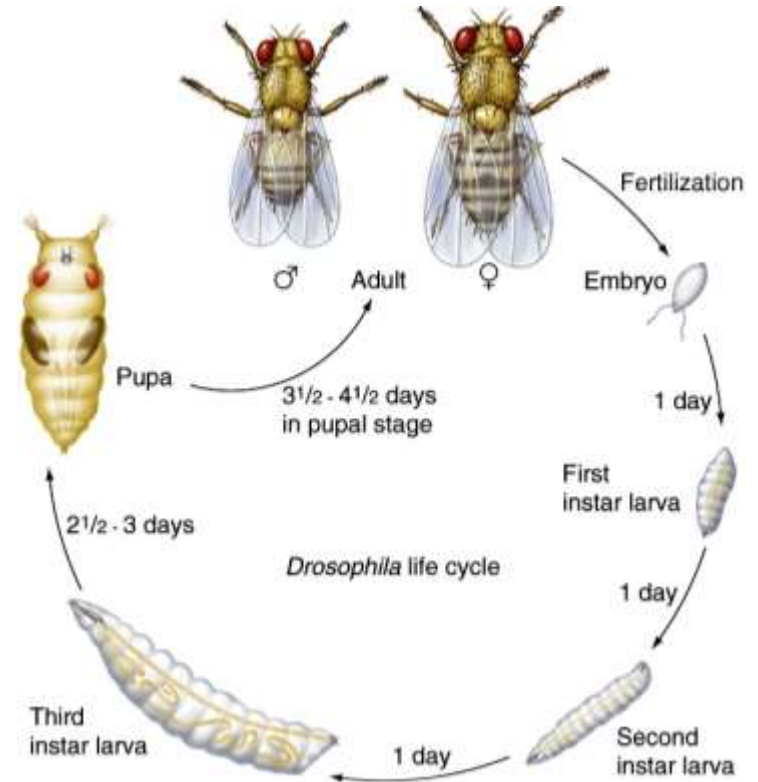
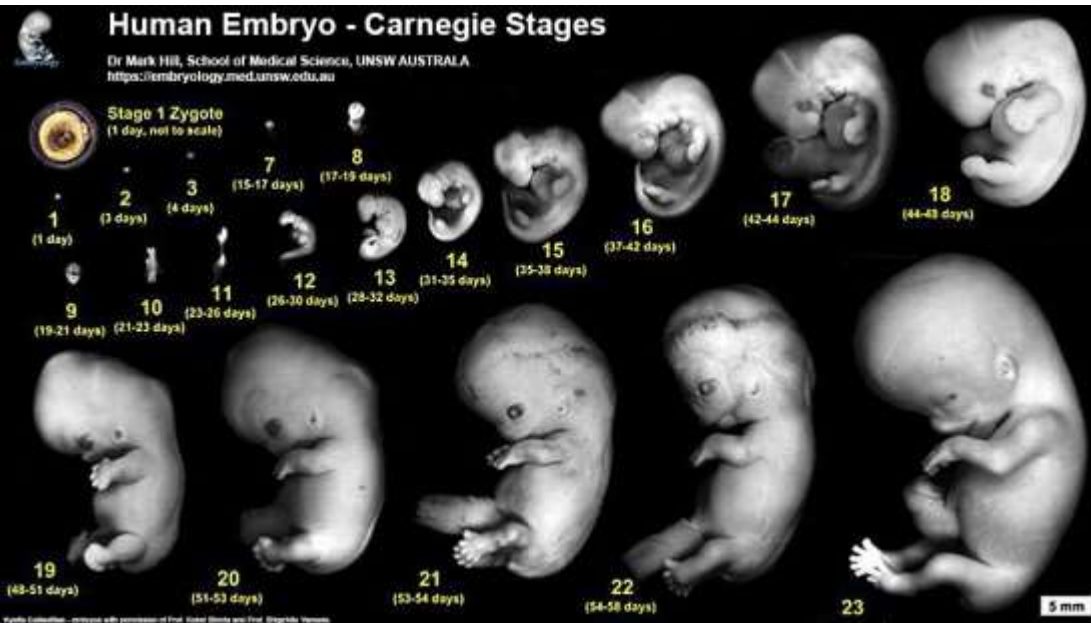


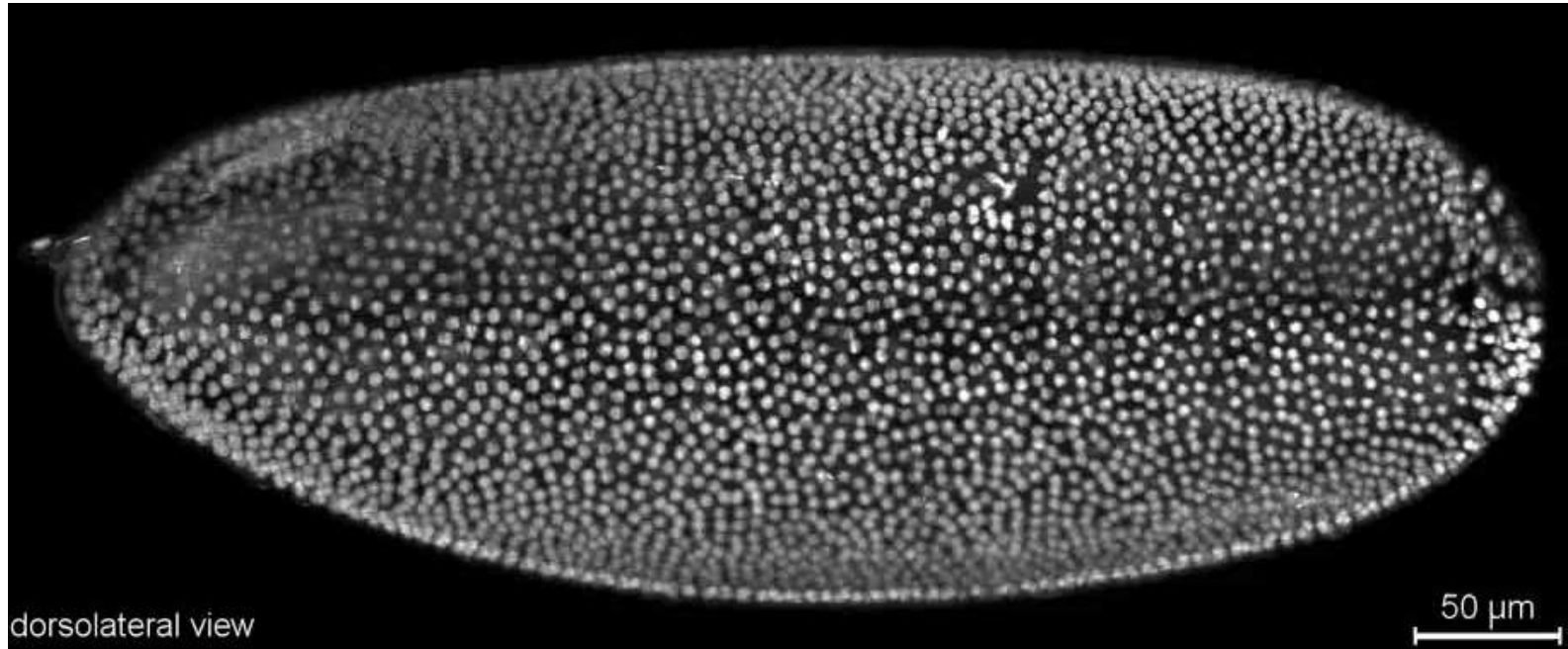
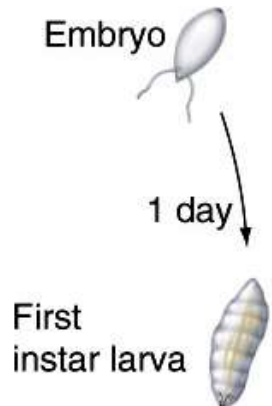
**Many hands make light work:  
How cells use tiny forces to shape big tissues**

Steve Del Signore  
QB Bootcamp  
1/12/2017

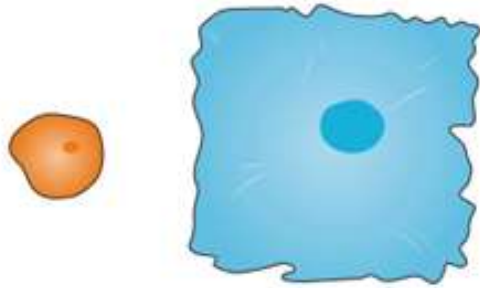
# How do we get assembled?



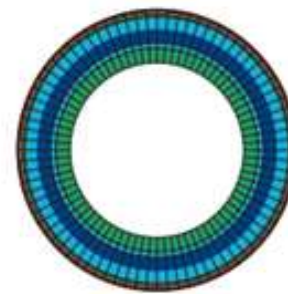
# Diverse tissue dynamics shape the developing embryo



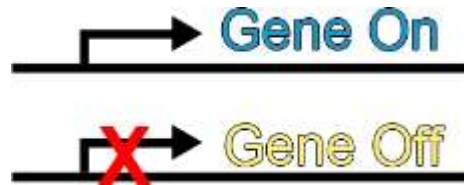
# Mechanical inputs can modulate diverse cell behaviors



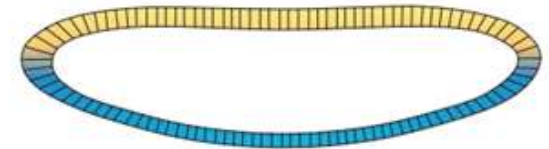
Cell Shape



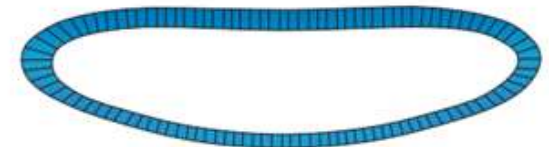
Proliferation



Gene expression



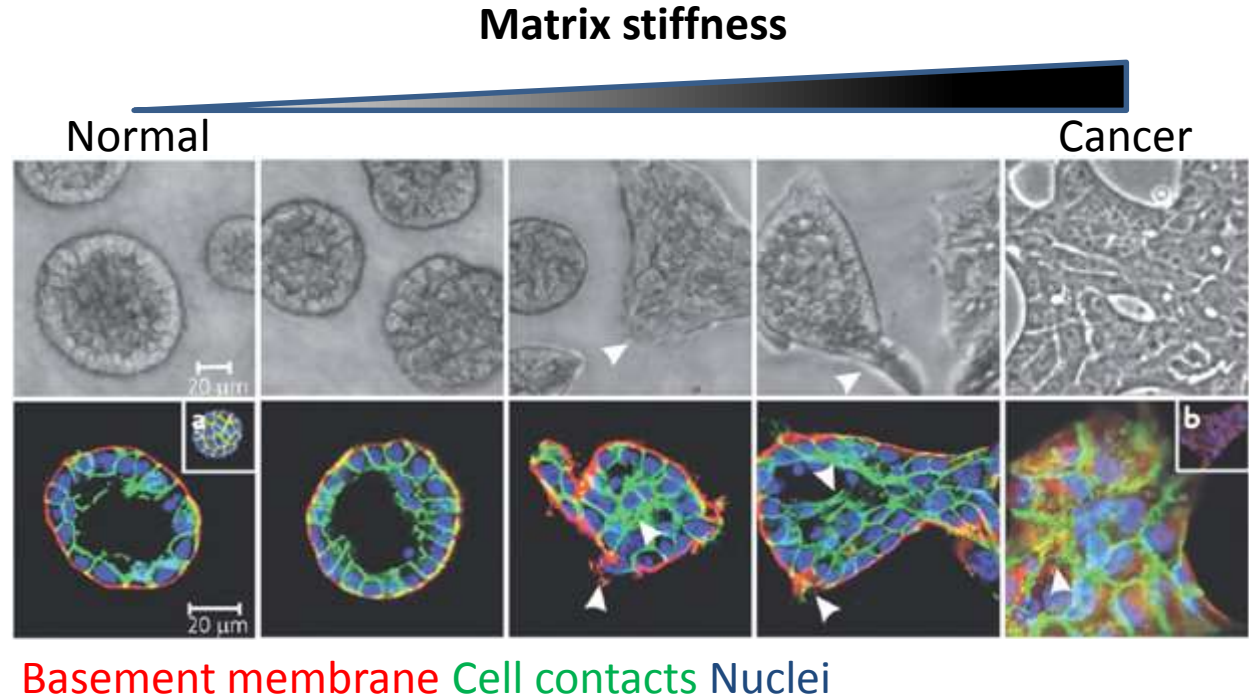
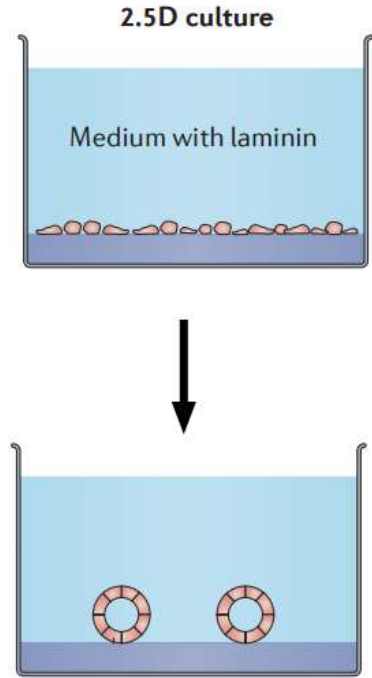
Constrained 4 minutes



