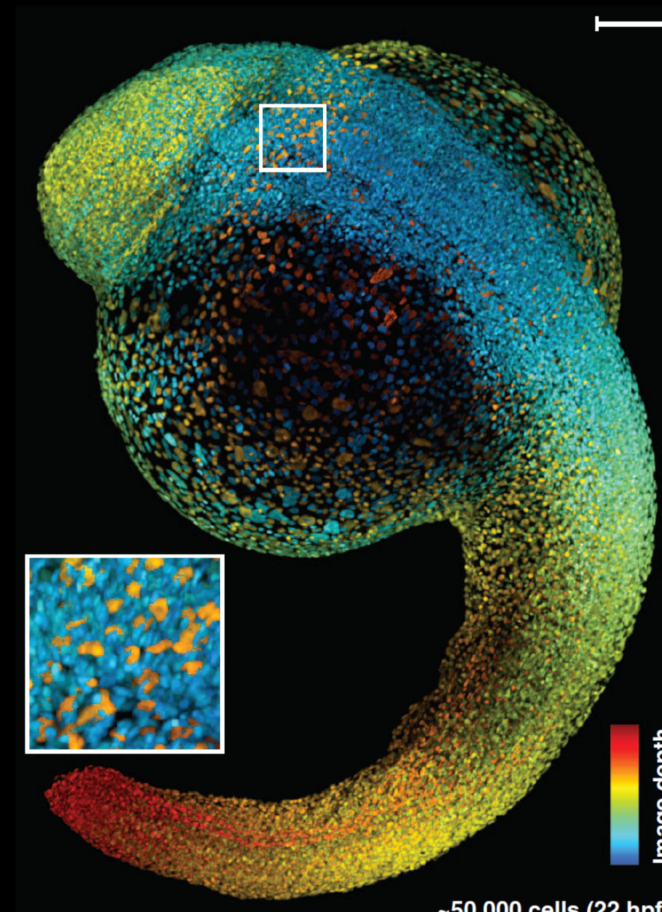
Dynamics of Multi-cellular Living Matter

Koichi FUJIMOTO
(Osaka Univ., Dept. of Biological Sci.,
Lab. of Theoretical Biology)

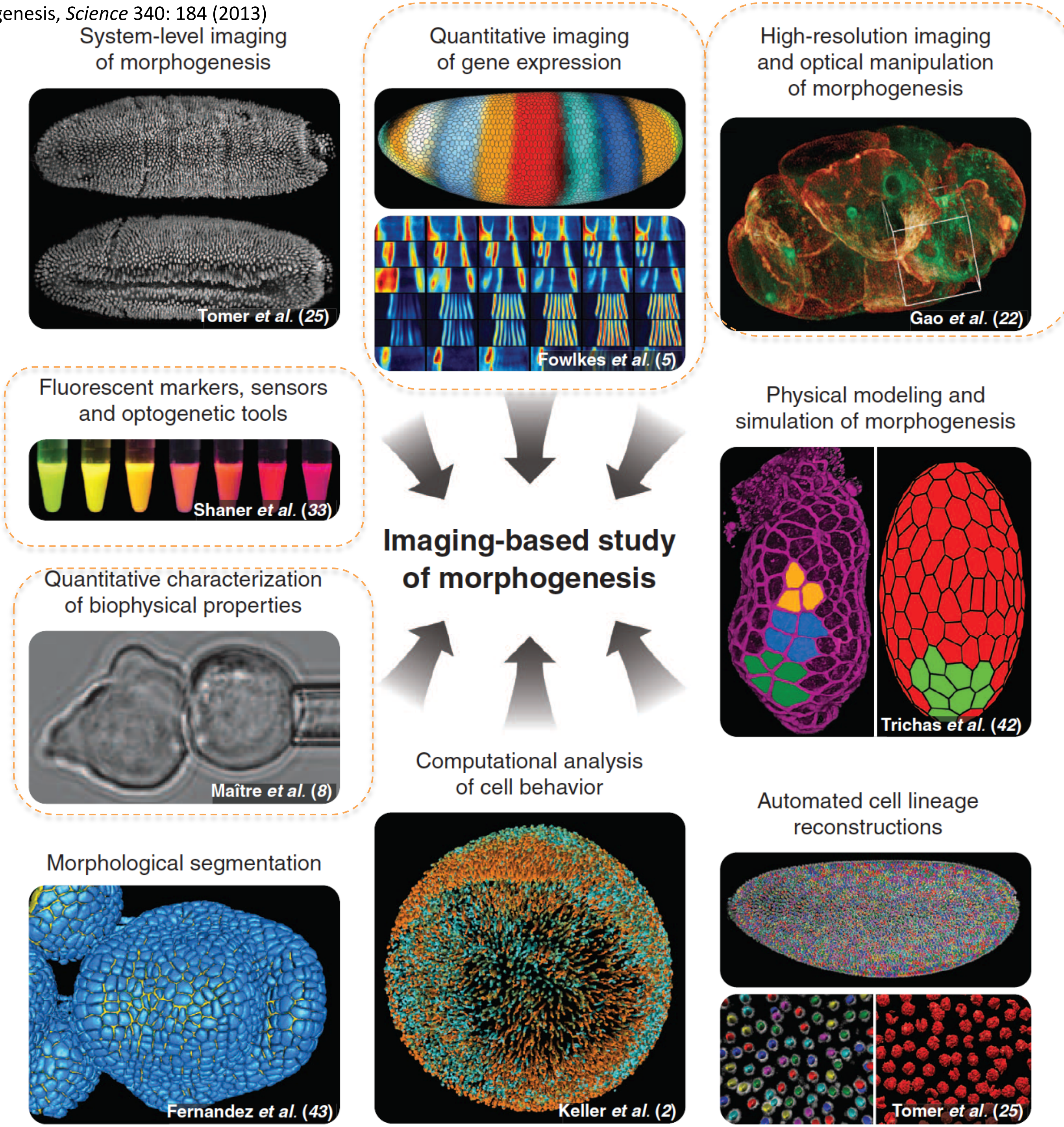
Theoretical background:
Nonlinear Dynamics,
Physics of Complex Systems

Development of Multicellular systems



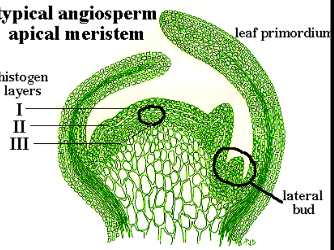
Keller, et al, *Science* 322: 1065 (2008)

Keller, Imaging morphogenesis, *Science* 340: 184 (2013)

