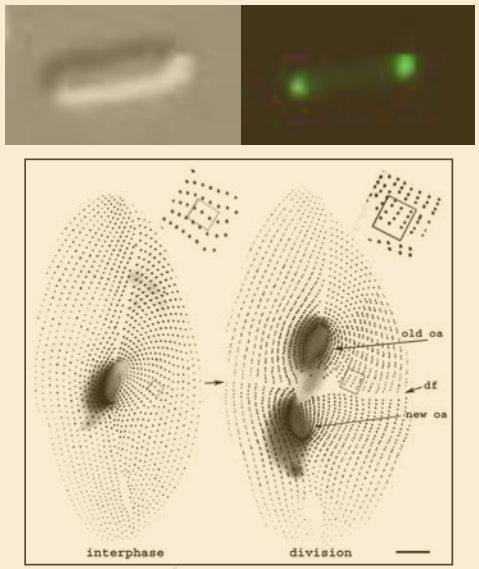
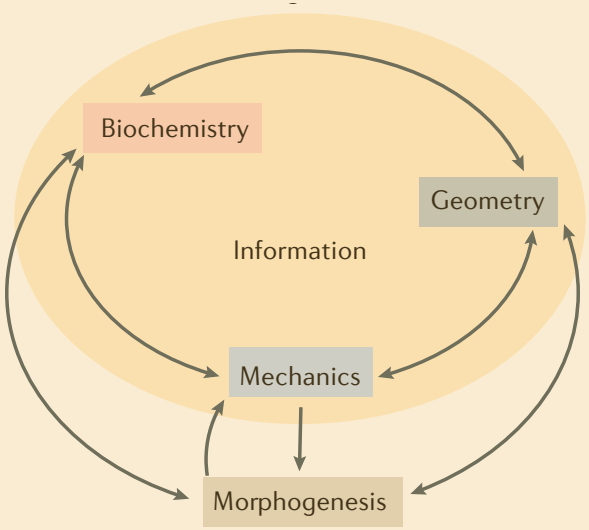
What is biological information?





Course 5: Structural and geometric information

Thomas Lecuit

chaire: Dynamiques du vivant

COLLÈGE DE FRANCE
1530

Plan

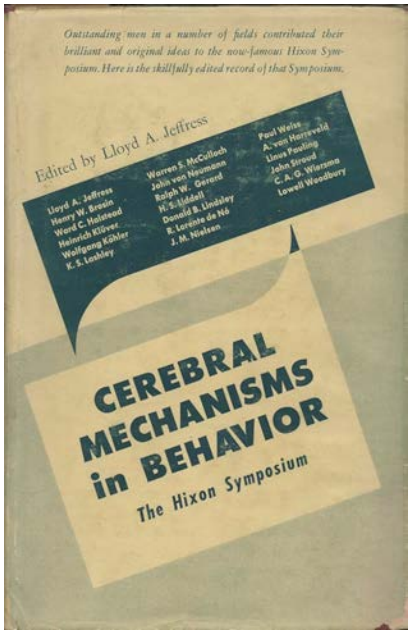
- Structural cellular heredity and cellular self-organisation
- Geometric information in cells:
  - decoding cell shape via signalling
  - decoding cell shape via mechanics
- Geometric information in development and morphogenesis
  - Geometric guidance
  - Geometric feedback

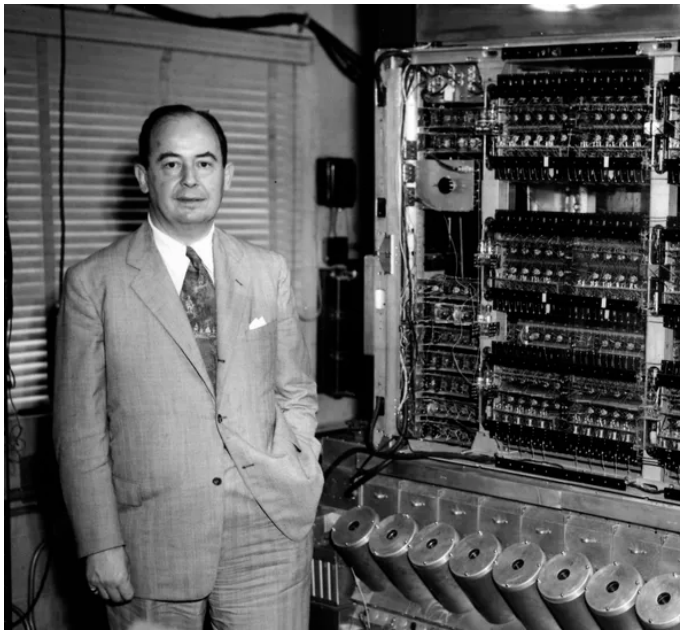
Self-reproducing automata

The General and Logical Theory of Automata

John von Neumann (1903-1957)

conference, 1948. publication,1951





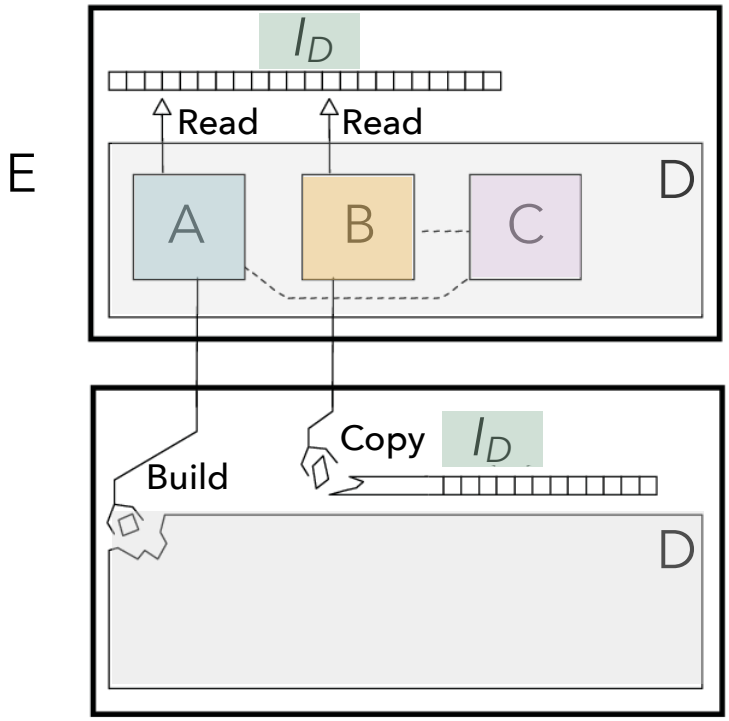
- Established a link between the ability of cells and organisms to self-reproduce and the theory of universal computation in automata/machines developed by Turing (1936).

- *According to this view, Life is intimately linked to computation and information processing*

Von Neumann, J., 1951. In: Jeffress, L.A. (Ed.), *Cerebral Mechanisms of Behavior: The Hixon Symposium*. John Wiley and Sons, New York, pp. 1–41.

Self-reproducing automata - What is the set of instructions I_D

- Requirements (to avoid degenerate complexity):
  - Copying the machine (A)
  - Copying the instructions to make the machine (B)



(a) **Automaton A, which when furnished the description of any other automaton** in terms of appropriate functions, **will construct that entity**.

A description in this sense will be called an instruction and denoted by a letter *I*

(b) **Automaton B, which can make a copy of any instruction *I***

that is furnished to it.

This automaton is nothing more subtle than a **« reproducer »**. (c)

(c) Combine the automata A and B with each other, and **with a control mechanism C.**

C will first cause A to construct the automaton which is described by this instruction *I*. Next C will cause B to copy the instruction *I*, and insert the copy into the automaton, which has just been constructed by A. Finally, C will separate this construction from the system A + B + C.

(d) denote D = A + B + C. D requires an instruction *I*.

Form an instruction I_D, which describes this automaton D, and insert to into A within D. Call the aggregate which now results E.

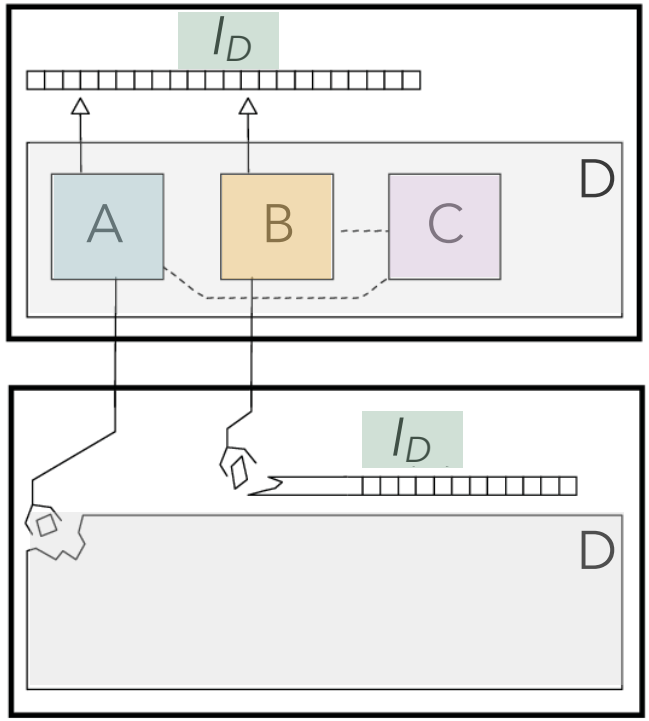
E is self-reproductive

$$E = D + I_D = A + I_D + B + C$$

Self-reproducing automata - What is the set of instructions in I_D?

Is the heritable information strictly in the DNA?

Is the information complete in the genome and its chemical derivatives?



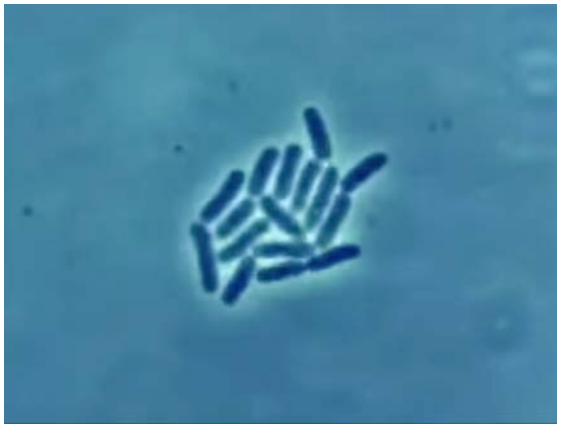
- *Underlying hypotheses:*
- I_D encodes A, B and C.
- A, as it builds D, the cell, provides building blocks that, with an energy source, self-assemble or self-organise into a cell (membrane, organelles etc).

- Cell organisation is fully transmitted via the synthesis of chemical components of a cell and given self-organisation property.

Propagation and transmission of organisation at cell division

- First sign of life on earth ~ 3.48B years ago

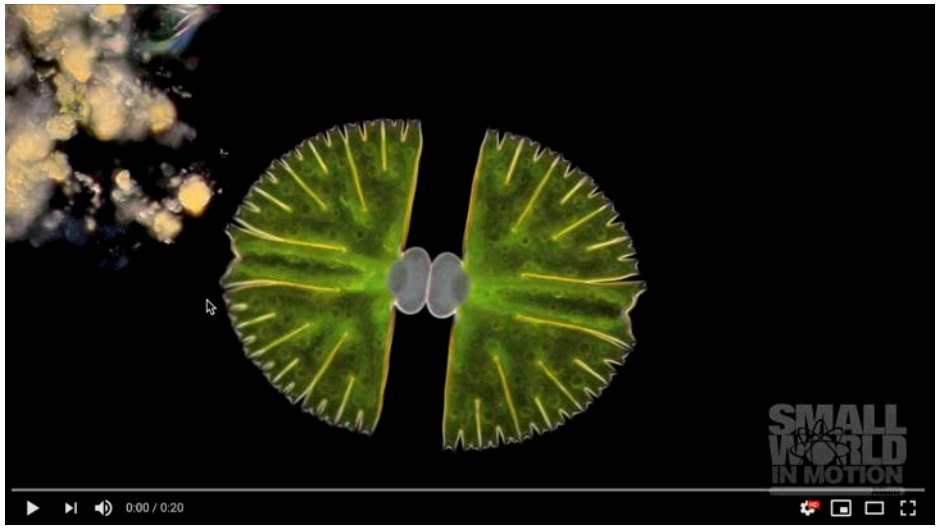
- For billions of years, bacteria propagated by cell division



Doubling time ~60 min

- How is cellular organisation transmitted from one cell to its descendants?

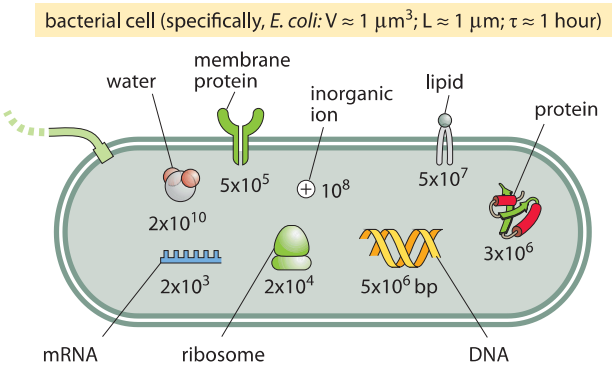
Propagation and transmission of organisation at cell division

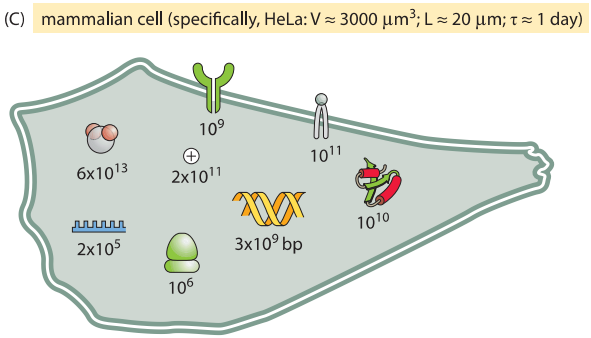


Green alga – *Micrasterias rotata*

Are cells purely self organised? – A thought experiment…

- What happens if a cell loses its organisation yet keeps the complete set of active molecules?





- Grind a cell to *complete* chemical homogeneity
- Keep high supply of energy (ATP), keep DNA.
- Chemical activity is preserved and complete

- Cells do not re-assemble/self-organise from the evolved chemical components
- The chemical information in a cell is not complete to ensure the propagation of organisation
- Cells need an organisation to propagate organisation

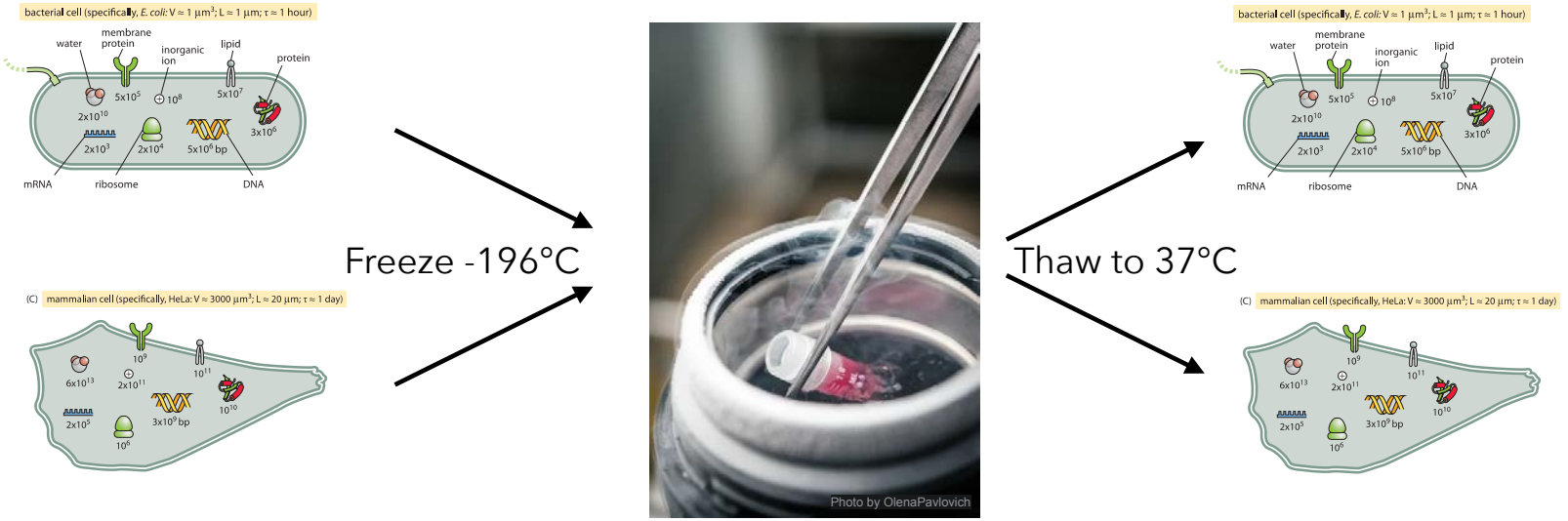
Cell Biology by the numbers. Ron Milo, Rob Phillips, 2012

Are cells purely self organised? – A thought experiment…

- *A contrario* what happens if molecular activity is stopped but cell organisation is preserved?

– Cell can lose completely molecular dynamics and activity, but they restart **if cell organisation is preserved**

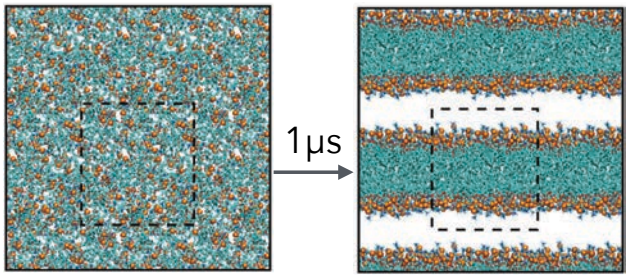
- Cells need an organisation to propagate organisation
- Cell organisation does not fully self-organise



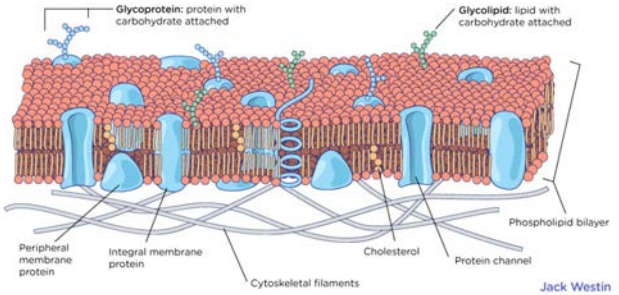
« Reproduction » of biological membranes

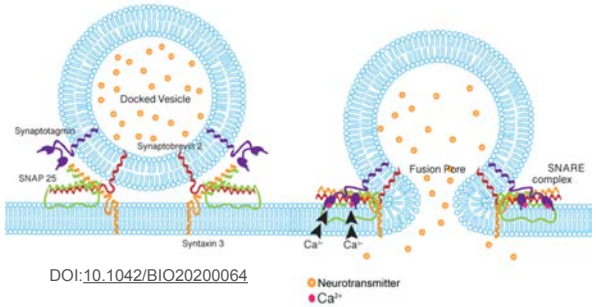
- Membranes have 50% lipids (5. $10^6/\mu m^2$), 50% proteins.
- Lipid bilayers can self-assemble in vitro.

