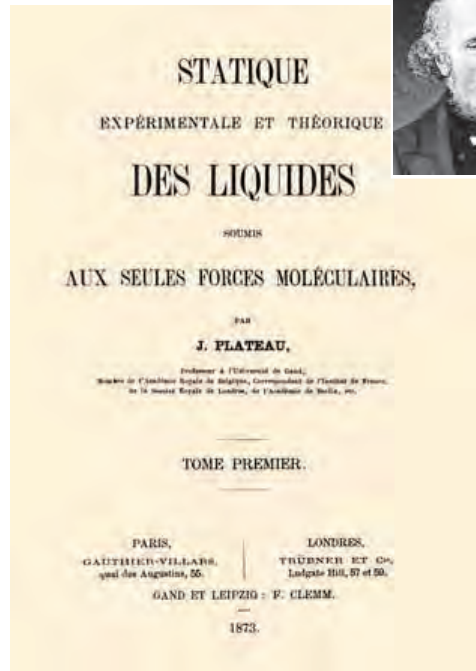


Equilibrium cell shapes

- surface tension: minimal surfaces

$$G_{\text{tot}} = \gamma \cdot A$$

(A)



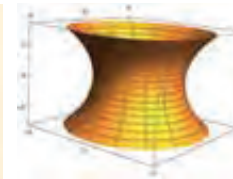
(B)



(C)

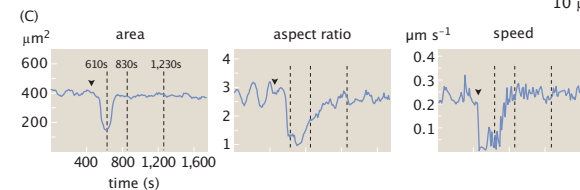
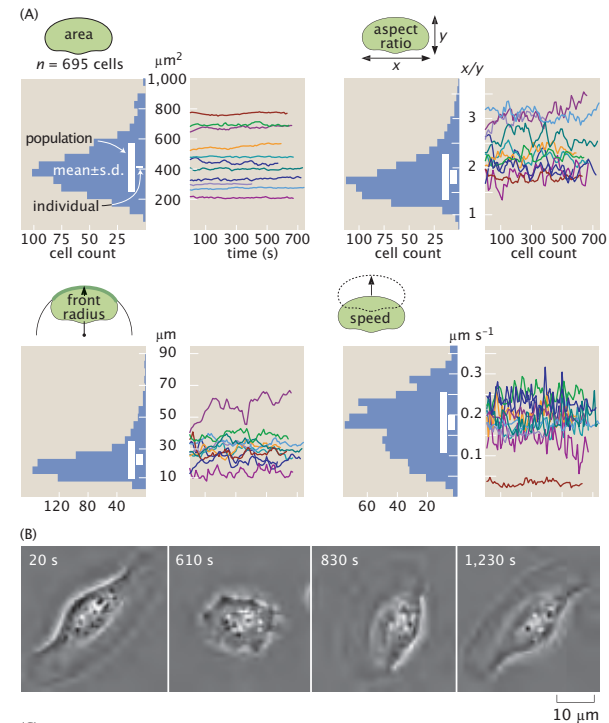
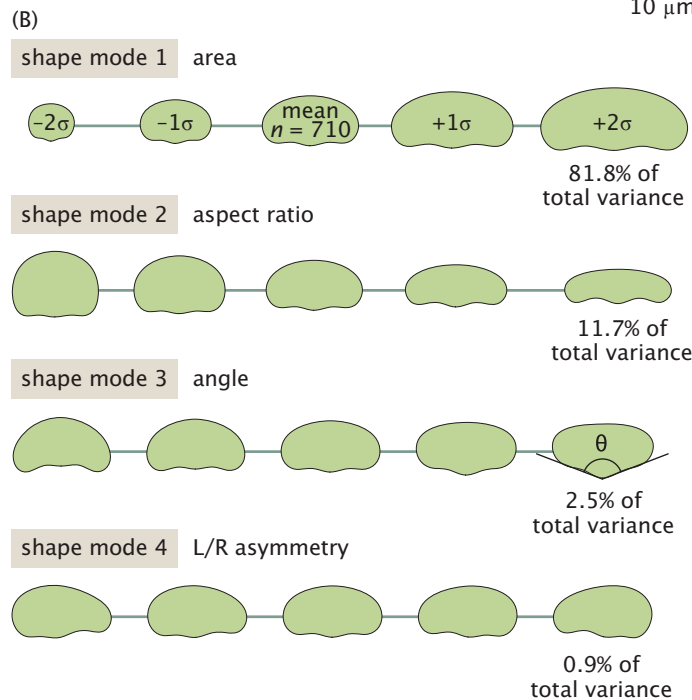
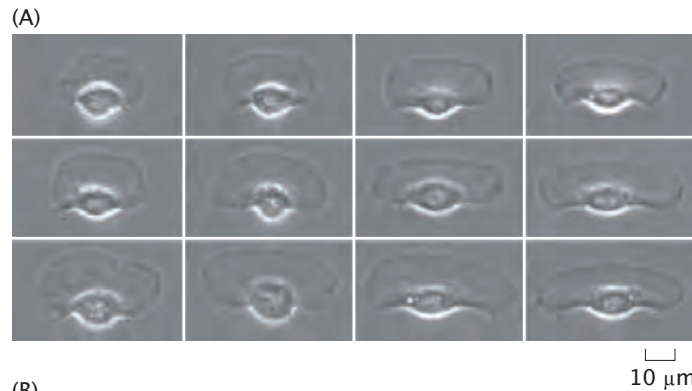


