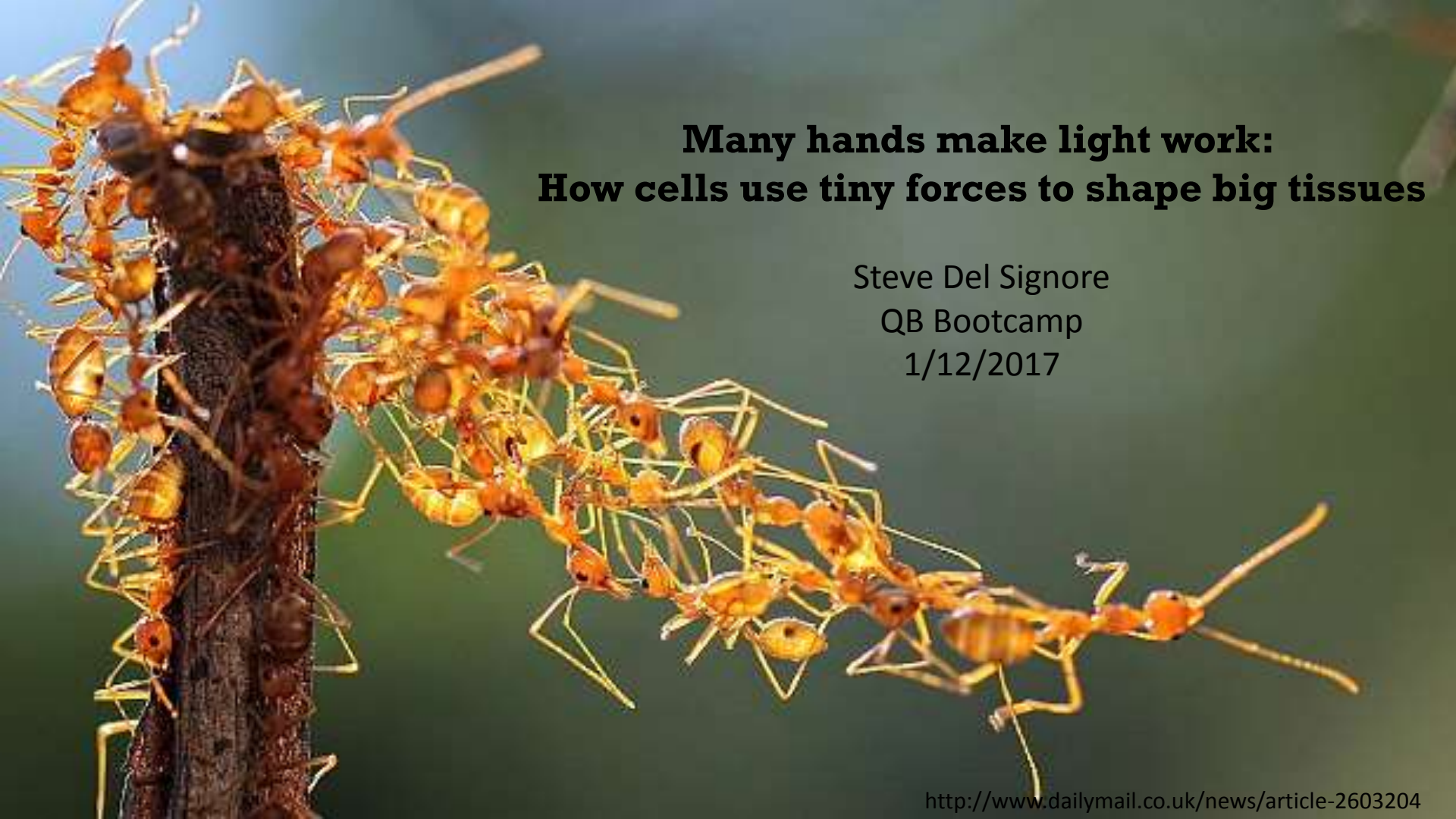


Many hands make light work: How cells use tiny forces to shape big tissues

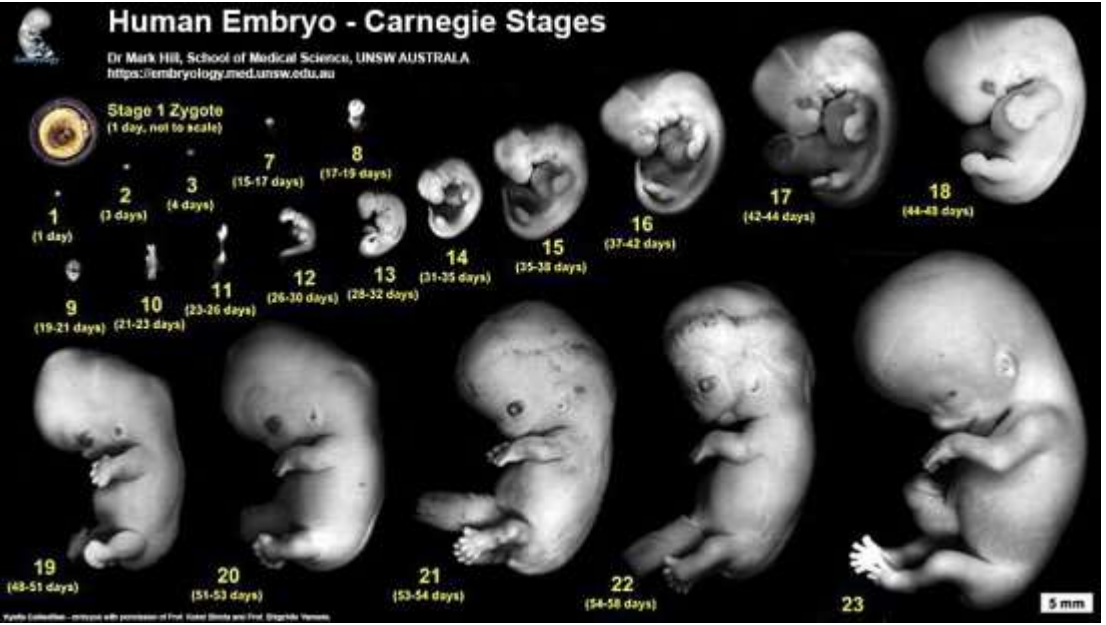
Steve Del Signore

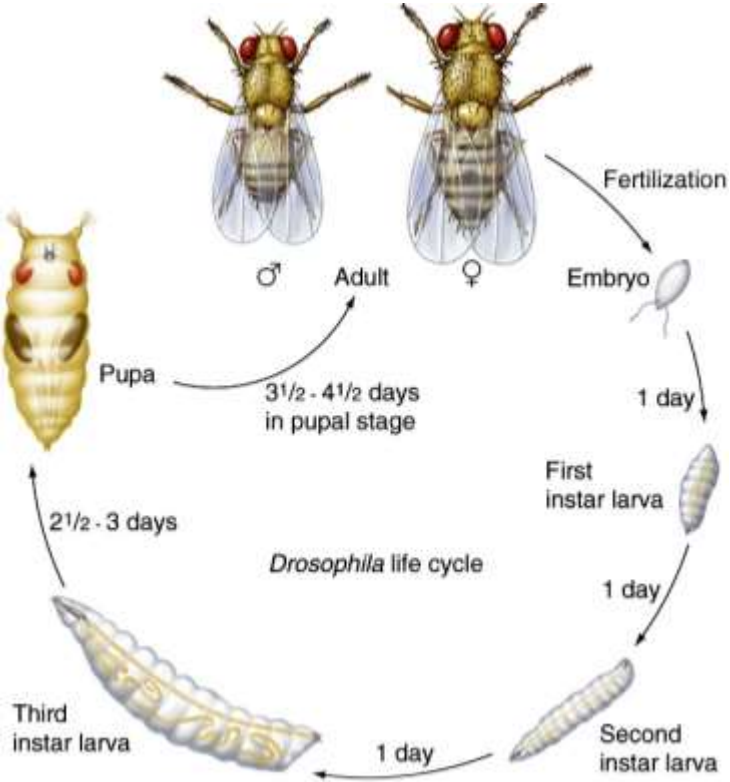
QB Bootcamp

1/12/2017

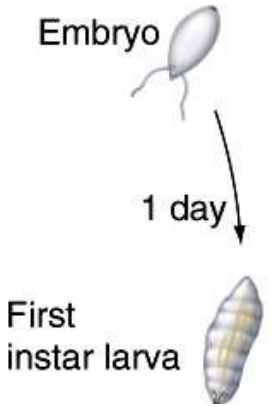
http://www.dailymail.co.uk/news/article-2603204

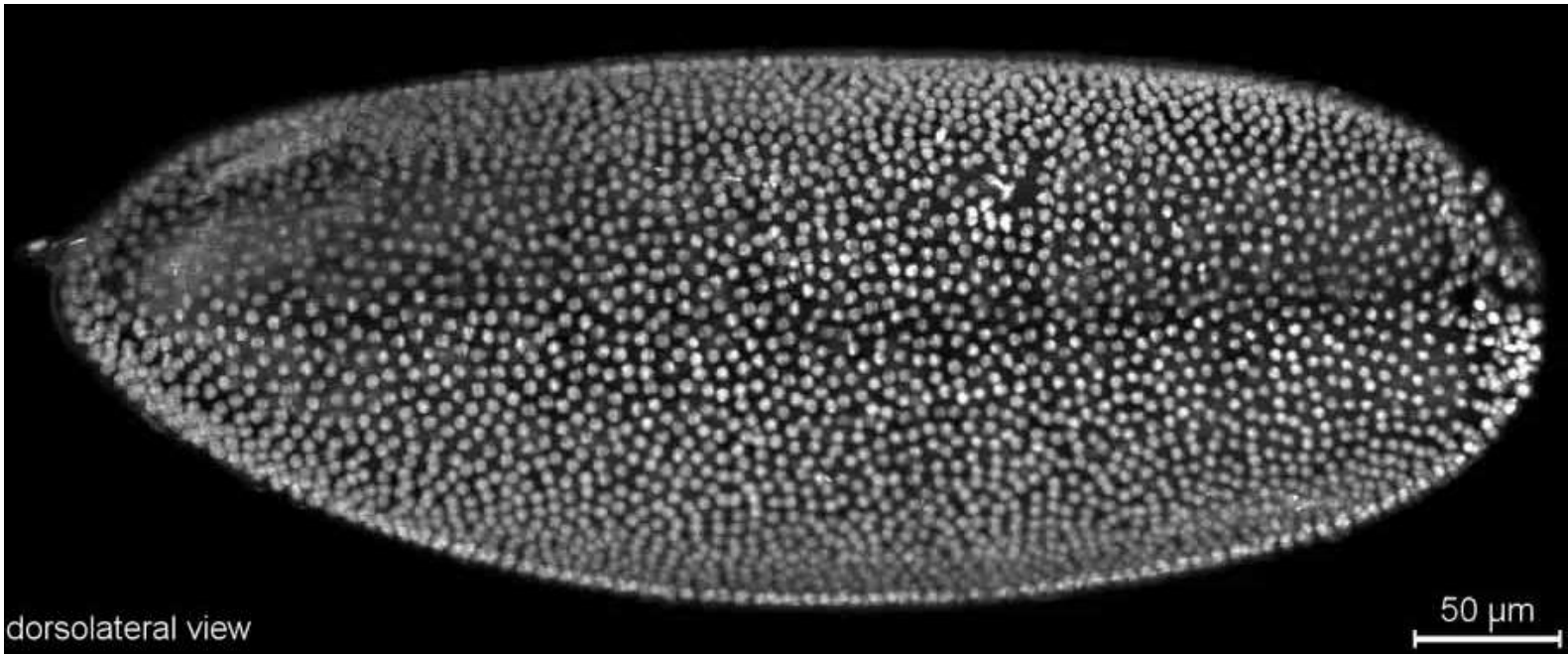
How do we get assembled?





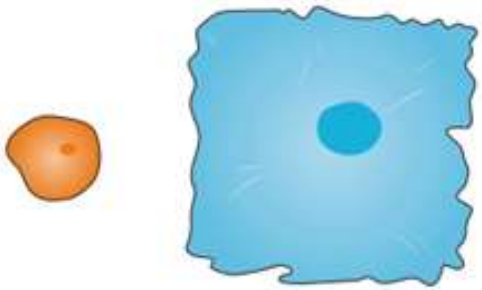
Diverse tissue dynamics shape the developing embryo



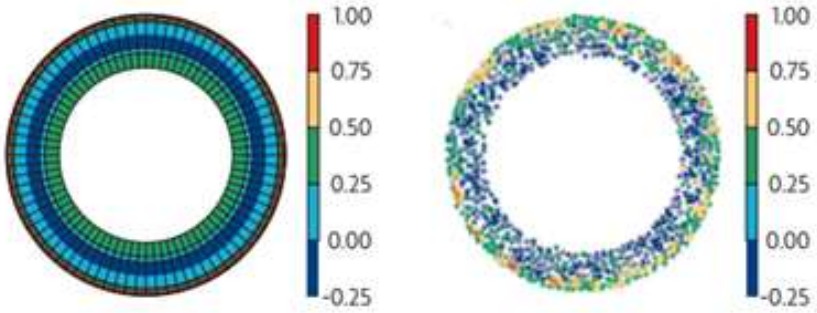


Nature Methods 9:755 (2012)

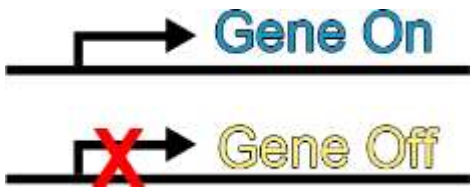
Mechanical inputs can modulate diverse cell behaviors