- **But in vivo, membranes do not self-assemble.**
- **Membranes grow by insertion of lipids, fusion of membranes etc.**
- **Moreover, membranes have specific protein compositions, topologies and orientations characteristic of different membrane systems, or membrane organelles.**



Skjevik et al *Phys.Chem.* 18,10573–10584 (2016)

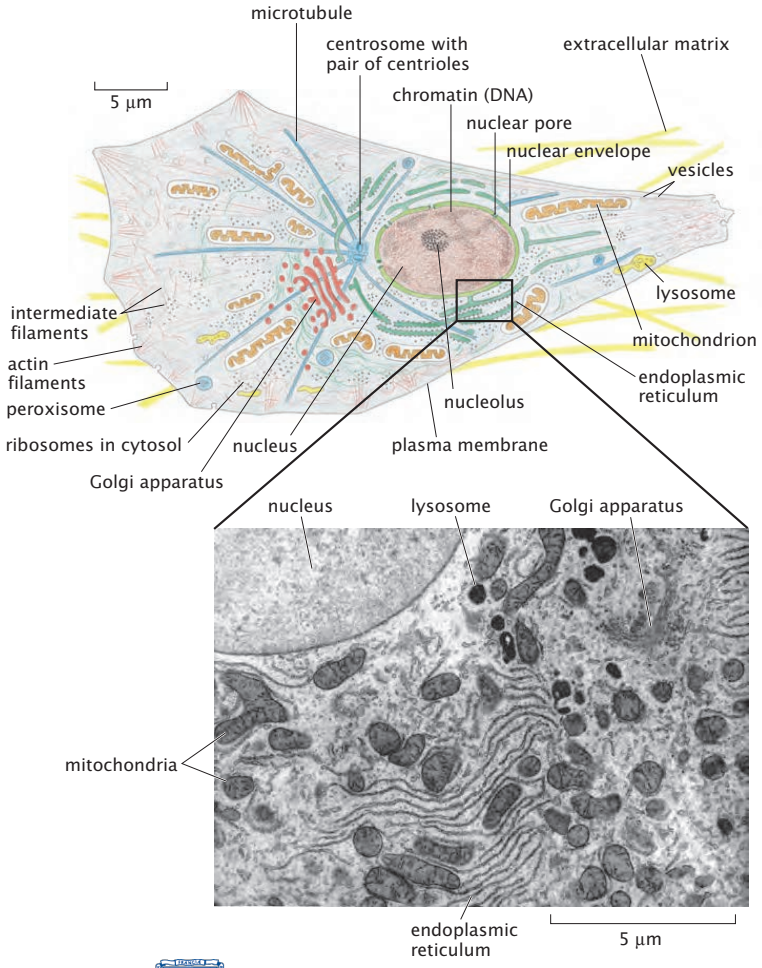




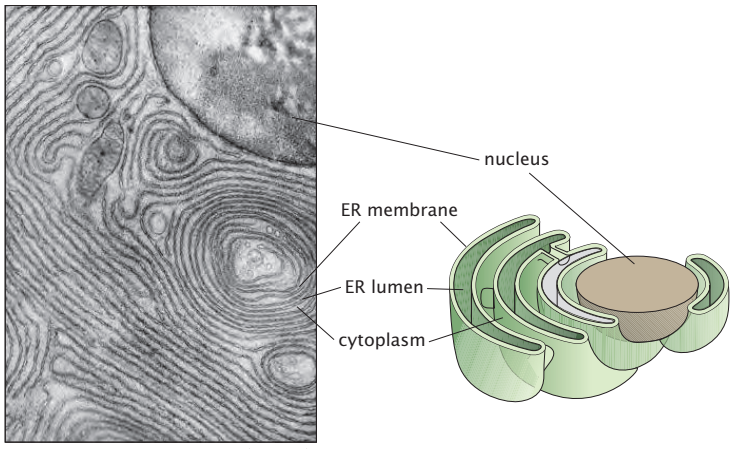
DOI:10.1042/BIO20200064

Membrane fusion: vesicle docking and fusing

« Reproduction » of membranes - Organelle inheritance



membrane type	percentage of total cell membrane	
	liver hepatocyte	pancreatic exocrine cell
plasma	2	5
rough ER	35	60
smooth ER	16	<1
Golgi apparatus	7	10
mitochondria outer	7	4
mitochondria inner	32	17
nucleus inner	0.2	0.7
secretory vesicle	-	3
lysosome	0.4	-
peroxisome	0.4	-
endosome	0.4	-



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

Membrane inheritance

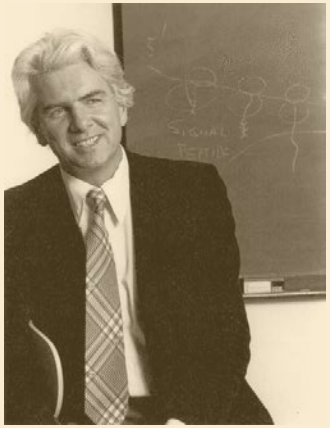
Protein insertion in lipid membranes and mechanisms of specific addressing

Intracellular protein topogenesis

GÜNTER BLOBEL

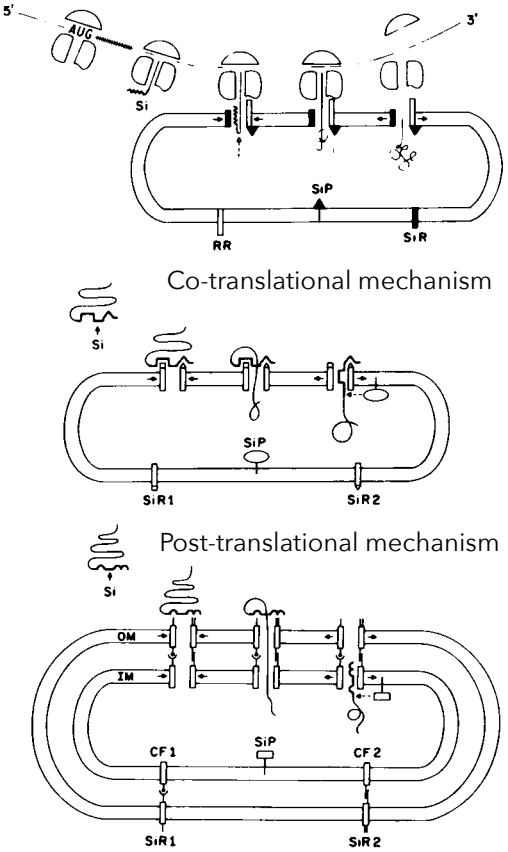
Laboratory of Cell Biology, The Rockefeller University, New York, New York 10021

- Protein translocation mechanisms in membranes.
- Integral membrane proteins (IMPs) require internal signal sequences and selective translocation mechanisms.
- Translocator proteins on receiving membrane
- Since IMPs need a target IMP to recognise where to be inserted, specific membranes cannot self-organise and must arise from a pre-existing membranes.
- A « genetic membrane » propagates its own information content: Membrane inheritance.



Günter Blobel (1936-2018)
Nobel 1999

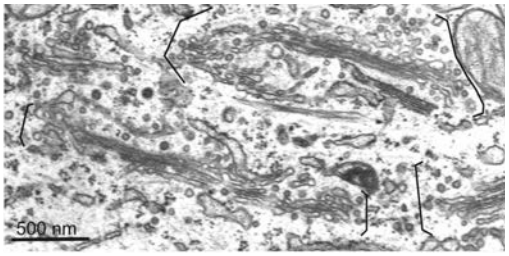
Thus, most IMPs can be integrated directly only into translocation-competent membranes. Because the translocators themselves are likely to consist of IMPs (see Fig. 1) that require translocation for their integration into the membrane, it follows that Virchow's paradigm on the ontogeny of cells could be extended to membranes and paraphrased to *omnis membrana e membrana*.



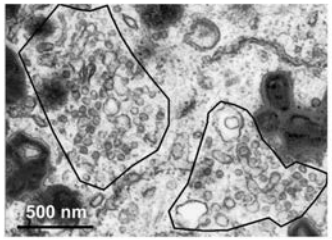
G. Blobel. *PNAS*. 77: 1496-1500 (1980)

Organelle inheritance

- **How are organelles transmitted in daughter cells during mitosis?**
- Disassembly into vesicles and tubules and reassembly after mitosis
- **Random partitioning vs Ordered partitioning**

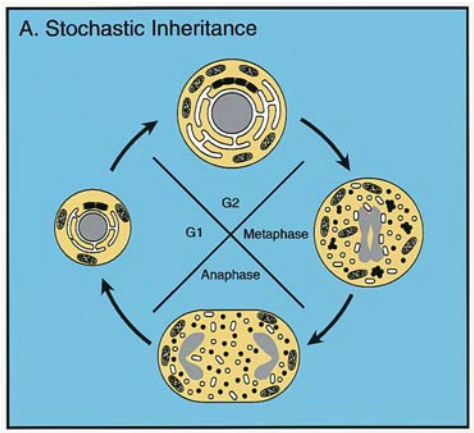


Golgi stacks

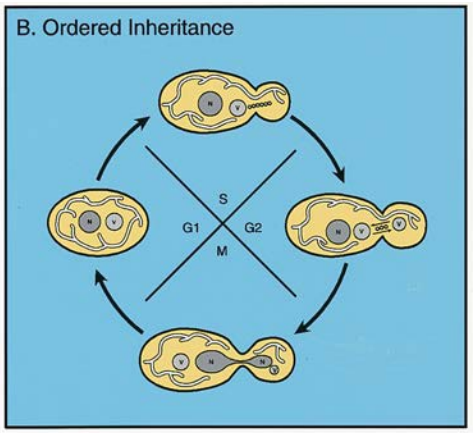


Dispersed Golgi vesicles/tubules

C. Rabouille & Jokitalo. *Mol. Membrane Biol.*, 20, 117 127 (2003)

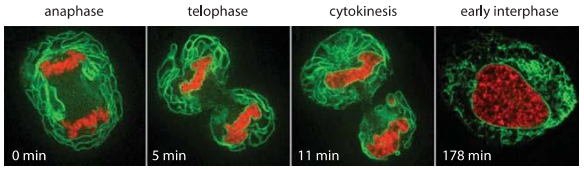


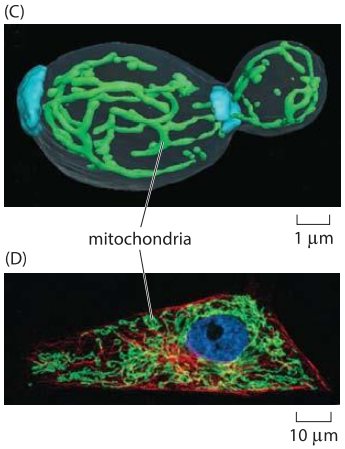
- Mitochondria
- Golgi apparatus
- Endosomes
- Nuclear envelope



- Endoplasmic reticulum
- Mitochondria
- Nuclear envelope

G. Warren & W. Wickner. *Cell*, 84, 395–400 (1996)





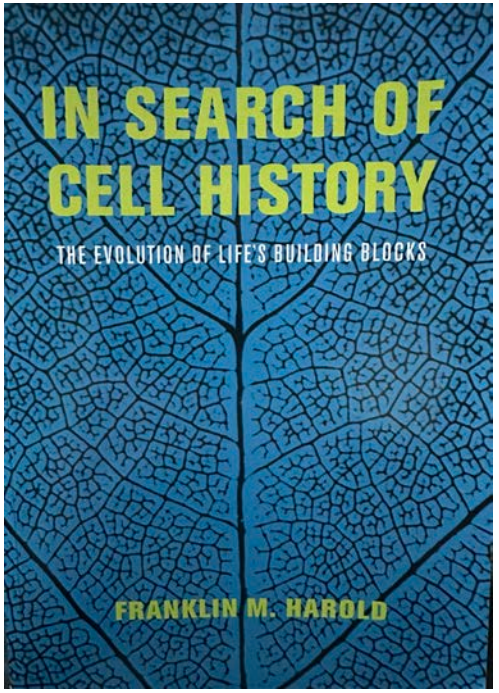
Cell Biology by the numbers. Ron Milo, Rob Phillips, *Garland Science* 2012

Structural and cellular heredity

- Physical and structural continuity between mother cell and daughter cells.
- Since the dawn of the first cells such an architectural continuity has pervaded.
- Structural Heredity
- *Cellular heredity independent of genetic heredity*

« Two universal constituents of cells never form de novo: chromosomes and membranes. ... Just as DNA replication requires information from a preexisting DNA template, **membrane growth requires information from preexisting membranes-their polarity and topological orientation relative to other membranes.**... Genetic membranes are as much part of an organism's germ line as DNA genomes; they could not be replaced if accidentally lost, even if all the genes remained. »

T. Cavalier-Smith. *Trends in Plant Science*. 5: 174-182 (2000)



Franklin M. Harold

Also author of:
The vital force
The way of the cell

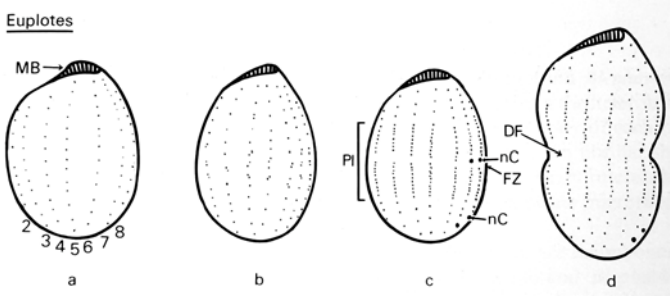
Structural inheritance

Cortical inheritance in ciliates

- The ciliate *Euplotes minima* contains 8 (36% of cells) or 9 (64%) rows of cilia on the dorsal surface.
- These rows of cilia propagate during cell division, following duplication of basal bodies.

- The number of cilia in clones from 8-row founder cells is statistically biased with a large majority of cells with 8 rows, and symmetrically of founder cells with 9 rows of cells.

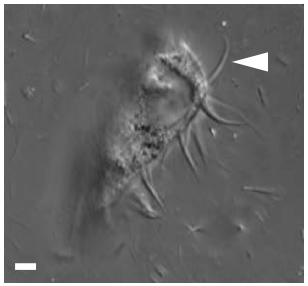
- The cells are all genetically identical (clonal related).
- **This is a manifestation of non genetic heredity**



Starting clone	Presumed number of rows in "founder" cell	A. Zero fidelity[a] 8	A. Zero fidelity[a] 9	B. Perfect fidelity 8	B. Perfect fidelity 9	C. Observed at 30 fissions 8	C. Observed at 30 fissions 9	p
	8 →	16	24	40	0	40	0	<0.001
	8 →	21	19	40	0	40	0	<0.001
	8 →	24	16	40	0	39	1	<0.001
	8 →	16	24	40	0	37	3	<0.001
	9 →	24	16	0	40	21	19	>0.2
36%—8	9 →	18	22	0	40	19	21	>0.2
64%—9	9 →	18	22	0	40	18	22	>0.2
	9 →	16	24	0	40	6	34	<0.001
	9 →	13	27	0	40	5	35	<0.001
	9 →	17	23	0	40	3	37	<0.001
	9 →	13	27	0	40	2	38	<0.001
	9 →	20	20	0	40	2	38	<0.001
						232	248	

Distribution of number of ciliary rows; Expected on the basis of:

[a]Random samples from a binomial distribution in which the respective proportions of 8-rowed and 9-rowed cells is the same as the observed *overall* frequency of 8-rowed and 9-rowed cells at 30 fissions (derived from the sums shown at the bottom of column C). For further explanation, see the text. From Table 1 of Frankel 1975b, with permission.

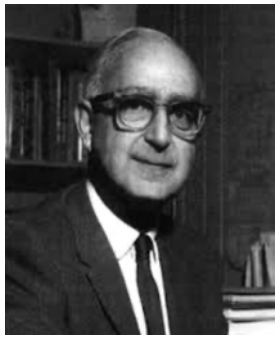


BT. Larson, et al *Current Biology* 32 (17), 3745-3757.e7

J. Frankel. *Pattern formation, Ciliate studies and Models*. 1989. *Oxford Univ. Press*.

Structural inheritance – cytotaxis

Janine Beisson
(1931-2020)



Tracy Sonneborn
(1905-1981)
developed *Paramecium*
as a model organism

*CYTOPLASMIC INHERITANCE OF THE ORGANIZATION OF THE CELL CORTEX IN PARAMECIUM AURELIA**

By Janine Beisson† and T. M. Sonneborn

Department of Zoology, Indiana University

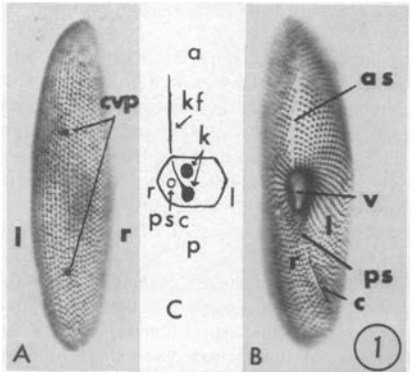
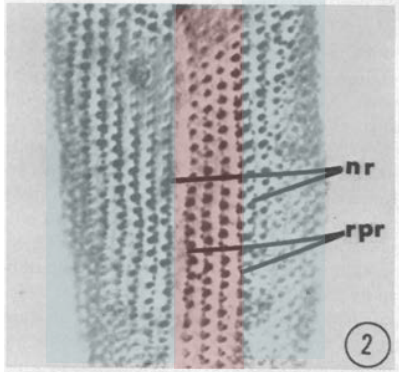
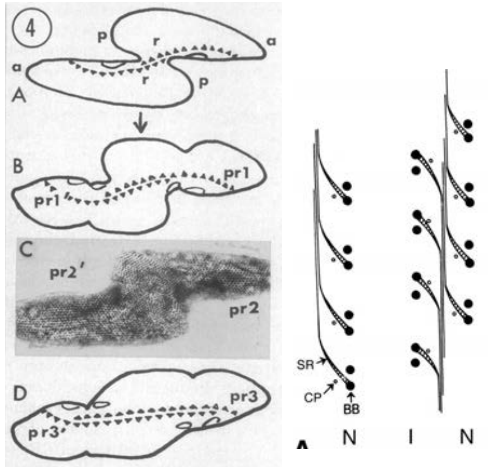


Fig. 1.—Normal cortical geography of *Paramecium aurelia*.



« Twisty » clone after 300 generations



« Observations on the role of existing structural patterns in the determination of new ones in the cortex of *Paramecium aurelia* should focus attention on the **informational potential of existing structures** and stimulate explorations, at every level, of the developmental and genetic roles of cytoplasmic organization. »

- *Paramecium aurelia* have multiple cilia at their surface.
- Perturbations in the orientation of cilia arise from aberrant separation of conjugating cells with reversed orientations.
- Perturbations in the orientation of cilia are transmitted clonally over 100s of generation.
- The orientation of cilia depends on the organisation of the environment that imparts polarisation.

