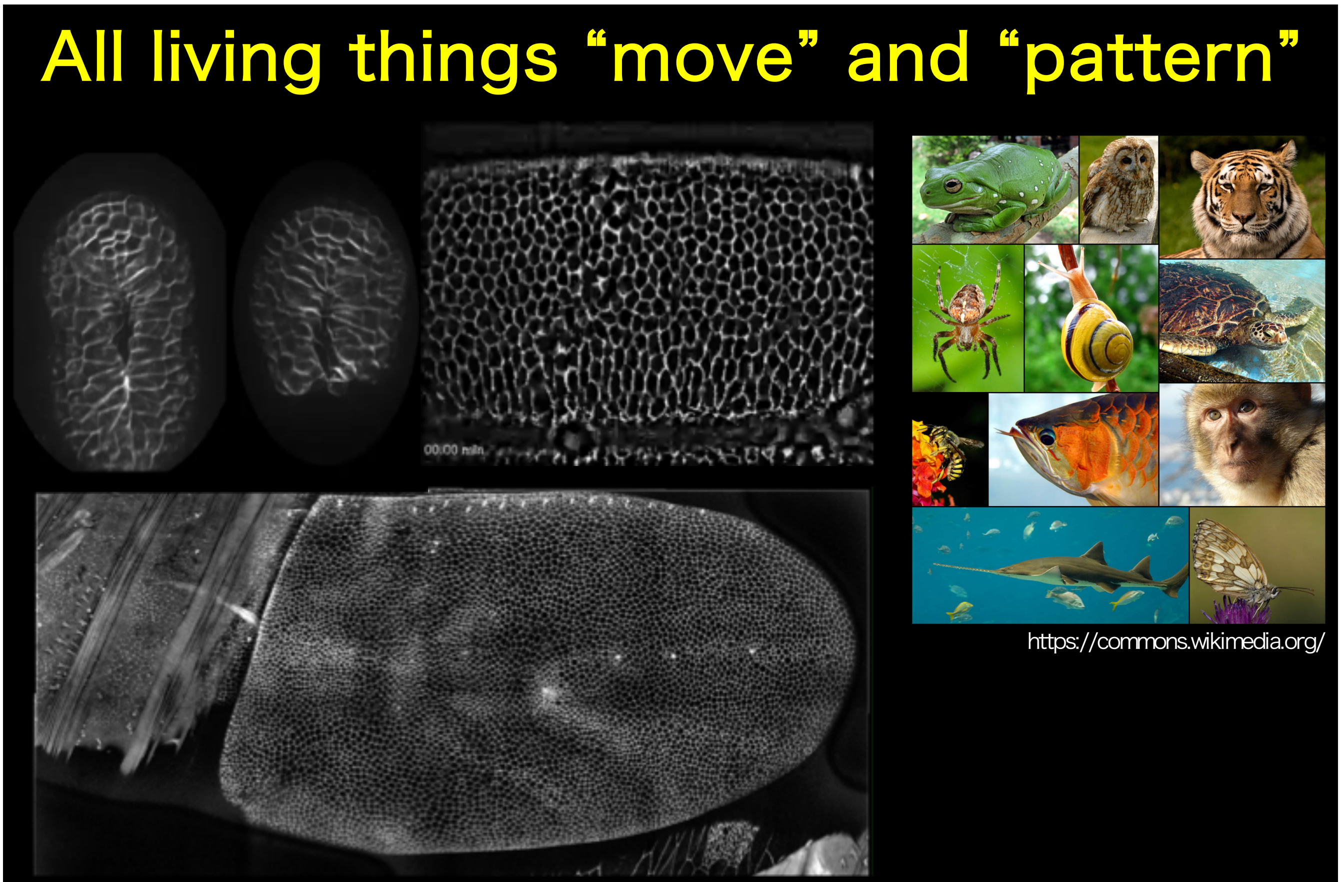
Quantifying and modelling epithelial morphogenesis

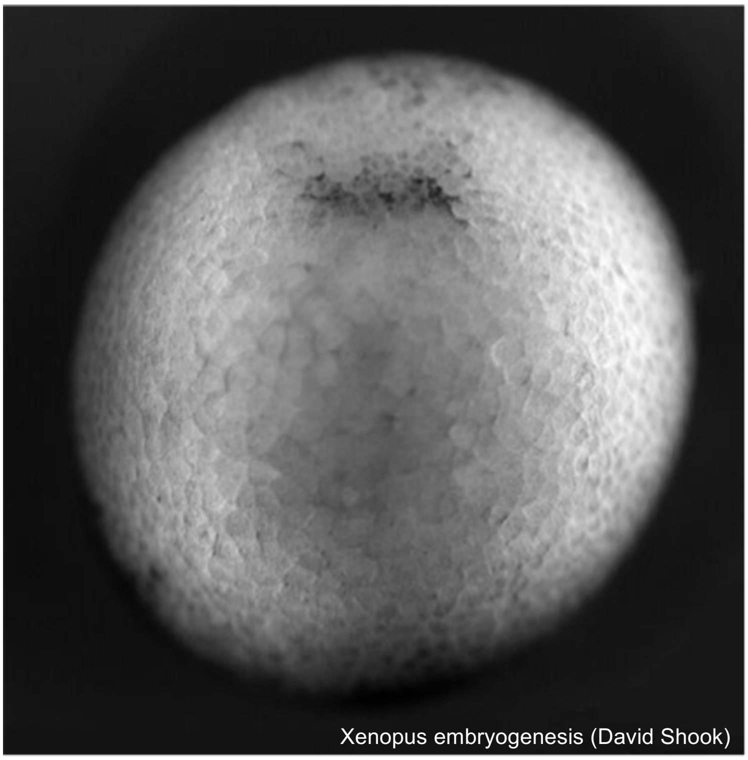
Kaoru Sugimura[1], Philippe Marcq[2], Shuji Ishihara[3]
(1: WPI-iCeMS, Kyoto Univ., 2: Inst. Curie, 3: Univ. Tokyo)



Ascidian neural tube closure: Hashimoto et al. *Dev. Cell*, 2015
Drosophila germband elongation: de Matos Simões et al. *J Cell Biol.*, 2014
Drosophila pupal wing morphogenesis.

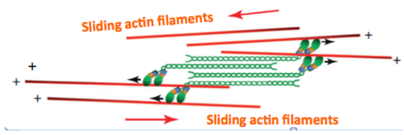
Mechanics of morphogenesis

the biological process to shape a tissue



Xenopus embryogenesis (David Shook)

Molecular forces



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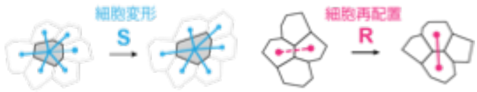
Deformation of cells/tissues



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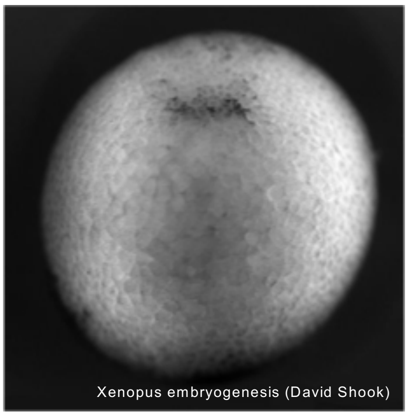
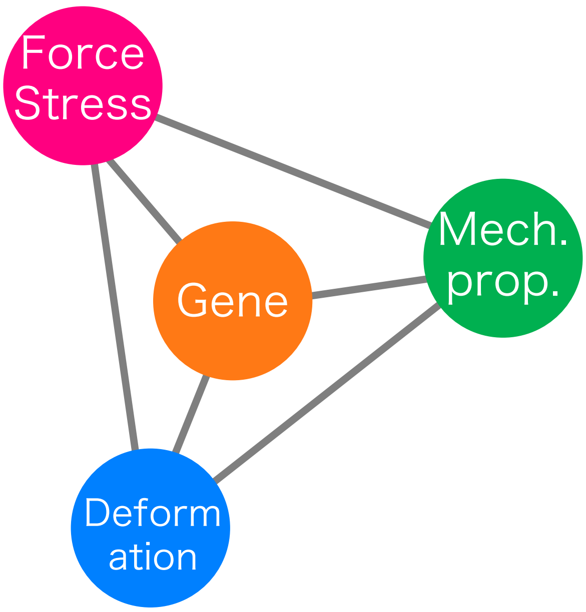
Body shape

Mechanics of morphogenesis

the biological process to shape a tissue



Xenopus embryogenesis (David Shook)



➡ How are mechanics and genetics integrated to shape an animal body?