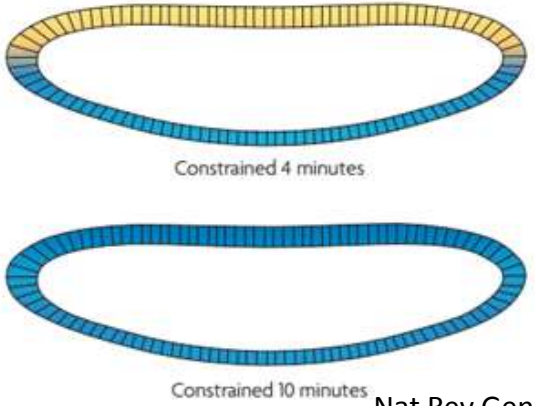
Cell Shape



Proliferation

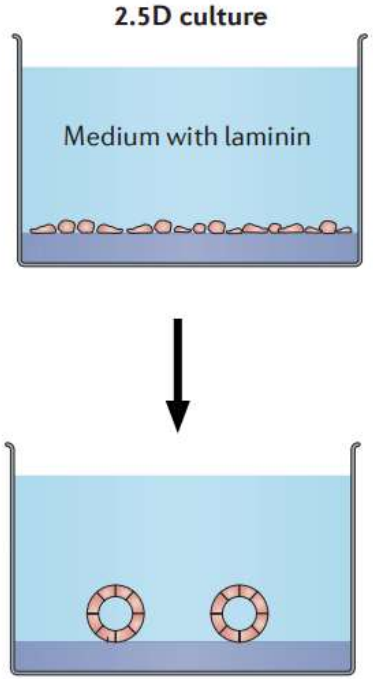


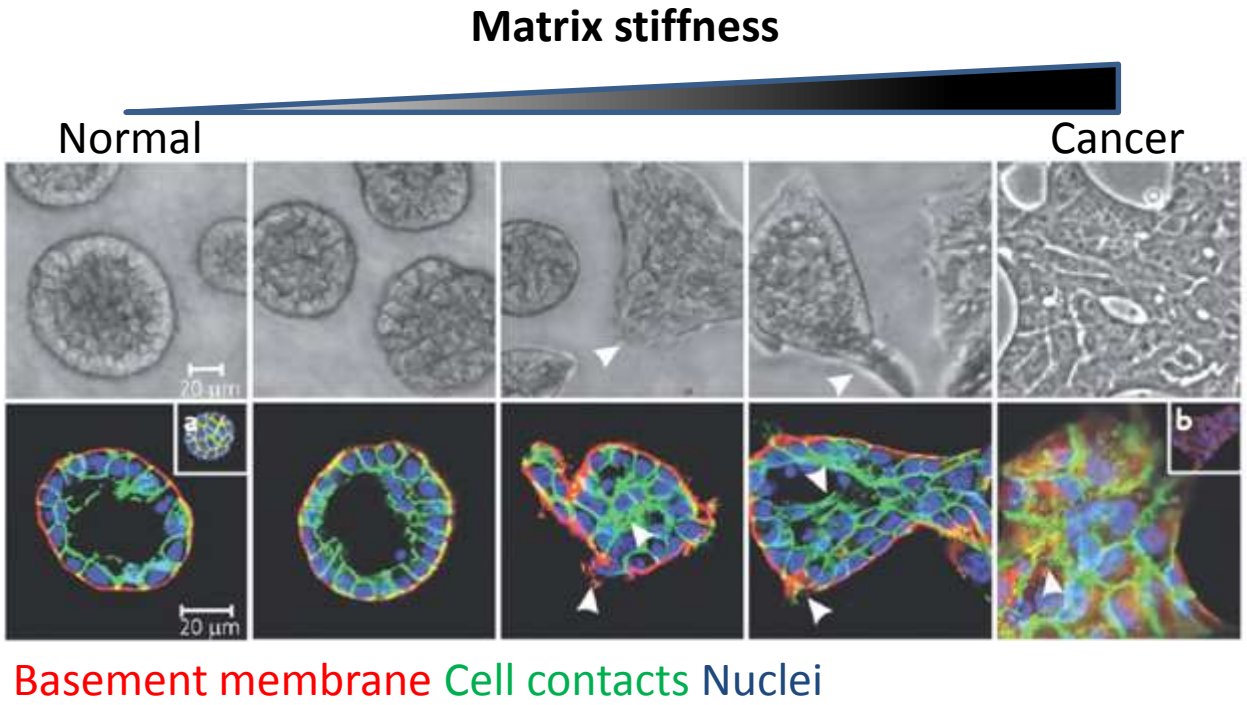
Gene expression



Nat Rev Gen 10:517

Mechanical inputs can drive pathological cell behaviors

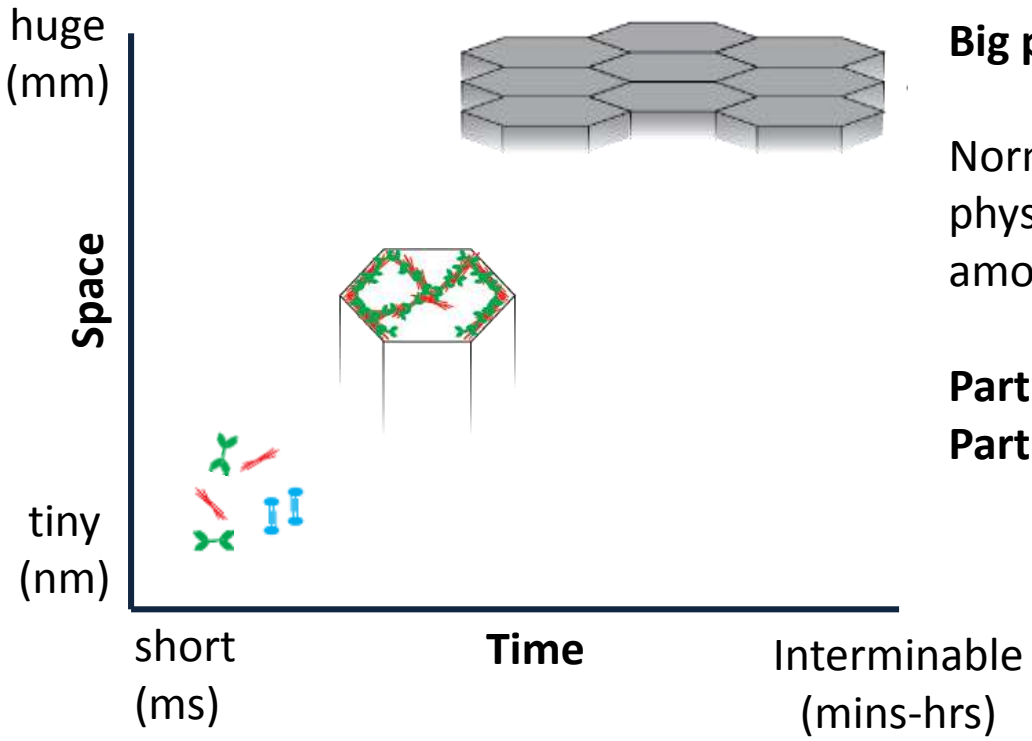




Basement membrane Cell contacts Nuclei

Nat Rev MCB 25:647 (2014)
Cancer Cell 8:241 (2005)

Morphogenesis is a multiscale process

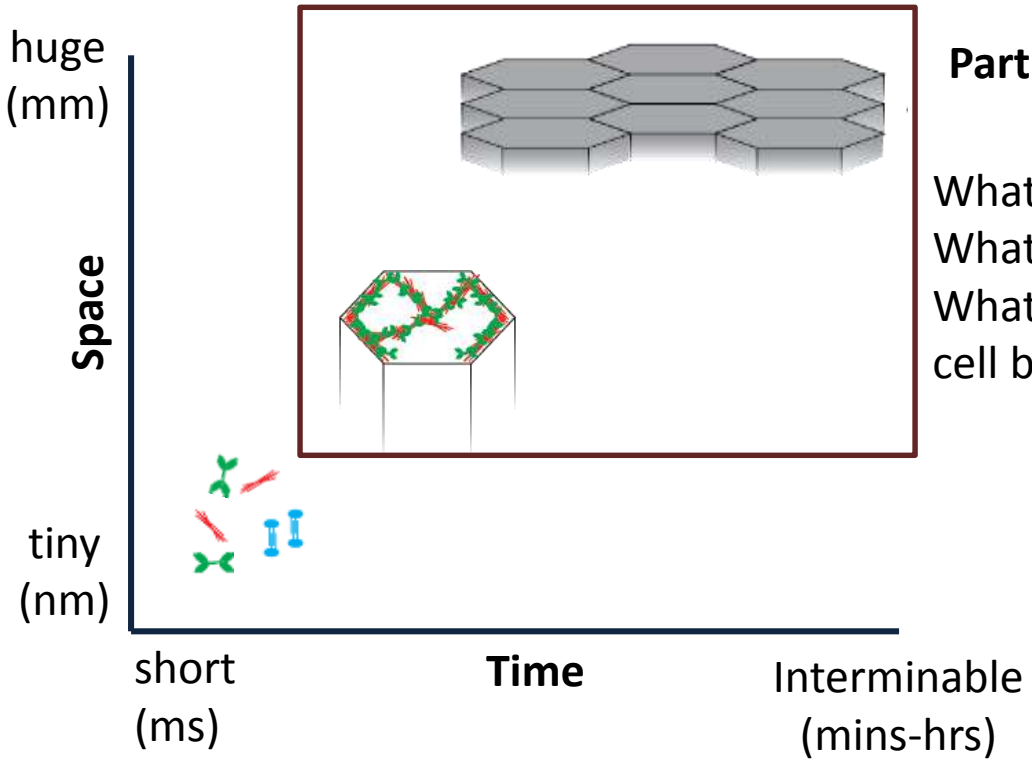


Big picture message:

Normal development depends on real physical mechanisms that mediate interaction among these space and time scales

Part I: The players
Part II: The game

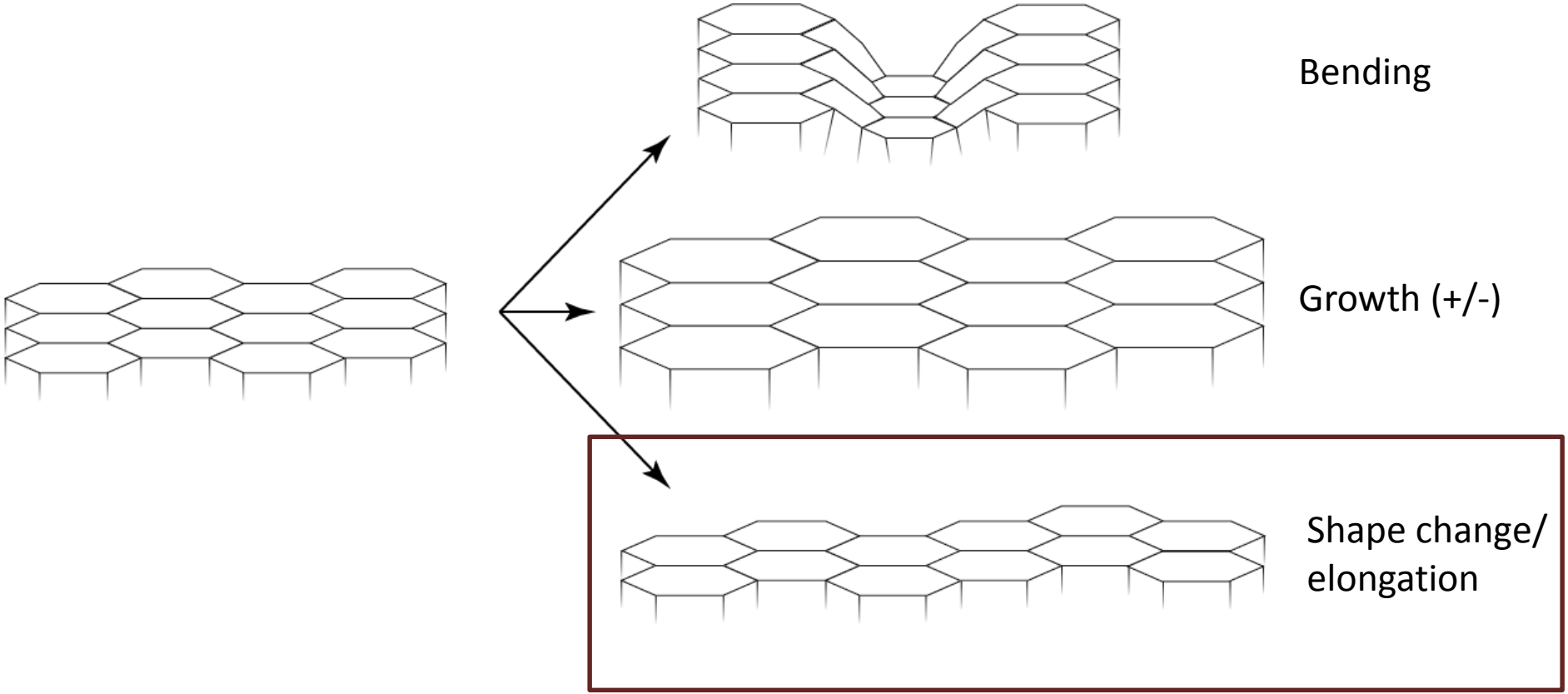
Morphogenesis is a multiscale process



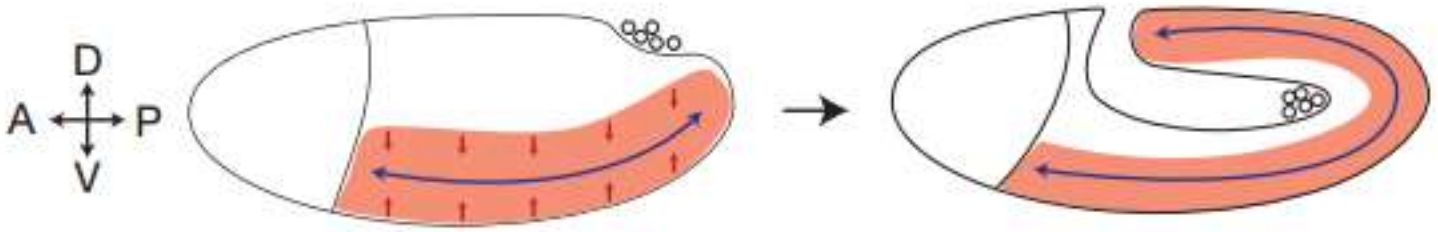
Part I: The players

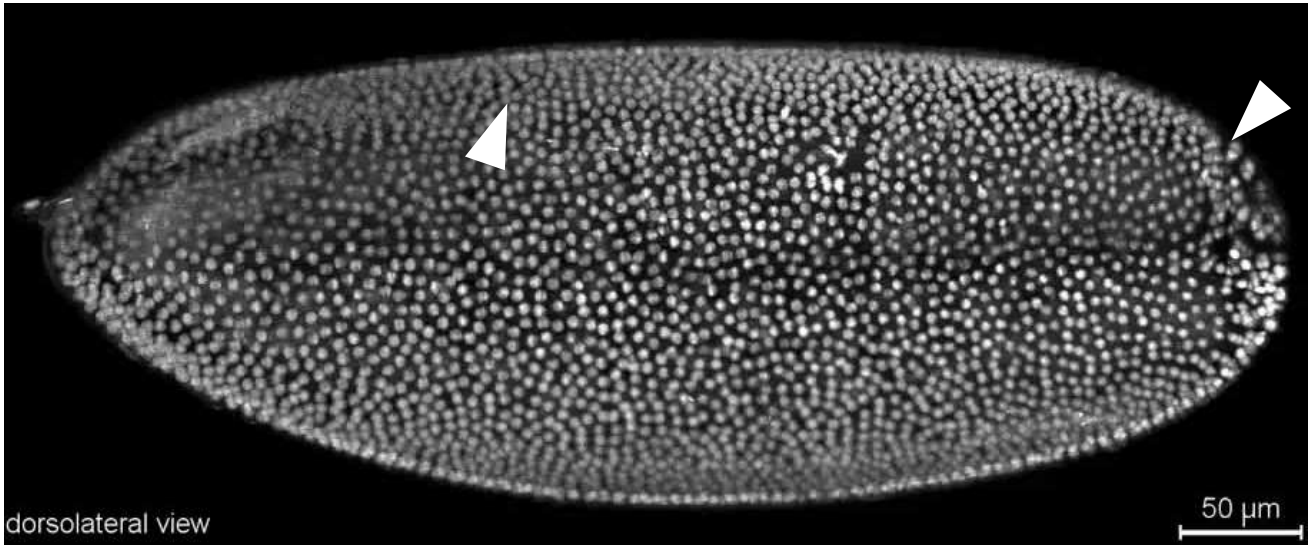
What tissue movements promote development?
What cell behaviors drive tissue dynamics?
What are the molecular forces that underlie cell behavior?

What tissue behaviors sculpt the developing organism?



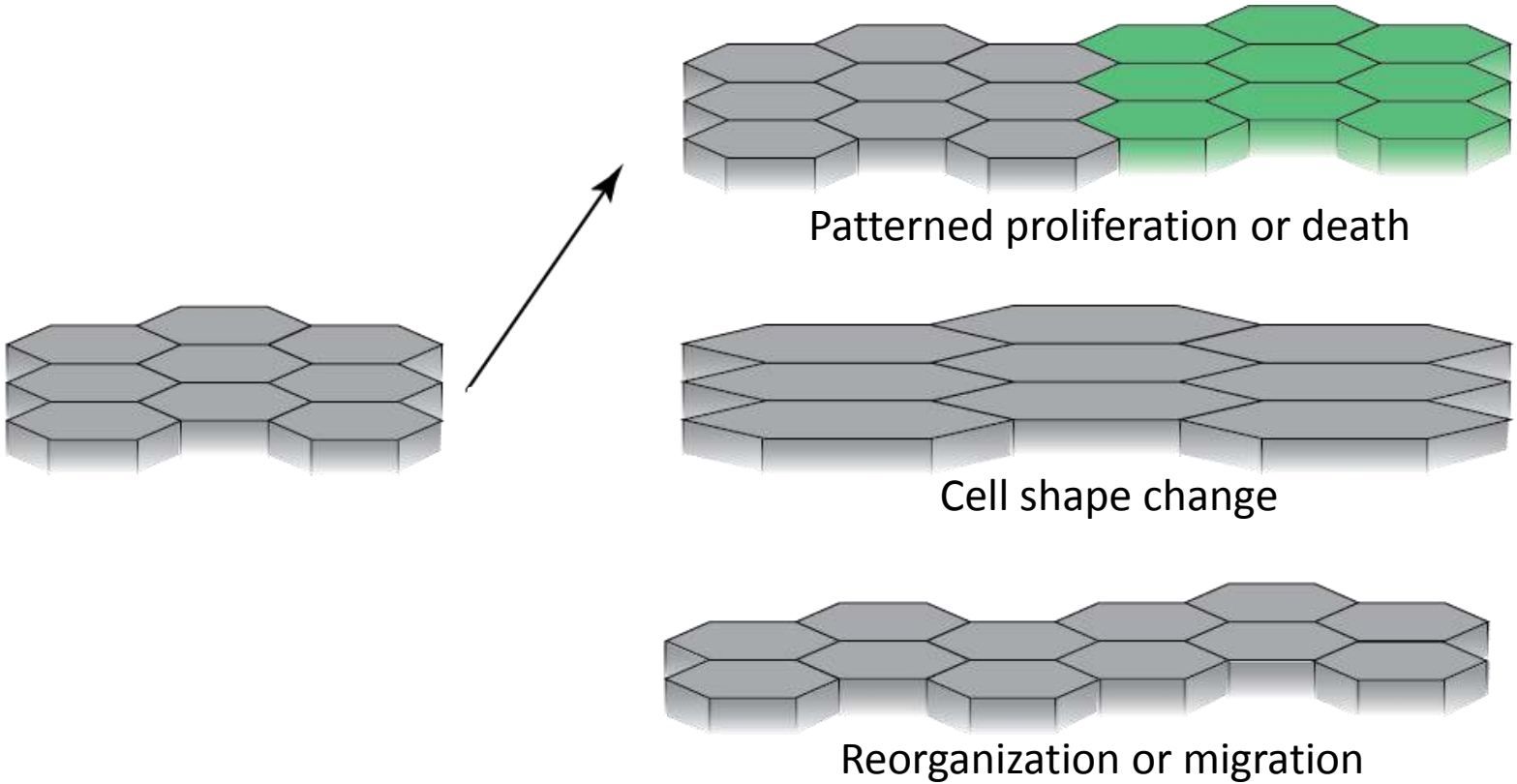
Tissue elongation: Drosophila germband extension