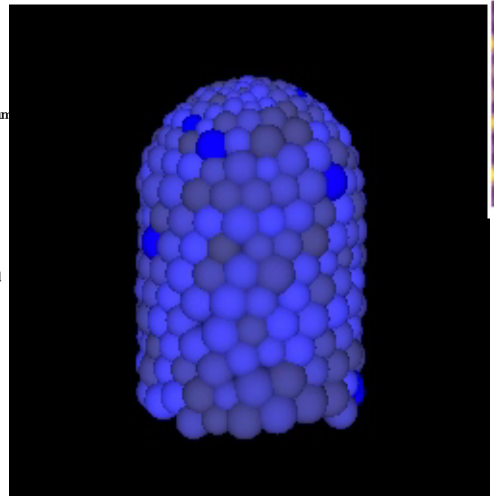


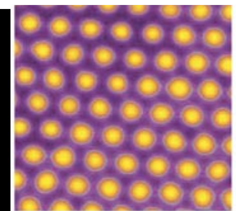
Four Bases of Morpho-genesis (形づくり)

Chemical



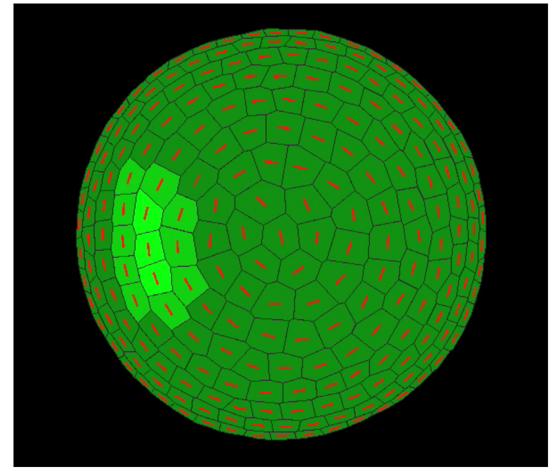
Vertical section of
Plant shoot
植物の地上部





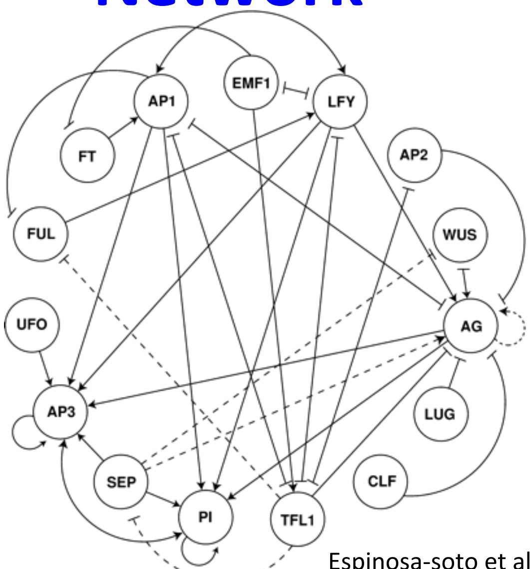
Turing 1952;
Jonsson, et al, PNAS 2006;
Smith et al, PNAS 2006, etc.

Mechanical



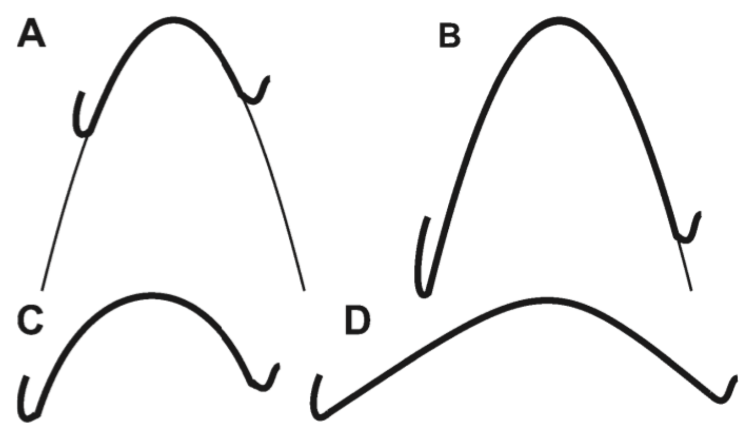
Hamant, 2009; Odell, Dev. Biol. 1981

Network



Espinosa-soto et al, *Plant Cell* 2004

Geometrical



Kwiatkowska, J. Exp. Bot. 2008; Morishita & Suzuki, J. Theor. Biol. 2014

A beginners' guide for research strategy of theoretical biology

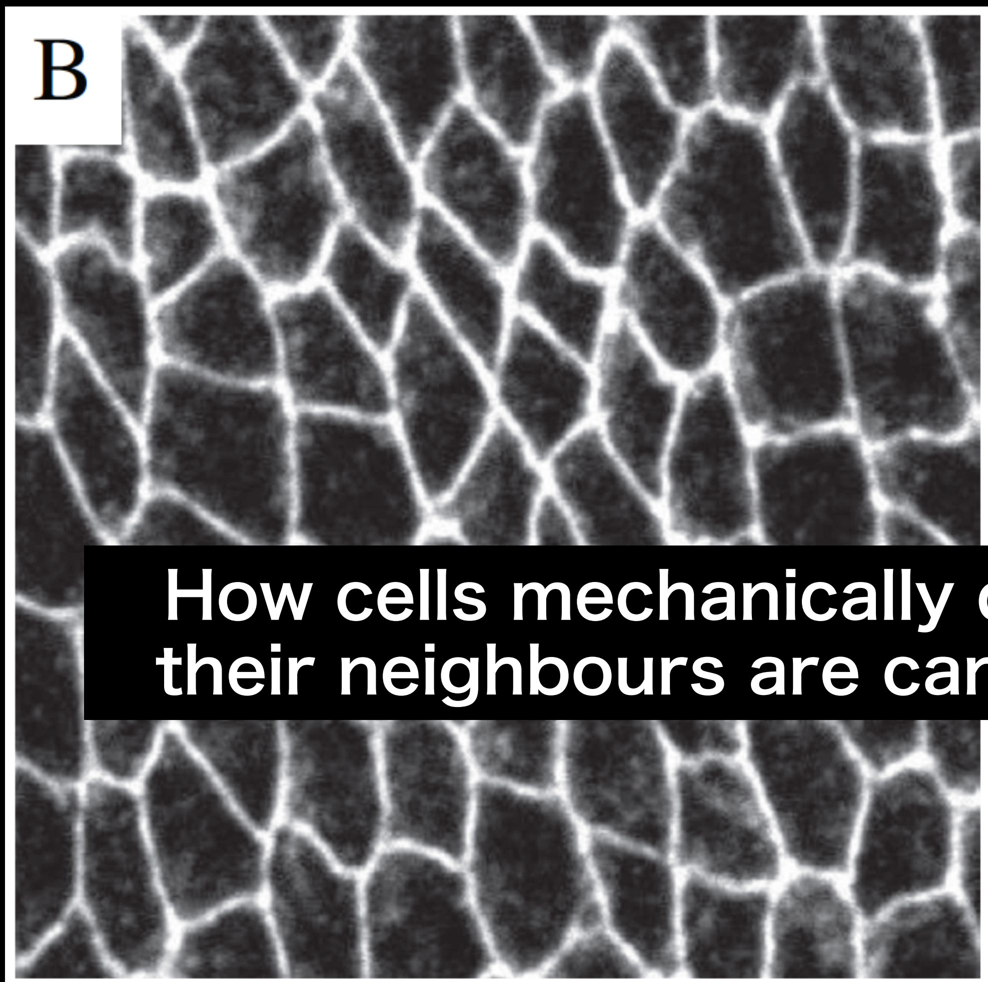
- Exploring analogy in spatio-temporal properties between multicellular matter and physico-chemistry, since the first principle is mostly absent.
- Theoretical prediction of the spatio-tempiral properties from a phenomenological model.
- Experimental verification.
- We could find the next predictions that are more non-trivial.