J. Beisson and T.M. Sonneborn. *PNAS*, 53: 275-282 (1965)

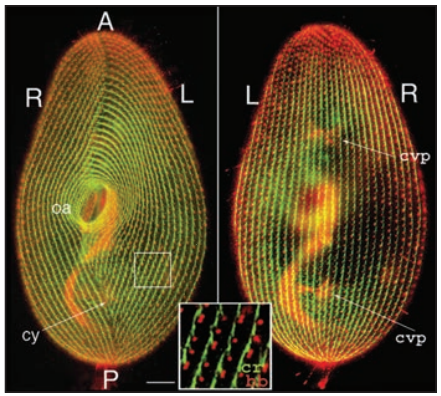
Structural inheritance – cytotaxis

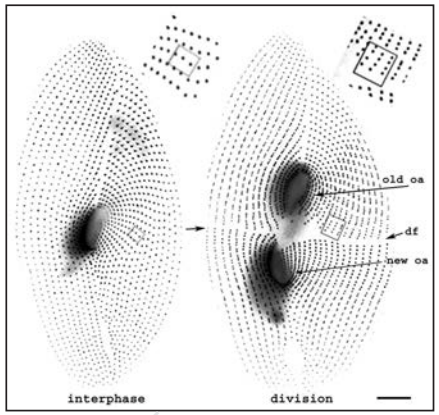
Preformed cell structure and cell heredity

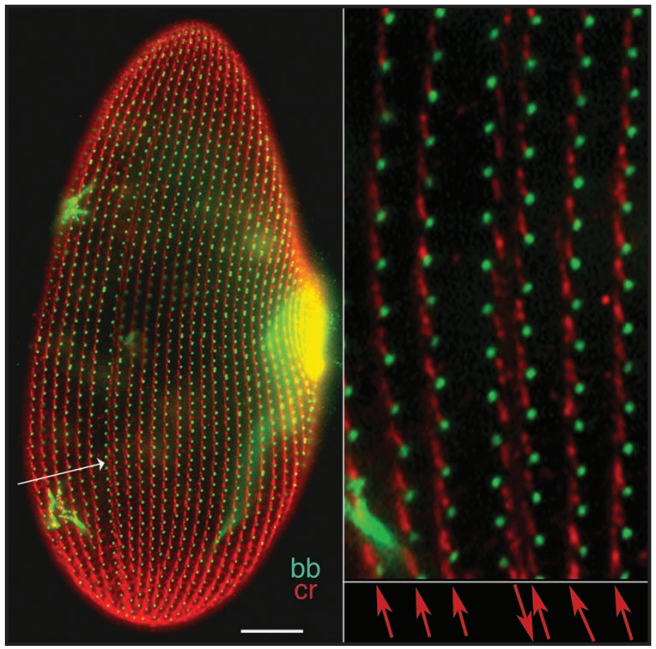
Janine Beisson

Centre de Génétique Moléculaire; Centre National de la Recherche Scientifique; Gif-sur-yvette, France

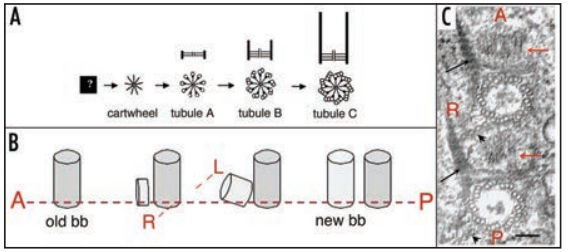
- Duplication of the basal body and of cortical patterns.
- **Preformed structures are used as templates** and are essential in the formation of new ones.

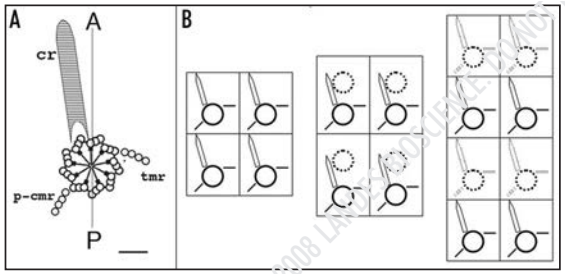






bb: basal body
cr: cililary rootlet





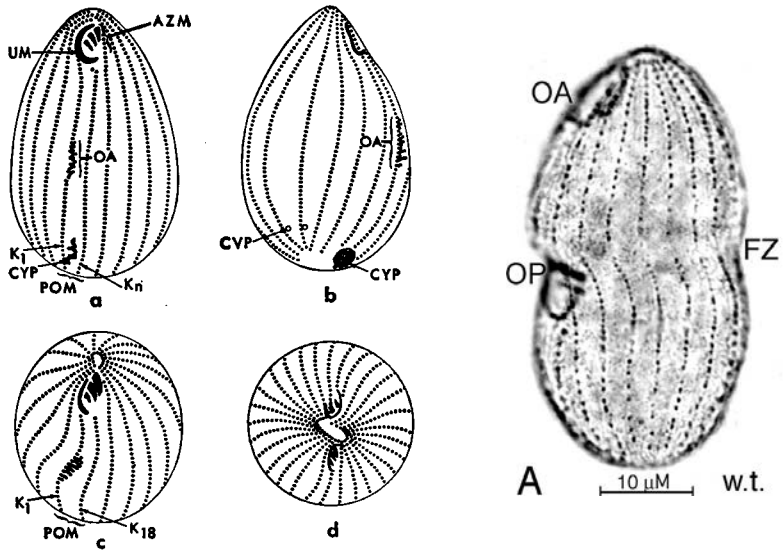
J. Beisson. *Prion*. 2(1):1-8. (2008) doi: 10.4161/pri.2.1.5063.

Structural inheritance – cytotaxis

Cortical Patterns in Cellular Morphogenesis

Differences in cortical patterns in ciliates may be hereditary, but independent of genic differences.

David L. Nanney



Tetrahymena thermophila

DL. Nanney *Science* 160: 496-502 (1968)

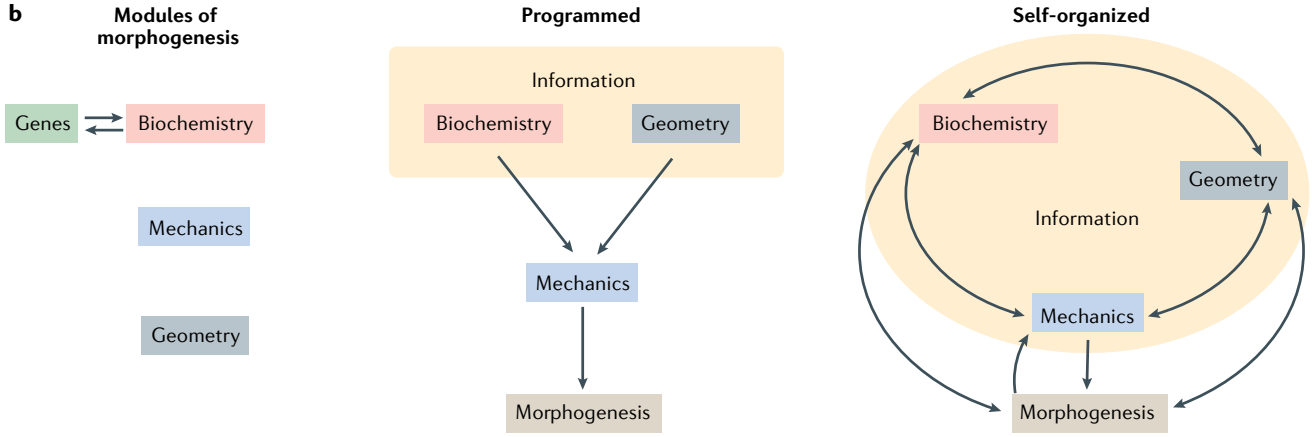
I have surveyed the studies bearing on the determination of cortical patterns in *Tetrahymena*. A variety of pattern permutations can be established on a common genic basis, and these permutations have sufficient stability to be designated *hereditary* variants. The mechanisms of hereditary maintenance apparently do not involve genic differences—either nuclear or cytoplasmic, either structural or functional—but involve rather, a multidimensional information storage and transmission system whereby the pattern, in a sense, maintains itself.

J. Frankel. *Eukaryotic cell*. 1617–1639 (2008)

Structure and Geometry as information

Implications:

- Such cellular structures and overall organisation and geometry **are not reducible to their molecular chemical constituents**.
- **They form entities of their own** that characterise cells, fertilised eggs etc.
- Cellular structures and cell geometry guide and constrain mechanochemical reactions and processes in cells and thereby orient their future evolution.
- As such, **structures and geometry constitute a module of information per se** that interacts with chemical and mechanical information in cells and during development

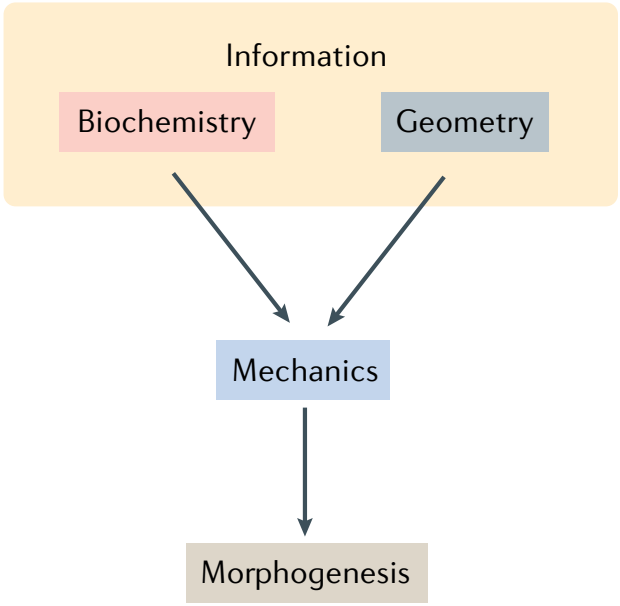


Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021

Structure and Geometry as information

PROGRAM

- hierarchy
- modularity
- heredity (template, initial conditions, genome)
- deterministic rules

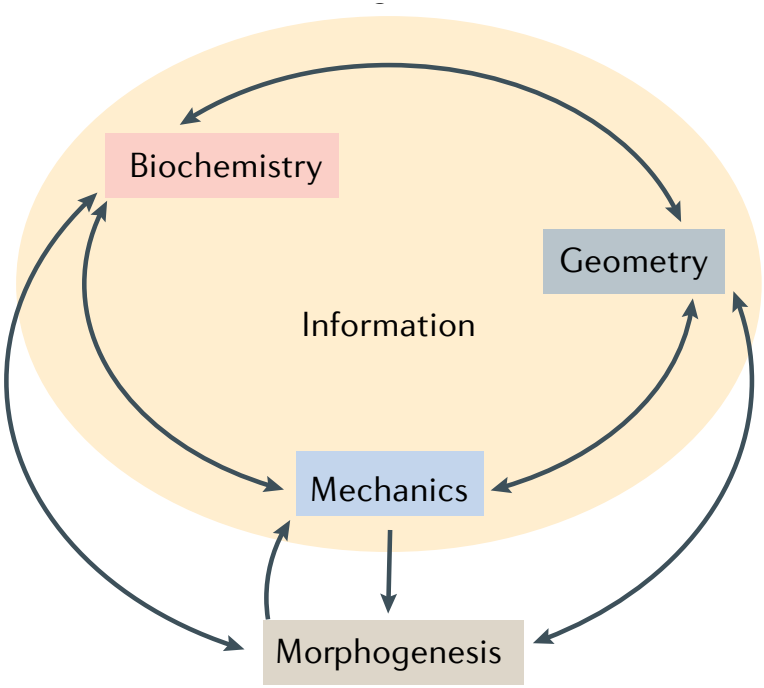


Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021

Structure and Geometry as information

SELF-ORGANIZATION

- no hierarchy
- stochastic processes/ statistical rules
- feedbacks



Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021

Plan

- Structural cellular heredity and cellular self-organisation

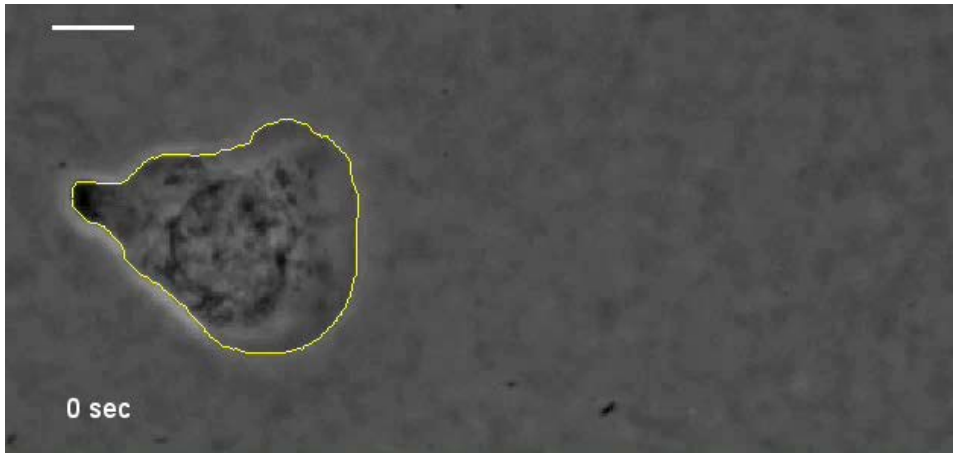
- **Geometric information in cells:**
  - decoding cell shape via signalling
  - decoding cell shape via mechanics

- Geometric information in development and morphogenesis
  - Geometric guidance
  - Geometric feedback

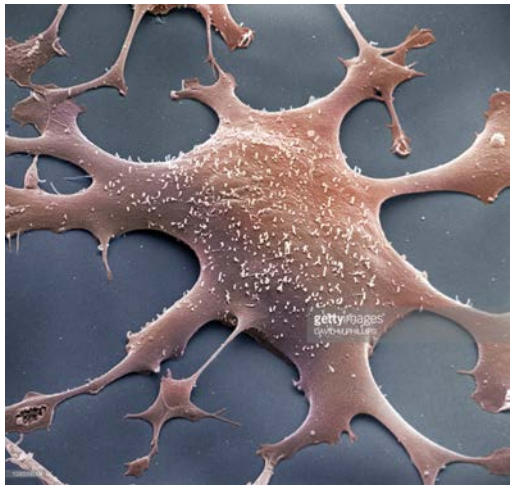
Decoding cell shape information via chemical signalling

Cells have complex and diverse morphologies and change shape dynamically

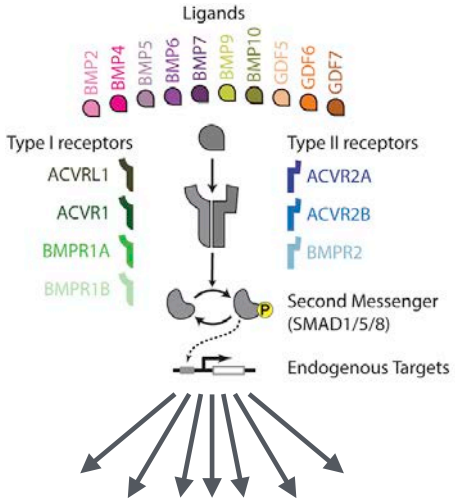
- Question: how does this affect cell signalling?



HL60 cell: human leukocyte



Human Fibroblasts

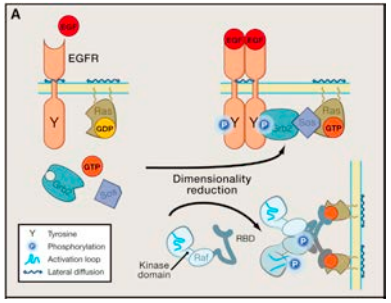


T. .Tsai et al. and J. Ferrell and J. Theriot, *Developmental Cell* 49, 189–205 (2019)

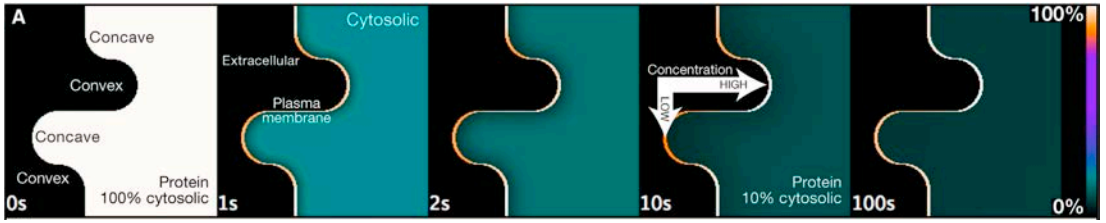
Decoding cell shape information via chemical signalling

Signalling on curved membrane surfaces

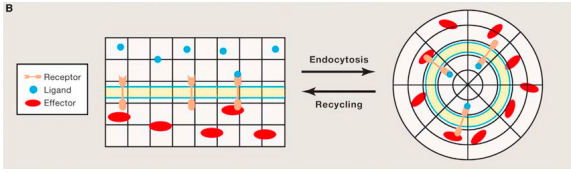
- **Membrane recruitment of proteins elicits signalling:** enhanced concentration in 2D overcomes reduced mobility compared with 3D diffusion.



- **Impact of membrane curvature:**
  - In convex membrane (invagination): surface to volume ratio of cytosol is lower, ie. *The pool of cytosolic proteins per unit of membrane is increased*, which increases binding to membrane receptor.
  - In concave membrane (protrusion), conversely, surface to volume ratio is increased, and membrane recruitment is decreased



- **In vesicle, signalling increased** due to ligand trapping and increased binding of cytosolic transducer.



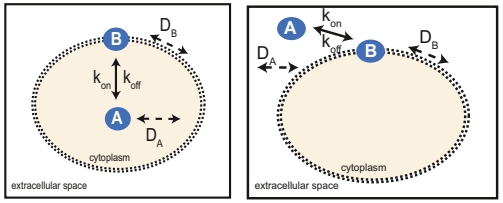
M. Schmick and P.H. Bastiaens. *Cell*, 156:1132-1138 (2014)

Decoding cell shape information via chemical signalling

Modelling reaction and diffusion on curved surfaces

- A is a component in solution (extracellular or cytoplasmic component) and X is a membrane component. When A binds to X on the membrane, it forms B, which is also a membrane component.

$$A + X \underset{k_{on}}{\overset{k_{off}}{\rightleftharpoons}} B$$



- Boundary condition: $D_A(\mathbf{n}\cdot\nabla C_A) = -k_{on}C_A|_{\partial\Omega}N_X + k_{off}N_B$

C_A is concentration of A in cytosol, $C_A|_{\partial\Omega}$ is concentration of A at boundary:

N_X and N_B are the concentrations of X and B on the membrane.

