What is biological information? nd **hinloni** s Molog

Course 5: Structural and geometric information <u>course of</u> structure ral and geometric information rai and geometric information <u>Community Co</u> <u>urse 5:</u> Structural Course 5: Stru

Thomas Lecuit **Thomas** signalized can regulate the stiffness $\mathcal{L}_{\mathcal{C}}$

chaire: Dynamiques du vivant (*k*) define the local concentration and thus the length scale (λ) and timescale (τ) of the cellular and tissue level processes driving shape changes. These challe. Dynamiques ou vivant

- 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 *ID*

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

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(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.

E

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* chemi_{ssale}homp@saneitys of the major components
- Keep high supply of energy $(A_{\text{peak}}^{\text{off the three model cells we employ often in the lab and in this case}}$
- Chemical activity is preserved and complete
- Cells do not re-assemble/self-organise from the evolved chemical components
- \bullet The chemical information in a cell is not complete to ensure the propagation of organisation
- Cells need an organisation to propagate organisation

COLLÈGE

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. 106/µm2), 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.
- Published on 01 M
 \sim Download 2017 O1: ϵ O1: ϵ f_{m} and are induced snapshots from one of the simulations. Phosphology shown are shown as stick models, with the shown as stick models, with the simulations. Phosphology with the simulations are shown as stick model and orientations characteristic of different membrane systems, or $\frac{1}{2}$ P ublished on 01 March 2016. Download by University of Newcastle on 17.1 : 17.1 • Moreover, membranes have specific protein compositions, topologies membrane organelles.

Published on 01 M

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View Article Online

Skjevik et al $Phys.Chem. 18,10573-10584(2016)$

DOI[:10.1042/BIO20200064](http://dx.doi.org/10.1042/BIO20200064) $ACab$

Membrane fusion: vesicle docking and fusing

Thomas LECUIT 2024-2025

will be discussed in detail later, additional $\frac{2}{\pi}$ simulations were performed using a similar force switch functions q as in the original C36 paper (Table 1, denoted as fsw in Table 2a, denoted as fsw in Table 2a, denoted as fsw and b). One out of three DPPC force switch repeats showed the

10 possible premature pore compared to all three repeats \tilde{z}

$\frac{1}{2}$ in the ER can compute $\frac{1}{2}$ es - Organe \bigcap ribosomes in cytosol nucleolus \sim nucleus \sim « Reproduction » of membranes - Organelle inheritance

The symbol '-' indicates that the value 12-1. **Figure 2.23:** Eukaryotic cell and its cell approximately equivalent to the top of the the top of the top portion of the nucleus can be seen Golgi apparatus
mitochondria outer most prominent organelles visible in mitochondria inner reticulum, and the Golgi apparatus. (Eukaryotic cell from Alberts et al., lysosome peroxisome 0.4 0.4 endosome

Table 1: The percentage of the total cell membrane of each membrane type in two model cells.

mitochondrion

Golgi apparatus

larger than the outer surface area of the cell its larger surface area of the plasma members of the plasma members T distribution of \mathbb{Z} and \mathbb{Z} and \mathbb{Z} are a among different organisms of \mathbb{Z} \mathcal{L} and \mathcal{L} is quantitatively detailed in Table 1. The \mathbb{R}^n shows that the member area area as a set of \mathbb{R}^n $m = \frac{1}{\sqrt{2}}$ followed by the Golgi and mitochondria. The cell plasma $\frac{1}{\sqrt{2}}$ \sim 10 μ mass to be a small fraction of less tensor of less tensor

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 sequences. δ and δ and δ and δ itic addressing matter made to list to \ldots order of the polynomial starting the polypeptide channels σ

Intracellular protein topogenesis membranes/protein integration into membranes/posttranslocation integration in

GÜNTER BLOBEL

Cell Biology

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 memar signal sequences and selective
translocation mechanisms. thesis on ribosomes, numerous specific proteins are unidirec-
- **•** Translocator proteins on receiving membrane I ranslocator proteins on receiving membrane proteins need to be sorted from each other and routed for export $\frac{1}{2}$ or targeted to other intracellular membranes or comparison or compariso Iranslocator proteins on receiving membrane
- Sinco IMPs nood a target IMP to recognise Internation for the theory is the international formation for the processes processes where to be inserted, specific membranes is predicted to be inserted, specific membranes \mathcal{L} sequences that constitute a permanent or transient particle a permanent or transient particle particle particle cannot self-organise and must arise from a pi sequences is predicted to be relatively small because $\frac{1}{2}$ existing membranes. We top and the topological Since IMPs nood a target IMP to recognise $\bullet\,$ Since IMPs need a target IMP to recognise $\frac{d}{dt}$ and the topological behavior would be topologically equivalent-i.e., tarcannot self-organise and must arise from a preof topogenic sequences would be decoded and processed by decoded and processed by \mathcal{L} existing membranes. Four topogenic sequences could be existing membranes. Ω
- geted to the same intracellular address. The information content A « genetic membrane » propagates its own distinct effects. For types of topogenic sequences \mathbf{f} to \mathbf{f} to \mathbf{f} to \mathbf{f} to \mathbf{f} to \mathbf{f} information content: Membrane inheritance. distinguished: signal sequences, stop-transfer sequences, sorting • A « genetic membrane » propagates its own information content: Membrane inheritance.

It is proposed that all of these orientations could be accom-

the determinant for intermed to the determinant \sim $\begin{array}{r} \textsf{Nobel 1999} \end{array}$ $\frac{1}{2}$ are permanent or transient or Günter Blobel (1936-2018) \sim ferent proteins whose common denominator $\bar{\mathbf{G}}$ σ the polypeptide channels in Fig. 3. It is clear from in Fig. 3. It is clear from σ

 S is S Thus, most IMPs can be integrated directly only into translocation-competent membranes. Because the translocators the member was are likely to consist of IMPs (see Fig. 1) that require
translocation for their integration into the membrane, it follows $\frac{1}{\text{d}}$ that Virchow's paradigm on the ontogeny of cells could be extended to membranes and paraphrased to *omnis membrana* $\setminus \setminus \setminus$ T increases and T and T and T and T across membranes across membranes across membranes across T themselves are likely to consist of IMPs (see Fig. 1) that require p is the chain action of \mathcal{L} e membrana.

 $S_{\rm eff}$ programs are conceivable also for conceivable also for conceivable also for cotra into P M, imm, and TKM as well as for posttrain integrational integrational integrational integrational integration

Thomas LECUIT 2024-2025 **G. Blobel.** *PNAS***. 77: 1496-1500 (1980)** G. Blobel (M*iddle*) or two members of members (polypeptide chain across one (or two) membrane(s), proceeding proteins (e.g., toxins such as the colicins or diphtheria toxin) quence) to integrate bitopic IMPs may have concluded the $U.$ DIVOCI $.$ I H then could biological members with the intervals with the intervals with the intervals \mathbb{R}

Organelle inheritance and molecular molecular molecular molecular molecular molecular molecular molecular mole \mathbf{M}

- yielding two equal fragments in each daughter cell. $\mathbf{a} \cdot \mathbf{b}$ \bullet How are organelles transmitted in daughter cells during mitosis? \bullet How are organelles transmitted in daughter cells during mitosis? \overline{a} probability such as endowed as endocytosis and phagocytosis and phagocytosis
	- budding yeast Saccharomyces cerevisiae. The mito-· Disassembly into vesicles and tubules and reassembly after mitosis $\bullet\,$ Disassembly into vesicles and tubules and reassembly after mitosis
	- $\bullet\,$ Random partitioning vs Ordered partitioning **• Random partitioning vs Ordered partitioning** cell. One of this former life is the remainder of the presence of a small size is the presence of a small size

Golgi stacks

tubules constitute the mitotic Golgi clusters (black lines). Dark areas around structures are lysosomes, which also accumulate to the same regions as MGCs. (C) MGC at higher magnification. Dispersed Golgi vesicles/tubules

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

G. Warren & W. Wickner. *Cell*, 84, 395–400 (1996) $\text{Cell}, 84, 395-400 (1996)$ *City* Orders 2014 Carl population of the spatial population of the spatial population of the endoplasments of the endoplasment of the endopla

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the ER can be sandwiched between the trans cisternae and

13 Figure 1: Shapes and sizes of mitochondria. (A) Electron microscopy image of a rat liver cell highlighting ma the results obtained for mitochondria by cytochemistry Figure 1: Shapes and sizes of mitochondria. (A) Blectron imicroscopy image of a rat jiven cell man This mage is
The numbers experiment of a rat jiven cell hugh it and the sizes of mitochondria. (A) Blectron imicroscopy ima organelles. The ER (which is a nuclear envirope) is a numerous property in yeast cell. Bud scars are labeled separatedly in blue. (D) Reticular mitochondrial network in a PtK2 kangaro yeast cell. Bud scars are labeled separatedly in blue. (D_h Retigular mitochondrial network in a PtK2 ka
cell. The mitochondria are visible in green and were labeled separatedly in the separated of motor in a PtK2 ka
the t_{noncont} of organization occurs the mitochondrial mombre transport of proteins across the mitochondrial membrance is the tubulin of the microtubules are labeled in rec reconstruction of the structure of a lamellar mitochondrion. (C) Reticular structure of mitochondria in a buddi reticulum. This image is a volumetric rendering of images of
al ViGLsc Gdenoughnuigh Lun! the numbers represent percent of
the important organelles and illustrating the size and shape of mitochondria. (B) Crythe all Echines represent percent of
from G. Schneider et al., Nat. cell. The mitochondria are visible in green and were labeled with an antibody against the proteins responsible

1981).

 ER marker (Sec61 β)
chromosome marker (H2B

 $A\subset \mathbb{R}$ that powers many cellular processes. It is now that \mathbb{R} is now that \mathbb{R}

mitophase the conditions of the conditions of the second seco

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of the Cell $20:347$

organelles.

course of the cell cycle.