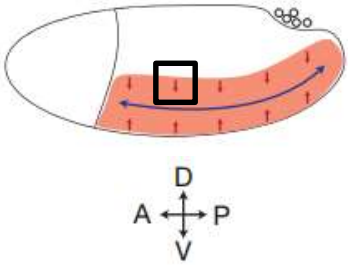


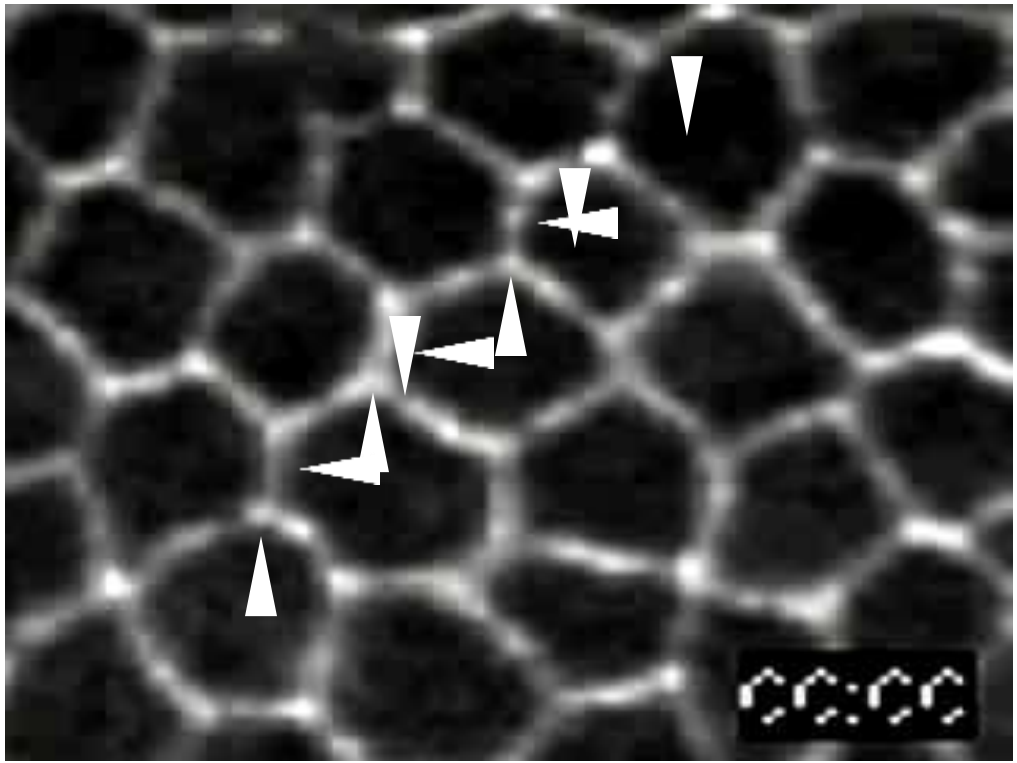
Nat Cell Bio 17:1247 (2015)

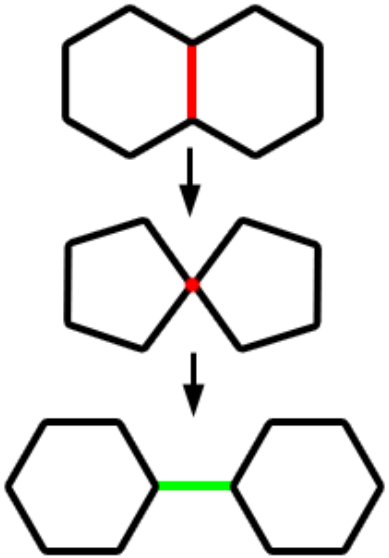
What cell behaviors drive tissue morphogenesis?



Cell reorganization drives germband extension: Single cell contact remodeling

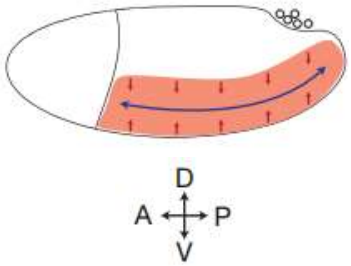


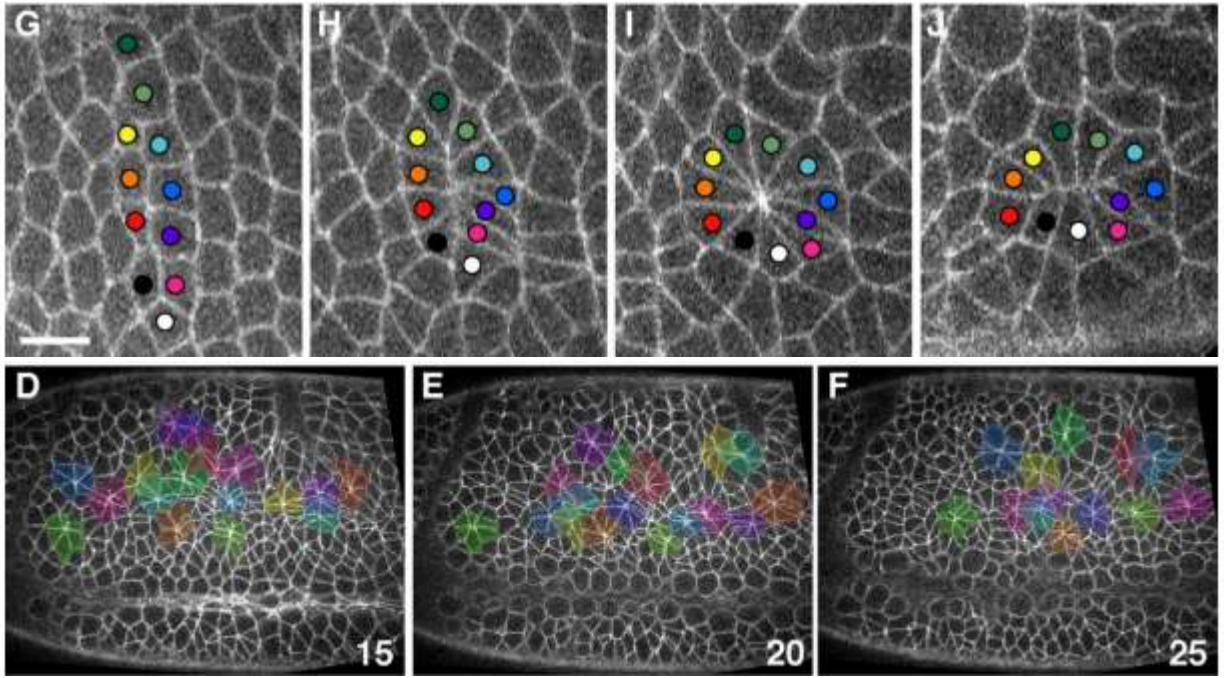




Nature 429:667

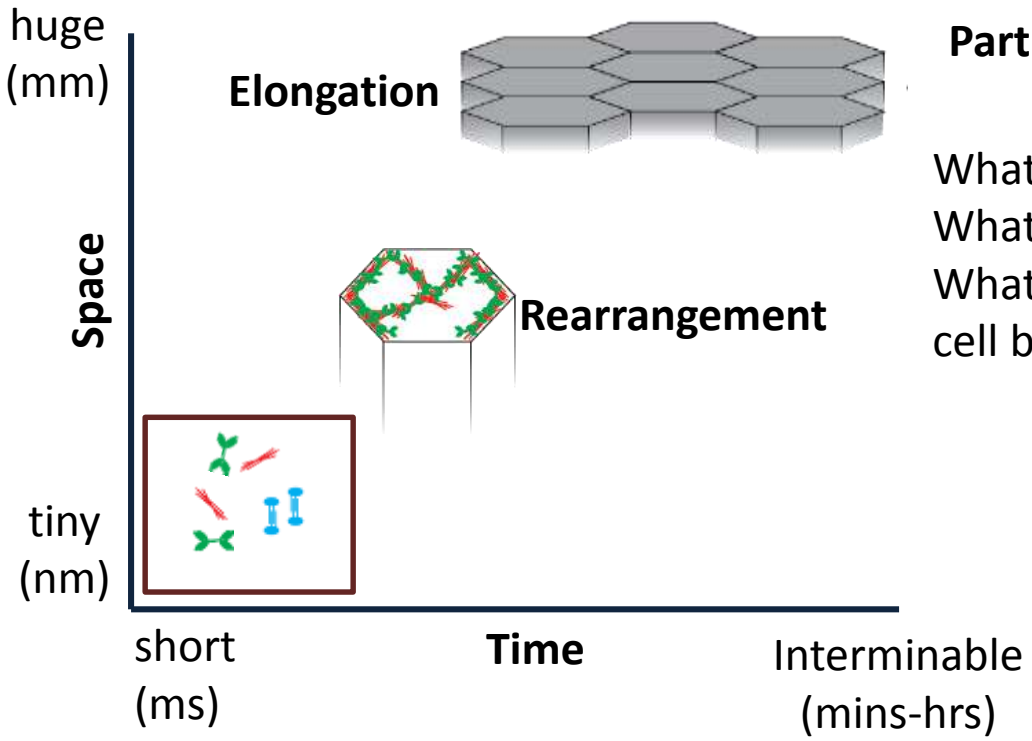
Cell reorganization drives germband extension: Multicellular contact remodeling





Dev Cell 11:459

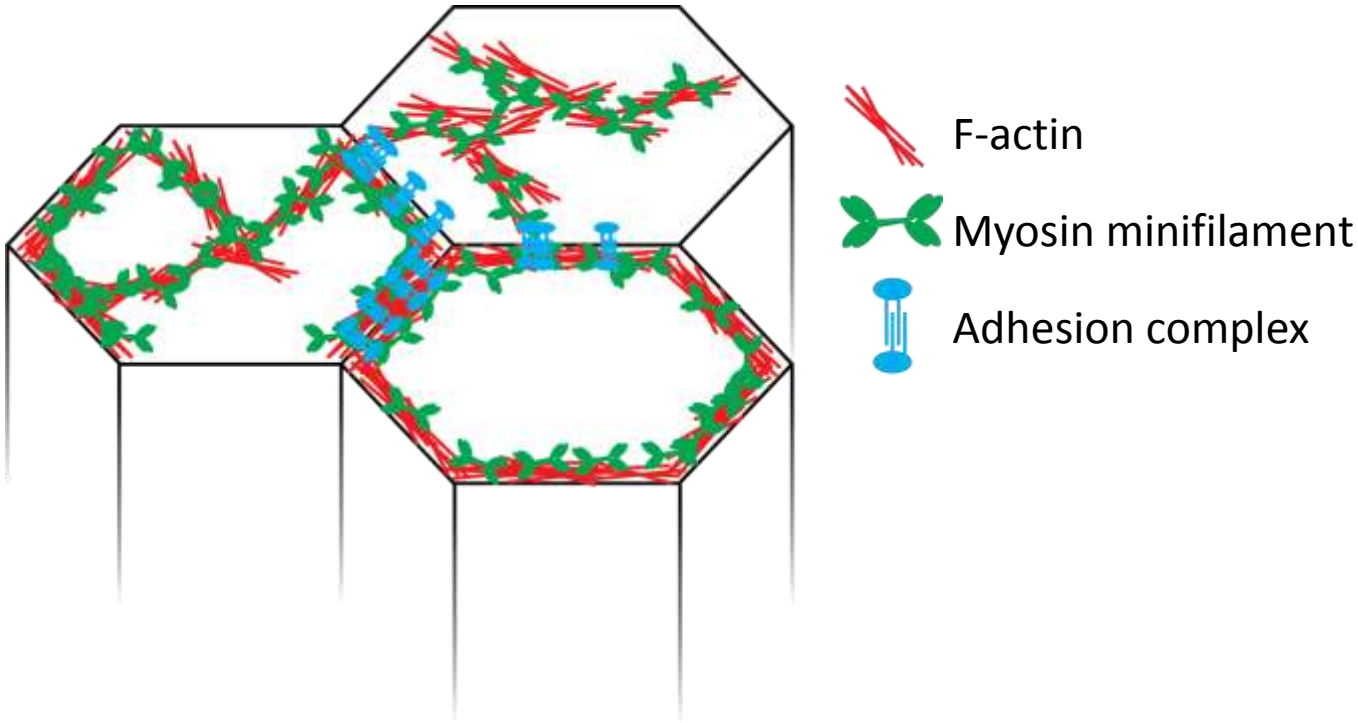
Morphogenesis is a multiscale process



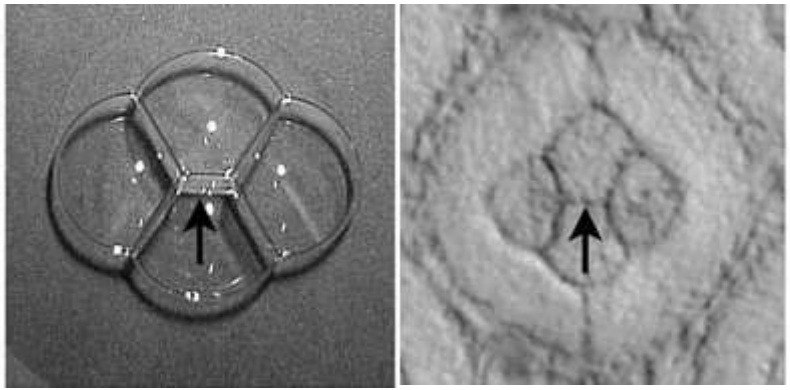
Part I: The players

What tissue movements promote development?
What cell behaviors drive tissue dynamics?
What are the molecular forces that underlie cell behavior?