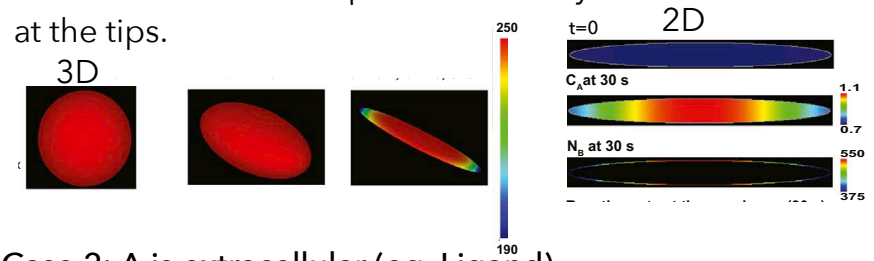
- Reaction/Diffusion of X and B at the membrane:

$$\frac{\partial N_X}{\partial t} = D_X\nabla^2 N_X - k_{on}C_A|_{\partial\Omega}N_X + k_{off}N_B$$

$$\frac{\partial N_B}{\partial t} = D_B\nabla^2 N_B + k_{on}C_A|_{\partial\Omega}N_X - k_{off}N_B$$

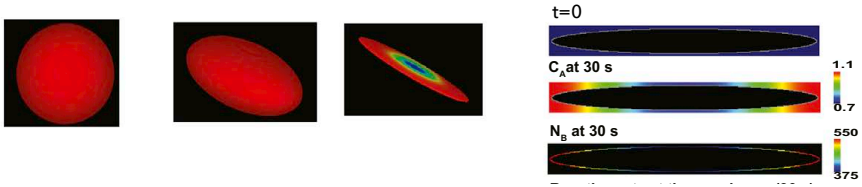
- Solve these equations on spherical and elliptical geometries and numerical simulations
- **Case 1: A is in the cytoplasm:**

  Uniform distribution on sphere. As the eccentricity of the ellipsoid increases, the membrane distribution becomes curvature dependent at early times. B is lower at the tips.



- **Case 2: A is extracellular (eg. Ligand)**

  Curvature dependence is reversed: B is higer at poles



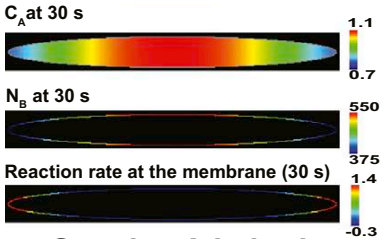
NB: These gradients of concentration are transient

P. Rangamani et al, R. Iyengar. *Cell* 154, 1356–1369 (2013)

Decoding cell shape information via chemical signalling

Competition between reaction and diffusion and impact of surface to volume ratio

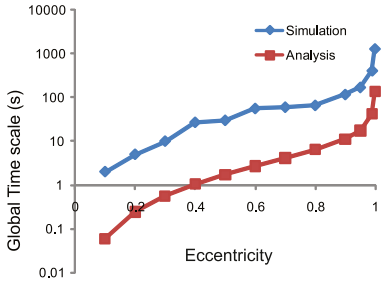
- Diffusion homogenises concentrations. $A + X \underset{k_{on}}{\overset{k_{off}}{\rightleftharpoons}} B$
- **But, reactions occur along the membrane and the local surface to volume ratio produces concentration differences in elliptic geometries.**
- At the tip, the available 3D cytoplasm for a given surface is less than in the center. Conversely, the volume of extracellular space is more than in the center
- **At the pole:** high curvature, and high surface to volume ratio. Depletion of A in cytosol due to the fact that reaction is faster than diffusion in cytosol.
- **Reaction dominates over diffusion**, the process is diffusion limited.
- **At the center:** diffusion time to membrane is much reduced so the process is not diffusion limited. **Diffusion dominates.**



- **These gradients of concentration are transient. This depends on the relaxation time scale of the gradient which can be computed by comparing the difference in diffusion at the major and minor axis.**

$$t = \frac{r_1^2 - r_2^2}{4D_A}$$

- The duration of the transient gradient is longer on more eccentric geometries.



P. Rangamani et al, R. Iyengar. *Cell* 154, 1356–1369 (2013)

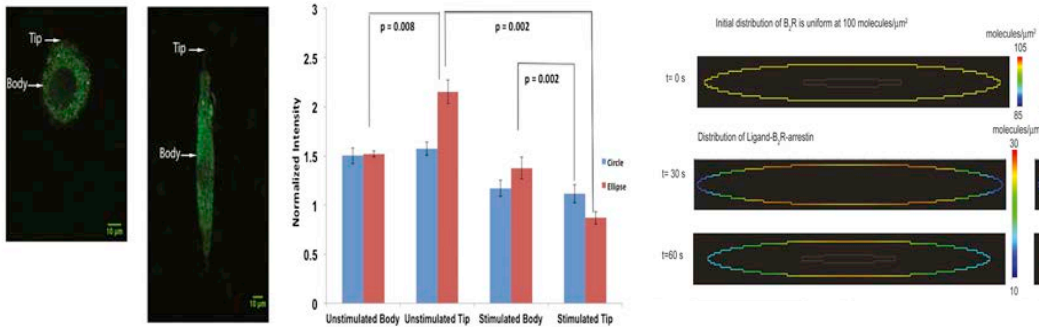
Decoding cell shape information via chemical signalling

Experimental tests: transient gradients of signalling

bradykinin receptor, a $G_{q/11}$- coupled receptor

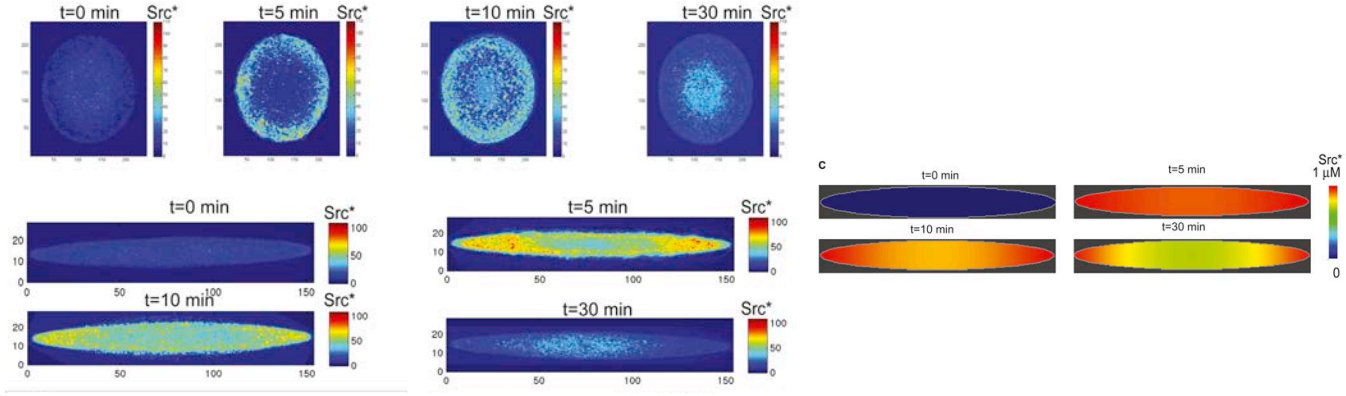
Cells plated on substrates of different geometries

Distribution of B2R in cells at the tips and body



PDGF receptor and activation of Src

Src is transiently enriched at the tip membranes in elliptical cells

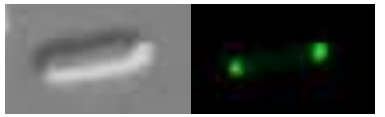


P. Rangamani et al, R. Iyengar. *Cell* 154, 1356–1369 (2013)

Decoding cell shape information via chemical signalling

A model for geometry-induced chemical gradients that are both stable and robust

A model inspired to account for polarity of MinD/MinE system in *E. coli,* and AtMinD in absence of MinE.



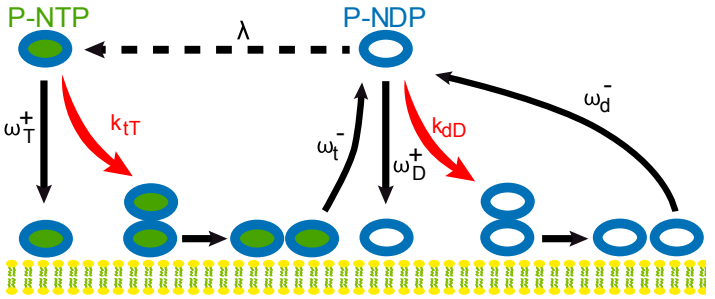
AtMinD-GFP

Direct ($w^{+}_{T;}\, w^{+}_{D}$) and cooperative (k_{tT}, k_{dD}) membrane association.

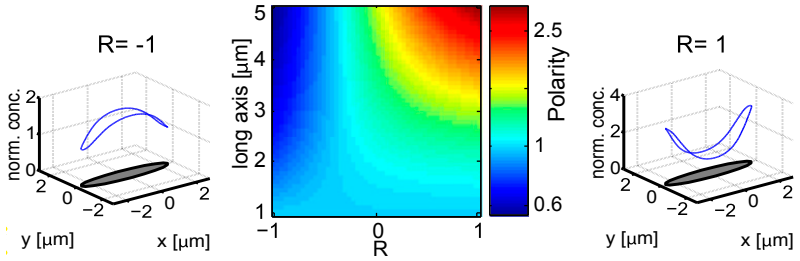
Polarity: $P = u_{pole}/u_{midcell}$.

Degree of cooperatively: $R = (k_{dD} - k_{tT})/(k_{dD} + k_{tT})$

2D simulation using known rate constants and diffusivities.



Proteins accumulate at poles (P > 1) if there is a preference for cooperative binding of P_{NDP} (R > 0).
When cooperative binding favors P_{NTP} (R < 0), proteins accumulate at midcell (P < 1)



Thalmeier D. J. Halatek and Erwin Frey. *PNAS* 113, 548–553 (2016).
Zhang et al. *BMC Microbiology* 2009, 9:101

Decoding cell shape information via chemical signalling

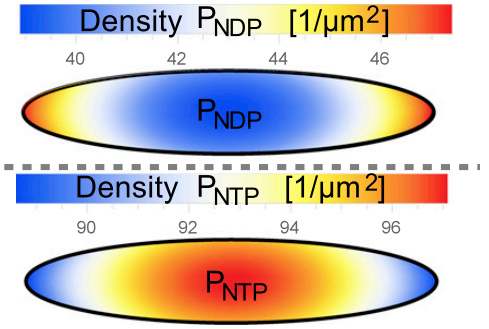
A model for geometry-induced chemical gradients that are both stable and robust

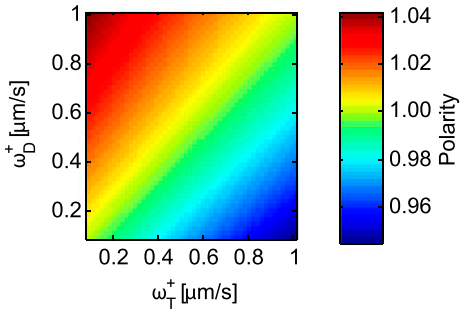
- **Without cooperativity, simulations reveal concentration gradients of the P_{NDP} and P_{NTP} in the cytosol.**

  These cytosolic gradients form seeds for membrane distribution which depends on the respective values of membrane binding constants w^{+}_{T} and w^{+}_{D}.

  This weak polarisation is amplified with cooperativity.

  Cannot be accounted for by geometry-dependent exchange kinetics





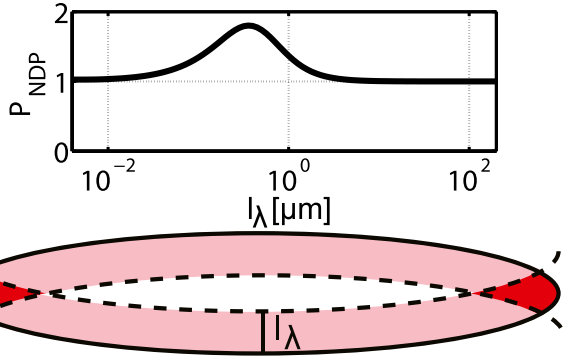
$$P = u_{pole}/u_{midcell}.$$

- **Cytosolic reaction volume (for nucleotide exchange) determines the pattern:**

  Role of diffusive coupling of membrane association/dissociation kinetics.

  1. The membrane is a *source* for cytosolic P_{NDP} via dissociation
  2. P_{NDP} is converted to P_{NTP} at rate λ (sink)

  Exponential decay length: $l_\lambda = \sqrt{D_c/\lambda}$

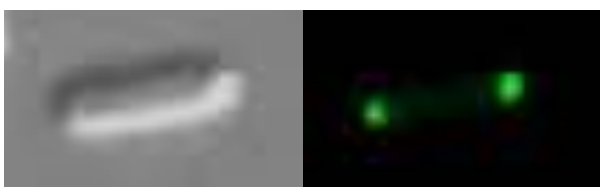


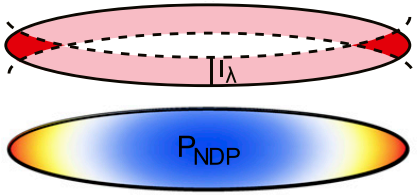
  These **reaction volumes overlap at poles leading to concentration of P_{NDP}.**
  As l_λ increases beyond l the overlap also occurs at mid cell. If l_λ too small, no overlap: there is an optimum value of l_λ

Thalmeier D. J. Halatek and Erwin Frey. *PNAS* 113, 548–553 (2016).

Decoding cell shape information via chemical signalling

A model for geometry-induced chemical gradients that are both stable and robust





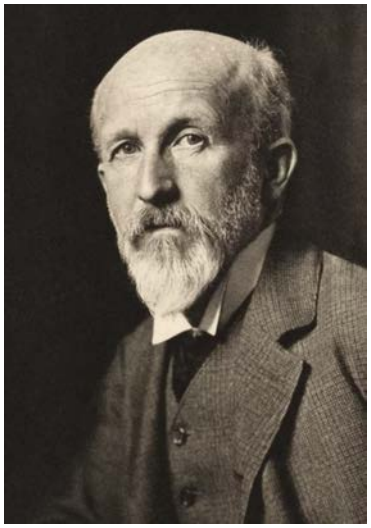
- A well mixed cytoplasm due to diffusion prevents establishment of a stable geometry-induced chemical gradient
- However, **the existence of a nucleotide exchange in a protein alters the state of the protein and introduces a decay length that interacts with the geometry to produce a stable enrichment.**

- Given that nucleotide exchange (or other posttranslational modification of protein) is very common, this may have general applicability.
  The model is very generic (not fine tuned, unlike chemical instabilities eg. Turing).
- **The pattern does not have a characteristic length scale** and depends rather on cell size.

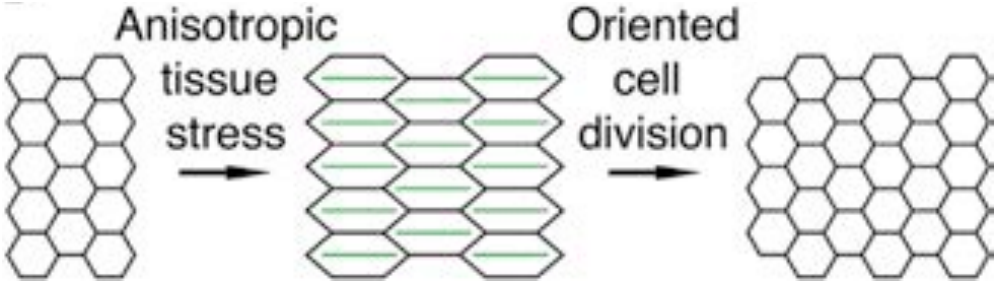
Cell division orientation

Hertwig's rule or « long axis rule » of cell division orientation

Cells tend to divide along their long axis



Compression of frog embryos

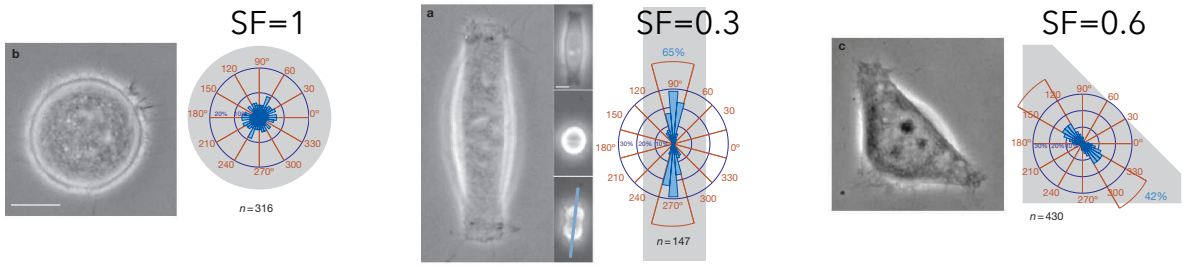


Hertwig O (1884). "Das Problem der Befruchtung und der Isotropie des Eies. Eine Theorie der Vererbung". *Jenaische Zeitschrift für Naturwissenschaft*. 18: 274

Mechanical decoding of cell & environment geometry

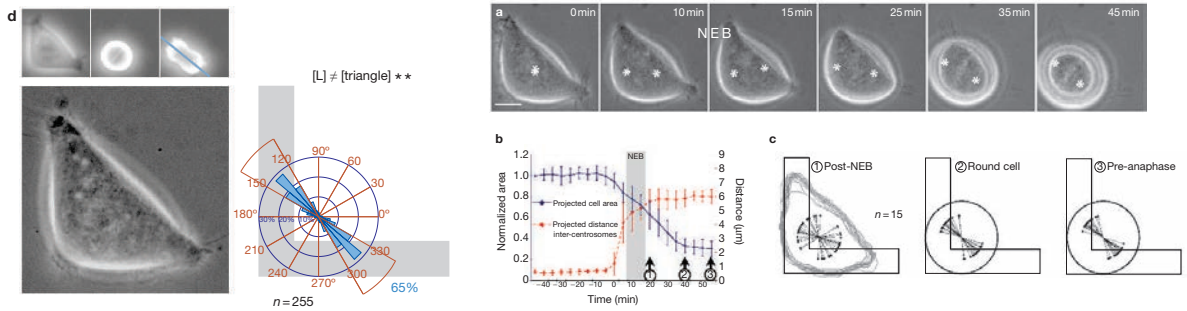
Cell geometry affects the orientation of cell division
But other factors contribute as well…

- Cells adhere to fibronectin substrates with different geometries
- Cells adopt different shapes
- Cell division axis correlates well with long axis of ellipse fitting cell shapes



Shape Factor (SF): ratio of minor to major axis of ellipse fitting cell shape

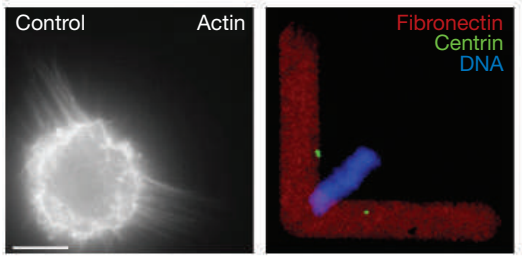
- Yet, cells on L shaped substrate have a similar triangular shape than on a triangular substrate, yet division axis is far more constrained.
  This suggests that additional factors contribute to division orientation.
- Moreover the orientation of the spindle occurs when cells are round.

