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

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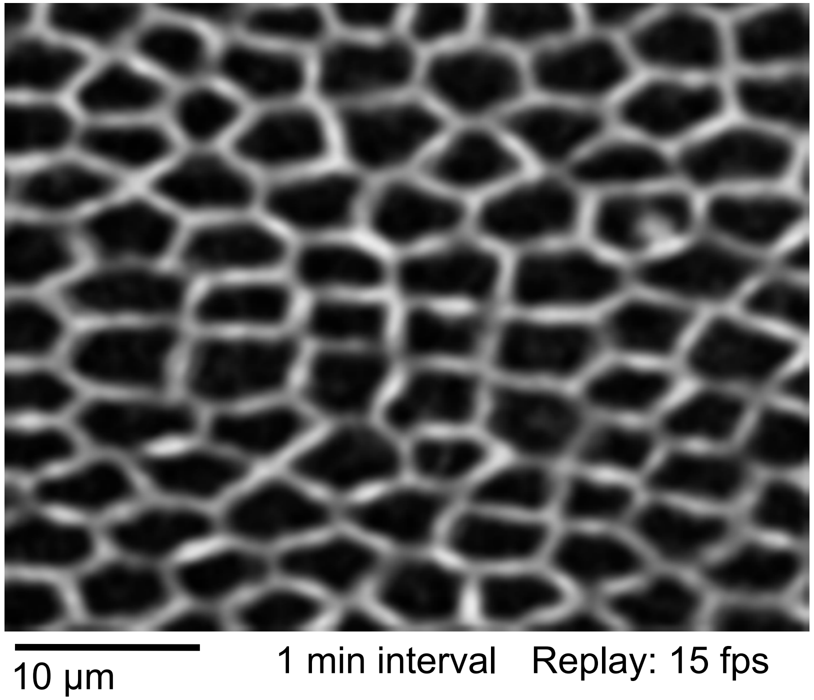
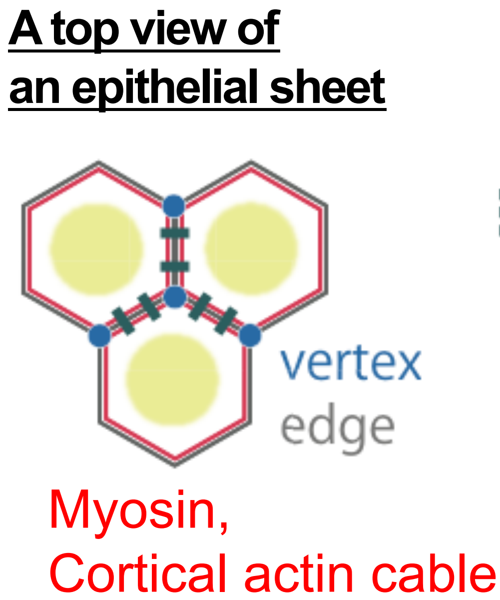
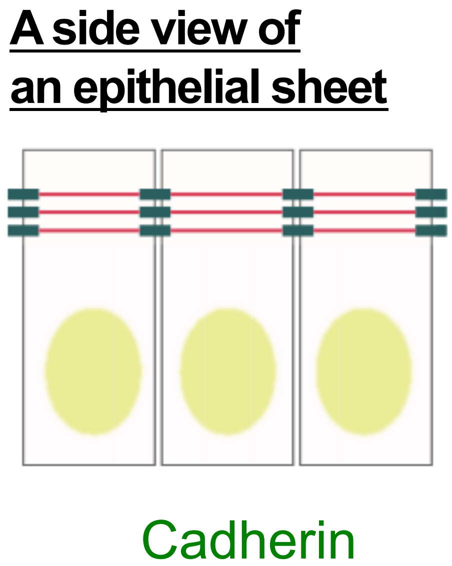
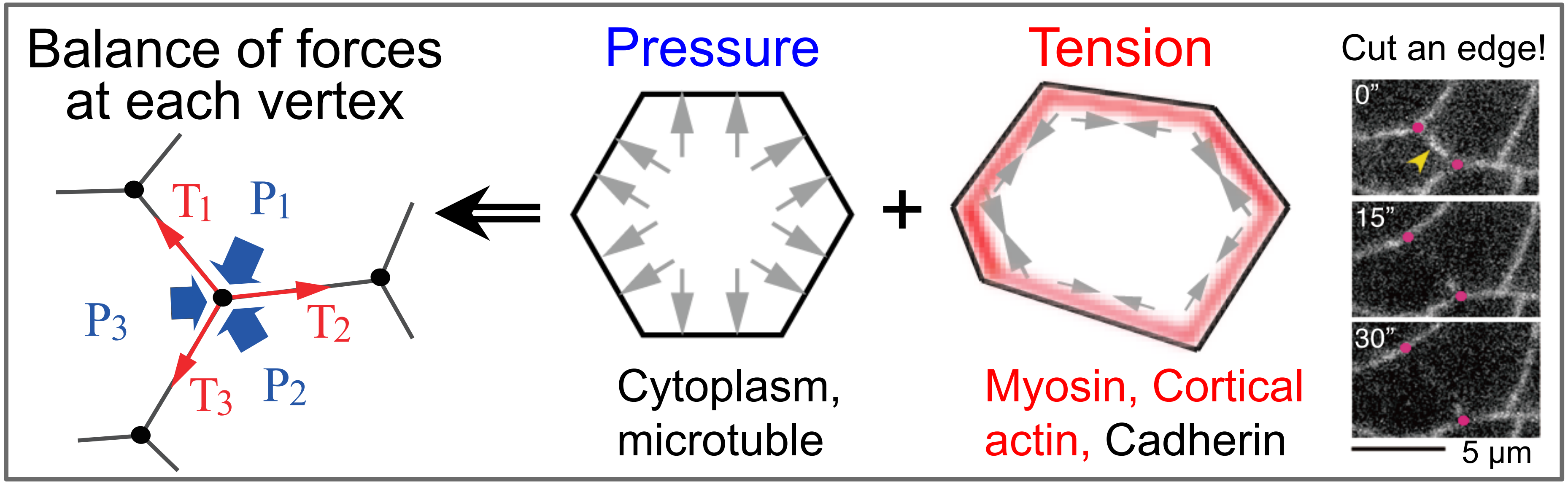
Pressure of a cell and tension of an edge