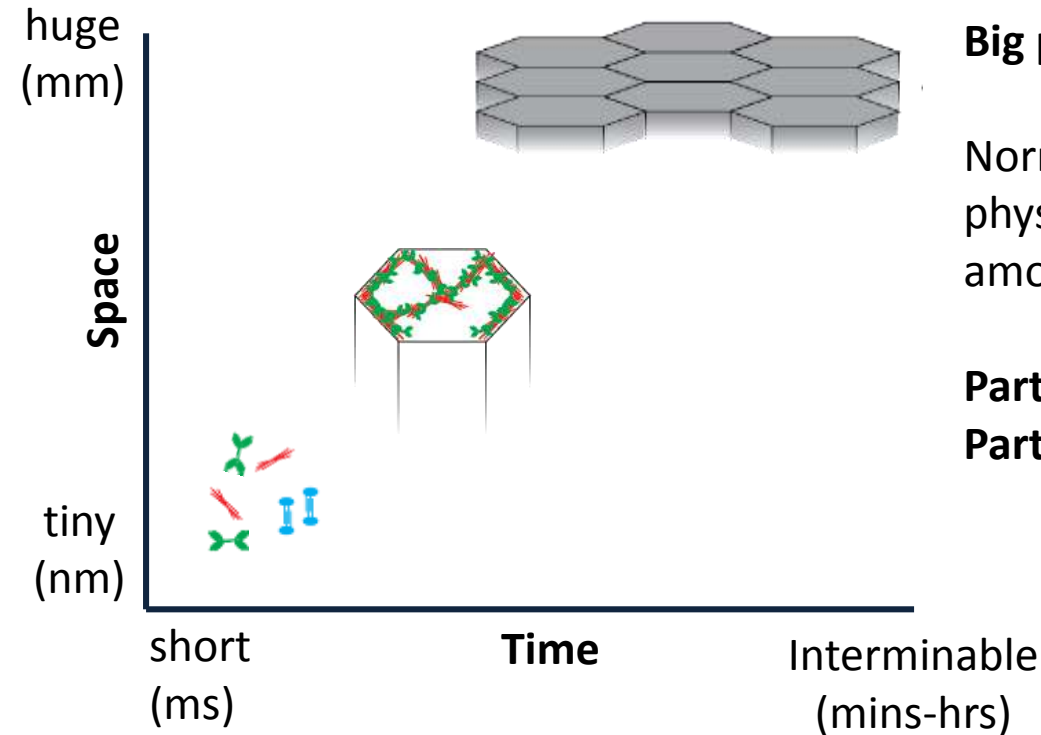
Constrained 10 minutes



# Mechanical inputs can drive pathological cell behaviors



# Morphogenesis is a multiscale process



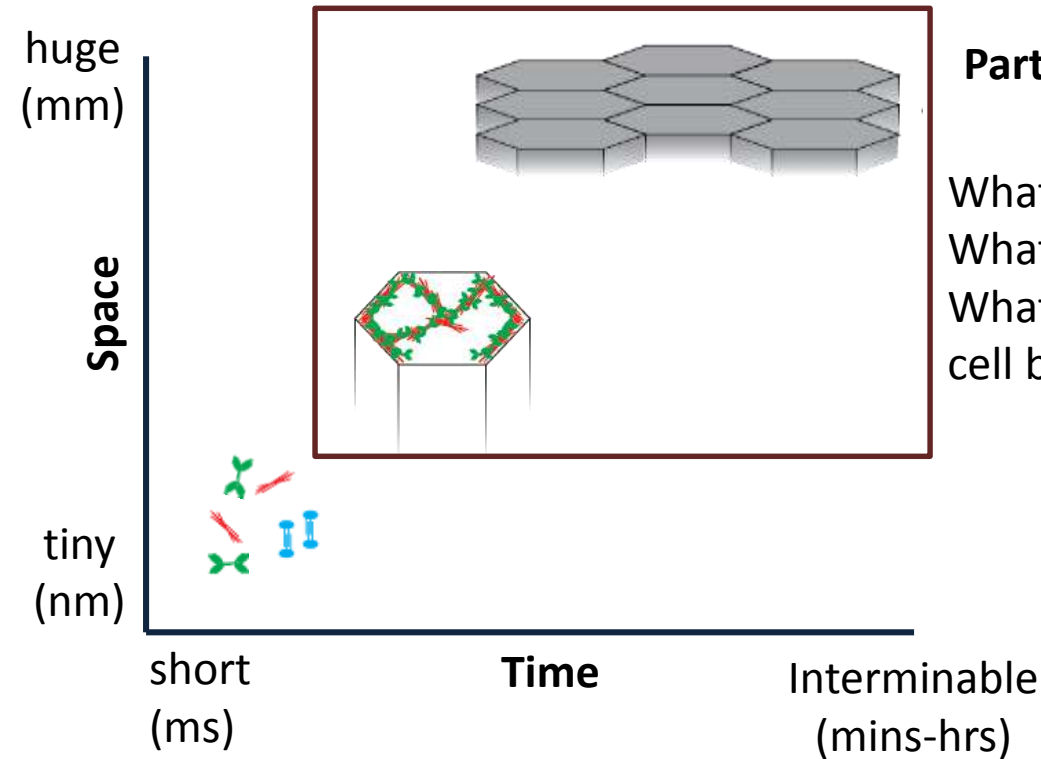
## Big picture message:

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



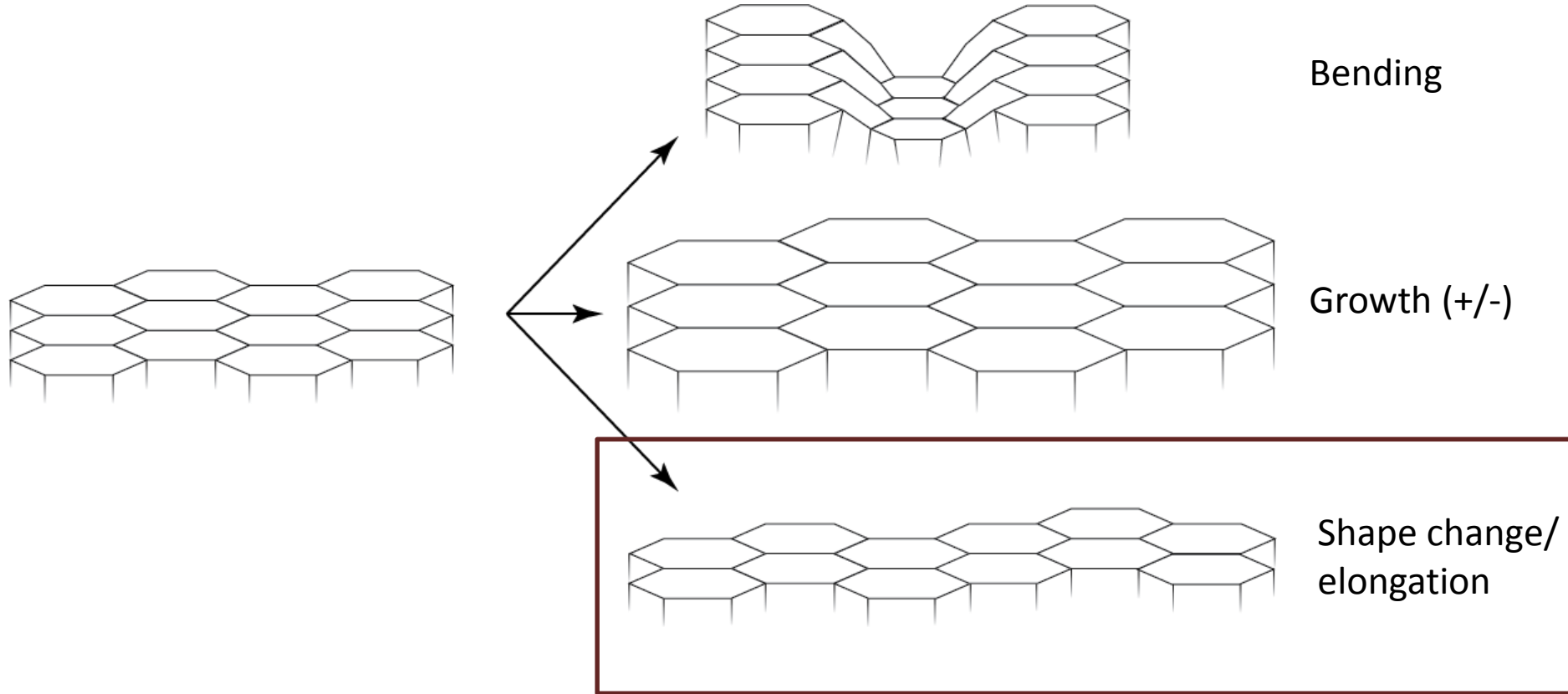
## Part I: The players

What tissue movements promote development?

What cell behaviors drive tissue dynamics?

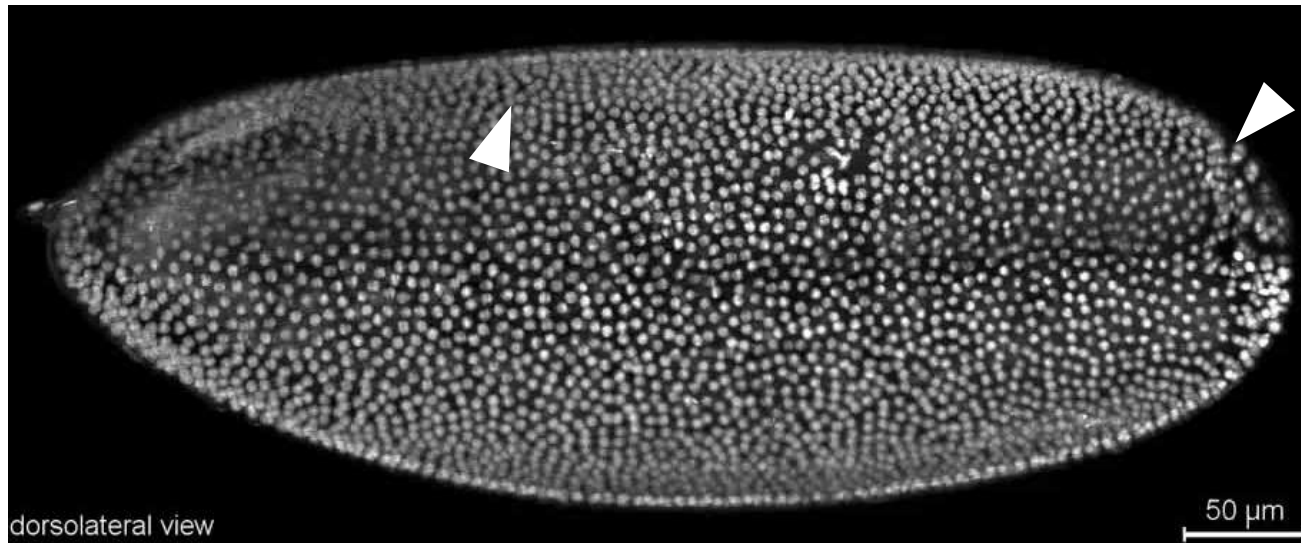
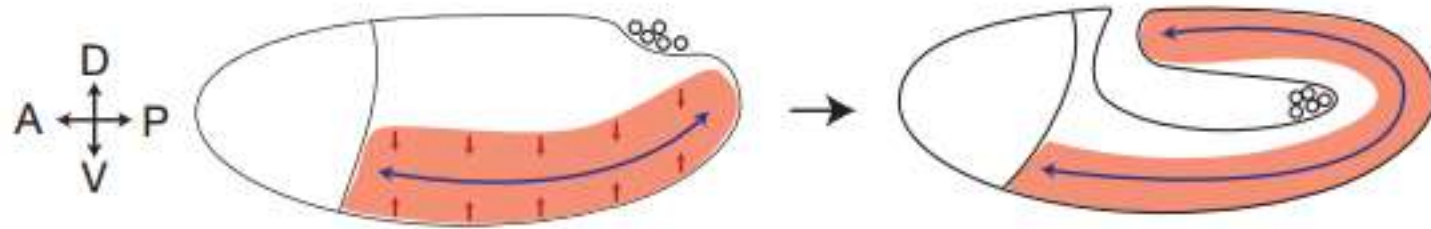
What are the molecular forces that underlie cell behavior?