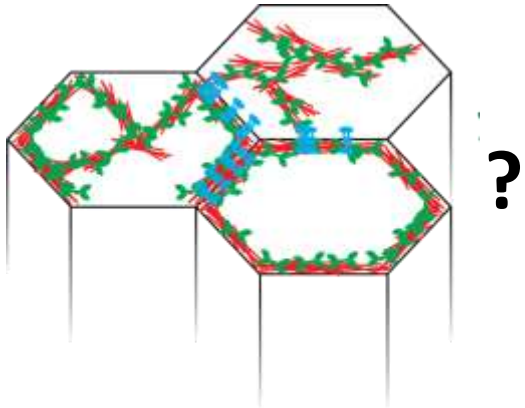
Cell adhesion and actomyosin tension drive cell dynamics



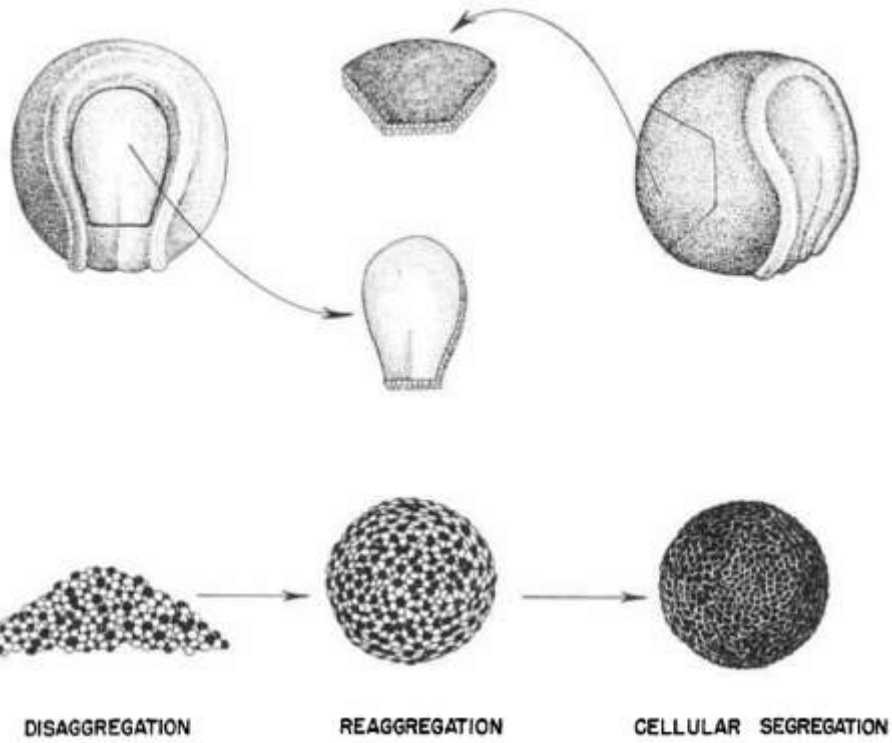
Adhesion originally considered dominant force



Nature 431:647 (2004)



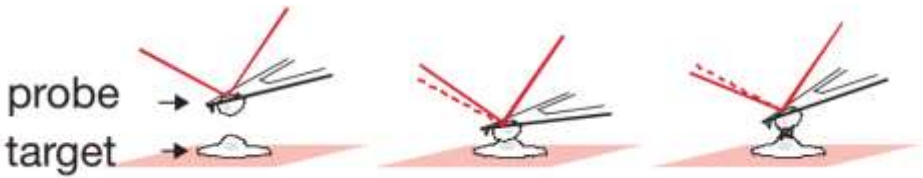
?

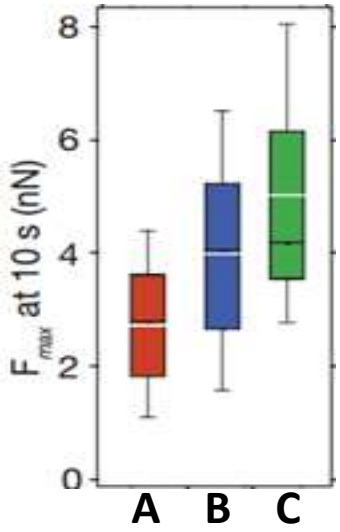


J Exp Zoo. 128:53 (1955)

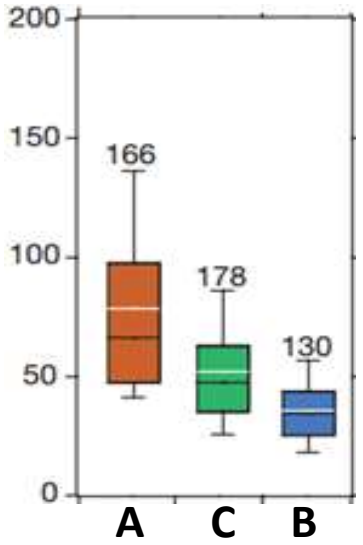
Quantification of adhesion and cortical tension in cells

Adhesion



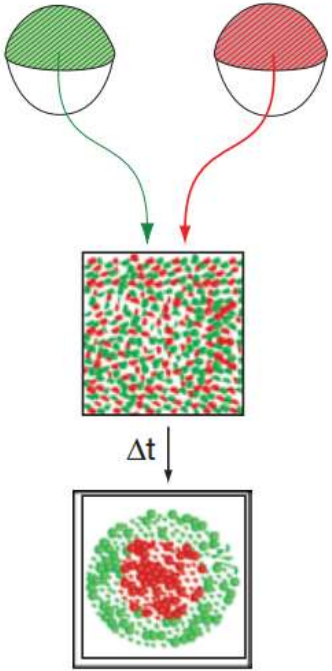


Tension



Nature Cell Biol 10:429 (2008)

Does surface tension or adhesion predict sorting behavior?

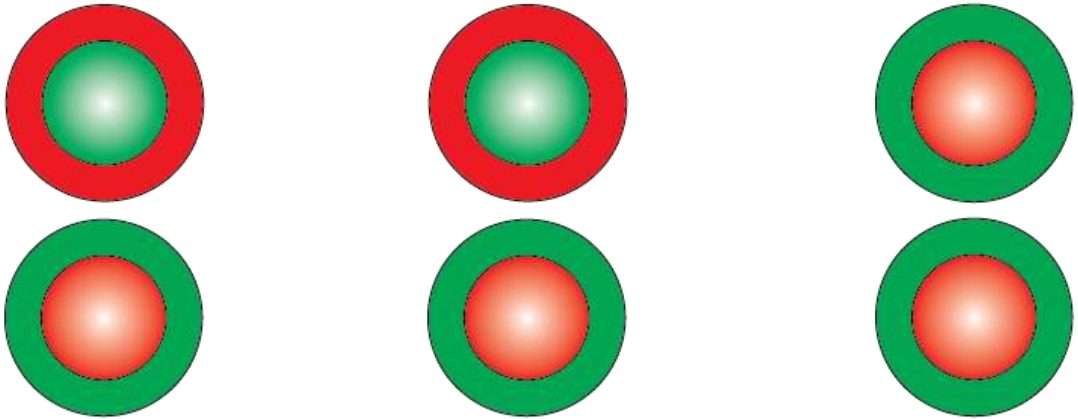


Adhesion

C>B>A

Surface Tension

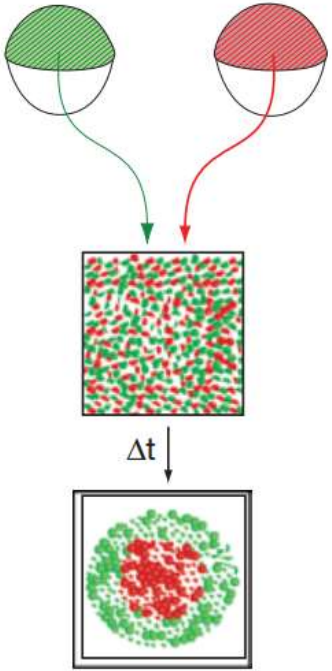
A>C>B

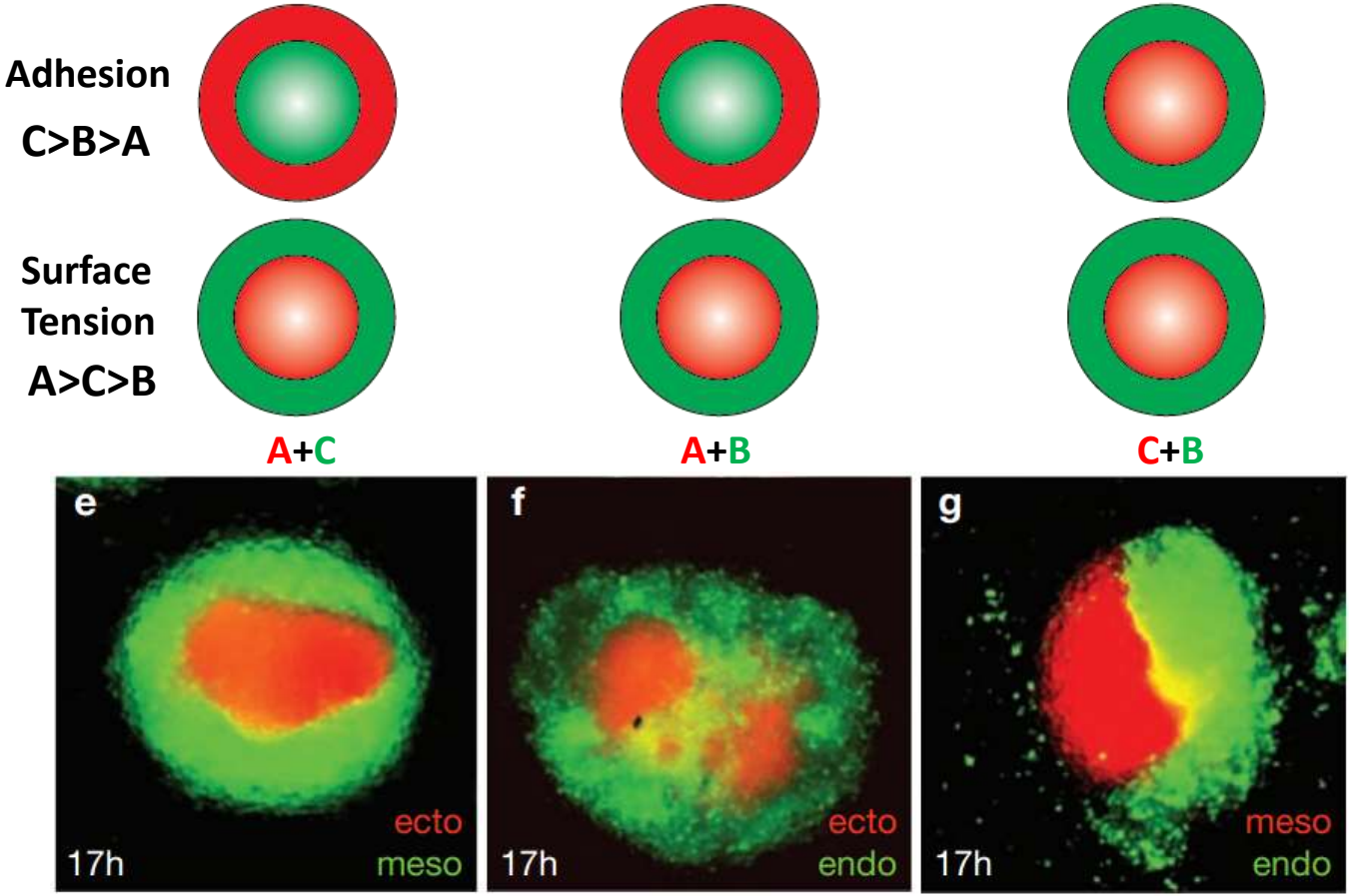


A+C A+B C+B

Nature Cell Biol 10:429 (2008)

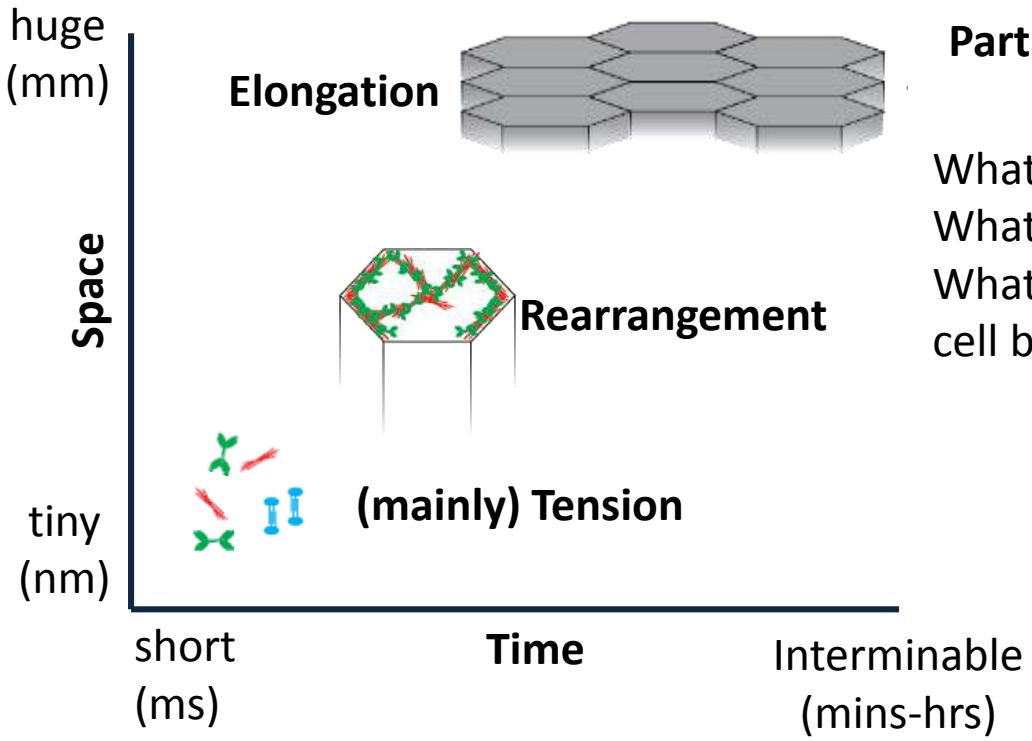
Surface tension predicts sorting; adhesion does not





Nature Cell Biol 10:429 (2008)

Morphogenesis is a multiscale process



Part I: The players

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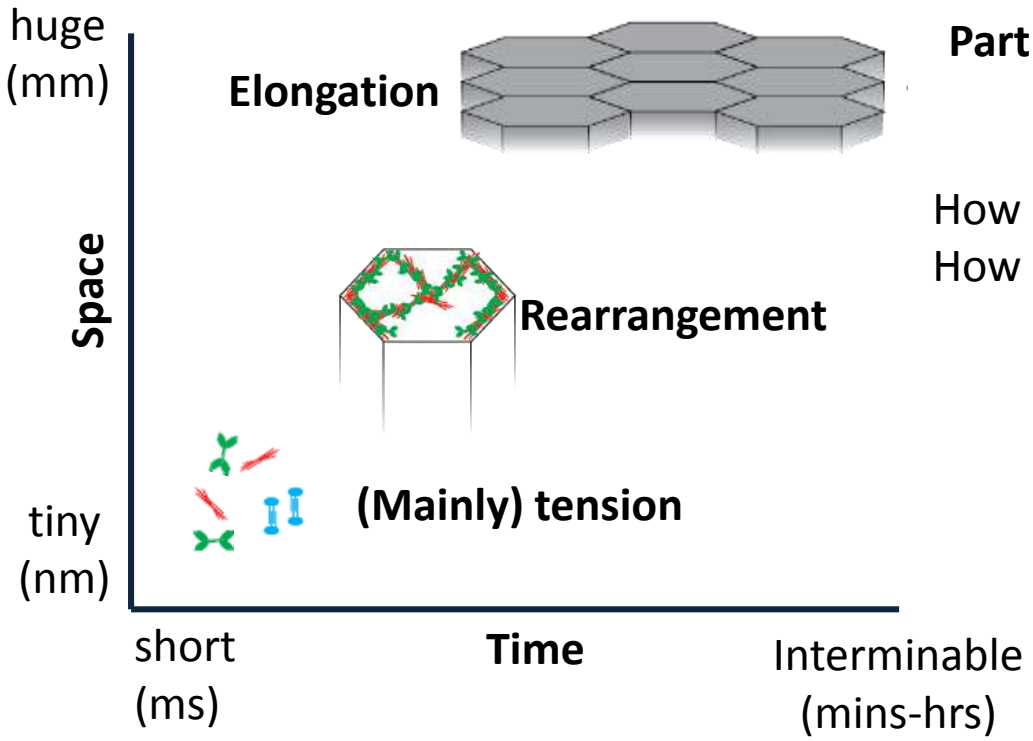
Morphogenesis is a multiscale process

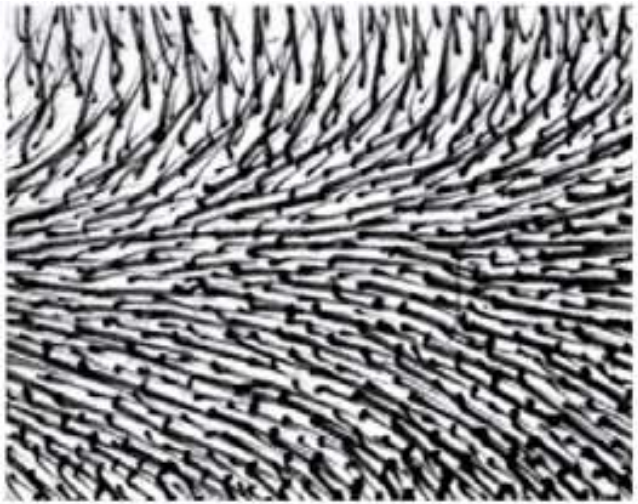


Part II: The game

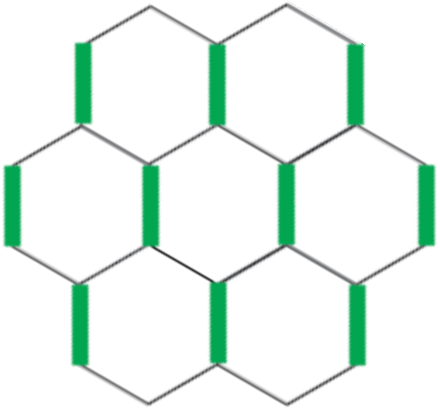
How are forces controlled in space and time?
How are forces integrated across the tissue?