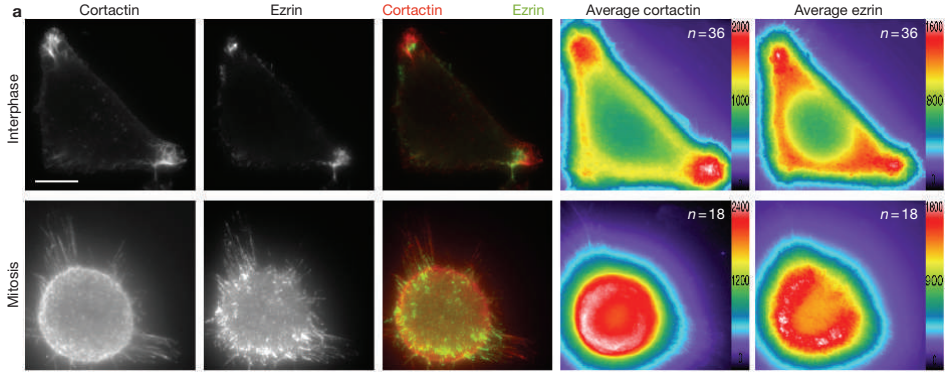


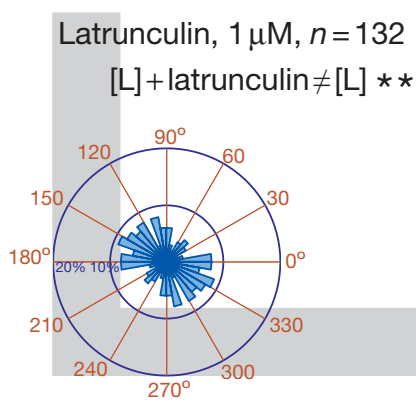
M. Théry et al and M. Bornens. *Nature Cell Biology* 7:947–953 (2005)

Mechanical decoding of cell & environment geometry

- Cortical marks associated with adhesion foci are distributed symmetrically along an axis that correlates with cell division orientation
- **Depolymerization of actin filaments leads to the randomisation of cell division orientation.**







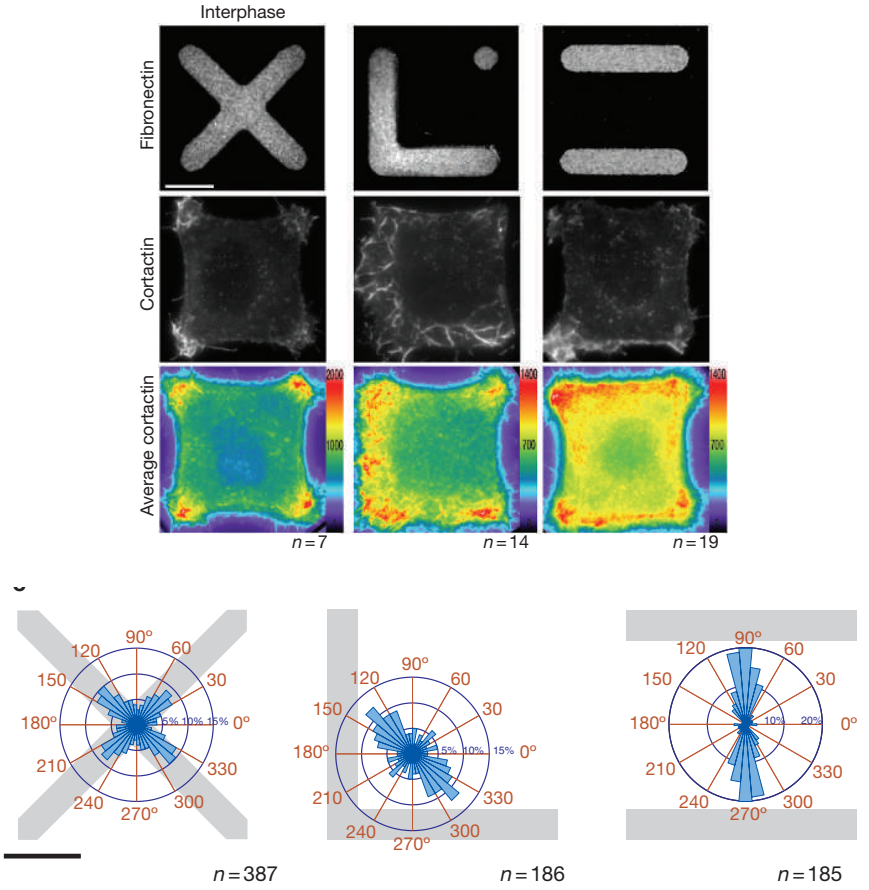
- *Hypothesis*: the geometry of adhesion/actin foci on the ECM orients cell division

M. Théry et al and M. Bornens. *Nature Cell Biology* 7:947–953 (2005)

Mechanical decoding of cell & environment geometry

The geometry of the adhesive environment orients cell division

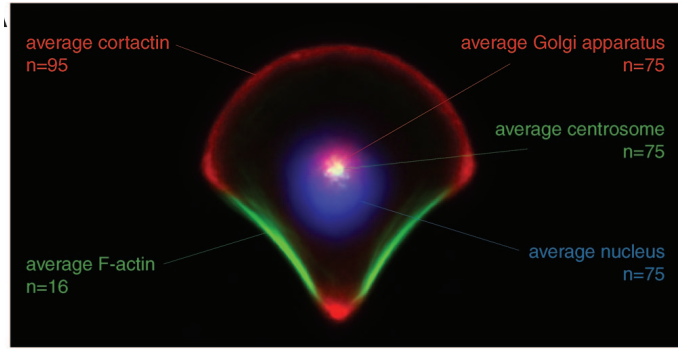
- Adhesive substrates that lead to similar cell shapes lead to different geometries of cortical marks.
- Cell division orientation is affected by the geometry of the ECM.
- It is directed perpendicular to the axis of symmetry of the ECM

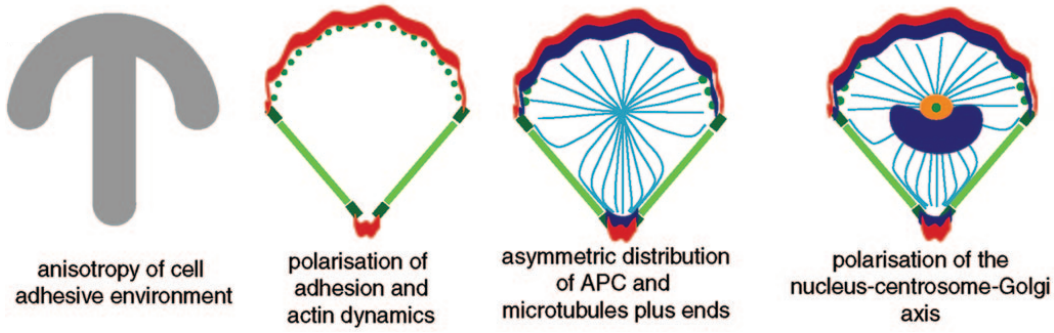


M. Théry et al and M. Bornens. *Nature Cell Biology* 7:947–953 (2005)

Mechanical decoding of cell & environment geometry

The geometry of the adhesive environment orients internal cell organisation



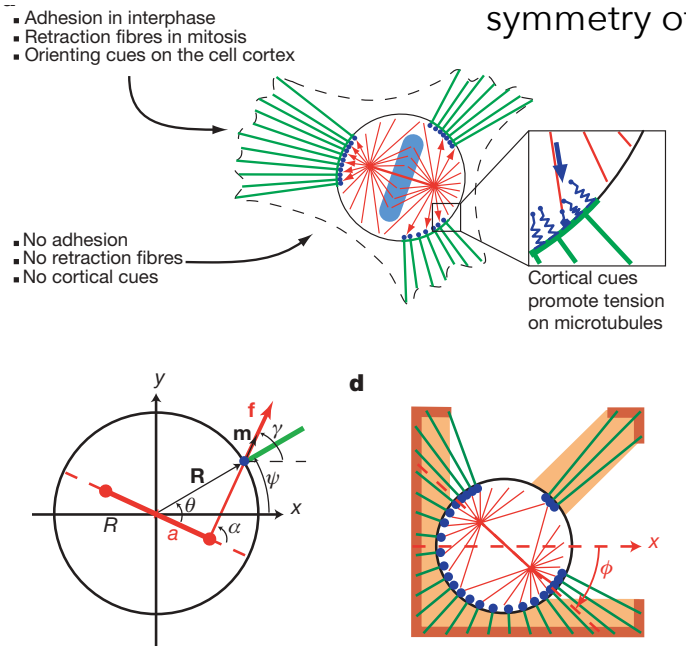


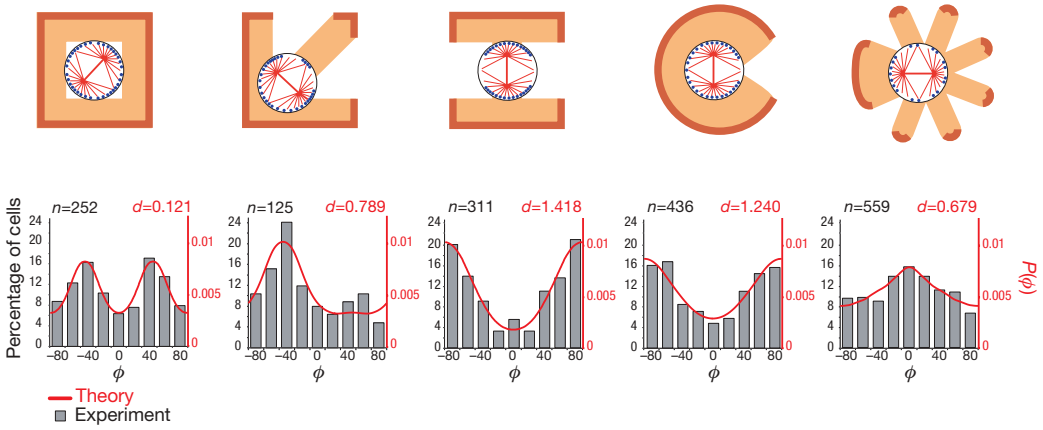
M. Théry et al and M. Bornens. *PNAS* 103:19771–19776 (2006)

Mechanical decoding of cell & environment geometry

Mechanical model of environment geometry sensing

- Retraction fibers at mitosis produce orienting cues at cell cortex.
- Role of cortical forces pulling on astral microtubules.
- Force balance leads to equilibrium position of spindle that reflects the symmetry of adhesive clusters



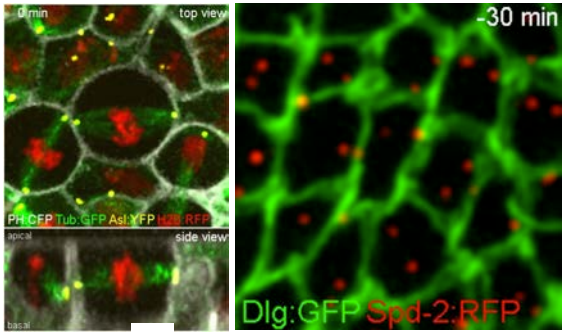


M. Théry et al and M. Bornens and F. Jülicher. *Nature* 447: 493-496 (2007)

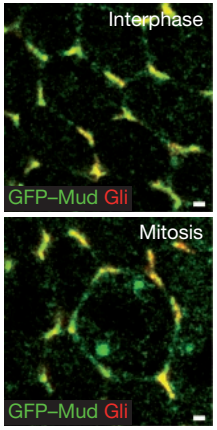
Mechanical decoding of cell & environment geometry

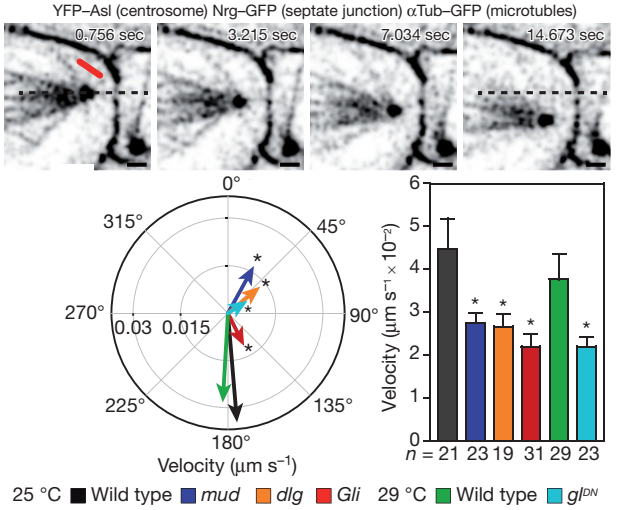
What cellular feature orients epithelial cell division?

- Epithelial cells tend to divide along the long axis in interphase.
- Cells round up during division.
- **How do they keep a memory of cell long axis prior to division?**

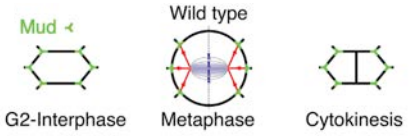


- The protein Mud, which is known to bind the -end directed motor Dynein, is located at tri-cellular junctions. Through this association, Mud mediates pulling forces on microtubules who direct their +ends to the cell cortex.





- *Hypothesis*: **Cortical pulling forces orient the mitotic spindle and thereby cell division in epithelial cells.**



Floris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016)

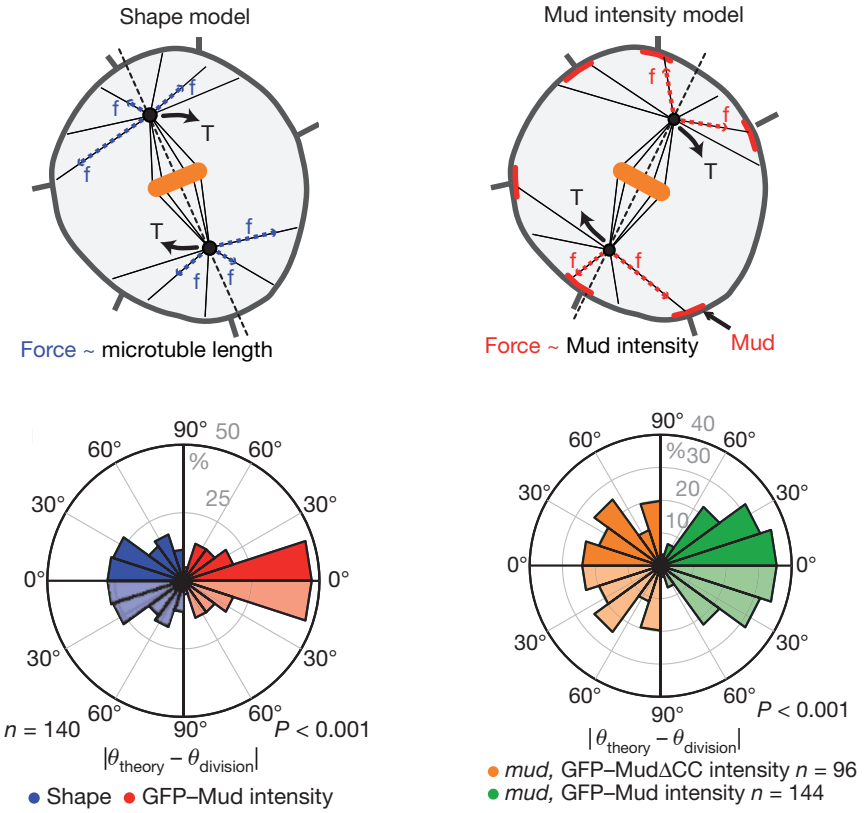
Mechanical decoding of cell & environment geometry

Tricellular junctions predict cell division orientation

- *Models/hypothesis*:
- **Shape model:** the pulling forces exerted by astral microtubules *scale with microtubule length* and, as a consequence, the model predicts the preferred spindle orientation along the long axis of the cell.
- **Mud intensity model:** astral microtubules pull with a force proportional to the *cortical GFP–Mud intensity* and independent of microtubule length.

- **Data: Measurement of orientation angle difference between data and predictions based on the specific models shows a better alignement with the Mud intensity per se than cell shape.**

- A mud mutant that cannot exert pulling forces leads to a lower alignement of spindle with Mud localisation at junctions



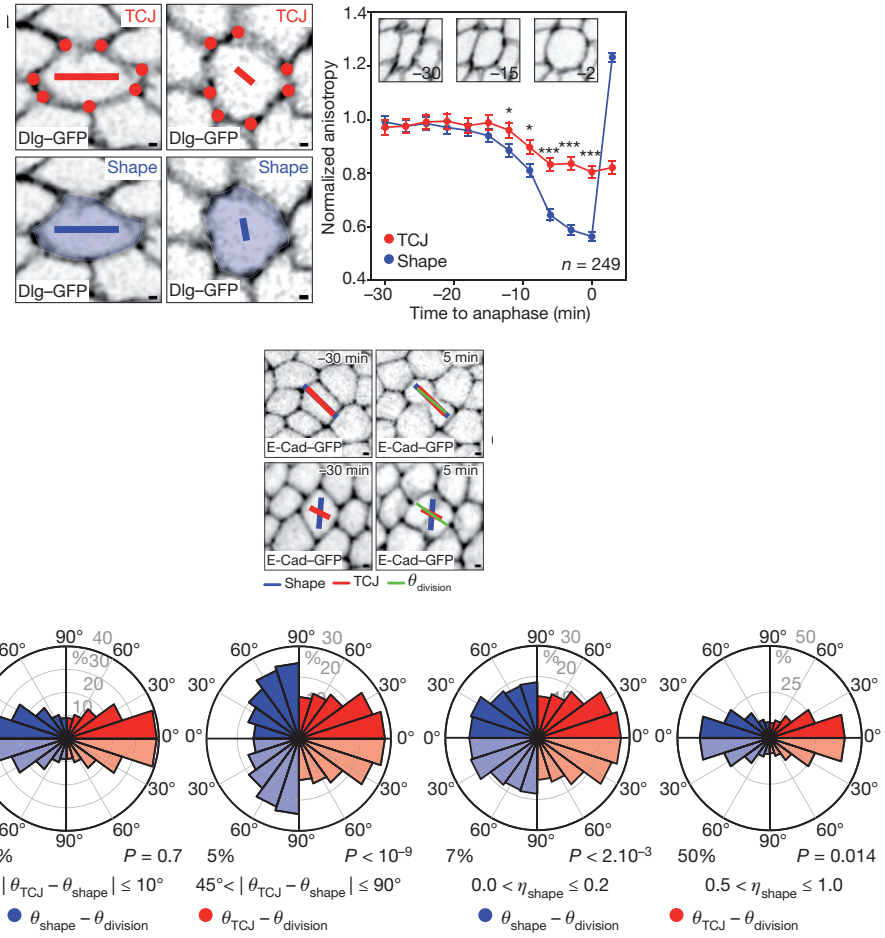
Floris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016)

Mechanical decoding of cell & environment geometry

Encoding of cell shape by tricellular junctions

- Measurement of two cell anisotropies:
  - Cell shape anisotropy: η_{shape}
  - TCJ distribution anisotropy: η_{TCJ}
- Orientation of anisotropy: θ_{shape} and θ_{TCJ}.

- During division, cell shape anisotropy reduces significantly, while TCJ anisotropy remains relatively unchanged, suggesting that **TCJ retain more information for the positioning of the mitotic spindle.**
- When shape and TCJ anisotropies have very similar orientations, they predict equally well cell division axis.
- **When shape and TCJ anisotropies have different orientations, TCJ anisotropy predicts very well division orientation, but not shape anisotropy.**
- When cells are more round (ie. low shape anisotropy η_{shape}), TCJ anisotropy predicts cell division orientation better than shape.