This is a very dynamic process, with the mitochondrion moving in a process that is a process that is a process that is a process of the interval in the interval in the interval interval in the interval in the interval interval interval in the interval interval interval in the \mathcal{L} stopped by the september of the separation of the

These two strategies are not mutually exclusively exclusively exclusively exclusively are not mutually exclusively both can operate the copy of t number of the organisation of the organisation of species of scor-

re 2: Structural dynamics of the endoplasmic reticulum during the cell cycle. Confocal imag Figure 2: Structural dynamics of the endoplasmic reticulum during the cell cycle. Confocal images
of HeLa cells. The chiconomes are labeled in red using a fusion of a fluorescent protein with
biotono H2P. The ED the state

e Cell 20:3471, 20 \mathcal{A} stochastic mechanism (Birky, 1983b) but \mathcal{A}

morphology as a function of the cell cycle. (Adapted from L. Lu et al., Molecular Biology

-GFP). The sequence of images shows the changes in ER

like \mathcal{L} and tangled arrangement of organization \mathcal{L} $\mathbb{E}[\mathbf{v}]$ microscopy of the ER and other ubiquitous members in the cell. In this cell type and growth conditions that the reconstructions that the reconstruction reconstruction reveals that the reconstruction reconstruction relations of the reconstruction relations of the reconstruction relatio mitochondria and lysosomes are more dominant in terms of volume than the ER. The cytoplasm itself occupies more than half of the volume even if $\sum_{i=1}^{\infty}$ is definitions that take $\sum_{i=1}^{\infty}$ with take a wide slice $\sum_{i=1}^{\infty}$ with \sum \overline{a} and project it is into a dense 2D image. Structural into a dense 2D image. Structural image. Structural images in \overline{a} like these serve as a jumping off point for tackling the utterly mysterious m_{max} and m_{max} and m_{max} and m_{max} structures of the ER and other organelles are set up and change during the ER and change during t

The introduction of the electron microscope confirmed \mathcal{L} the results obtained for mitochemistry \mathcal{A} mitochondria and intracellum

The ER (which is a second includes the nuclear envelope) is a second the nuclear envelope) is a second term of \mathcal{L}

highlighting the endoplasmic

not as an ordered one.

Morphological Studies

- 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

A B C

Fig. 1. *Euplotes* **exhibits highly polarized, complex cellular architecture and walks** 3745-3757.e7 **BT.** Larson, et al **across surfaces using microtubule-based organelles called cirri, some of which are** *Current Biology* 32 (17),

			Distribution of number of ciliary rows						
Presumed number of rows in "founder"		Expected on the basis of:							
		A. Zero fidelity ^a		B. Perfect fidelity		C. Observed at 30 fissions			
cell			8	9	8	9	8	9	p
	8	-1	16	24	40	θ	40	$\mathbf{0}$	< 0.001
	8	TOMBER	21	19	40	$\mathbf{0}$	40	$\mathbf{0}$	< 0.001
Starting	8	make.	24	16	40	$\bf{0}$	39		< 0.001
clone	8	\rightarrow	16	24	40 [°]	$\overline{0}$	37		< 0.001
	9	\rightarrow	24	16	Ω	40	21	19	> 0.2
$36\% - 8$	9		18	22	$\mathbf{0}$	40	19	21	> 0.2
$64% - 9$	9	-	18	22	$\bf{0}$	40	18	22	>0.2
	Q	-	16	24	$\bf{0}$	40	6	34	< 0.001
	9	$\qquad \qquad \blacksquare$	13	27	$\bf{0}$	40	5	35	< 0.001
	9	\rightarrow	17	23	$\mathbf{0}$	40	3	37	< 0.001
	Q	-1	13	27	$\mathbf{0}$	40		38	< 0.001
	9	-	20	20	θ	40		38	< 0.001
							232	248	

^aRandom 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 cells is the same as the observed *overall* frequency of 8-rowed and 9-rowed cells a
sums shown at the bottom of column C). For further explanation, see the text. Fi with permission

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

Structural inheritance – cytotaxis uctural inneritance – cytotax

Janine Beisson (1931-2020)

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

« 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. » downloaded from https://www.production.com/
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r~~~~~~~~ $\begin{array}{ll} \text{ZATION OF THE} \end{array}$ DRN CYTOPLASMIC INHERITANCE OF THE ORGANIZATION OF THE CELL CORTEX IN PARAMECIUM A URELIA* ²⁷⁸ GENETICS: REISSON AND SONNEBORN Puoc. N. A. S. $\mathbf{R} \mathbf{N} = \mathbf{N} \mathbf{N}$ BY JANINE BEISSON† AND T. M. SONNEBORN 161818 DEPARTMENT OF ZOOLOGY, INDIANA UNIVERSITY downloaded from https://www.pnas.org/ INIST-CNRS CS10310, INT address 193.54.110.55.110.55.110.55.11 ~.,'.mr [~] [~] [~] . * Fe \sim r^* will now be demonstrated by a second type of observation. rxy and property The cortex of Paramecium aurelia exhibits a high degree of structural differentia-In a pair of exconjugants united by a cytoplasmic bridge, one exconjugant was n-A~ [~] [~] a cut (Fig. 5A, B) so as to remove roughly the anterior 2/3 of the cell including the cell $f_{\rm eff}$ at each level of organization observable with the limits of resolution observable within the limits of resolution of r β \rightarrow β $\frac{1}{2}$ in gullet in $\frac{1}{2}$ and $\$ $t_{\rm max}$ of the corresponding is remarkable pattern is remarkably constant and remarkably constant and re- 1.444 p and p is function \mathbb{R} is function of the amputated cell (represented in black) is function of the amputated in black \mathbb{R} is function of the amputated in black \mathbb{R} is function of the amputated in black For a set of the set of the set r_{\star} . \blacksquare t_{max} and t_{max} are the side notation of the side notation \mathcal{L} ts* produces faithfully through a regular contract of changes during growth and fissions. The changes of $\sqrt{\frac{1}{2}}$ \mathcal{N} in the figure \mathcal{N} remains of the posterior right field of the amputated cell of the amputated cell However, this highly stable organization can be experimentally modified. Sonneis fused to the host in the host field. The host is vestible field. The host is very state of the host of the born $\mathcal{O}(\mathcal{O}_\mathbf{X})$, the normal pattern by function of material pattern $\mathcal{O}(\mathcal{O}_\$ Download
Download $\frac{1}{\sqrt{2}}$ $\frac{1}{\sqrt{2}}$ $\frac{1}{\sqrt{2}}$ $\frac{1}{\sqrt{2}}$ $\frac{1}{\sqrt{2}}$ $\frac{1}{2}$ and is surrounded on both sides by only host circumoral material. Figures and $\frac{1}{2}$ \sum_{rpr} $v = \frac{1}{2}$ 5C, D, E shows the development of the graft during the first three fissions. In the **A pr2** pr2 $\frac{1}{\sqrt{2}}$ by partial loss of supernumerary structures, and by $\frac{1}{\sqrt{2}}$ and \frac first two successive opisthes (ol, 2), the cortical growth accompanying fission en accident of separation in which one of the material \sim larged the graft forward to the vestibular region. Then by the third fission (Fig. n-A~ [~] [~] \sum_{c} ps $\frac{1}{\sqrt{\frac{6}{\pi}} \cdot \frac{6}{\pi}}$
y » clone after 300 generations
whitiple cilia at their surface. $A \rightarrow A \rightarrow B$ $\frac{1}{2}$
sty » clone after 300 generations \mathbb{R} its partner. Sonneborn' showed, by all available methods of genetic analysis, \mathbb{R} 5E) the "daughter" vestibule, which goes to the opisthe, came to lie at the juncture of the right field (ri) of the host with the left field (12) of the graft. At the other # .4't ^A that these ability of these ability of these ability of the second mutations. The cortical mutations of the second mutations. In the cortical mutations of the cortical mutations. In the cortical mutations. In the cortical Fo> a, K' j uncture (1800 away) between host and graft cortex, the whole ingestatory apparations apparations appara-A
Pro. 1.—Normal cortical geography of *Paramecium aurelia*. (A) Wisty » clone after 300 go proved to be here \bigcap \sim comoral or vestibular fields developed; but at both \sim vestibular fields developed; but at both \sim N A **B** \cup **R** \cup A is an of the other features and B is and cytopyge, see Fig. is and cytopyge, see Fig. is and cytopyge, see Fig. is a set of the set of the see Fig. is a set of the see Fig. is a set of the see Fig. is a se type, as though the existing pattern of cortical organization itself determined the

w Twisty » clone after 300 generations
source white logalize at the incounts view, of ^a silver nitrate impregnated cell. Magnification: X 416. A cell's right and left sides

 \mathbf{r} structures, which has been called "macrocrystallinity" \mathbf{r} or "cytotaxis" \mathbf{r} $_{\rm e\, cortex}$ $\quad \bullet$ *Paramecium aurelia* have multiple cilia at their surface. · Paramecium aurelia have multiple cilia at th α and α and two sets of contractions of contractions indicate structures (CVP2). Dashed lines indicate structures (CVP2). Dashed lines indicate structures indicate structures (CVP2). Dashed lines indicate structures behind the plane of view. (C) Ventral surface of a mirror image doublet of a spirotrich (formerly hypotrich) ciliate such as *Oxytricha* or *Stylonychia*,

- on the \bullet Besturbations in the exientation of eilia and on the **•** Perturbations in the orientation of cilia arise from aberrant separation **•** and of conjugating cells with reversed orientations. m an it a a chinn ann an
Domhnulo o tionn a fudhl ple cilia at their surface.
1 of cilia arise from aberrant sep
sed orientations.
1 of cilia are transmitted clonally errant separation reference 38 with permission of the publisher. • Perturbations in the orientation of o
- stock 51 (syngen 4) of P. aurelia. All of these arose from conjugating pairs which we have \sim 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 t \sim and \sim 100s of generation. ² » clone after 300 generations
2 ltiple cilia at their surface.
3 ion of cilia arise from aberrant separ
3 ersed orientations.
3 ion of cilia are transmitted clonally c
2 ends on the organisation of the gitudinally to yield two nucleated moieties, the normally arranged mointensy produced a clone of \mathcal{L} • Perturbations in the orientation of or
	- $\bullet\,$ The orientation of cilia depends on the organisation of the 100s of generation.

	• The orientation of cilia depends on the

	environment that imparts polarisation.