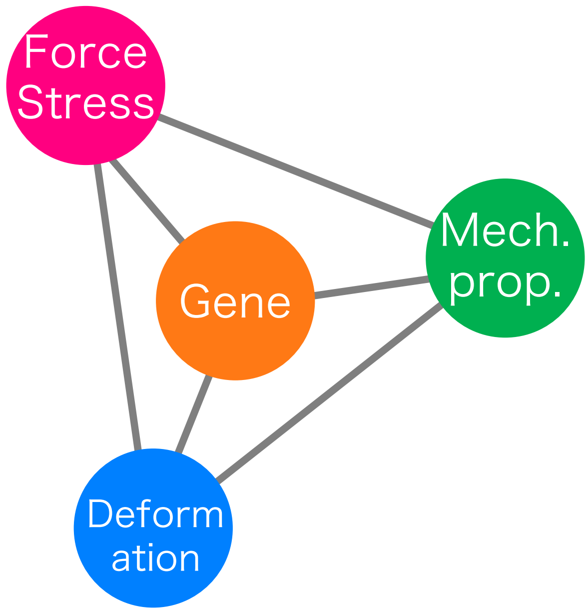
Outline

0. Questions

1. Quantifying
   epithelial morphogenesis

2. Modelling
   epithelial morphogenesis

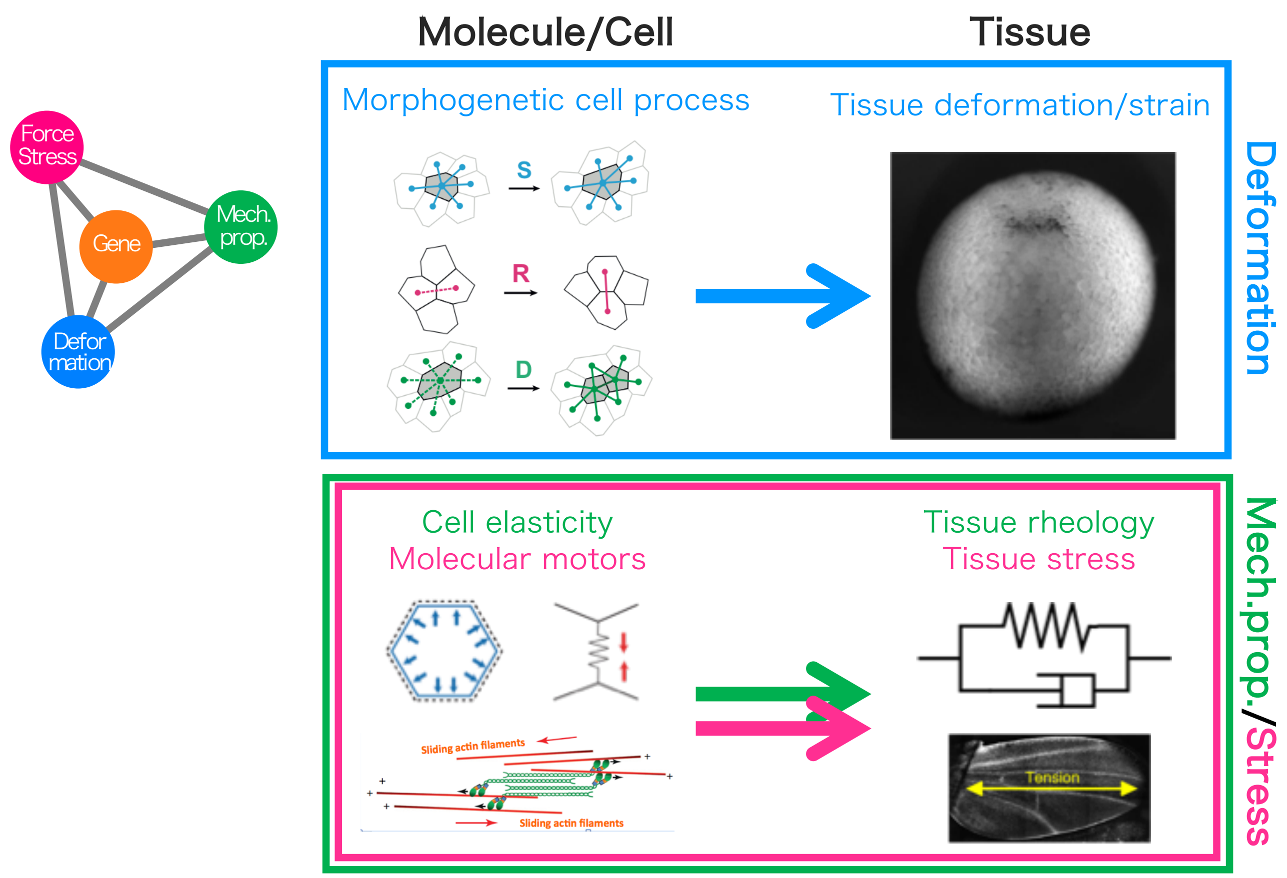
3. Future research plans



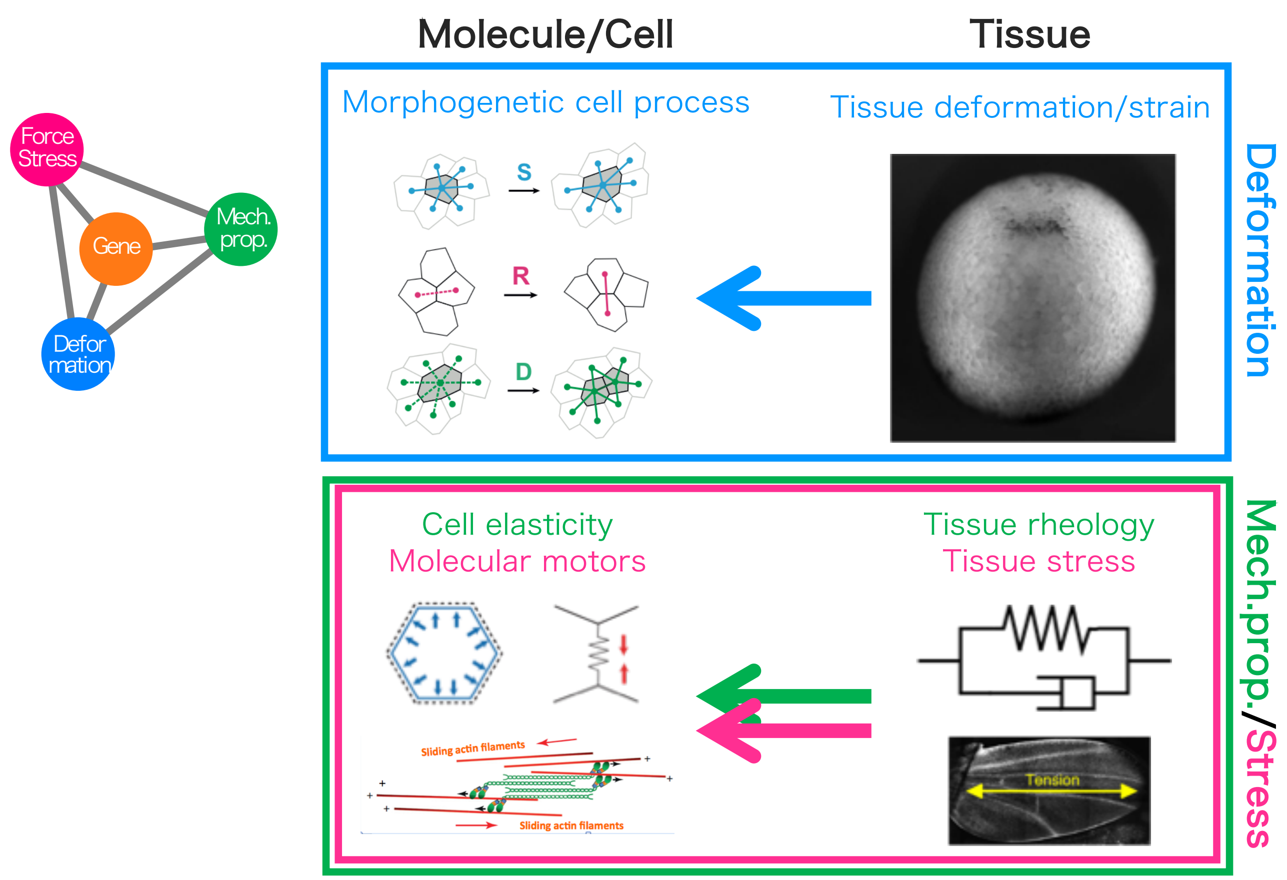
0. Questions:

Bridging cellular and tissue scales

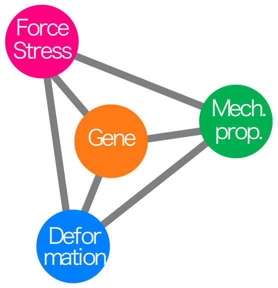
Molecular/Cell → Tissue

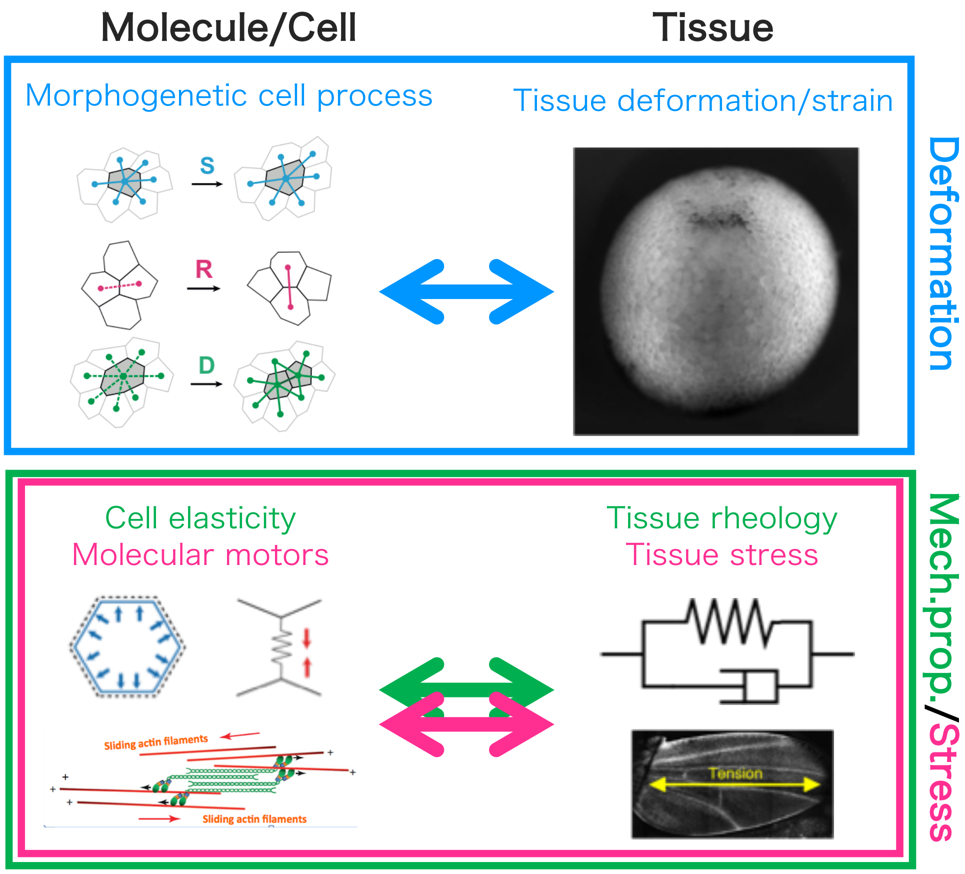


Molecular/Cell ← Tissue



Molecular/Cell ⇄ Tissue

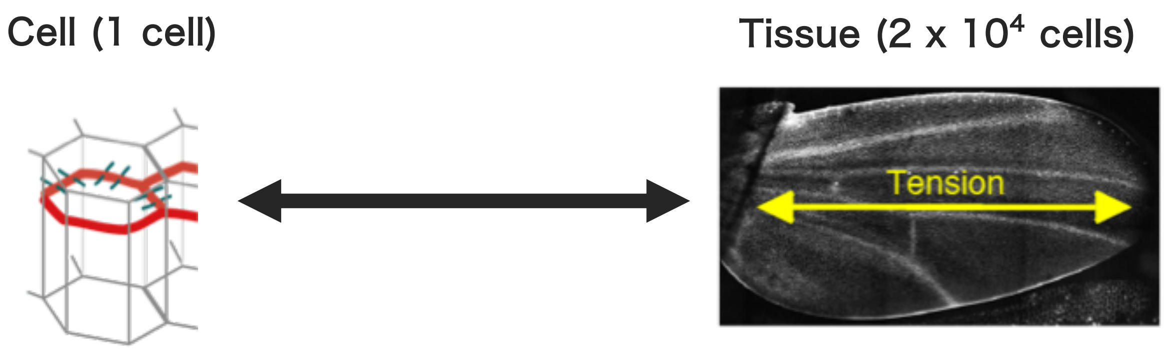




Our questions:
Multi-scale integration in a developing tissue

How do morphogenetic processes of each individual cell collectively lead to the development of a tissue with its correct shape and size?

How are cellular-level mechanical determinants, such as cell-junction tension and cell area elasticity, related to tissue rheology?