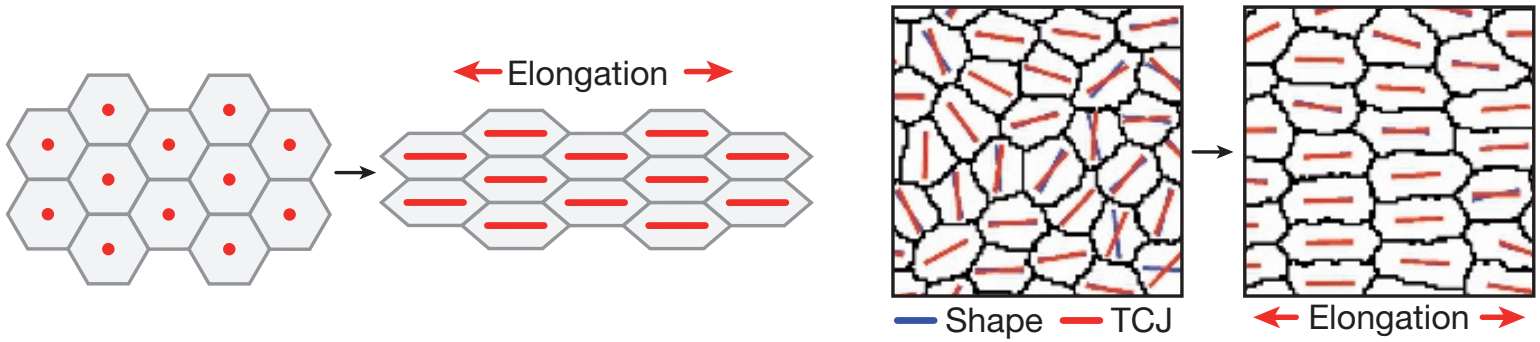


Floris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016)

Mechanical decoding of cell & environment geometry

Encoding of cell shape by tricellular junctions.

Decoding of cell shape by mechanical pulling forces exerted on astral microtubules



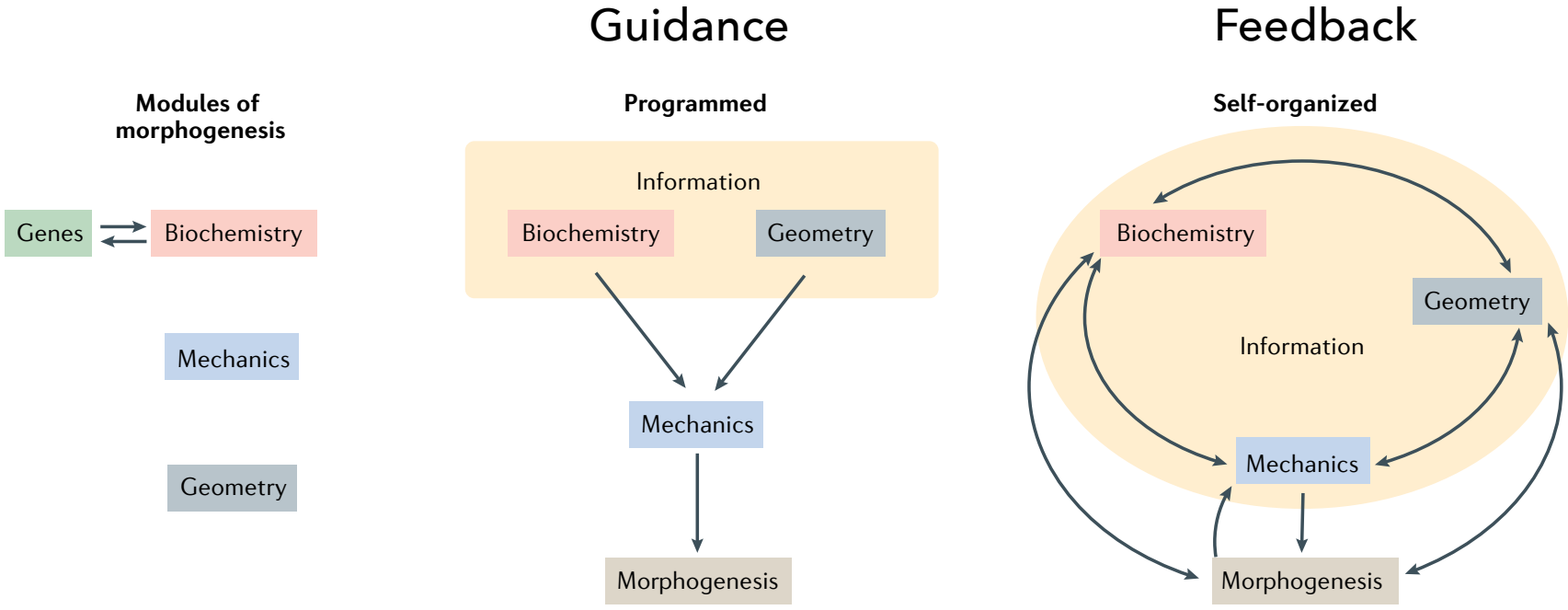
Floris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016)

Plan

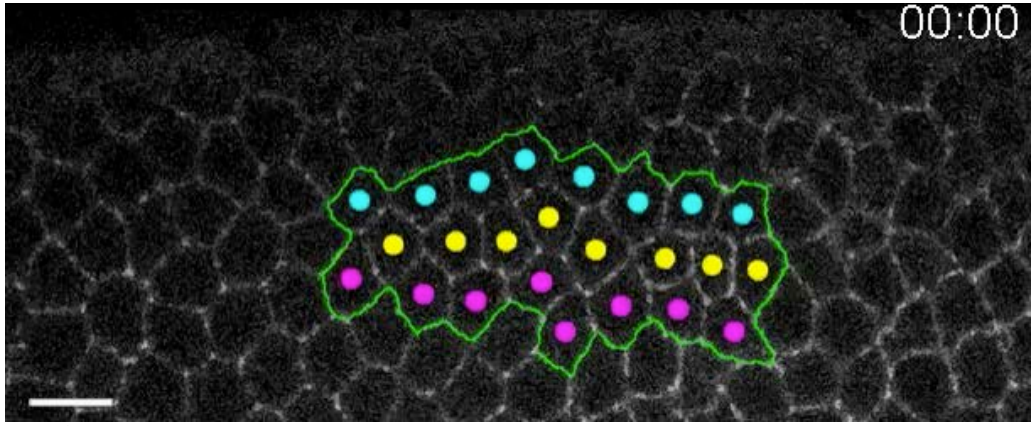
- Structural cellular heredity and cellular self-organisation
- Geometric information in cells:
  - decoding cell shape via signalling
  - decoding cell shape via mechanics
- **Geometric information in development and morphogenesis**
  - Geometric guidance
  - Geometric feedback

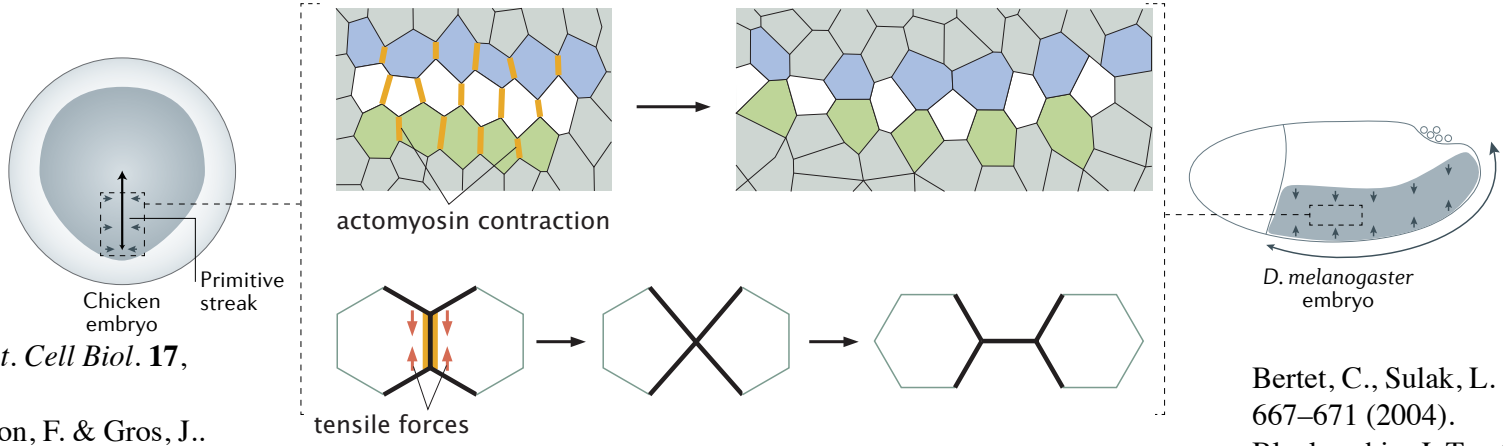
Geometrical information during development

Geometry specifies: initial and boundary conditions that could affect signalling and mechanics



Active viscous cell flows driven by anisotropic cell contractility



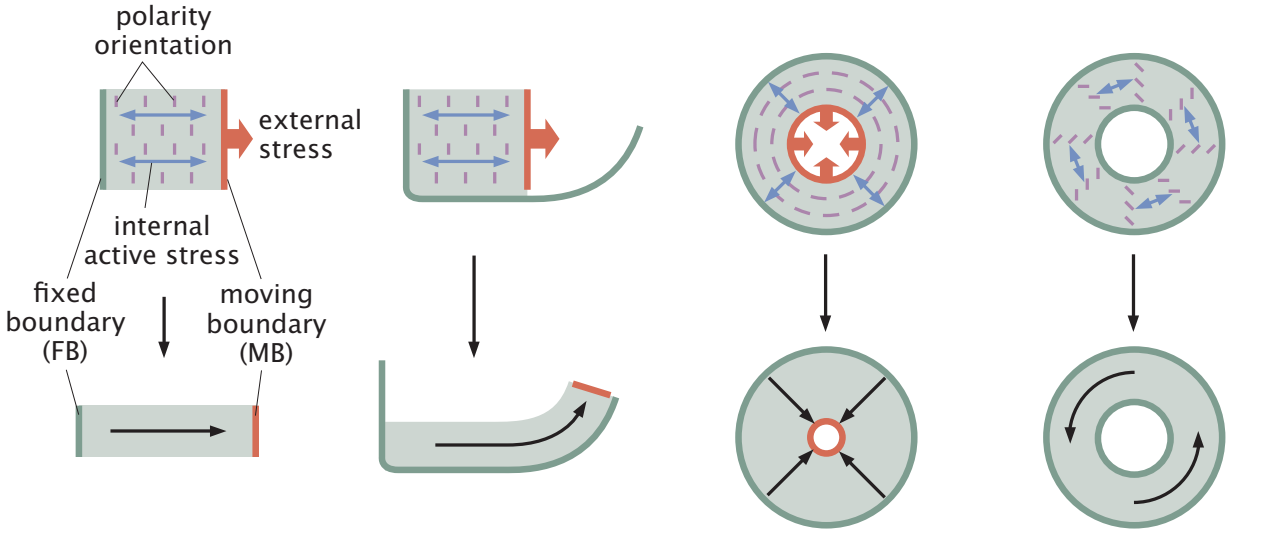


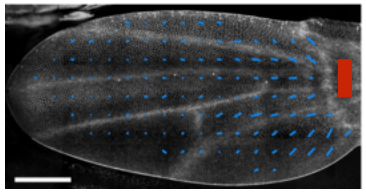
Rozbicki, E. et al. C. *Nat. Cell Biol.* **17**, 397–408 (2015).
Saadaoui, M., et al, Corson, F. & Gros, J.. *Science* **367**, 453–458 (2020).

Bertet, C., Sulak, L. & Lecuit, T. *Nature* **429**, 667–671 (2004).
Blankenship, J. T., et al. & Zallen, J. A. *Dev. Cell* **11**, 459–470 (2006).
Rauzi, M, et al, T. Lecuit and PF Lenne, *Nat. Cell Biol.* **10**, 1401-1410 (2008)

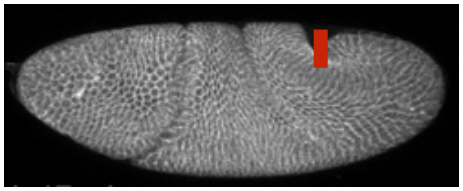
Geometry constrains tissue flow

- Geometry defines boundary conditions and constrains tissue flow

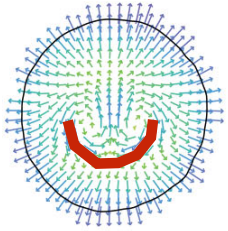




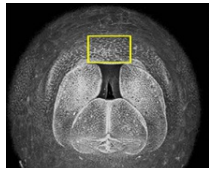
M. Merkel, R Etournay et al 2015



Drosophila germ band
Tribolium gastrulation



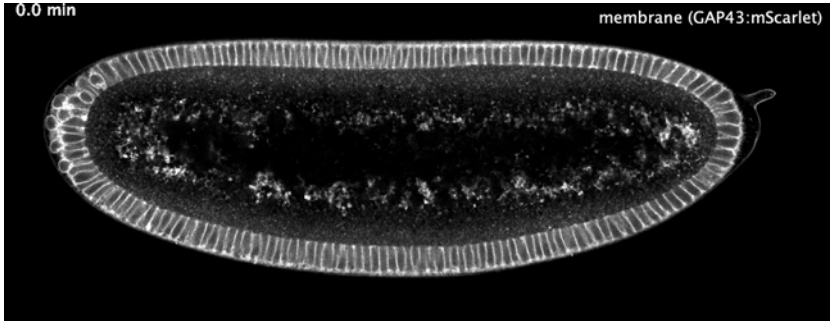
Chick gastrulation
Saadaoui M et al 2020

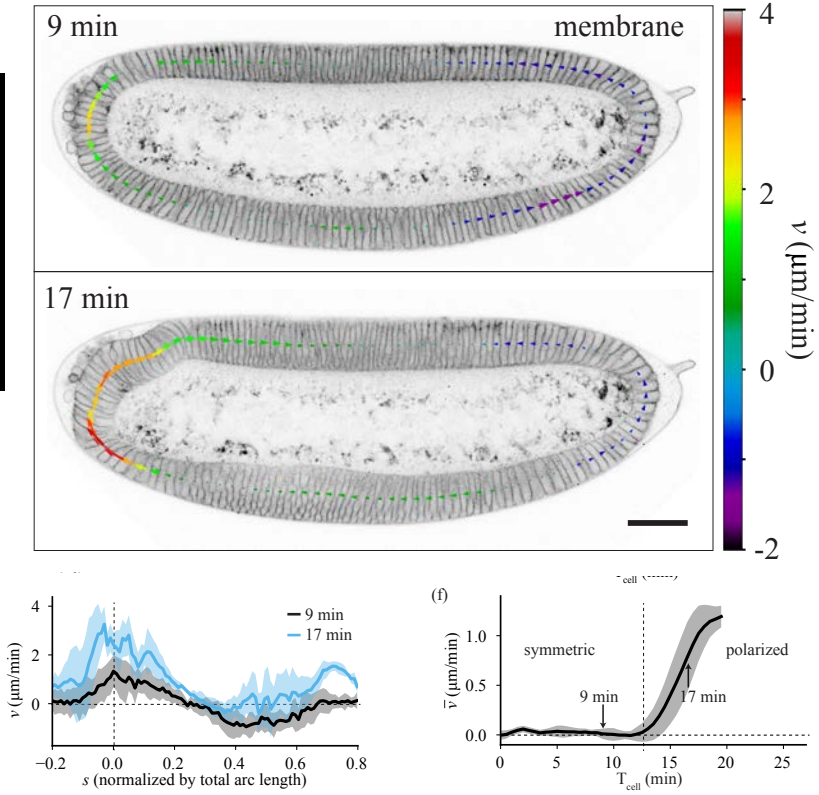


Genitalia rotation
Sato et al, 2015

C. Collinet and T. Lecuit. *Nature Reviews Molecular Cell Biology*, 2021

Geometry guides tissue flow

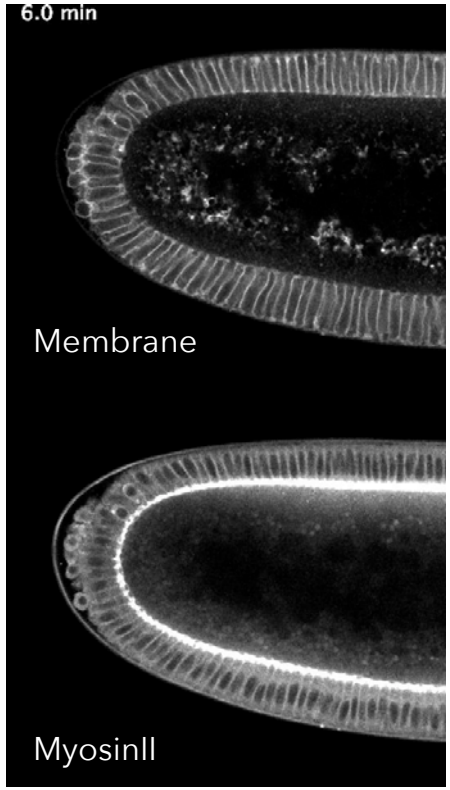


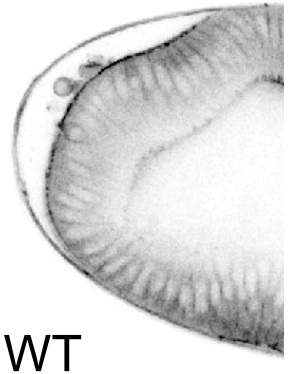


Gehrels EW, Chakrabortty B, Perrin ME, Merkel M, Lecuit T. *PNAS*. 120(6):e2214205120 (2023)

Geometry guides tissue flow

Polarized tissue flow requires contractility

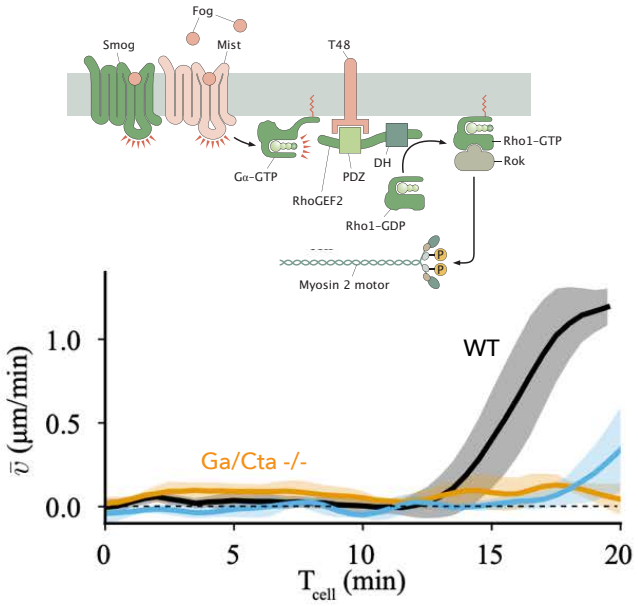




WT

Ga/Cta $^{-/-}$

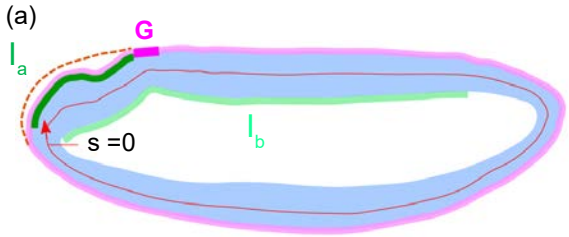
- Polarized (asymmetric) flow requires apical MyosinII contractility



