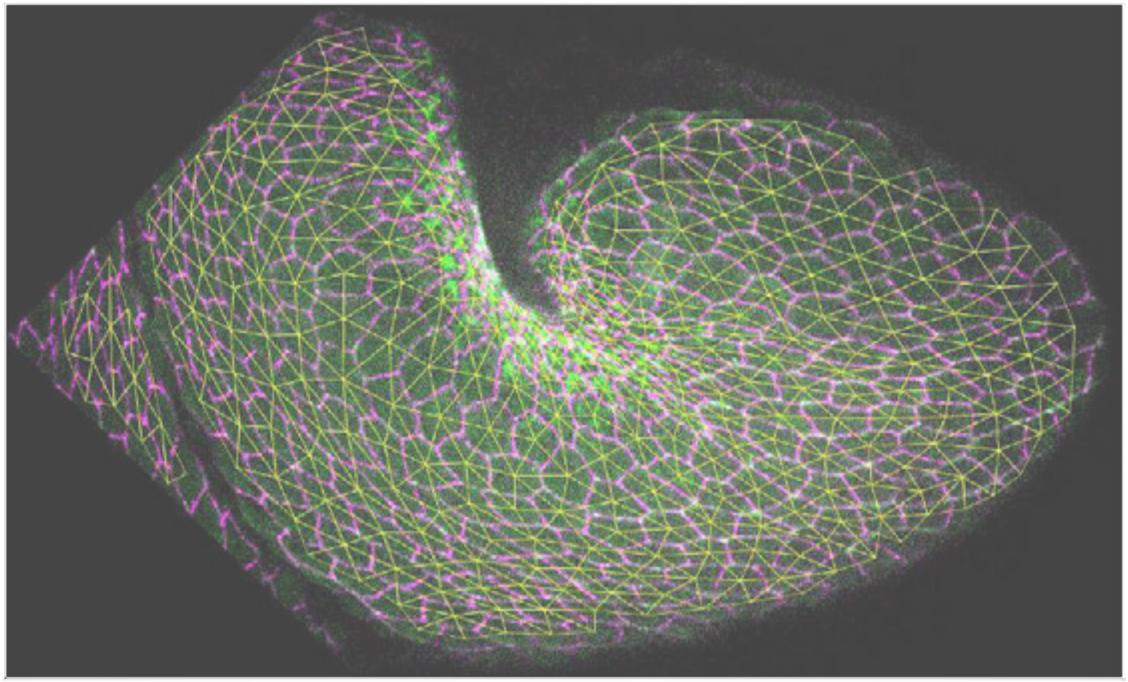
Morphogenesis: space, time, information



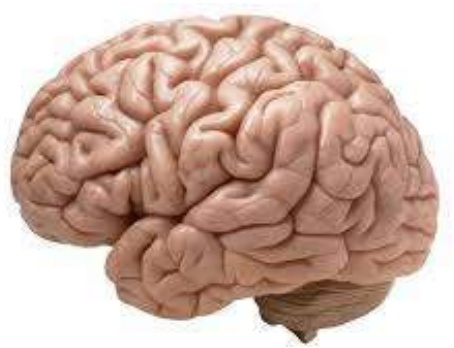
Course 4: Folding, Invagination

Thomas Lecuit
chaire: Dynamiques du vivant

COLLÈGE DE FRANCE
1530

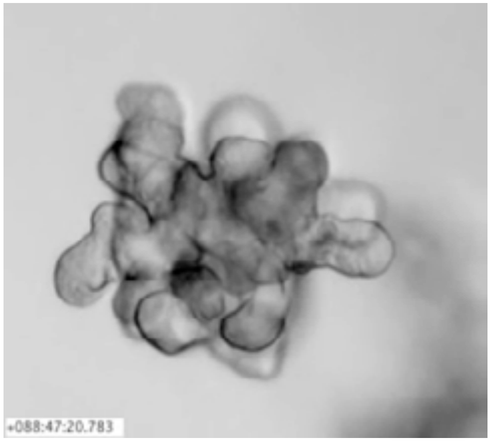
Tissue curvature: control and self-organisation

1. Stress induced curvatures during tissue folding , looping, branching



Cortex convolution

Gut villi

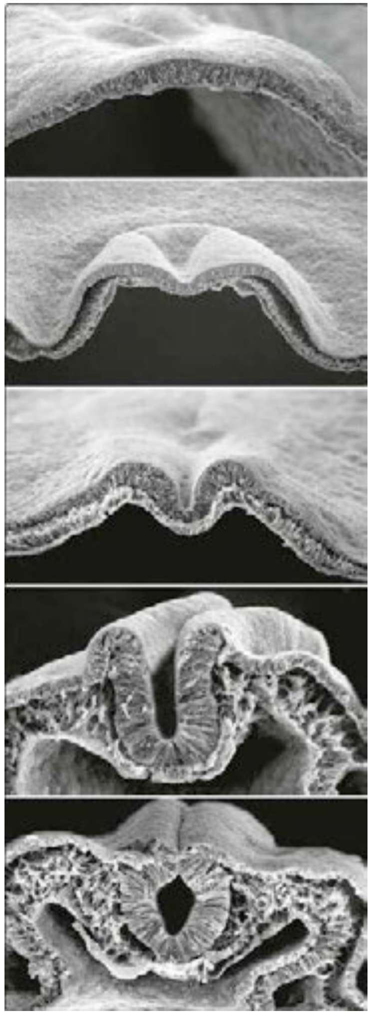


lung branching

Gut looping

Tissue deformations: control and self-organisation

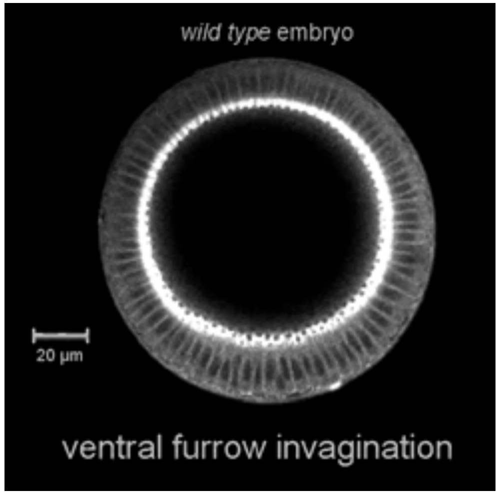
2. Tissue invagination



G. Schoenwolf U. Utah School of Medicine

Chick neural tube

Sea Urchin endoderm



Drosophila mesoderm

Stress induced curvatures during tissue folding , looping etc

1. Self-Organised mechanical instabilities

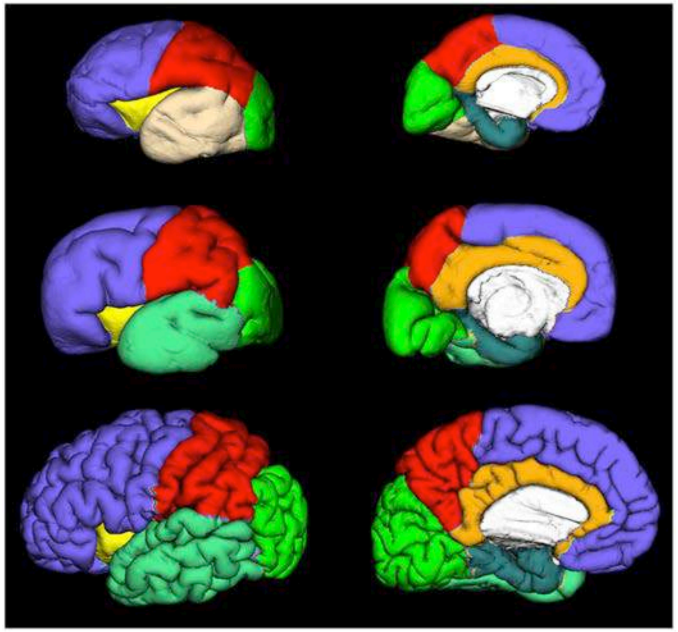
General Framework:

- Elastic material
- Internal stress: eg. growth
- External stress: boundary conditions
- Stress relaxation

Use of continuous/coarse grained models

Growth induced mechanical instabilities: Cortex convolutions

- Mechanics of Brain convolutions
  - — Development
  - — Evolution



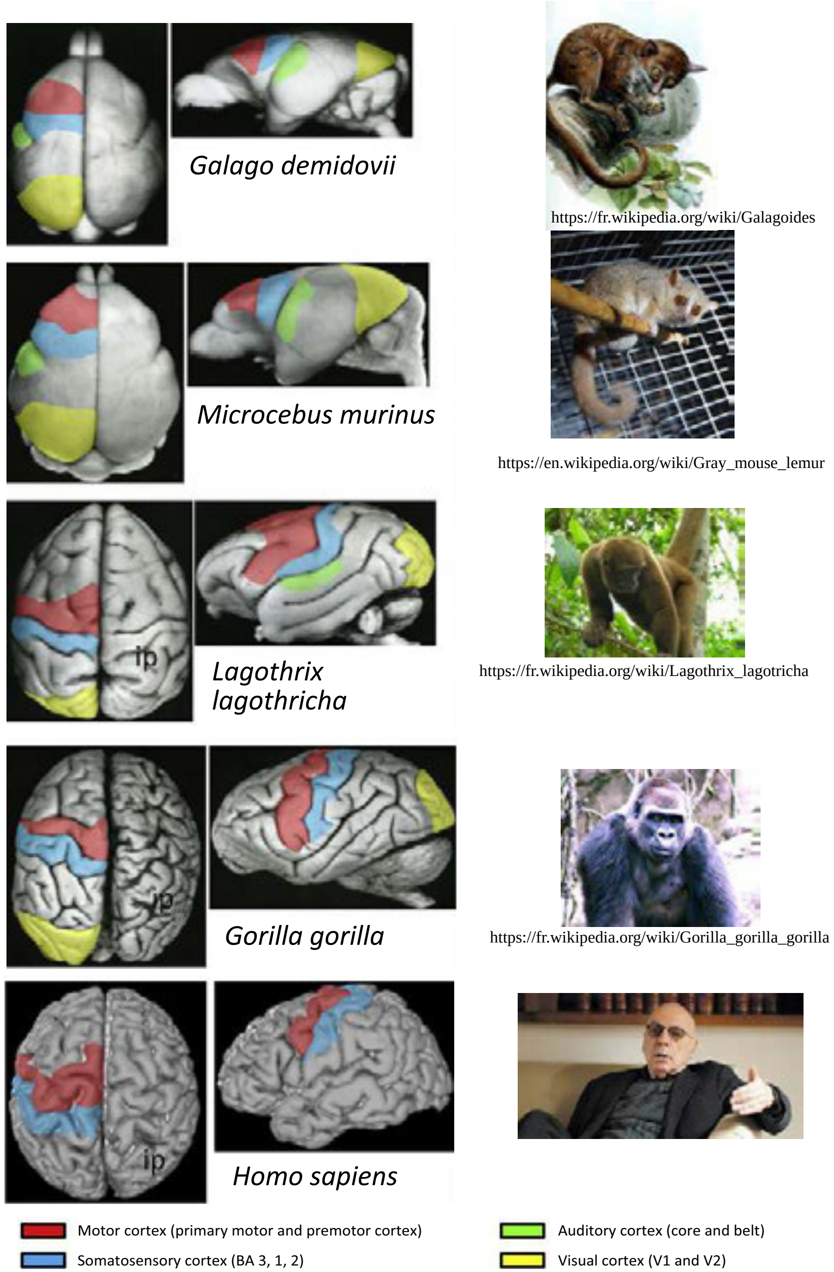
25 week

30 week

40 week

Homo sapiens

Vasung L, et al and Kostovic I (2016) *Front. Neuroanat.* 10:11. doi: 10.3389/fnana.2016.00011

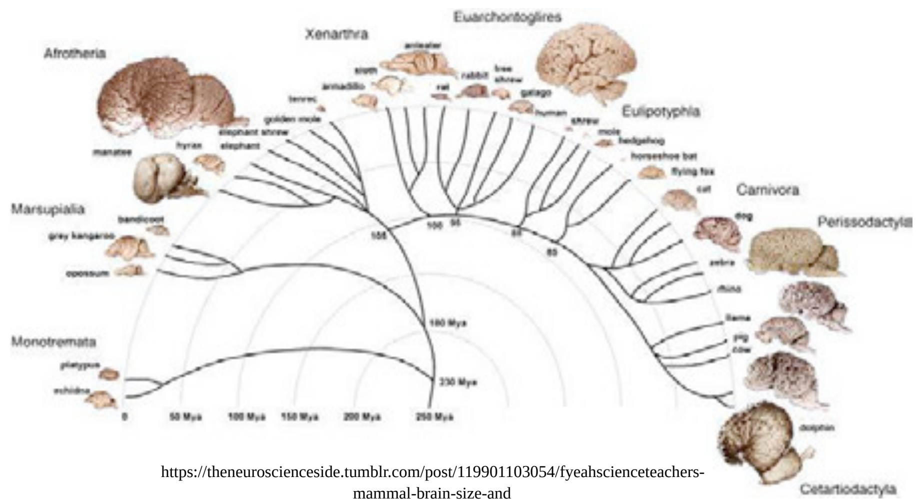


K. Zilles, N. Palomero-Gallagher and K. Amunts. *Trends in Neurosciences* (2013), 36:275-284

Growth induced mechanical instabilities: Cortex convolutions

- Mechanics of Brain convolutions
- Cortical folding scaling laws

1. Folding index generally increases with brain mass.
2. But there are a number of outliers (cetacea, marsupials, humans)



https://theneuroscienceside.tumblr.com/post/119901103054/fyeahscienceteachers-mammal-brain-size-and

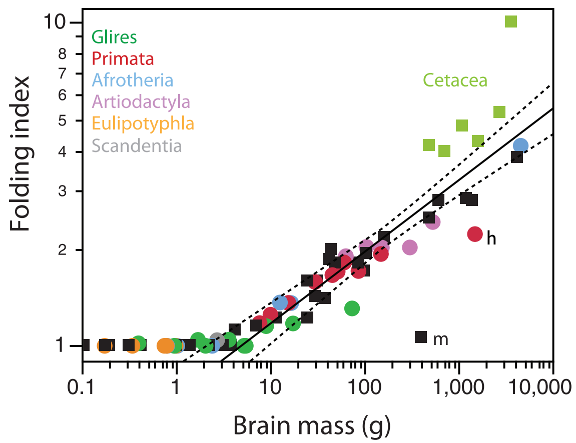
3. Two different scaling laws for smooth and folded cortices

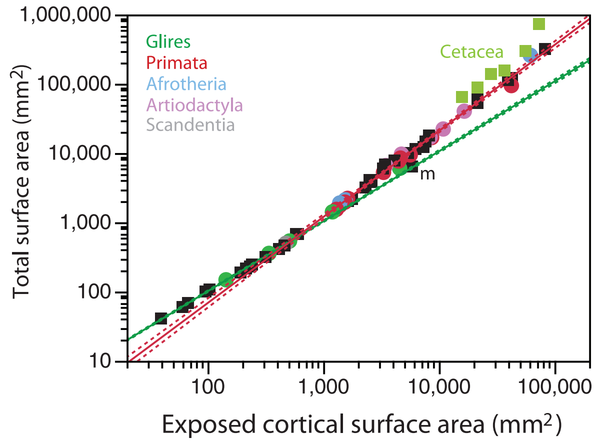
folded cortex

$S_T = S_E^{1.24}$

smooth cortex

$S_T = S_E$





Self-similar fractal configuration (fractal dimension d= 2.48)

Similar to crumpled paper (fractal dimension d= 2.5)

B. Mota and S Herculano-Houzel *Science* (2015) 349:74-77

Growth induced mechanical instabilities: Cortex convolutions

- A mechanical model of cortex folding: minimisation of stresses

1. Folding of a sheet of paper: Self-avoiding (non-intersecting) surface that minimises its free energy

(minimisation of internal and external stresses)

$$T^{1/2}A_G = kA_E^{1.25}$$

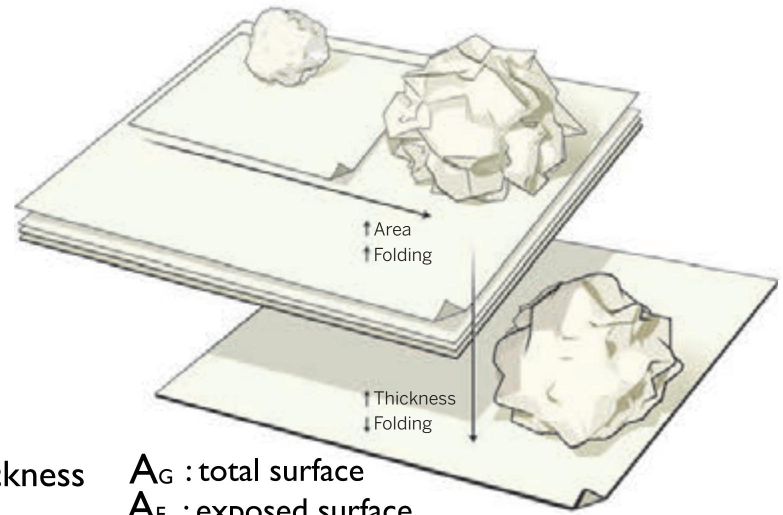
T: thickness

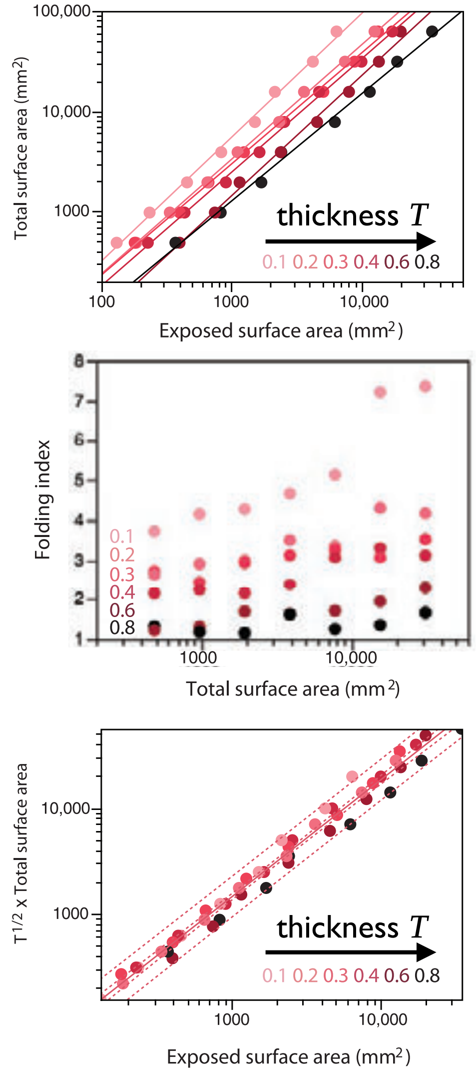
(1.25 exponent so that k is dimensionless)

A_G : total surface

A_E : exposed surface

- a thinner sheet folds more





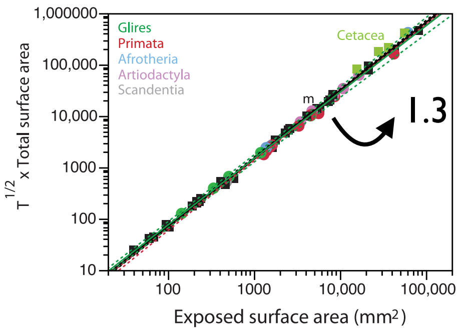
2. All cortices (gyrencephalic and lissencephalic) follow a unique power law where folding scales universally with surface area and thickness

3. The exponent is nearly the same as for folded paper

$$T^{½}A_G = A_E^{1.3}$$

lissencephaly if $T = k^2 A_G^{1/2}$ $(A_G = A_E)$

gyrencephaly if $T < k^2 A_G^{1/2}$ $(A_G > A_E)$



B. Mota and S Herculano-Houzel *Science* (2015) 349:74-77

G. Strieder and S Srinivasan *Science* (2015) 349:31-32

Growth induced mechanical instabilities: Cortex convolutions

- A mechanical model of cortex folding: minimisation of stresses

1. Universality of scaling law across folded and unfolded cortices calls for intrinsic property of cortex

2. Follows minimisation of internal and external stresses

3. Depends on relative rate of lateral expansion of total surface (progenitor expansion) relative to its thickness (radial neurogenesis, cell migration)
4. Evolution of brain shape reflects evolution of mechanisms regulating T relative to A_G

5. What is the origin of internal stresses that emerge during development of brain?

B. Mota and S Herculano-Houzel *Science* (2015) 349:74-77
G. Strieder and S Srinivasan *Science* (2015) 349:31-32

Growth induced mechanical instabilities: Cortex convolutions

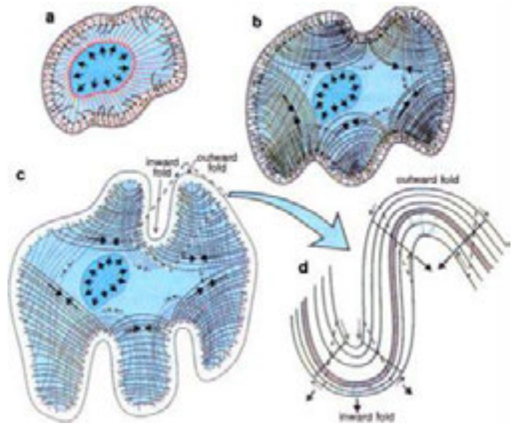
- Models of brain convolutions: internal stresses

1. Tensile forces of axons (white matter) onto cortex (grey matter)

A tension-based theory of morphogenesis and compact wiring in the central nervous system

David C. Van Essen

DC Van Essen *Nature (*1997) 385:313

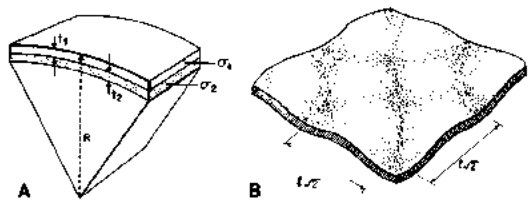


2. Differential growth rate in grey matter compared to white matter: compressive stress

Mechanical Model of Brain Convolutional Development

Pathologic and experimental data suggest a model based on differential growth within the cerebral cortex.

David P. Richman, R. Malcolm Stewart, John W. Hutchinson, Verne S. Caviness, Jr.