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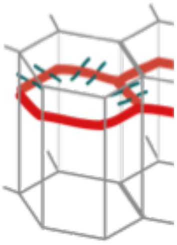
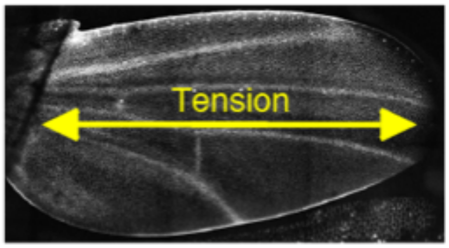
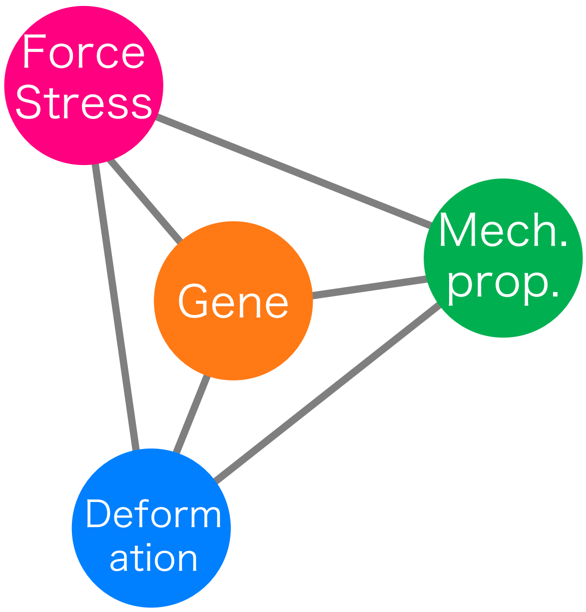
Cell (1 cell)



Coarse-graining

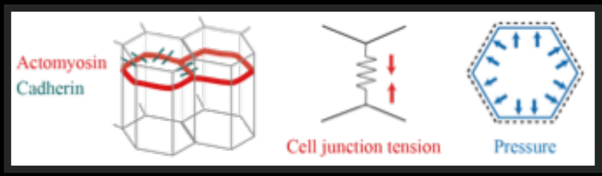
Tissue (2×10^4 cells)

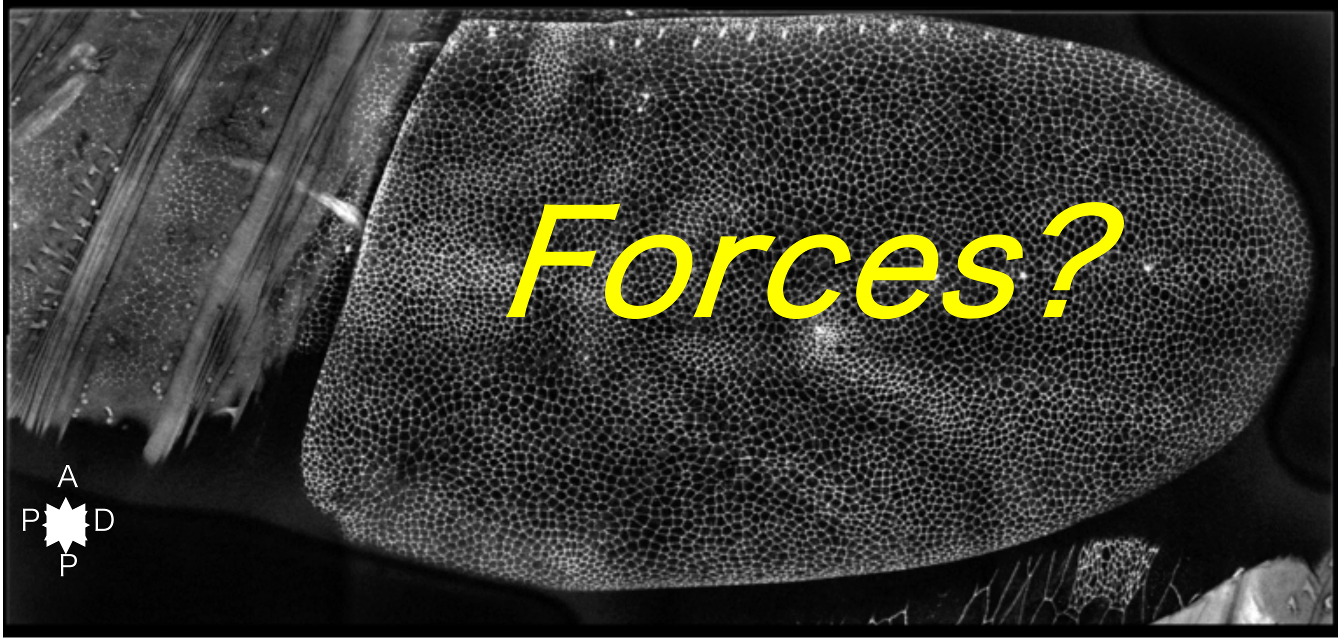




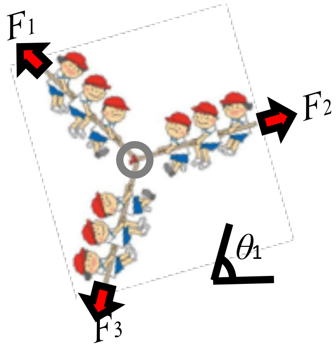
1. Quantifying epithelial morphogenesis

Our model system:
Drosophila pupal wing epithelium





Inverse problem between forces and shapes



$$F_1\cos\theta_1+F_2\cos\theta_2+F_3\cos\theta_3=0$$
$$F_1\sin\theta_1+F_2\sin\theta_2+F_3\sin\theta_3=0$$

3 unknowns, 2 conditions

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Relative values of forces

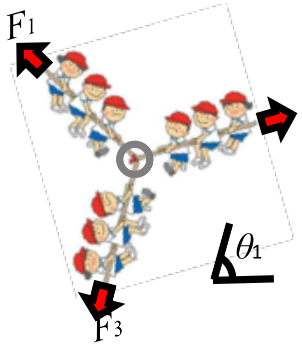
$F_2/F_1 \quad F_3/F_1$

Force

⬆

Shape

Inverse problem between forces and shapes



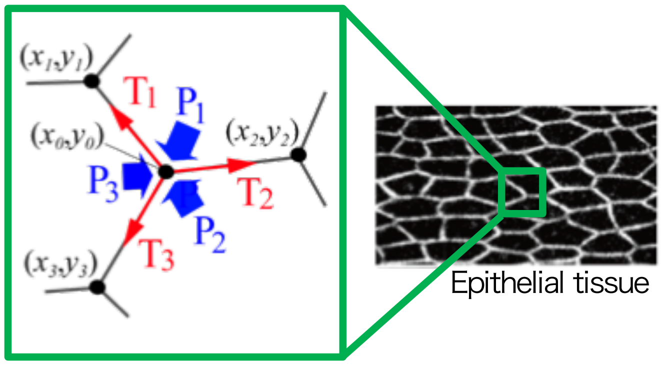
$$F_1\cos\theta_1+F_2\cos\theta_2+F_3\cos\theta_3=0$$
$$F_1\sin\theta_1+F_2\sin\theta_2+F_3\sin\theta_3=0$$

3 unknowns, 2 conditions

⇓

Relative values of forces

$F_2/F_1 \quad F_3/F_1$



Force balance equations

\# of unknowns > # of conditions

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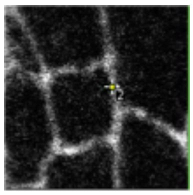
Relative values of cell junction tension and difference of cell pressure

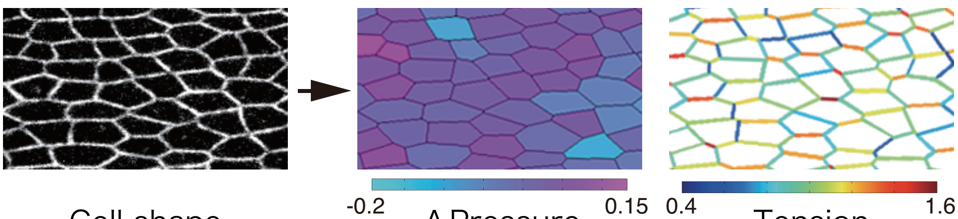
$T_{ij} \quad \Delta P_i$

Bayesian force/stress inference

Force balance-eq. positive tension

$$\underbrace{P(\text{Force}\,|\,\text{Shape})}_{\text{Posterior}} \propto \underbrace{P(\text{Shape}\,|\,\text{Force})}_{\text{Likelihood}}\ \underbrace{P(\text{Force})}_{\text{Prior}}$$





Cell shape ΔPressure Tension

$$\sigma = \frac{1}{A}\left(-\sum_i P_i A_i \mathbf{I} + \sum_{[ij]} T_{ij}\frac{\boldsymbol{r}_{ij}\otimes\boldsymbol{r}_{ij}}{|\boldsymbol{r}_{ij}|}\right)$$