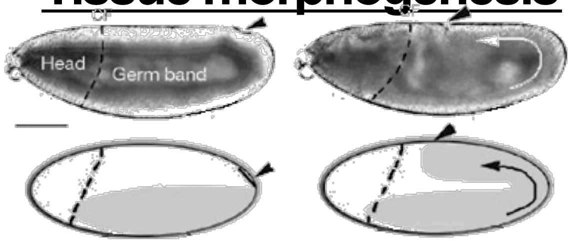




Questions *Morphology ⇔ Mechanical force*

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?**

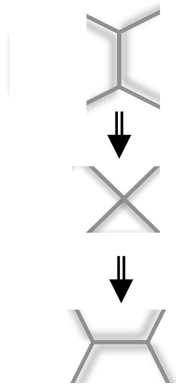
Tissue morphogenesis



Germband elongation in the *Drosophila* embryo

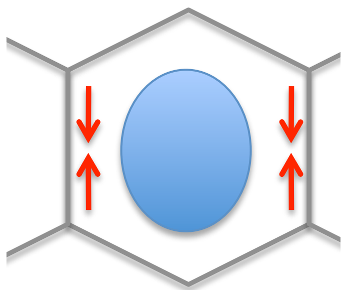
Bertret et al. (2004)

Cellular behaviors



Cell Rearrangement

Molecular dynamics

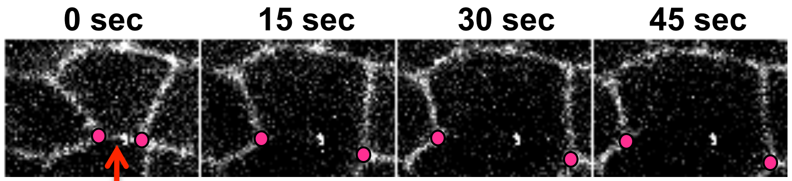


Myosin Cadherin

Lecuit lab, Zallen lab etc.