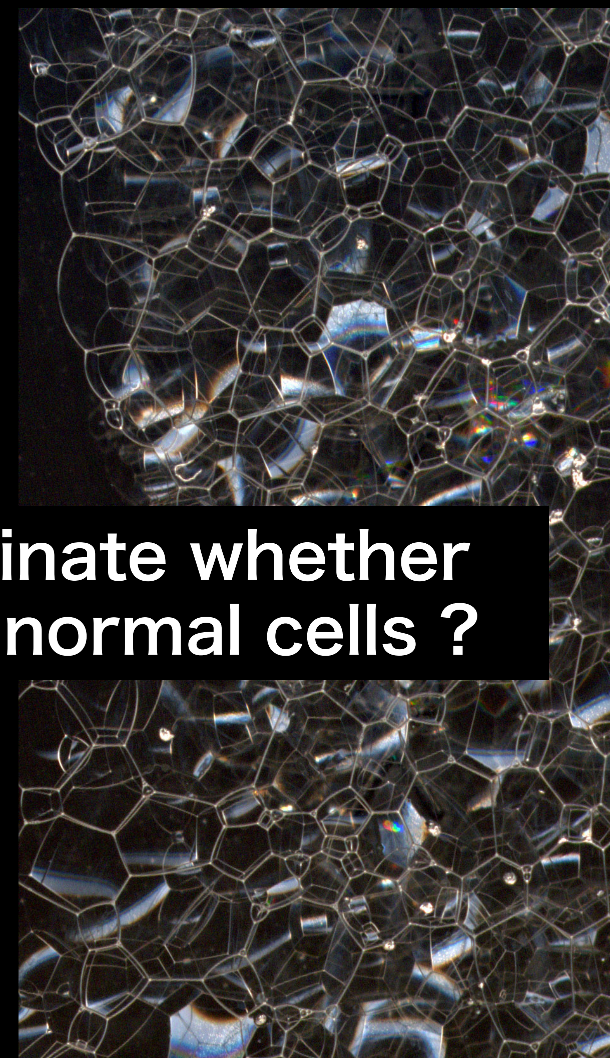
Here I show

☆ Two research examples of the strategy.

☆ Two future problems for Theoretical Biology.

Analogous shape of polygonal “cells”



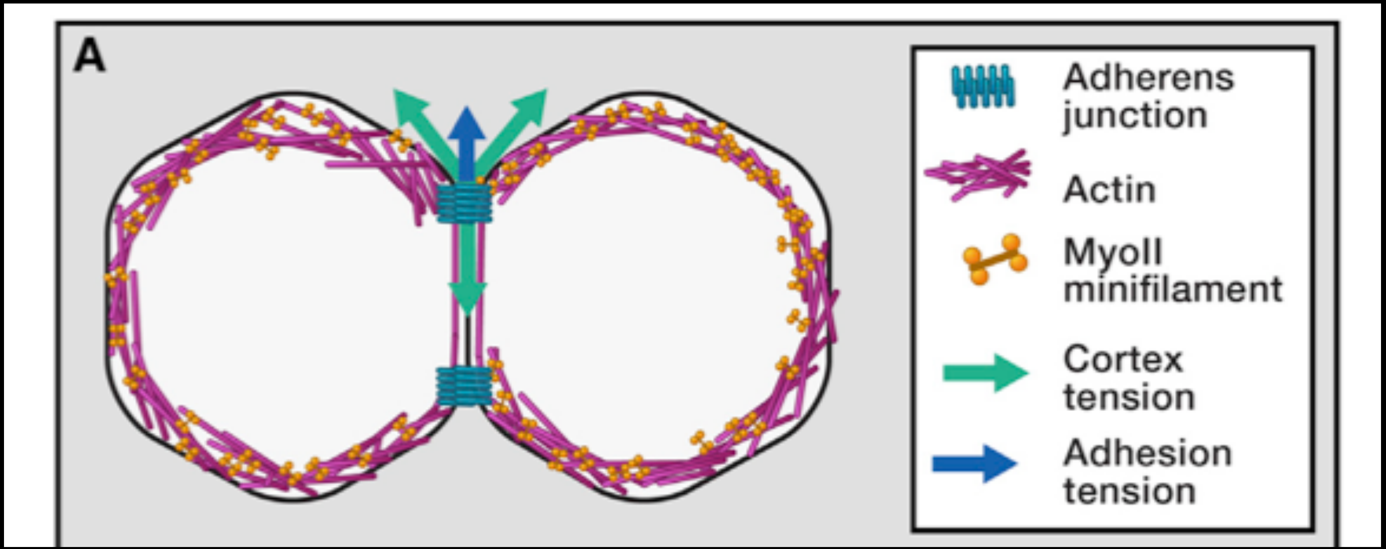


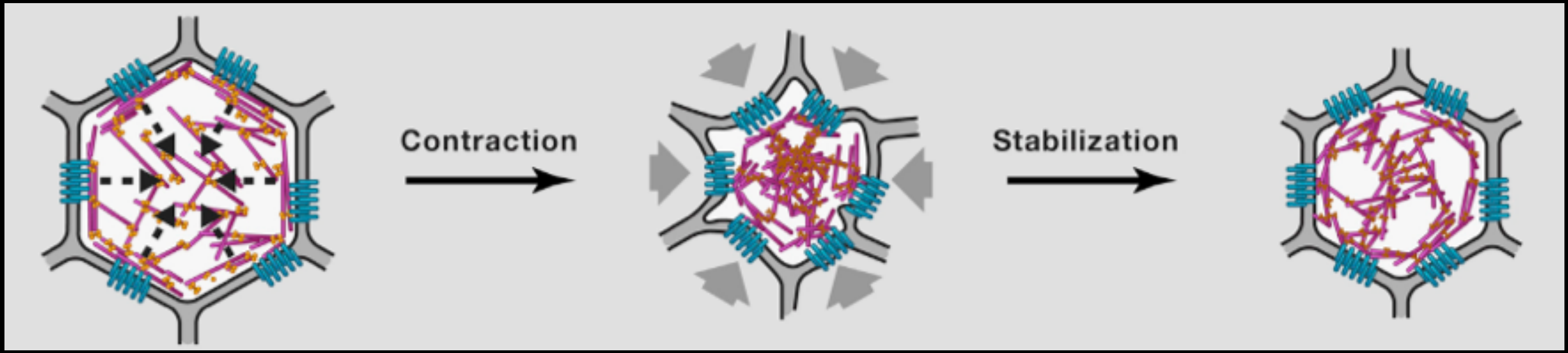
How cells mechanically discriminate whether their neighbours are cancer or normal cells ?