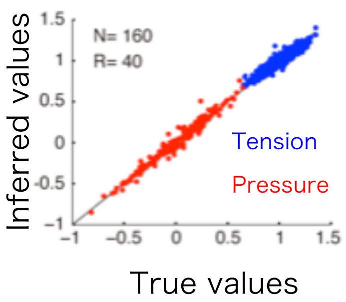
Stress tensor

Ishihara and Sugimura. *J. Theor. Biol.* (2012); Sugimura and Ishihara. *Development* (2013); Ishihara et al. *EPJE* (2013); Sugimura et al. *IEEE EMBC* (2013)

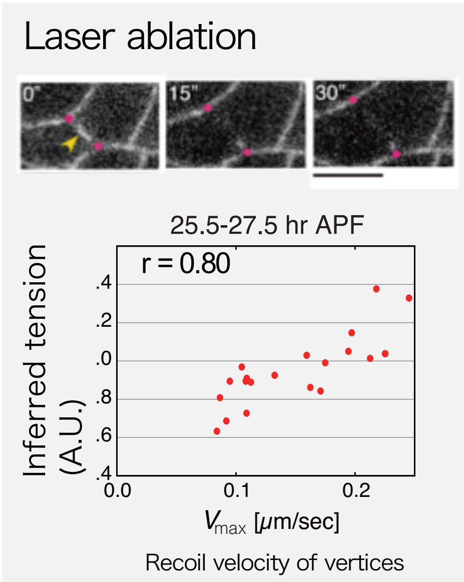
In silico and *in vivo* Validation

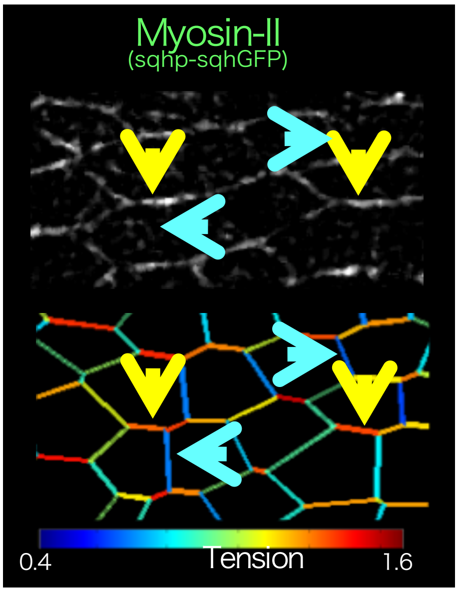
In silico

Numerical data



In vivo



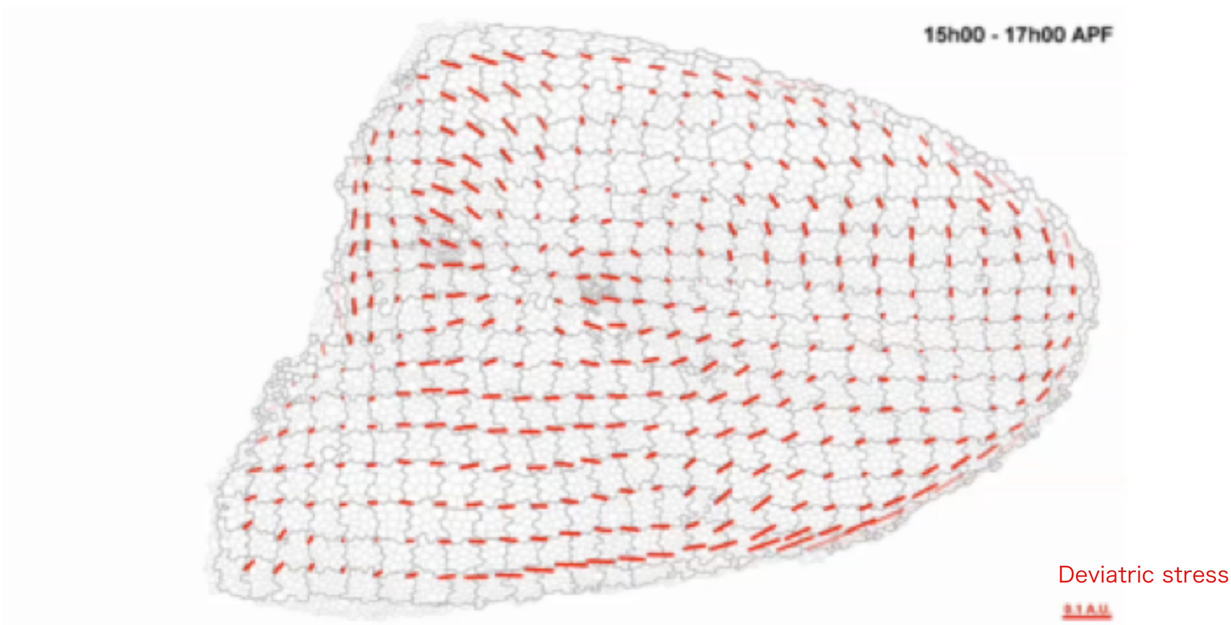


Laser ablation **Myosin-II distribution** **Photo elasticity**

Robust against the image processing error **Temporal smoothness**

Coarse-grained measurement of stress

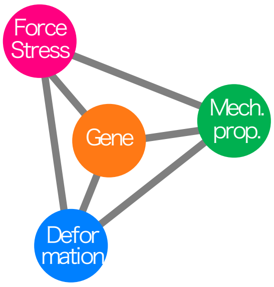
Stress tensor $\sigma = \frac{1}{A}\left(-\sum_i P_i A_i \mathbf{I} + \sum_{[ij]} T_{ij} \frac{\mathbf{r}_{ij} \otimes \mathbf{r}_{ij}}{|\mathbf{r}_{ij}|}\right)$



First to quantify space-time maps of stresses in a whole tissue

Stress anisotropy in the wing

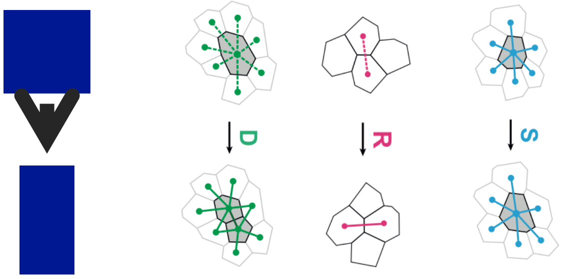
Coarse-grained measurements of kinematics (deformation)



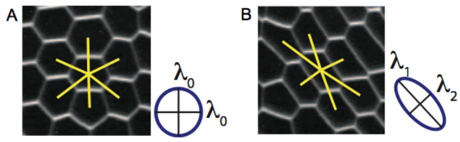
Yohanns Bellaïche Boris Guirao François Graner

$$G = D + R + S + A$$

Tissue growth | Cell Division | Cell Rearrangement | Cell Shape Change | Cell Death (Apoptosis)