Measuring dynamics of forces *in vivo* is very difficult

A relative value of tension measured by laser cutting



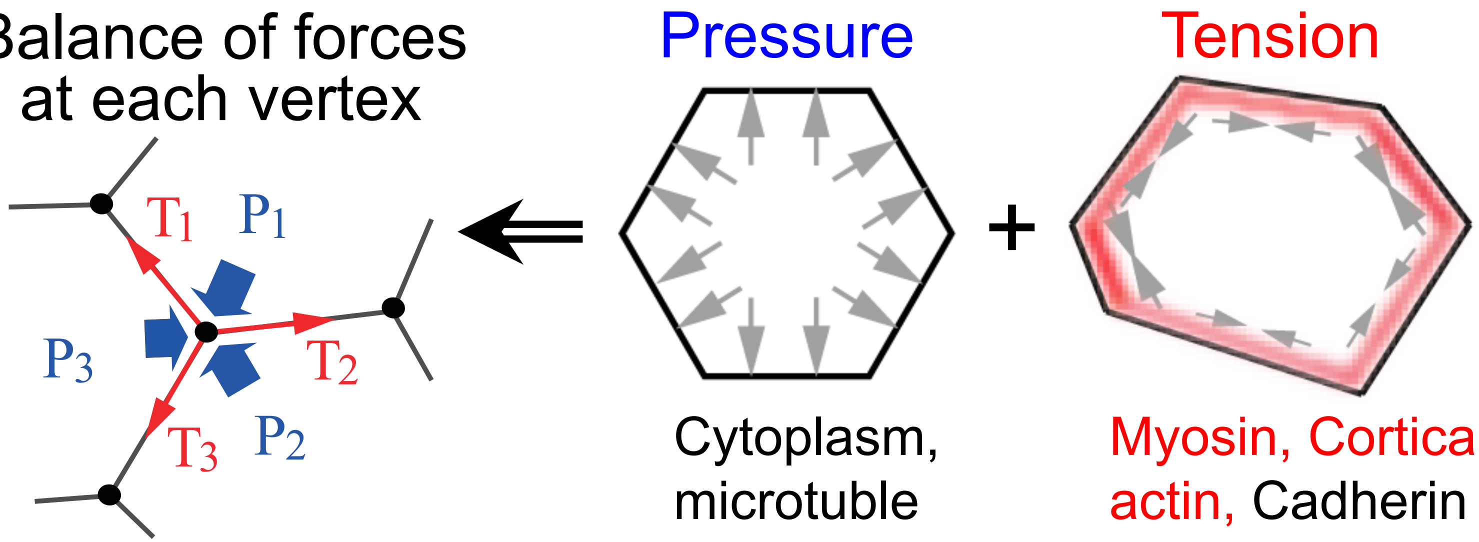
Destroy cortical actin network

“invasive”

