成長する組織の力学過程
Mechanical control of epithelial pattern formation

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Acknowledgement

Atsushi Miyawaki (RIKEN BSI)
RIKEN BSI-Olympus Collaboration Center

Shuji Ishihara, Kunihiko Kaneko (Univ. of Tokyo)

Tomoyuki Higuchi, Kazuyuki Nakamura (Inst. Math. Stat.)

Tadashi Uemura, Toshiyuki Harumoto (Kyoto Univ.)

Hideki Oda (BRH)

Roger Karess (CNRS)

Funding:
JST PRESTO (S. Ishihara)
RIKEN SPDR program, RIKEN Incentive Research Grant and Grant-in aid for young scientists (K. Sugimura)
Pressure of a cell and tension of an edge

A top view of an epithelial sheet

A side view of an epithelial sheet

Myosin, Cortical actin cable

Cadherin

Balance of forces at each vertex

Pressure

Tension

Cut an edge!
Questions

1. How does mechanical force that drives tissue deformation emerge in light of the molecular properties of the constituent cells?

2. How does the generated forces regulate the correct patterning of a tissue?

Tissue morphogenesis

Germband elongation in the *Drosophila* embryo

*Bertret et al. (2004)*

Cellular behaviors

Cell Rearrangement

Molecular dynamics

Myosin Cadherin

Lecuit lab, Zallen lab etc.
Measuring dynamics of forces \textit{in vivo} is very difficult.

A relative value of tension measured by laser cutting:

- 0 sec
- 15 sec
- 30 sec
- 45 sec

Destroy cortical actin network

“invasive”

Vertices move faster $\rightarrow$ Larger tension

Balance of forces at each vertex:

- Pressure
- Tension

Cytoplasm, microtubule

Myosin, Cortical actin, Cadherin

No appropriate method to directly and repeatedly measure forces in a multi-cellular tissue.

Cut an edge!
1. Our new method to estimate forces
2. Forces in the *Drosophila* wing
3. How forces regulate epithelial pattern formation
Outline of our new method to estimate forces

**Input:** image of cells

**Output:** “relative” values of forces

### Position of vertex

- $v_1(x_1, y_1)$,
- $v_2(x_2, y_2)$,

### Conditions

$< \text{unknowns}$

### Balance of Forces at Each Vertex

\[
\begin{align*}
\alpha^1 T_1 + \alpha^2 T_2 + \alpha^3 T_3 + \beta^1 P_1 + \beta^2 P_2 + \beta^3 P_3 &= \gamma \dot{X}_0 \\
\alpha^1 T_1 + \alpha^2 T_2 + \alpha^3 T_3 + \beta^1 P_1 + \beta^2 P_2 + \beta^3 P_3 &= \gamma \dot{Y}_0 \\
T_1^x &= \frac{x_1 - x_0}{||\vec{x} - \vec{x}||} \times T_1 \\
P_1^x &= \frac{y_2 - y_1}{2} \times P_1
\end{align*}
\]

### Inverse Problem

“minimize $F = |Ap - \gamma V|^2 + \mu |Bp - f|^2$”

- $\mu$ is determined by Bayesian statistics
- Positive tension

- Pressure & tension
- Drag

- Expected features of system $\mu$
Indefiniteness and its physical interpretation

- N+R cells, v+R vertices, and M+2R edges
- If all vertices are 3-way junction, M=(3/2)v
- Note Euler’s theorem v-M+N=1

Conditions: (num. of vertex) × 2 = 2(v+R)
Unions: (num. of cell + edge) = M+N+3R

\[ R+1 \text{ indefiniteness} \]

$\text{I} \text{ definiteness by hydrostatic pressure}$

\[ A\vec{p}_{iso} = 0, \]
\[ \vec{p}_{iso} = (0, \ldots, 0, 1, \ldots, 1) \]

$\text{R} \text{ definiteness by boundary condition}$

Estimate relative values of forces

\[ P_i = c p_i + p_{hs}, T_j = c t_j \]

Becomes less significant as N increases
True and estimated forces in artificial data

**Numerical simulation:**

\[ U = \sum_{Cell:i} U_e(A_i) + \sum_{Contact:j} U_a(l_j) + \sum_{Cell:i} U_c(L_i) \]

Cell: \( i \)

Area

elasticity

Cell adhesion,

Contraction

Cortical

elasticity

Calculate true values of forces

**Estimation:**

Estimated values

- pressure
- tension

※ The prior (positive tension) that we adopted yielded the best results among priors tested (e.g. L2-norm, spatial smoothness).
Advantages of our new method

**Input:** image of cells

**Output:** distribution of forces

- Single cell resolution
- Applicable to a tissue-scale
- Noninvasive
- No assumption of forms of the potential energy
**Drosophila** epithelial tissues (notum and wing)

**Larva**

Wing disc of *Drosophila* 3rd instar larva

**Embryo**

http://flybase.org/

**Pupa**

Wing at 15.5 hr APF (after puparium formation)

**Adult**

Wing
Application to the *Drosophila* pupal wing

**Input:** image of cells

![Image of cells](image)

**Output:** “relative” values of forces

![Color map of forces](image)

**balance of forces at each vertex**

\[ \vec{A} p = \gamma \vec{V} \]

- pressure & tension
- drag

\[ \vec{p} = (T_i, T_M, P_1, \ldots, P_N) \]

\[ \vec{V} = \vec{X} \]

Bayesian formulation

\[ \nabla a(x_a, y_a), \quad \nabla b(x_b, y_b), \]

get positions of vertices
The summary of results

1. Our new method to estimate forces

2. Forces in the *Drosophila* wing
   - stronger tension along the PD axis
   - nature of tension: external force stretching the wing
   - “force-generating” and “force-responding” properties of myosin

3. How forces regulate epithelial pattern formation
   - hexagonal packing in the wing and notum
   - more strongly biased tensile force -> more hexagons?
   - biased external force accelerates hexagonal pattern formation both *in silico* and *in vivo*
**Anisotropic external force instructs directional arrangement of cells for efficient hexagonal packing**

**Anisotropic stretch**

Anisotropic tensile forces may avoid the mismatch in orientations of small group of cells by setting the unique axis of cell rearrangement.

**Control and isotropic expansion**

This mismatch in orientations of small group of cells produces non-hexagonal cells.

**Aligned!!**

Faster relaxation of the energy

**Mismatch!!**

Slower relaxation of the energy
Mechanical basis of pattern formation: feedback regulations that connects molecular, cellular, and tissue dynamics

Tissue
- Stress field of a tissue
- Hexagonal packing

Cell
- Junctional remodeling

Molecule
- Myosin

Low Tension
High Tension

100µm