	J. Beisson and

	16 3. Beisson and
3. Beisson and
3. Beisson and
3. Beisson relationships with the state of the rotationally permuted oral structures beat in the wrong direc-• The orientation of cilia depends or fissions of the heteronolar doublet cell. prl and prl', pr2 and pr2', pr3 and pr3', are the three pairs of

J. Beisson and T.M. Sonneborn. *PNAS*, 53: 275-282 (1965) particles, over $p = 1$ and $p = 1$ and $p = 1$ \ddot{o} is first three first three first three figures leading invariant to the mouth and m

Structural inheritance — cytotaxis

Preformed cell structure and cell heredity

Janine Beisson

Review

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

 \mathbb{Z} and ventral side is matrix. The ventral side is matrix in \mathbb{Z}

 b_5 $\frac{E \cdot G}{E}$ Thomas LECUIT 2024-2025

- Duplication of the basal body and of cortical patterns.
- **Key words:** Parameter of the formation of new ones. • Preformed structures are used as templates and are essential

bb: basal body a bacterial endosymbiont, or the alternative expression of mating Figure 1 depicts the organization of the cortex of *P. tetraurelia* cr: cililary rootlet $t_{\rm{max}}$ does not between precisely when such bridges between conju-

cr: cililary rootlet J. Beisson. Prion. 2(1):1-8. (2008) doi: 10.4161/pri.2.1.5063. $\sum_{i=1}^n$

on March 27, 2016

polytene chromosomes in insects, and

colleagues concluded ruefully that generalize that generalize α

Cortical Patterns in **Cellular Morphogenesis** ciated and abundantly documented first $\sum_{i=1}^{n}$ solution \mathbf{r} $\ddot{}$ cleic acid and sand. In view of the no-

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

Tetrahymena thermophila ing sand graphs to get the cellular state α cellular state α

DL. Nanney *Science* 160: 496-502 (1968). of doublet cell. AZM, adoral zone of \mathcal{Q}_1 paratus, for example, is not usually ciliary row. This figure and all subsequent figures are printed so that the printed so that the printed so tha
This figures are printed so that the printed so that the printed so that the printed so that the printed so th t (1) and the cell corresponds to the cell state bar in this and scale bar in this and

studies described. Indeed, it was enun-

 e more susceptible to a more susceptible to

readily identified with ciliary units, are common genic basis, and these permutathe pores of the contractions tions have sufficient stability to be designated *hereditary* variants. The cytoproct, or the cytopyge by different policytopyge by different mechanisms of hereditary maintenance apparently do not involve genic differ- $\sum_{i=1}^{n}$ ences—either nuclear or cytoplasmic, be encompassed in a consideration of either structural or functional—but involve rather, a multidimensional inforthrough several levels of organizations of organizations of organizations of organizations of organizations of mation storage and transmission system compared the protter whereby the pattern, in a sense, maintains itself. permutations can be established on a I have surveyed the studies bearing on the determination of cortical patterns in Tetrahymena. A variety of pattern

nisms. At least a recognition of the

OAs and OPs of both cells in the final stage of development. FZ References and Notes J. Frankel. *Eukaryotic cell.* 1617–1639 (2008) indicates the fission zone. The arrow in panel B marks an incomplete

Structure and Geometry as information was and Ocometry a $\tau_{\rm{23.5}}$ and $\tau_{\rm{23.5}}$ and $\tau_{\rm{23.5}}$ and $\tau_{\rm{23.5}}$ where $\tau_{\rm{23.5}}$ \inf inionii audit

Implications:

- **•** Such cellular structures and overall organisation and geometry are not reducible to their molecular chemical constituents. \sim Cuid $\overline{}$
- \bullet They form entities of their own that characterise cells, fertilised eggs etc. Applied **n entities of their own** that characterise cells, fertilised eggs etc. n
C

the local concentration depends on the production depends on the production–

- Cellular structures and cell geometry guide and constrain mechanochemical ε reactions and processes in cells and thereby orient their future evolution. ns and processes in cells and thereby orient their future evolution. $\overline{}$ cen geometry guide and constrain mechanochemical $\overline{}$ ierici Length scale and thoroby origin the ta pr Distance *x* iti uc
- As such, structures and geometry constitute a module of information per se that interacts with chemical and mechanical information in cells and during development **Biochemistry Mechanics** stitute a n Mechanotransduction

 A s another example, Turing instabilities control pal- \mathcal{A}

DE FRANCE

PROGRAM

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

More viscous

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

IVI f_{max} Structure and Geometry as information

- 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

23

Cells have complex and diverse morphologies and change shape dynamically

• Question: how does this affect cell signalling?

HL60 cell: human leukocyte

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

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Human Fibroblasts

Type I receptors **Type II receptors** ACVRL1 ACVR₂A ACVR1 ACVR2B BMPR1A **RMPR2**

S

Second Messenger (SMAD1/5/8) Endogenous Targets

V

BMPR1B

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.

initial generation of the concentrations. Cell, $156:1132-1138$ (2) M. Schmick and P.H. Bastiaens. Cell, 156:1132-1138 (2014)

proding cell shane information via che the membrane. The dynamics of *A* in the cytoplasm are govv2 *U* shape information via chemical signalling *V CA* (Equation 2) Here, *U(*m*)* and *V(*n*)* are the radial and angular functions for *NB*, $\overline{}$ Decoding cell shape information via chemical signalling variation along a single axis. However, all results can be readily as \mathcal{A} extended to the three-dimensional (3D) models, and although the \mathcal{J}_1 fon via chemical signaling λ

Modelling reaction and diffusion on curved surfaces erned by \mathbf{S} vn² # ð*^l* # ²^u *cosh*ð2nÞÞ*^V* ⁼ ⁰ (Equation 7) whole *CA* is the concentration of α and α and α and α Here, *U(*m*)* and *V(*n*)* are the radial and angular functions for *NB*, where *CA* is the concentration of *A* (in molecules/mm³), and *DA* is \mathbf{P} lling reaction and diffusion on curved surface ס פ \sim Activated Signaling Components Modelling reaction and diffusion on curved surfaces. The angle-dependent wave function α ponents may vary depend on the eccentricity and size of α and size of α of α

• A is a component in solution (extracellular or cytoplasmic • Solve component) and X is a membrane component. When A binds to X component, and λ is a membrane component. When λ binds to λ geometries and num
on the membrane, it forms B, which is also a membrane \bullet Case 1: A is in the c component. where P_B **Q** $\frac{k_m}{k_m}$ of P_B D_{B} **^A** kon **(i) Schematic A b** A is a component in solution (extracemular or cytopiasmic

$$
A + X \stackrel{k_{\text{off}}}{\overline{k_{\text{on}}}} B
$$

 $D_A(\mathbf{n} \cdot \nabla C_A) = -k_{on}C_A\big|_{\partial\Omega}N_X + k_{off}N_B$ 3 • Boundary condition: \overline{D} $\mathbf{u} \cdot \nabla C_A$) = $-K_{on}C_A|_{\partial \Omega}N_X + K_{off}N_B$ 3D on

 N_X and N_B are the concentrations of X and B on the membrane. C_A is concentration of A in cytosol, $\mathsf{C}_\mathsf{A}|_{\partial\Omega}$ is concentration of A at boundary: $\frac{1}{\sqrt{2}}$ (in molecules), respectively (in molecules), n is the molecules/ molecules/ mm2 ntration of A in cytosol, $\left. \mathsf{C}_{\mathsf{A}} \right|_{\partial \Omega}$ is concentration of A at boundary: **(iii) 2D simulations (iii) 2D simulations** N_X and N_B are the concentrations of X and B on the membrane. $\hfill{\blacksquare}$ ca is concentration of A in cytosol. Cal is concentration of A at boundary: c_A is concentration of A in cytosol, $\mathsf{c}_{A|\partial\Omega}$ is concentration of A

), *NX* and *NB* are the concentrations of *X* and *B* • Reaction/Diffusion of X and B at the membrane: Similarly, membrane components *X* and *B* satisfy the following

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

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

 $\sum_{i=1}^{n}$ **DE FRANCE** Thomas LECUIT 2024-2025 T boundary condition accounts for the balance between T the balance between T

a (extracellular or cytoplasmic **and the secular space** of extracellular or cytoplasmic $\frac{1}{3}$ and numerical simulations \overline{O} **X** seometries and numerical simulations **(ii) 3D simulations •** Solve these equations on spherical and elliptical and **s •** Solve these equations on spherical and elliptical **(i) Schematic (iii) 2D simulations (iii) 2D simulations (i) Schematic**

the Supplemental Information.

 \sim \sim \sim \sim geometry because it allows us to study the effect of curvature in \mathcal{L}

angular coordinates take the following form:

 \mathbb{Z}^2 *V*

 \blacksquare

B DB

vn² # ð*^l* # ²^u *cosh*ð2nÞÞ*^V* ⁼ ⁰ (Equation 7)

respectively; m is the equivalent of the radius for the ellipse,

Species A is in the cytoplasm

Species A is in the cytoplasm

vm² # ð*^l* # ²^u *cosh*ð2mÞÞ*^U* ⁼ ⁰ (Equation 6)

 \bigcap \bigcup \bigcap \bigcap • Case 1: A is in the cytoplasm:

375

numerically.

550

 \mathcal{A} Signaling from the cytoplasmic component A binds to the plasma membrane to the plasma membrane component \mathcal{A} diffuse in the cytoplasmic volume, whereas \mathcal{L}

2

^u⁼ *^a*²g*DA*

respectively; m is the experiment of the radius for the electronic section of the electronic n distribution on sphere. As the eccentricity of **angle going from 1. Example 2018** the ellipsoid increases, the membrane distribution $t = 0$ **t**=0 2D Uniform distribution on sphere. As the eccentricity of للمصرى المستشرق المستشر **at the tips. a** ^u⁼ *^a*²g*DA* ver **250**

Cell *154*, 1356–1369, September 12, 2013 ª2013 Elsevier Inc. 1357

 θ

ponents to Transient Inhomogeneities in the Membrane and the Membrane and the Membrane and the Cytoplasm in the Cytopla

Reaction rate at the membrane (30 s)

G and G a Decoding cell shape information via chemical signalling Consider the following reaction, where *A* is a component in soluthe ellipsoid, the angle-dependent wave function remains intact.

brane component. When *A* binds to *X* on the membrane, it forms

Competition between reaction and diffusion and impact of surface to volume ratio **B**, which is also a member component. This is shown in the component of the component. This is shown in the component of the component o tion bet in elliptic coordinates and Bessel functions (Arscott, 1964) in surface to volume ratio

- Diffusion homogenises concentrations. $A + X \stackrel{k_{off}}{\longrightarrow}$ *kon koff kon koff*
- But, reactions occur along the membrane and the local surface to volume ratio produces concentration differences difference in _' in elliptic geometries. ρ members members and are free to diffuse and are free to diffuse along the plane of ρ
- \bullet 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 **B** than in the center ν ersely, the volume of extracellular sp
- 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.
- and B on the groson.
• Reaction dominates over diffusion, the process is diffusion limited. es over diffusion, the process is diffusion if
c_aat 30 s
- At the center: diffusion time to membrane is much reduced so the process is not N_a at 30 s and reduced so the process is not diffusion limited. Diffusion dominates.