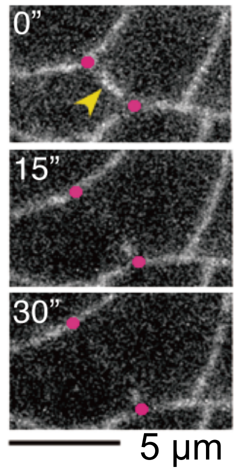
Vertices move faster ⇒ Larger tension

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

Balance of forces at each vertex

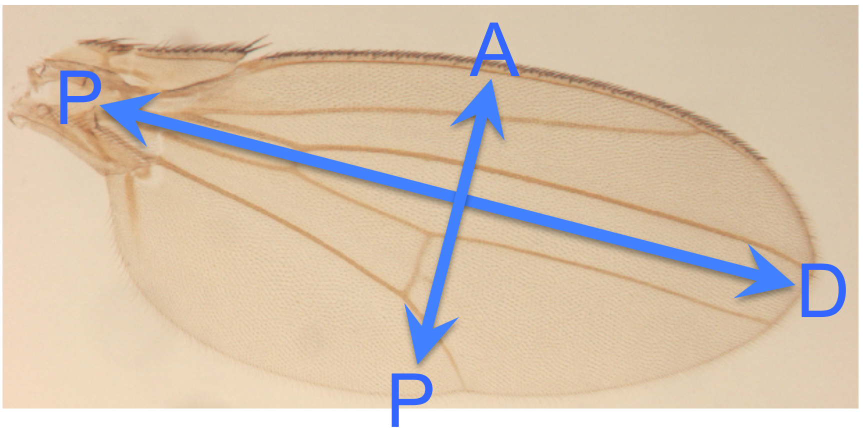


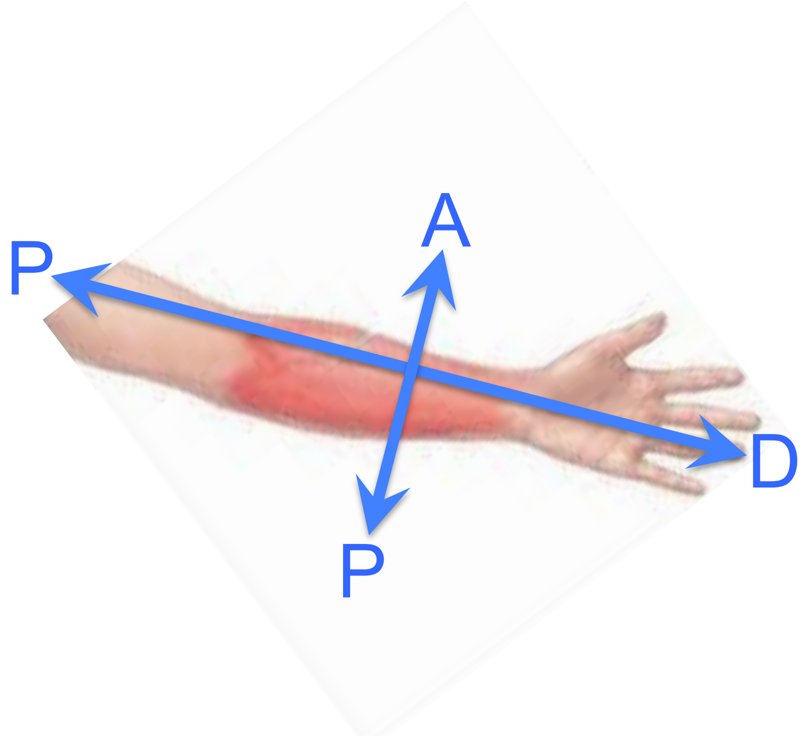
Cut an edge!



Outline

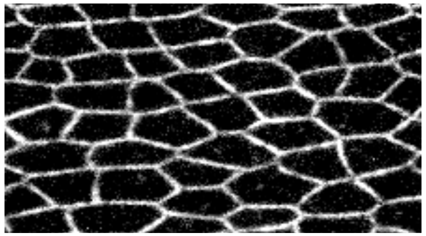
1. Our new method to estimate forces
2. Forces in the *Drosophila* wing
3. How forces regulate epithelial pattern formation

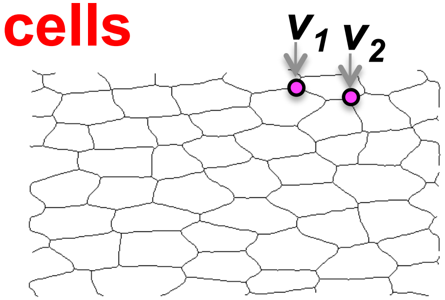




Outline of our new method to estimate forces

Input: **image of cells**



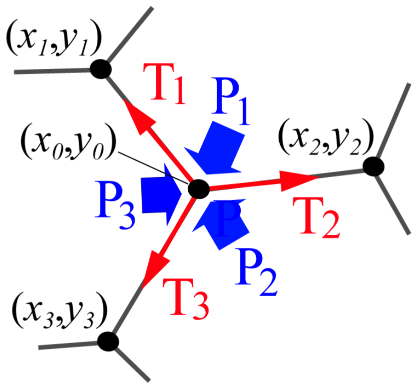


position of vertex

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

conditions < unknowns

balance of forces at each vertex



$$\alpha_x^1 T_1 + \alpha_x^2 T_2 + \alpha_x^3 T_3 + \beta_x^1 P_1 + \beta_x^2 P_2 + \beta_x^3 P_3 = \gamma \dot{X}_0$$

$$\alpha_y^1 T_1 + \alpha_y^2 T_2 + \alpha_y^3 T_3 + \beta_y^1 P_1 + \beta_y^2 P_2 + \beta_y^3 P_3 = \gamma \dot{Y}_0$$

$$T_1^x = \frac{x_1 - x_0}{\|\vec{x}_1 - \vec{x}_0\|} \times T_1 \qquad P_1^x = \frac{y_2 - y_1}{2} \times P_1$$

$$A\vec{p} = \gamma \vec{V}$$

pressure & tension — drag

$$\vec{p} = (T_1 \cdots, T_M, P_1, \cdots, P_N)$$

$$\vec{V} = \dot{\vec{x}}$$

Inverse problem

" minimize

$F = |Ap - \gamma V|^2 + \mu |Bp - f|^2$ "