DP. Richman et al. and V. Caviness S*cience (*1975) 189:18

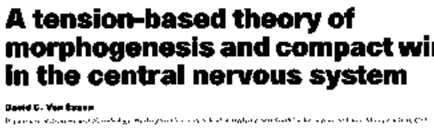
3. Chemical Turing pattern pre-pattern the cortex and induce growth heterogeneities

Lefèvre & Mangin *Plos Comp. Biol*. 2010

Growth induced mechanical instabilities: Cortex convolutions

- Models of brain convolutions: internal stresses

1. Tensile forces of axons (white matter) onto cortex (grey matter)


A tension-based theory of morphogenesis and compact wiring in the central nervous system

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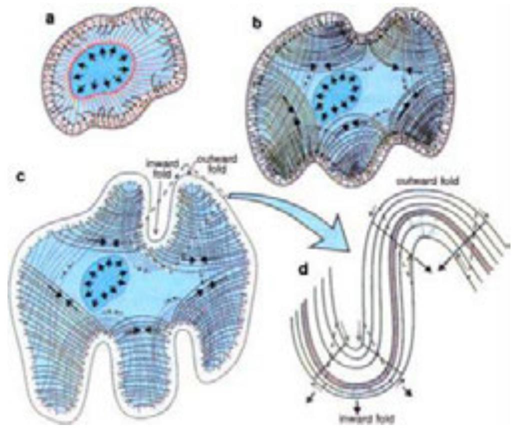
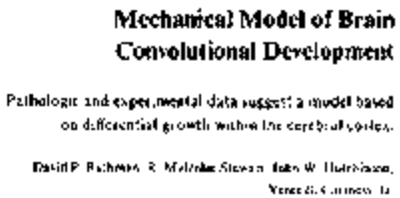


Experiments mapping distribution
of tensile stress is not consistent
Xu et al, L. Taber *J. Biomech. Eng.* (2010) 132: 0710131

2. Differential growth rate in grey matter compared to white matter: compressive stress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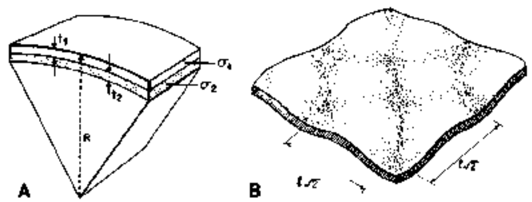
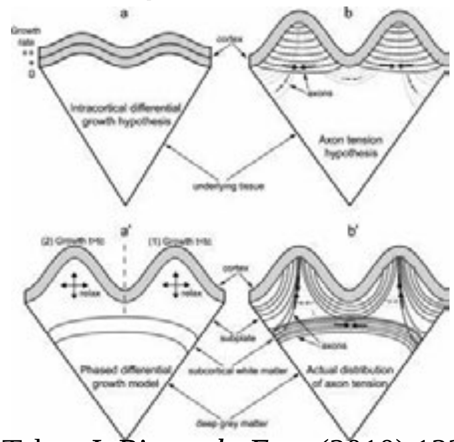


DP. Richman et al. and V. Caviness S*cience (*1975) 189:18



Xu et al, L. Taber *J. Biomech. Eng.* (2010) 132: 0710131

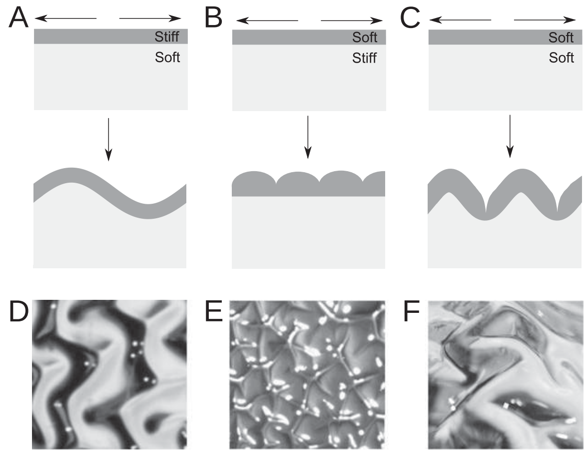
3. Chemical Turing pattern pre-pattern the cortex and induce growth heterogeneities

no evidence: Lefèvre & Mangin *Plos Comp. Biol*. 2010

Growth induced mechanical instabilities: Cortex convolutions

- Cortical folding (gyrification) arises as a mechanical instability due to heterogeneous growth of a soft tissue

1. Brain best modelled as soft tissue (both in white and grey matter)
2. Elastic solid
3. Differential growth of white (g=1) and grey matter (g=1+ x)

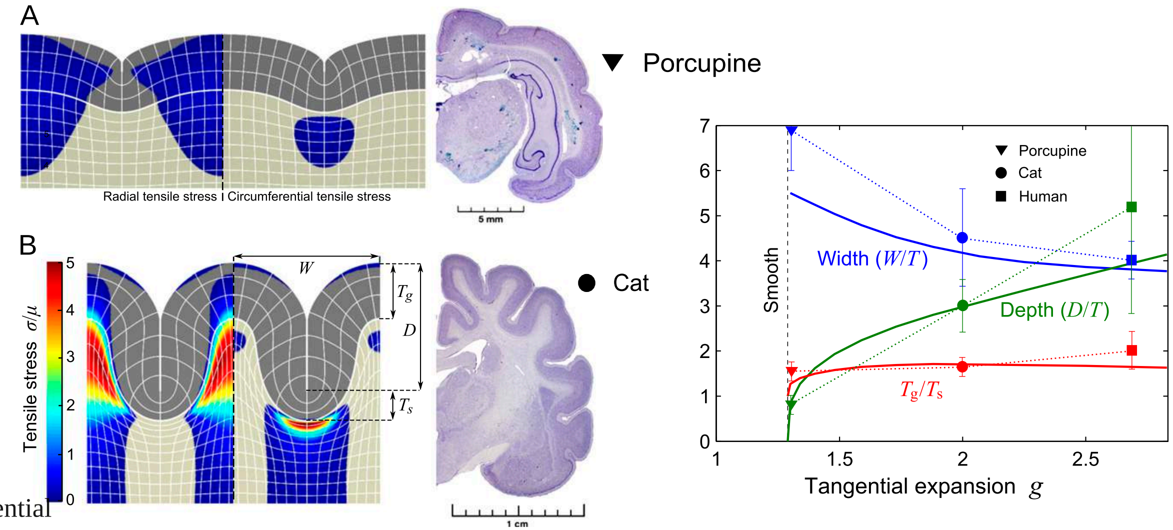


wrinkles cusps wrinkles & cusps

g = 1.30

g = 2.25

radial and circumferential tensile stress



T. Tallinen et al and L. Mahadevan. *PNAS* (2014) 111:12667

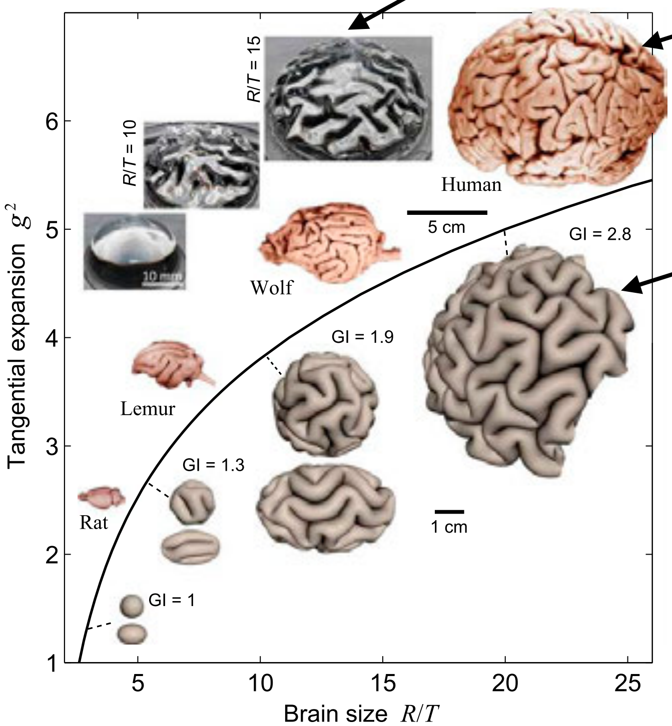
Growth induced mechanical instabilities: Cortex convolutions

- Cortical folding (gyrification) arises as a mechanical instability due to heterogeneous growth of a soft tissue

physical mimic of brain

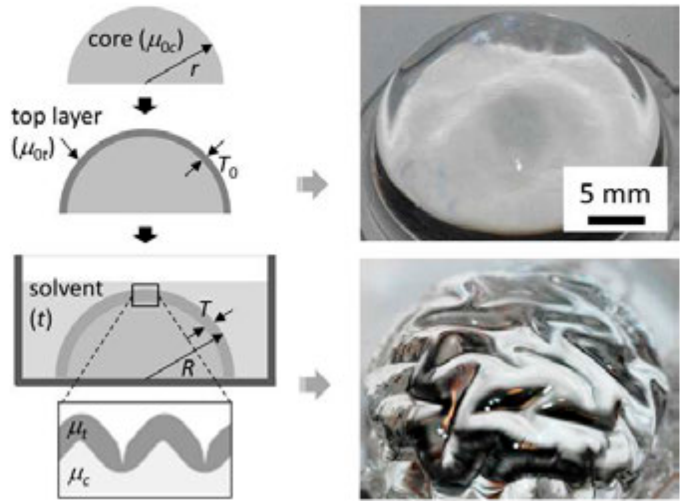
brain

simulations



GI: gyration index (total area/exposed area)

physical model of brain like instability

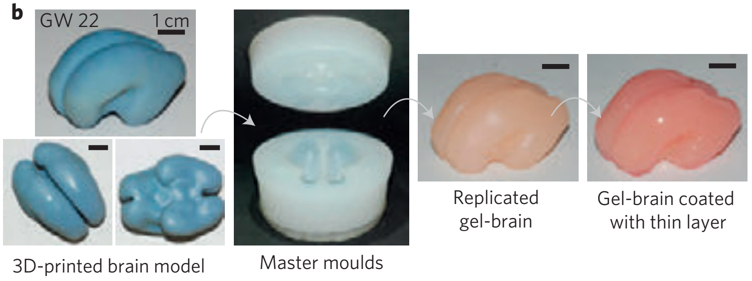


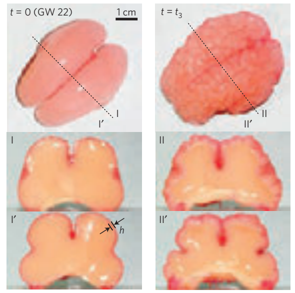
swelling of outer layer (growth)

T. Tallinen et al and L. Mahadevan. *PNAS* (2014) 111:12667

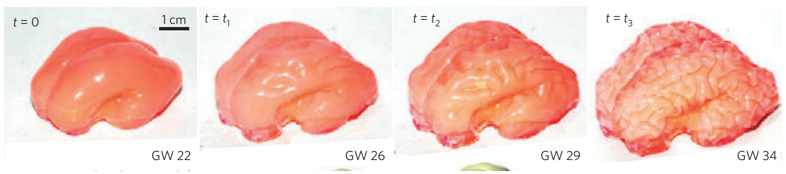
Growth induced mechanical instabilities: Cortex convolutions

- 3D model of brain folding: impact of initial geometry

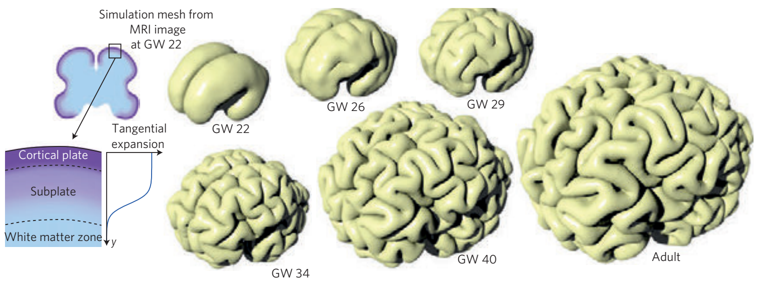


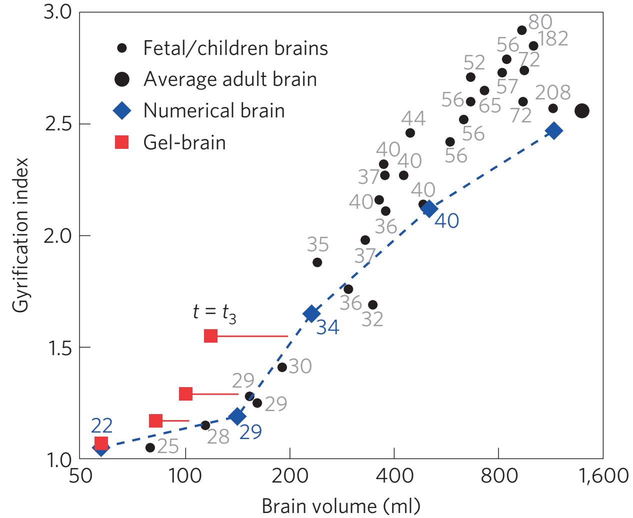


brain mimic



numerical brain





T. Tallinen et al, and L. Mahadevan. *Nature Physics* 12: 588–593 (2016)

Growth induced mechanical instabilities: Cortex convolutions

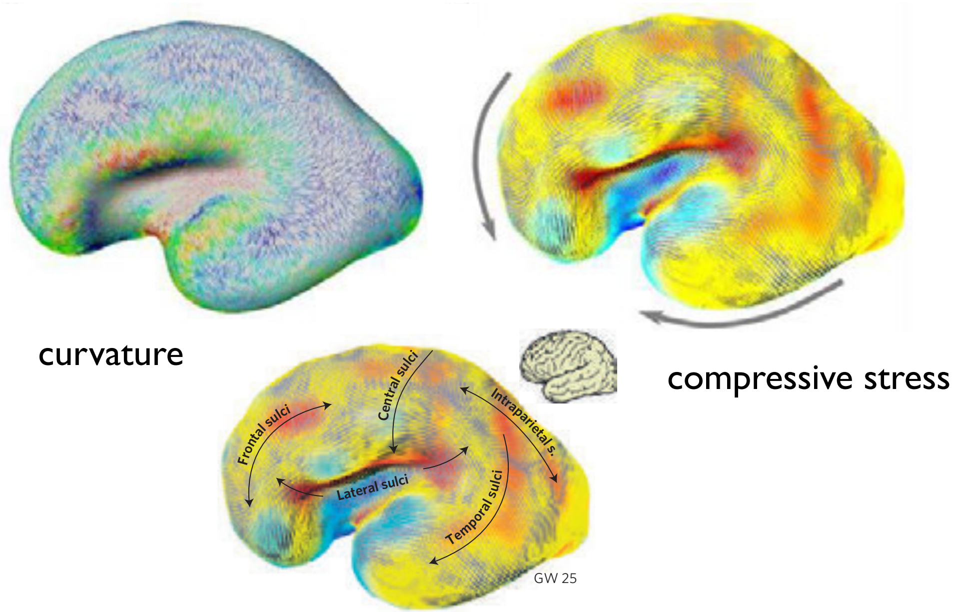
- 3D model of brain folding: impact of initial geometry

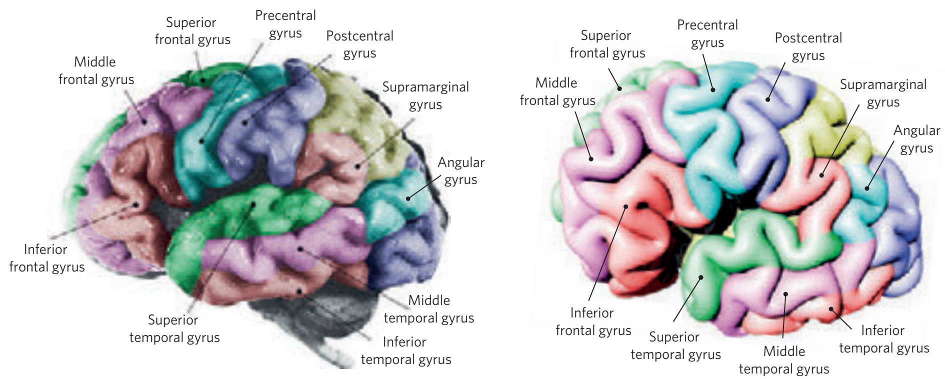
Initial geometry characterised by curvature map

High (Low) curvature associated with Low (High) compressive stress

Main gyri result from compressive stress

Other smaller gyri are less reproducible in terms of their position.

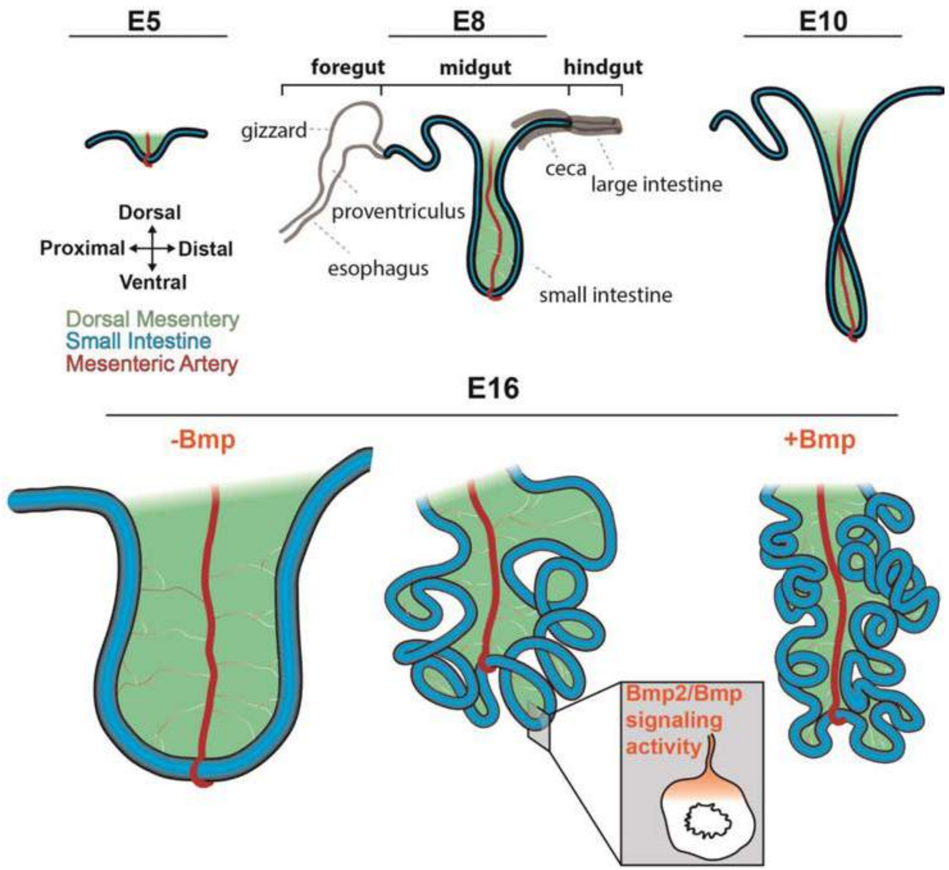




T. Tallinen et al, and L. Mahadevan. *Nature Physics* 12: 588–593 (2016)

Growth induced mechanical instabilities: Gut looping

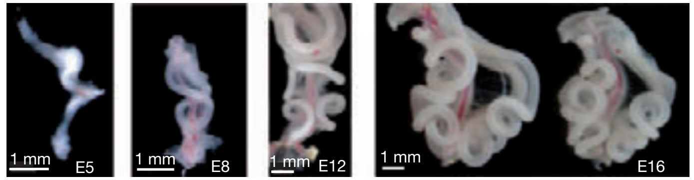
- Gut morphogenesis involves looping and coiling

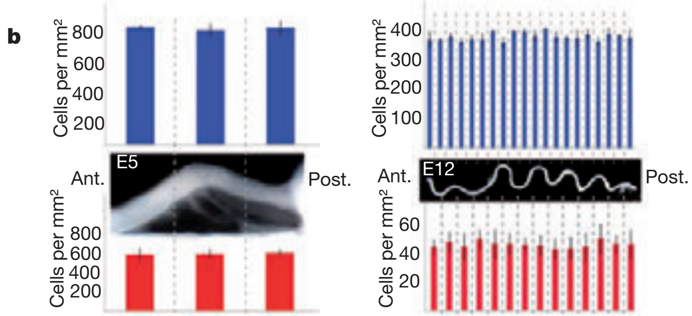


T. Huycke and C. Tabin. *Int. J. Dev. Biol*. 62: 109-119 (2018)
https://doi.org/10.1387/ijdb.170325ct

Growth induced mechanical instabilities: Gut looping

- Gut looping arises as a mechanical instability due to differential tissue growth



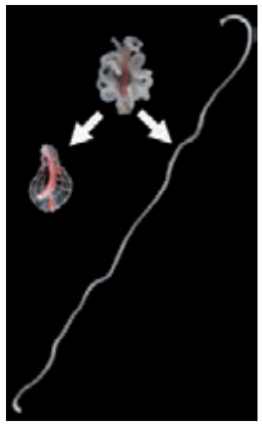


Gut

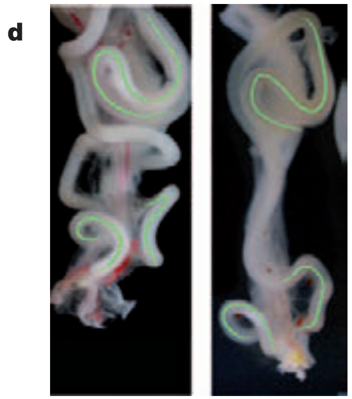
Mesentery

- Formation of stereotypical looping patterns
- The gut shows uniform proliferation
- Mechanical dissociation of mesentery and gut leads to gut relaxation by decoiling and mesentery relaxation: gut is normally compressed and mesentery is stretched.
- So the gut and mesentery are elastic, isotropic tissues.
- Hypothesis: Differential uniform growth underlies differential strain.

Mechanical dissociation of mesentery



Mesentery removed *in vitro*



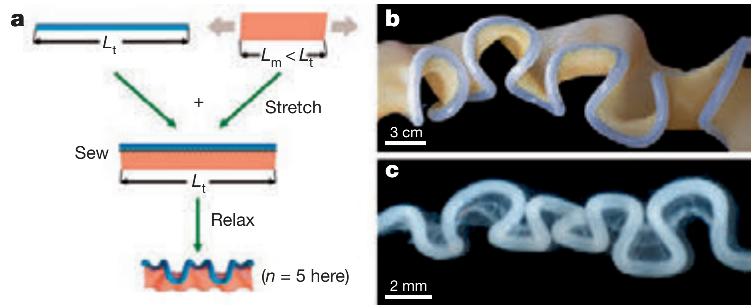
With mesentery

Partial mesentery removal *in ovo*

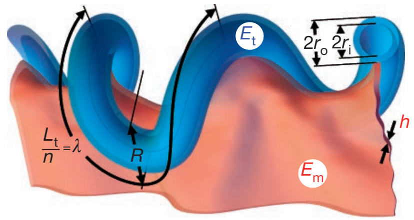
Thierry Savin, et al, L. Mahadevan and Cliff Tabin. *Nature* (2011) 476:57-62.

Growth induced mechanical instabilities: Gut looping

- A physical simulacrum of the gut and mesentery is similar qualitatively to gut looping in vivo



- An elastic theory predicts tissue geometry given elastic moduli of tube (gut) and sheet (mesentery), strain and force balance.
- When strain ε (due to differential growth) is above critical value ε_*, the gut buckles and loops.
- Geometry/Elasticity relations:



onset of looping:

$$\lambda \propto \left(\frac{E_t I_t}{E_m h}\right)^{1/3}$$

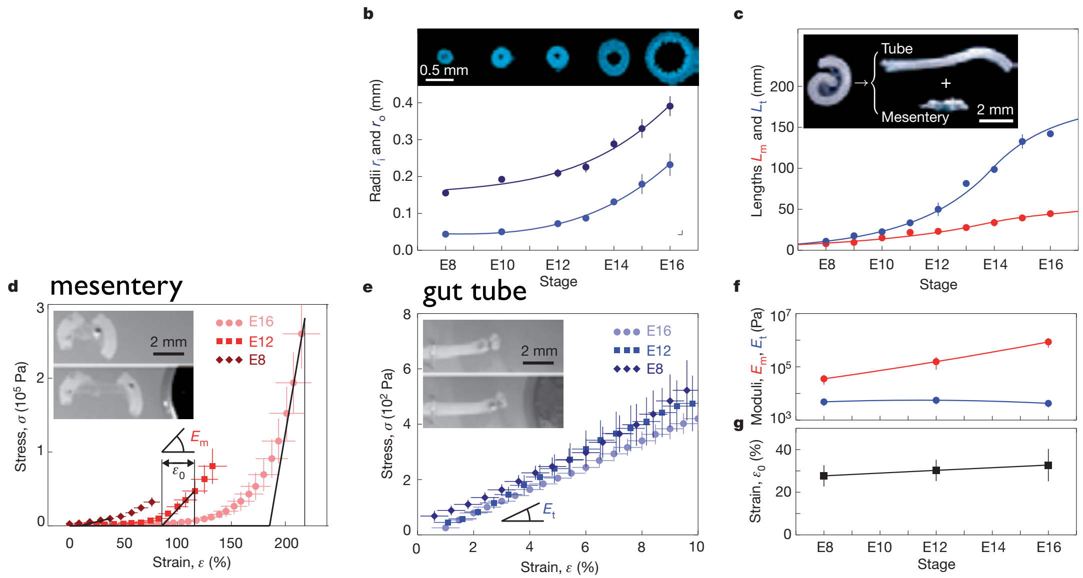
complete looping:

$$R \propto \left(\frac{E_t I_t}{E_m h \varepsilon_0^2}\right)^{1/3}$$

with $\varepsilon_* \propto A/\lambda$ — A: amplitude, λ : length

$\varepsilon = \varepsilon_0 \gg \varepsilon_*$ — E_t, E_m: Young's moduli, I_t: quadratic moment

- Geometric measurements
- Mechanical measurements (stress/strain relations) of mesentery and gut (using magnetic force on steel ball)

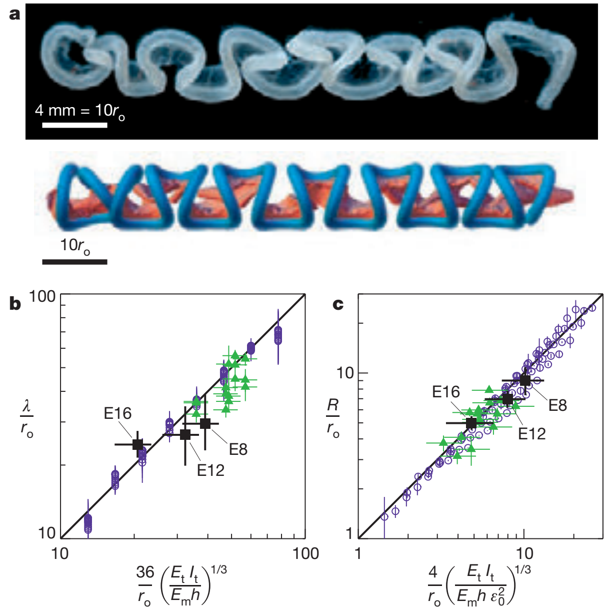


Thierry Savin, et al, L. Mahadevan and Cliff Tabin. *Nature* (2011) 476:57-62.