# What tissue behaviors sculpt the developing organism?

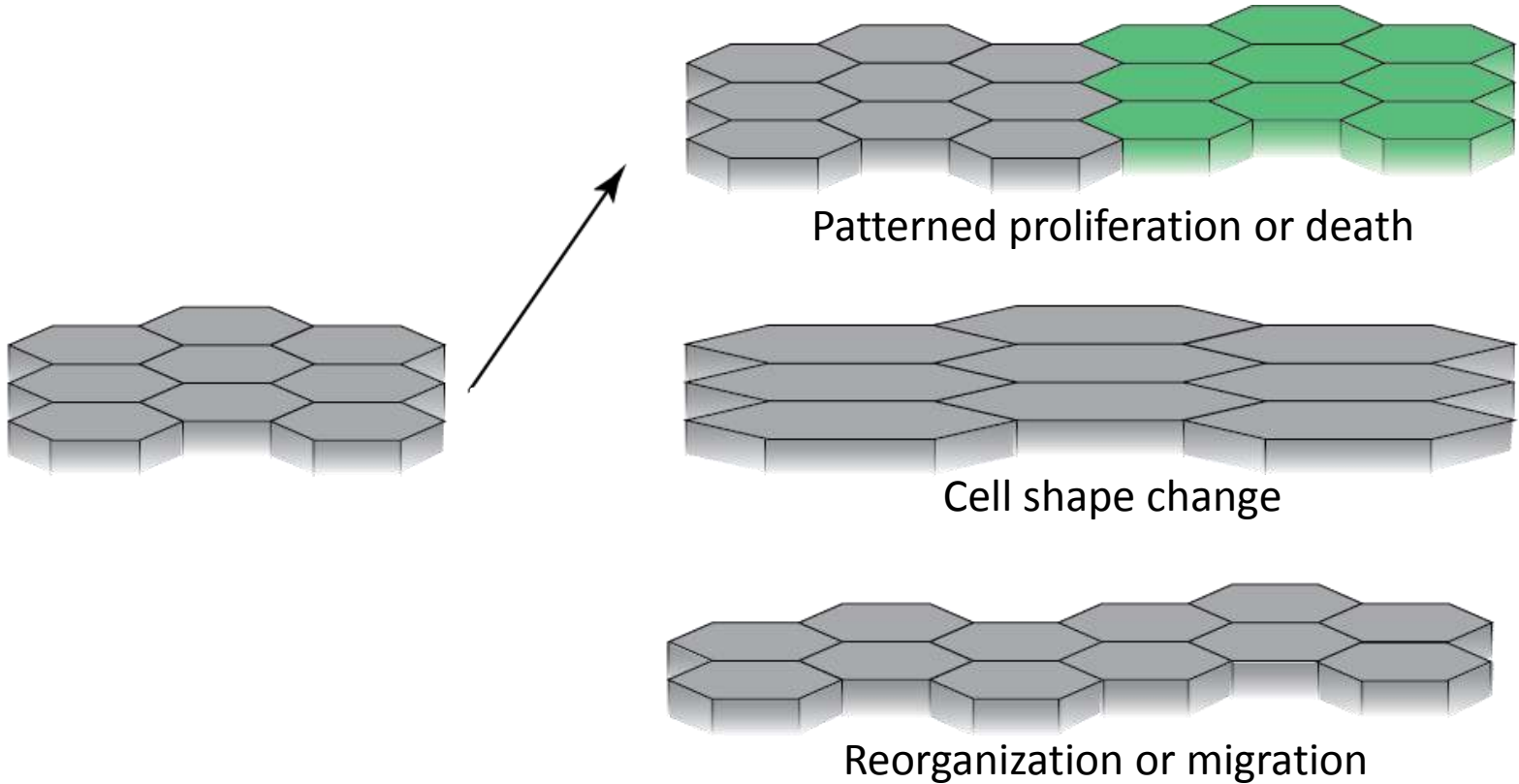




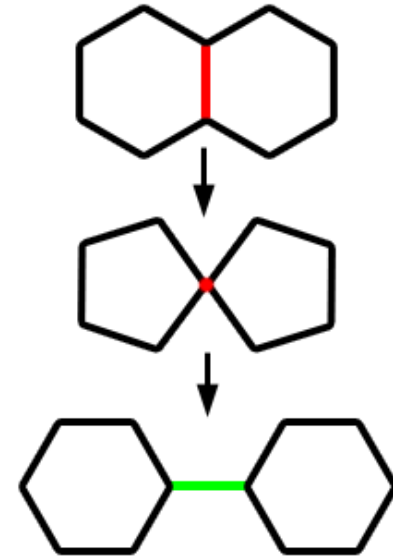
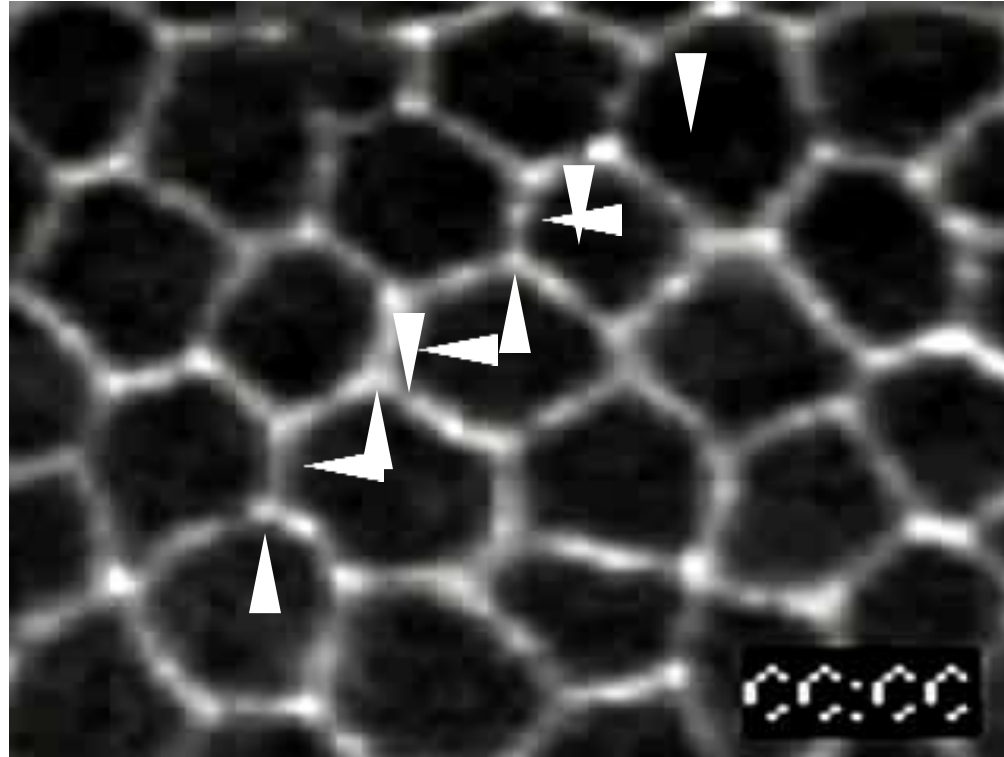
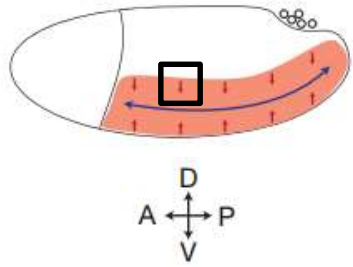
## Tissue elongation: *Drosophila* germband extension



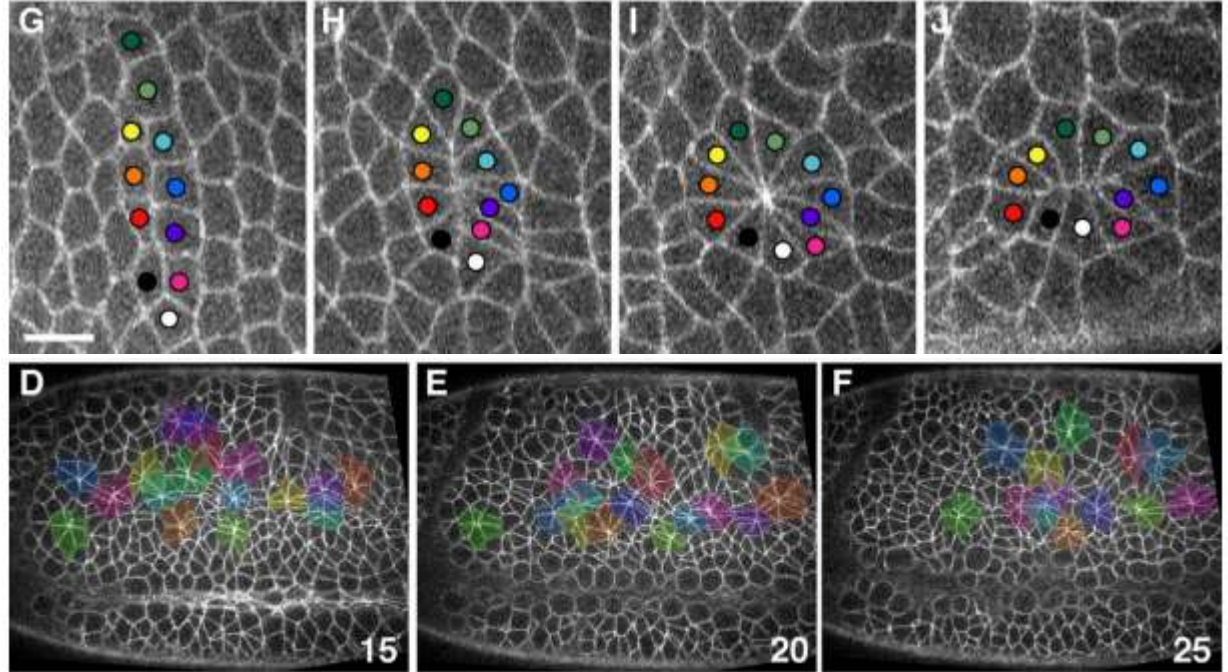
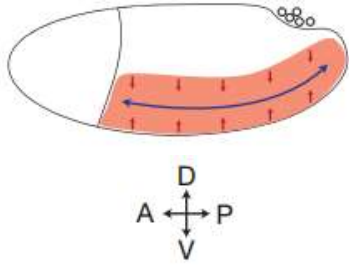
# What cell behaviors drive tissue morphogenesis?



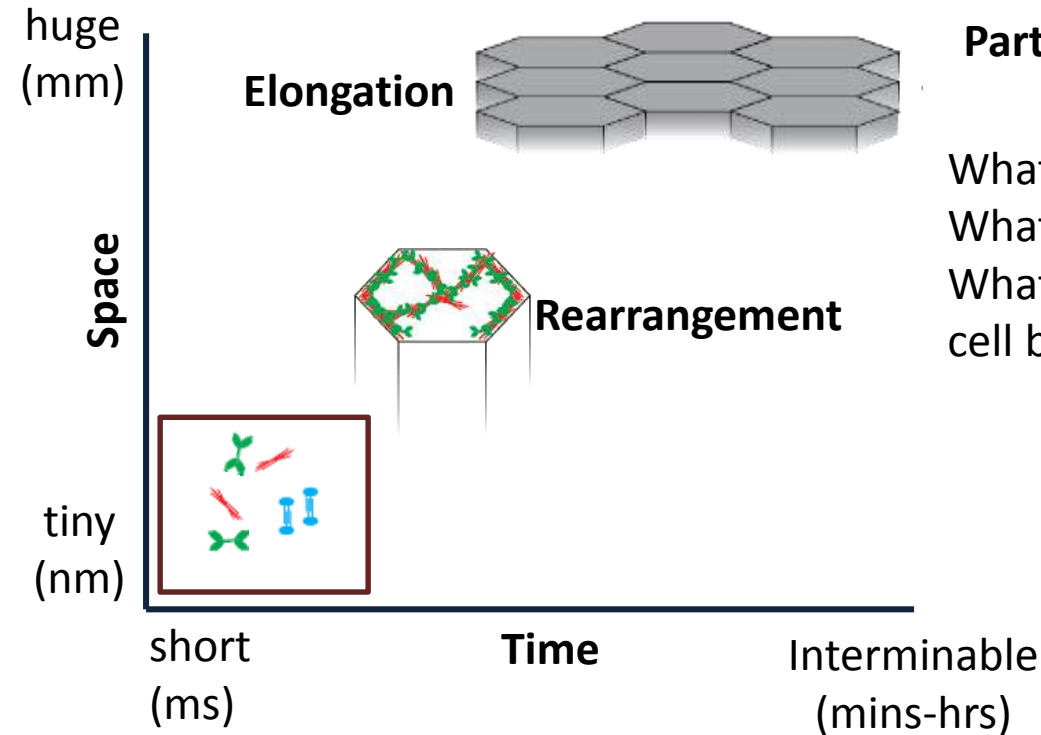
# Cell reorganization drives germband extension: Single cell contact remodeling



# Cell reorganization drives germband extension: Multicellular contact remodeling



# Morphogenesis is a multiscale process



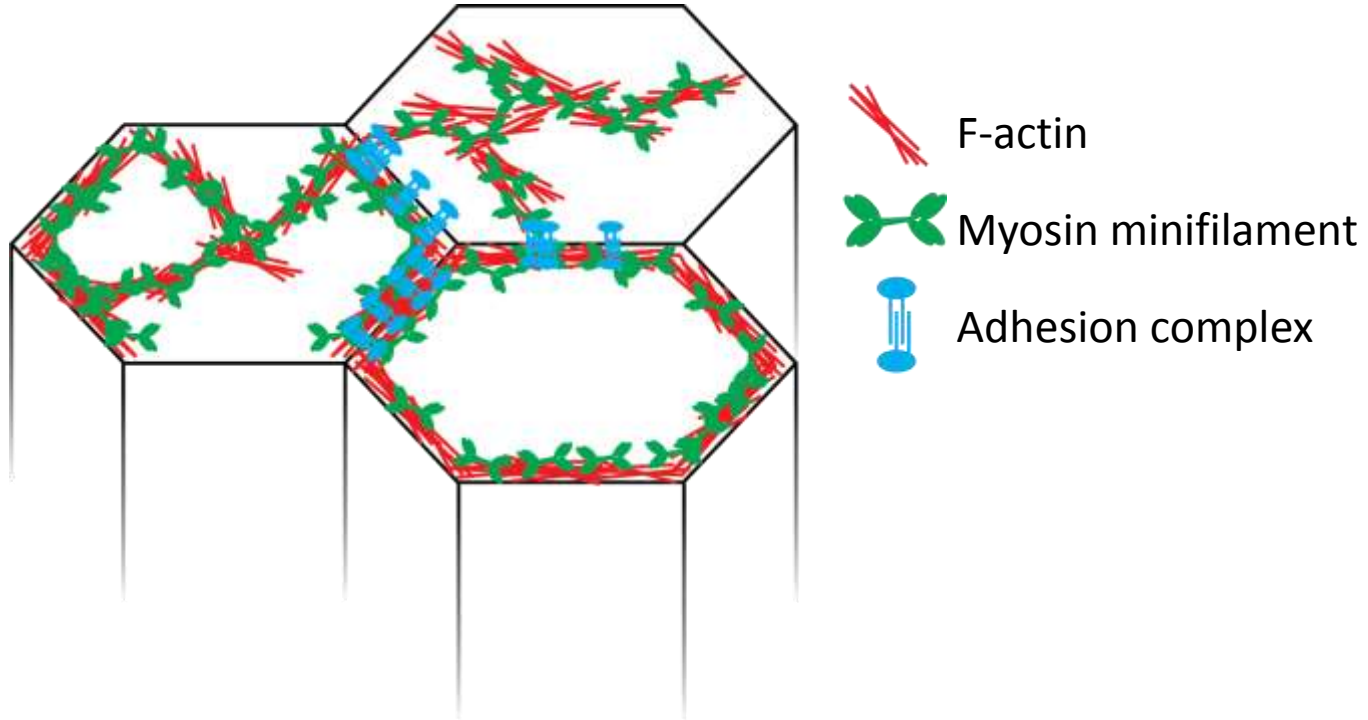
## Part I: The players

What tissue movements promote development?

What cell behaviors drive tissue dynamics?

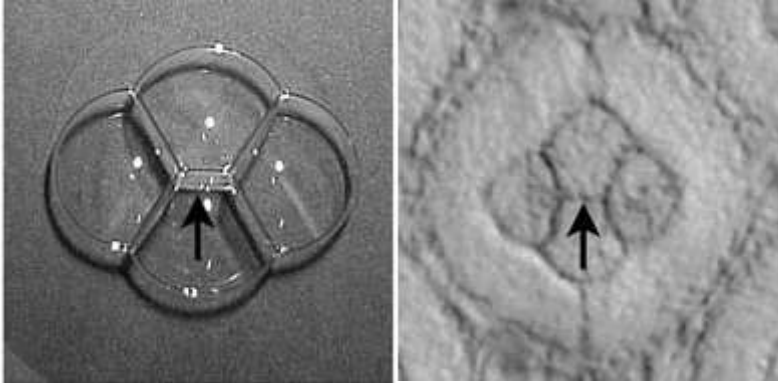
What are the molecular forces that underlie cell behavior?