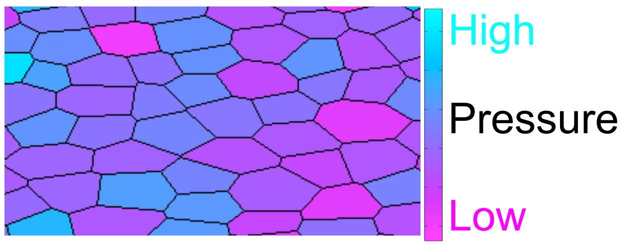
Expected features of system

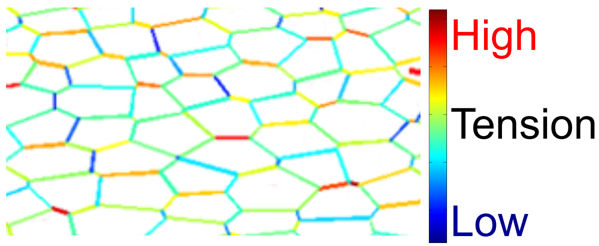
II

Positive tension

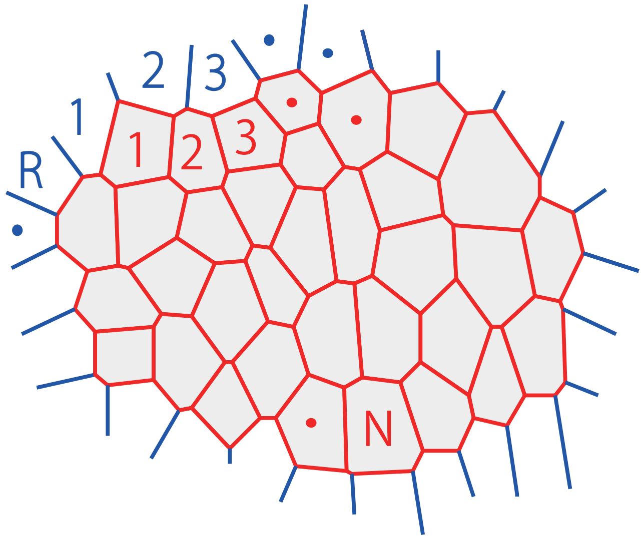
μ is determined by Bayesian statistics

Output: **"relative" values of forces**





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 vetex)×2 = 2(v+R)
Unknowns: (num. of cell + edge) = M+N+3R

⇒ **$R+1$ indefiniteness**

■ **1 indefiniteness by hydrostatic pressure** ⇒ **Estimate relative values of forces**

$$A\vec{p}_{iso} = 0,$$

$$\vec{p}_{iso} = (0,\cdots,0,1,\cdots,1)$$

$$P_i = cp_i + p_{hs}, T_j = ct_j$$

■ **R indefiniteness by boundary condition** ⇒ **Becomes less significant as N increases**

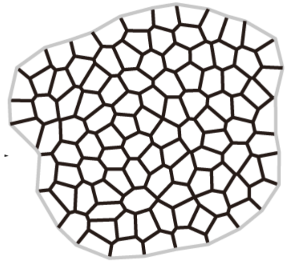
True and estimated forces in artificial data

Numerical simulation :

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

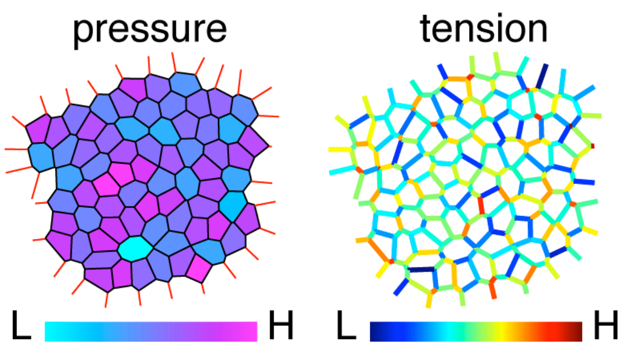
Area elasticity | Cell adhesion, Contraction | Cortical elasticity

