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

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QB Bootcamp
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http://www.dailymail.co.uk/news/article-2603204
How do we get assembled?
Diverse tissue dynamics shape the developing embryo
Mechanical inputs can modulate diverse cell behaviors

Cell Shape

Proliferation

Gene expression
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

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

Part I: The players
What tissue behaviors sculpt the developing organism?

- Bending
- Growth (+/-)
- Shape change/elongation
Tissue elongation: Drosophila germband extension
What cell behaviors drive tissue morphogenesis?

- Patterned proliferation or death
- Cell shape change
- Reorganization or migration
Cell reorganization drives germband extension:
Single cell contact remodeling
Cell reorganization drives germband extension: Multicellular contact remodeling
Morphogenesis is a multiscale process.

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

Part I: The players

Elongation
Rearrangement

Space

Huge (mm)
Tiny (nm)

Time

Short (ms)
Interminable (mins-hrs)
Cell adhesion and actomyosin tension drive cell dynamics

- F-actin
- Myosin minifilament
- Adhesion complex
Adhesion originally considered dominant force
Quantification of adhesion and cortical tension in cells

Adhesion

probe → target

Tension

bead → cell

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

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

Part I: The players

Elongation

Rearrangement

(mainly) Tension
Morphogenesis is a multiscale process

Part II: The game

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

Elongation

Rearrangement

(Mainly) tension

Space

 Huge (mm)

 tiny (nm)

 Time

 Short (ms)

 Interminable (mins-hrs)
Cells can systematically polarize

Control

Polarity gene mutant

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!
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.
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

References:
Cell 137:1331 (2009)
COGD 21:671 (2011)
Blocking pulsed constriction disrupts cell & tissue dynamics

[Diagram showing molecular interactions and cellular responses with graphs and images of cellular structures]
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
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

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Cell junction tension suggests hinge pulls on wing

Cell bond tension

Bond angle:

15 hours  
17 hours  
23 hours  
26 hours  

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?
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