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B • These gradients of concentration are transient. This depends on the relaxation time scale of the al state of an be computed by comparing the state o difference in diffusion at the major and minor axis.

ary (i.e., plasma membrane) arise? The transient membrane in-transient membrane) arise? The transient membrane
The transient membrane in-transient membrane in-transient membrane in-transient membrane in-transient membrane

solutions to the reaction-diffusion system as Mathieu functions

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

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

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

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P. Rangamani et al, R. Iyengar. Cell 154, 1356-1369 (2013) *(legend continued on next page)*

Decoding cell shape information via chemical signalling la chemical signaling membrane, membrane, ϵ responding recruitment rates kdD for PNDP and ktT for PNTP; (iv) \overline{a} $T_{\rm eff}$ and recruitment is switched of the membrane profile of the total of t ϵ rell shape information via chemical signalling ϵ bourdinape information wat chomical organisming Deseding soll changinfermation via chamical signalling protein density (blue) is flat, whereas membrane-bound PNDP (protein) and PNP (protein) and PDP (red \mathbf{b} function of \mathbf{b} for \mathbf{b} for \mathbf{b} for \mathbf{b} $\overline{}$ The recruitment rate recruitment rate restores polarity. (F) D density profiles of \mathcal{D} and same bound profiles of \mathcal{D} coll chano information via ten snape moduled man bacterial pattern-forming systems. instead of and line basic symmetries as the real geometry of an E. coli cell. Importantly, in contrast to a 1D model, it fully accounts for the different di-

 $\mathcal{P}_{\mathcal{P}}$ as in Eq. () as in Eq. () with kdD $=0.1$ um $\mathcal{P}_{\mathcal{P}}$

A model for geometry-induced chemical gradients that are both stable and robust leased to the cytosol with details with the control with the control with α much more pronounced than the corresponding patterns in the absence of cooperative membrane binding. The density of PNTP (blue) is comparatively flat, and there lel for geometry-induced chemical gradients that are both stable and robust are much less membrane-bound proteins in this nucleotide state than in the PNDP state. The overall protein pattern is strongly dominated by PNDP. A Generic Reaction Module for Sensing of Cell Geometry try-induced chemical gradients \sim essential for the ability of the system to generate protein patterns hat are both stable and robust

A model inspired to account for polarity of MinD/MinE system in *E. coli,* The Colimbia of the SI Appendix, Eqs. 1–6. and AtMinD in absence of MinE. \mathbf{D} I \mathbf{D} and \mathbf{n} is \mathbf{D} $\mathsf{MinF}_{\mathsf{max}}$ bound (PNTP) state (Fig. 1A). Both forms are allowed to freely for polarity of MinD/MinE system in *E. col* D \mathbf{u} cytosolic PNDP undergoes nucleotide exchangewith a rate \mathbf{v} both protein species can bind to the membrane \mathbf{v}

Direct (w^{\perp} _{T;} w^{\perp} _D) and cooperative (k_{tT} , k_{dD}) membrane association. α (α _l, α _d_l) membrane association.

recruitment of either PNTP or PNDP to the membrane, defined as cooperatively: $R = (k_{dD} - k_{tT})/(k_{dD} + k_{tT})$ ω_{τ}^{\pm} ω_{τ}^{\pm} $P = u_{pole}/u_{middle}$ Degree of cooperatively: $R = (k_{dD} - k_{tT})/(k_{dD} + k_{tT})$ Polarity: c and c \sim c $\$ $-\frac{\mu a D}{\mu I}$ $\frac{\mu a D}{\mu a D}$

2D simulation using known rate constants and diffusivities. cooperative binding of PNDP (R). Moreover, the polarity P of PNDP (R), and polarity P of PNDP (R), the polarity P of PNDP (R), and the polarity P of PNDP (R), and the polarity P of PNDP (R), and the polarity P of PNDP (R), has been reported to dimerize (19, 21). This process thus provides

Am
9:101 mode
101 http://www.biomedia.com/1471
101 mode in 1471-2181
101 mode in 1471-1530
1530 models $\frac{1}{2}$ $\frac{28}{10}$ E _E
 $\frac{E}{\pi}$ th $\frac{1}{2}$ cumulate at poles (P > 1) if there is a preference for $P = 1$ and $P = 1$ $\mathsf{E}(\mathsf{R} > 0)$ $\begin{bmatrix} 1 & 1 & 1 & 1 \ 1 & 1 & 1 & 1 \end{bmatrix}$ When cooperative binding favors $P_{\text{NTP}}(R < 0)$, proteins $\begin{bmatrix} \frac{2}{3} & \frac{2}{3} \\ \frac{2}{3} & \frac{2}{3} \end{bmatrix}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ Downloaded from https://www.pnas.org/bookult.com/iP address 193.54.110.55.110.55.110.55.110.55.110.5 Proteins accumulate at poles (P > 1) if there is a preference for cooperative binding of P_{NDP} (R > 0). $\frac{1}{2}$ accumulate at midcell (P < 1) $\frac{20}{20}$ Downloaded from https://www.pnas.org/by "INIST-CNRS" on November 20, 2021 from IP address 193.54.111 > 0*).*
Drs P_{NTP} (R < 0), proteins Downloaded from https://www.pnas.org/con/cnRS contractors.com/
Profilist-CNRS contractors.com/

/s. The density of PNDP (red) as well as the overall protein density (green) exhibit strongly bipolar patterns, which are

The Impact of Cell Geometry on Protein Gradients in Elongated Cells.

Thalmeier D. J. Halatek and Erwin Frey. PNAS 113, 548-553 (2016). *AtMinD is localized to puncta in* **E. coli** *and chloroplasts* $\frac{d}{dt}$ $\mathbb{E}[\mathbf{H}, \mathbf{H}, \mathbf{H}, \mathbf{H}]$ $24-2025$
24.2025 (FIGT D. J. Halatek and ETWIN FIEY. FIVAS 113, 346–333 (2010). ^T where it recruits further PNTP with rate ktT . At the membrane, hydrolysis triggers de-Thalmeier D. J. Halatek and Erwin Frey. *PNAS* 113, 548–553

Erwin F
ng et al. Zhang et al. *BMC Microbiology* 2009, 9:101 \mathcal{L} $t = 1.5MCM$; $t = 1.1$, 2000, 0.101 Zhang et al. *BMC Microbiology* 2009, 9:101 -2025 Z hang et al. *BMC Microbiology* 2009 $r_{\rm g}$ ellipse). The membrane density of the protein is divided by its minimum concentration (Left: 113 μ σ_{ν}

Decoding call shane information vi **Decoung consider information vi** chamical cianalling Decoding cell shape information via chemical signalling

(recruitment) serves to a more serves to a more serves to a more profiles weakly non-nuniform profiles α

A model for geometry-induced chemical gradients that are both stable and robust protein density (green) is flat, whereas membrane-bound PNTP (blue) accumulates at midcell and PNDP (red) forms a bipolar pattern. (E) Polarity P of the membraneadel for geemetry induced chemical gradients that are beth stable and reby