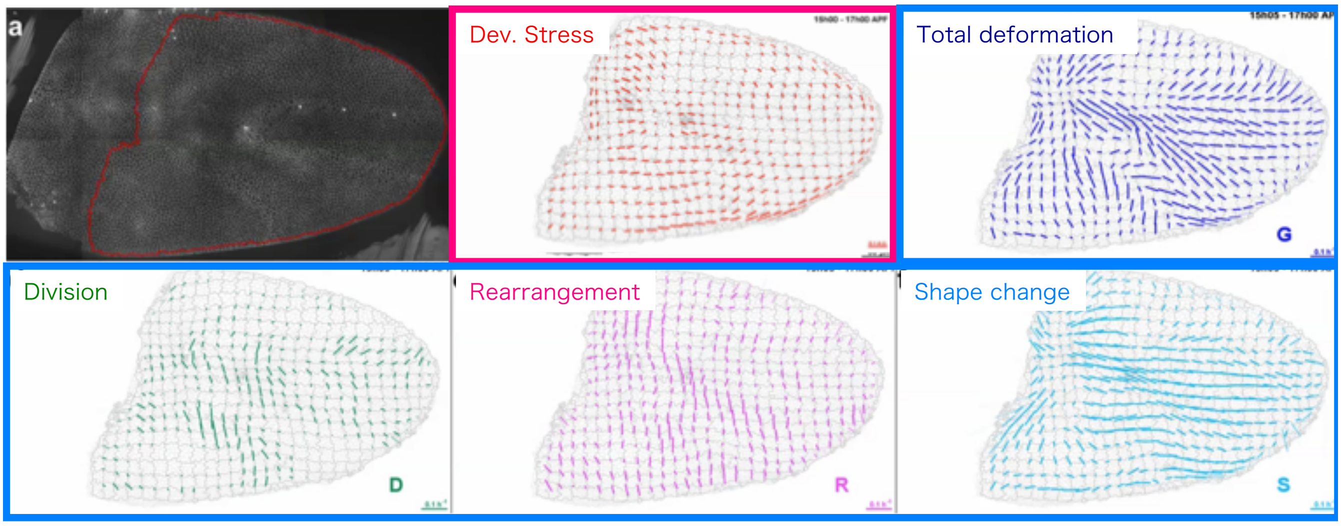


Texture tensor



$$M = \left\langle \frac{1}{2} \sum_{link} \vec{\ell} \otimes \vec{\ell} \right\rangle$$

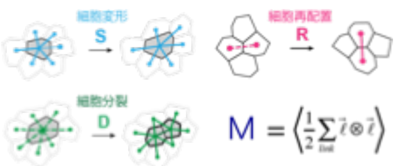
Unified quantification of stress and deformation



Stress tensor

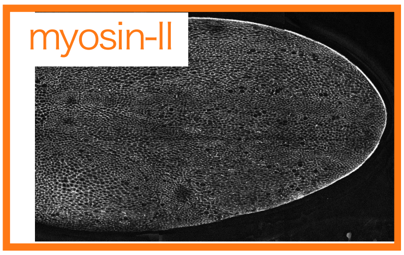
$$\sigma = \frac{1}{A}\left(-\sum_i P_i A_i \mathbf{I} + \sum_{[ij]} T_{ij} \frac{\mathbf{r}_{ij} \otimes \mathbf{r}_{ij}}{|\mathbf{r}_{ij}|} \right)$$

Texture tensor

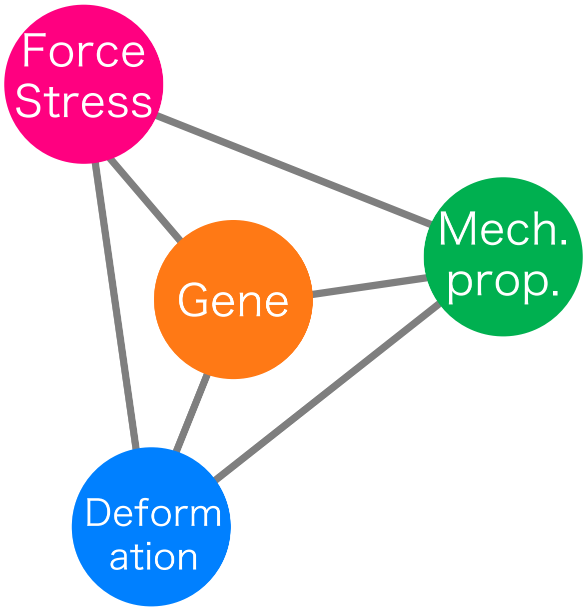


$$M = \left\langle \frac{1}{2} \sum_{link} \vec{\ell} \otimes \vec{\ell} \right\rangle$$

myosin-II



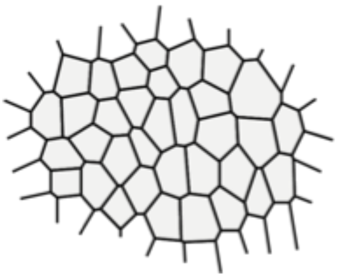
Guirao et al. *eLife* (2015); Sugimura et al. *Unpublished*



2. Modelling epithelial morphogenesis

Mechanical models for epithelial tissue

Discrete model (e.g., CVM)



- Cell shape is explicitly represented
- Cell geometry is determined by minimizing energy function

$$V = \underbrace{\sum_{cell} \frac{K}{2}\left(A_i - A_0\right)^2}_{\text{cell area elasticity}} + \underbrace{\sum_{membrane} \gamma_0 L_j + \sum_{cell} \frac{\kappa_0}{2} \ell_i^2}_{\text{linear and elastic tension of junctions}}$$

- Useful for including experimental data obtained at cellular level, such as the laser ablation of cell junctions and subcellular distribution of proteins

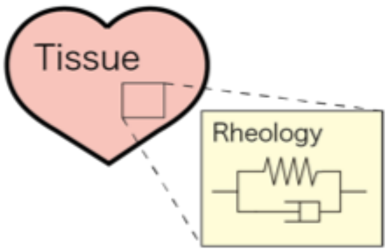
- Relationship between cell morphogenetic processes and cell mechanics and tissue scale deformation and rheology are not directly tractable

Mechanical models for epithelial tissue

- in-depth analysis of tissue rheology

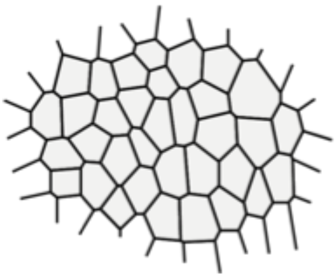
- do not include the information of the cellular structure by construction

Continous model

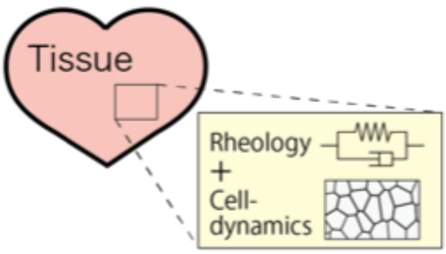


Mechanical models for epithelial tissue

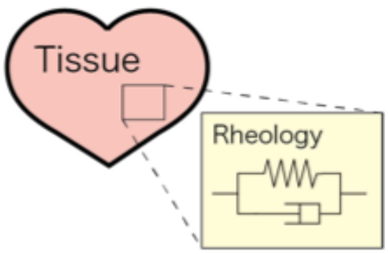
Discrete model (e.g., CVM)



New continuous model



Continous model



Continuum model with DOFs representing cell shape and cell rearrangement

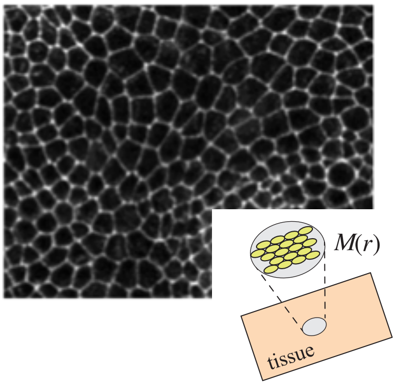
Comparable with experimental data (stress tensor, texture tensor)

Shuji Ishihara

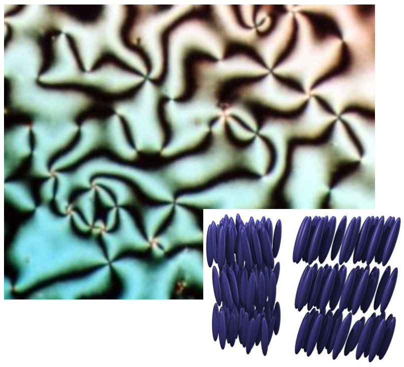
Philippe Marcq

Tissue as soft matters : material with internal DoF
Similar, but different structures and kinematics