# Cell adhesion and actomyosin tension drive cell dynamics

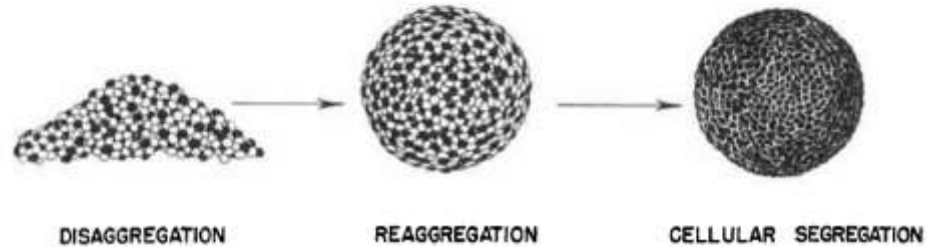
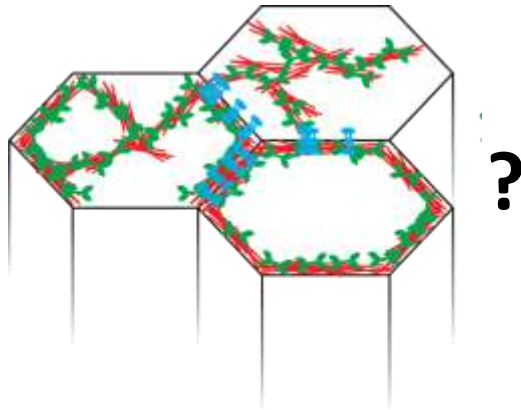
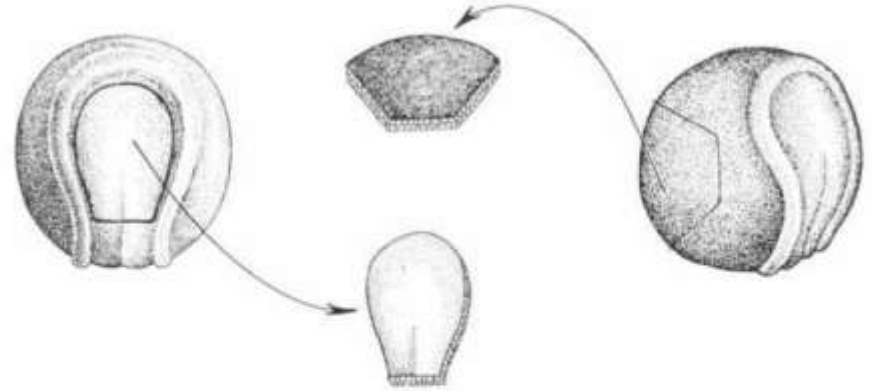




# Adhesion originally considered dominant force



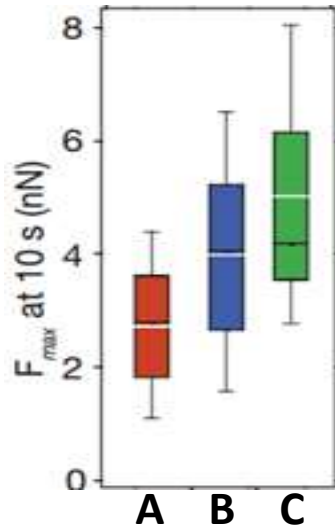
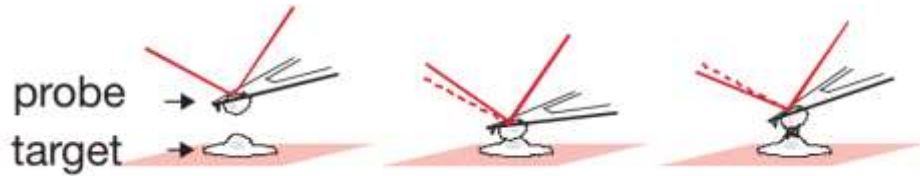
Nature 431:647 (2004)



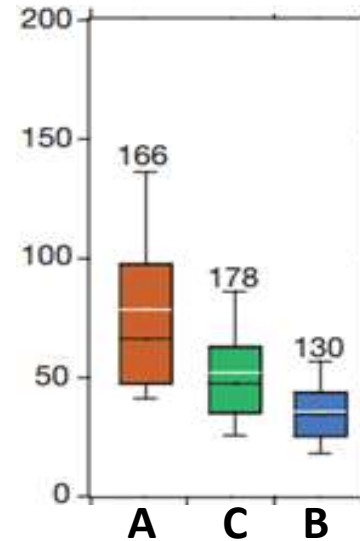
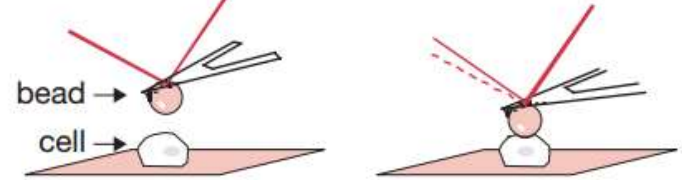
J Exp Zoo. 128:53 (1955)

# Quantification of adhesion and cortical tension in cells

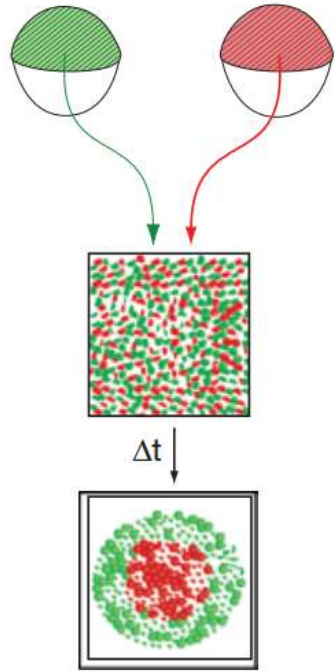
## Adhesion



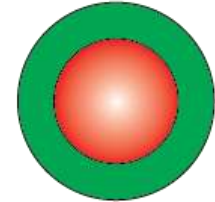
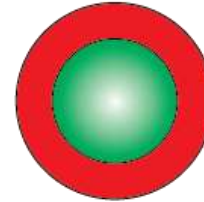
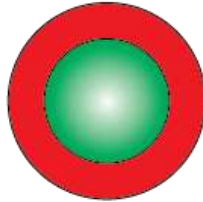
## Tension



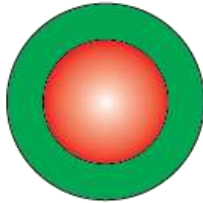
# Does surface tension or adhesion predict sorting behavior?



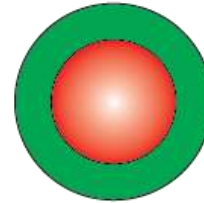
Adhesion  
 $C > B > A$



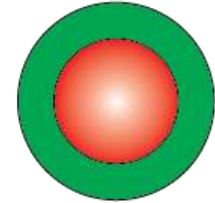
Surface  
Tension  
 $A > C > B$



$A+C$

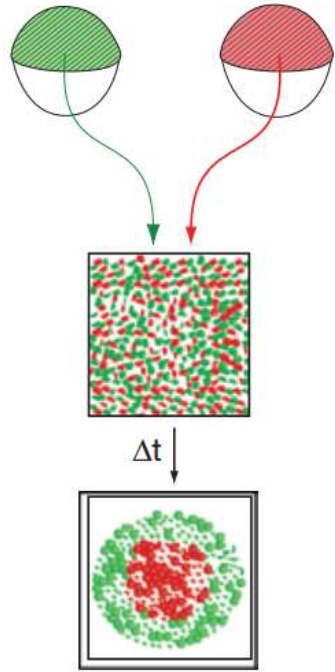


$A+B$

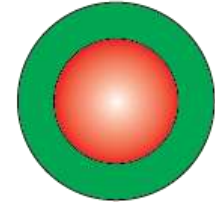
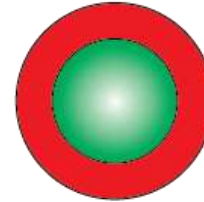
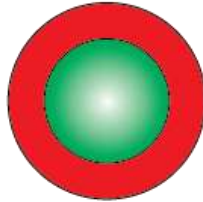


$C+B$

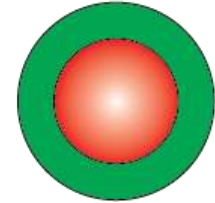
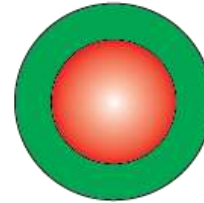
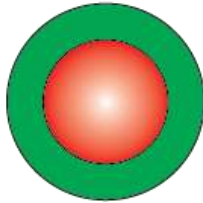
# Surface tension predicts sorting; adhesion does not



Adhesion  
 $C > B > A$



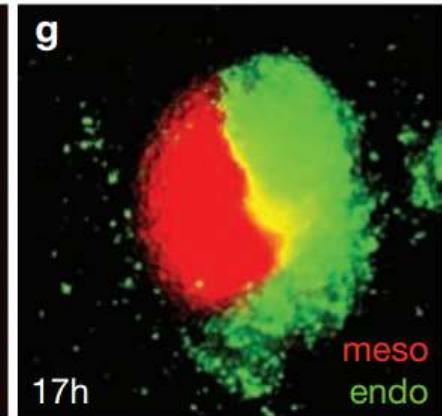
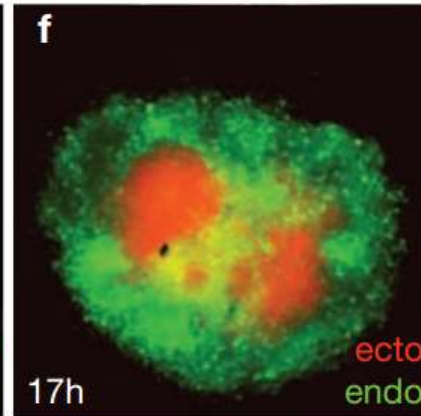
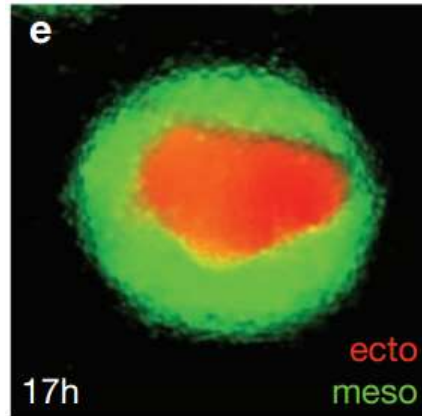
Surface  
Tension  
 $A > C > B$