Growth induced mechanical instabilities: Gut looping

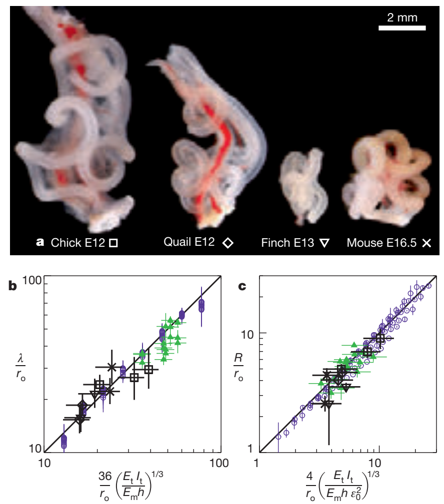
- No free parameter
- The elastic model predicts relationship between geometry and stiffness parameters.

$$\lambda \propto \left(\frac{E_t I_t}{E_m h}\right)^{1/3} \qquad R \propto \left(\frac{E_t I_t}{E_m h \varepsilon_0^2}\right)^{1/3}$$



Chick
Rubber model
Simulations

- The same elastic model explains the gut looping in different bird species and the mouse.
- Tuning parameters (from evolutionary perspective) are relative stiffness of tube and mesentery, differential growth rate (strain).



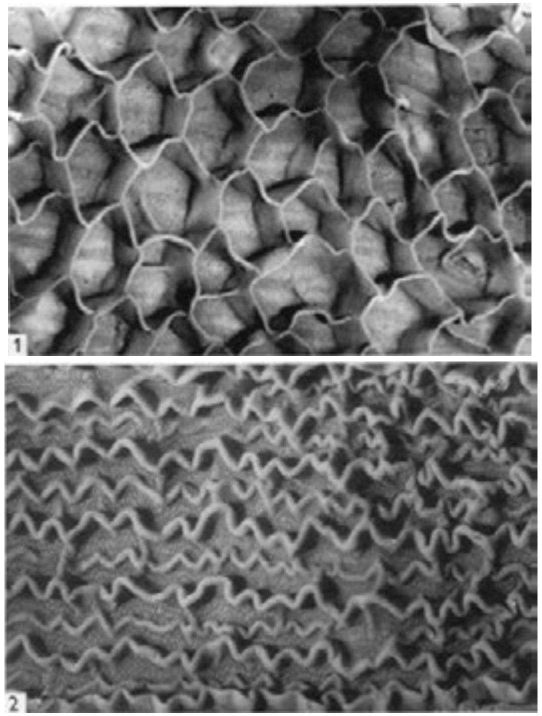
Thierry Savin, et al, L. Mahadevan and Cliff Tabin. *Nature* (2011) 476:57-62.

Growth induced mechanical instabilities: Gut vilification

- Self-organised mechanics: chick gut
- Self-organised biochemistry: Turing field in mouse gut

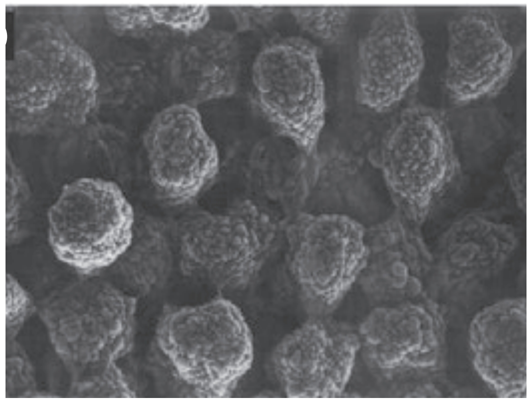
Growth induced mechanical instabilities: Gut vilification

snake



snake: gut

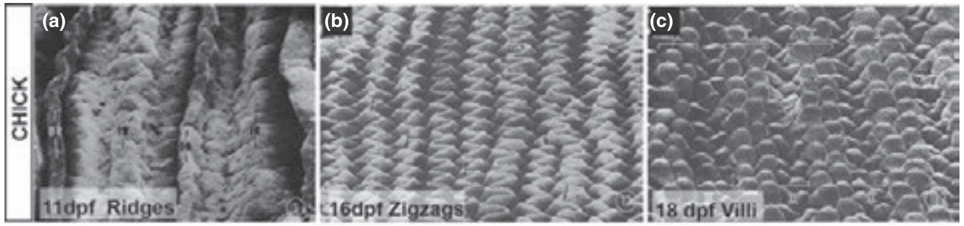
chick: duodenum



rat: gut

Growth induced mechanical instabilities: Gut vilification

- Gradual development of folding patterns in the gut of birds

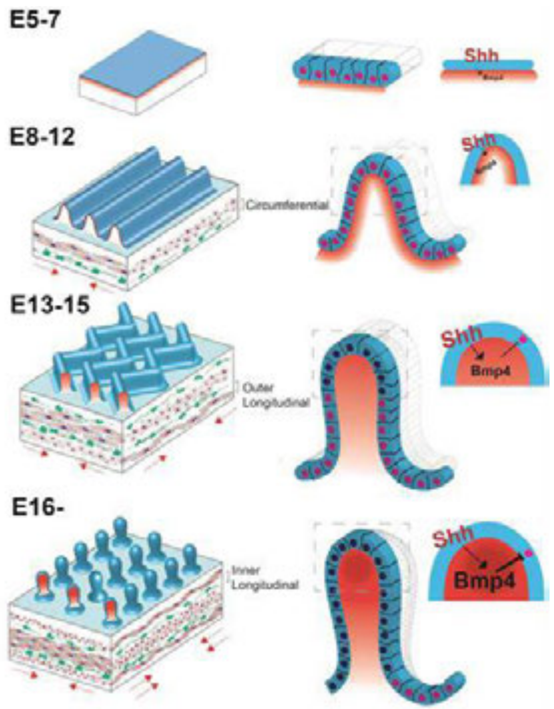


Epithelium and mesenchyme form annealed surfaces

Formation of ridges in epithelium and mesenchyme parallel formation of circumferential smooth muscles

Formation of Zigzags parallels formation of longitudinal muscles

Formation of Villi

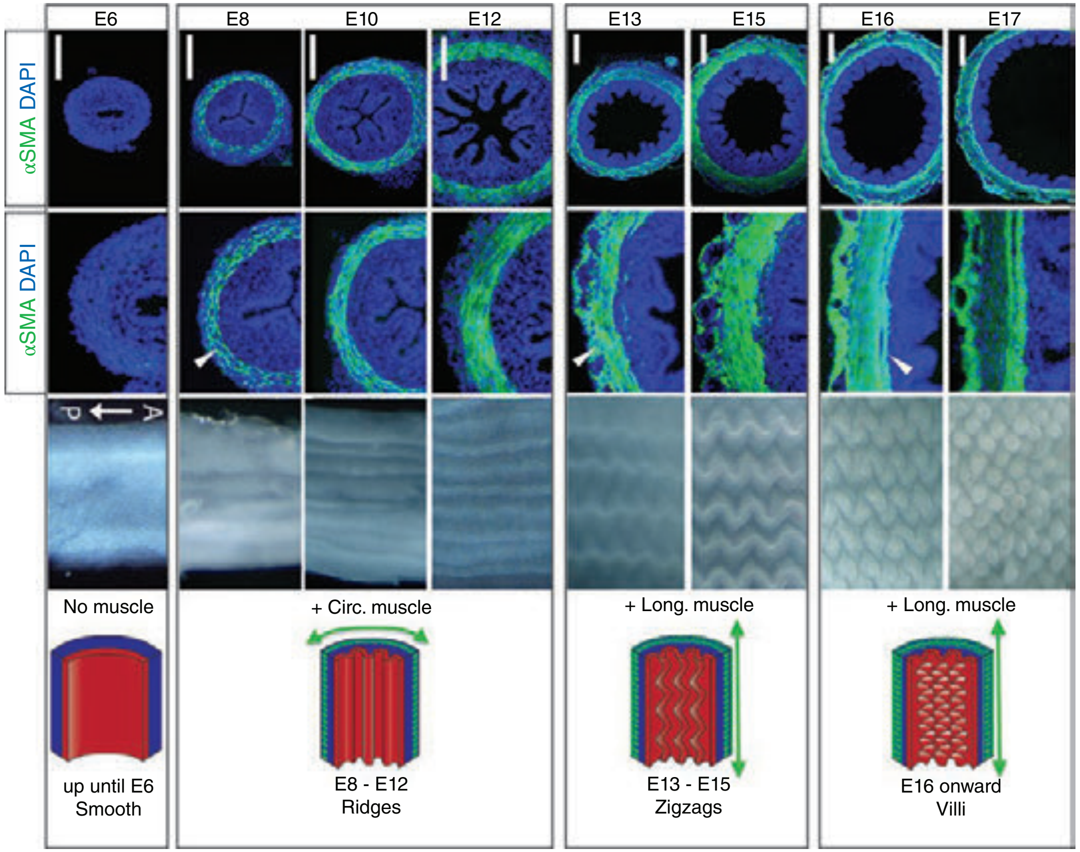


K Walton et al., C. Tabin and D. Gumucio *WIREs Dev Biol*. 2018;e317.

Growth induced mechanical instabilities: Gut vilification

- Gradual development of folding patterns in the gut

- Epithelium and mesenchyme form annealed surfaces ensheathed by sequential layers of smooth muscles
- Formation of R**idges** in epithelium and mesenchyme parallel formation of circumferential smooth muscles
- Formation of **Zigzags** parallels formation of longitudinal muscles
- Formation of **Villi** formation of longitudinal muscles



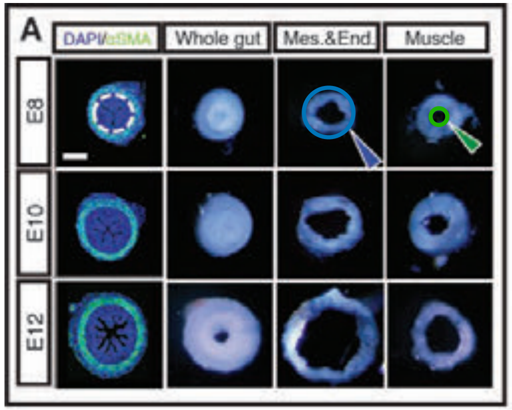
Ridges Zigzag Villi

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

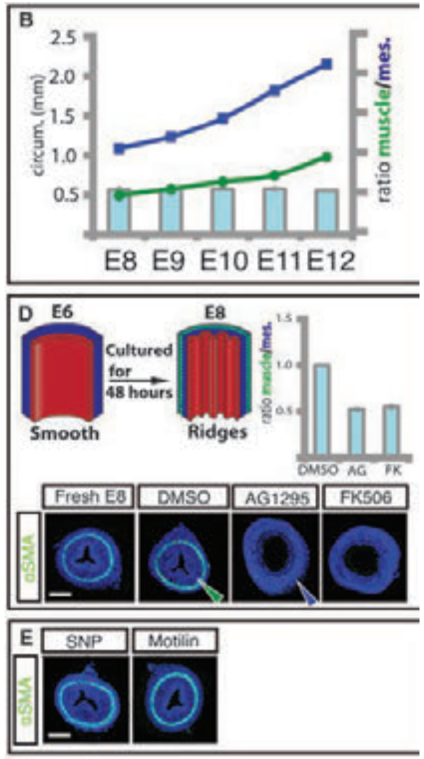
Growth induced mechanical instabilities: Gut vilification

- Tissue ridges arise from mechanical instability caused by differential growth and constraints

compression ratio

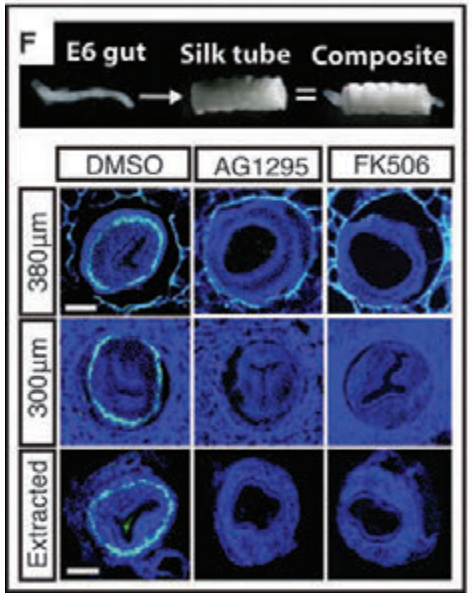


Mechanical removal of constraint



Pharmacological removal of constraint
(inhibition of smooth muscle differentiation)

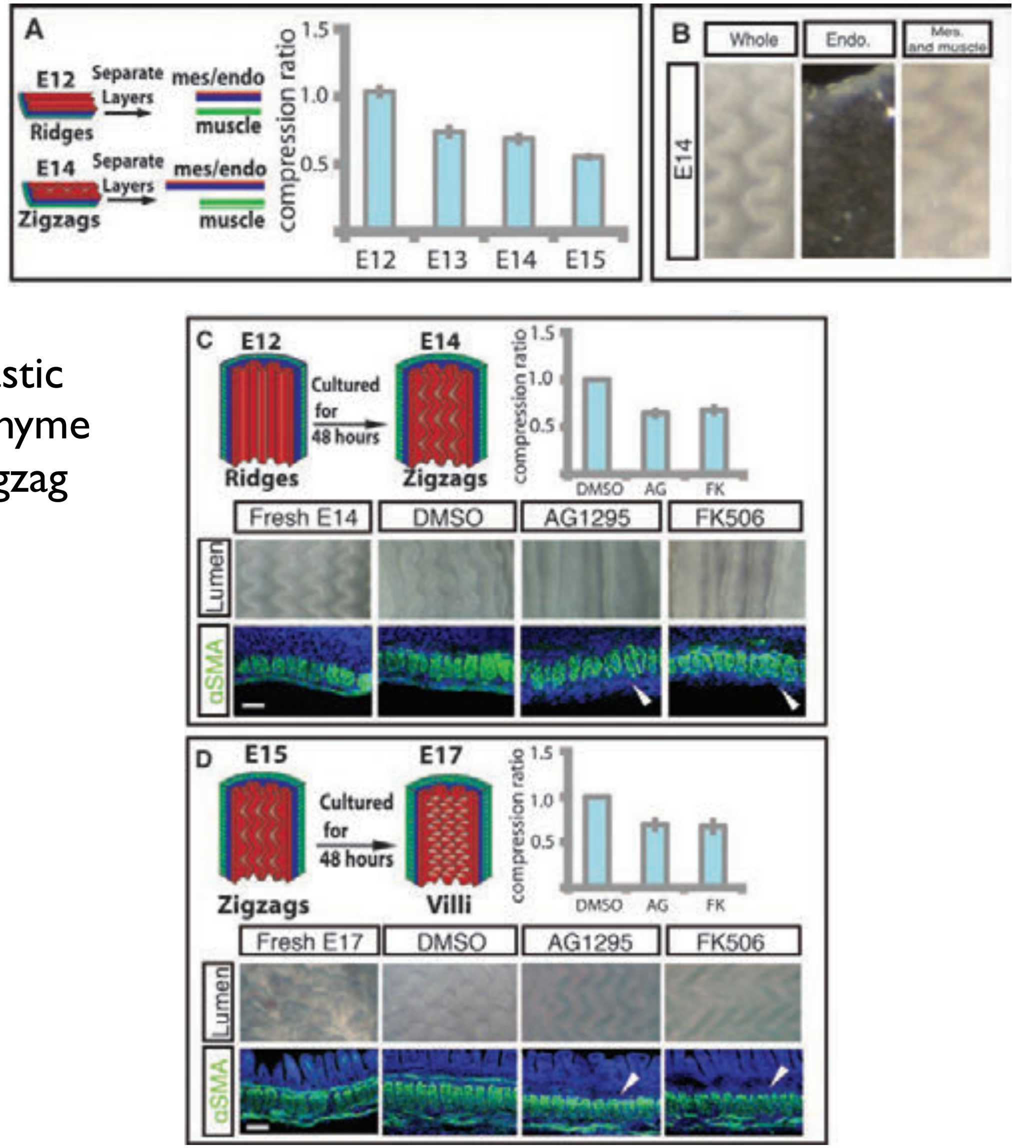
- Mesenchyme and Epithelium grow more than surrounding smooth muscles and are consequently constrained and compressed.
- Removal of smooth muscles leads to elastic unfolding of epithelium and mesenchyme
- Addition of artificial mechanical constraint rescues the need for surrounding smooth muscles
- Role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



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

Growth induced mechanical instabilities: Gut vilification

- Tissue zigzags and villi arise from mechanical instability caused by differential growth and constraints



- Removal of smooth muscles leads to elastic lengthening of endothelium and mesenchyme
- Longitudinal muscles are required for zigzag and villi formation
- Role of longitudinal constraints

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

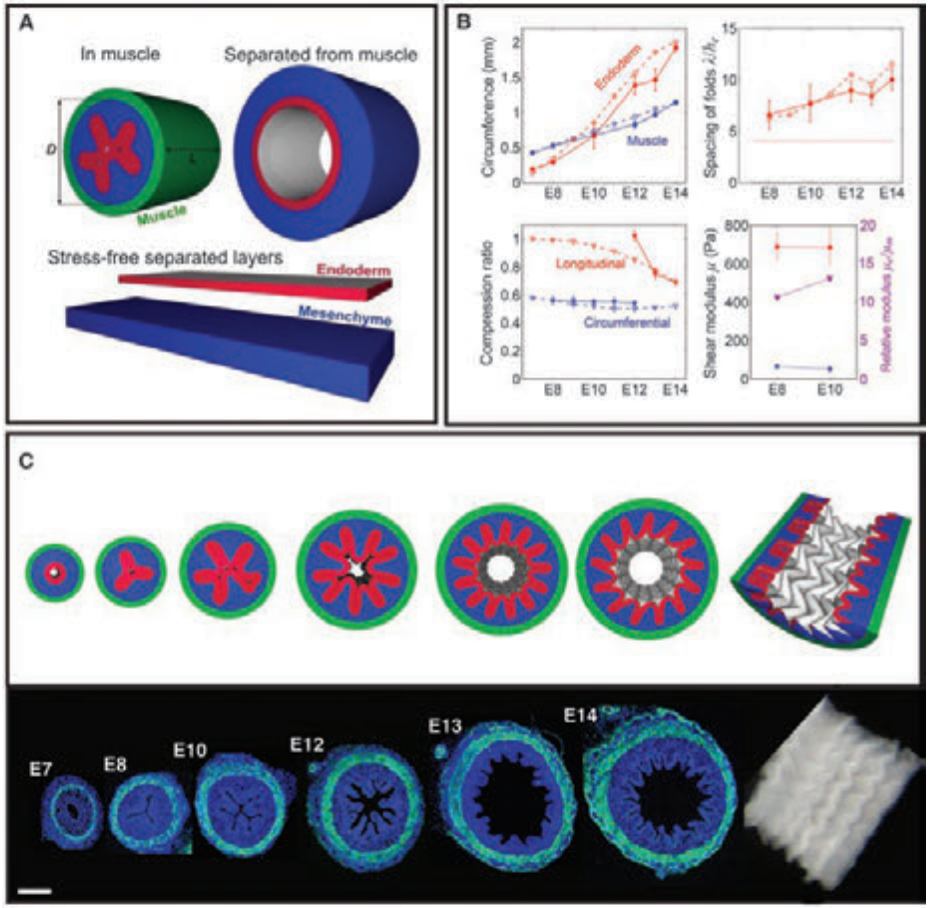
Growth induced mechanical instabilities: Gut vilification

- Tissue zigzags and villi arise from mechanical instability caused by differential growth and constraints

E. Hannezo J. Prost and J-F. Joanny *PRL* 107, 078104 (2011)

- Computation model

Similar earlier theoretical studies: M. Ben Amar and F. Jia. *PNAS* 110: 10525–10530 (2013)

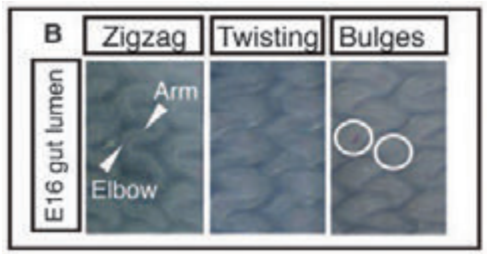


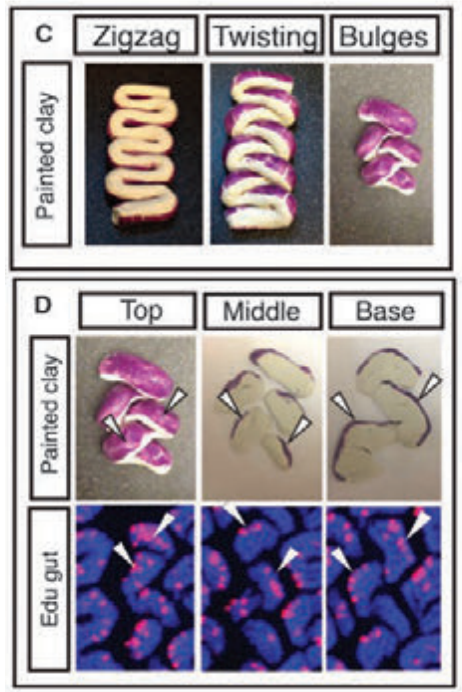
A. Shyer et al, C. Tabin and L. Mahadevan. *Science* 342: 212-218 (2013)

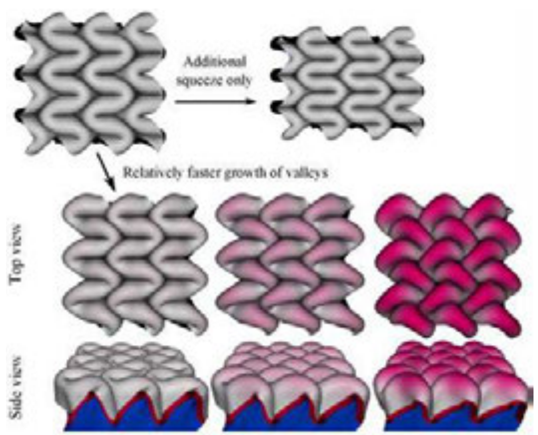
Growth induced mechanical instabilities: Gut vilification

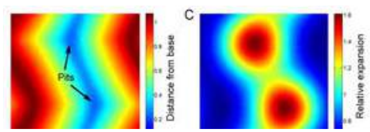
- Non-uniform growth also underlies formation of villi

- Proliferation concentrated in furrows
- Proliferating cells cause twisting and upward movement of proliferating cells
- Leads to formation of villi
- Computer simulations recapitulate this transition





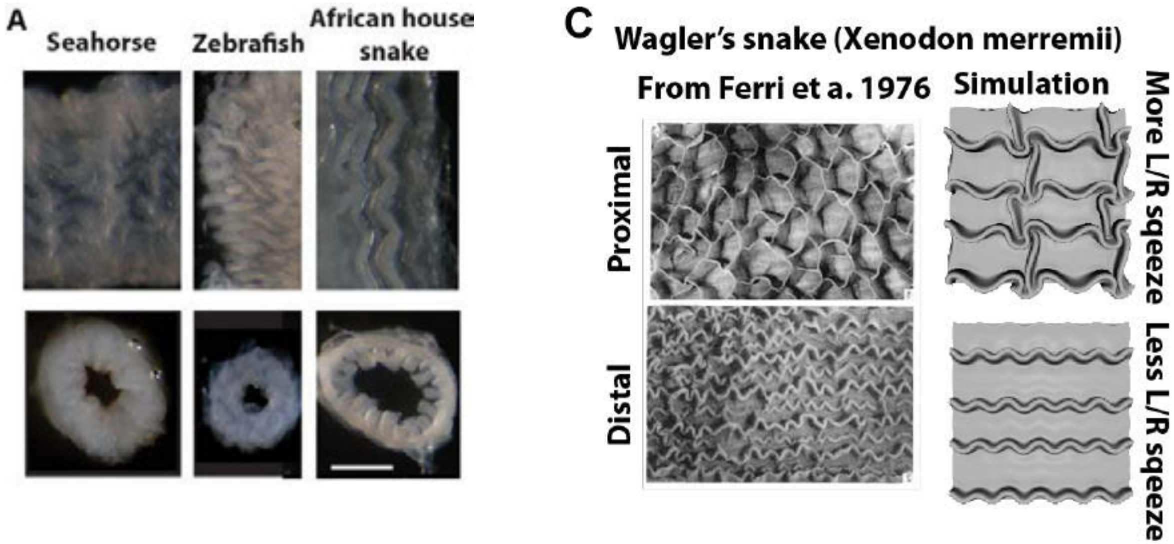




A. Shyer et al, C. Tabin and L. Mahadevan. *Science* 342: 212-218 (2013)

Growth induced mechanical instabilities: Gut vilification

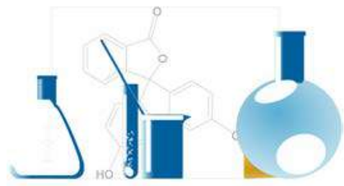
- Exploring the morphospace of vilification with mechanical instabilities