Gehrels EW, Chakrabortty B, Perrin ME, Merkel M, Lecuit T. *PNAS*. 120(6):e2214205120 (2023)

Geometry guides tissue flow

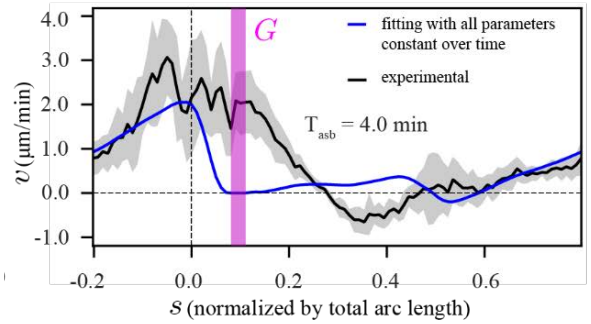
Localized friction or adhesion is not required for flow



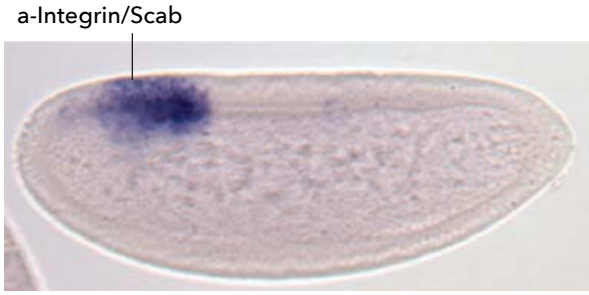
viscosity heterogeneous friction active tension

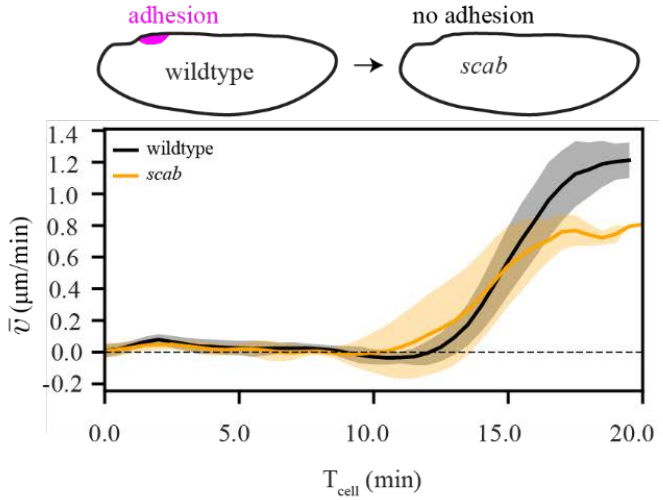
$$\eta \frac{d^2 v}{ds^2} - \gamma(1 + g\Theta_G)v = -\frac{dt_{act}}{ds} \quad (2)$$

$$t_{act} = f_a I_a + f_b I_b$$



S. Münster et al., S. Grill and P. Tomancak. *Nature* 2019

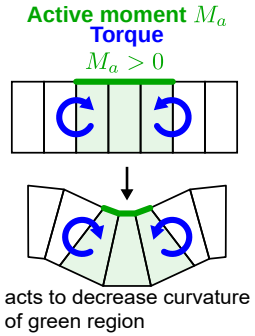


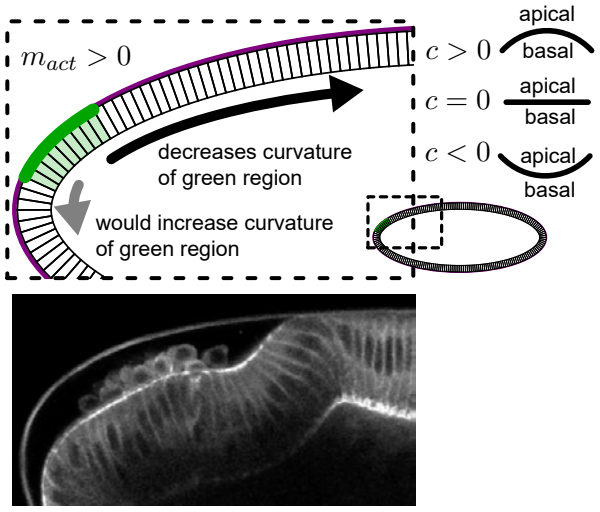


Gehrels EW, Chakrabortty B, Perrin ME, Merkel M, Lecuit T. *PNAS*. 120(6):e2214205120 (2023)

Geometry guides tissue flow

Flow emerges from interaction between egg curvature gradient and contractility





- When apical MyosinII is at higher level than basally, a positive active moment emerges that creates torque on neighboring tissue
- Positive active moment in region of apical contractility acts to decrease curvature
- The egg shell imposes a positive curvature to the tissue
- Flow arises from reduction of curvature away from embryo pole

Gehrels EW, Chakrabortty B, Perrin ME, Merkel M, Lecuit T. *PNAS*. 120(6):e2214205120 (2023)

Geometry guides tissue flow

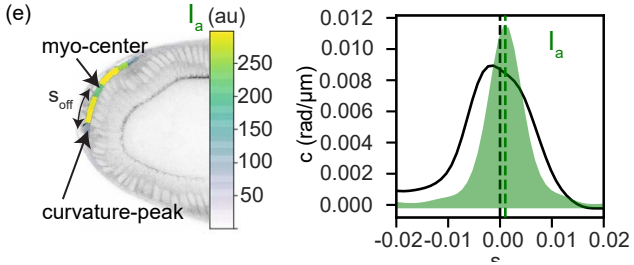
Flow emerges from interaction between egg curvature gradient and contractility

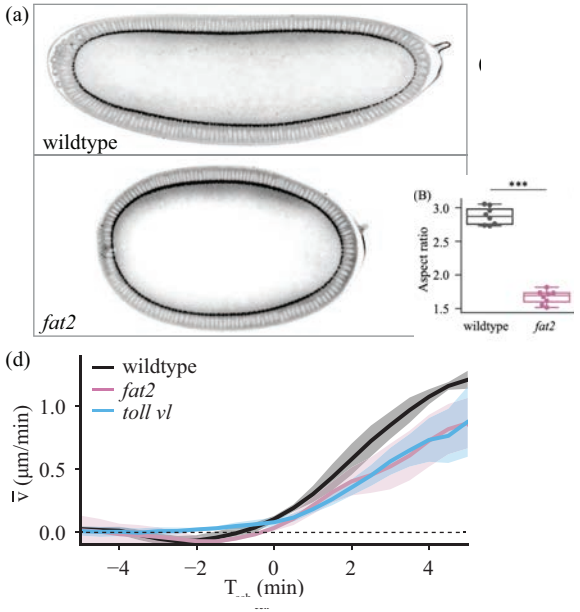
viscosity friction active tension curvature active moment

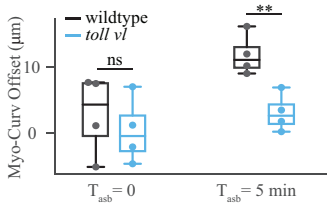
$$\eta \frac{d^2 v}{ds^2} - \gamma v = -\frac{dt_{act}}{ds} - c\frac{dm_{act}}{ds} \quad (3)$$

$$t_{act} = f_a I_a + f_b I_b$$

$$m_{act} = (f_a I_a - f_b I_b)\frac{h}{2}$$







Key parameters in the model:

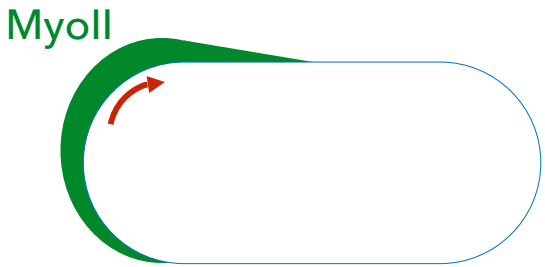
- *curvature profile*
- *offset* between curvature and contractility gradients (s_{off})

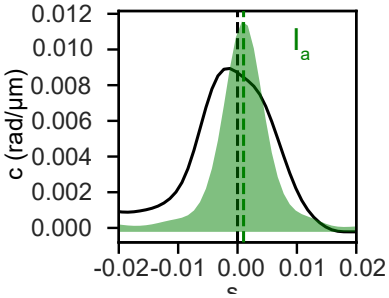
Gehrels EW, Chakrabortty B, Perrin ME, Merkel M, Lecuit T. *PNAS*. 120(6):e2214205120 (2023)

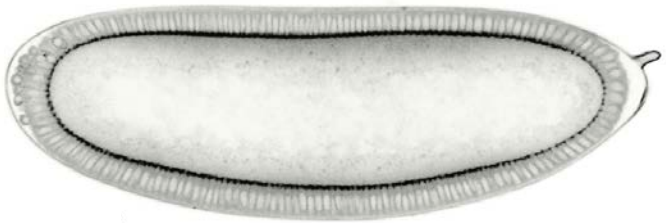
Salbreux, G. & Jülicher, F. Mechanics of active surfaces. Phys. Rev. E 96, 1–20 (2017).

Geometry guides tissue flow

Flow emerges from interaction between egg curvature gradient and contractility







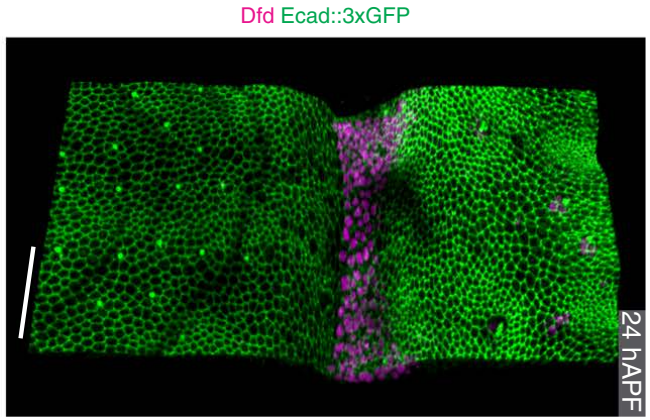
Genetics → Biochemistry → Mechanics → **Morphogenesis**

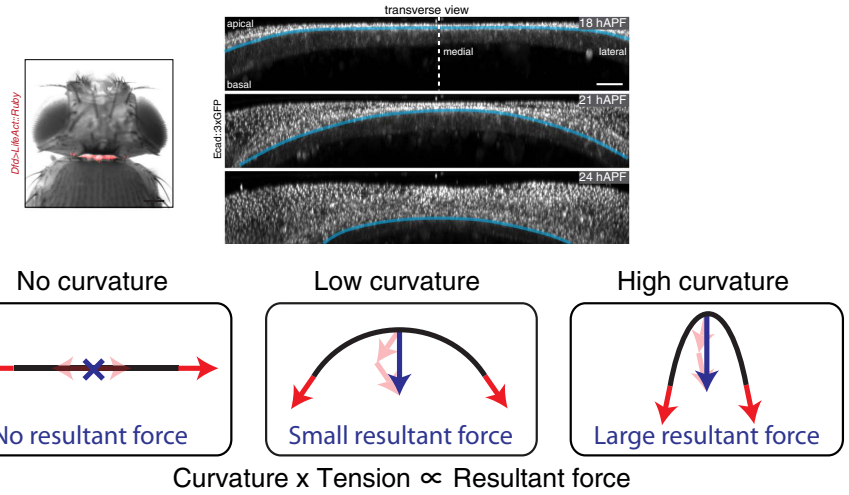
Geometry → Mechanics

Gehrels EW, Chakrabortty B, Perrin ME, Merkel M, Lecuit T. *PNAS*. 120(6):e2214205120 (2023)

Geometry guides tissue infolding

Tissue curvature translates in plane tension into invagination force





Genetics → Biochemistry

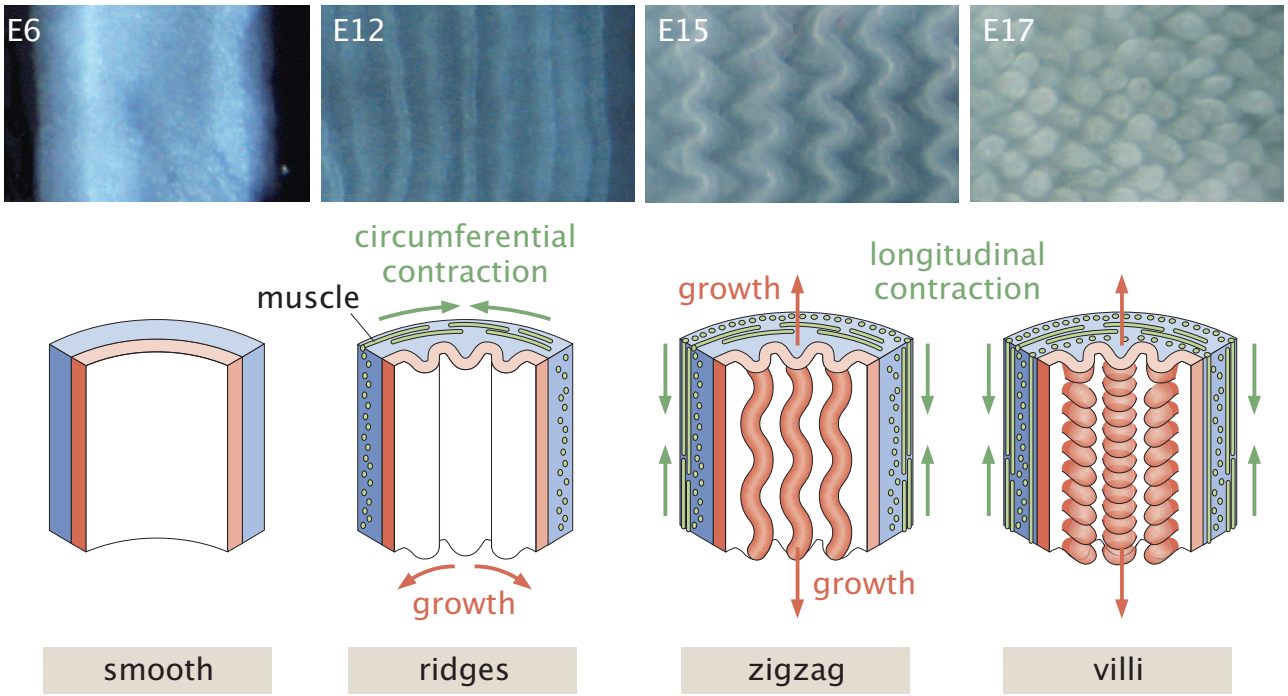
Mechanics → Shape changes

Geometry

A. Villedieu et al, and F. Bosveld & Y. Bellaïche, *Nature Communications* | (2023)14:594

Growth induced mechanical instabilities: Gut vilification

Tissue geometry as a mechanical constraint

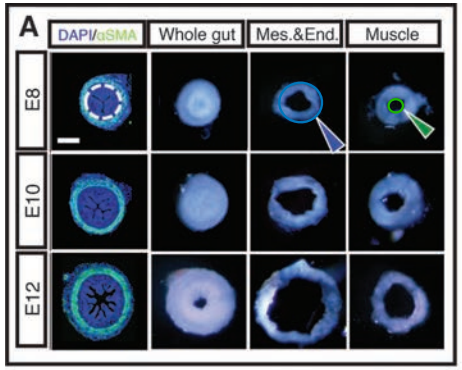


Adapted from
A. Shyer et al, C. Tabin and L. Mahadevan. *Science* 342: 212-218 (2013)

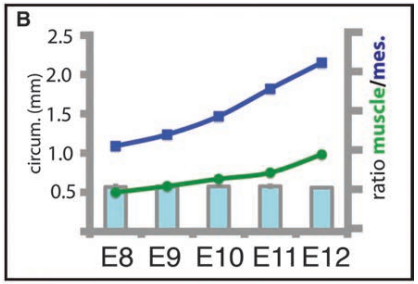
Growth induced mechanical instabilities: Gut vilification

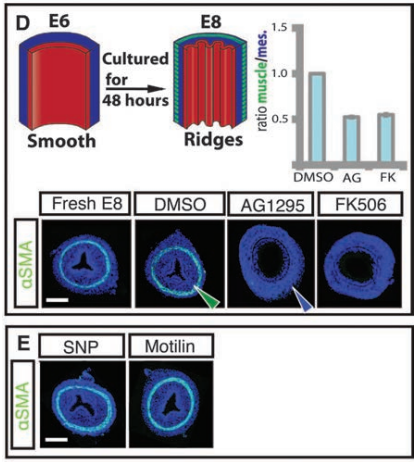
Villi arise from mechanical instability caused by differential growth and constraints

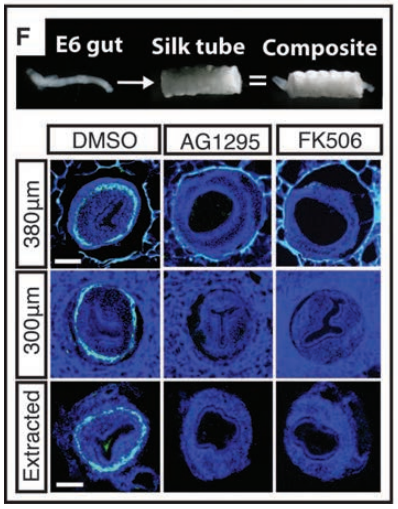
- Mesenchyme and Epithelium grow more than surrounding smooth muscles and are consequently constrained and compressed.
- Removal of smooth muscles leads to elastic unfolding of epithelium and mesenchyme
- Addition of artificial mechanical constraint rescues the need for surrounding smooth muscles
- **Role of circumferential constraints**



Mechanical removal of constraint



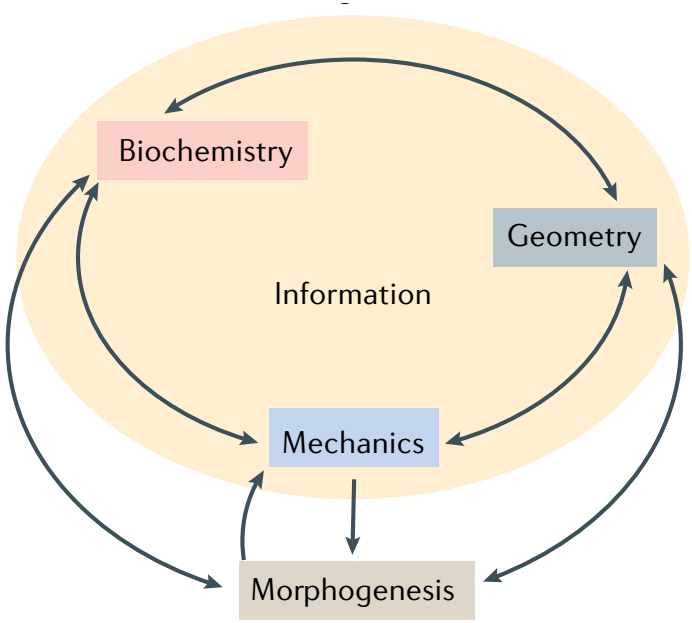




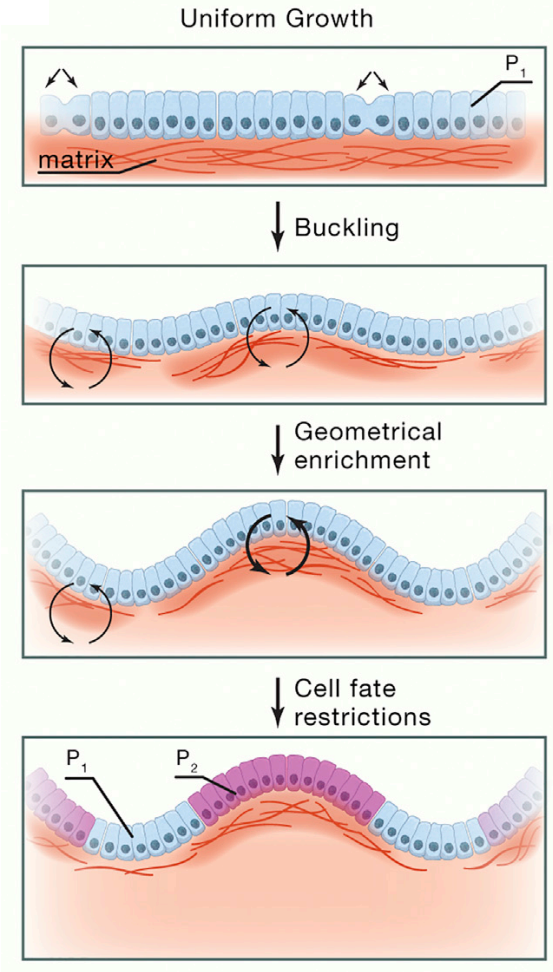
Pharmacological removal of constraint (inhibition of smooth muscle differentiation)