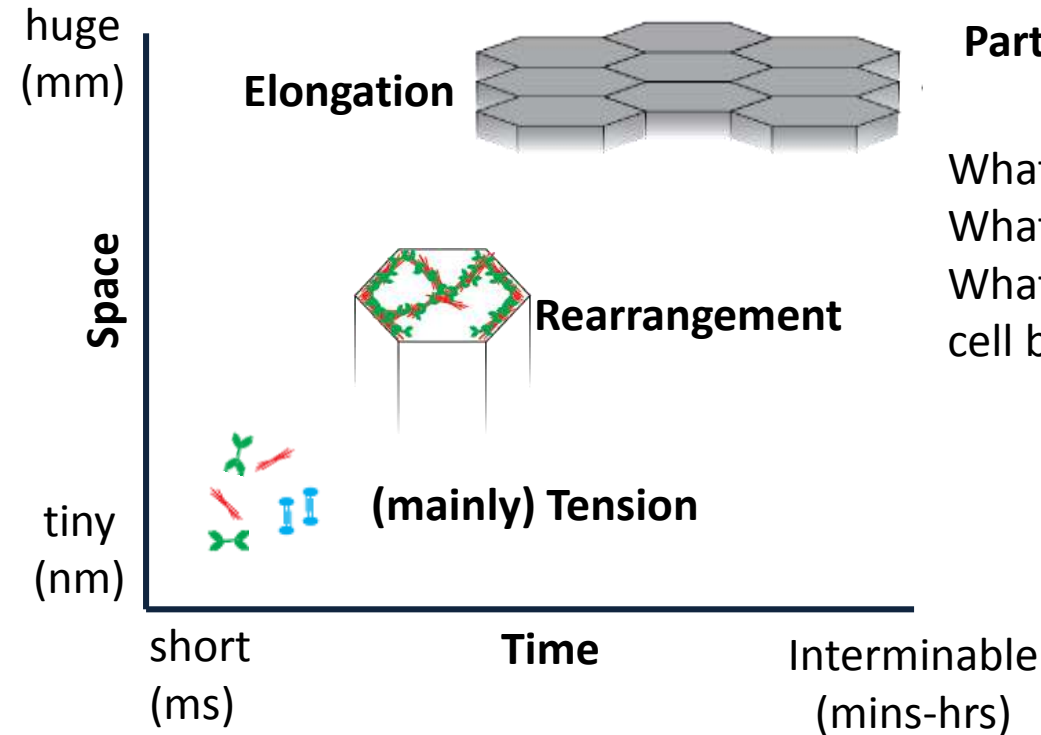
A+C

A+B

C+B



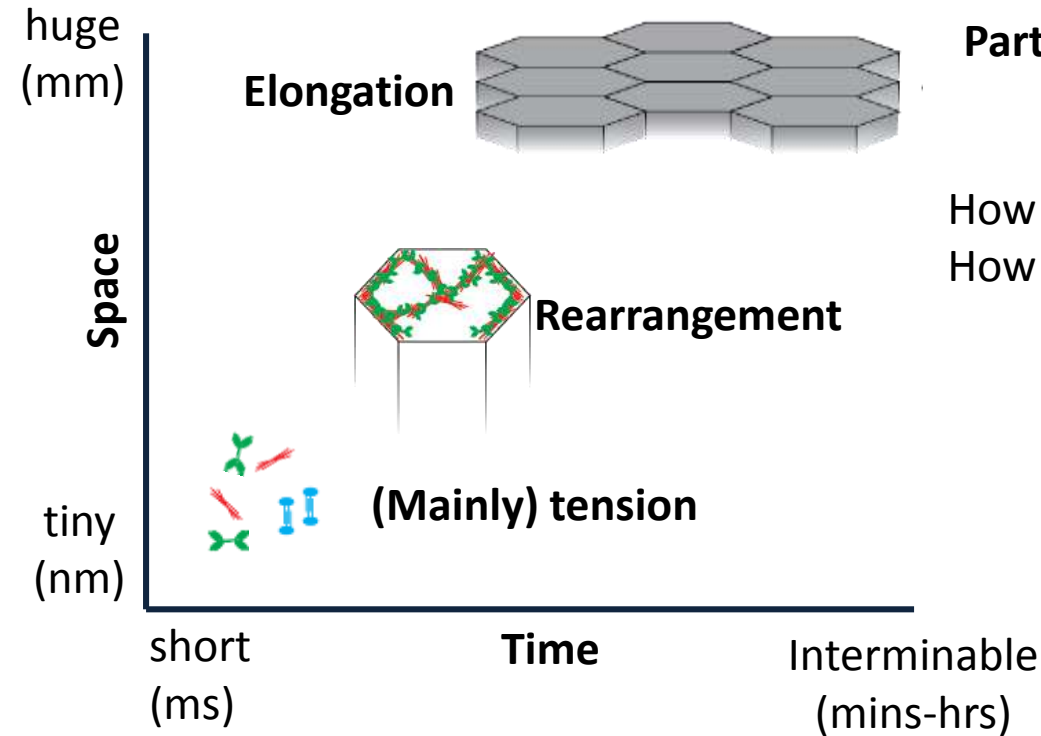
# Morphogenesis is a multiscale process



## Part I: The players

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

# Morphogenesis is a multiscale process



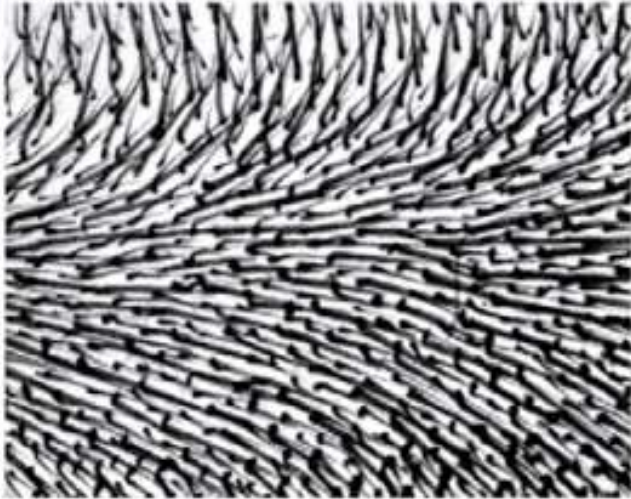
## Part II: The game

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

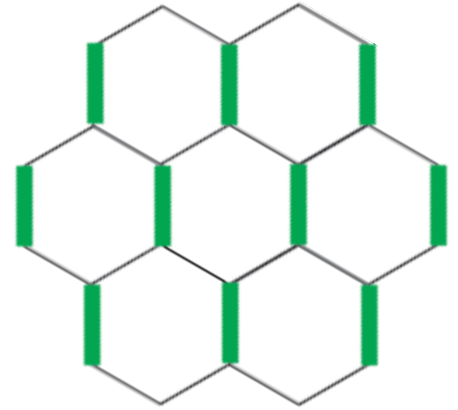


# Cells can systematically polarize

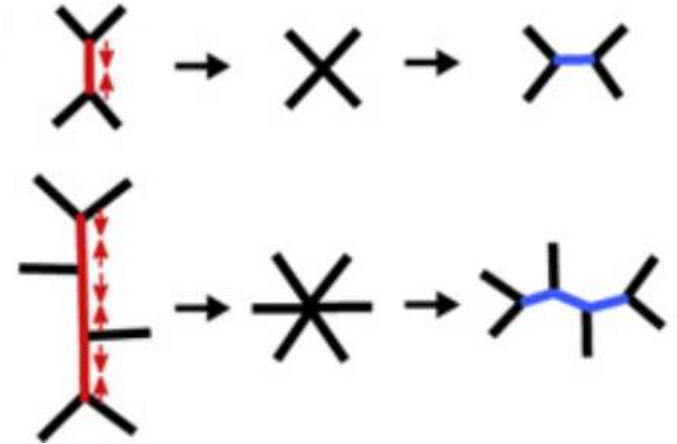
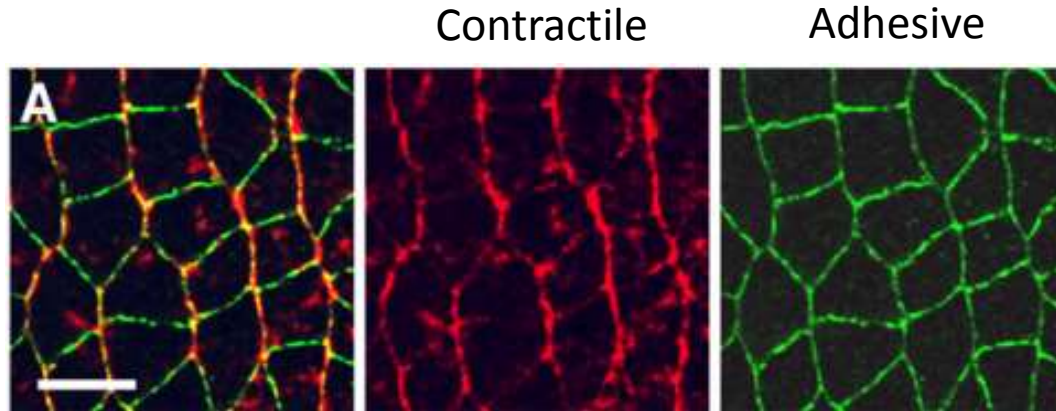
**Control**



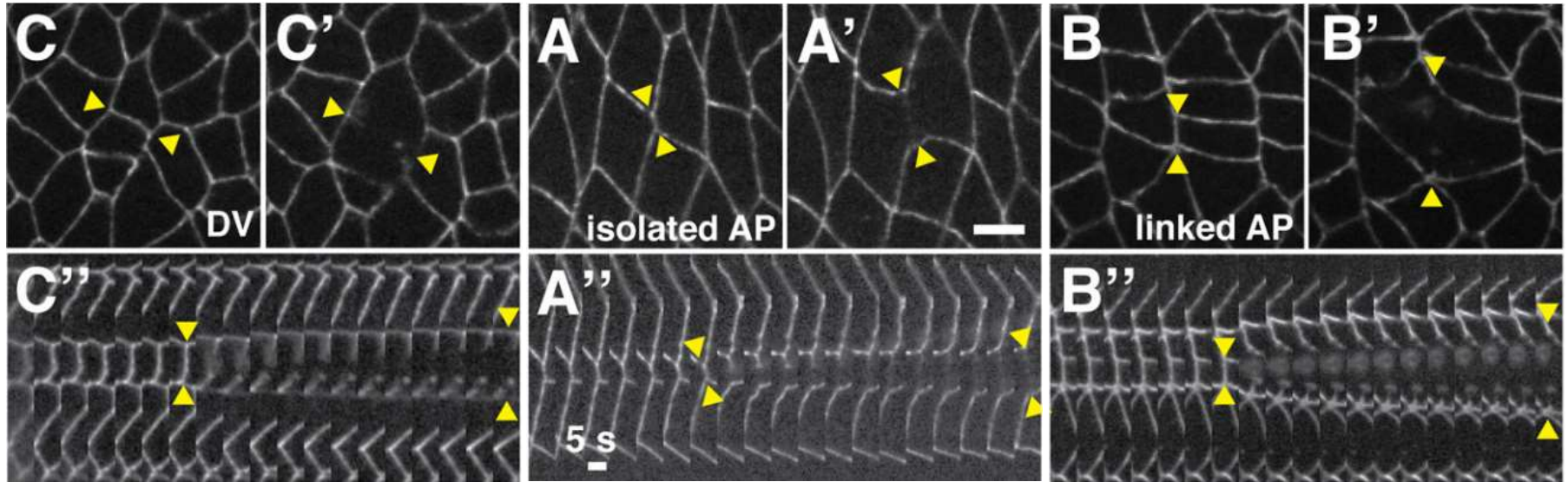
**Polarity gene mutant**



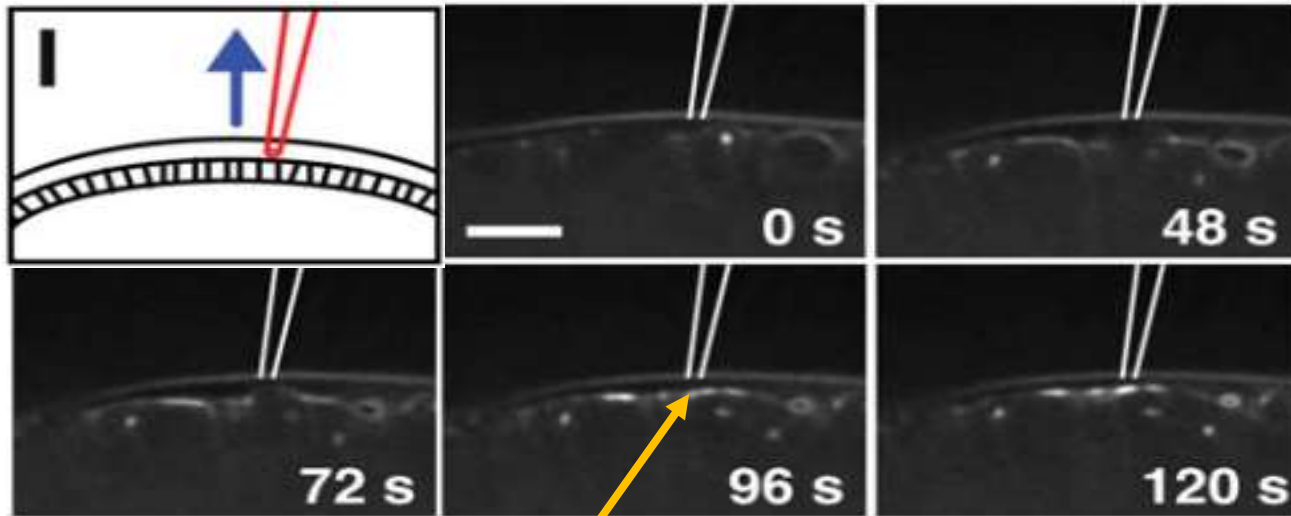
# Adhesion and contractile proteins polarize during cell intercalation



# Contractile proteins increase tension on vertical junctions

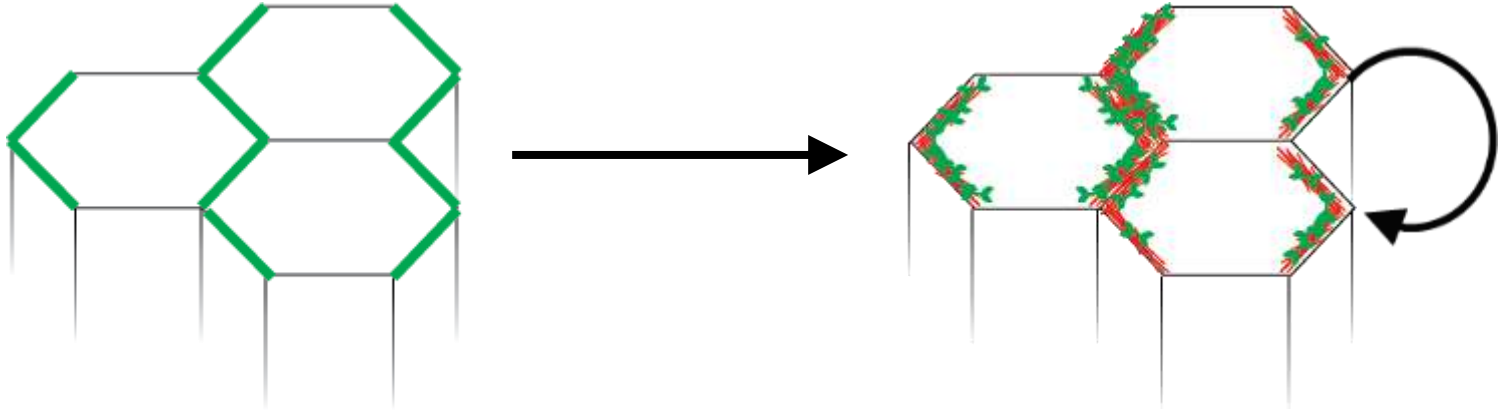


## Tension itself enhances recruitment of Myosin!



Myosin recruitment

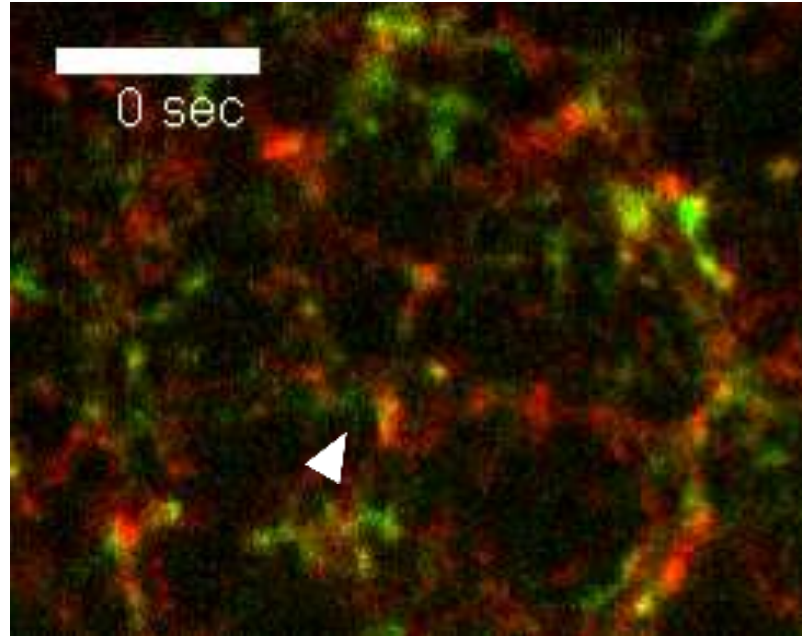
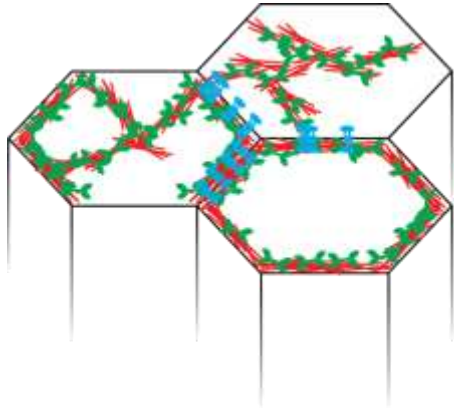
## Molecules and forces are organized across subcellular & multicellular domains



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

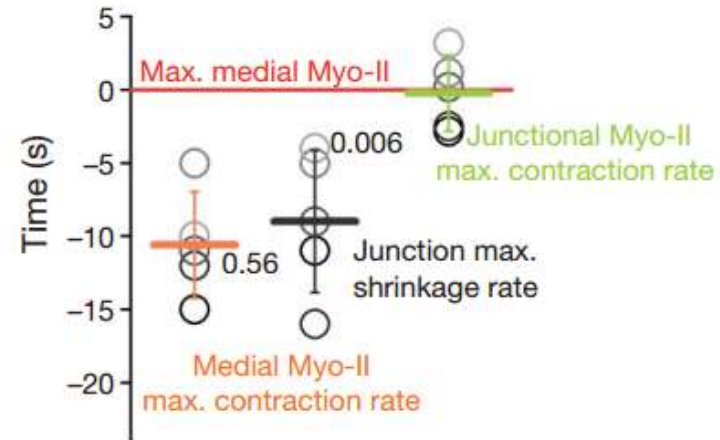
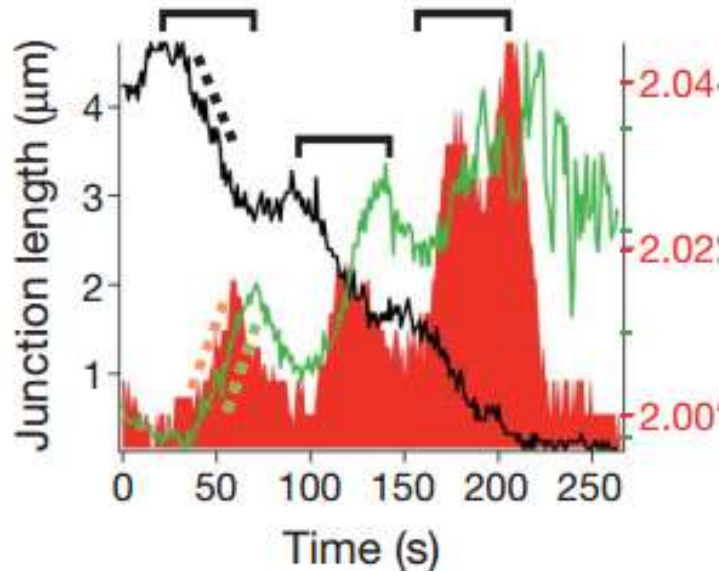
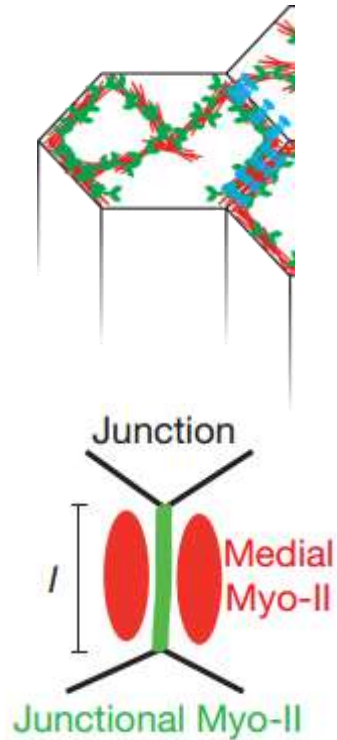