Gut vilification with Turing instabilities

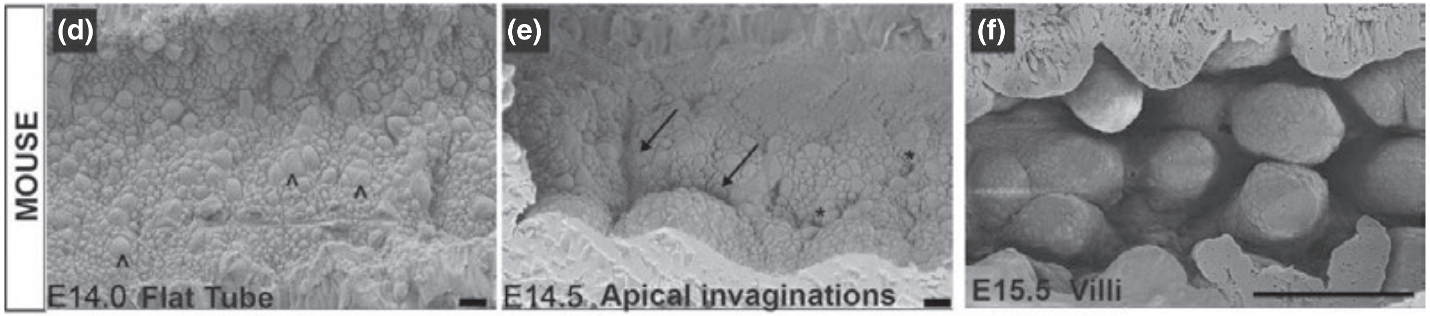
- Self-organised mechanics: chick gut

- Self-organised biochemistry: Turing field in mouse gut



Gut vilification with Turing instabilities

- Direct villus emergence from a flat epithelium in mammals

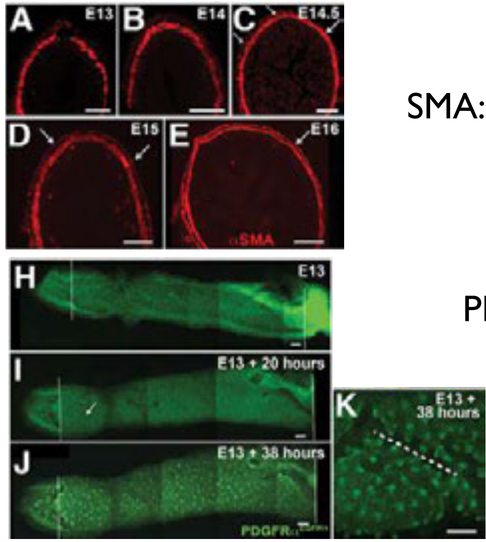


K Walton et al., C. Tabin and D. Gumucio *WIREs Dev Biol*. 2018;e317.

Katherine.D. Walton et al and Deborah L. Gumucio. *Development* (2016) 143, 427-436

Gut vilification with Turing instabilities

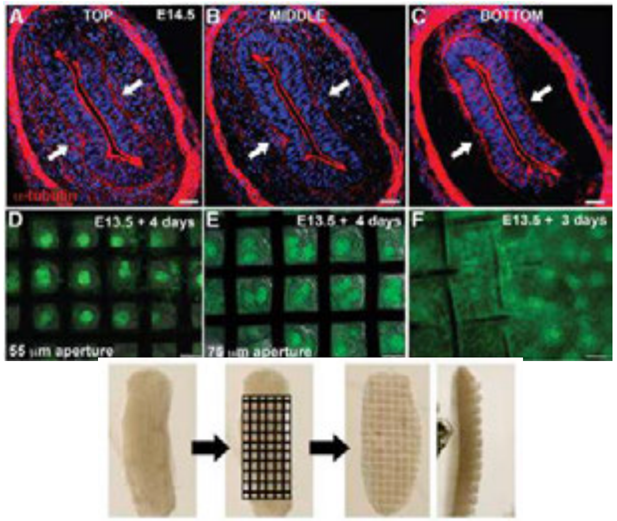
- No evidence of mechanical constraints governing vilification in the mouse



SMA: marker of smooth muscles

PDGFRa: marker of mesenchymal condensation

- Villus emergence precedes (by 24h) formation of longitudinal muscles
- Mechanical dissection of the gut does not affect timing of villi formation (circularity of gut affected by longitudinal cut)



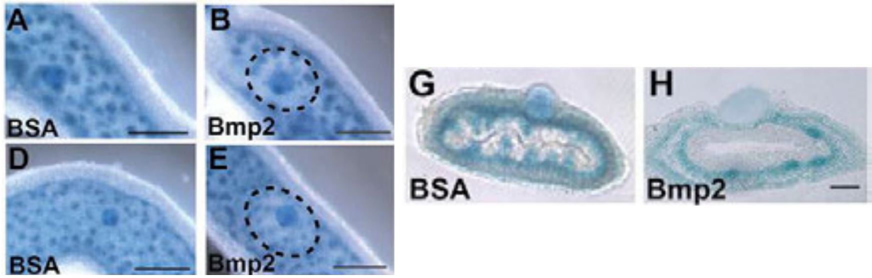
- Mesenchymal condensation at the base of epithelium are visible before any deformation of epithelial layer.
- Thus, mesenchymal condensation is an inducer of epithelial vilification
- Mechanical constraints on epithelial layers do not affect villi size.
- Must be controlled by mesenchymal signal

Katherine.D. Walton et al and Deborah L. Gumucio. *Development* (2016) 143, 427-436
A. Shyer et al. C. Tabin *Cell* (2015) 161:569-581

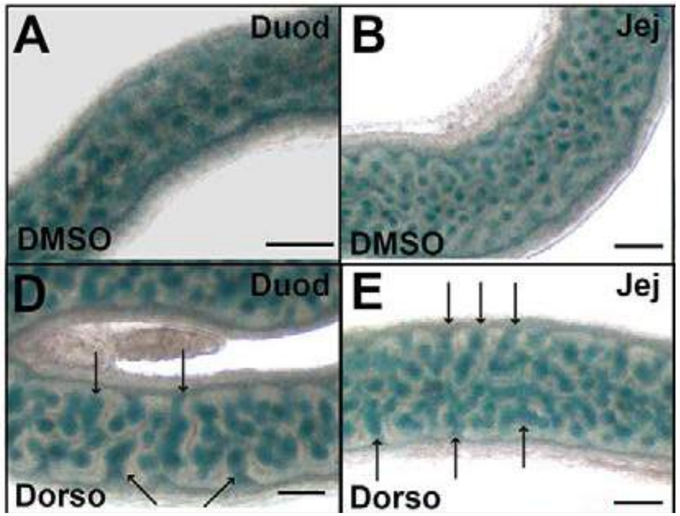
Gut vilification with Turing instabilities

- Spatial patterns of vilification by developmental signalling (BMP)

Ptc marks mesenchymal condensates



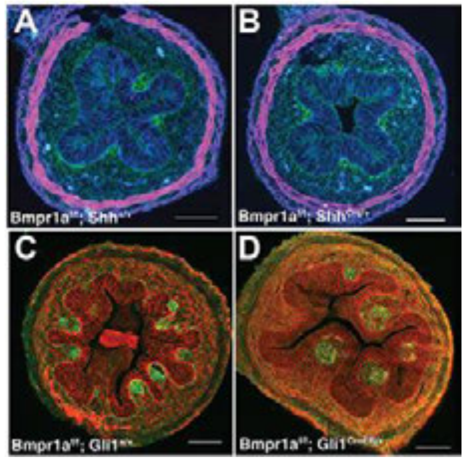
- BMP signals control vilification:
  - BMP2 beads inhibit mesenchymal condensation and vilification
  - BMP inhibitor causes enlargement of mesenchymal condensates (spots become stripes).
  - BMP signalling affects vilification in the mesenchyme but not in epithelium



Dorsomorphin: BMP inhibitor

Epithelium BMPr1a -/-

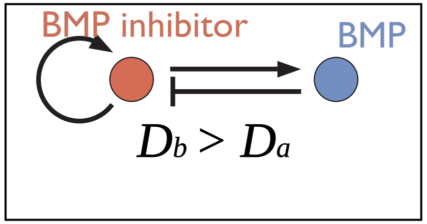
Mesenchyme BMPr1a -/-



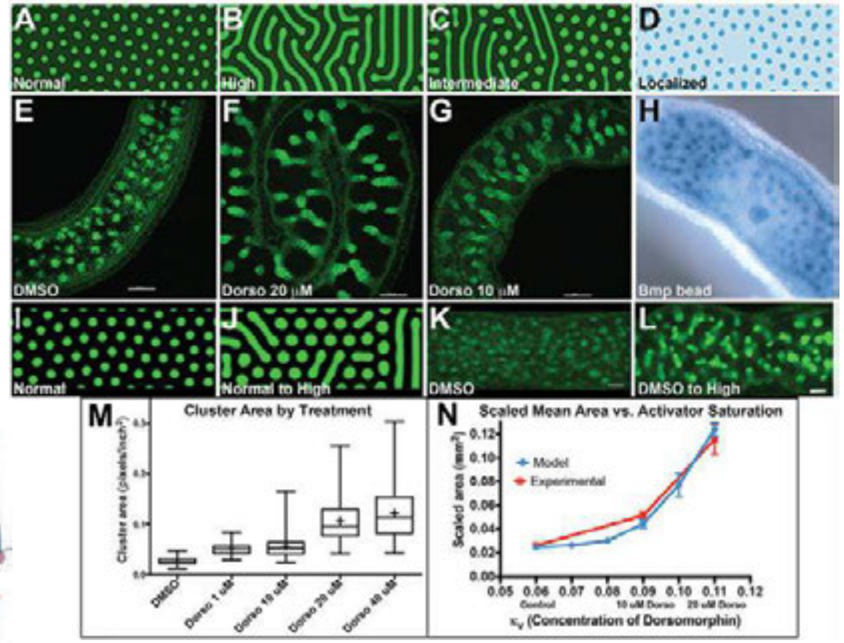
Katherine.D. Walton et al and Deborah L. Gumucio. *Development* (2016) 143, 427-436

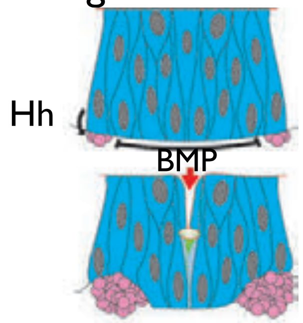
Gut vilification with Turing instabilities

- A Turing reaction-diffusion model of vilification



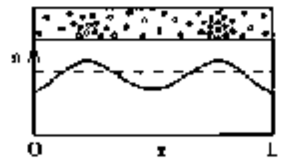
- Turing activator: BMP inhibitor
- Turing inhibitor: BMP signals
- BMP regulators are co-expressed as required for Turing model
- Saturation of activator produces stripes in simulations and experiments
- Dynamic adaptation of pattern to dose of Turing activator (BMP inhibitor).





- However, mesenchymal condensation also emerge from Turing-like mechanical instabilities.
- Possibility of mechanical amplification of chemical instability (or vice versa).

Course 27 November



See: G.F. Oster, J.D. Murray, and A.K. Harris. *J. Embryol. esp. Morph.* 1983. 78:83-125
A.K Harris, D. Stopak and P. Warner. *J. Embryol exp. Morph.* 1984. 80:1-20
A. Shyer et al, R. Harland. *Science* 357: 811-817 (2017)

Katherine.D. Walton et al and Deborah L. Gumucio. *Development* (2016) 143, 427-436

How is the position of curvatures specified?

- Curvatures are not positioned deterministically (by upstream pre-pattern)
- They are self-organised due to mechanical or mechano-chemical instabilities
- Stereotypical pattern specified by geometry (shape of brain) and elastic properties.

✓Organ morphogenesis

- But:
- Curvatures also arise in precisely defined position, following a highly reproducible pattern.

✓ Embryonic gastrulation and neurulation

Tissue invagination

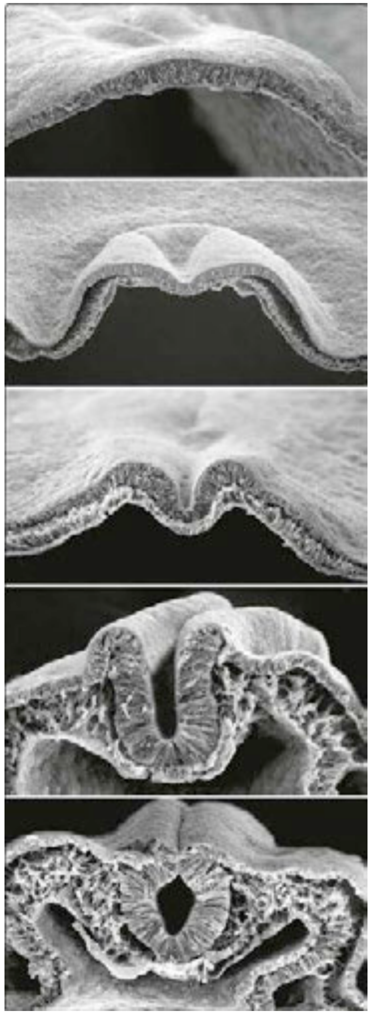
1. Controlled and Self-Organised mechanical instabilities

- Internal stress: eg. contractility
- External stress: boundary conditions (e.g. constraints associated with tissue geometry)

- Goal: Predict tissue morphogenesis (invagination) from cellular behaviours (cell contractility).

Tissue deformations: control and self-organisation

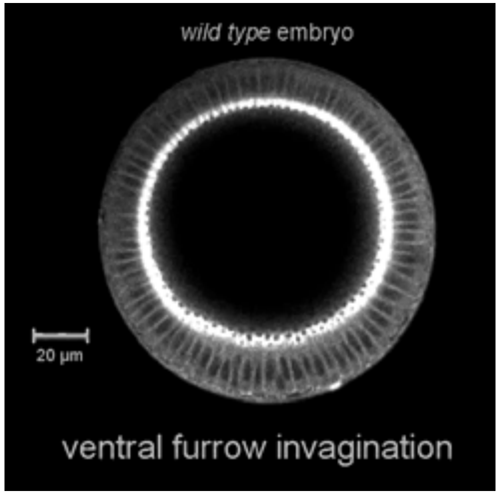
2. Tissue invagination



G. Schoenwolf U. Utah School of Medicine

Chick neural tube

Sea Urchin endoderm

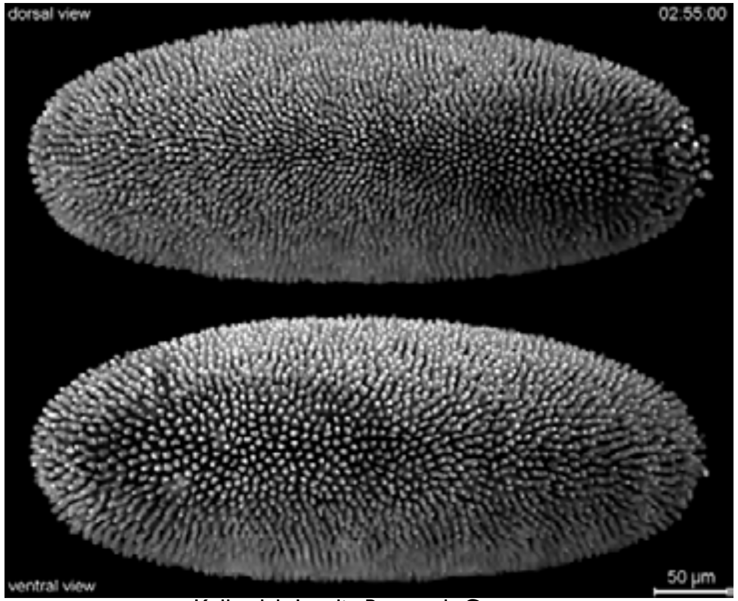


Drosophila mesoderm

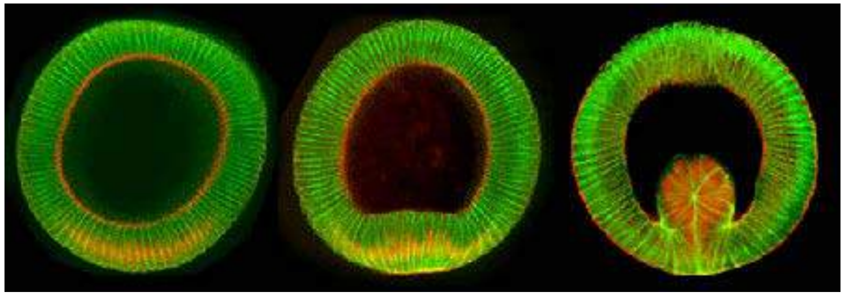
Programmed tissue invagination: Gastrulation

- Tissue invagination during gastrulation: the *Drosophila* embryo

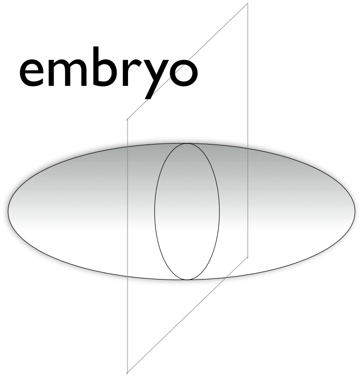
- Gastrulation: separation of tissue layers (ectoderm, mesoderm and endoderm)
- The ventral epithelium (presumptive mesoderm) forms a furrow
- and invaginates
- Leads to the formation of two distinct tissues

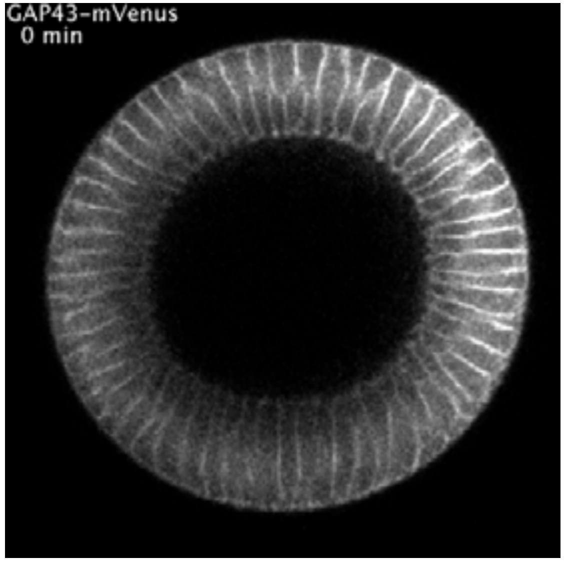


Keller lab Janelia Research Campus



Twist



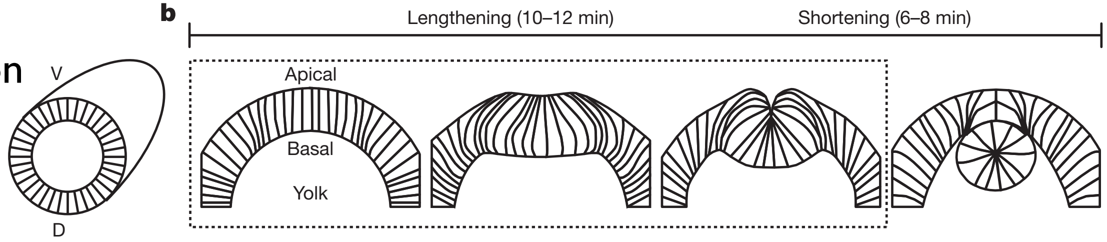


Programmed tissue invagination: Gastrulation

3D cellular model

Cell shape changes:

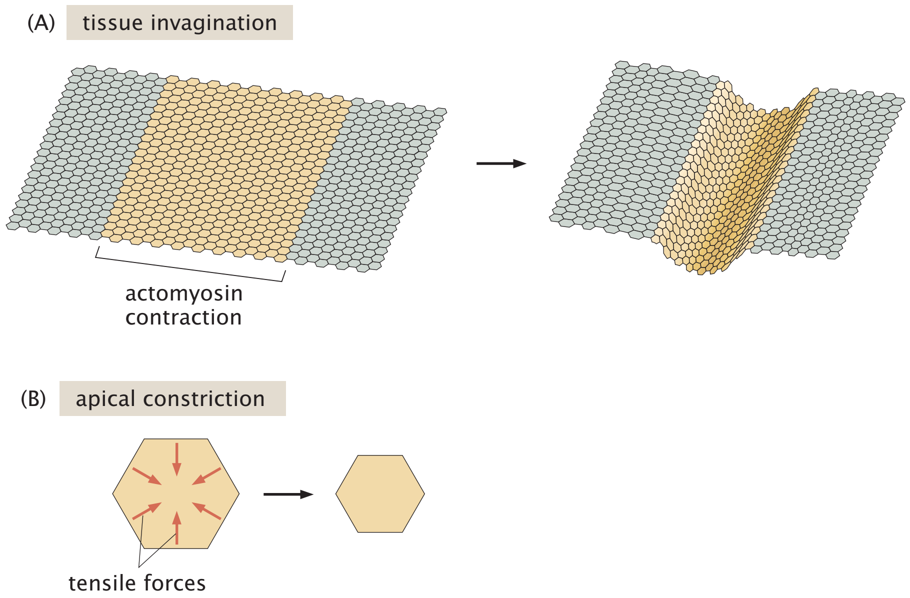
- Cell apex constriction
- Cell lengthening
- Basal expansion



2D cellular model

Cell shape changes:

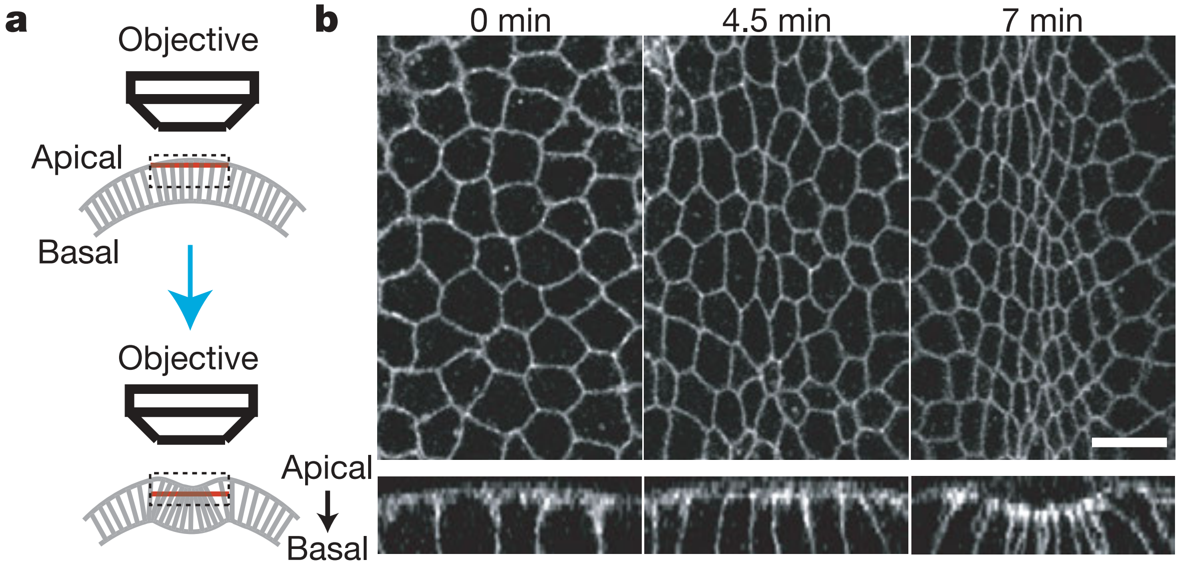
- Apical cell constriction



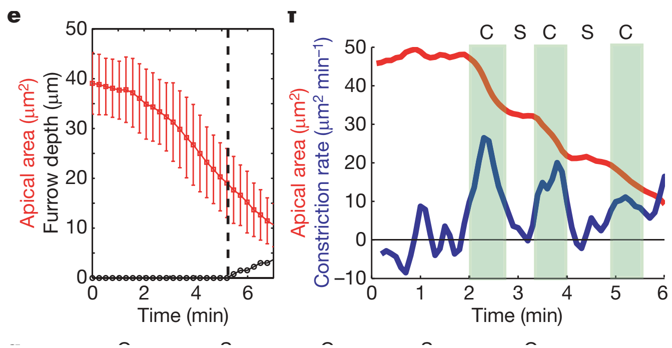
ill. Nigel Orme

Programmed tissue invagination: Gastrulation

2D cellular model — Tissue furrowing correlates with apical cell constriction



- Constriction is pulsatile

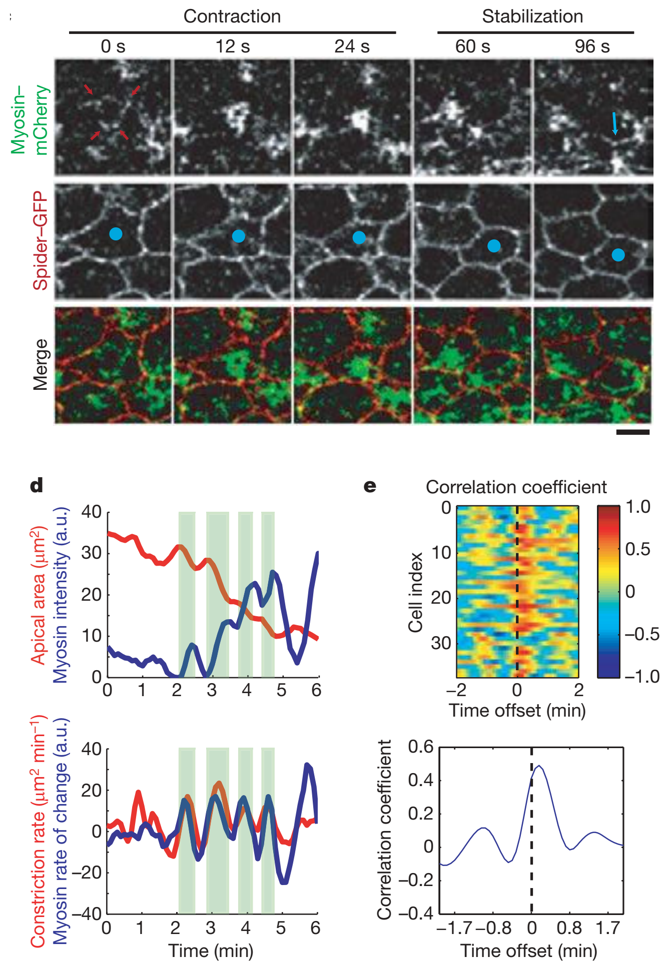


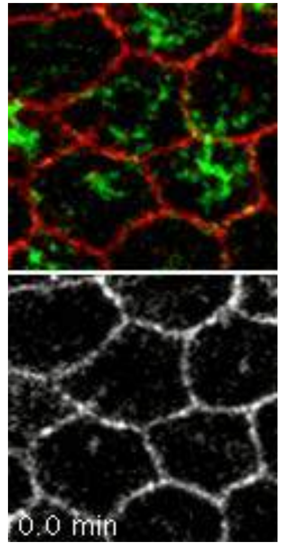
A. Martin,, M. Kaschube and E. Wieschaus, *Nature* (2009) 457:495-499

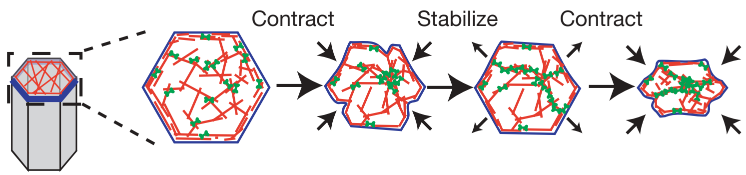
Programmed tissue invagination: Gastrulation

2D cellular model — Apical cell constriction is driven by contractile actomyosin pulses

- Myosin-II contractility is pulsatile
- Cell apical constriction correlates with Myosin-II pulsation
- Phases of constriction alternate with phases of stabilisation of cell shape
- A « mechanical ratchet » ensures irreversible cell and tissue deformations





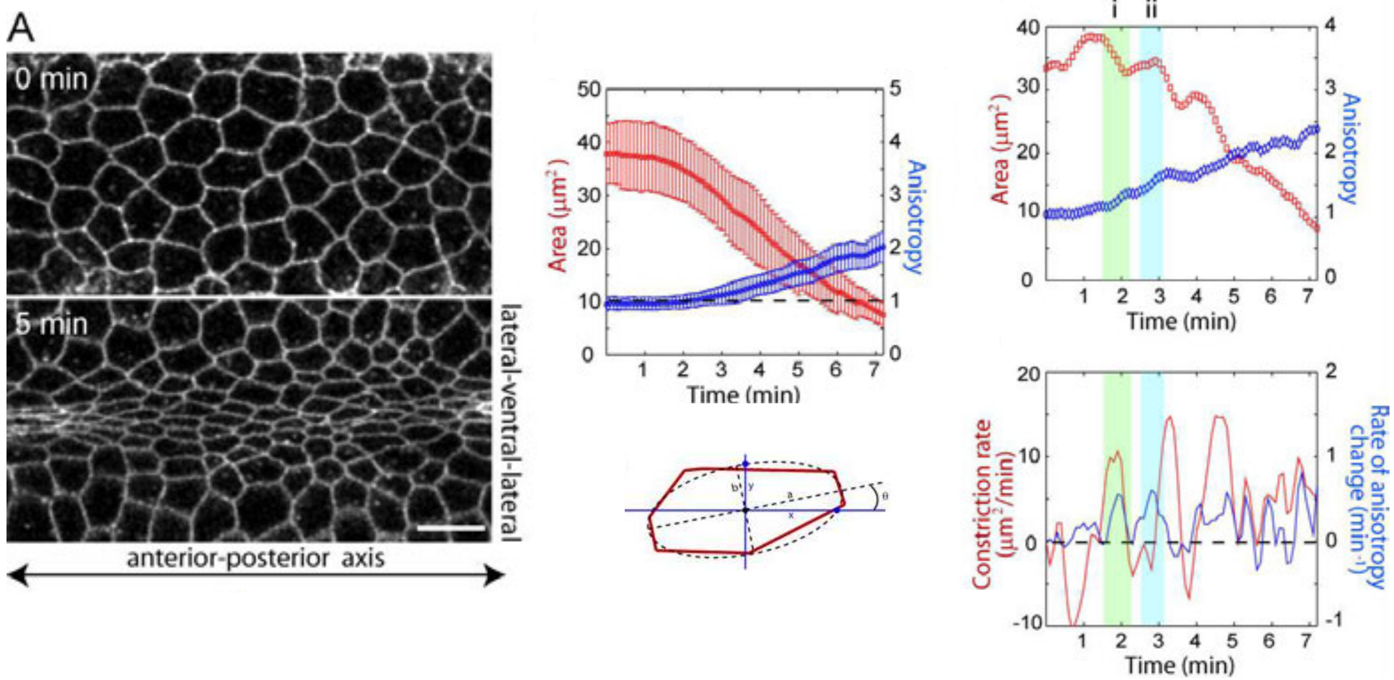


A. Martin,, M. Kaschube and E. Wieschaus, *Nature* (2009) 457:495-499

Programmed tissue invagination: Gastrulation

2D cellular model — Cell-Cell mechanical coupling

- Cells are strained along the anteroposterior axis
- Anisotropic cell constriction

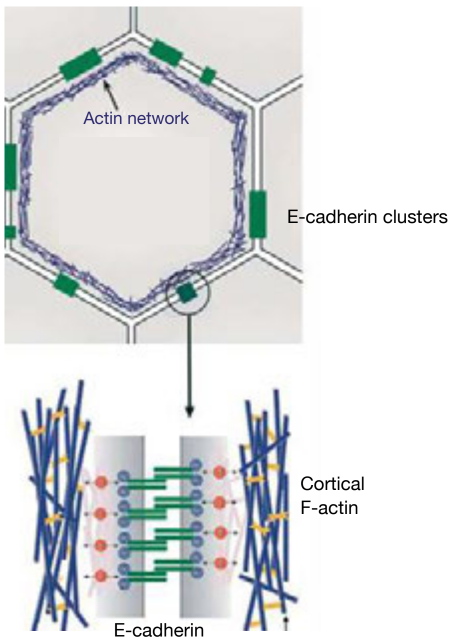


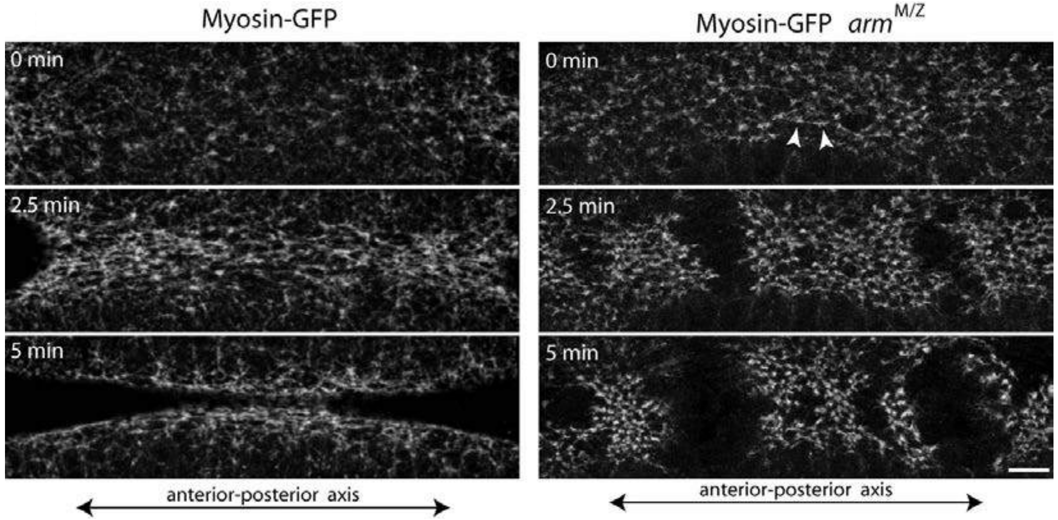
A. Martin et al. and E. Wieschaus. *J. Cell Biol.* (2010) 188 (5):735–749

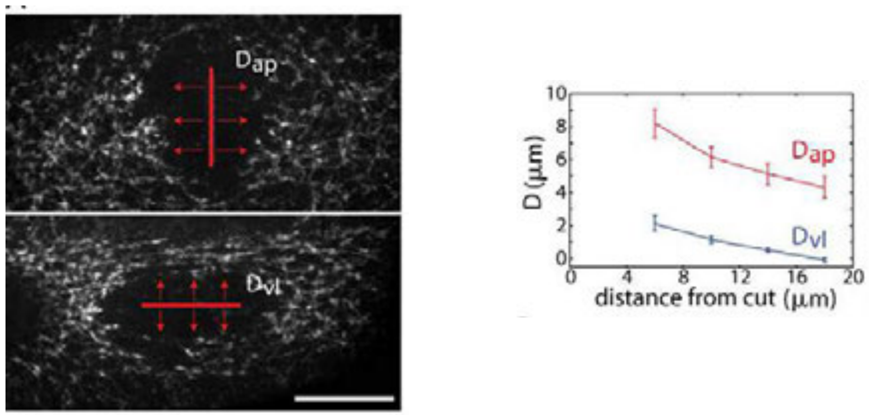
Programmed tissue invagination: Gastrulation

2D cellular model — Anisotropic apical cell constriction is due to increased tension along the anteroposterior axis

- Integrity of cell-cell junctions underlies tension build up via cell mechanical coupling





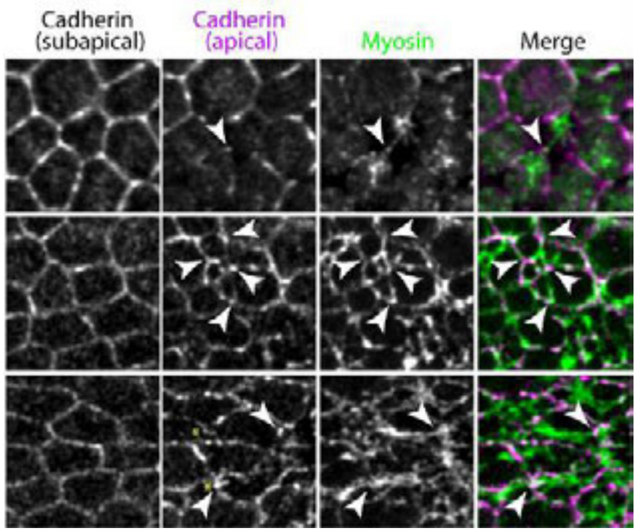


Laser ablation experiments: relaxation kinetics is related to total mechanical stress

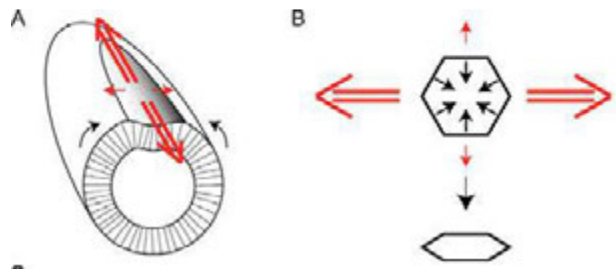
A. Martin et al. and E. Wieschaus. *J. Cell Biol.* (2010) 188 (5):735–749

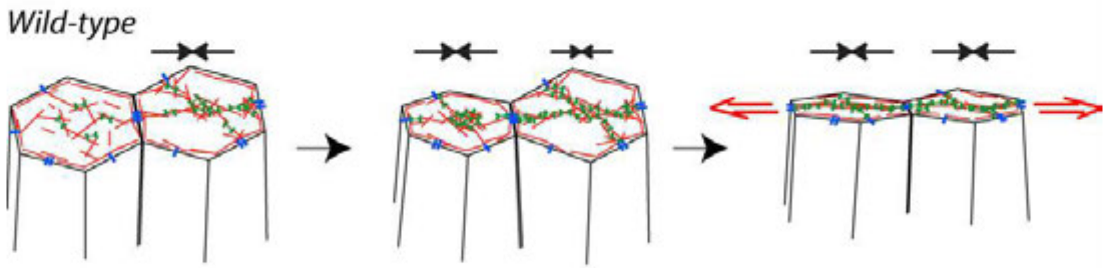
Programmed tissue invagination: Gastrulation

2D cellular model — Cell-cell mechanical coupling requires actomyosin coupling to cell junctions



- Multicellular actomyosin network underlies cell mechanical coupling



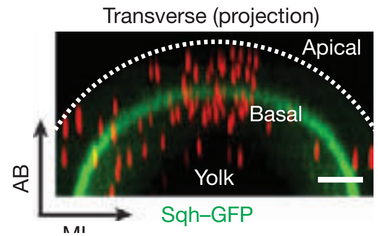


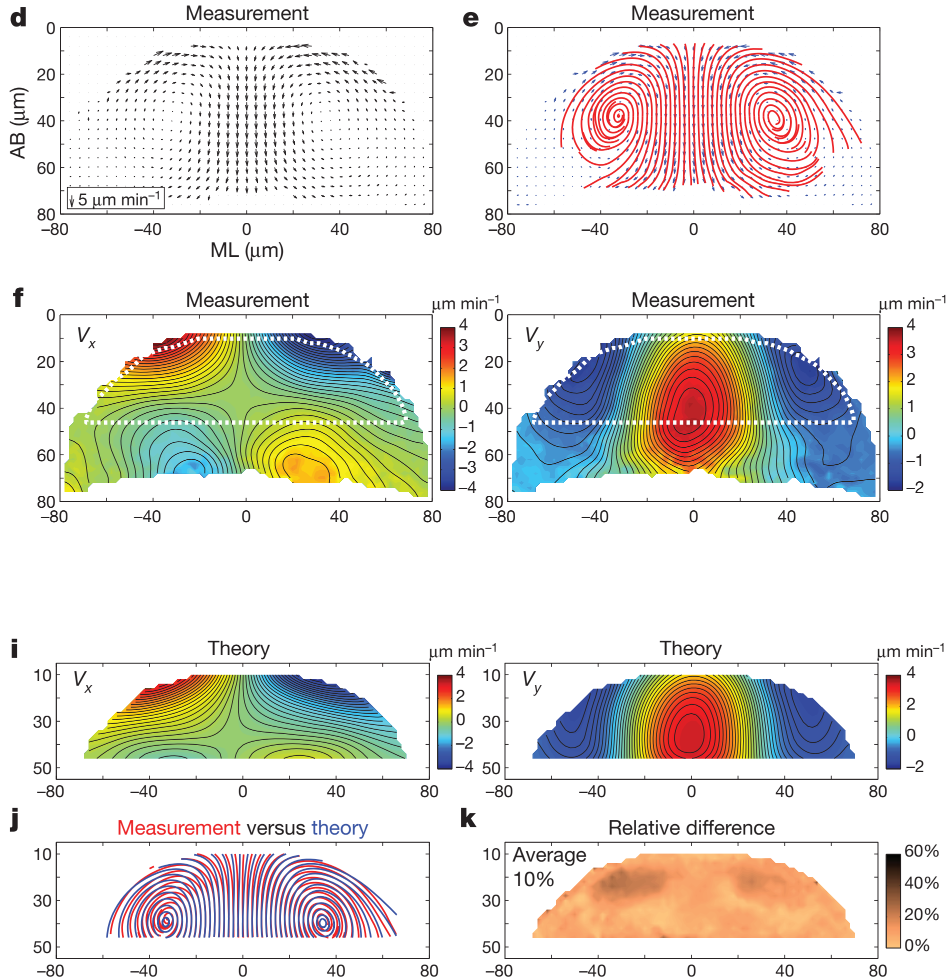
A. Martin et al. and E. Wieschaus. *J. Cell Biol.* (2010) 188 (5):735–749

Programmed tissue invagination: Gastrulation

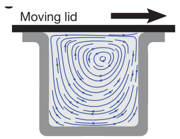
2D cellular model: apical constriction drives tissue scale hydrodynamic flow

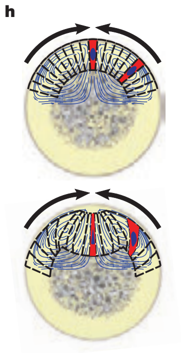
- Accounts for tissue flow at the onset of tissue invagination (furrowing)





- Stokes equations predict viscous flow at low Reynolds number regime:
- flow velocity at the interior of a domain is uniquely determined by velocities at the domain boundary.
- Suggests that tissue flow arises from shear forces associated with apical contractility at tissue scale

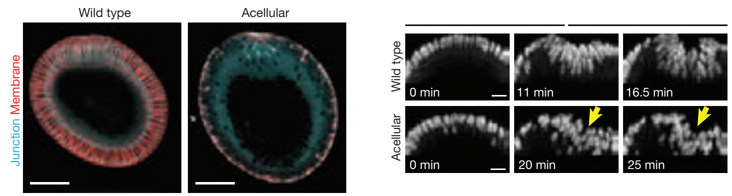




He et al. and E. Wieschaus. *Nature* (2014) 508:392-396

Programmed tissue invagination: Gastrulation

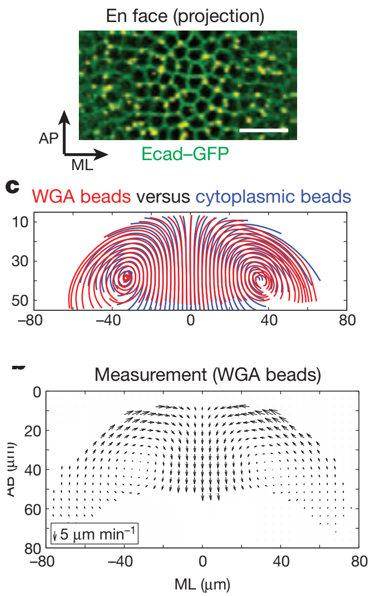
2D cellular model: apical constriction drives tissue scale hydrodynamic flow

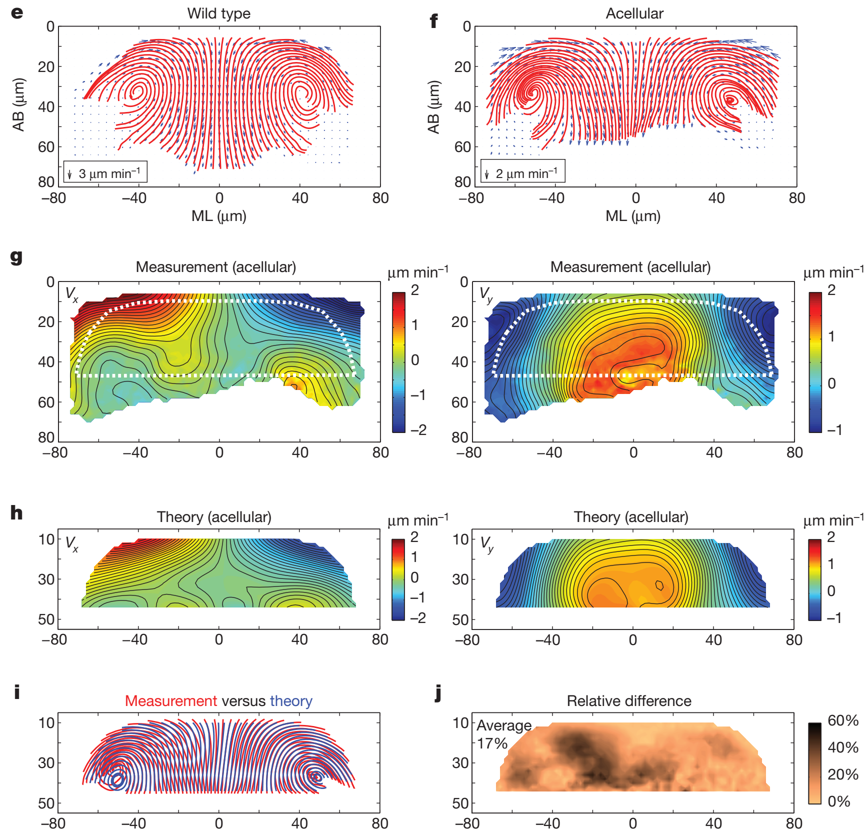


Acellular embryos

- Flows of cytoplasmic beads and membrane bound beads are similar suggesting that cells passively respond to cytoplasmic flow

- The individuality of cells is not necessary for tissue hydrodynamic flow: flow in acellular embryo is similar to normal embryos





He et al. and E. Wieschaus. *Nature* (2014) 508:392-396

Programmed tissue invagination: Gastrulation

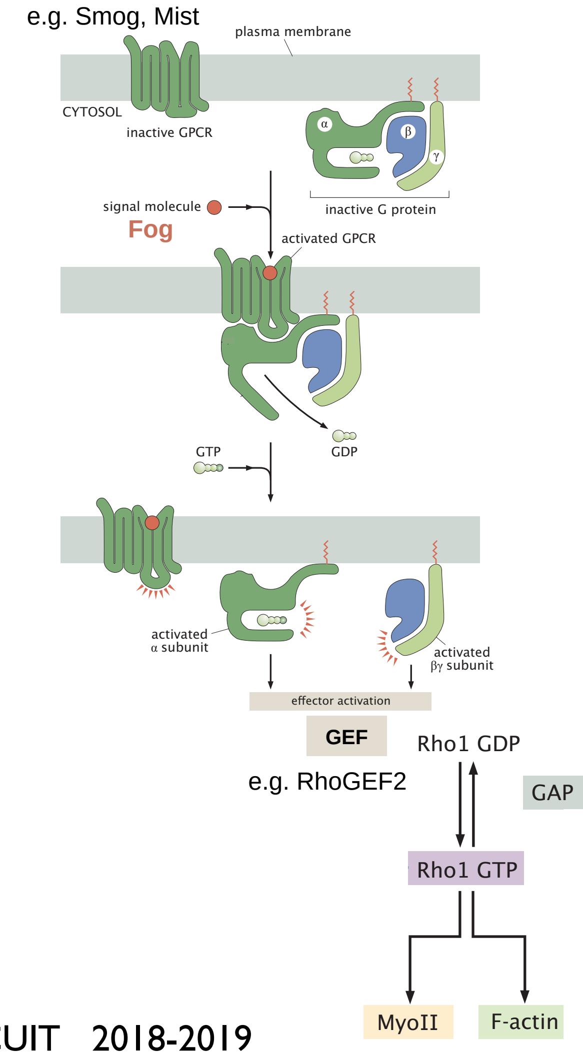
2D cellular model: The spatial program controlling apical cortical mechanics