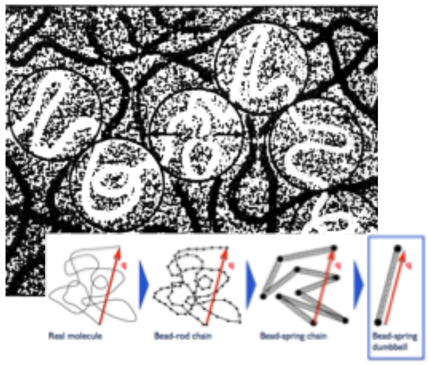
Tissue



Liquid crystal

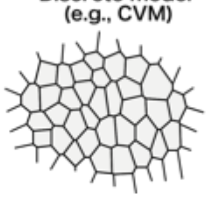


Polymer melts



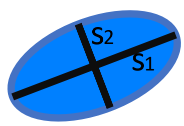
New continuum model for epithelial mechanics

Discrete model (e.g., CVM)



$$V=\sum_{cell}\frac{K}{2}\left(A_i-A_0\right)^2+\sum_{membrane}\gamma_0 L_j+\sum_{cell}\frac{\kappa_0}{2}\ell_i^2$$

Approximate a cell by an ellipse M



M : cell shape tensor
$M = S^T S$

Energy as a function of M

$$f(M)=\frac{1}{\pi|M|^{1/2}}\left(\frac{K}{2}\left(\pi|M|^{1/2}-A_0\right)^2+\frac{\pi\gamma_0}{\sqrt{2}}\sqrt{\mathrm{Tr}M}+\pi^2\kappa_0\mathrm{Tr}M\right)$$

Elastic stress

$$\sigma_e=K\left(\pi|M|^{1/2}-A_0\right)I+\left(\frac{\gamma_0}{\sqrt{2\mathrm{Tr}M}}+2\pi\kappa_0\right)\frac{M}{|M|^{1/2}}$$

Kinematics for cell deformation

Decomposition of deformation rate

$$\underbrace{\nabla v}_{\text{tissue deformation}}=\underbrace{\Omega+D_s}_{\text{cell shape change}}+\underbrace{D_r}_{\text{cell rearrangement}}$$

Kinematic for cellular shape M
(co-deformational to deformation rate)

$$\dot{M}=(\nabla v-D_r)M+M(\nabla v-D_r)^T$$

Tlili et al. 2015

Kinetics: Thermodynamic formalism

Entropy production rate

$$T\dot{s}=\sigma_p:D+\sigma_e:D_r\ +r\Delta\mu$$

Constitutive relationship

$$\sigma_p=\chi_{ss}D-\chi_{sr}\sigma_e\ +\sigma_a$$

$$D_r=\chi_{rs}D+\chi_{rr}\sigma_e\ +D_a$$

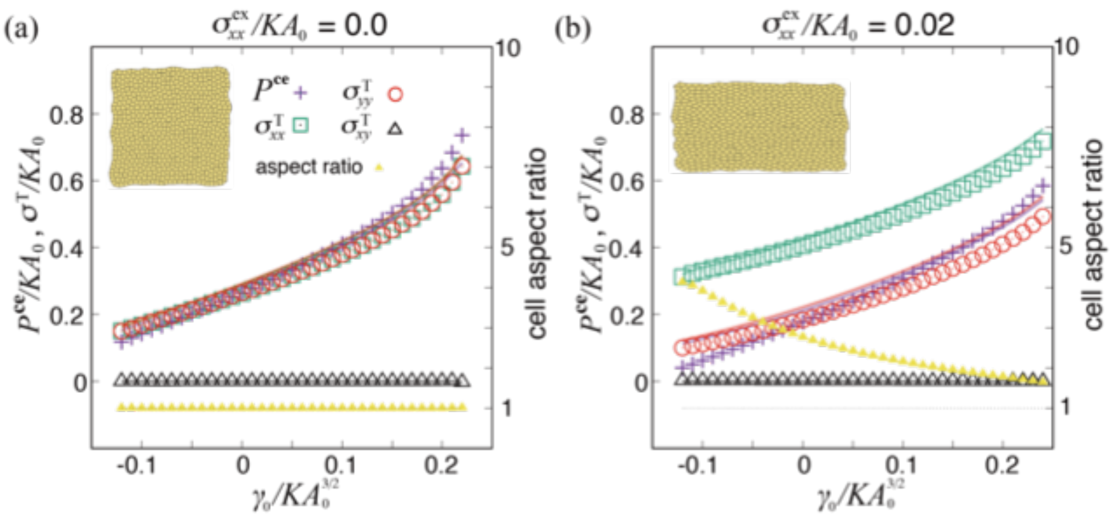
Ishihara, Marcq, Sugimura. *Phys. Rev. E* (2017).

New continuum model retains essential features of Cell vertex model (CVM)

◇ Comparison of macroscopic stress expressions

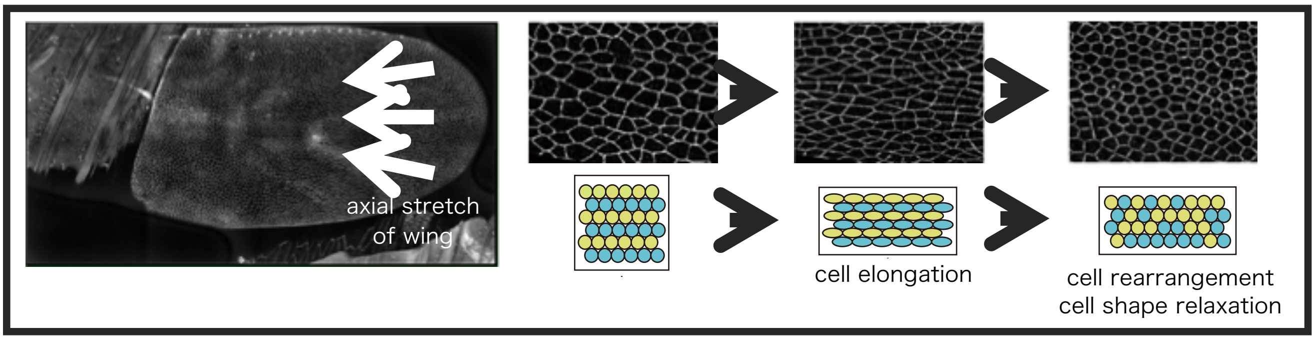
Ones calculated from coarse-grained cellular shape tensor M (symbols)

the true ones obtained using the CVM simulations (solid lines)



◇ We also recovered two instabilities described for the CVM.