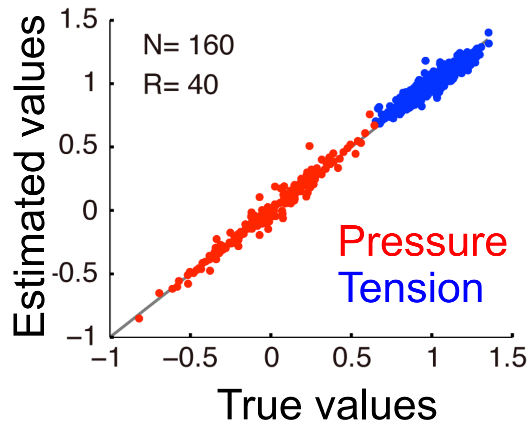
係数を振る



Calculate true values of forces

Estimation :





※ 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**

⇓

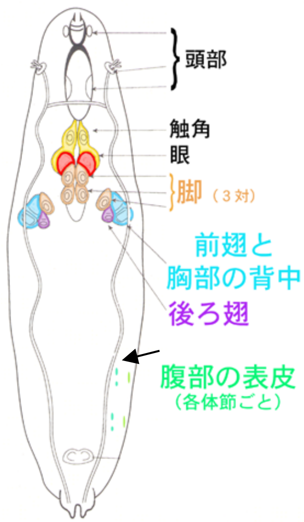
Output: **distribution of forces**

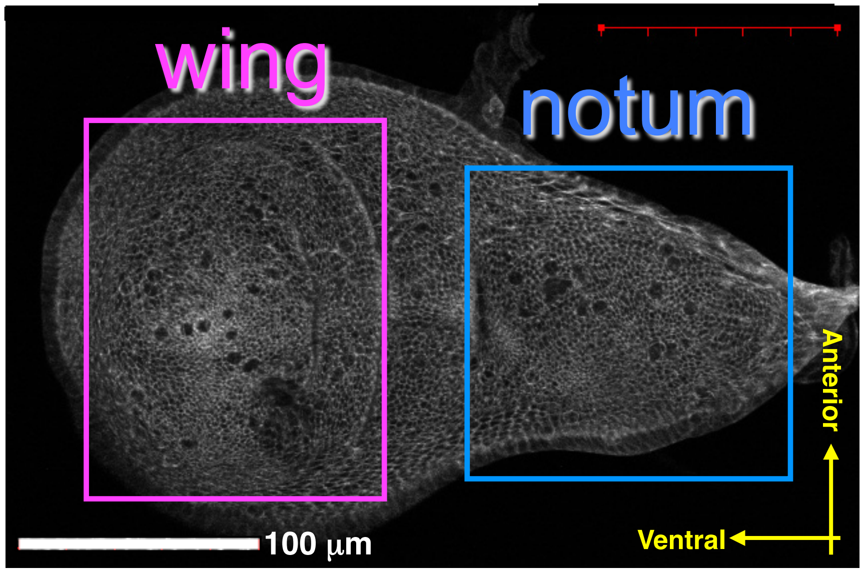
- **Single cell resolution**
- **Applicable to a tissue-scale**
- **Noninvasive**
- **No assumption of forms of the potential energy**

Drosophila epithelial tissues (notum and wing)