ショウジョウバエのサナギ期の上皮細胞
Reza Farhadifar, Ph. D. Thesis, Dresden, 2009.

http://en.wikipedia.org/

Forces in Cells



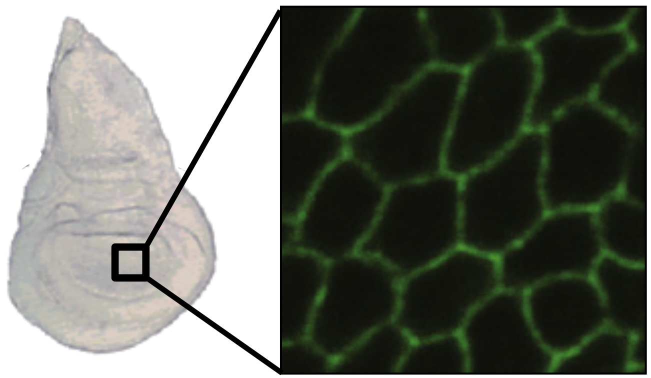


Heisenberg & Bellaiche, "Forces in Tissue Morphogenesis and Patterning" Cell (2013);
Guillot & Lecuit, "Mechanics of Epithelial Tissue Homeostasis and Morphogenesis" Science (2013)

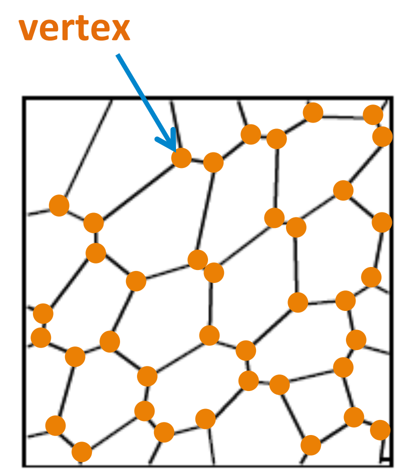
Phenomenological model of Multicellular Mechanics

Cell vertex model (Honda 1983)

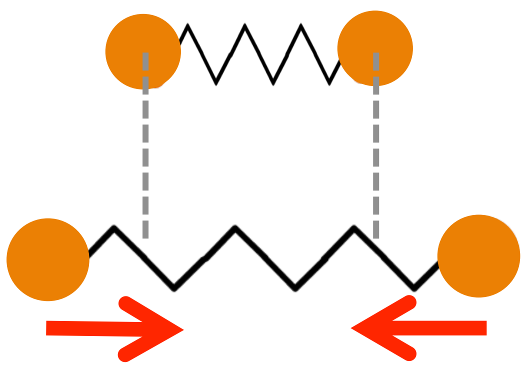
Multicellular tissue

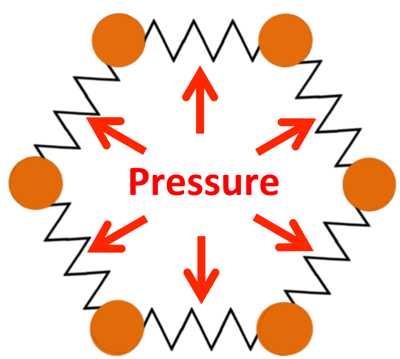


Polygonal cells in 2D space



Potential energy

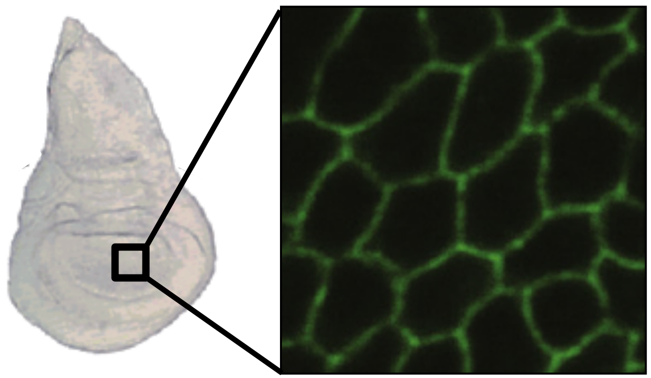




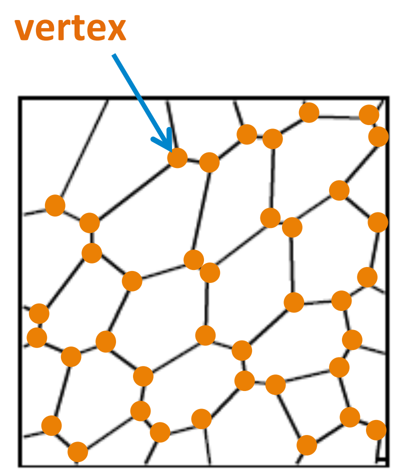
Phenomenological model of Multicellular Mechanics

Cell vertex model (Honda, 1983)

Multicellular tissue



Polygonal cells in 2D space



Equation of Motion of a single vertex

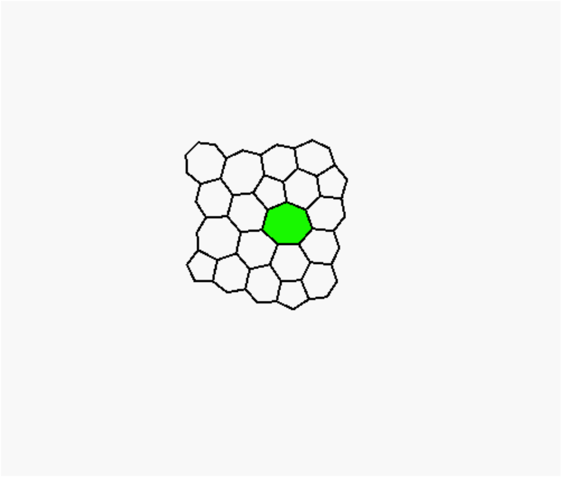
$$\dot{\vec{r}}_i = -\frac{\partial U}{\partial \vec{r}_i}$$

$$U = \sum_{\alpha} \frac{K_\alpha}{2}\left(A_\alpha - A_\alpha^{(0)}\right)^2 + \sum_{<i,j>} \Lambda_{ij}\ell_{ij} + \sum_{\alpha} \frac{\Gamma_\alpha}{2} L_\alpha^2$$