Application1: relaxation upon tissue stretching



$$\dot{c} + \eta^{-1}\Gamma(c)\sinh(c) = (1 - v_1)\partial_x v_x$$

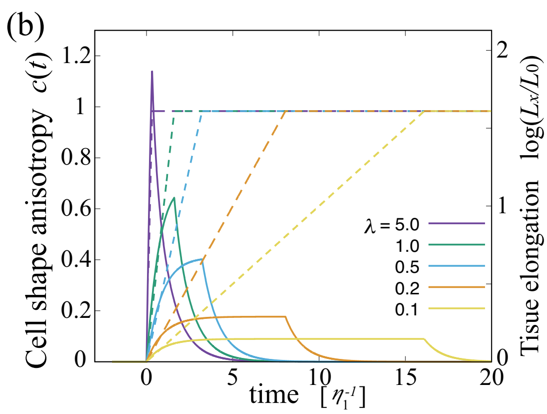
relaxation time scale:

$$\boxed{\tau = \eta \frac{2\pi S_0}{\pi\gamma_0 + 4\pi^2\kappa_0 S_0}}$$

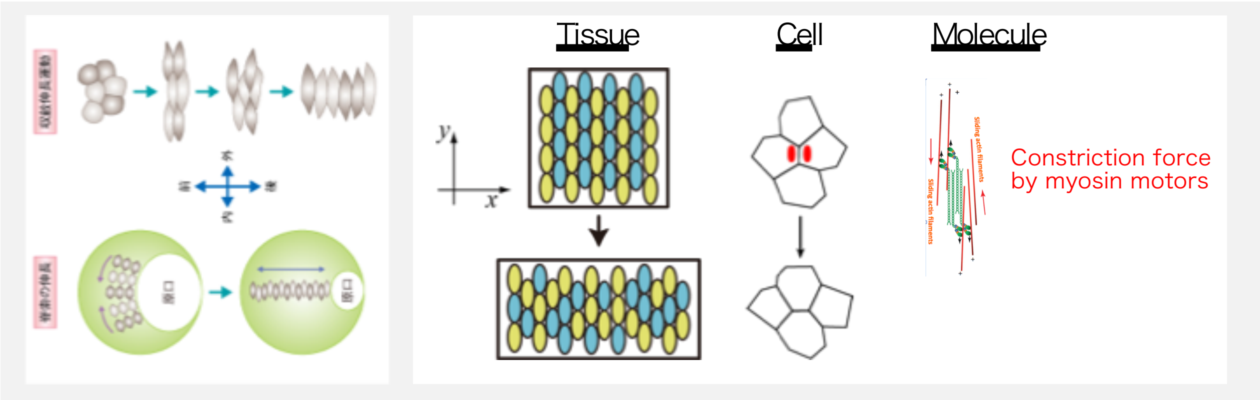
S_0 : cell size

γ_0, κ_0: cell tension parameter of Cell Vertex Model

$$V = \sum_{cell} \frac{K}{2}(A_i - A_0)^2 + \sum_{membrane} \gamma_0 L_j + \sum_{cell} \frac{\kappa_0}{2} \ell_i^2$$



Application2: active contraction-elongation (CE)



Kinetics: Thermodynamic formalism (c.f. active gel theory in Kuruse et al. PRL, 2005)

Entropy production rate

$$T\dot{s} = \sigma_p : D + \sigma_e : D_r \; + r\Delta\mu$$

Coupling reaction that supplies energy to the system

r : the reaction rate

$\Delta\mu$: difference of chemical potential by the reaction

Constitutive relationship

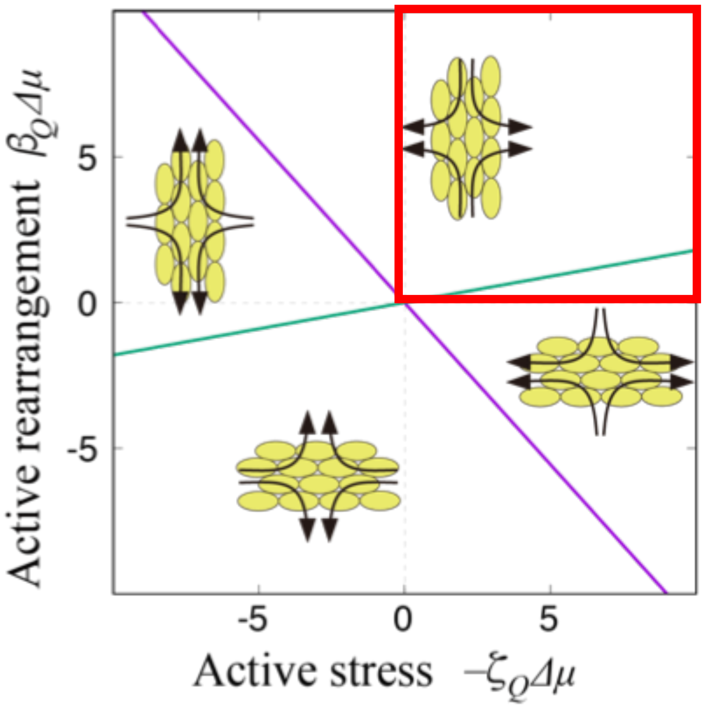
$$\boxed{\begin{aligned} \sigma_p &= \chi_{ss} D - \chi_{sr}\sigma_e \; + \sigma_a \\ D_r &= \chi_{rs} D + \chi_{rr}\sigma_e \; + D_a \end{aligned}}$$

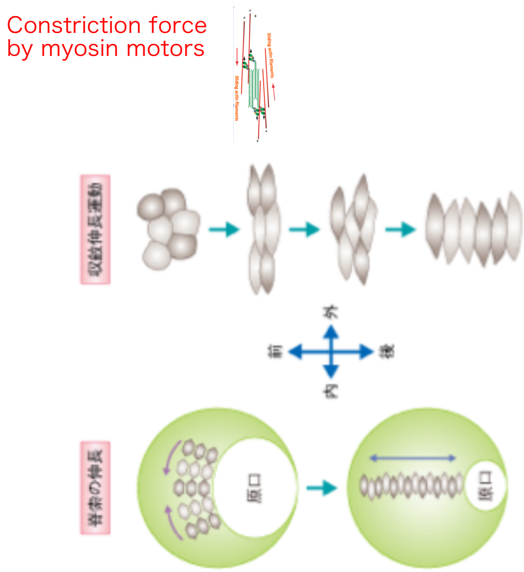
σ_a Active stress

D_a Active cell rearrangement

$$\sigma_a \propto \Delta\mu, \quad D_a \propto \Delta\mu$$

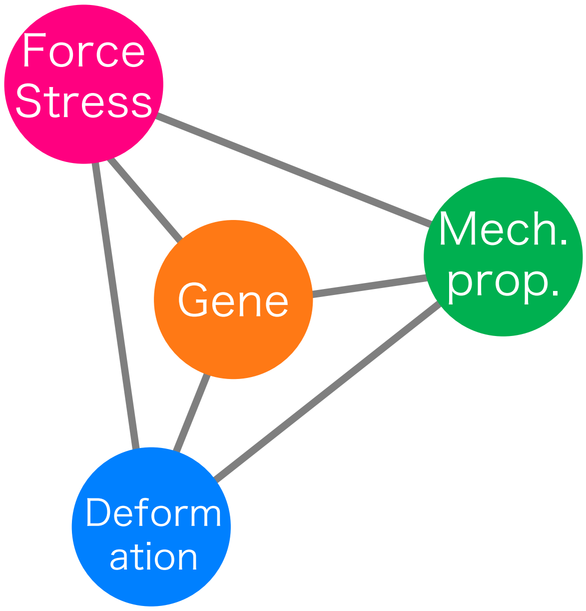
Application2: active contraction-elongation (CE)





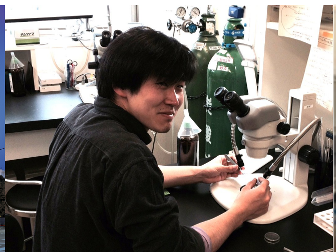
http://first.lifesciencedb.jp/archives/8436

Our model predicts a mechanism for contraction-elongation, whereby tissue flows perpendicularly to the axis of cell elongation.

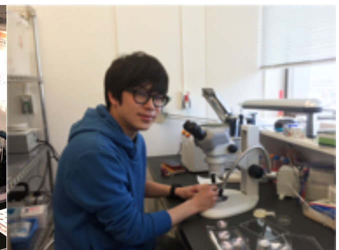


3. Future research plans

Sugimura group, WPI-iCeMS, Kyoto Univ.



Keisuke Ikawa (2014.4~)



Goshi Ogita (2018.4.~)

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