Information (genetics/ biochemistry)

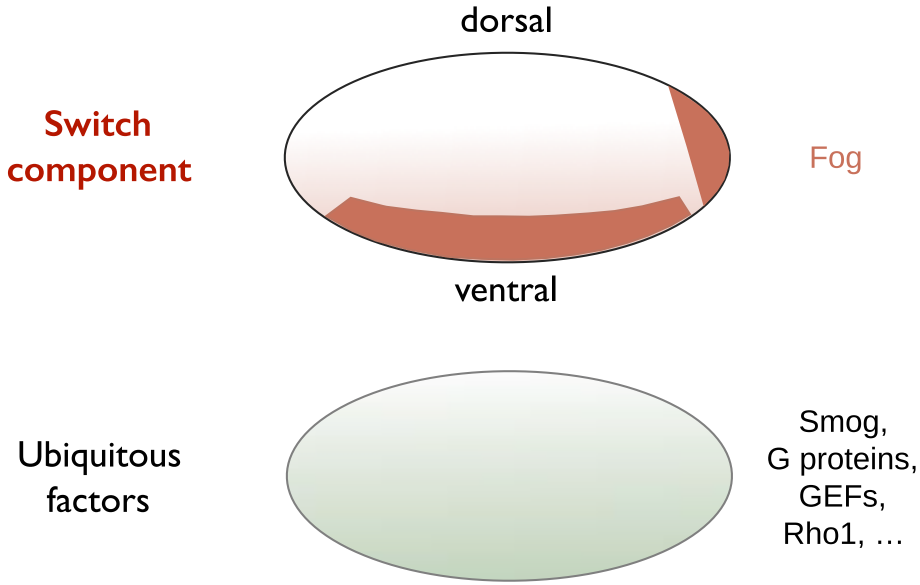
↓

Mechanics

The pathway:
GPCR and G protein signalling underlies Myosin2 activation



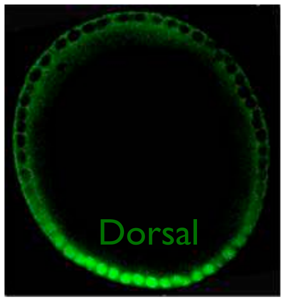
The program:
Embryonic prepattern spatially controls signalling



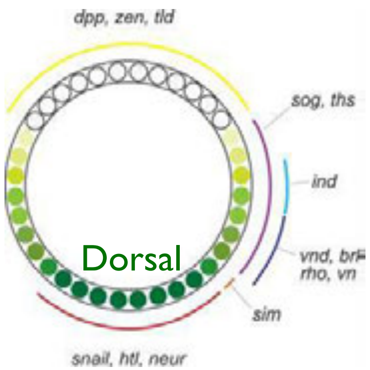
Programmed tissue invagination: Gastrulation

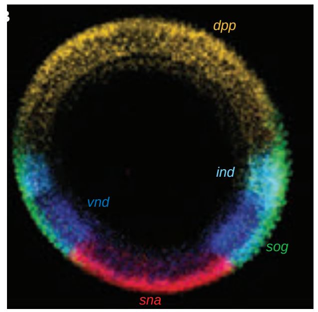
2D cellular model: The spatial program controlling apical cortical mechanics

The pathway:
Positional information and spatial activation of Myosin2

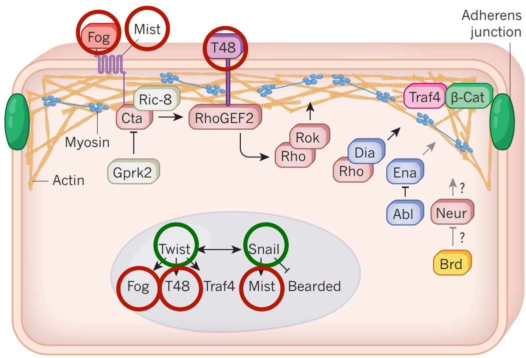


B. Shilo lab

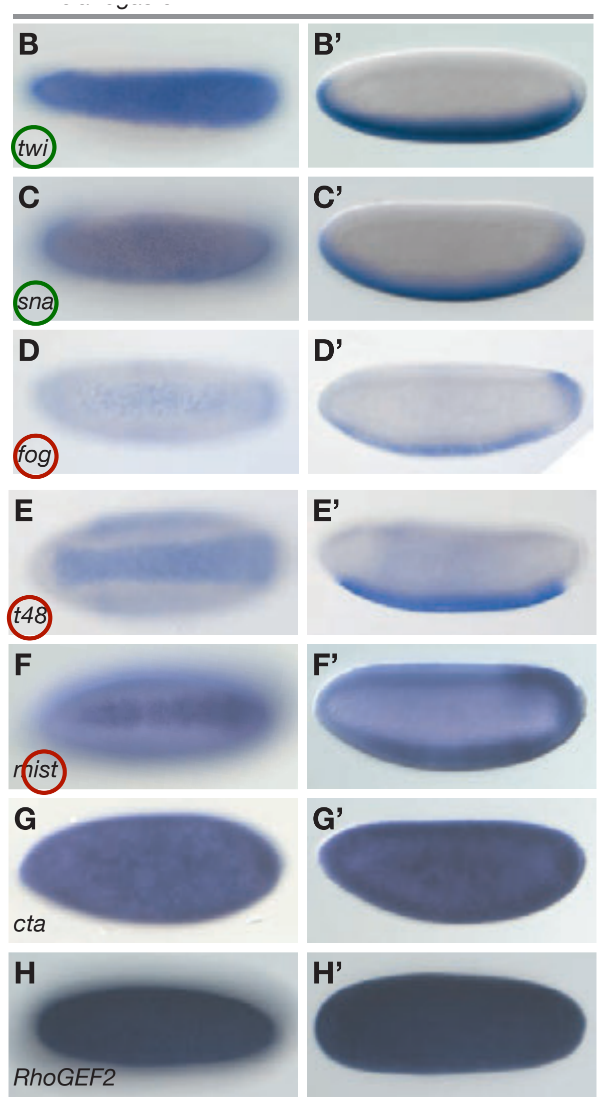




M. Levine. PNAS, 2008 105 (51) 20072-20076;



D. Gilmour, M. Rembold and M. Leptin. *Nature* 541:311-320 (2017)

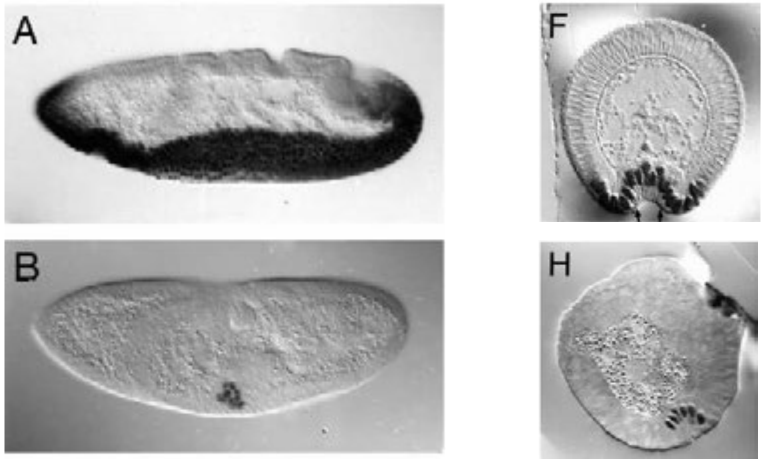


Urbansky et al. S. Lemke. *eLife* 2016;5:e18318

Programmed tissue invagination: Gastrulation

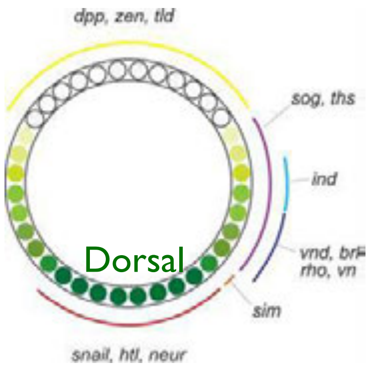
2D cellular model: The spatial program controlling apical cortical mechanics and invagination

Snail positive cells can invaginate on a cell-autonomous basis. Indicates that cell autonomous activation of the « invagination program » is sufficient to induce proper invagination.



host snail/twist -/-

donor wt



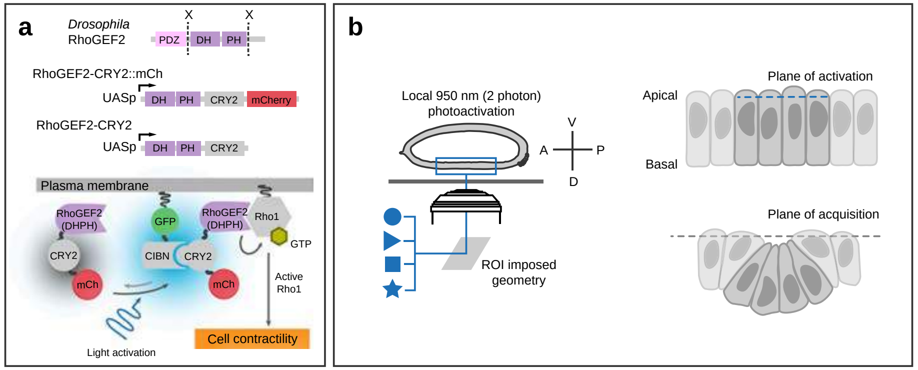
host Toll -/-

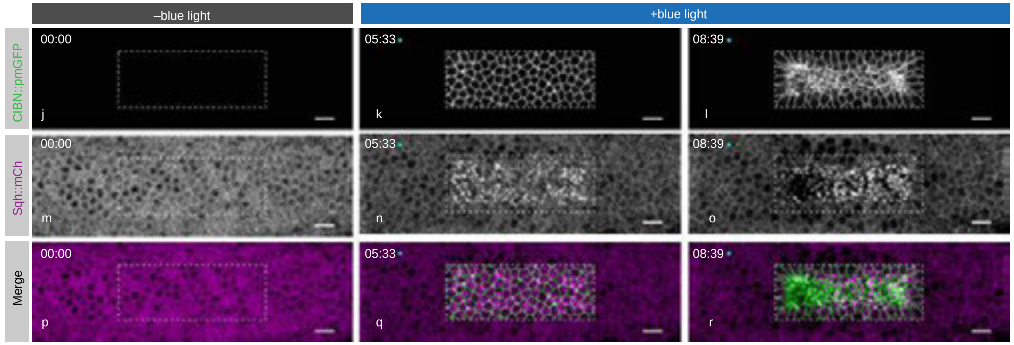
donor wt

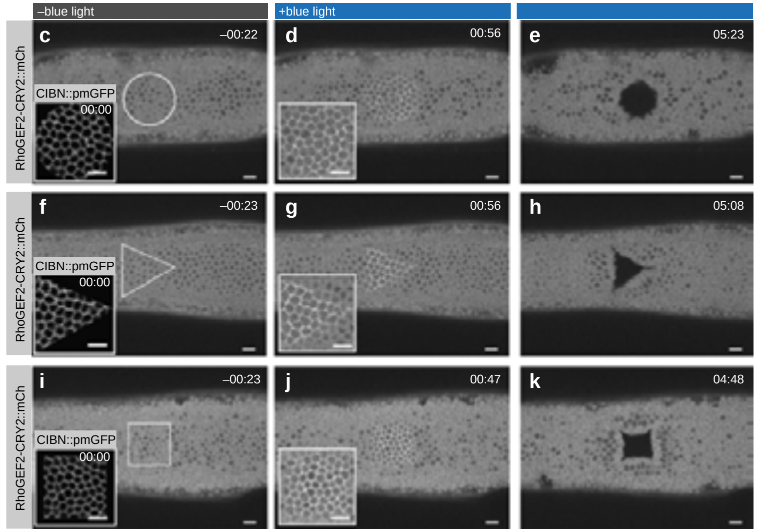
M. Leptin and S. Roth *Development* 120, 853-859 (1994)

Programmed tissue invagination: Gastrulation

2D cellular model: The spatial program controlling apical cortical mechanics and invagination







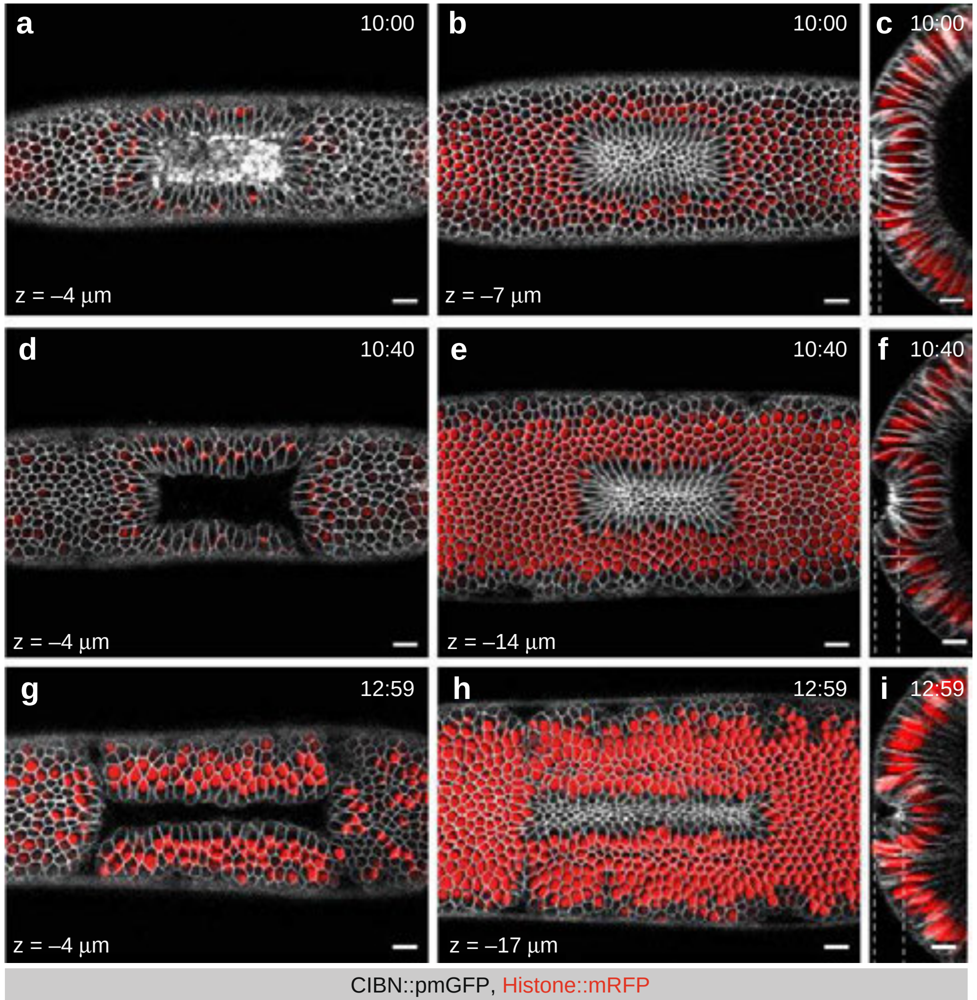
- Optogenetic activation of the Rho1GTP pathway
- Rho1 activation causes MyosinII activation cell autonomously
- Rho1 activation is sufficient to induce tissue invagination. The geometry of activation directs the geometry of invagination

E Izquierdo, T. Quikler and S. de Renzis *Nature Communications*. (2018)9:2366 | DOI: 10.1038/s41467-018-04754-z

Programmed tissue invagination: Gastrulation

2D cellular model: The spatial program controlling apical cortical mechanics and invagination

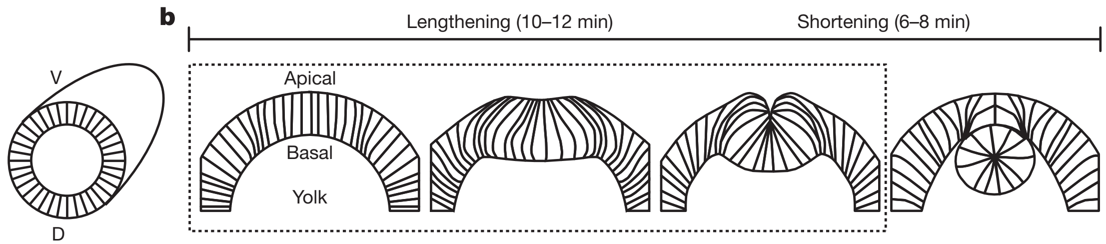
- Optogenetic activation of the Rho1GTP pathway causes *complete* tissue invagination, suggesting that apical contractility is sufficient for complete invagination



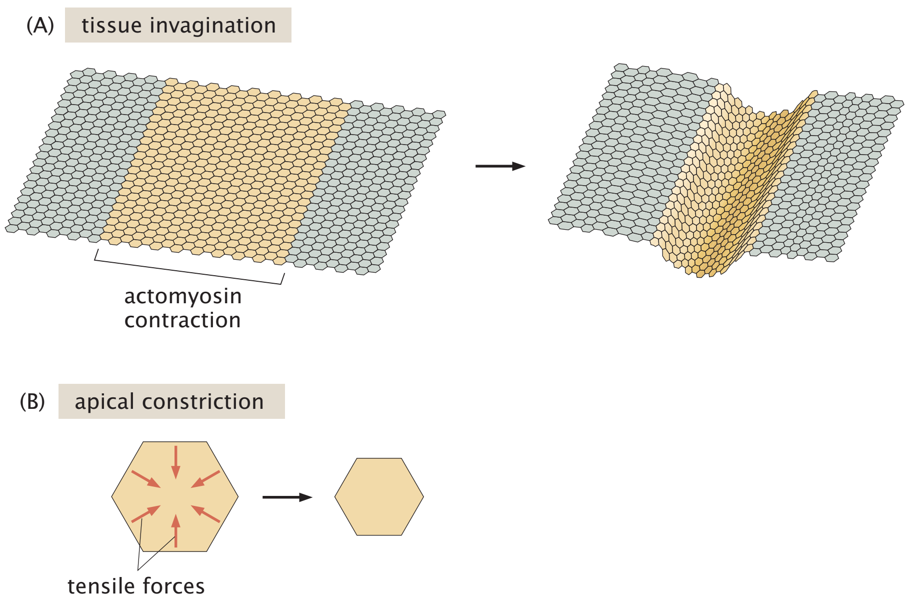
E Izquierdo, T. Quikler and S. de Renzis *Nature Communications.* (2018)9:2366 | DOI: 10.1038/s41467-018-04754-z

Programmed tissue invagination: Gastrulation

3D cellular model

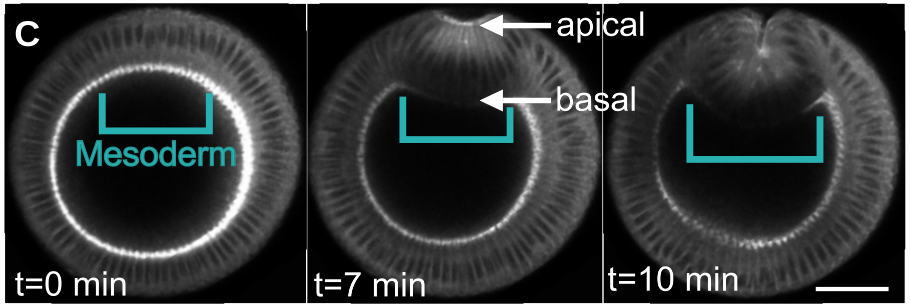


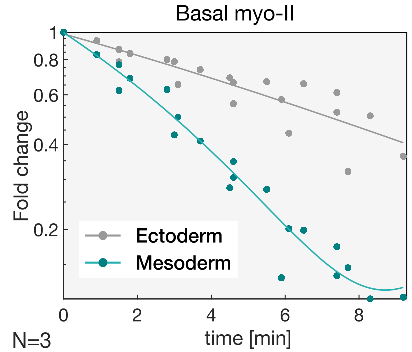
2D cellular model

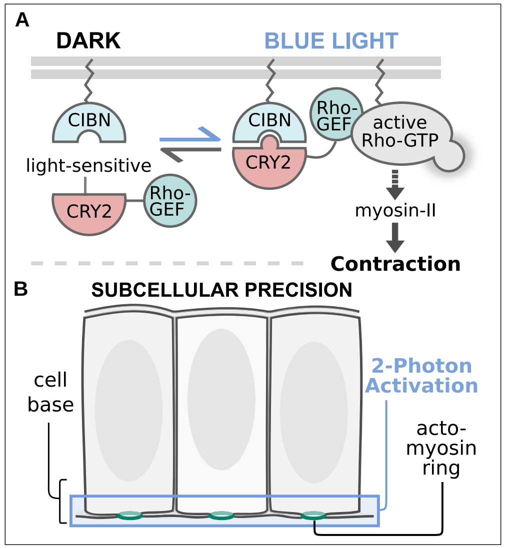


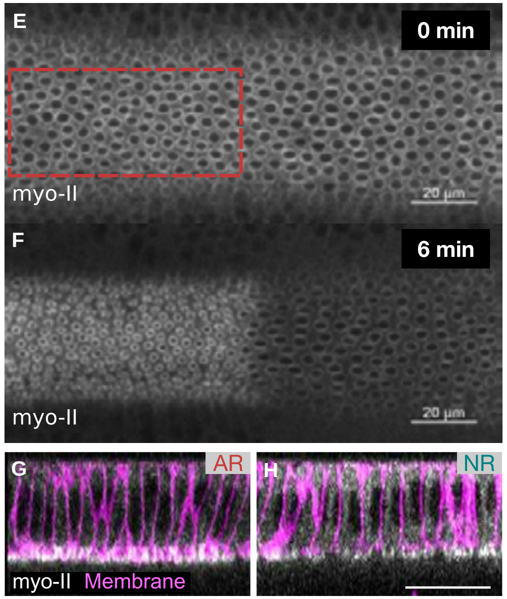
Programmed tissue invagination: Gastrulation

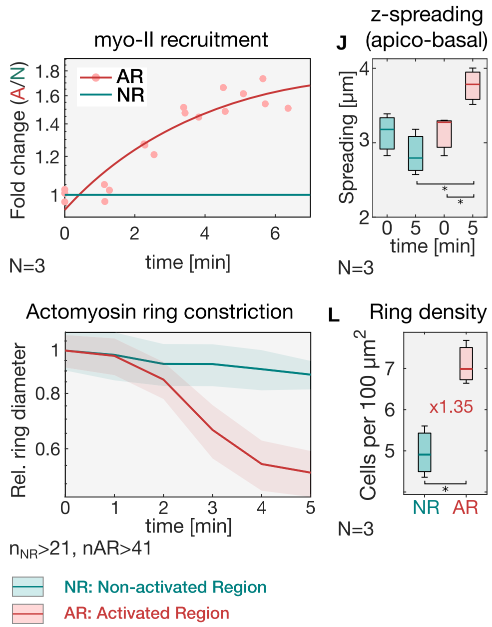
3D cellular model: basal inhibition of Myosin-II is required for invagination