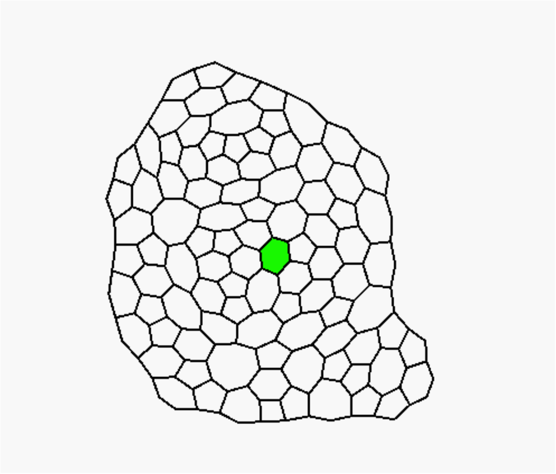
U: **Potential energy**

Differential Growth smoothens the boundary shape

Cell division (growth) rate (/hour) 1 : 1



Cell division rate 3 : 1



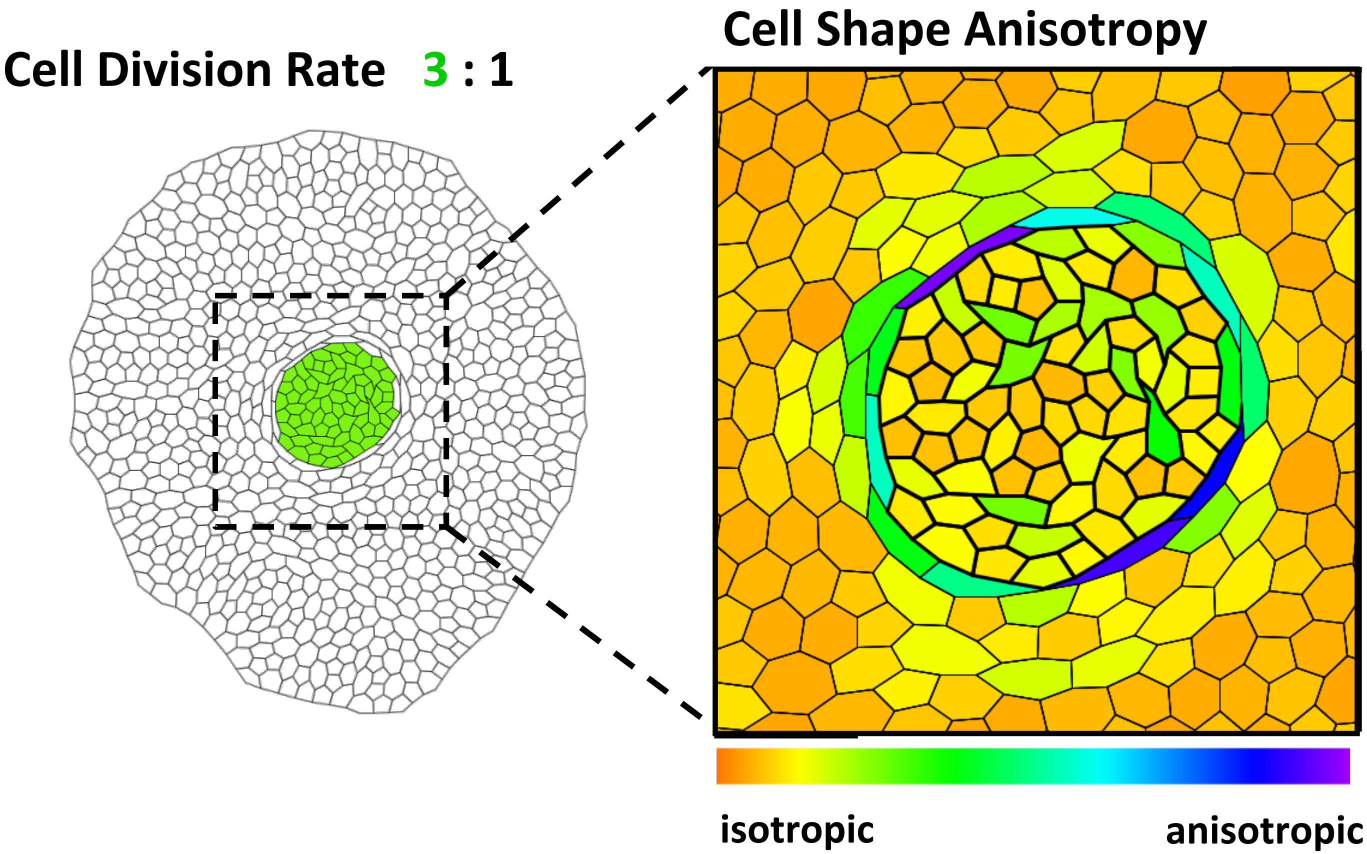
The boundary shapes qualitatively reproduces experiment