Cells can systematically polarize

Control

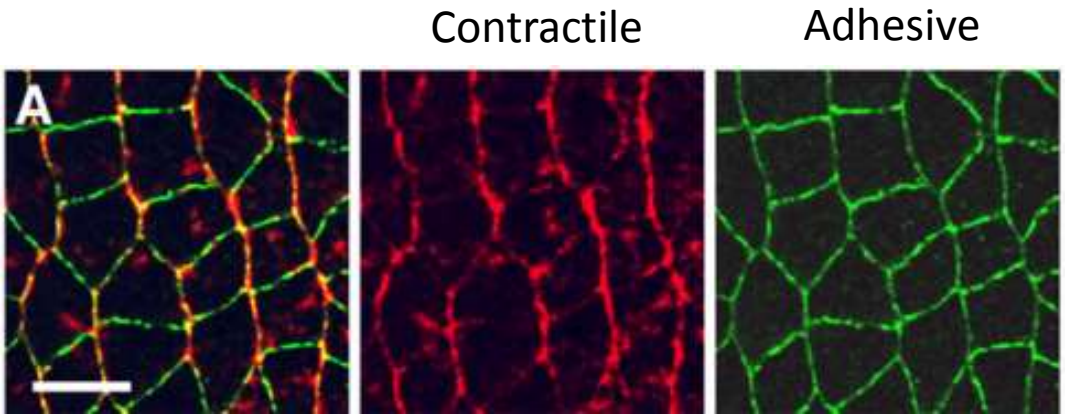


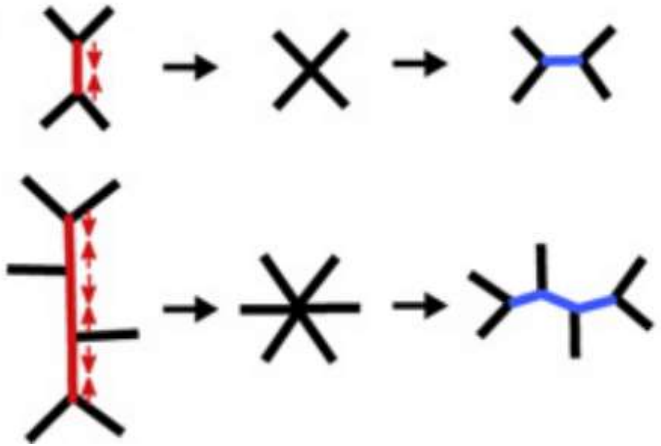
Polarity gene mutant



Development 134:647 (2007)

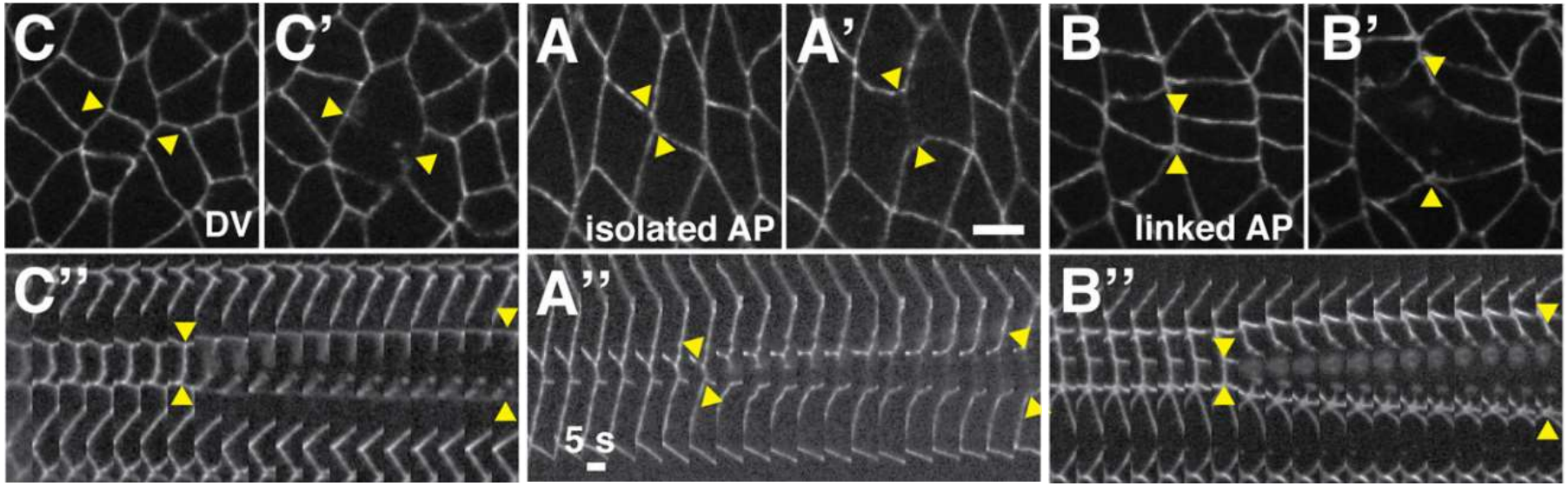
Adhesion and contractile proteins polarize during cell intercalation

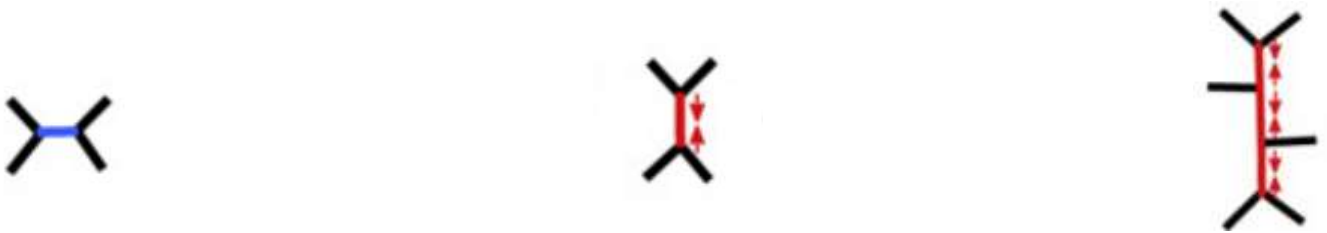




Dev Cell 11:459 2006
Dev Cell 17:736 (2009)

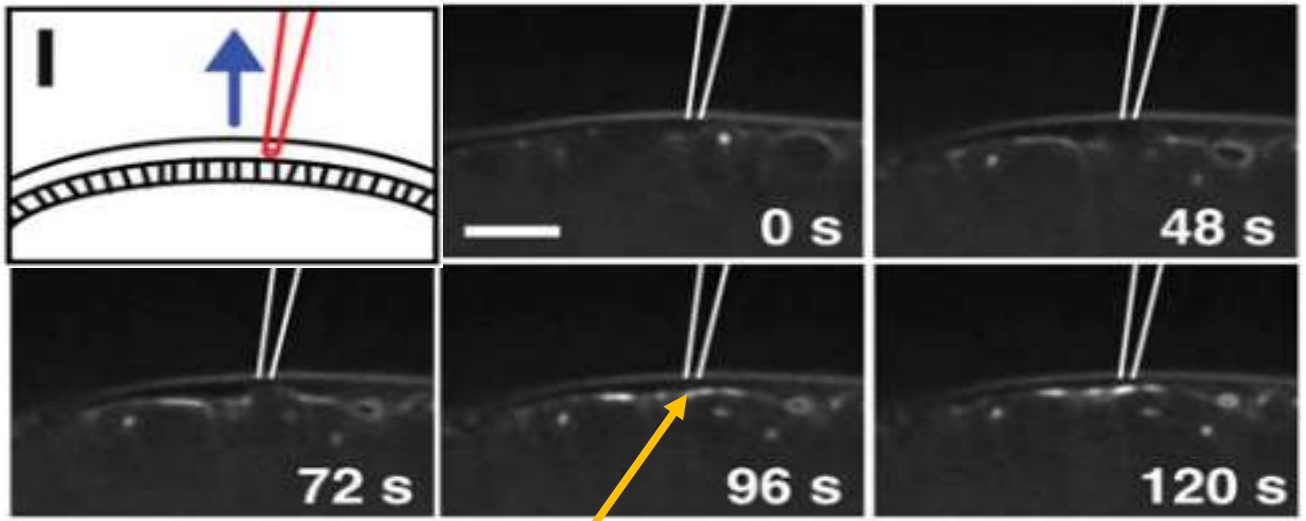
Contractile proteins increase tension on vertical junctions





Dev Cell 17:736 (2009)

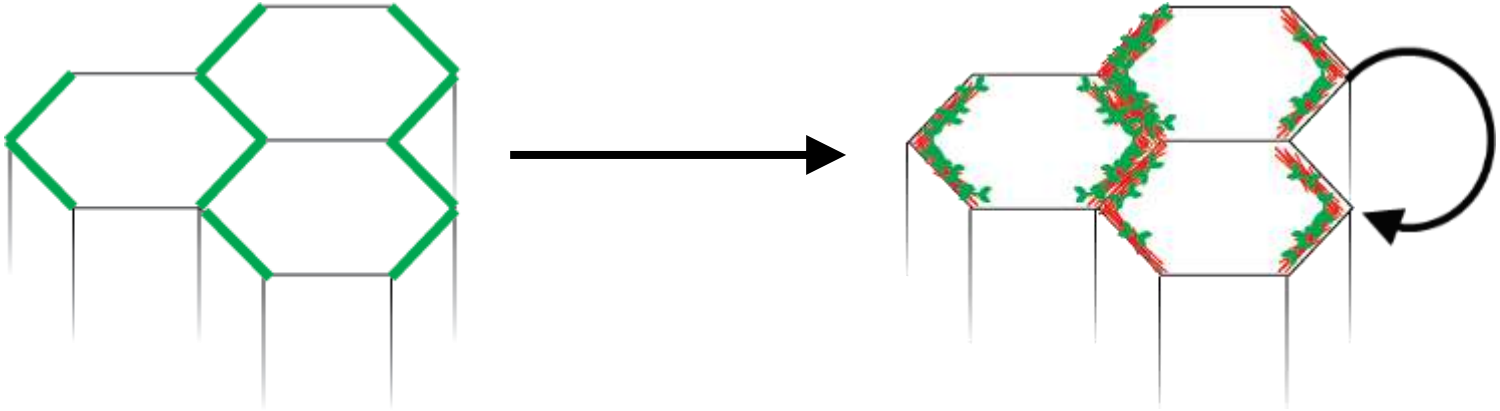
Tension itself enhances recruitment of Myosin!



Myosin recruitment

Dev Cell 17:736 (2009)

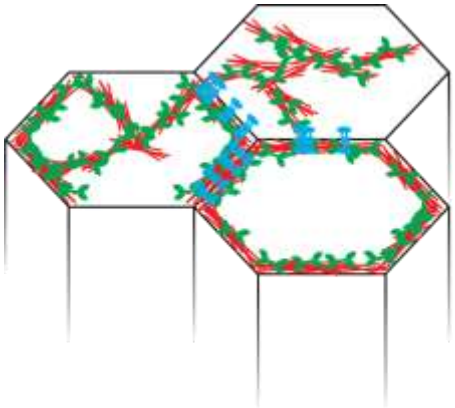
Molecules and forces are organized across subcellular & multicellular domains

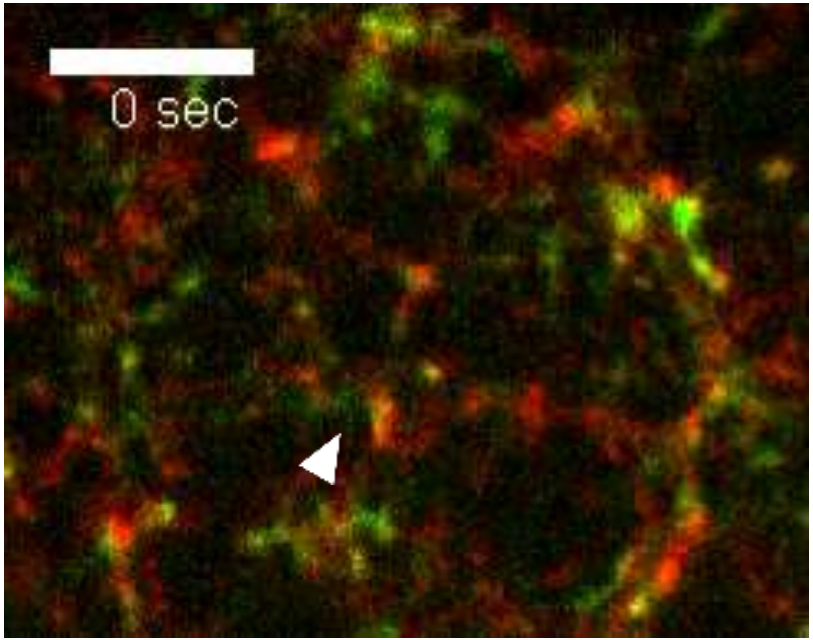


Molecules and forces are polarized within the cell
Tissue level polarity cues and local forces both organize

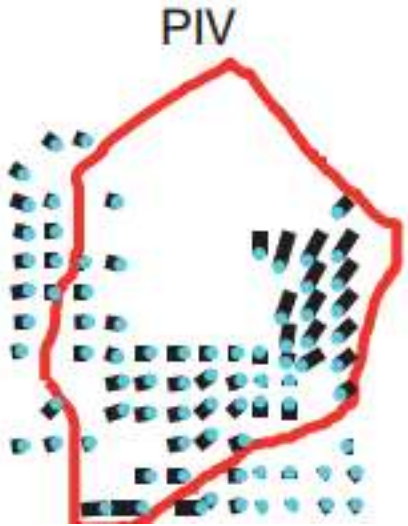
Suggests model in which stable tension biases rearrangements to favor vertical intercalation and horizontal elongation