A Boundary Sensity P_{NDP} [1/µm²] de la construcción de la construcc
De la construcción de la construcc $\frac{1}{\sqrt{1-r}}$ with of l \sim 1 \sim 2 \sim 1 \sim 1 poles and is depleted at midcell. In contrast, PNTP exhibits high concentration at midcell and a low concentration at the poles. The attachment and detachment rates are set to 1 μm/s and 1 s−¹ , respectively, which gives a penetration depth la \mathcal{S}_1 segregation of cytosolic PNDP and PNTP. All proteins that detach from the membrane are in an NDP-bound state and can undergo nucleotide exchange; the range of PNDP in the cytosol is limited to a penetration depth l^λ (dashed lines); here, l^λ =0.35 μm. At the poles, this reaction volume receives input from opposing faces of the $P(A \cap B)$ is a penetration depth landshed lines; here, this reaction volume receives input from opposing faces of the poles, the poles, this receives in put from opposite faces of the poles, the poles of the poles, the pol If k too smalle polarch redsheep is an antimum value of l_0 $\parallel \iota_{\lambda}$ too small, no overlap. there is an opumum value of ι_{λ} μ_{P} Pologies: The Holotek and Frygin Fray, PNAS 113, 548, 553 (2016) Downloaded from https://www.pnas.org by "INIST-CNRS CS10310, INEE & INSB" on November 20, 2024 from IP address 193.54.110.55. gradients of the P_{NDP} and P_{NTP} in the cytosol. $\overline{}^{40}$ D E fusive coupling of these biochemical processes. Fig. 2. Membrane affinity controls, and recruitment and recruitment amplifies geometry adaption. The cells used for the numerical studies μ SINR) Even when recruitment is turned of the cytosology profiles in the cytosol. PNDP and PNDP accumulates control \mathcal{R} poles and is dependent at middell. In contrast, \mathcal{L} and a low concentration at the poles. The attachment and detachment and detachment at the poles. The attachment and detachment and detachment and detachment and det , respectively, which gives a penetration of the source depth labels of the source degradation mechanism for the spatial mechanism for the spatial mechanism for the spatial mechanism for the spatial mechanism for the spat segregation of cytosolic PNDP and PNTP. All proteins that detach from the membrane are in an NDP-bound state and can undergo nucleotide exchange; the range of p_N and accumulation of P_NDP and P_N and P_N accumulation depends on the penatration depends on the penaltry on the penaltry on the penaltry on the penaltry of the penaltry of t Iso occurs at mid cell. If l_λ too small, no overlap: there is an optimum value of l_λ $\sum_{i=1}^{n} I_{i}$ and $\sum_{i=1}^{n} I_{i}$ and I_{i} and I_{i} are I_{i} and $I_{$ Thalmeter D. J. Halatek and Erwin Frey. $PNAS$ 113, 548–553 (2016). $\frac{1}{2}$ $\bullet\,$ Without cooperativity, simulations reveal concentration and the pattern formation These cytosolic gradients form seeds for membrane distribution which depends on the respective values of **The Little** membrane binding constants w_{T} and w_{D} . This weak polarisation is amplified with cooperativity. $\color{red} \diagdown$ $\frac{1}{\sqrt{2}}$ two distinct types of patterns either $\frac{1}{\sqrt{2}}$ accumulate at $\frac{1}{2}$ $\frac{1}{2}$ $\frac{0.98}{0.96}$ sities at both cell poles. The poles patterns is \sim 10.96 $\,$ t_4 0.6 0.8 1 $\omega_{\textsf{T}}^{\textsf{t}}$ [µm/s] $P = u_{pole}/u_{midcell}$. recruitment of either PNTP or PNDP to the membrane, defined as $\mathcal{L}=\frac{1}{\mathcal{L}}\int_{\mathcal{L}}\mathcal{L}(\mathbf{r})\mathcal{L}(\mathbf{r})$ accumulate at the cell poles (P \sim 1) if there is a preference for a preference for a preference for a preference for cooperative binding of P $\sqrt{10^2}$ $\overline{}$ observed in mutant Eq. EcMinE (18). In contrast, when cooperative binding favors PNTP $\overline{}$ $m \cdot m$ \cdot alue of L $\sum_{k=1}^{\infty}$ value of ℓ_{k} much more proponding patterns in the absence of corresponding patterns in the absence of cooperative members α are much less membrane-bound proteins in the PNDP state than in the 1.04 Downloaded from https://www.pnas.org by "INIST-CNRS" on November 20, 2022 from IP address 193.54.110.55.110.55 • Cytosolic reaction volume (for nucleotide exchange) determines the pattern: $\sqrt[2]{\begin{array}{c} \Delta \end{array} }$ $\frac{1}{2}$ and decay at this committy, to defining the oriental $\frac{1}{2}$. Role of diffusive coupling of membrane association/dissociation kinetics. spatial segregation of PNTP and PNDP in the cytosol? Because these ytosolic gradients form seeds for membrane $\color{red}\blacktriangleleft$ $\overline{}$ constants \overline{m} and \overline{m} p. Cannot be accounted for by geometry-dependent exchange kinetics is released from the members of the latter acts as a source acts as a source acts as a source acts as a source α iffusive coupling of membrane association/dissociation kil 1. The membrane is a source for cytosolic P_{NDP} via dissociation $\sum_{k=1}^{n}$ density profile for PNDP in the cytosol is exponential with the 2. PNDP is converted to PNTP at rate *λ* (sink) Exponential decay length: $l_\lambda\!=\!\sqrt{D_c/\lambda}$ these reaction volumes overlap close to the cell poles (Fig. 2B, These reaction volumes overlap at poles leading to concentration of $\mathsf{P}_{\mathsf{NDP}_{\mathsf{L}}}$ $\frac{42}{46}$ element of the method is th $\overline{P_{\text{max}}}$ geometry sensing. To put this result in perspective with $\overline{P_{\text{max}}}$ and $\overline{P$ particle mechanisms based on $\sum_{i=1}^{\infty} 0.6$ and $\sum_{i=1}^{\infty} 1.00 \geq$ $\begin{array}{ccccc}\n & P_{\text{NDP}} & \text{where}\n\end{array}$ $\begin{array}{ccc} \text{S} & \text{S} \\ \text{S} & \text{S} \end{array}$ and $\begin{array}{ccc} \text{S} & \text{S} \\ \text{S} & \text{S} \end{array}$ P_{NTP} $\begin{array}{|c|c|c|c|c|}\n\hline\n\textbf{NTP} & \textbf{0.2} & \textbf{0.4} & \textbf{0.6} & \textbf{0.8} & \textbf{1} \\
\hline\n\textbf{1} & \textbf{1} & \textbf{1} & \textbf{1} & \textbf{1} & \textbf{1} \\
\hline\n\end{array}$ ω_{τ} [μ minis] α distribution of nodes in the cytosol, which ensures in the cytosol here the middle stations are the middle stations are \sim $\mathsf{SCS.}$ with respect to both symmetry axes, we can further axes, we can further axes, we can further axes, we can further axes of C $0^{1/2}$ to 10^{2} λ [μ m] at middle \overline{a} α and the cytosologic nodes whose distribution α $\frac{1}{\sqrt{2}}$ poles and middle \overline{p} E Thalmeier D. J. Halatek and Erwin Frey. *PNAS* 113, 548–553 (2016). **Decoding cell shape information**
 A model for geometry-induced chemical gradivity

Without cooperativity, simulations reveal concentration

Iradients of the PNDP and PNTP in the cytosol.

These cytosolic gradients form 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*

29

 p_{Ω}

Thanneler D. J. Haratek and Erwin Piey. Tivas 115, 340–555 (2010).

parameter ranges where patterns with several maxima, not neces-

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מר

 p in the limit where the attachment rates of the two species are equal, ω

 \mathcal{L} much more proponent binding patterns in the density of P

Decoding cell shape information via chemical signalling

A model for geometry-induced chemical gradients that are both stable and robust $\mathcal{A} = \mathcal{A} \cup \mathcal{A}$ and $\mathcal{A} = \mathcal{A} \cup \mathcal{A}$ and $\mathcal{A} = \mathcal{A} \cup \mathcal{A}$ C

D Experimental property of the second second

• A well mixed cytoplasm due to diffusion prevents establishment of a stable geometryinduced chemical gradient x [um]

- $\bullet\,$ 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. eotide excritinge in a protein alters the state of the control profiles in the cytosol. PNDP accumulates control segregation of cytosolic PNDP and PNDP-bound state are in an ADP-bound state and can undergo nucleotide exchange; the range of α
- $\bullet\,$ Given that nucleotide exchange (or other posttranslational modification of \mathbf{q}_{in} atein) is very common, this may have general applicability. The same of the state of the state of the state of the state of t The model is very generic (not fine tuned, unlike chemical instabilities eg. Turing). or other posttranslational modification of **pro**tein) is very ie tuned, unithe chemical instabilities eg. Turing). The absence of P Download
Download
Download $\mathbf{P} = \mathbf{P} = \mathbf{P} = \mathbf{P}$ even when records in the cytosological offs, PNTP and PNDP form in the cytosol. PNDP accumulates control points in the cytosol. PNDP accumulates control points control points control points c poles and is depleted at midcell. In contrast, PNTP exhibits high concentration at midcell and a low concentration at the poles. The attachment and detachment

are much less membrane-bound proteins in this nucleotide state than in the PNDP state. The overall protein pattern is strongly dominated by PNDP.

 $\overline{\mathbf{A}}$

P_{NDP}

 \bullet The pattern does not have a characteristic length scale and depends rather on cell size. rates are set to 1 μm/s and 1 s−¹ , respectively, which gives a penetration depth la \mathbb{R}^2 is the source degradation of the spatial mechanism for PM depends rather on consize. Download

Cell division orientation

Hertwig's rule or « long axis rule » of cell division orientation of stress (Figure 1D). This is consistent with situations of the previous observations of the previous observations of the previous observations of

Cells tend to divide along their long axis

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

Compression of frog embryos

LE^T **a c** Mechanical decoding of cell & environment geometry

- Cells adhere to fibronectin substrates with different geometries
- \bullet Cells adopt different shap
- \bullet Cell division axis correlate long axis of ellipse fitting
- This suggests that additional factors contribute to $\begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \end{array} \end{array}$ **b** yet division axis is far more constrained. • Yet, cells on L shaped substrate have a similar triangular shape than on a triangular substrate, division orientation.
- Moreover the orientation of the spindle occurs when cells are round.

Cell geometry **and orientation** of cell division But other factors contribute as well...

60

90º 120

Shape Factor (SF): ratio of minor to major axis of ellipse fitting cell shape division (blue line). Circular graphs, superimposed on micro-pattern drawings, to the corresponding micro-pattern. The distributions of spindle orientation were 30 300 μ 300 μ 300 μ 300 μ 300 μ

M. Théry et al and M. Bornens. Nature Cell Biology 7:947-953 (2005) significant and the absence of cell geometrical bias indicated that spin-M. Théry et al and M. Bornens. Nature Cell Biology 7:947-953 (2005)

- 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.

microtubules for spindle positioning on [L]. (**a**) Cortactin and activated ezrin

on the , cells fixed and immunolabelled for cortactin and activated ezrin are shown. • *Hypothesis*: the geometry of adhesion/actin foci on the ECM orients cell division

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M Théry et al and M Dernang Nature Cell Dislam 7.047 $\sum_{i=1}^{n}$ and $\sum_{i=1}^{n}$ control control conditions (left) and in control control conditions (left) and in control co M. Théry et al and M. Bornens. *Nature Cell Biology* 7:947–953 (2005) σ ϵ σ

a based on the control of the control of

a b The geometry of the adhesive environment orients cell divisionInterpretational control of the control of Fibronectin

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

 M The orientation of the spin determines in interpretation M \mathbf{M} . There \mathbf{U} are and \mathbf{M} . Domens. *Ivalure* \mathbf{U} $\frac{1}{1}$ = 0.47 0.52 (0.005). M. Théry et al and M. Bornens. *Nature Cell Biology* 7:947–953 (2005) Figure 5**1** The spatial distribution of ECM government corresponding to ECM government corresponding to the ECM go

Thomas LECUIT 2024-2025 and the orientation of the spindle. (**a**) Membrane ruffles in interphase, as $\overline{}$ core located upon the additional periphery. Cell periphery. Cells

 $\mathbf{f}(\mathbf{r}) = \mathbf{f}(\mathbf{r})$ The geometry of the adhesive environment orients internal cell organisation

zation. (*A*) Cell surface polarity propagates to cell internal polarity. This map anisotropy of cell **polarisation of** asymmetric distribution anisotropy of cell care adhesion and of APC and adhesive environment adhesion and actin dynamics microtubules plus ends distribution of combination of combination \mathbf{r} .

adhesive micropatterns, such as the one we describe, as the one we describe, as the one we describe, are a simple and cost-effective way to control internal organization of the control internal organization of cultured and cultured α polarisation of the
nucleus-centrosome-Golgi s is a cell biology analyses are based on the parallelization and parallelizati

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Thomas LECUIT 2024-2025 of internal cell organization on the crossbow micropattern is the combination on the combination \mathcal{C} of several average distributions of cell organelles. Nuclei, centrosomes, or

M. Théry et al and M. Bornens. *PNAS* 103:19771-19776 (2006) and cost-effective way to control $(1, 1, 2)$

study both experimental decade cortical cues and spindle mechanics that governs spindle orientation. force exerted per microtubule acts in a direction tangential to the force generators, implies that the force F(y) is proportional to rr(y), $\mathsf{call} \ \& \ \mathsf{anviron}$ ment geomi ten a chwironnicht geometry $\frac{1}{2}$ \mathbf{r} at angle h \mathbf{r} w relative to the spinthe total wise number that the total number α Mechanical decoding of cell & environment geometry where \mathbf{y}

force generatively account for the observed \mathbf{f} is proportional to reflect that the force \mathbf{f} environment geometry sensin Mechanical model of environment geometry sensin<mark>g</mark>

 $\overline{}$ Detus that are associated by corresponding $\overline{}$ \bullet Retraction fibers at mitosis produce orienting cues at cell cortex. \bullet

Supplementary Information).