Larva

Wing disc of *Drosophila* 3rd instar larva

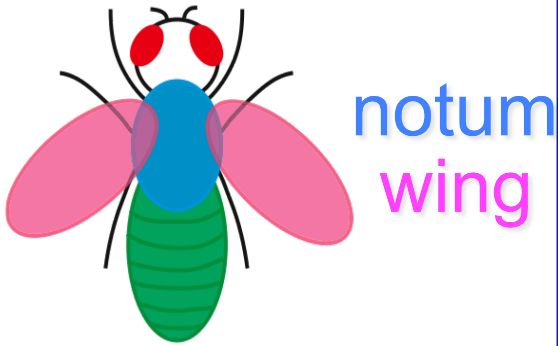




Embryo

http://flybase.org/

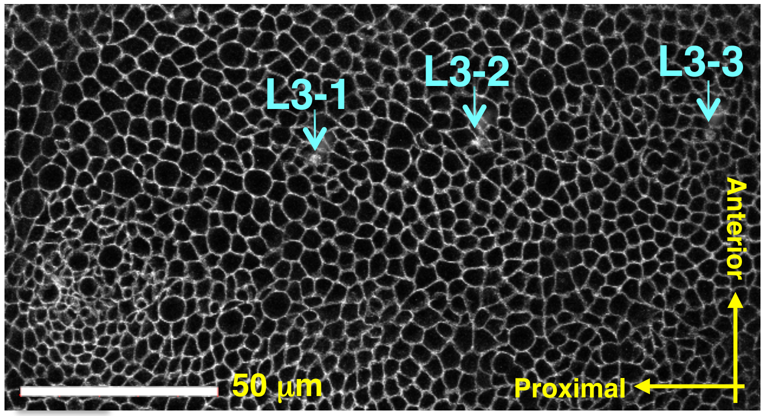
Adult



Wing

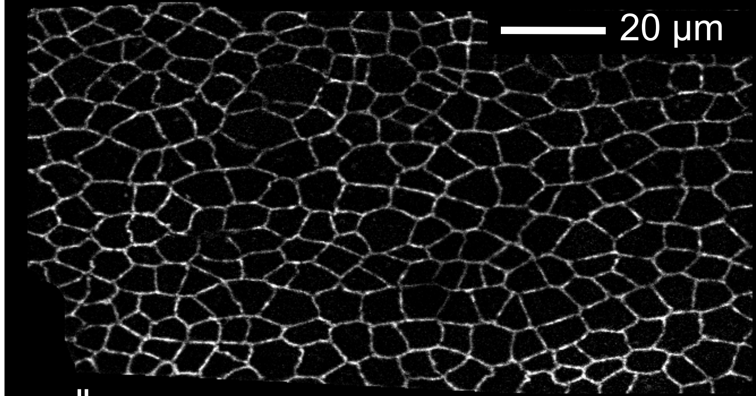
Pupa

Wing at 15.5 hr APF (after puparium formation)