(D)



Cell shape as a dynamical steady-state

- Cell shape is dynamically but not genetically encoded. It is self-organised



The cell as a complex organism

4 big problems

- Cell internal heterogeneity: compartmentation of activities
- Cell polarity: vectorial organisation
- Cell motility
- Cell size: 2020

Cell size – volume

Statement of the problem:

- **Cell size varies between cell types** in Animals but **within a given cell type there is very little size variation** (ex. epithelial cell). So cells control their volume tightly.
—Why is cell size regulated?
- **Cell size is tightly coupled to cell function**, for example, neuron, oocyte, red blood cells, Ciliates etc.
- **Cell size is physically constrained**, e.g.:
 - diffusion of metabolites limits cell size.
 - surface to volume ratio for exchange with environment
 - diffusion of signalling molecules limits communication within cells (unless other transport mechanisms operate such as motor driven or by trigger waves)
 - energetically: synthesis of ribosomes and translational capacity limits cell growth. Given maximal rate of rRNA transcription, there is a limit to cell growth, unless polyploidy or multinucleation (ex. muscle cells, ciliates etc).
- **Cell size is governed by protein synthesis, osmotic flow and cell cycle** which operate at different time scales: how is this integrated?

Cell size – scaling

Statement of the problem:

- Cell size is tightly regulated but varies strongly during embryonic cleavage (by a factor of 2^N for N divisions)
- Cells grow 2-fold before they divide or may grow while they increase their ploidy
- As cells change their volume do internal organelles scale? What are the mechanisms of scaling?
- When cells display symmetric structures (eg. flagella or cilia) how is the size of these structures controlled



Thomas LECUIT

Taille, croissance et organisation cellulaires

Cours les mardis de 10h à 11h30
Amphithéâtre Guillaume Budé

Cours :

- 17 novembre 2020** Du tissu à la cellule : taille et complexité
- 24 novembre 2020** Volume cellulaire : déterminants physico-chimiques et régulation
- 01^{er} décembre 2020** Croissance et division cellulaires : la cellule mesure-t-elle ses dimensions ?
- 08 décembre 2020** Lois de proportions cellulaires

Colloque :

Contraintes et plasticité au cours du développement et de l'évolution
(avec Denis Duboule, chaire Évolution des génomes et développement)

Les 03 & 04 juin 2021
Amphithéâtre Maurice Halbwachs