F-actin Myosin

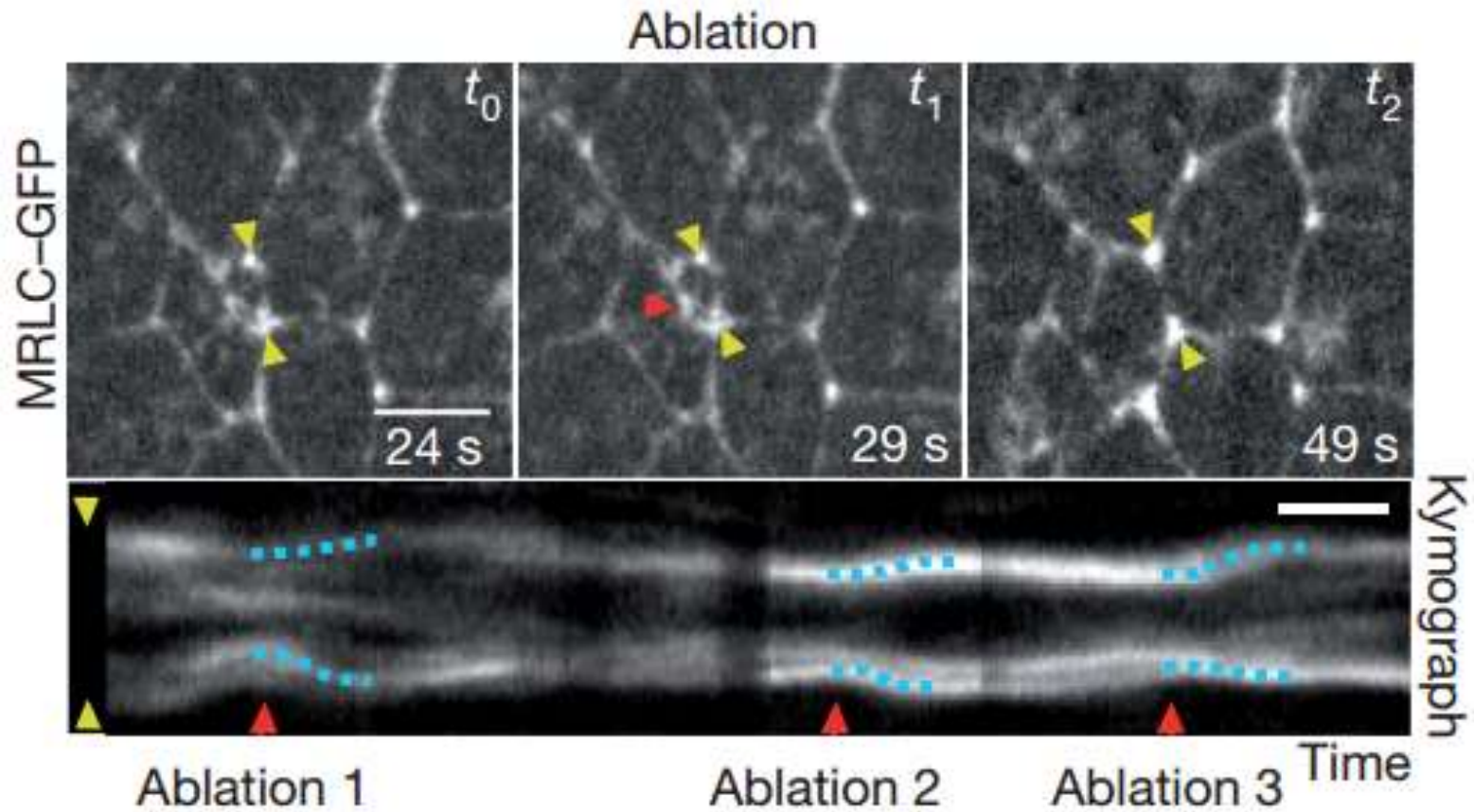




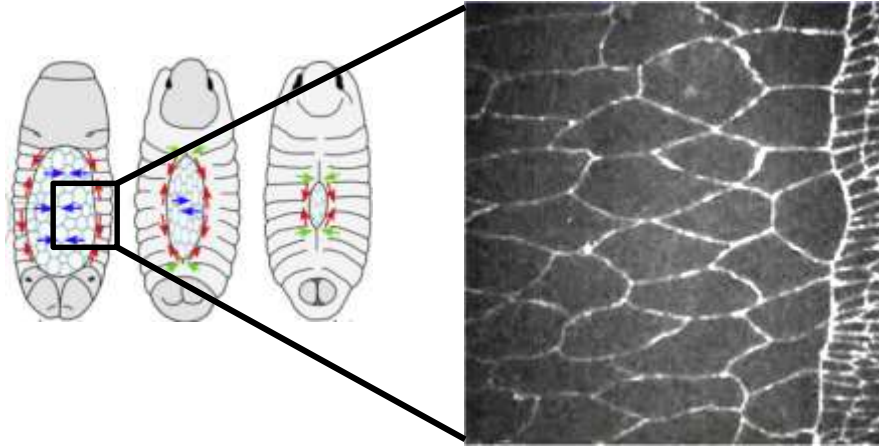
# Cell surface actomyosin correlates with junction shrinking



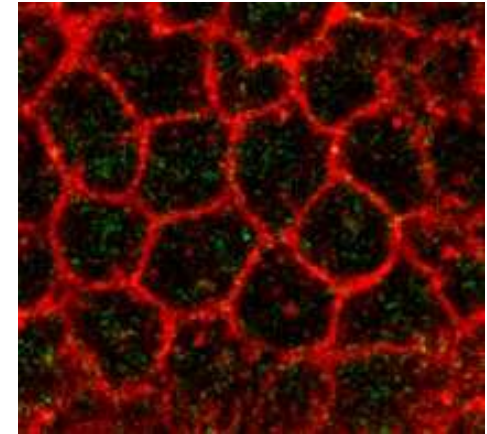
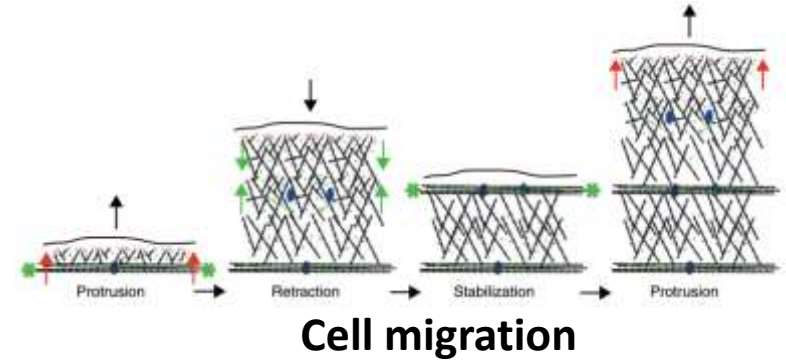
## Laser ablation of surface myosin reverses junction constriction



# Pulsed cell and molecular dynamics are everywhere!

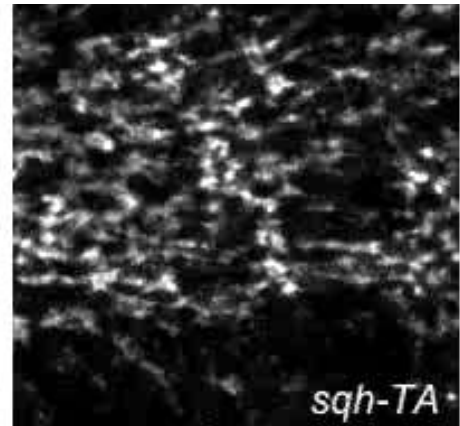
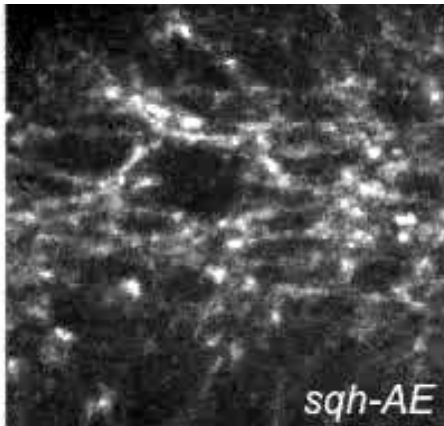
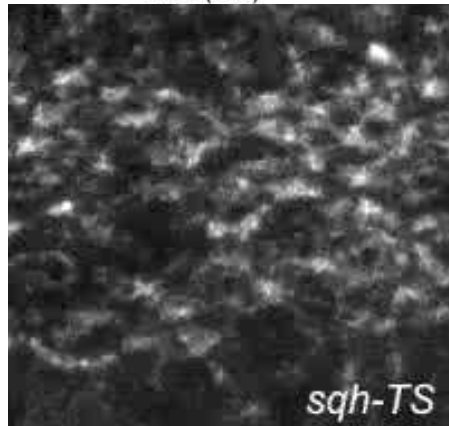
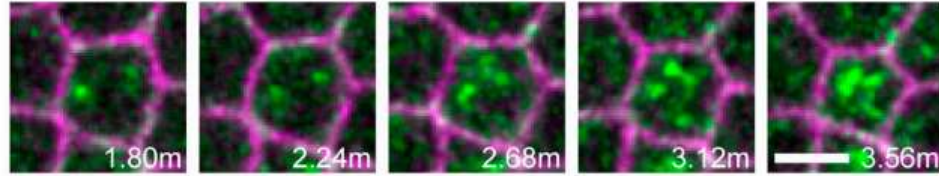
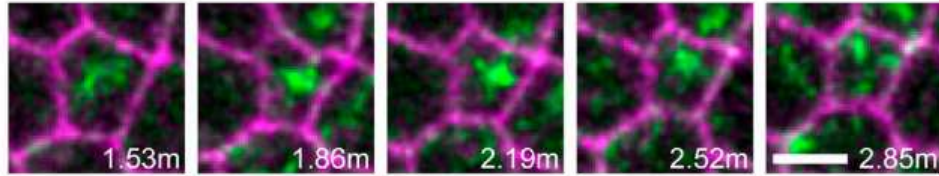
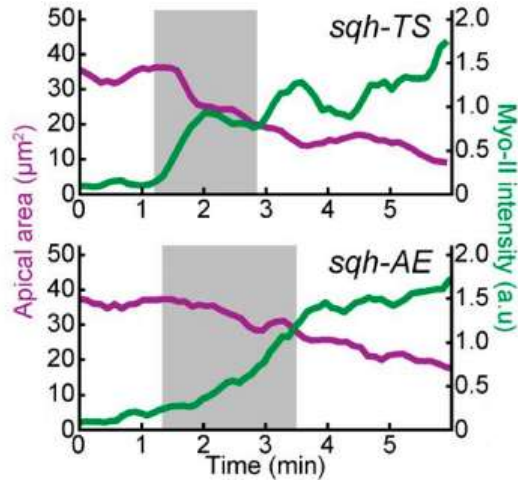
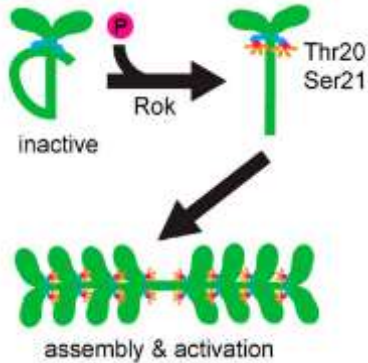


**Dorsal closure/ “wound healing”**



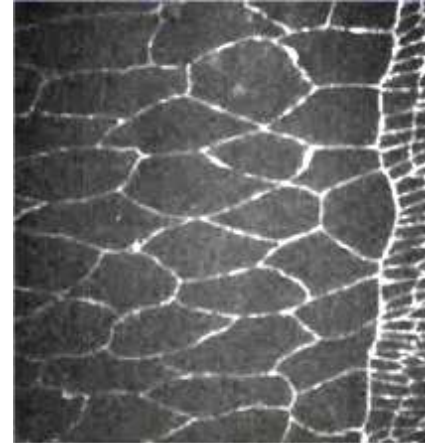
**Gastrulation/EMT**

# Blocking pulsed constriction disrupts cell & tissue dynamics



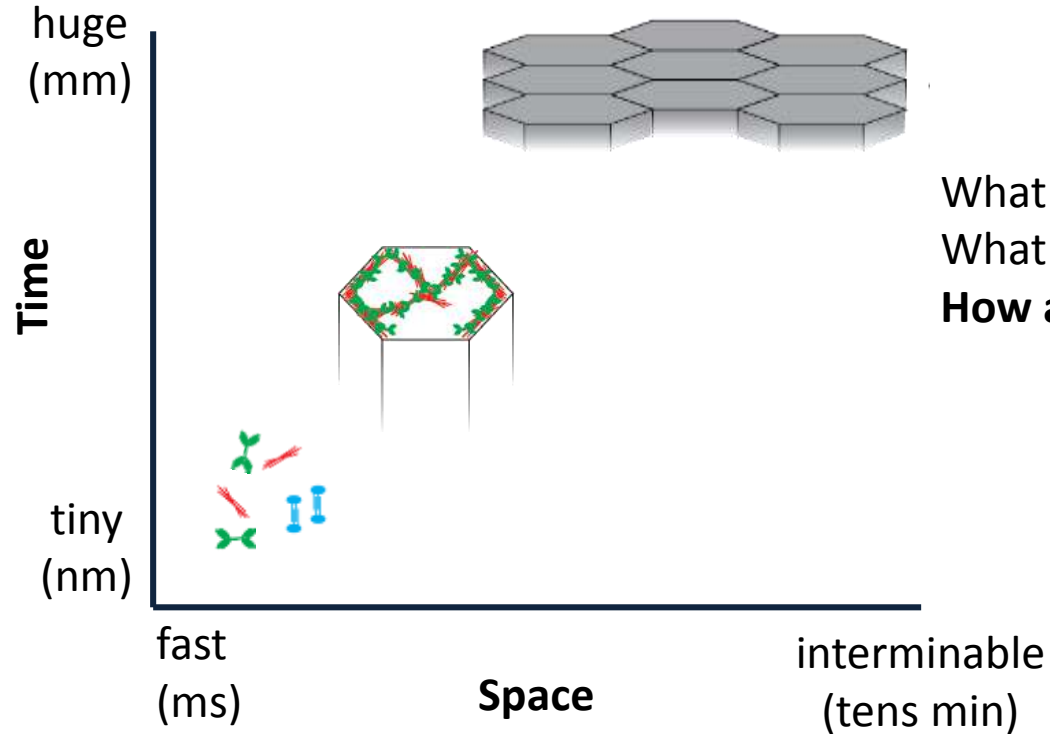
## Why are pulsed dynamics so important?