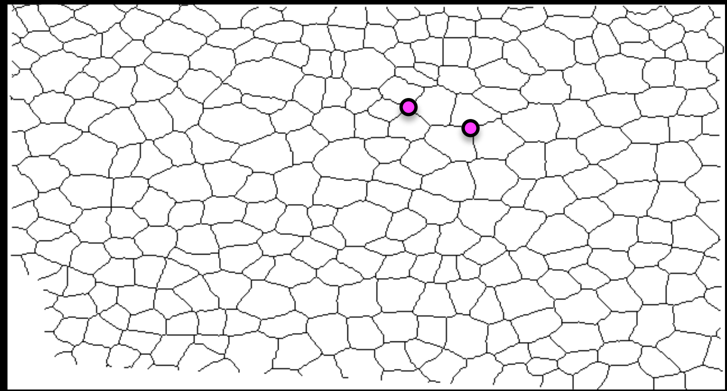


Application to the *Drosophila* pupal wing

Input: **image of cells**



get positions of vertices



$v_a(x_a, y_a)$,
$v_b(x_b, y_b)$,

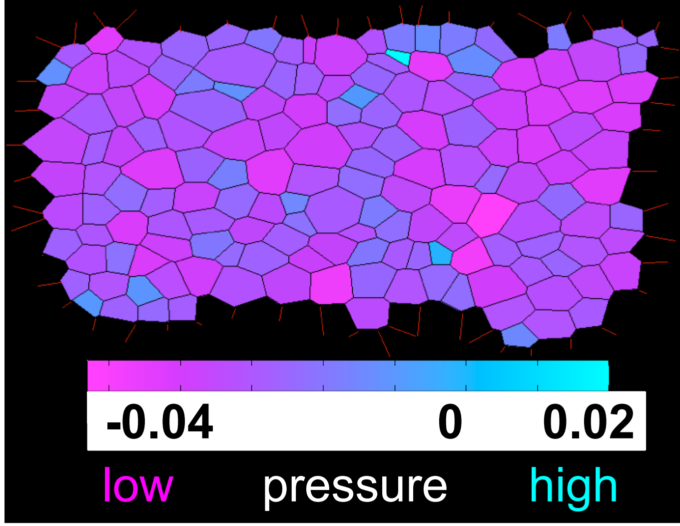
balance of forces at each vertex

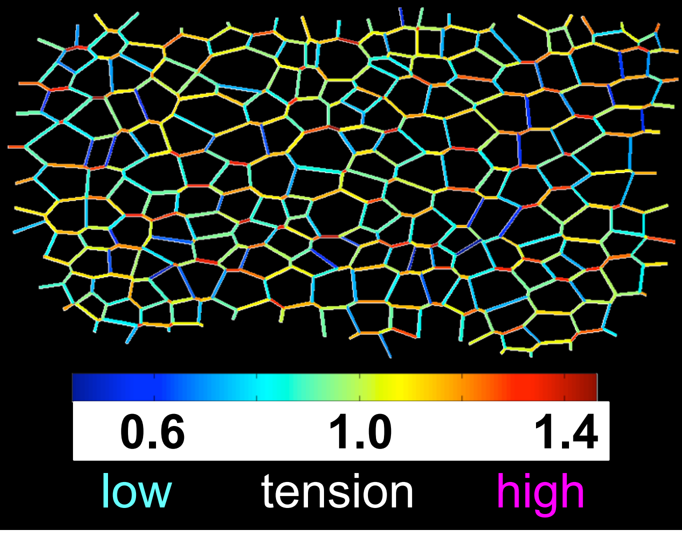
$$A\vec{p} = \gamma\vec{V} \qquad \vec{p} = (T_1 \cdots, T_M, P_1, \cdots, P_N) \qquad \vec{V} = \dot{\vec{X}}$$

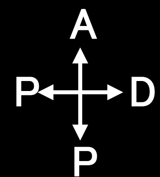
pressure & tension — drag

\+ Bayesian formulation

Output: **"relative" values of forces**





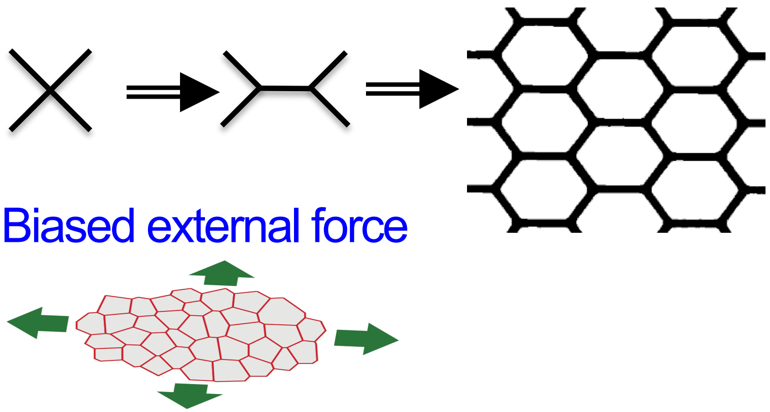


The summary of results

1. **Our new method to estimate forces**
2. **Forces in the *Drosophila* wing**
   - stronger tension along the PD axis
   - nature of tension: <u>external force stretching the wing</u>
   - ”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

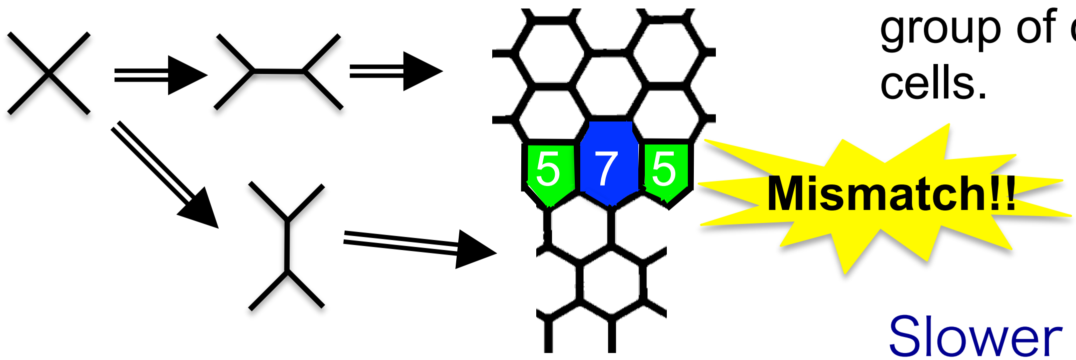


Anisotropic tensile forces may avoid the mismatch in orientations of small group of cells by setting the unique axis of cell rearrangement.

Aligned!!

Faster relaxation of the energy

Control and isotropic expansion



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

Slower relaxation of the energy

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