Our key assumption, that retraction fibres locally activate cortical

- in culture, these correlated with the presence of \mathcal{L}_max \bullet Role of cortical forces pulling on astral microtubules.
	- Cortical cues \bullet Force balance leads to equilibrium position of spindle that reflects the on microtubules b symmetry of adhesive clusters

is a dimensionless energy landscape, R is the cell radius and d=(2pD)=(CNMTR) is a dimensionless coefficient, which combiness coefficient, which coefficient α the effects of the noise strength and the strength of the strength of the strength of the strength of the coupling of the cou retraction fibres to the activity of force generators as well as the

numbers of force generators and microtubules.

 \mathcal{L}_{max} spin denote that \mathcal{L}_{max}

Cortical cues promote tension on microtubules

φ

spin de poles $3,4,12,13,13$ this results in a net torque on the spin dependence on the spin dependence on the spin \mathcal{A}

a Adhesion in interphase Retraction fibres in mitosis Orienting cues on the cell cortex

Adhesion in interphase Retraction fibres in mitosis

No adhesion No retraction fibres No cortical cues

 \mathcal{Y} d

y

α θ $R \diagup \bigwedge \psi$

f m γ

x

 R **a** $\left(\frac{a}{r}\right)$ *x* $\left(\frac{a}{r}\right)$ *x* $\left(\frac{a}{r}\right)$ *x* $\left(\frac{a}{r}\right)$ *x* $\left(\frac{a}{r}\right)$ *x* $\left(\frac{a}{r}\right)$

$Mechan^c$

- \bullet Epithelial cells tend to divide al interphase.
- Cells round up during division.

cortical tension, the authors show that as cell shape and as α creases (i.e., cells becoming more elongated) the long axis of the cell aligns with TCJ bipolarity. Moreover, global anisotropic tissue stresses result in the alignment of TCJ bipolarity with the orientation of stress (Figure 1). The stress (Figure 1D). This is consistent tent with the previous observations that anisotropic tissue stresses

GFP–Mud

GFP–Mud

*G*α*ⁱ*

• How do they keep a memory of cell long axis prior to division? tissues, but GFP–Mud∆C_C cannot restore as the cannot restore as t $\frac{1}{2}$ and $\frac{1}{2}$. Whereas the GFP–Mud \sim

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GFP–MUD FAST COMPANY GETTING FAST COMPANY COMPANY COMPANY

0.8

Cell shape potential (AU)

1.0

What \mathcal{C} cellular is the mudicipal cell division. tissues, but GFP–Mud∆CC cannot restore astral pulling forces in *mud* $\frac{1}{2}$ c **mudded** and the company of the company *G*α*ⁱ mud* GFP–Mud GFP–Mud German – German German – Germ
German – German – Ge GFP–Mud GFP–Mud GFP–Mud Fas3 GFP–Mud Fas3 GFP–Mud Fas3 GFP–MudΔPins shown in **e**) and TCJ intensities (**e**) in wild-type (WT), *Gli*, *dlg* and *pins* cells (mean±s.e.m.). Fas3, cell contours. Student's *t*-test; NS, not significant; ****P*<0.0005. Scale bars, 1µm (**a**–**d**). \mathbb{R}^2 \mathcal{N} $*$ 1.2 1.4 1.8 2.0 2.2 GFP–Mud intensity (at TCJs relative to septate junctions) 8 4 c **mudden** and the company of the company With **Gli** α distribution of α GFP–Mud Fas3 GFP–Mud Fas3 GFP–Mud Fas3

GFP–Mud GFP–Mud

 -0.4 and

GFP–Mud GFP–Mud

Figure 14.673 sec 3.215 sec 7.034 sec 14.673 s 0.756 sec 3.215 sec 7.034 sec 14.673 sec 1trosome) Nrg–GFP (septate junction) αTub–GFP (microtubles) Our finding that in metaphase the Mud distribution at TCJs is a $h = 7.034 \text{ sec}$ and $h = 14.673 \text{ sec}$

distribution of GFP–Mud∆C_C in *mud*ic in *muddature*ly, collectively, and c $\mathbf{f}(\mathbf{g})$ findings indicate that TCJs via $\mathbf{f}(\mathbf{g})$

epithelial tissues.

0°

45°

Velocity (μm s–1 × 10–2)

3

**

315°

 $\mathcal{L}=\mathcal{L}$

exert a torque (T, arrows). **e–g**, Experimental $s_n \rightarrow -\infty$

differ from wild type (Watson's *U*²

cells quantified in **b**. **b**, Mean centrosome velocity relative to microtubule ablation site (left), mean $\mathbb{E}\left[\mathbf{v}_k\right] = \mathbf{v}_k \mathbf{v}_k$ right) in wild-type, *mud*, *dlg* and *Gli* cells at 25 °C and in wild-type and *glDN* cells at 29 °C. Student's *t*-test; **P*<0.05. Orientations in *mud*, *dlg* and *glDN*

GFP–Mud intensity

c, GFP–Mud localization in *mud* (*n*=15), *pins* (*n*=22), *Gαi* (*n*=5) cells and GFP–Mud∆Pins in *mud* cells (*n*=18). **d**, **e**, GFP–Mud distribution

(**d**, images representative of quantifications

of microtubule pulling forces, specifying the spin-

With Glil and Delivery Company of the Com

GFP–Mud

 \mathcal{T}_{max}

37 1884). Future work will show use the show use of \sim further how the memory mechanism

 $\mathcal{F}^{\text{max}}_{\text{max}}$ intensity $\mathcal{F}^{\text{max}}_{\text{max}}$

d

GFP–Mud GFP–Mud

GFP–Mud GFP–Mud GFP–Mud GFP–Mud GFP–

Theory 0.6 and 0.6 and

mechanistic understanding of the state of the century-old Hertwig's rule (Hertwig,

is molecularly implemented and employed to control tissue architecture and shape during during development. It is in the control of the contro not going to take another century.

0.8

GFP–Mud potential (AU)

REFERENCES

f grunde de la componentación

f f

Force ~ microtuble length

Fig. 8d), planar mitotic spindles were not oriented according to the distribution of GFP–Mud∆C_C in an interest of GFP–Mud∆C_C in an interest of Collective light of Collective light Fig. 8d), planar mitotic spindles were not oriented according to the distribution of GFP–Mud∆CC in *mud* tissue (Fig. 2l). Collectively, \mathcal{L} and \mathcal{L} and \mathcal{L} and oriented according to the total to the distribution of GFP–Mud∆CC in *mud* tissue (Fig. 2l). Collectively,

b

T

315°

e

0°

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*

Mechanical decoding of cell & environment geometry <u>0.756 sec 3.215 sec 3.215 sec 3.215 sec 3.215 sec 7.034 sec 7.034 sec 14.673 sec 14.674 sec 14.674 sec 14.674 sec </u> a 0.056 sec 3.215 sec 3.215 sec 3.215 sec 14.673 sec 14.674 sec 14.674 Γ anical decoding of cell & en' \blacksquare f T

1.0

Tricellular junctions predict cell division orients

f

Force ~ microtuble length

- *Models/hypothesis*:
- Shape model: the pulling forces exerted by astral f microtubules *scale with microtubule length* and, as a T consequence, the model predicts the preferred spindle orientation along the long axis of the cell. f T <u>otubule length</u> and, as ce
Et
Cel $\frac{1}{1}$
- Mud intensity model: astral microtubules pull with a force proportional to the<u> cortical GFP-Mud intensity</u> and independent of microtubule length. 0 45 90 135 135 135 135 135)u e*nsity* and
- \bullet Data: Measurement of orientation angle difference between data and predictions based on the specific models shows a 0.6 better alignement with the **Mud intensity per se than cell shape.** f
ว_่
h an u $\frac{1}{\sqrt{2}}$ Tdivision Ttheory 0.6 0 360 a r c f
m
el n models sho di
C
r tte

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dle with Mud local • A mud mutant that cannot exert pulling forces leads to a
lower alignement of spindle with Mud localisation at Spindle orientation (°) lower alignement of spindle with Mud localisation at Spindle orientation (°) junctions

<u>0.756 sec 3.215 sec 3.215 sec 3.215 sec 3.215 sec 7.034 sec 14.674 sec 14.674 sec 14.674 sec 14.674 sec 14.67</u>

5 6

μm s–1 × 10–2) 3

90°

45°

* * *

–5 min –2 min –1 min 0 min

*

270°

315°

0.03 0.015

Figure 2 | **TCJs regulate Mud-dependent**

microtubule pulling forces to orient divisions. a, Ablation of astral microtubules (red line), *n*=21 cells quantified in **b**. **b**, Mean centrosome velocity relative to microtubule ablation site (left), mean

Floris Bosveld et al, and Y. Bellaiche. Nature 530: 495-49 $\frac{1}{9}$ $\frac{1}{2}$ Floris Bosveld et al, and Y. Bellaiche. Nature 530: 495-498 (2010) \mathbf{s} 16) contract a mud (16) Floris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016)

Encoding of cell shape by tricellular junctions

- Measurement of two cell anisotropies:
	- Cell shape anisotropy: *ηshape*
	- TCJ distribution anisotropy: *ηTCJ*
- Orientation of anisotropy: *θshape* and *θTCJ.*
- During division, cell shape anisotropy reduces a significantly, while TCJ anisotropy remains relati unchanged, suggesting that TCJ retain more information for the positioning of the mitotic spindle. **Definition**
- 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 divisions, orientation, but not shape anisotropy.
- When cells are more round (ie. low shape anisot *n*_{shape}), TCJ anisotropy predicts cell division orient better than shape. E-Cad–GFP

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loris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016) $|\theta_{\text{TCJ}}|$ Floris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016) 30: 495-498 (20 i $|\theta_{\rm TCJ}$ ·

 η_{TCJ}

 \sim

 \sim

 $E \subset \mathbb{R}$

 η_{TCI}

 \overline{a} $\theta_{\rm TC}$ **h**, Differences (green bars, mean±s.d.) between

0° 0°

*θ*shape and *θ*TCJ versus *η*shape

Encoding of cell shape by tricellular junctions.