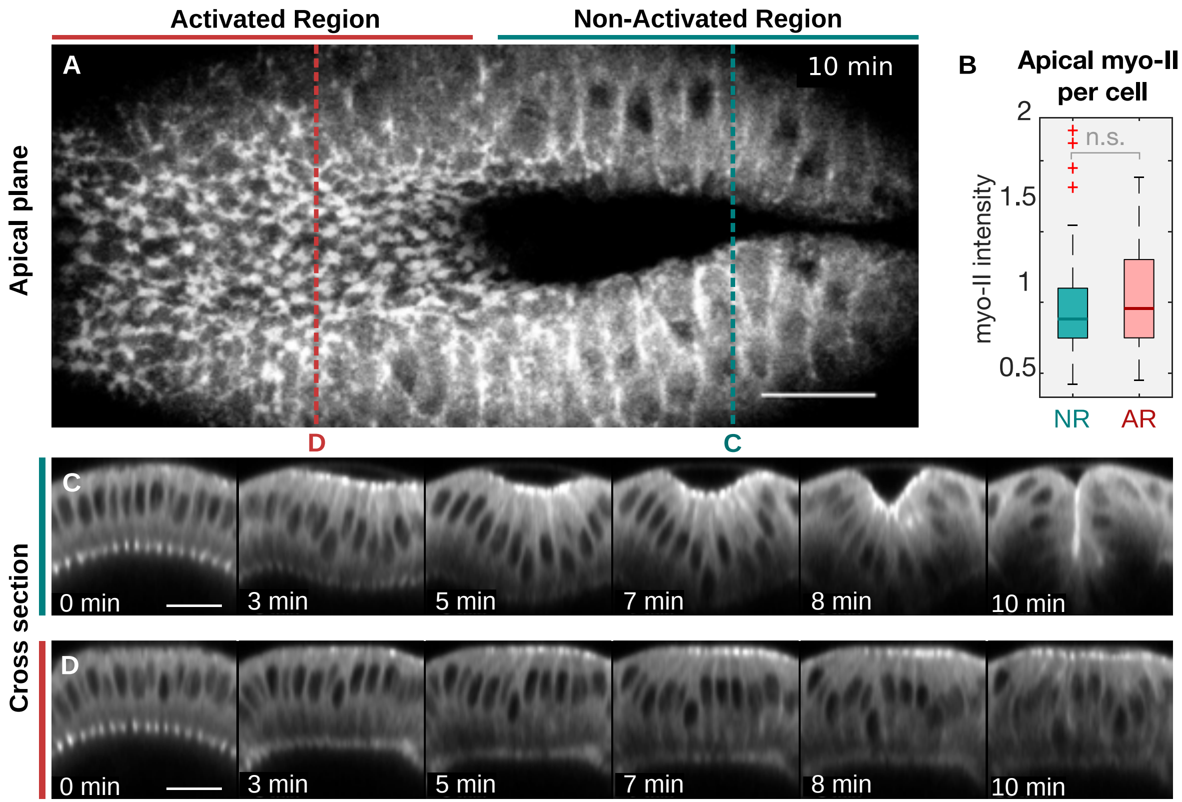




D. Krueger et al. and S. de Renzis *EMBO J.* (2018) pii: e100170. doi: 10.15252/embj.2018100170

Programmed tissue invagination: Gastrulation

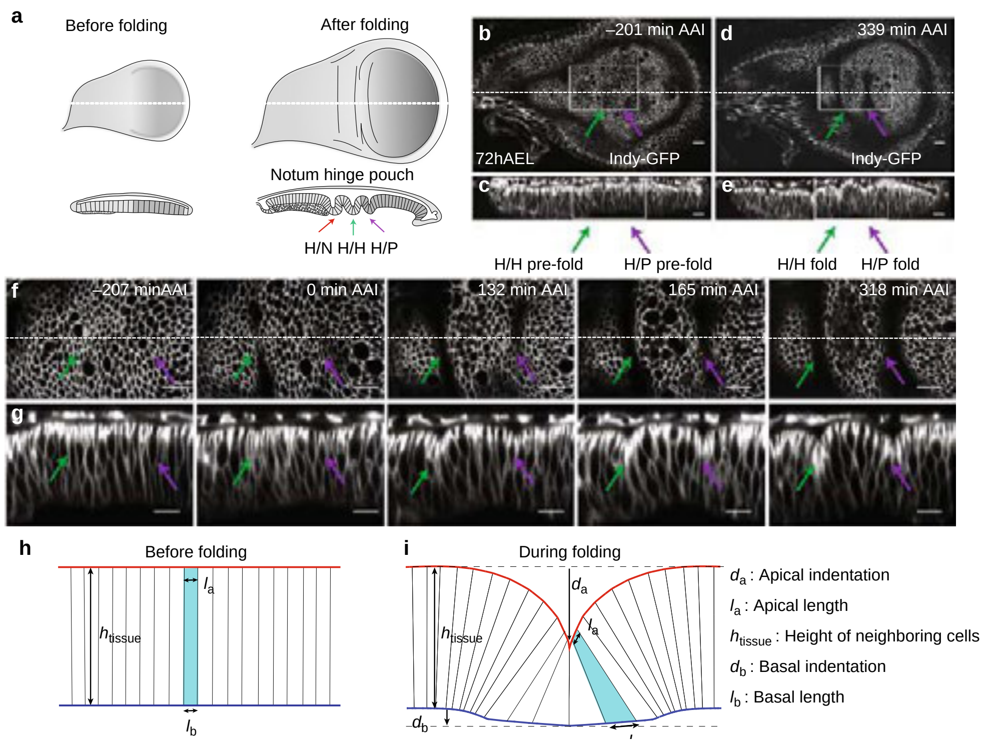
3D cellular model: basal inhibition of Myosin-II is required for invagination

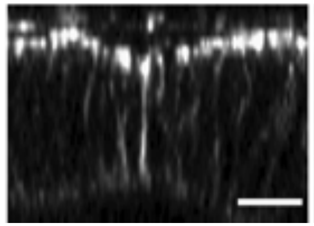


D. Krueger et al. and S. de Renzis *EMBO J.* (2018) pii: e100170. doi: 10.15252/embj.2018100170

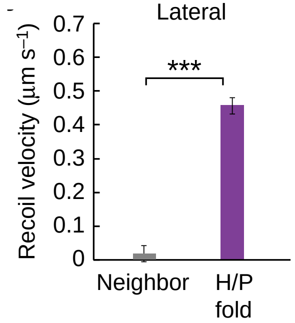
Programmed tissue invagination: Gastrulation

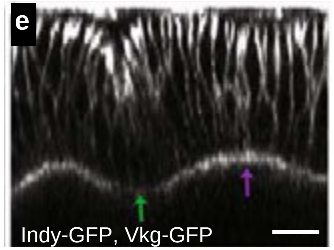
3D cellular model: increased lateral tension and basal tension relaxation induce tissue invagination



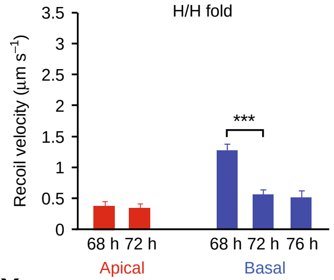


F-actin (UtrABD::GFP)

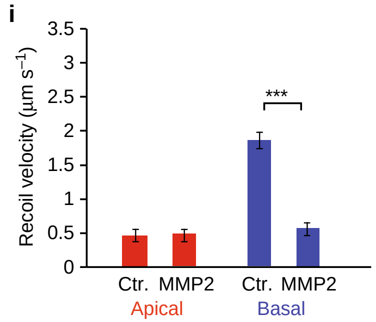


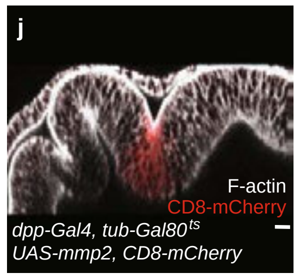


ECM: extra-cellular matrix



Tension inferred from ablation relaxation





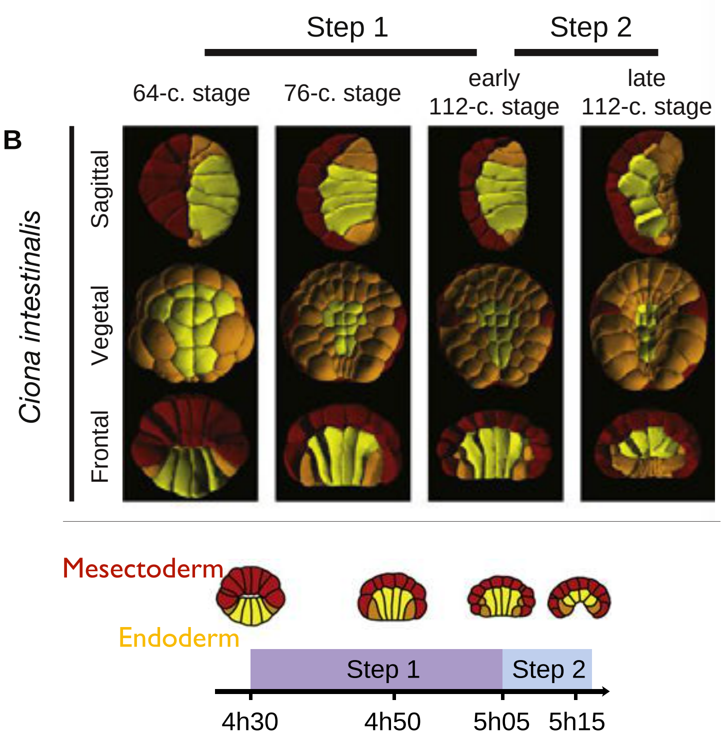
Ectopic furrow

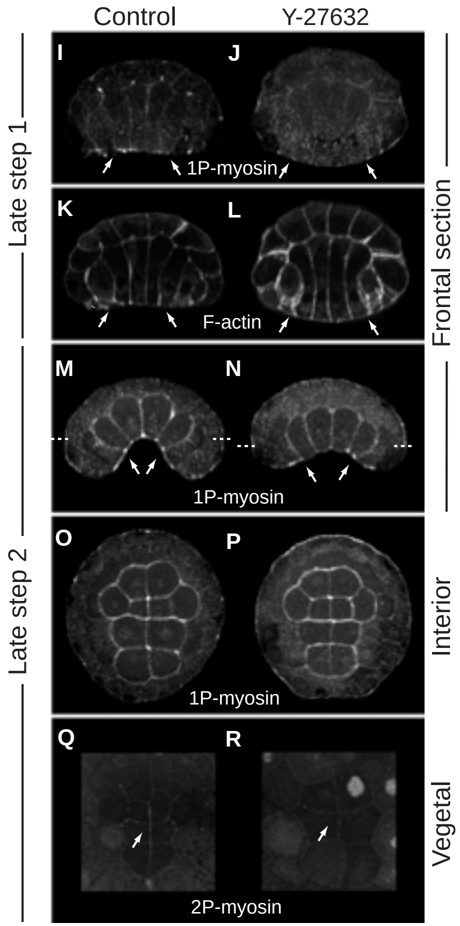
L Sui et al. G. Salbreux and C. Dahmann *Nature Communications.* (2018) (2018)9:4620 | DOI: 10.1038/s41467-018-06497-3

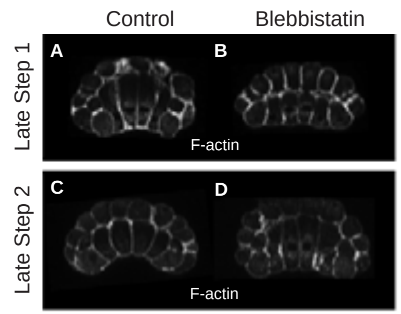
Programmed tissue invagination: Gastrulation

3D cellular model: increased apical and lateral tension induce tissue invagination

- Sequential apical and lateral recruitment of Myosin-II to cell cortex



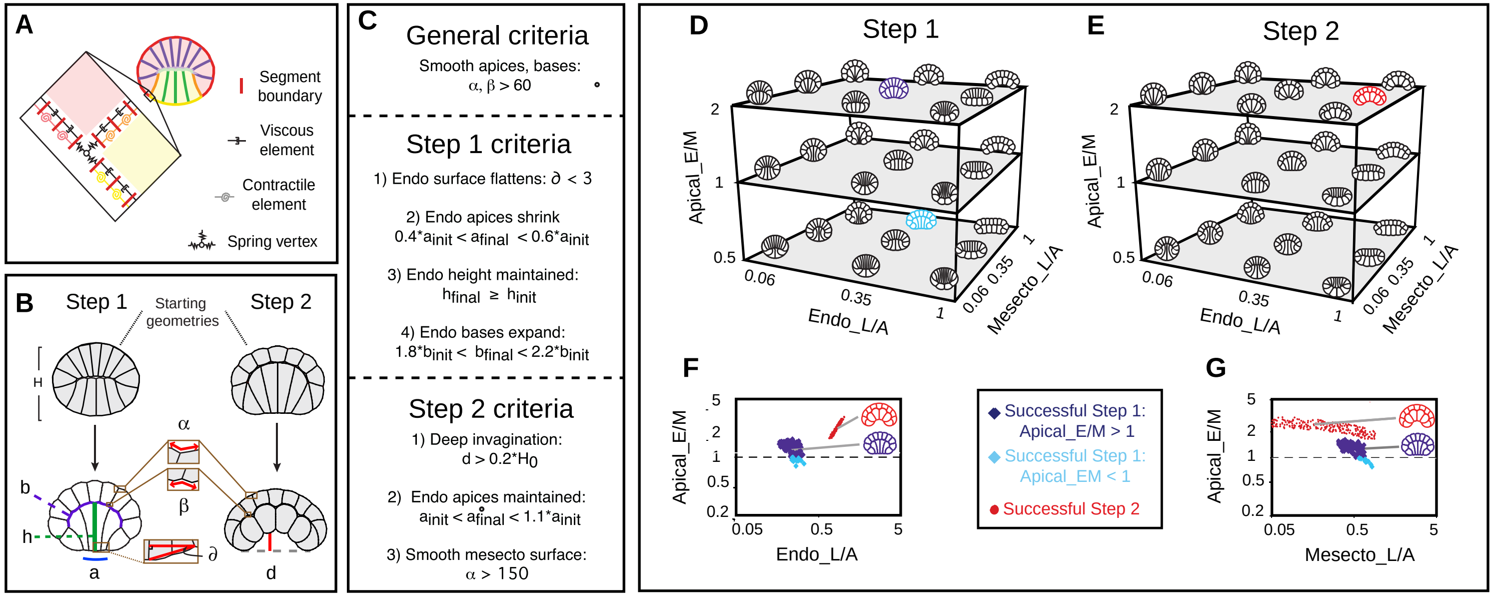


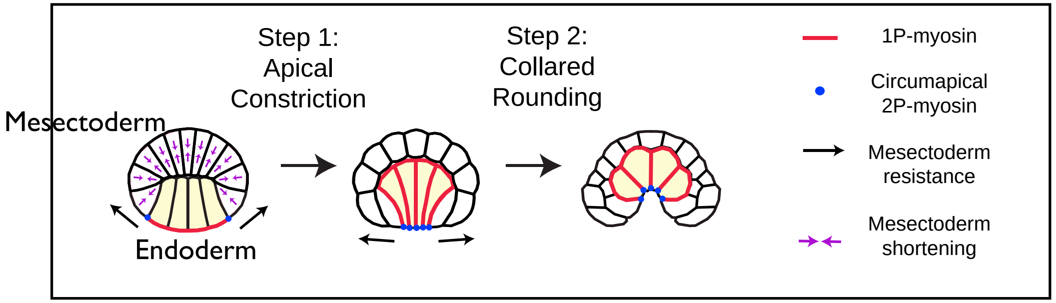


K. Sherrard, F. Robin, P. Lemaire and E. Munro. *Current Biology* 20, 1499–1510 (2010)

Programmed tissue invagination: Gastrulation

3D cellular model: increased apical and lateral tension induce tissue invagination





K. Sherrard, F. Robin, P. Lemaire and E. Munro. *Current Biology* 20, 1499–1510 (2010)

See also: M. Rauzi et al, and M Leptin. *Nature Communications* | 6:8677 | DOI: 10.1038/ncomms9677 |

Programmed tissue invagination: Gastrulation

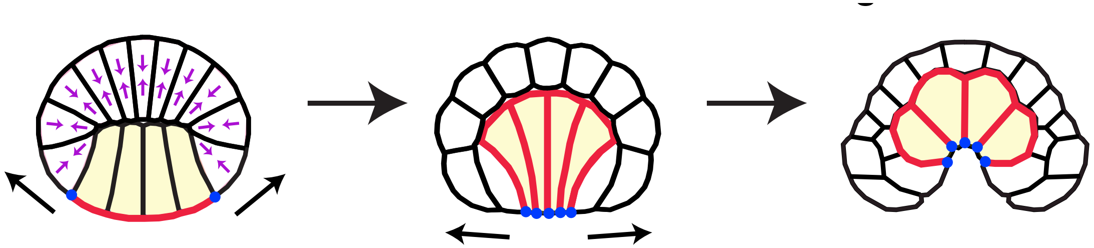
The program of Invagination:

Spatial and temporal control over cortical mechanics:
active stress generation (MyosinII contractility)

Information
(genetics/
biochemistry)

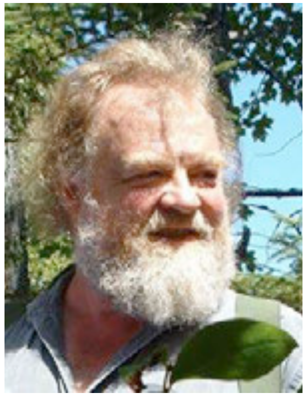
Mechanics

- Regionalisation
- Polarisation

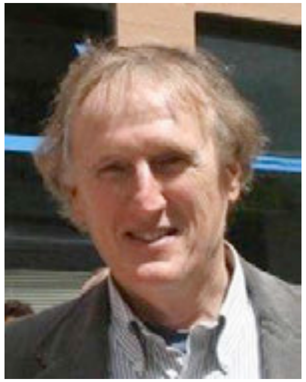


Self-organised tissue invagination

- **Self-organisation of invagination:**
given initial trigger, cell deformation and spatial pattern emerges from cell mechanical properties



Garrett Odell
1943-2018



George Oster
1940-2018

The Mechanical Basis of Morphogenesis

I. Epithelial Folding and Invagination

G. M. ODELL,[1] G. OSTER, P. ALBERCH, AND B. BURNSIDE

University of California, Berkeley, California 94720

In this study we want to minimize both the number of complex instructions (e.g., morphogens and clocks) as well as the genetic programming required to generate morphogenetic patterns.

In our model, coordination at the population level arises from the local behavior of each cell automatically; there is no need to introduce poorly understood devices such as morphogens and cellular clocks.

Second, we wanted to minimize the load of genetic preprogramming required to generate morphogenetic patterns. We felt that to equip each cell with an autonomous program, and a precise "clock" for activating that program, was unesthetic and probably unnecessary. At least part of the burden of pattern formation and regulation may be taken up by the equilibration of purely mechanical forces.

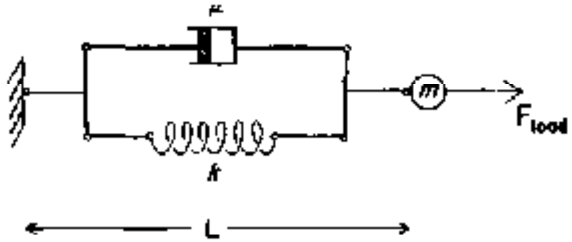
Our model, therefore, is built on Newton's laws of motion and consists of a dynamical system of ordinary differential equations whose solution determines the global time history of the cell sheet geometry, given its initial configuration.

G.M. Odell, G. Oster, P. Alberch and B. Burnside. *J. Math. Biol* (1980) 9:291-295
G.M. Odell, G. Oster, P. Alberch and B. Burnside. *Dev. Biol.* (1981) 85:446-462

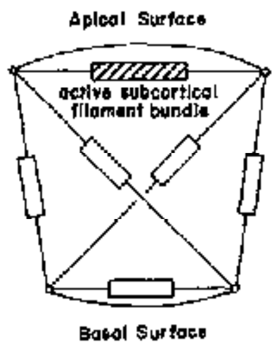
Self-organised tissue invagination

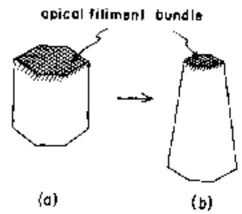
- Task: coordinating at population level (tissue) individual cell behaviours in space and time

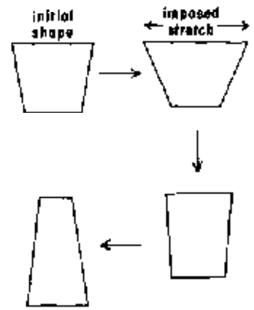
- Cells are mechanically coupled
- Apical contractility
- Volume incompressibility
- The apical cortex of cells is excitable (active spring):
- small cell stretching causes relaxation to rest configuration *Lo*
- above threshold, cell stretching causes cell « firing » of contractility and return to a new rest configuration



$$\frac{dL}{dt} = -\frac{k}{\mu}(L - L_0) + \frac{1}{\mu} F_{load}.$$



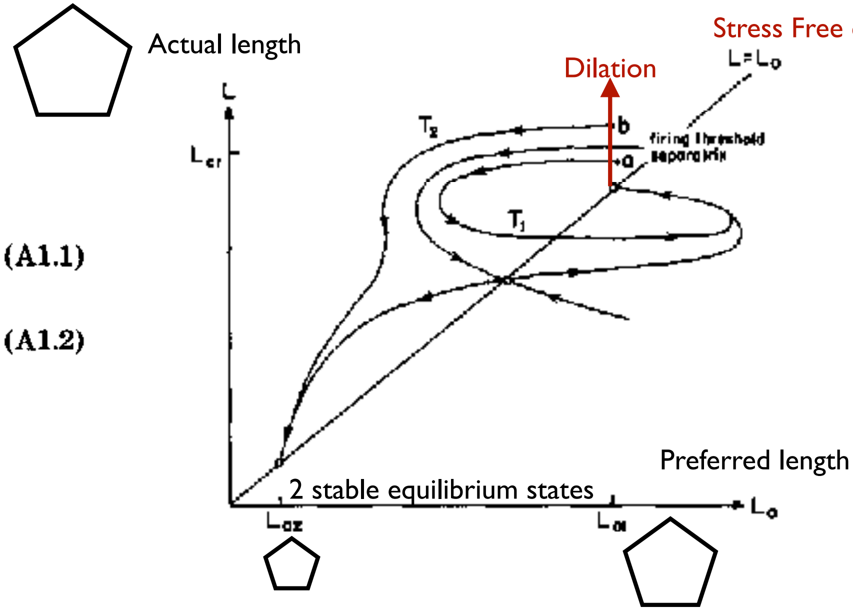




G.M. Odell, G. Oster, P. Alberch and B. Burnside. *J. Math. Biol* (1980) 9:291-295
G.M. Odell, G. Oster, P. Alberch and B. Burnside. *Dev. Biol.* (1981) 85:446-462

Self-organised tissue invagination

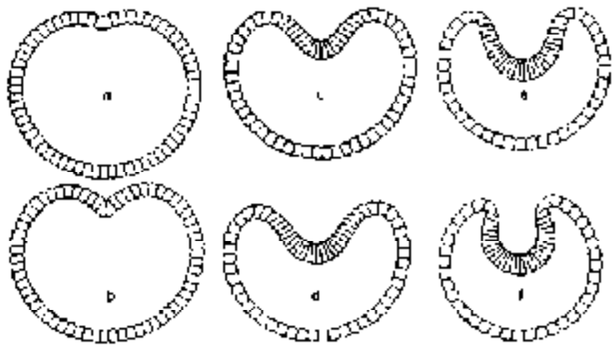
- Rest configuration is a fonction of cell deformation

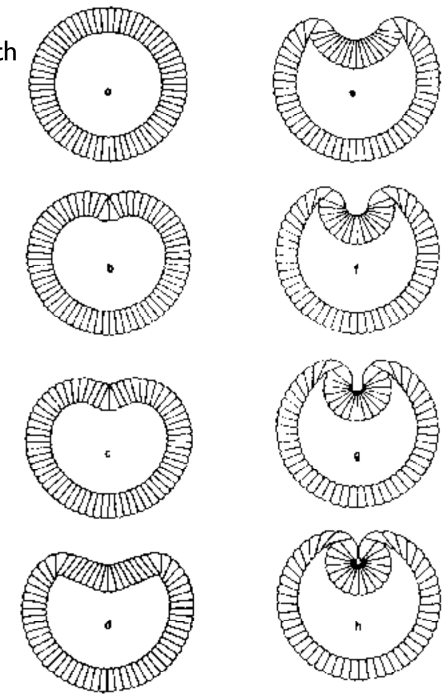


$$\frac{dL}{dt} = -\frac{k(\cdot)}{\mu}[L - L_0], \qquad \text{(A1.1)}$$

$$\frac{dL_0}{dt} = G(L, L_0). \qquad \text{(A1.2)}$$

- Predicts wave of contractility and cell deformation that give rise to tissue folding and invagination