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



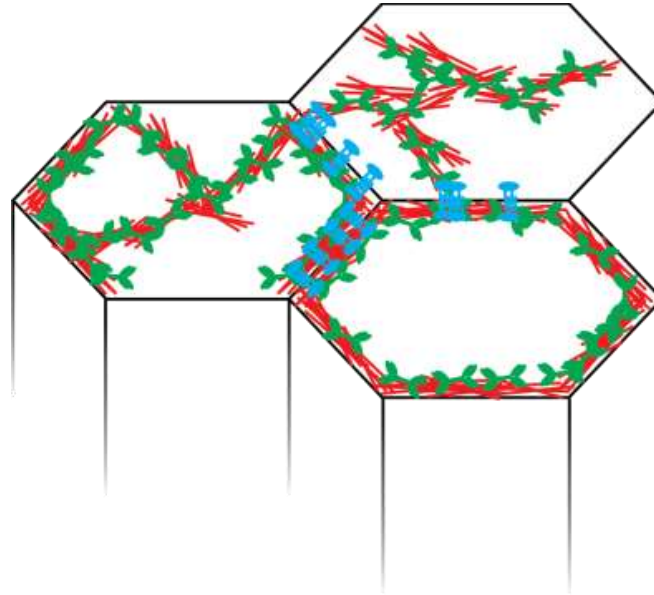


# Morphogenesis is a multiscale problem



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



F-actin



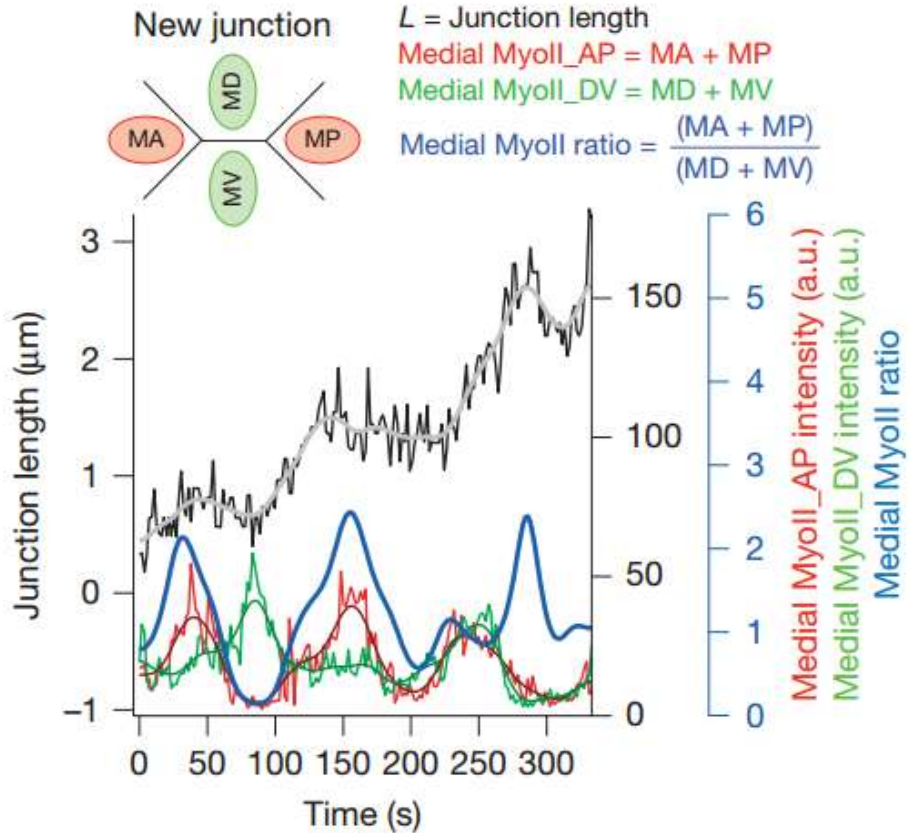
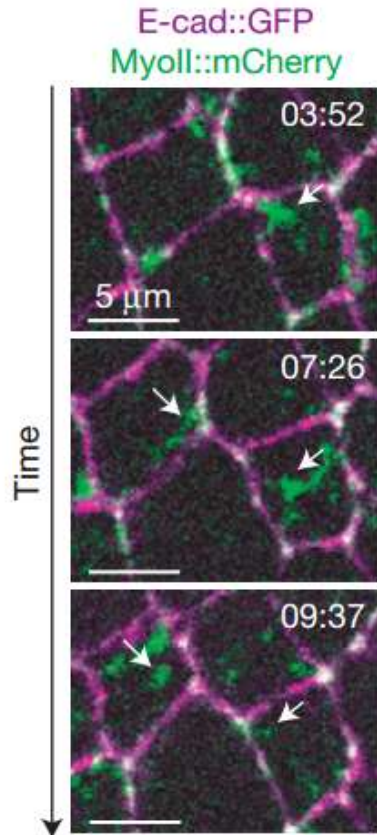
Myosin minifilament



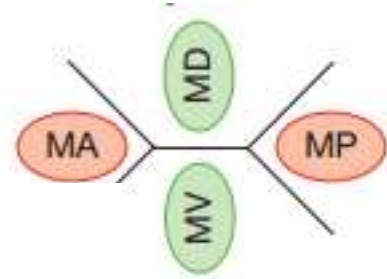
Adhesion complex



# Junction expansion requires help from neighbors

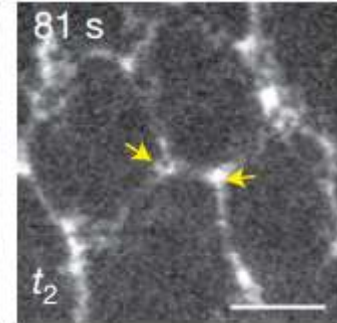
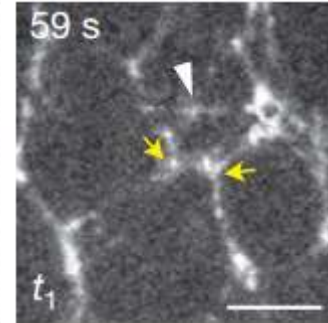
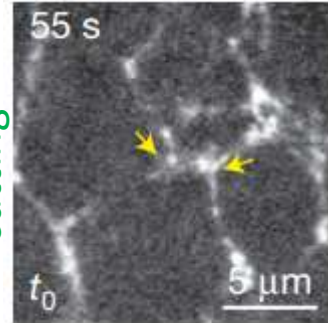


# Junction expansion requires constriction in left-right neighbors

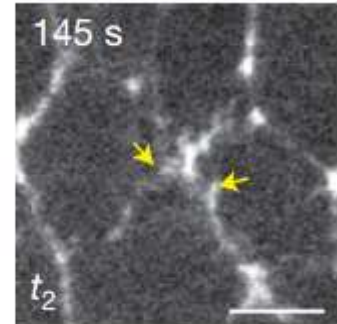
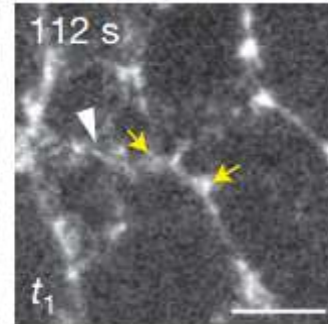
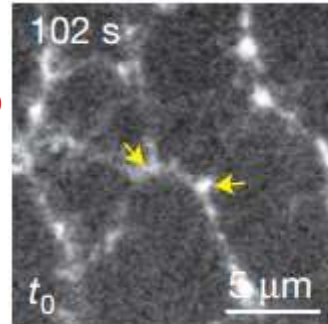


Myosin II::GFP

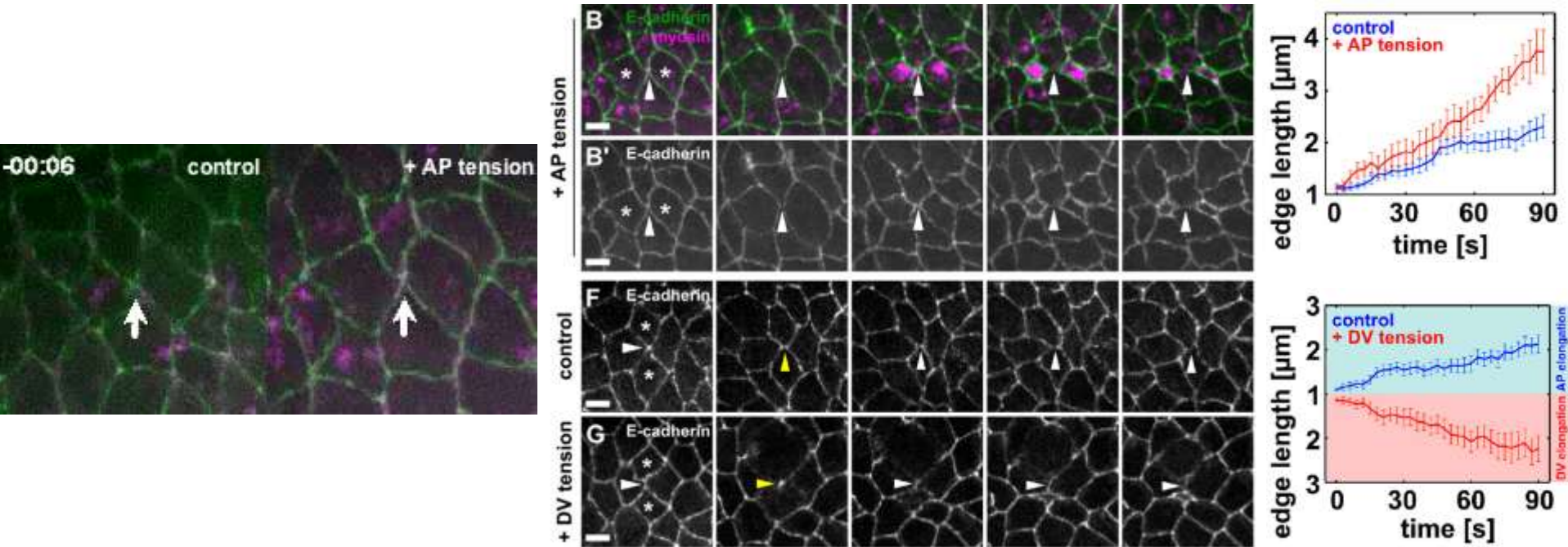
Top-bottom  
cutting



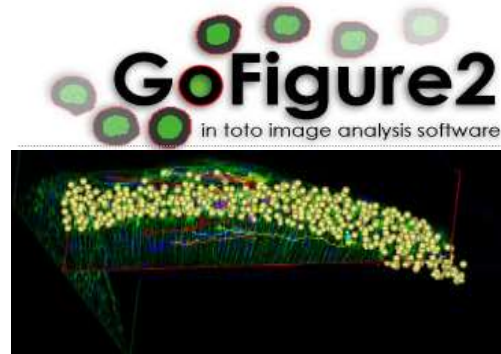
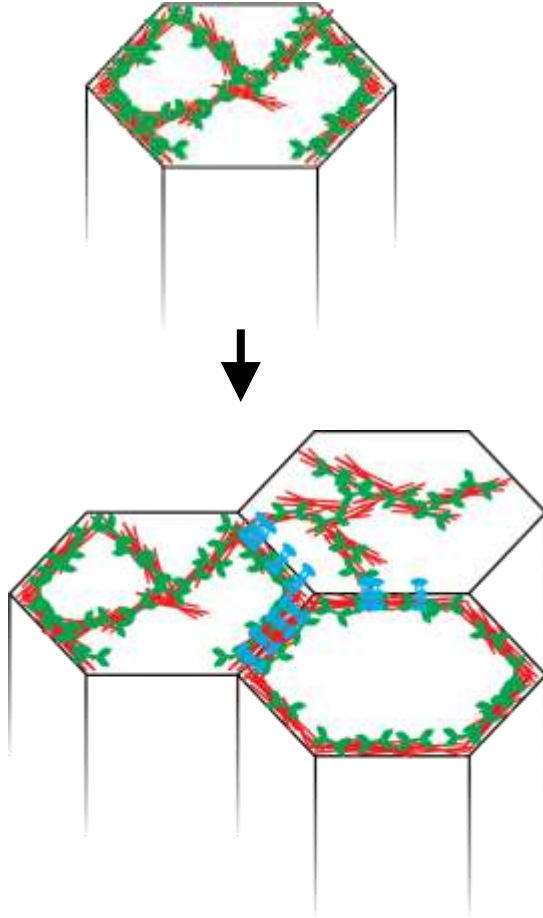
Left-right  
cutting



# Constriction in neighboring cells is sufficient to induce contact remodeling

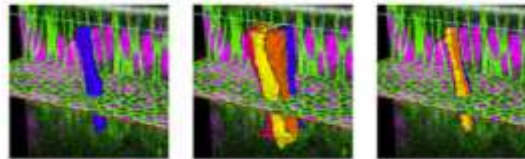


# We can do more biggerer



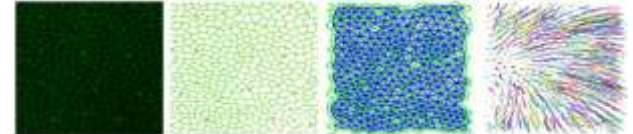
<http://www.gofigure2.org/>

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



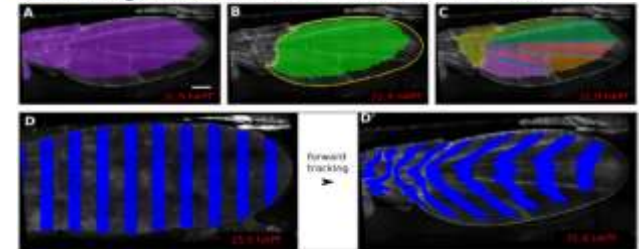
Development 2014 141: 2895

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

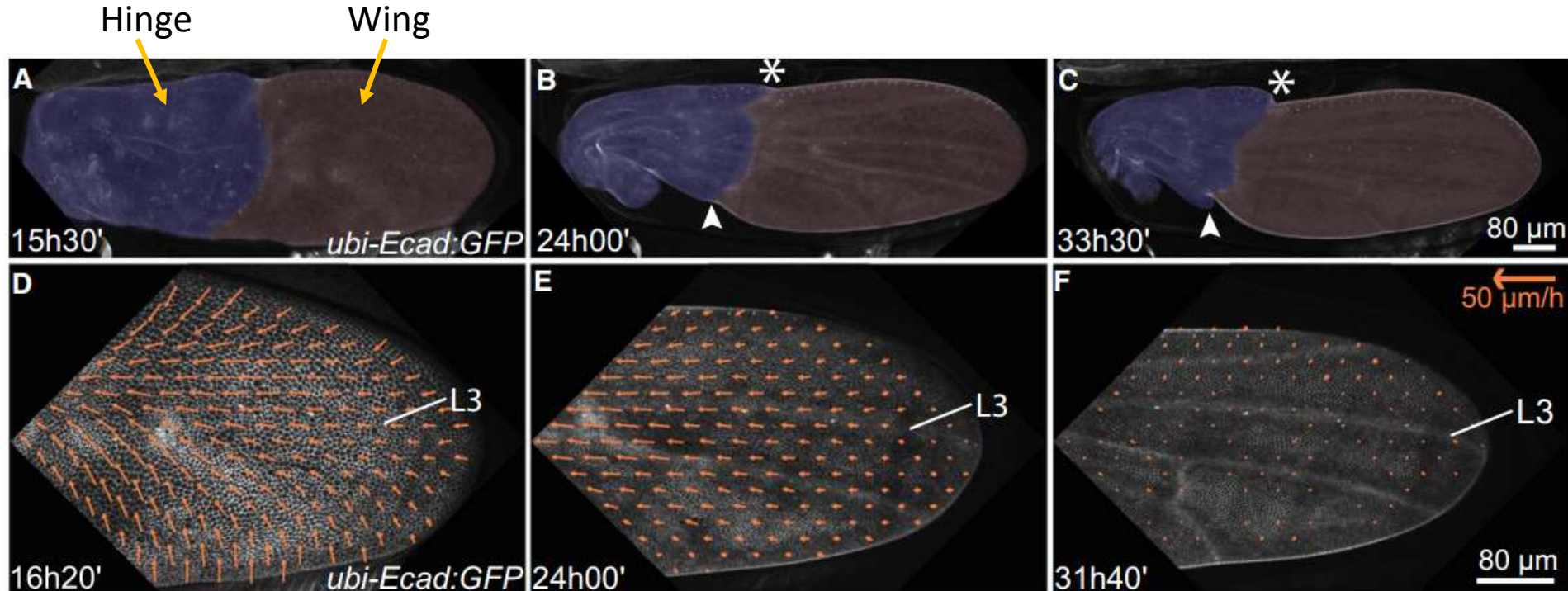
**TissueMiner: A multiscale analysis toolkit to quantify how cellular processes create tissue dynamics**