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

3-498 (2016)
etg Floris Bosveld et al, and Y. Bellaiche. *Nature* 530: 495-498 (2016)

- 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

Elastic Viscoelastic

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

Concentration

x

Geometry constrains tissue flow

• Geometry defines boundary conditions and constrains tissue flow \mathbf{r} intercalation between cells (see Supplementary Notes for the Supplementa ains tissue flow \blacksquare

incorporation the mechanical forces with α and the cells and the

 \sim

Posterior

(D and E) Tissue flows in the model as the model as the model as the model as the resultant of area changes of a

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Thomas LECUIT 2024-2025 Gehrels EW, Chakrabortty B, Perrin ME, Merkel M, Lecuit T. *PNAS*. 120(6):e2214205120 (2023)

symmetric polarized

 $\overline{1}$ min 17 mi

Polarized tissue flow requires contractility

E G E
ANCE Thomas LECUIT 2024-2025

WT ets

Localized friction or adhesion is not required for flow

3 **the polarized flow. (A)** Schematic representation of our model, equation (2), which is similar to equation

4 (1) in **Fig. 3 A**, but with an additional domain *G* (magenta) of localized increase in friction by a factor *g*. **(B,**

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

Flow emerges from interaction between egg curvature gradient and contractility

 \diagdown

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 \mathbf{z}

constant over time

1300

would increase curvature Geometry guides tissue flow

 α erges from i α Flow emerges from interaction between egg curvature gradient and contractility

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 $= 0$

1AOMAtry of green region Geometry guides tissue flow $= 0$

Flow emerges from interaction between egg curvature gradient and contractility

Geometry guides tissue infolding tissue
Internectional U
er $\frac{2}{\pi}$ les
<u>—</u> <u>9</u> $\overline{}$ **des tissue infoldir Geometry guides tissue infolding**

20

Tissue curvature translates in plane tension into invagination force $\frac{1}{\sqrt{2}}$ _
na .
ic folding(MyoII)tissues, SI ----
ne l abelis welling welling we
also into **3** $\overline{}$ \mathbf{r} lana tangjan into invasing ates in piane די!
ר

16

 14 hAPF \sim

(Fig. folding

apical

stereotypical

initial

Note).

Dfd Ecad::3xGFP

16

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)

ridges, zigzags, and villi with the sequential formand machanica cu mcchanica circumferential restriction of the outward expaninctabilitioc: C m stabilities. $\overline{}$ surgical separation of the layers, indit wilitiestian cle provides most of the circumferential constraint. Ridges Form Because of Muscle-**Triguced Med** \mathbf{t} can find the ratio of \mathbf{t} ical instablities. \sim could drive existence to, or \sim aut villilicationi might be linked. cular smooth muscle and formed luminal folds. anical instabilities: v $B = \frac{1}{2}$ Growth induced mechanical instabilities: Gut vilification

 $\mathcal{L}_{\mathcal{A}}$ the constraint provided by the music provided by the

of the muscle layer in the control samples to the

Constrained Azimuthal Growth of the Einstability C T notion that differential growth of layer of the muscle layer in the control samples to the o by cifferential instead of, functioning as a passive barrier to exirowth and const chanical inctability. plant ridge formation in health in health in health in health in health in the second in health in health in h Endoderm-Mesenchyme Composite m mechanical instabili Villi arise from mechanical instability caused by differential growth and constraints

 t_{max} row more in the embryonic group given situated the layers and \mathbb{E} fects on the morphologies. When the interest more more interest m s and are and m chymru and epithelial layers at different stages at different stages at different stages at different stages a \mathbb{F} from E8, when the circular muscle layer first \mathbb{F} forms, to E12 just before the first longitudinal problems of the first longitudinal problems of the first longitudinal problems. muscle layer forms, we found that the mesenfects on their respective morphologies. When the • Mesenchyme and Epithelium grow more $\|$ cost peugoles and exertile than surrounding smooth muscles and are \parallel $\frac{1}{2}$ inadended the first longitudinal local state $\frac{1}{2}$ $\begin{array}{ccc} \text{consequently} \text{ constrained} & \text{and} \end{array}$ chyme and attached epithelium unfold (Fig. 2A). This indicates that relative growth of these layers compressed. the ridge patterns in the embryonic gut, we sureding smooth muscles and are $\overline{}$ conbined and

The notion that differential growth of layered

Constrained Azimuthal Growth of the

- $s_{\rm s}$ indeed the ratio strained with the muscle layer; indeed the ratio $\frac{1}{\sqrt{2}}$ • Removal of smooth muscles leads to **F** muscle layer to the outer circumference of the elastic unfolding of epithelium and cumferential stretch ratio, consistently averages averages averages averages averages averages averages averages mesenchyme no o and attached epithelium unformation under the set of the set o ing of epithelium and
- mesenchyme (Fig. 2C). constraint <u>ide</u> that the circular muscle layer, once differentiated, $\mathbf{H} = \mathbf{V}^T$ urrounding smooth $\|\cdot\|$ the free azimuthal expansion of the mesenchyment \mathbf{f} $\frac{1}{2}$ and the time of these times times times the times times times the times times times the times times times the times of t relative to the muscle layer leads to azimuthal and muscle does not abolish ridge pattern in the \bullet Addition of artificial mechanical constraint rescues the need for surrounding smooth muscles muscle layer to the outer circumference of the rtificial mechanical constraint to or surrounding sincour
- Role of circumferential constraints $\sqrt{\frac{2}{3}}$ relative to the muscle layer leads to a muscle layer leads to a muscle layer to a muscle layer to a merential constraints

circumference of the unit of the unit of the unit of the unit of the inner and endoderm (blue arrowhead) is la

 $\frac{1}{2}$ muscle (dotted line). When separated from the muscle, the muscle, the mesenchyme and attached from the mesenchyme and attached the mesenchyme and attached the mesenchyme and attached the mesenchyme and attached endoderm und Science 342: 212-218 (2013)

stals it forms, the contraction of σ muscles on σ

instead of, functioning as a passive barrier to ex-

and parallel luminal folds, indistinguishable from in ovo E8 guts (Fig. 2D). When E6 guts were

Geometric feedback: how tissue folding affects signalling

 \overline{C} iii \overline{C} enough beyond a certain timescale. The application of \overline{C} Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021

Biochemistry Mechanics

 $\begin{array}{ll} \mathbb{Z}_M^* \quad \text{co}\ \texttt{L}\ \texttt{E}\ \texttt{S}\ \texttt{E} \quad \text{I} \quad \text{$

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

Geometric feedback: how tissue folding affects signalling

Spatial organisation of villi and stem cell populations

n^oCell **Paytrusion**

Flow

Crypt

Microvilli

 C_{el} proliferation

- 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.
- \bullet 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. $\overline{\mathbf{a}}$

A. Shyer et al. and C. Tabin, *Cell* 161, 569-580 (2015) π . shown using c. C_0 ll 161 560 580 (201 $tanh, Ceu 101, 505 - 500 (201$

processes (47, 48). For instance, polarization cells and polarized cells in the cells of the cells of the cells

pathway, namely Celse of Dro-California and Dro-California and Dro-

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Geometric feedback: how tissue folding affects signalling

- Model • *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.

 $+$ Grid

Artificial Villi

 $A = \frac{1}{2} \int_{0}^{1} \frac{1}{\sqrt{2}} \, \mathrm{d}x$

(A) Luminal views of the chick intestine from E13 to

- *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.

E10 gut

slab

Thomas LECUIT 2024-2025 A. Shyer et al. and C. Tabin, *Cell* 161, 569–580 (2015)

574 Cell *161*, 569–580, April 23, 2015 ª2015 Elsevier Inc.

 $\overline{=}13$

 $E15$

NATURE CELL BIOLOGY ARTICLES IN A SECOND ARTICLES IN A SECOND ARTICLES IN A SECOND ARTICLES IN A SECOND ARTICLES \mathcal{L} region-specific manner (Fig. 3a, b). The crypt morphology (Extended the crypt) morpholog for contriguents of ϵ inhibiting myosin increases organoid survival survival survival survival survival survival survival survival s residual stresses from contraction (Supplementary Crypton) Geometric control of organoid patterning

 $\mathcal{L}_{\mathcal{A}}$ and $\mathcal{L}_{\mathcal{A}}$ and $\mathcal{L}_{\mathcal{A}}$ and $\mathcal{L}_{\mathcal{A}}$ and $\mathcal{L}_{\mathcal{A}}$ and $\mathcal{L}_{\mathcal{A}}$ and $\mathcal{L}_{\mathcal{A}}$

in crypts and villi, we validated the involvement of myosin IIA in

- \bullet Spontaneous formation of crypt and villi in intestinal organoids (ie. derived from stem cells) $\mathcal{L}_{\mathbf{p}}$ If and villi in intestinal organoids (ie de *actomy crypt morphoedelling crypt morphoedelling* phogenesis and generation of spontaneous curvature. The generation of spontaneous curvature. We constructed mos
- \bullet This is characterised by a lack of reproducibility in terms of cell proportions, size and number of crypts and villi. inhibiting myosin increases organoid survival ϵ mumber of crypts and villi. Note). Nonetheless, as myosin IIA exhibits a differential pattern
- Organoids are embedded in Matrigel, in an isotropic environment.