Cell division (growth) rate Green = Black

Green > Black

Drosophila wing disc, Tsuboi, Ohsawa, Igaki, KF, unpublished

The differential growth elongates cells only at the boundary

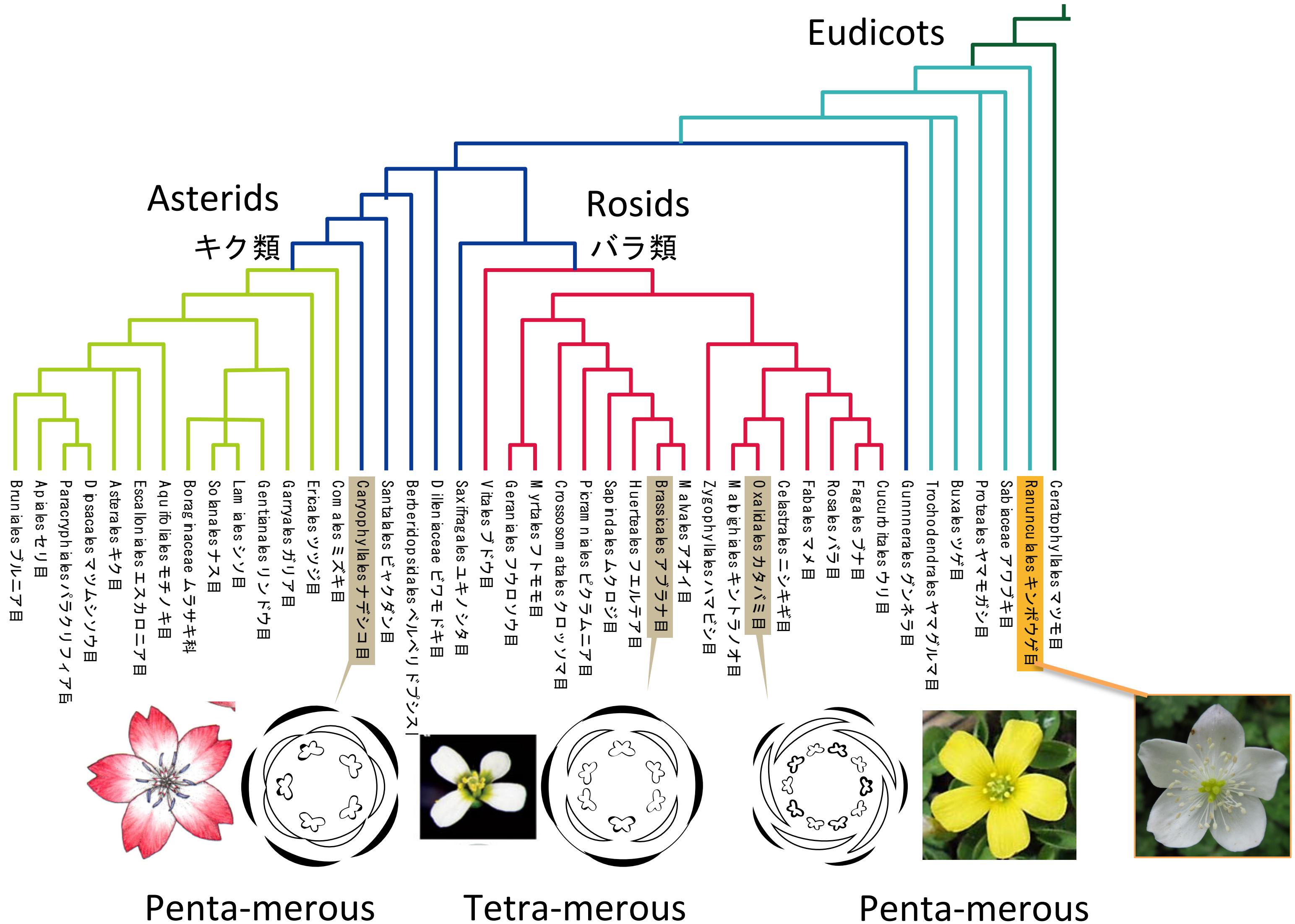


Boundary specificity
↓
Selective elimination of cells

- What we focus: Polygonal shape and tension.
- What we predict: Cells mechanically sense cell division rate difference from their neighbors.
- Experimental verification: Smoothed boundary and elongated cells.

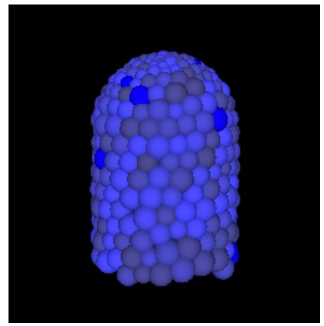
What developmental properties determine special organ numbers?

Floral organ numbers are mostly 4 or 5 in eudicots (双子葉植物)



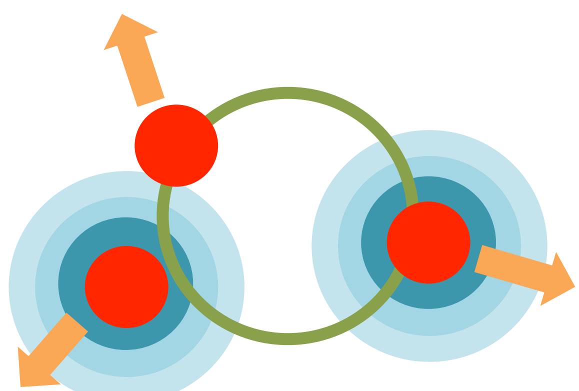
How to explore responsible properties for organ numbers

Biochemical patterning during organ arrangement

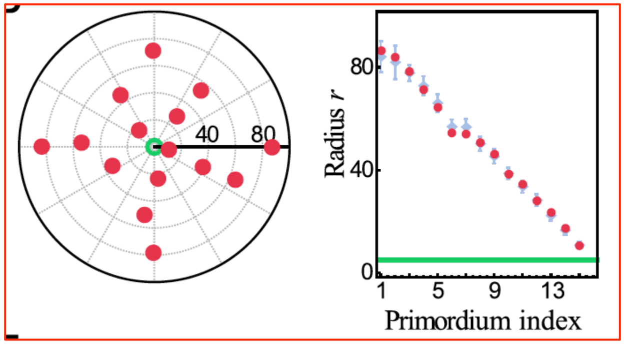


Coarse-graining of interaction between concentration spots.

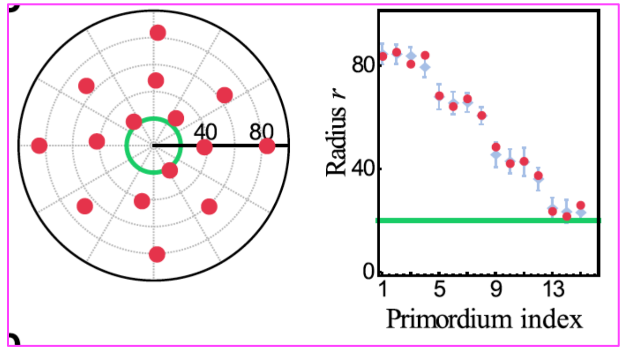
Organ positioning under repulsive potential