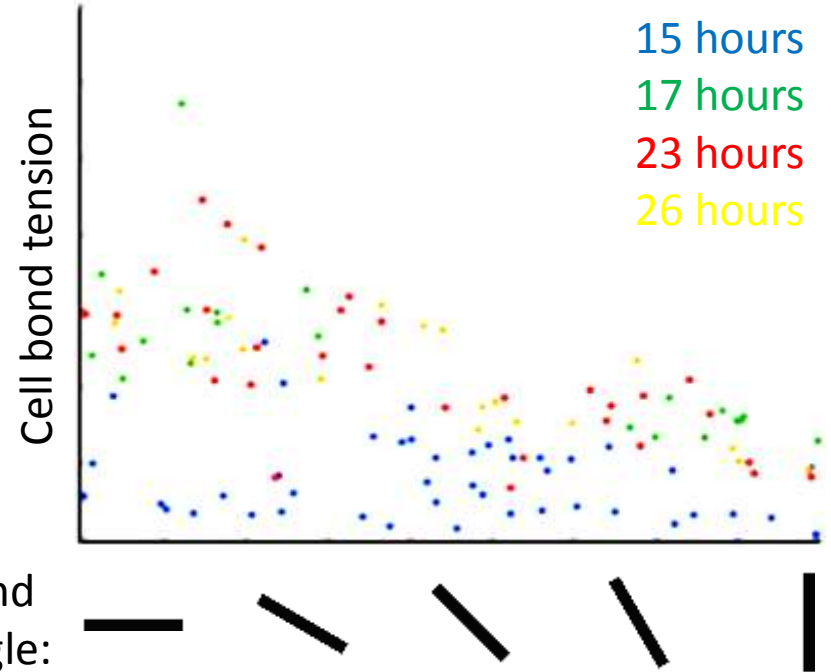
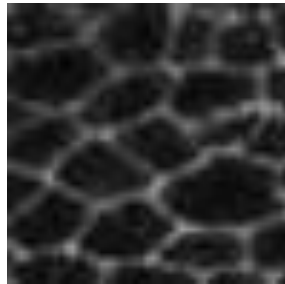
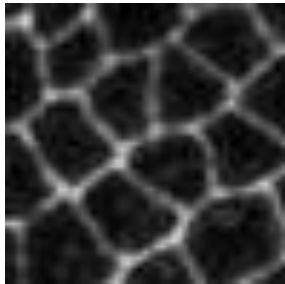
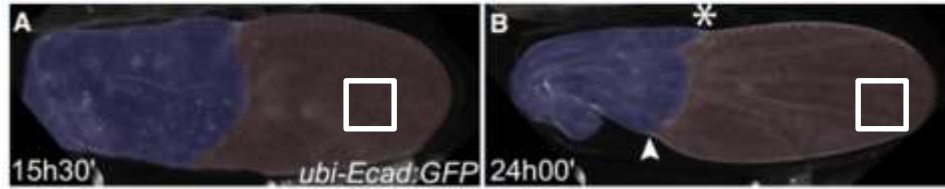
Elife 2016:e14334



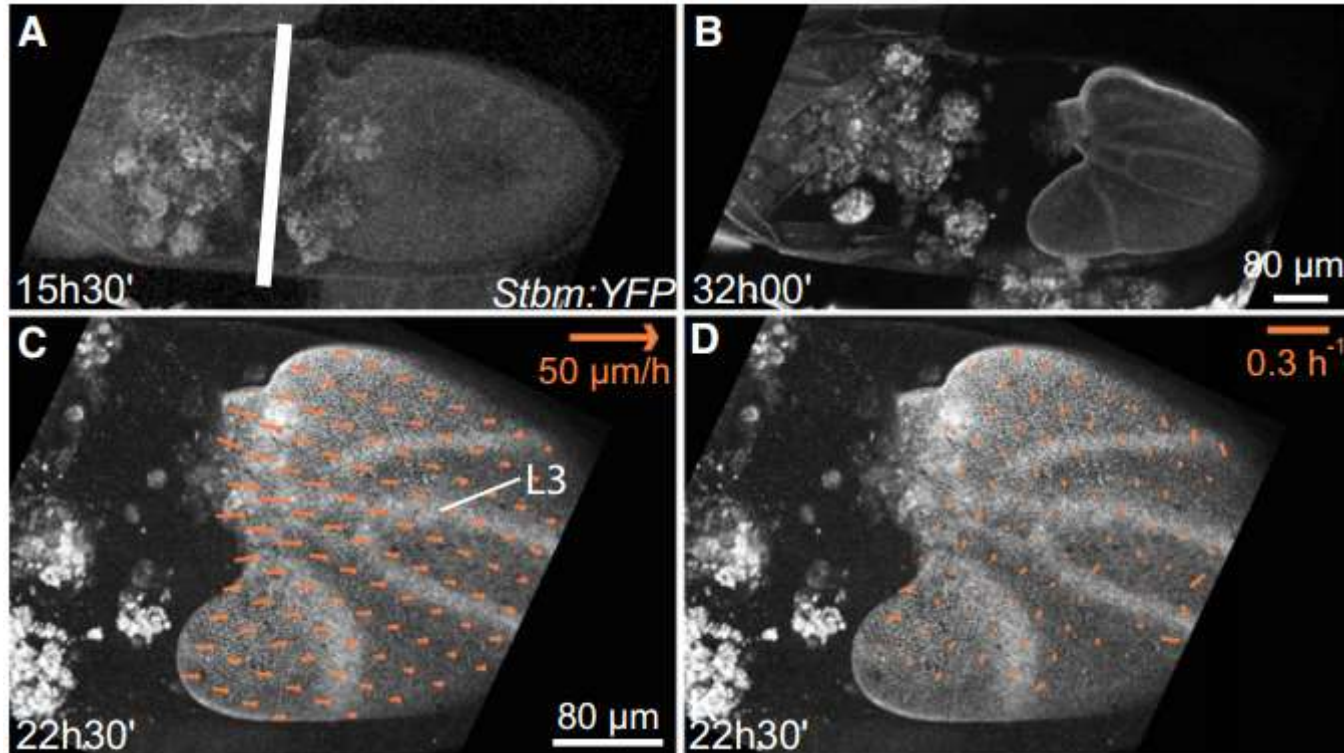
# Mechanical interactions between tissues regulate cell polarity and intercalation



# Cell junction tension suggests hinge pulls on wing

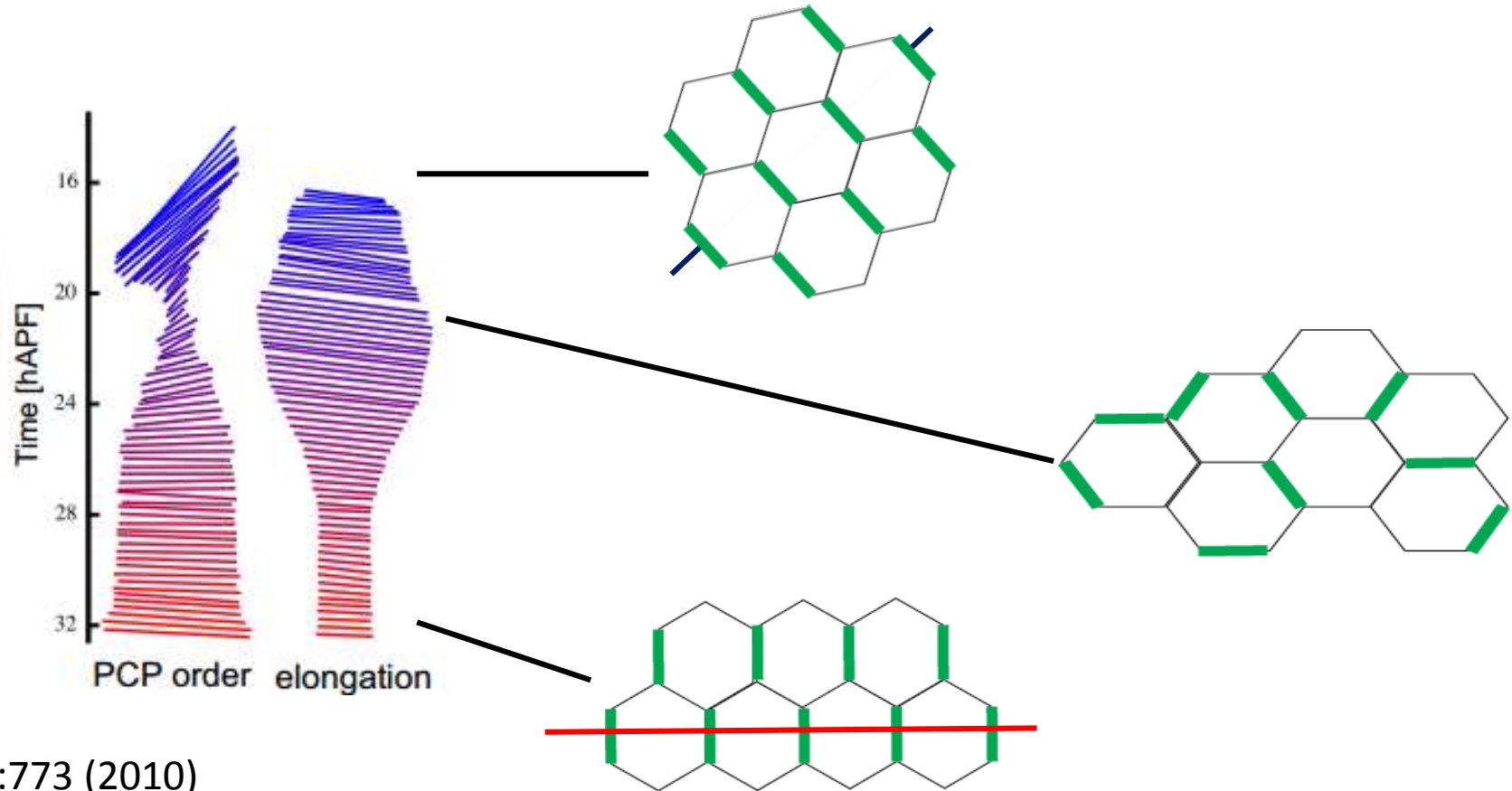


## Blocking tension input prevents tissue polarization, cell flow, and elongation

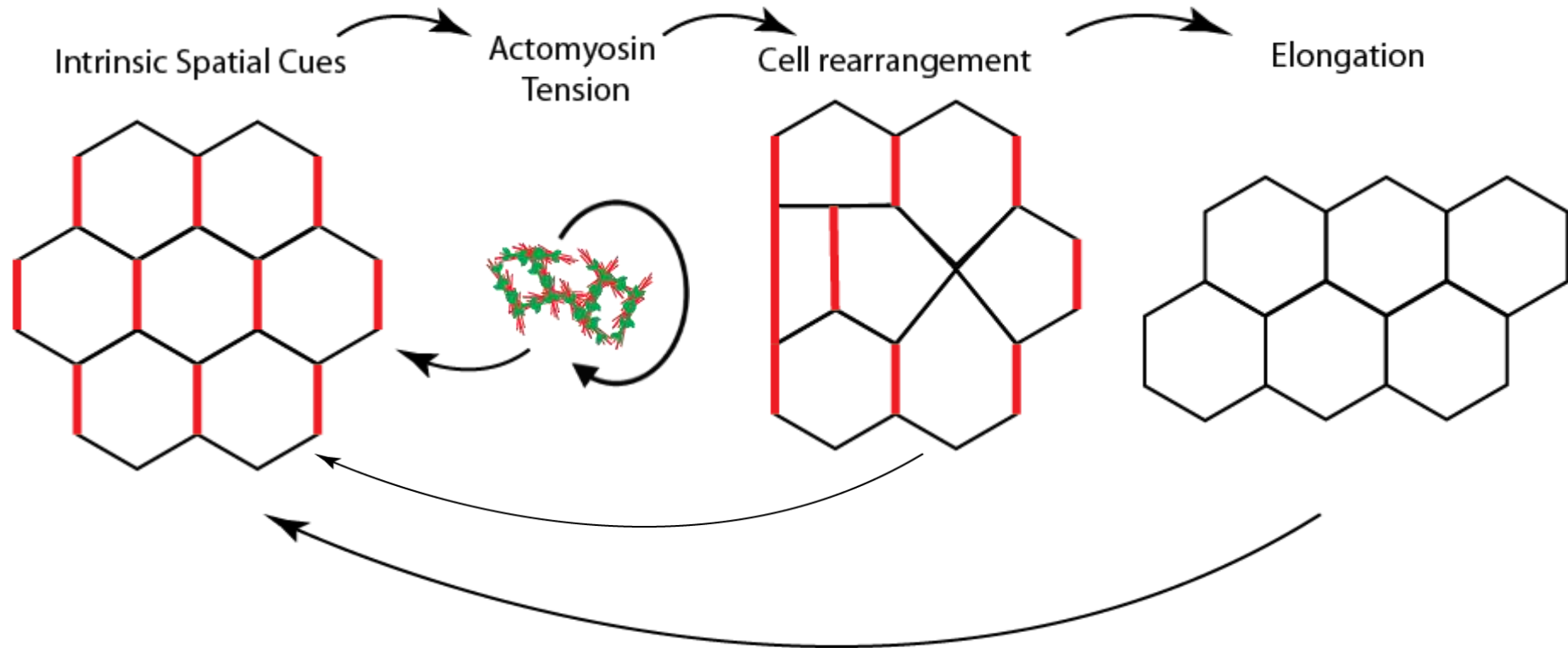




# Tension and cell flow reorganize the wing during elongation



## 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

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