 $\mathcal{L}_{\mathcal{P}}$ particles are in agreement with region-specific tension-specific tension-specific tension-specific tension

myosin contraction contraction at day 3 before bulging prevents crypt more bulging α

 \bullet *Hypothesis*: geometric and associated mechanical constraints could guide morphogenesis

RESEARCH | RESEARCH ARTICLE

RESEARCH | RESEARCH ARTICLE

- \bullet *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:
	- \circ Stem cells at the tip (Lgr5+)
	- Paneth cells at the tip (Lysozyme+)
	- Enterocytes on the sides (AldoB+)

Add discogiated cells

were preferentially localized to the same endlocations as the ISCs (Fig. 2, F and G), whereas the latter were on average excluded from the ends and confined to the middle of the tissue (Fig. 2, H and I). These findings suggest that \mathbf{H} and \mathbf{H} and I). These findings suggests that \mathbf{H}

microfabricated tissues of controlled size and shape. (B) An array of intestinal

~80 tissues. (D and E) An array of intestinal organoids at day 5 (D) and

microfabricated tissues of controlled size and shape. (B) An array of intestinal

~80 tissues. (D and E) An array of intestinal organoids at day 5 (D) and

microfabricated tissues of controlled size and shape. (B) An array of intestinal organoids formed from engineered intestinal tissues of rodlike geometry and magnification. (C) Frequency map showing average Lgr5 expression over ~80 tissues. (D and E) An array of intestinal organoids at day 5 (D) and

> lapse microscopy (Fig. 3, A to D, and movie S2). Lgr5 expression at the time of seeding and shortly thereafter (<2 hours) appeared uniformly low. As the organoids formed in the crypt-like space, Lgr5 was reeded strongly was related strongly was related strongly was related strongly was related to the control of the control at the ends of tissues, remaining low else-

lapse microscopy (Fig. 3, A to D, and movie S2). Lgr5 expression at the time of seeding and shortly thereafter (<2 hours) appeared uniformly low. As the organoids formed in the crypt-like space, Lgr5 was reexpressed strongly at the ends of tissues, remaining low else-form \mathcal{C}

N. Gjorevski et al. and M. Lutolf, Science gionalization, we observed a morphological YAP. Shortly after seeding, YAP was uniformly after seeding, YAP was uniformly after seeding, YAP was uniformly $\frac{1}{\sqrt{2}}$ substituting the generation of $\frac{1}{\sqrt{2}}$. If S_{ciance} 375 Δ (2022) \mathbf{r} ; such cell states that \mathbf{r} is \mathbf{r} and \mathbf{r} N. Gjorevski et al. and M. Lutolf, Science 375, 40 (2022) $\overline{}$

morphology between the different regions of the

nuclear throughout the tissue, except in some cases where cell crowding was observed early was observed as a straight of the control in the curved regions as a result of (stochastic) variations in cell density (fig. S4A). Between 12 and 24 hours after seeding, corresponding to the time when spatial differences in cell shape appear (and preceding the patterning of Lgr5), nuclear YAP localization became restricted to the lateral regions of the tissues. At the ends of the tissues, cytoplasmic translocation, and

in the array of intestinal organoids (F) and average Paneth cell distribution (G). (H and I) AldoB-expressing enterocytes within rod-shaped organoids (H) and average enterocyte distribution (I). The dashed lines indicate the average contour of the tissues. Scale bars, 100 mm [(B), (D), (F), (H)], 25 mm [(C), (G), (I)].

in the array of intestinal organoids (F) and average Paneth cell distribution (G). (H and I) AldoB-expressing enterocytes within rod-shaped organoids (H) and average enterocyte distribution (I). The dashed lines indicate the average contour of the tissues. Scale bars, 100 mm [(B), (D), (F), (H)], 25 mm [(C), (G), (I)].

> Yes-associated protein 1 (YAP) is a regulator of ISC fate (24–27), which is strongly influenced by cell shape and mechanics (28, 29). To ascertain whether the differences in cell morphology between the different regions correlated with differences in YAP activity,

Yes-associated protein 1 (YAP) is a regulator of ISC fate (24–27), which is strongly influenced by cell shape and mechanics (28, 29). To ascertain whether the differences in cell morphology between the different regions correlated with differences in $\mathcal{A}_\mathcal{A}$ activity, and the differences in $\mathcal{A}_\mathcal{A}$

in the array of intestinal organoids (F) and average Paneth cell distribution (G). (H and I) AldoB-expressing enterocytes within rod-shaped organoids (H) and average enterocyte distribution (I). The dashed lines indicate the average contour of the tissues. Scale bars, 100 mm [(B), (D), (F), (H)], 25 mm [(C), (G), (I)].

lapse microscopy (Fig. 3, A to D, and movie S2). Lgr5 expression at the time of seeding and shortly thereafter (<2 hours) appeared uniformly low. As the organoids formed in the crypt-like space, Lgr5 was reeded strongly was related strongly was related strongly was related strongly was r

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Downloaded from https://www.science.org at bibCNRS INSB on February 02, 2022

Several recent studies have in activation in the repression in the repression of canonical ISC and canonical signatures, including Lgr5, Olfm4, and EphB3, during intestinal regeneration and cancer $\mathcal{L} = \{1, 2, 3, 4\}$. Support the spatial and temporal and te

- led mechanical constraints quide tissue morp \bullet *Hypothesi*s: geometric and associated mechanical constraints guide tissue morphog minister and control of the internuclear distance, cell shape, and subcellular • *Hypothesi*s: geometric an<mark>d associated mechanical constraints guide tissue morphogenesis</mark>
	- $t_{\rm eff}$ the tissues. Individual side regions of the tissues. Individual side $t_{\rm eff}$ • The transcription factor YAP, which is also known to be \mathbb{R} α colleal contacts localized organoids and remain cytoplasmic at the tips.

(A and B) Bright-field and Lgr5-eGFP time-lapse imaging of the representative organoid development (A) and frequency maps showing average Lgr5 expression over ~80 tissues (B). (C and D) Relative changes in the Lgr5-eGFP expression in curved ends and flat sides of the original sides of

averaged tissue over time (D). (E) Immunofluorescence images showing the difference in

activity and induction of $F^{\mathcal{A}}$ between cells of the end and the side regions of the side regi activity and induction of Paneth cells at the tips.

and appearance of the first DLL+

representative organoids. (L) Schematic illustration

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 s small (100 mm) diameter, and large (100 mm) resulting in a packed or a spread system (fig. S_4 activity strongly correlated with S_4 cell spreading: Nuclear translocation was significant translocation was nificantly more frequent with 100-mm wells with 100-mm wells with 100-mm wells with 100-mm wells with 100-mm wells

 \overline{C}

| Geometric control of organoid patterning

- 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 terre, p. 60. -- 2. *La phase de coordination,* p. 61. A. La densit6 critique tion guides the behaviour of workers.

critique ; les situations des ouvriers, sur Funde in et sur l'autre, sont identité de la propriété de la propr ils sont soumis du pilier de l
ET LES COORDINATIONS INTERINDIVIDUELLES **CHEZ** *BELLICOSITERMES NATALENSIS* **External du sommet du pilier du sommet du pilier du sommet du pilier du pilier du pilier de la component du component du component du component du component du component du component du** support, l'autre ~ l'orienter vers l'autre pilier. Bien que les travaux soient ET *CUBITERMES SP.* SOCIAUX .. 76 accomplis *par des ou~riers qui changent d tout instant,* qui n'oat pas de LA THt~ORIE DE LA STIGMERGIE **:** VII. -- AUTEURS CIT#.S .. 80 rapports entre eux, du fair manuel de la qualit \sim des stimuli, les construers entre eux, les construers entre e tions, arees ou la message in the second response in the convergence of the COMPONE TUDE. DU COMPORTEMENT DES TERMITES CONSTRUCTEURS. de synth~se, p. 68.

des arceaux s'effectuel avec precision et apparement sans difficult^a de stimulation de stimulation par la cr6a
Il faut un changement de stimulation par la cr6ation de stimulation de stimulation de stimulation de stimulat nouvelles stimuli, en l'especialistica constructions modifiées par les par les par les par les par les par les

La conséquence de ce type de stimulation est de régler automatiquement la *marche de l'ouvrage.* et la signification de ce que nous nommons plus loin la *stigmergie. <u>In traduction</u>*

n*ene de t'ouvra*ge.
La coordination des tâches, la régulation des constructions ne dépendent pas directement des ouvriers, mais des constructions elles-mêmes. *L'ouvrier* pas uneccennent des ouvriers, mais des constructions enes-memes. L'ouvrier
ne dirige pas son travail, il est guidé par lui. C'est à cette stimulation d'un
tres porticulier que nous demans le para de grandes (tienes pinêtes ne airige pas son travait, à est galae par tat. G est à cette stimulation d'un
type particulier que nous donnons le nom de srigmeneraie *(stigma,* piqûre ; *ergon, travail, œuvre*=œuvre stimulante). ϵ inent des ouvriers, mais des constructions enes-memes. I orgon, travail, œuvre=œuvre stimulante). donn~ de l'espaee, pour devenir, *par elles-mdmes, des stimuli significati]s* (i). *boulettes de terre agit sur les ouvriers constructeurs d la maniire d'un centre*

R — *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 en nghe, enes ne declendient pas la meme reponse. La forme du sommatis acquiert le pouvoir, significatif, d'orienter la construction. Elle tient donc $\hat{\mathbf{n}}$ rôle capital pour le devenir de l'édifice. comportement bfitisseur a ~t6 fournie par l'observation de la conduite estanties
B. -- *La stigmergie et les stimulations simultanées*. -- Mais il y a portonomiente de la profondeur. Il profonde
Porton de la profondeur. Il profondeur de la profondeur. Il profondeur de la profondeur de la prof en ligne, elles ne déclenchent pas la même réponse. La forme du stimulus un rôle capital pour le devenir de l'édifice. Acanthonymes natalensis, de l'acametermes acanthonymes acanthonym
De la probabite mes natalensis, de l'academie de l'édifice.

INSECTES SOCIAUX. TOME VI. Nº 1. 1959. INSECTES SOCIAUX, TOME VI, $\mathbf{x}^{\mathbf{o}}$ 1, 1959.

stigmergie et les stimulations simulations simulations simulations simulations simulations simulations and

- 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.