Actomyosin exhibits pulsed flow at the surface of remodeling cells



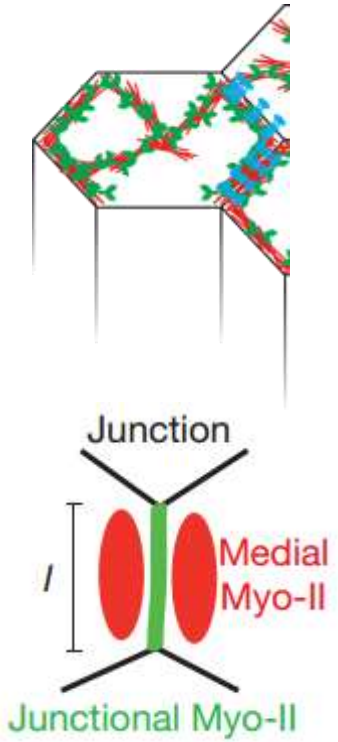


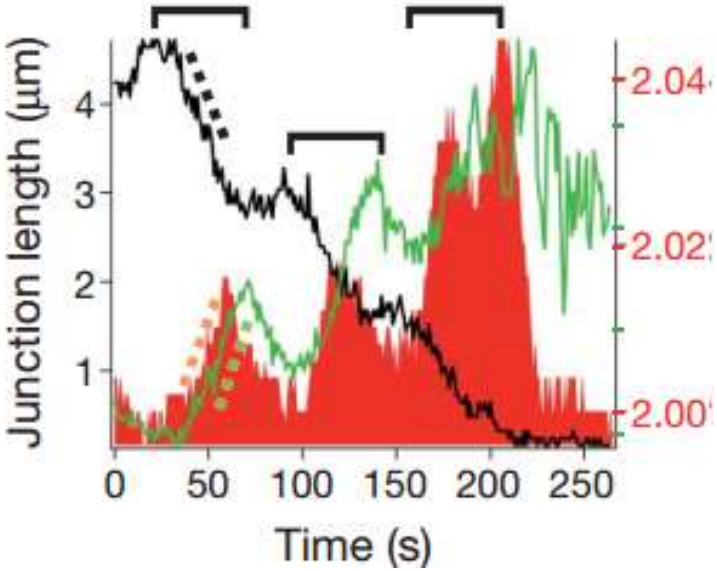
F-actin Myosin

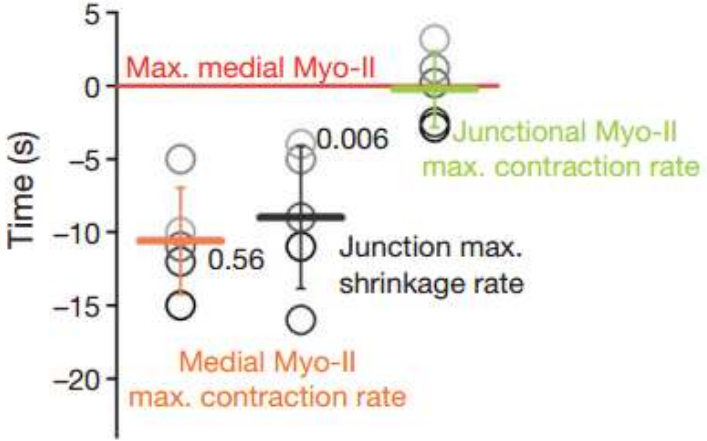


Nature 468:1110

Cell surface actomyosin correlates with junction shrinking

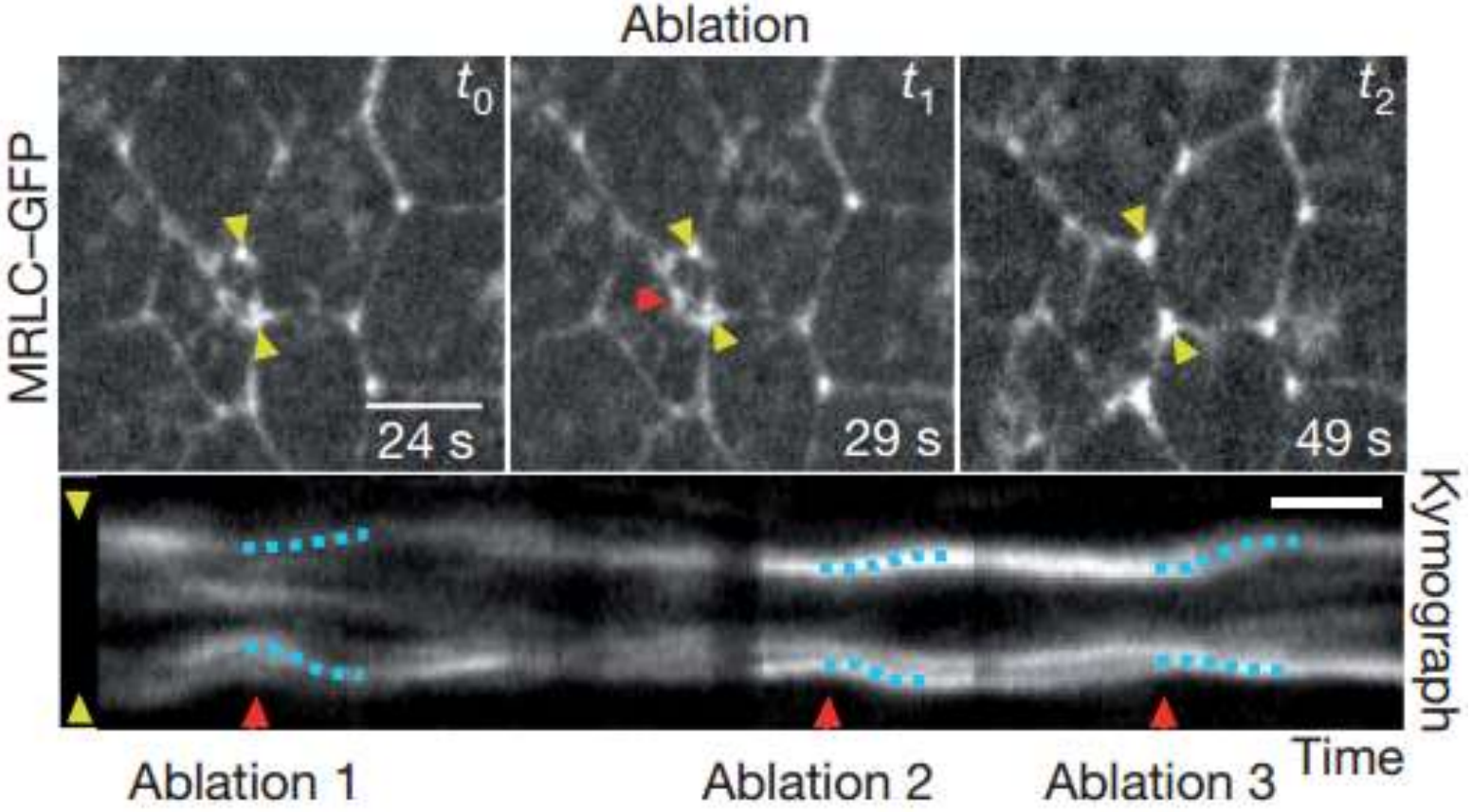




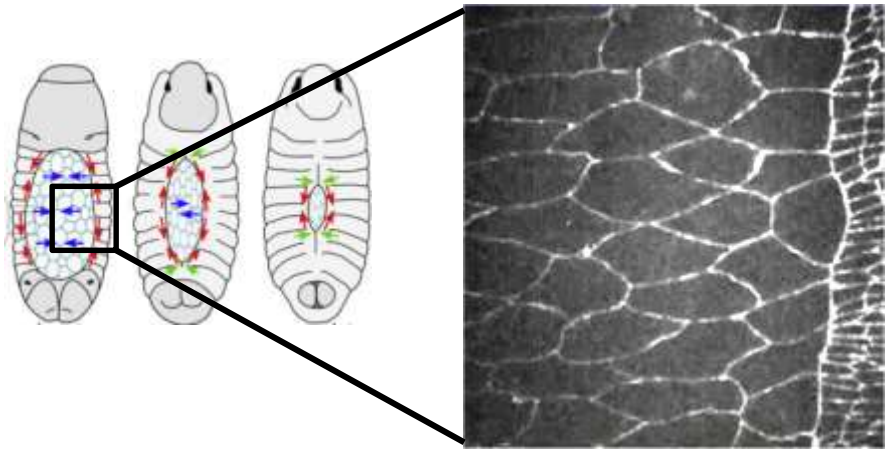


Nature 468:1110

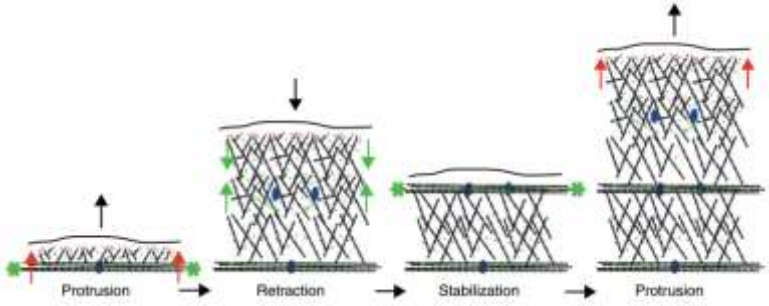
Laser ablation of surface myosin reverses junction constriction



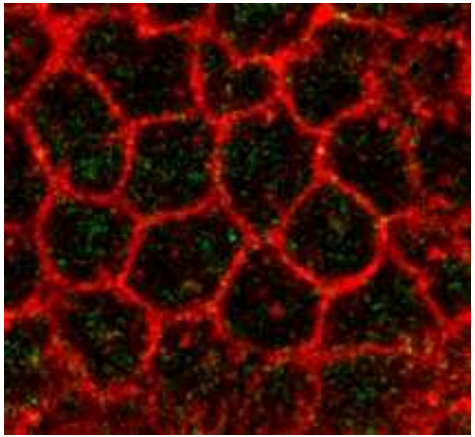
Pulsed cell and molecular dynamics are everywhere!



Dorsal closure/ “wound healing”



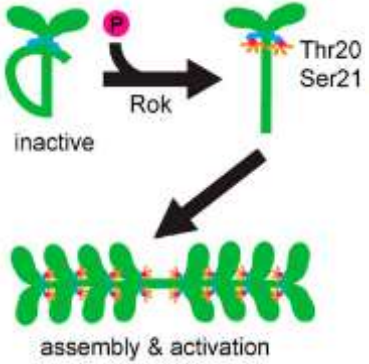
Cell migration

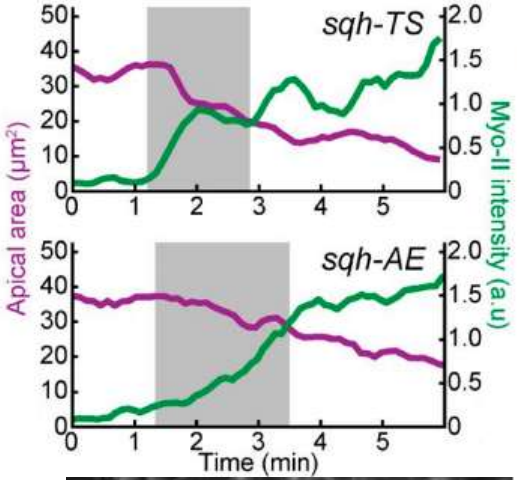


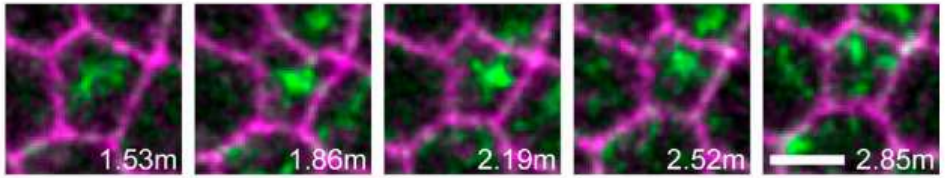
Gastrulation/EMT

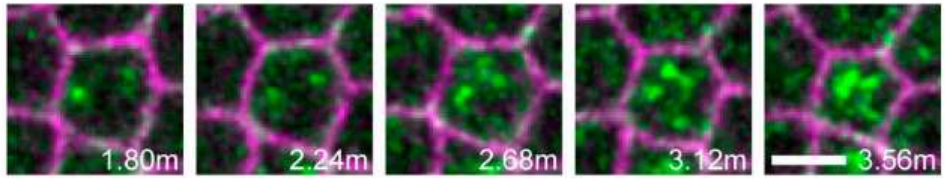
Cell 137:1331 (2009)
COGD 21:671 (2011)
Nature 457:495 (2009)

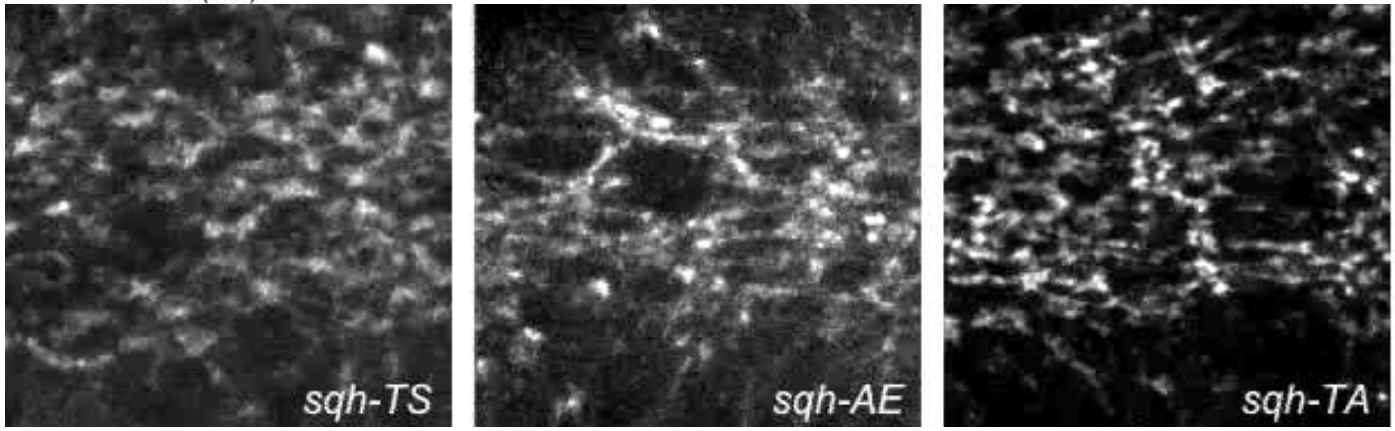
Blocking pulsed constriction disrupts cell & tissue dynamics







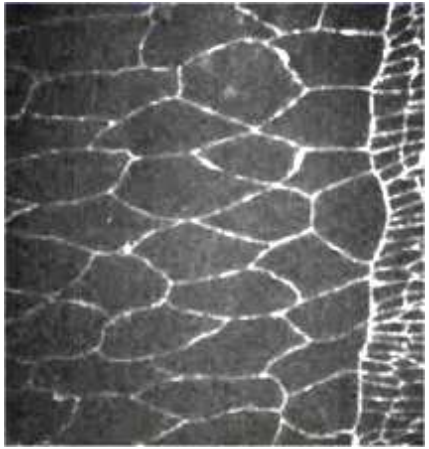




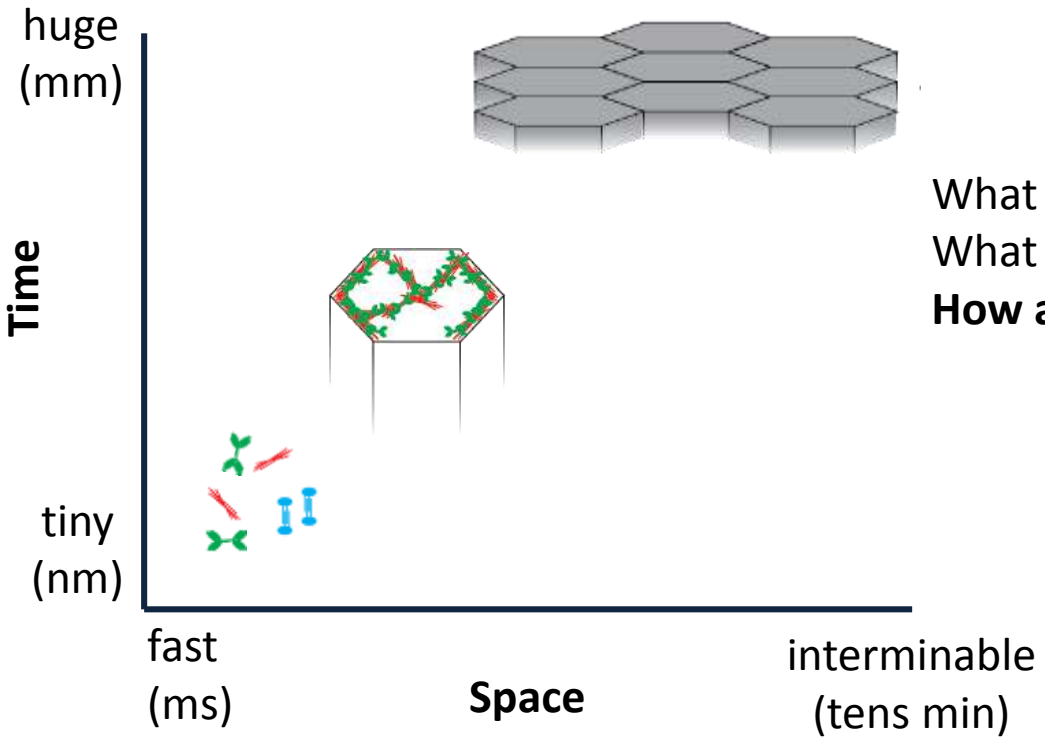
JCB 206:435 (2014)

Why are pulsed dynamics so important?