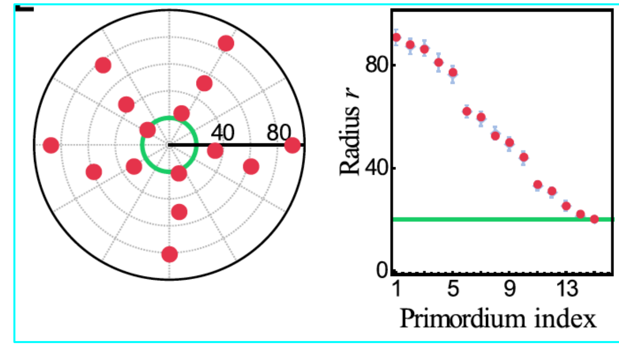
Emergence of concentric arrangement



Non-concentric



Tetra-merous <u>whorl</u>

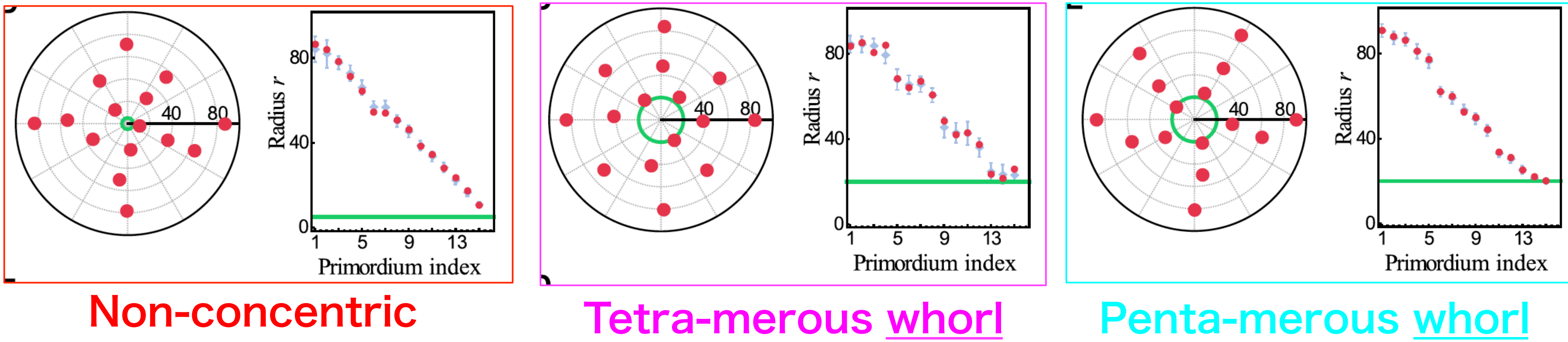


Penta-merous <u>whorl</u>

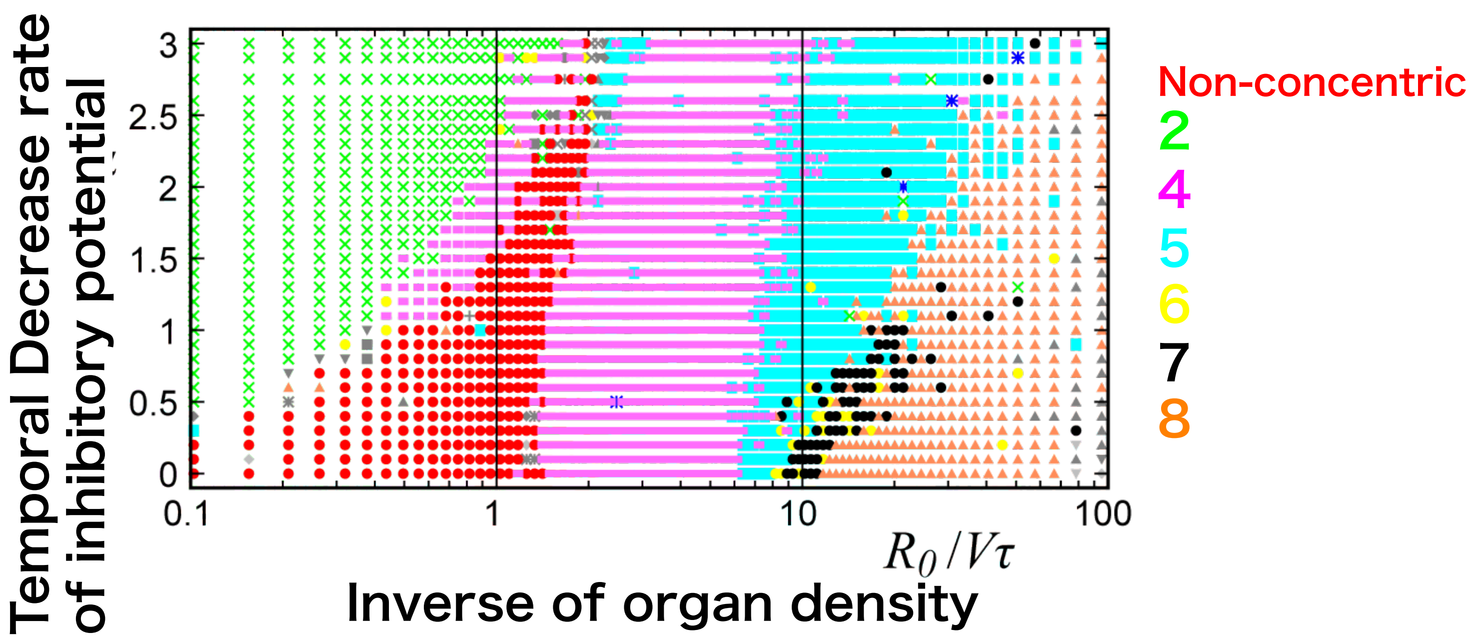
<u>Whorl</u>: concentric organ positioning