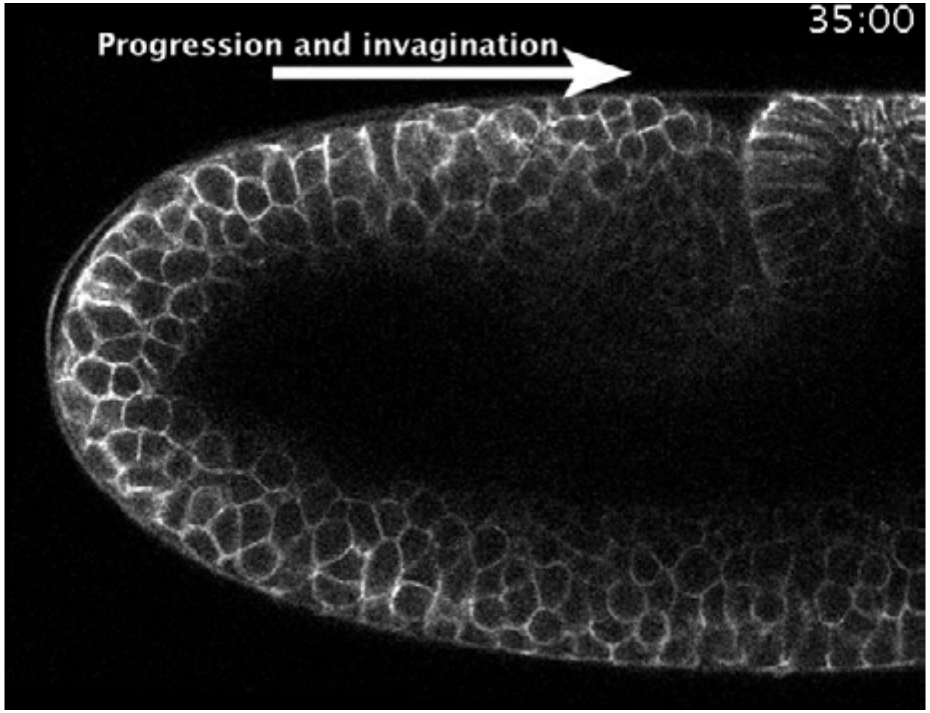


G.M. Odell, G. Oster, P. Alberch and B. Burnside. *J. Math. Biol* (1980) 9:291-295
G.M. Odell, G. Oster, P. Alberch and B. Burnside. *Dev. Biol.* (1981) 85:446-462

Programmed and Self-Organised Invagination

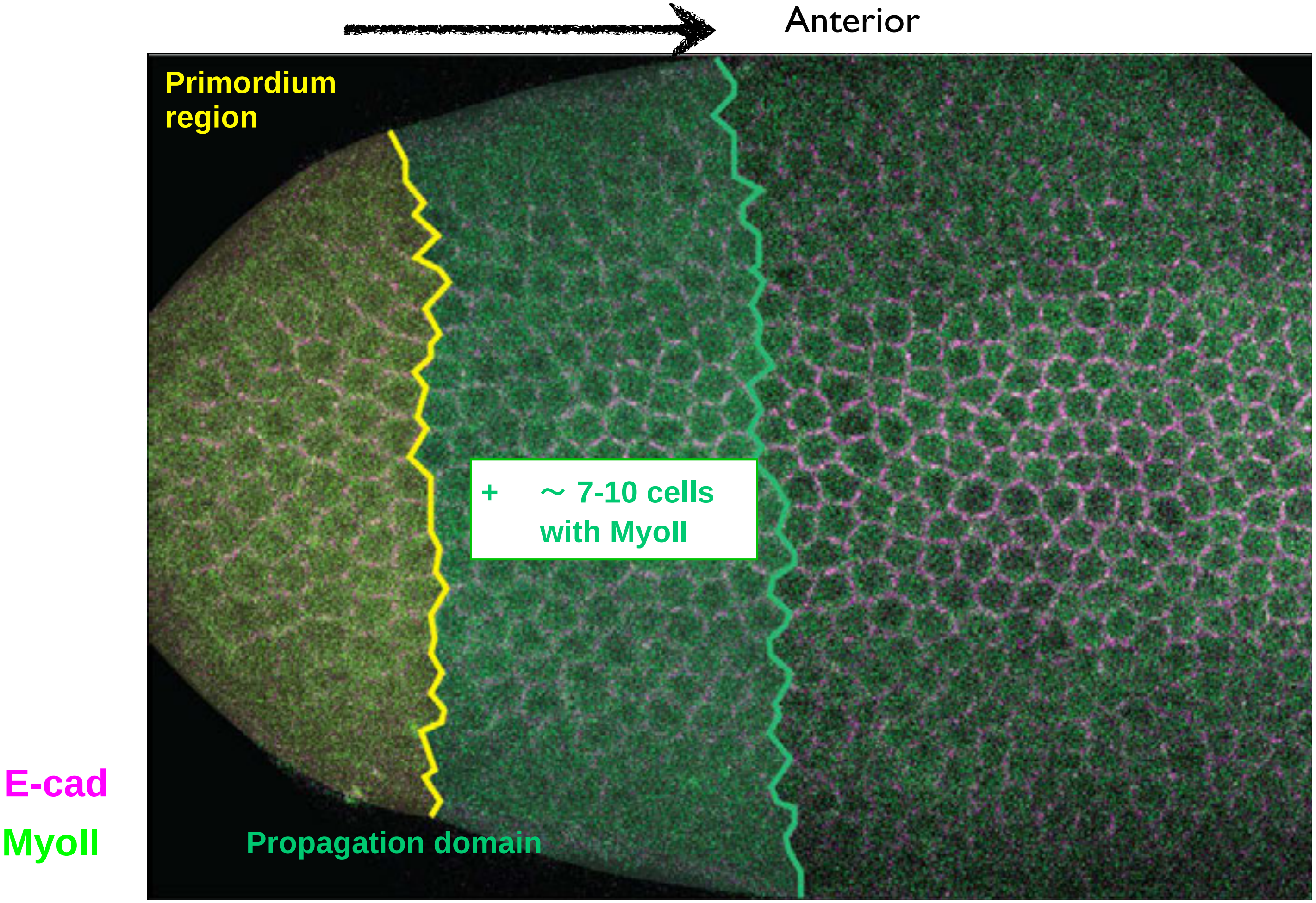
- Interplay between control and self-organisation of tissue morphogenesis

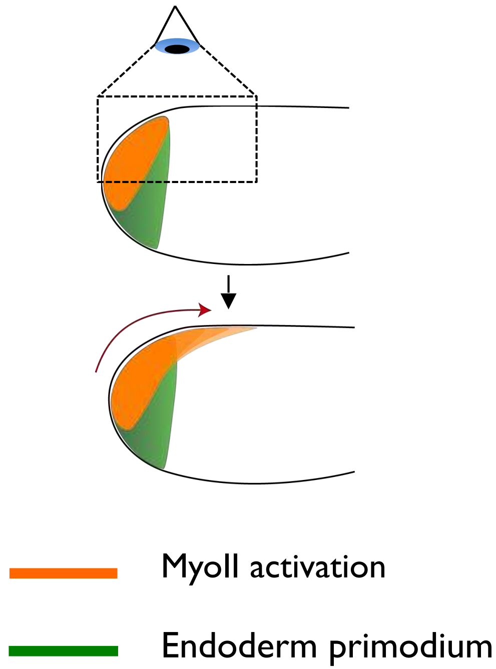
Endoderm morphogenesis in *Drosophila*



Programmed and Self-Organised Invagination

- A tissue scale wave of actomyosin activation is associated with wave of invagination

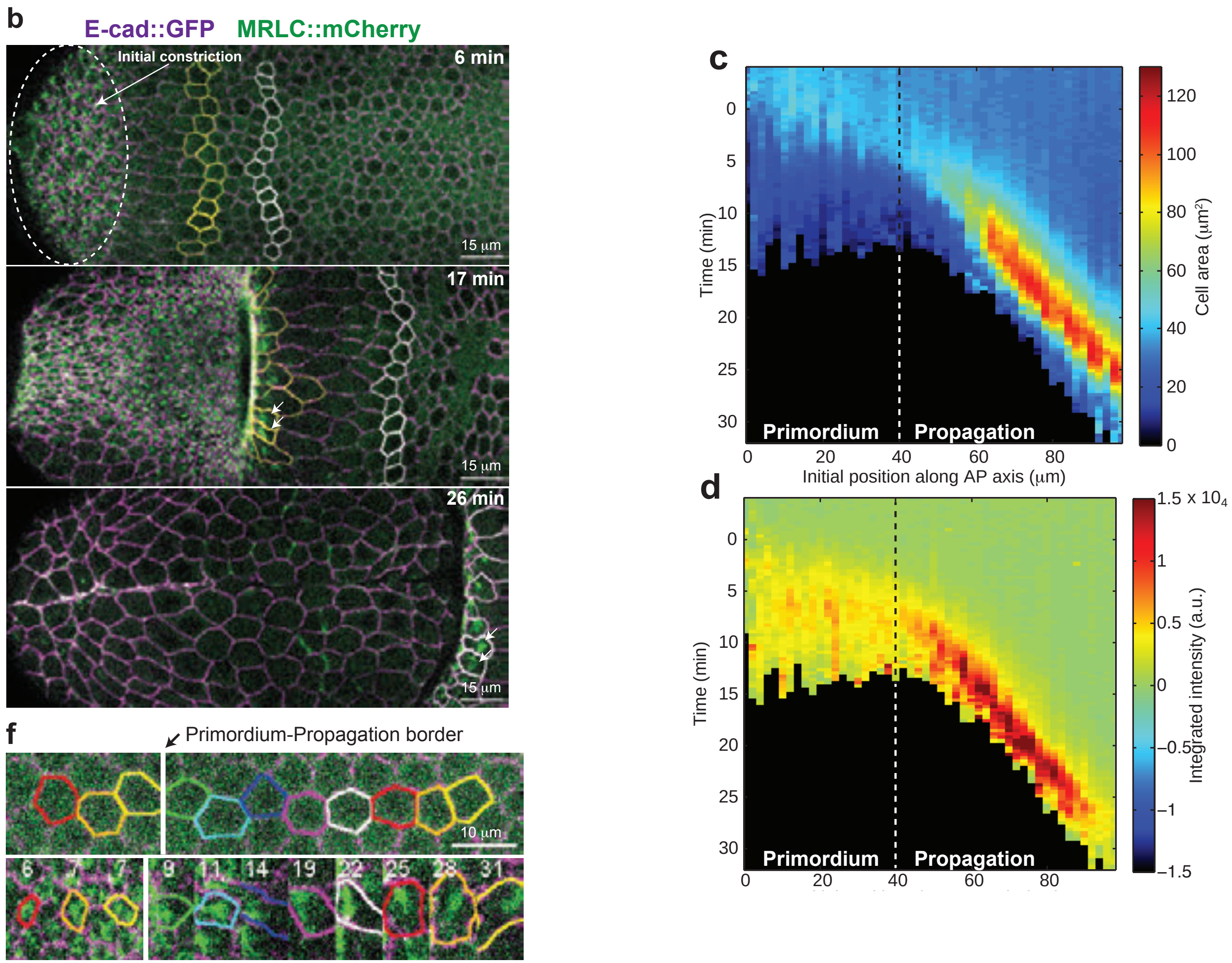




A. Bailles & C. Collinet et al, E. Munro and T. Lecuit. *bioRxiv* 430512; doi: https://doi.org/10.1101/430512

Programmed and Self-Organised Invagination

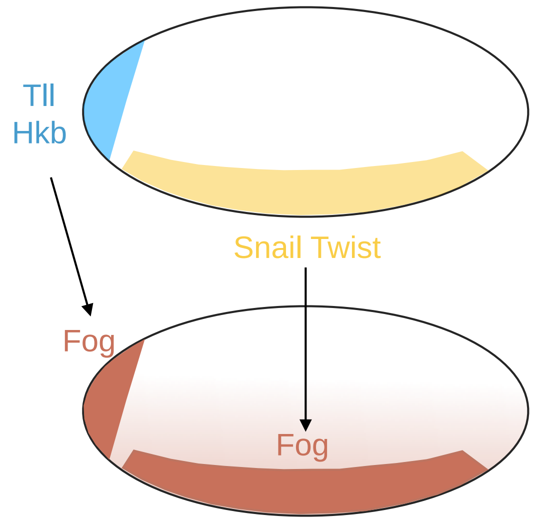
- A tissue scale wave of actomyosin activation is associated with wave of invagination

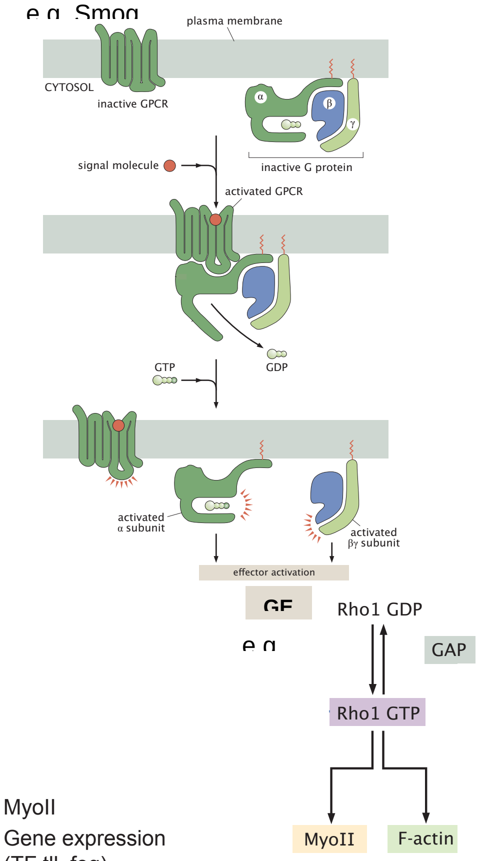


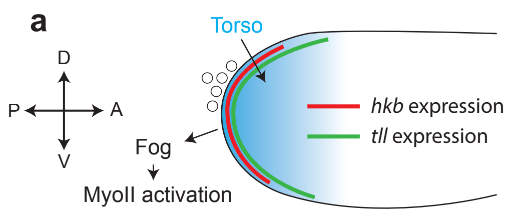
A. Bailles & C. Collinet et al, E. Munro and T. Lecuit. *bioRxiv* 430512; doi: https://doi.org/10.1101/430512

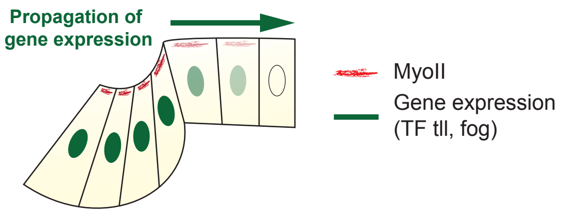
Programmed and Self-Organised Invagination

- Initiation of invagination: the transcriptional program





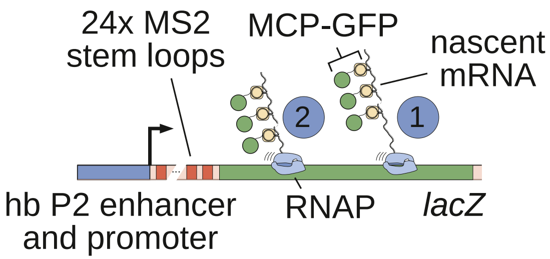


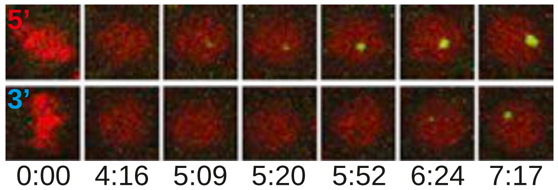


A. Bailles & C. Collinet et al, E. Munro and T. Lecuit. *bioRxiv* 430512; doi: https://doi.org/10.1101/430512

Programmed and Self-Organised Invagination

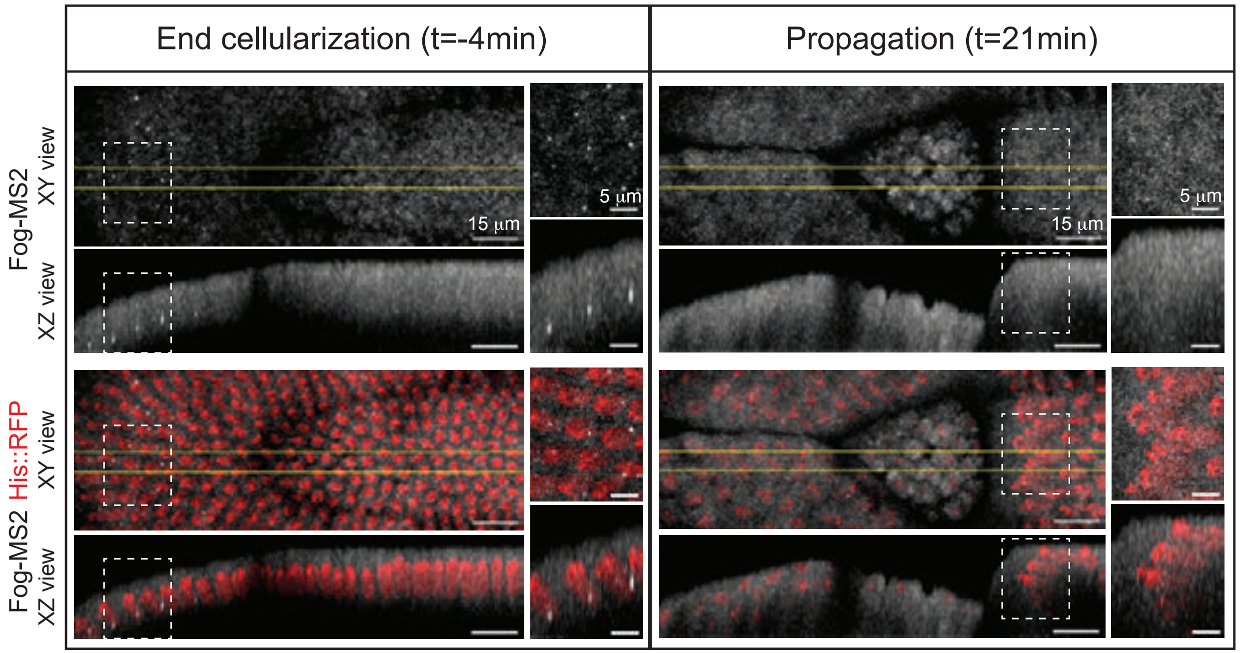
- The tissue wave of invagination is not controlled transcriptionally





H. Garcia et al., 2013

Monitoring the dynamics of transcription in vivo with the MS2/MCP::GFP system

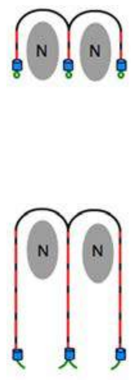


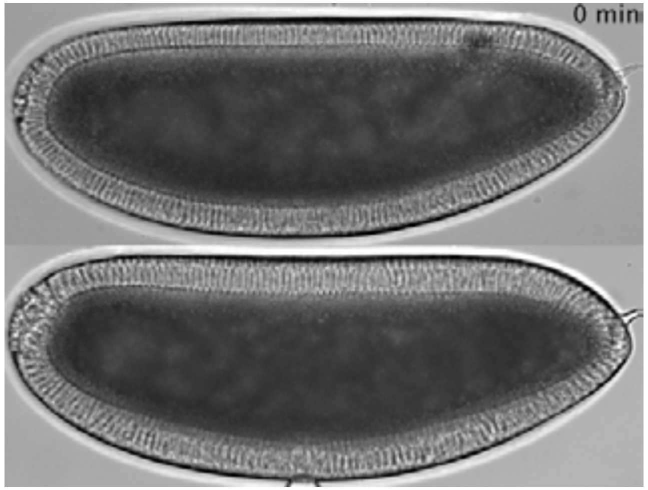
A. Bailles & C. Collinet et al, E. Munro and T. Lecuit. *bioRxiv* 430512; doi: https://doi.org/10.1101/430512

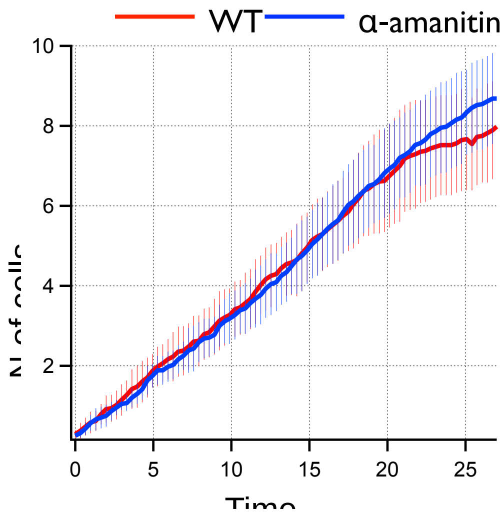
Programmed and Self-Organised Invagination

- The tissue wave of invagination is not controlled transcriptionally

  - α-amanitin is potent inhibitor of RNA Pol-II



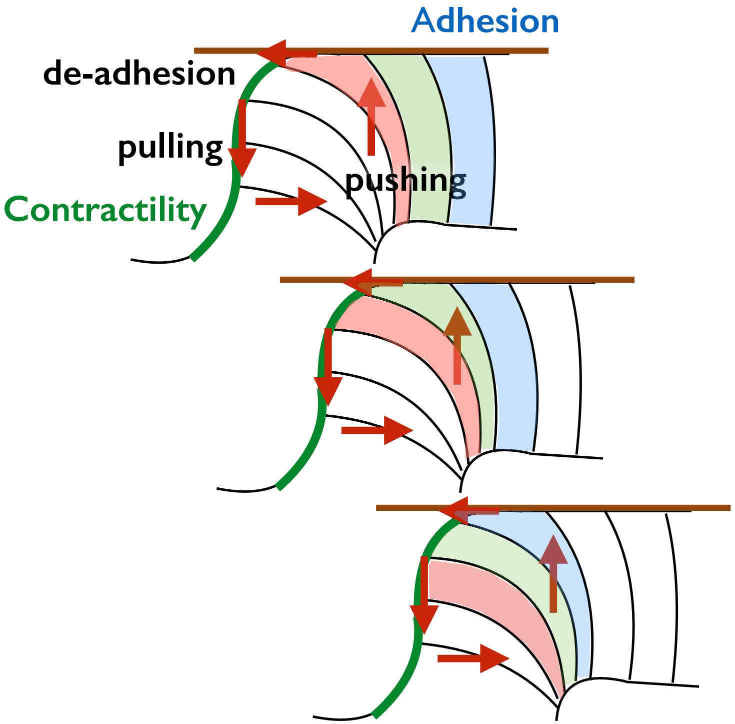




A. Bailles & C. Collinet et al, E. Munro and T. Lecuit. *bioRxiv* 430512; doi: https://doi.org/10.1101/430512

Tissue scale Model:

Self-propagating mechanical cycle



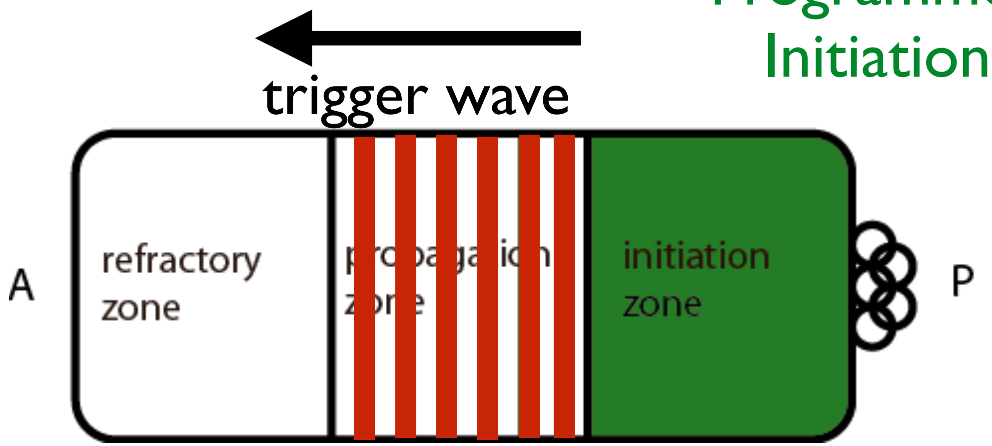
- Invagination compresses cells anteriorly and against vitelline membrane
- Cells adhere to vitelline membrane and subsequently detach as they join invagination
- New cycle begins

A. Bailles & C. Collinet et al, E. Munro and T. Lecuit. *bioRxiv* 430512; doi: https://doi.org/10.1101/430512

Self-organisation with mechano-chemical information

Information
(mechano-
chemistry)

Self-organized
propagation



Programmed
Initiation

Mechanical
Feedback

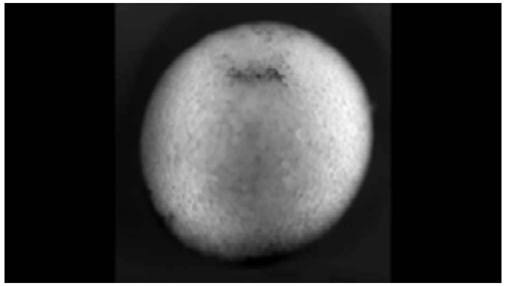
Quantitative
response
to GPCR/Rho1
signalling

Information

(genetics/
biochemistry)

A. Bailles & C. Collinet et al, E. Munro and T. Lecuit. *bioRxiv* 430512; doi: https://doi.org/10.1101/430512

Next Course 18 December



Tissue extension and growth: control and self-organisation