Integrate time scales
‘Sample’ energy states?
Allow for more dynamic/robust regulation?
Coordination of cell behavior

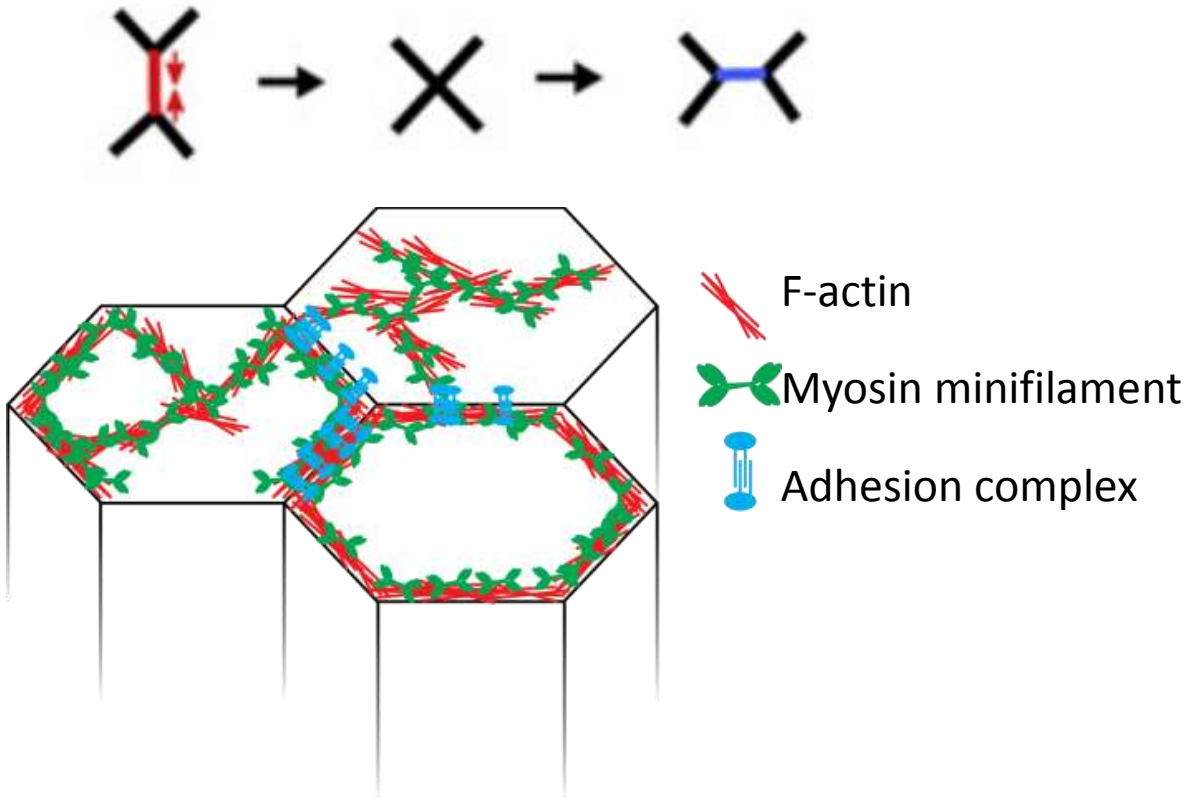


Morphogenesis is a multiscale problem

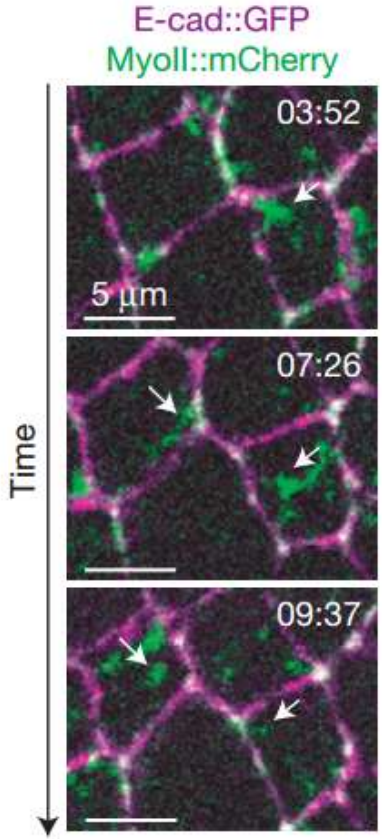


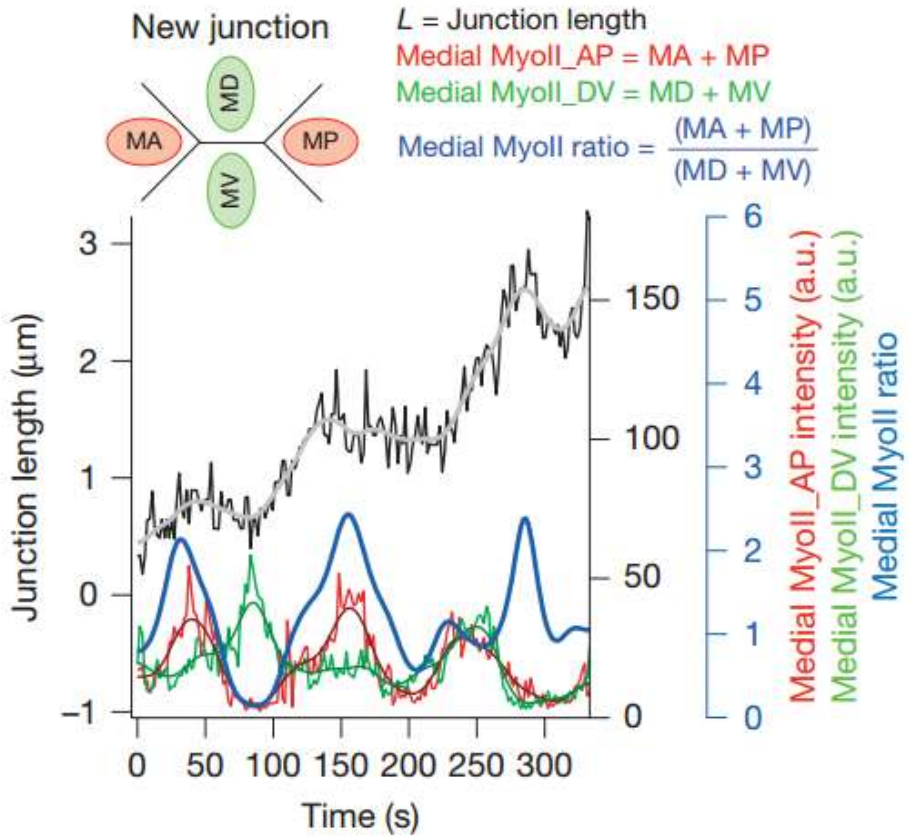
What are the forces that deform cells?
What controls these forces in space and time?
How are forces integrated across the tissue?

No (epithelial) cell is an island



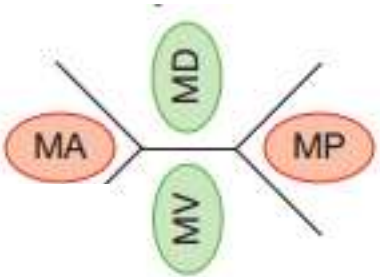
Junction expansion requires help from neighbors

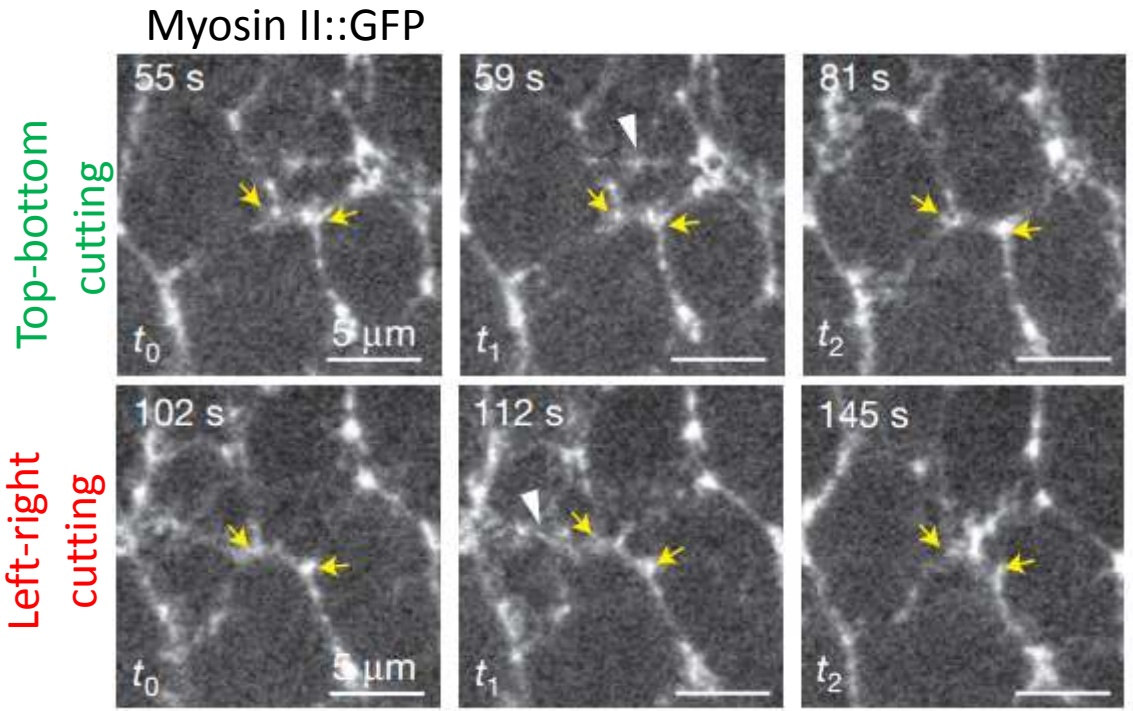




Nat Cell Bio 17:1247 (2015)

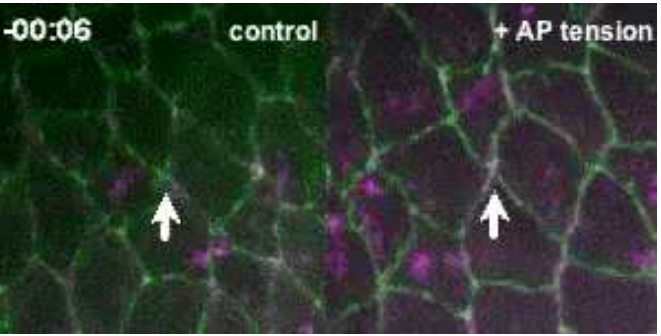
Junction expansion requires constriction in left-right neighbors

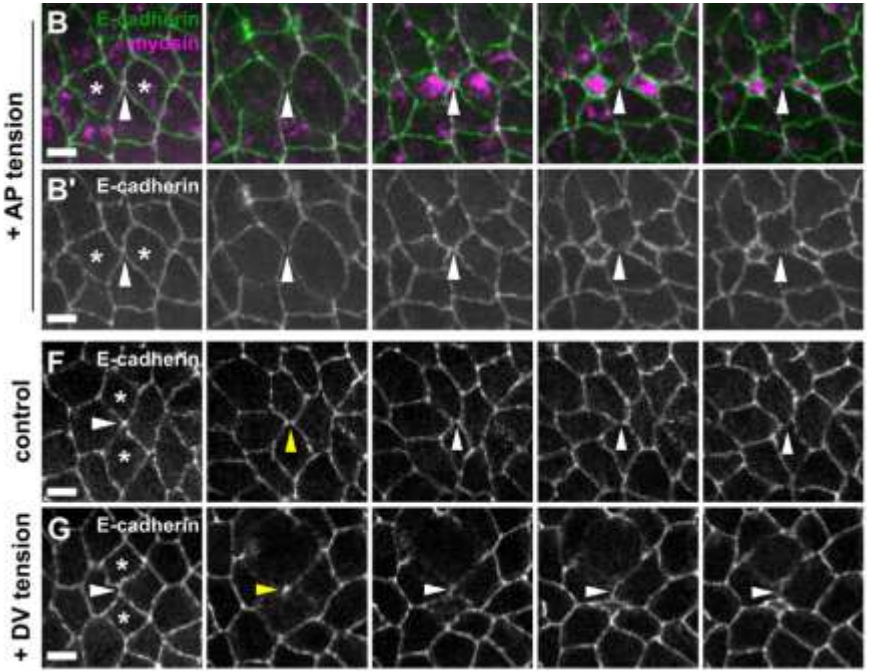


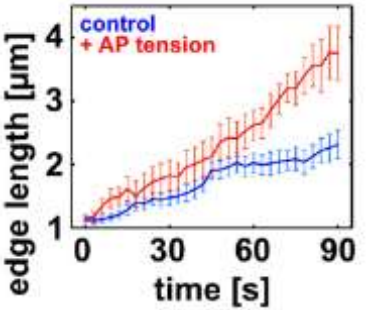


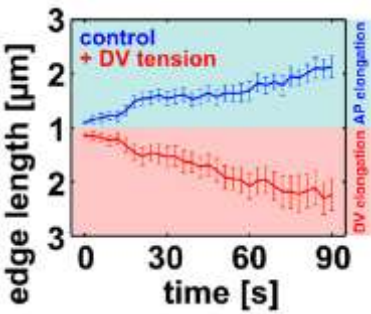
Nat Cell Bio 17:1247 (2015)

Constriction in neighboring cells is sufficient to induce contact remodeling



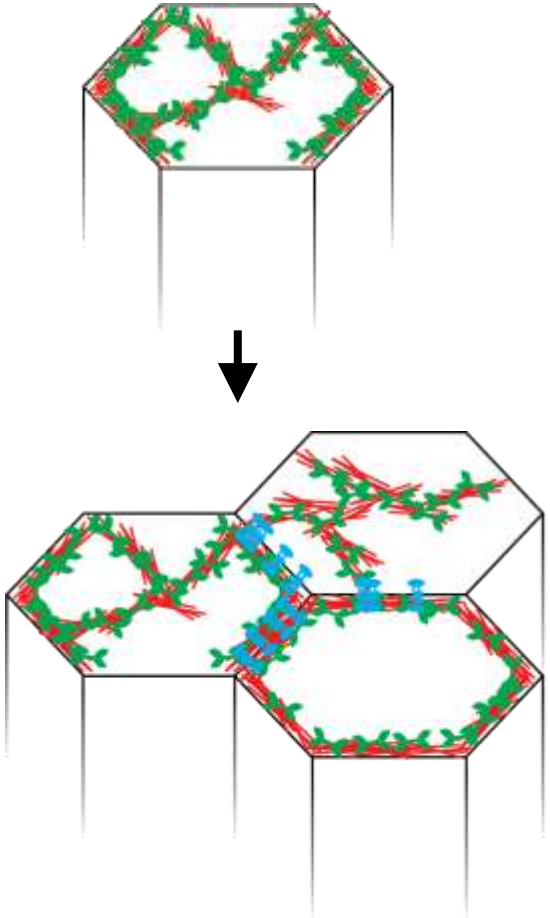




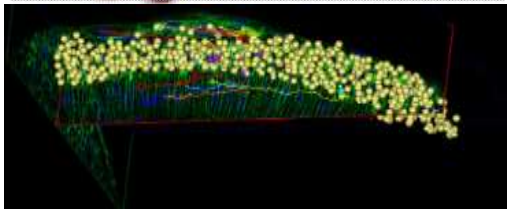


eLife 2016;5:e10757

We can do more biggerer

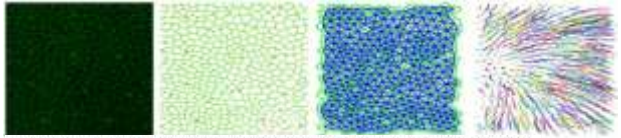


GoFigure2
in toto image analysis software



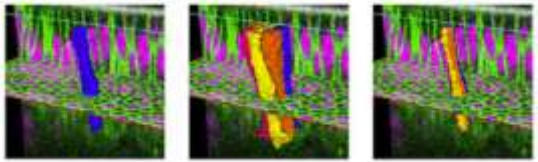
http://www.gofigure2.org/

Segmentation and Tracking of Adherens Junctions in 3D for the Analysis of Epithelial Tissue Morphogenesis



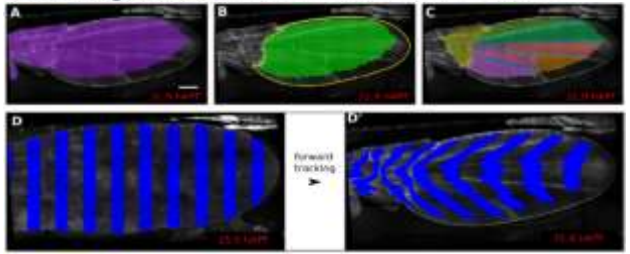
PLOS Computational Biology | DOI:10.1371/journal.pcbi.1004124 April 17, 2015