A. Shyer et al, C. Tabin and L. Mahadevan. *Science* 342: 212-218 (2013)

Geometric feedback: how tissue folding affects signalling



Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021

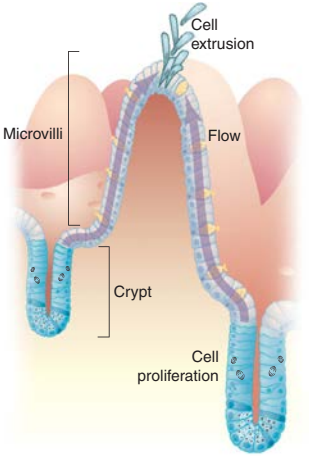


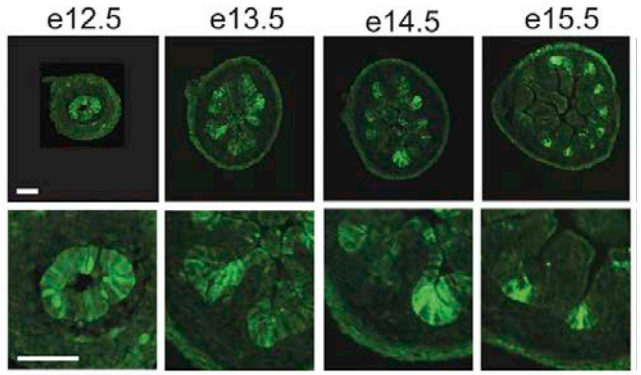
Hannezo and Heisenberg, *Cell* 178, 13-25 (2019)

Geometric feedback: how tissue folding affects signalling

Spatial organisation of villi and stem cell populations

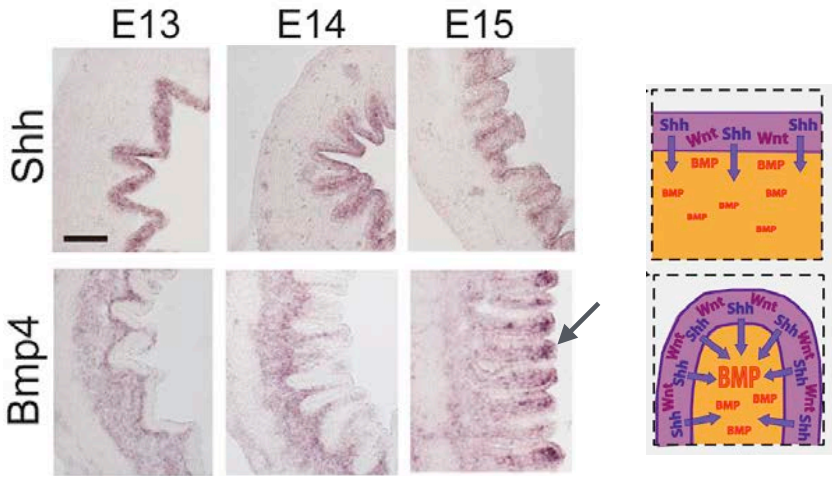
- Proliferating intestinal stem cells (ISC) form a niche at the base of villi (crypt).
- Lgr5, a marker of ISC, is first expressed in the entire epithelium, and is later restricted to regions at the base of villi.





Lgr5

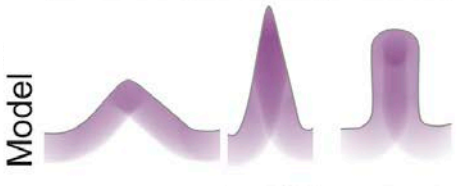
- Shh, is expressed uniformly in the intestine epithelium during formation of the villi.
- BMP4, another growth factor expressed in the underlying mesenchyme, is first expressed uniformly, but later on is restricted to the distal tip of the villi.
- BMP4 subsequently represses ISC induction at the villi tip.

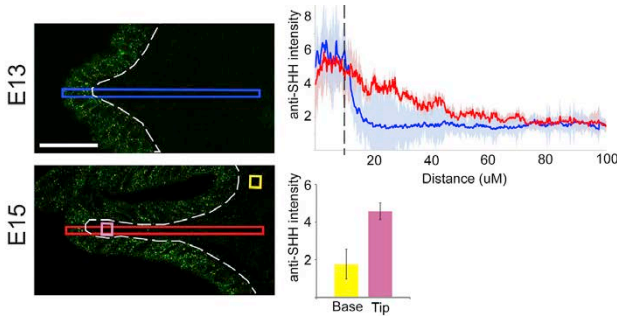


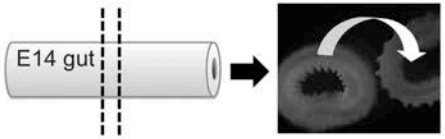
A. Shyer et al. and C. Tabin, *Cell* 161, 569–580 (2015)

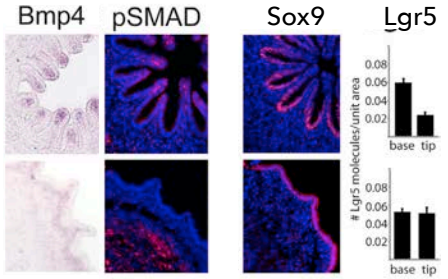
Geometric feedback: how tissue folding affects signalling

- *Hypothesis*: **Impact of surface to volume ratio on concentration of Shh.** Shh concentrates in mesenchyme surrounded by a higher surface of epithelium.
- The concentration profile of Shh changes as the tissue folds and [Shh] increases at the tip.

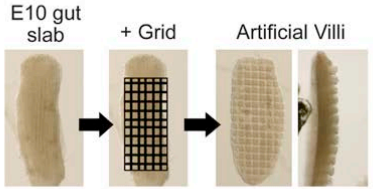


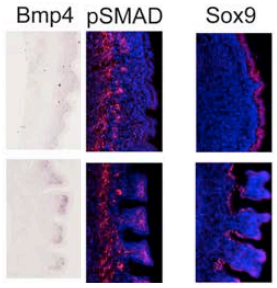






- *Testing* the role of tissue curvature:
  - ***Necessity:*** Inversion of gut curvature flattens the villi and causes loss of BMP signal and of the restriction of ISC induction at base of villi.
  - ***Sufficiency:*** induction of premature folding with a grid causes earlier BPM signalling and ISC induction at base of villi.



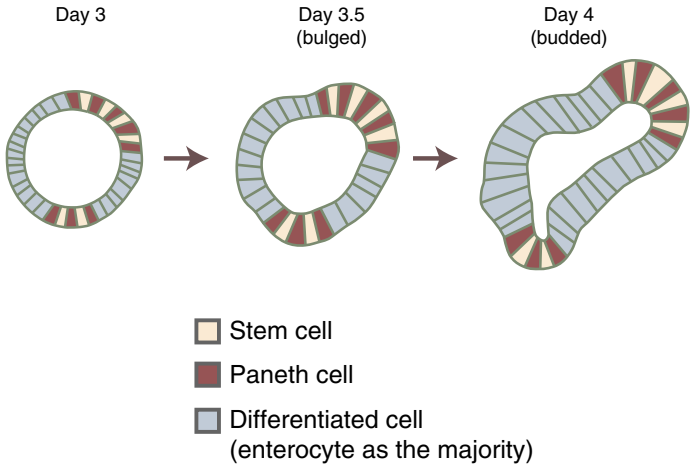


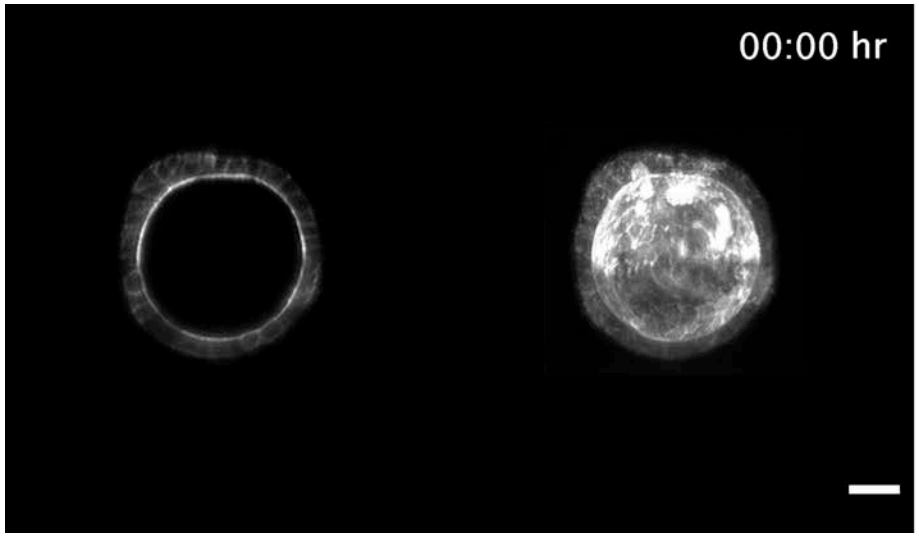
A. Shyer et al. and C. Tabin, *Cell* 161, 569–580 (2015)

Geometric control of organoid patterning

- **Spontaneous formation of crypt and villi in intestinal organoids (ie. derived from stem cells)**
- This is characterised by a lack of reproducibility in terms of cell proportions, size and number of crypts and villi.
- Organoids are embedded in Matrigel, in an isotropic environment.

- ***Hypothesis*: geometric and associated mechanical constraints could guide morphogenesis**





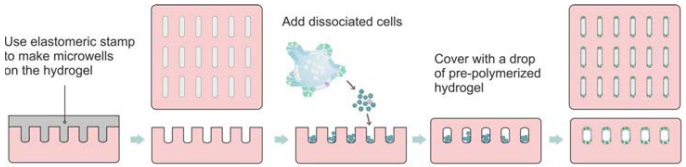
20µm

Q. Yang et al, E. Hannezo and P. Liberali, *Nature Cell Biol*. 23, 733-744 (2021)

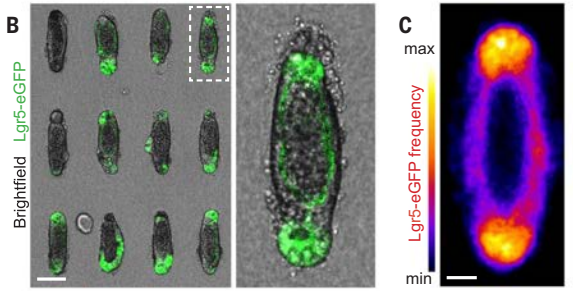
Geometric control of organoid patterning

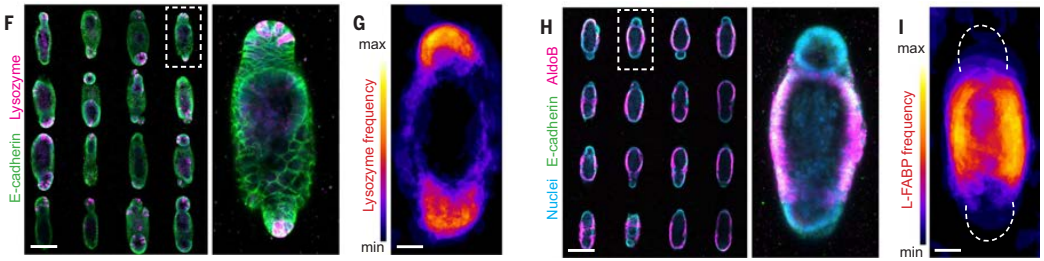
- *Hypothesis*: geometric and associated mechanical constraints guides morphogenesis

- Use of in geometric moulds to constrain and guide the self-organisation of intestinal organoids



- This gives rise to reproducible localisation of cell fate markers:
  - Stem cells at the tip (Lgr5+)
  - Paneth cells at the tip (Lysozyme+)
  - Enterocytes on the sides (AldoB+)

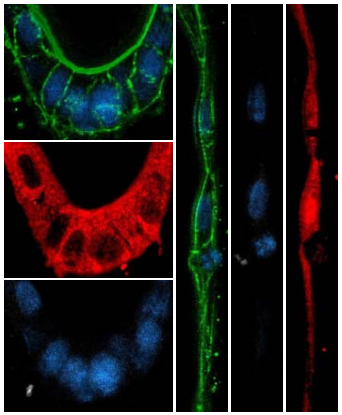




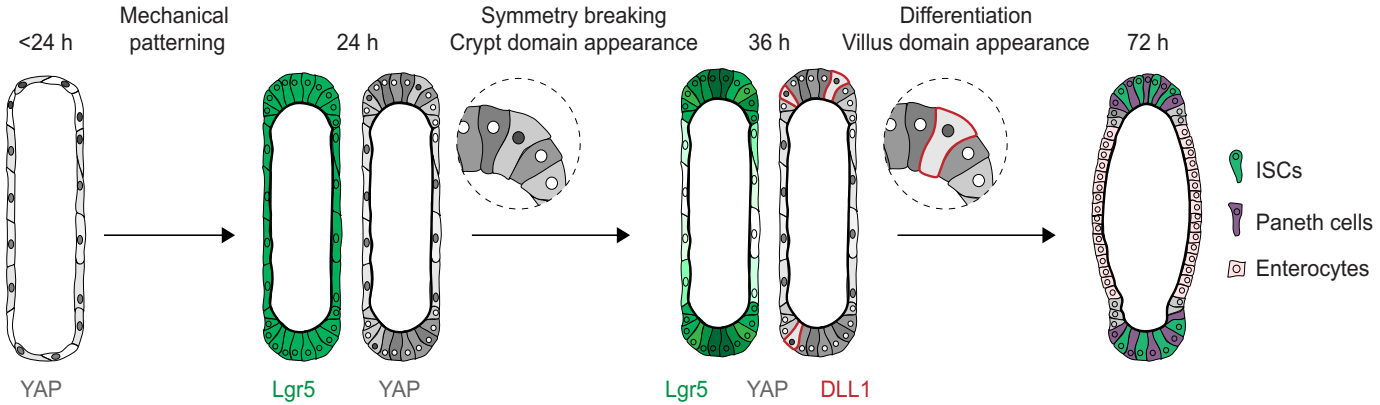
N. Gjorevski et al. and M. Lutolf, *Science* 375, 40 (2022)

Geometric control of organoid patterning

- *Hypothesis*: geometric and associated mechanical constraints guide tissue morphogenesis



- The transcription factor YAP, which is also known to translocate in the nuclei of cells under tension, eg.via ECM or cell cell contacts, localises to the nucleus on the sides of organoids and remain cytoplasmic at the tips.
- This results in repression of ISC on the side due to YAP activity and induction of Paneth cells at the tips.



N. Gjorevski et al. and M. Lutolf, *Science* 375, 40 (2022)

Conclusions - Perspectives

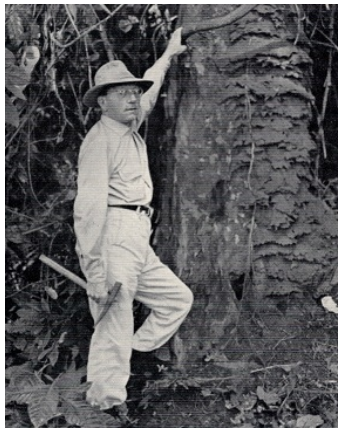
- **Structural cellular heredity and cellular self-organisation**
  - The cells are not self-organised and require heredity of structures (organelles, membranes, cortical elements etc) to perpetuate their organisation at cell division.
  - « Rehabilitation » of heredity beyond genomes.

- **Geometric information in cells:**
  - decoding cell shape via signalling: surface to volume ratio and diffusion/reaction coupling
  - decoding cell shape via mechanics: memory of cell shape during division. Begs the question of structural memory.

- **Geometric information in development and morphogenesis**
  - Serves as initial and boundary conditions that constrain mechanochemical processes.
  - Geometric guidance
  - Geometric feedback

Stigmergy: the construction guides the behaviour of workers

Structural and geometric guidance



LA RECONSTRUCTION DU NID
ET LES COORDINATIONS INTERINDIVIDUELLES
CHEZ *BELLICOSITERMES NATALENSIS*
ET *CUBITERMES SP.*
LA THÉORIE DE LA STIGMERGIE :
ESSAI D'INTERPRÉTATION
DU COMPORTEMENT DES TERMITES CONSTRUCTEURS.

par Pierre-P. GRASSÉ

La conséquence de ce type de stimulation est de régler automatiquement la marche de l'ouvrage.

La coordination des tâches, la régulation des constructions ne dépendent pas directement des ouvriers, mais des constructions elles-mêmes. *L'ouvrier ne dirige pas son travail, il est guidé par lui.* C'est à cette stimulation d'un type particulier que nous donnons le nom de STIGMERGIE (*stigma*, piqûre ; *ergon*, travail, œuvre=œuvre stimulante).

B. — ***La stigmergie et les stimulations simultanées.*** — Mais il y a plus encore. Selon que les boulettes sont rassemblées en tas ou disposées en ligne, elles ne déclenchent pas la même réponse. La forme du stimulus acquiert le pouvoir, significatif, d'orienter la construction. Elle tient donc un rôle capital pour le devenir de l'édifice.

INSECTES SOCIAUX, TOME VI, N° 1, 1959.

Conclusions - Perspectives

- **Mechanochemical information is transmitted in a geometrically constrained channel that affects transmission per se.**
- Cell and tissue shape/geometry exerts a feedback on the mechanisms from which shape/geometry emerges: tissue geometry, cell geometry (eg. in epithelial cells)
- Manifests during and tissue/organ/embryo morphogenesis:

- Geometry specifies the initial and boundary conditions.

- In development: inheritance of geometry and structures that are subsequently updated as morphogenesis progresses.

- In self-organisation, emergent shape can be a new initial & boundary condition for next process which is then guided by it.