Quantitative 4D analyses of epithelial folding during *Drosophila* gastrulation



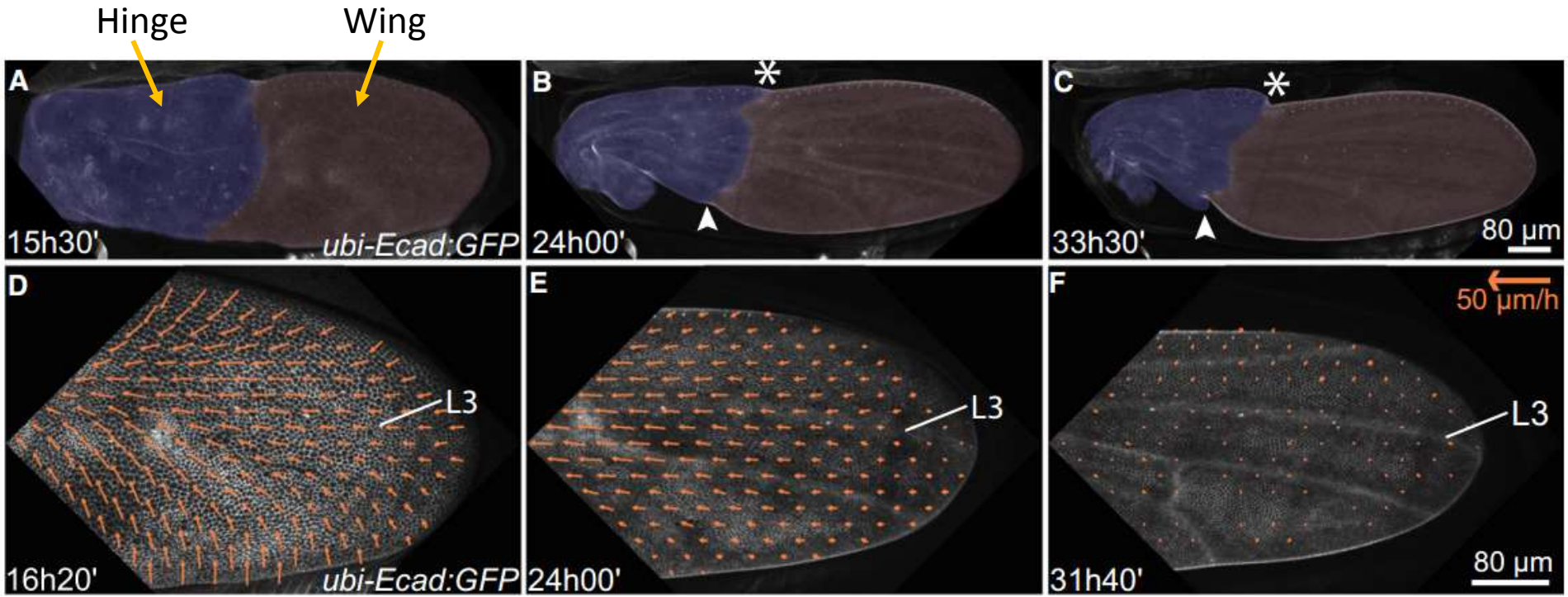
Development 2014 141: 2895

TissueMiner: A multiscale analysis toolkit to quantify how cellular processes create tissue dynamics



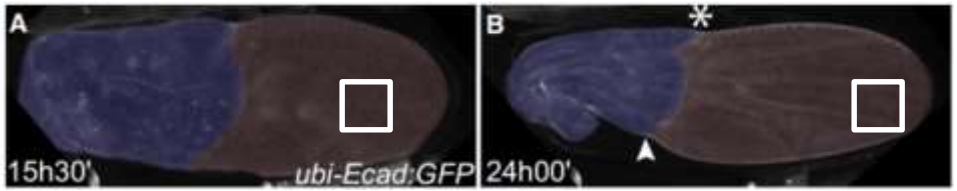
Elife 2016:e14334

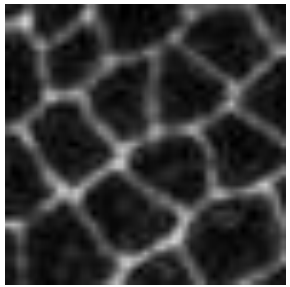
Mechanical interactions between tissues regulate cell polarity and intercalation

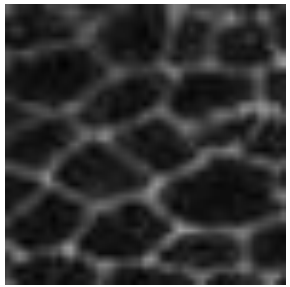


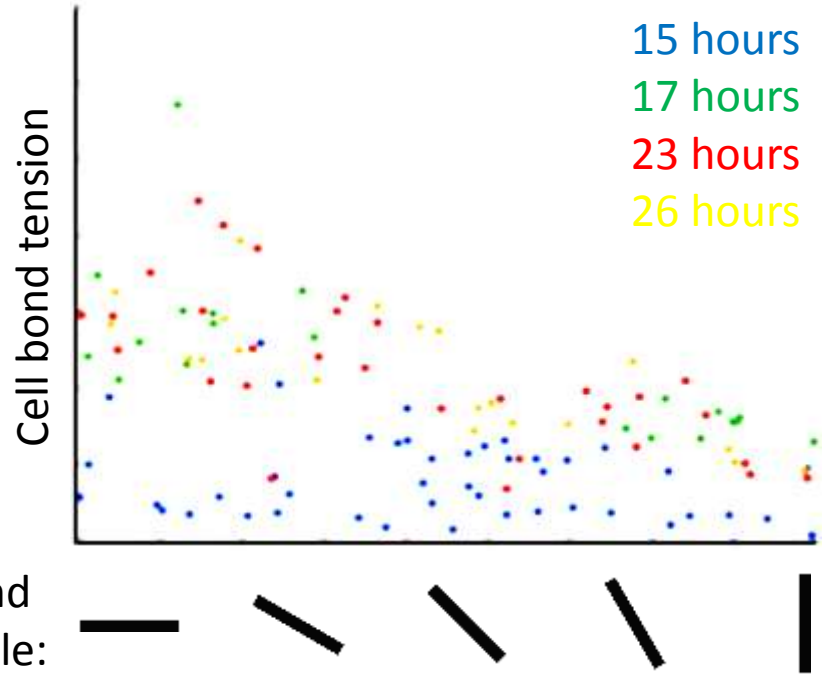
Cell 142:773 (2010)

Cell junction tension suggests hinge pulls on wing



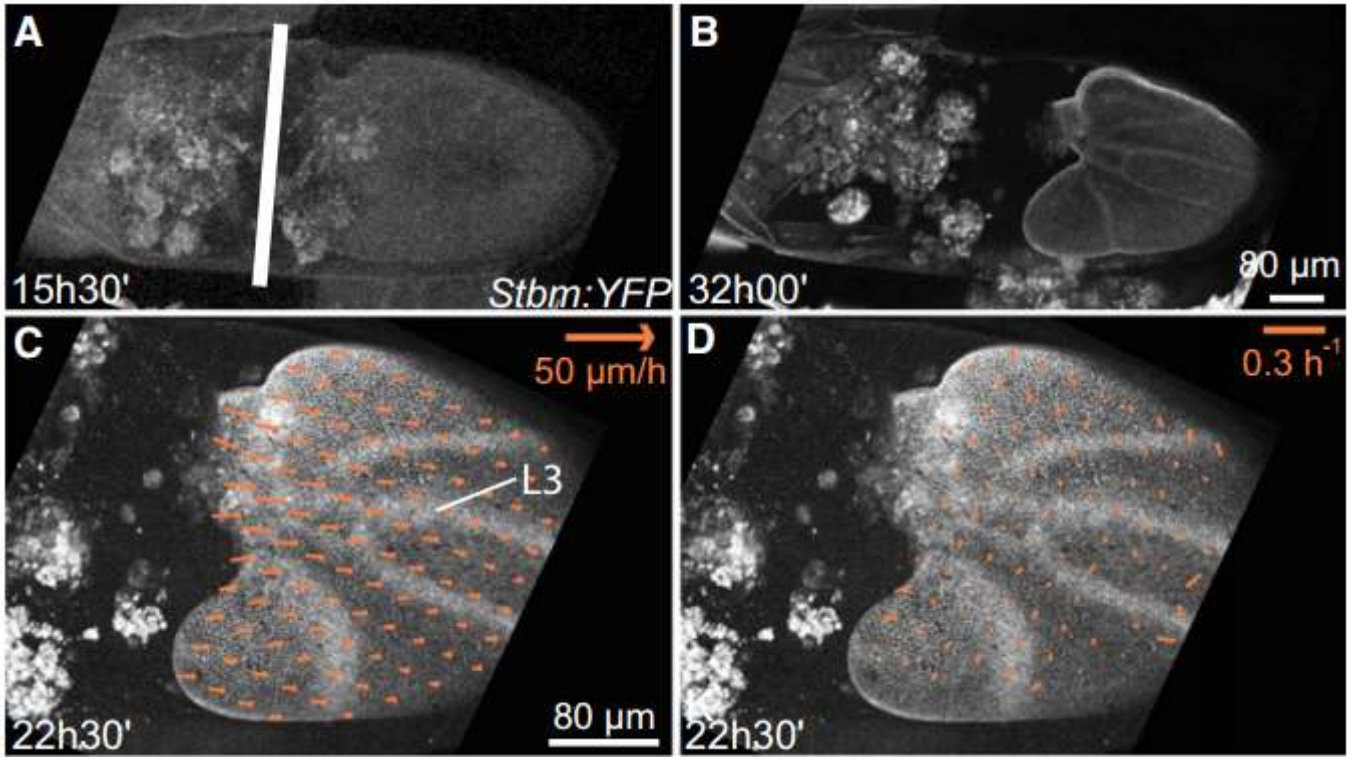






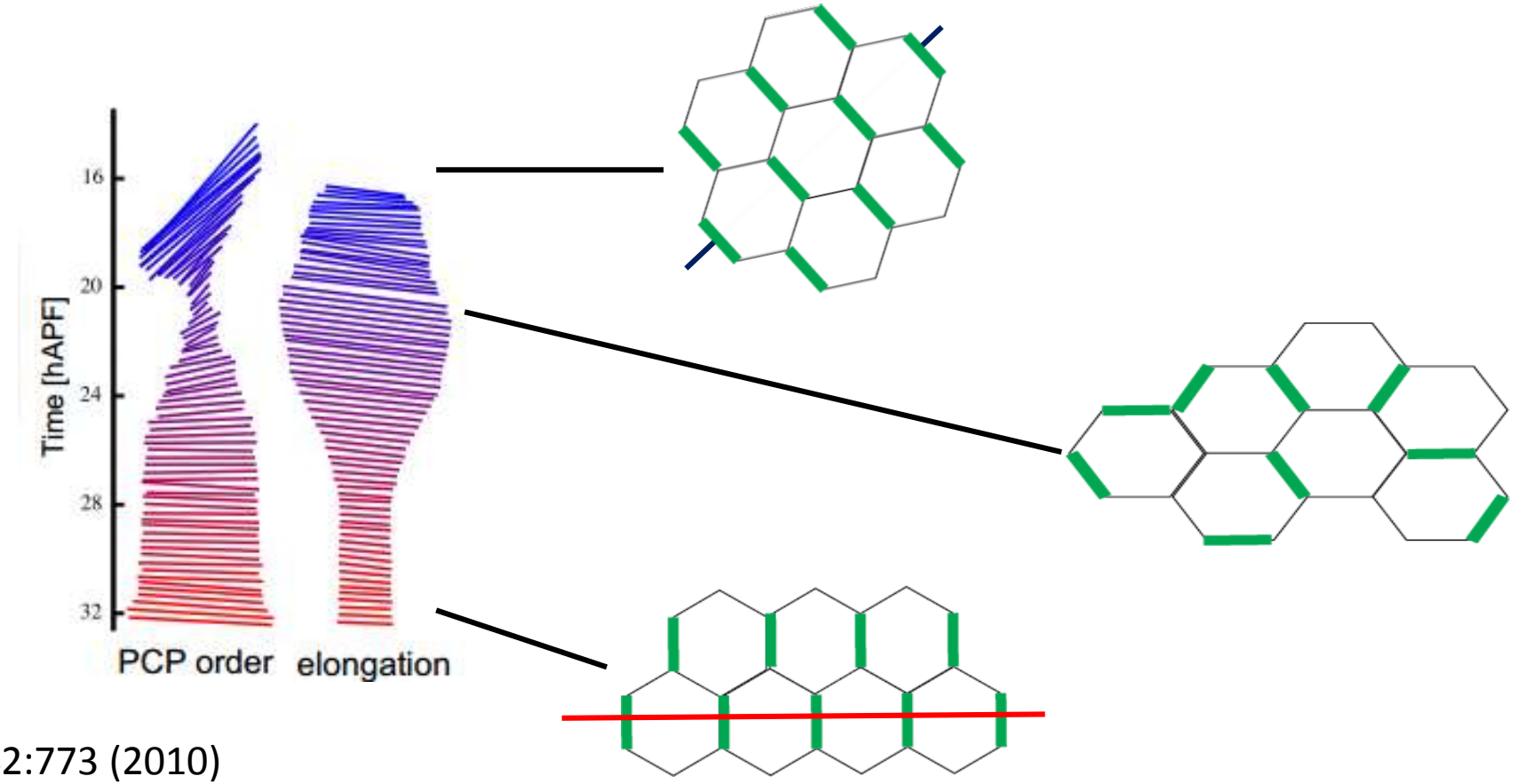
Cell 142:773 (2010)

Blocking tension input prevents tissue polarization, cell flow, and elongation



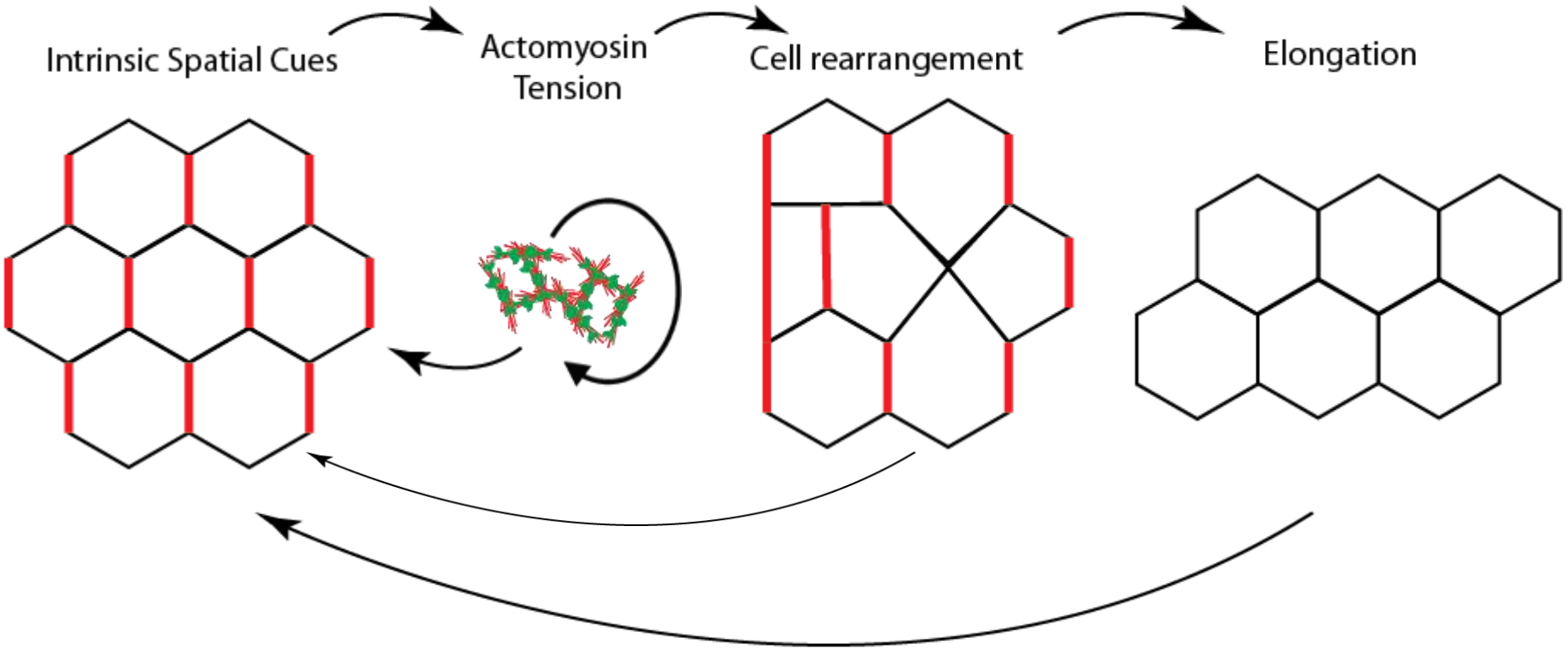
Cell 142:773 (2010)

Tension and cell flow reorganize the wing during elongation



Cell 142:773 (2010)

Trying to put it all together…



Some unanswered questions

Which are the initiating events?
What mechanisms control pulsed forces?
How do other mechanical properties such as stiffness or protrusion contribute?
Lots of positive feedback mechanisms, but how do these pathways get attenuated?

Acknowledgements

QB Program
Jane Kondev
Avi Rodal
Rodal Lab