Kitazawa & KF, *Submitted.*

Dominance of 4 and 5

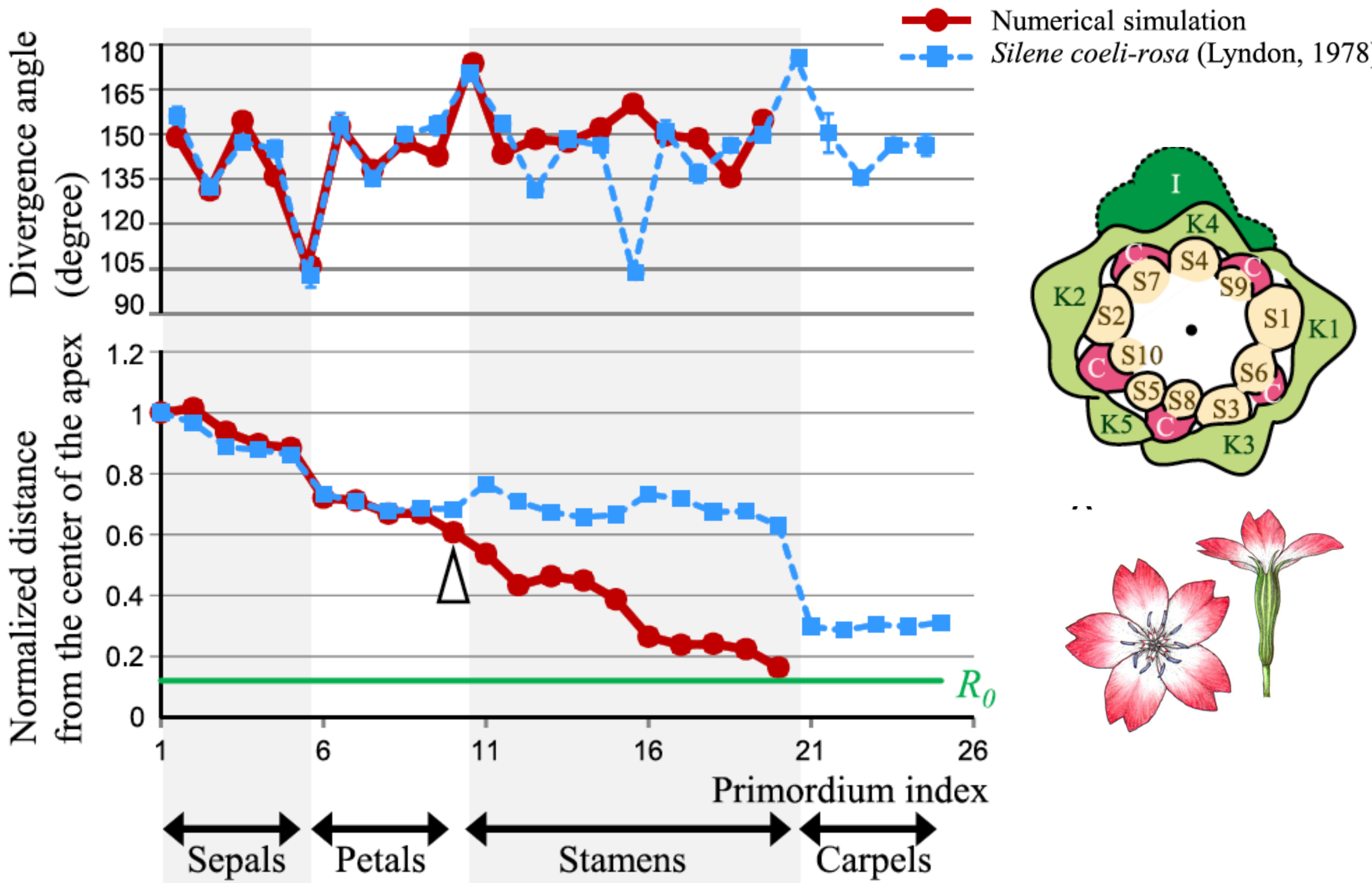


Whorl: concentric organ positioning



Kitazawa & KF, *Submitted.*

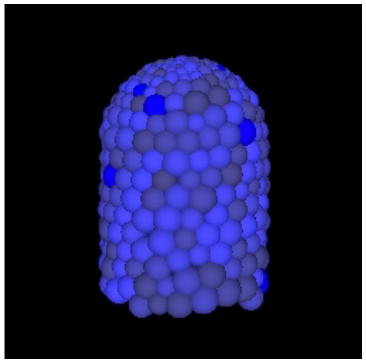
Reconstructing penta-merous floral organ positioning



Kitazawa & KF, *Submitted.*

How to verify the predictions

Biochemical and mechanical patterning during organ arrangement

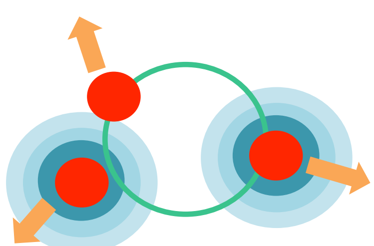


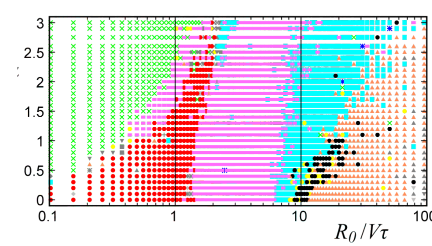
Alternation of organ positioning by perturbation into gene networks

Coarse-graining

1. Inferring genes from their spatio-temporal patterns and roles on organ positioning.
2. Comparing the gene mutants with the model predictions.

Organ positioning under repulsive potential

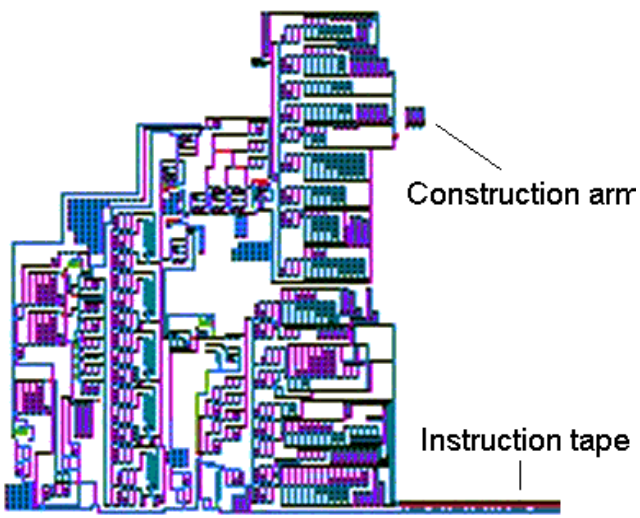




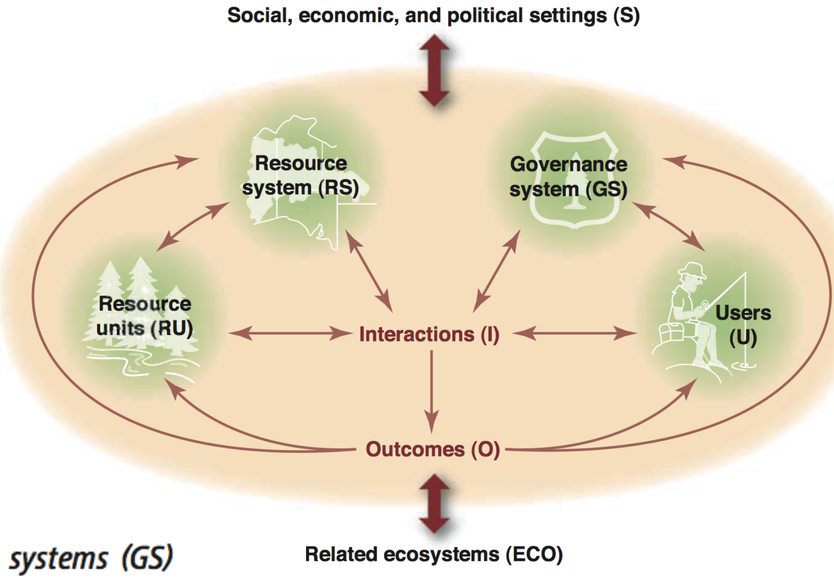
Two Future problems for Theoretical Biology

1. Complementarity of “mathematics-oriented” and “phenomena-oriented” approaches

Examples

Mathematics-oriented	Phenomena-oriented
Theory of Self-reproduction (J. von Neumann)  www.srm.org.uk	Theory of Evolution (C. Darwin)   http://www.biomedware.com/

2. How to "Self-organize" Sustainability of Socio-Ecological Networks



ramework for analyzing social-ecological systems.

Resource systems (RS)

RS1 Sector (e.g., water, forests, pasture, fish)
RS2 Clarity of system boundaries
RS3 Size of resource system*
RS4 Human-constructed facilities
RS5 Productivity of system*
RS6 Equilibrium properties
RS7 Predictability of system dynamics*
RS8 Storage characteristics
RS9 Location

Resource units (RU)

RU1 Resource unit mobility*
RU2 Growth or replacement rate
RU3 Interaction among resource units
RU4 Economic value
RU5 Number of units
RU6 Distinctive markings
RU7 Spatial and temporal distribution

Governance systems (GS)

GS1 Government organizations
GS2 Nongovernment organizations
GS3 Network structure
GS4 Property-rights systems
GS5 Operational rules
GS6 Collective-choice rules*
GS7 Constitutional rules
GS8 Monitoring and sanctioning processes

Users (U)

U1 Number of users*
U2 Socioeconomic attributes of users
U3 History of use
U4 Location
U5 Leadership/entrepreneurship*
U6 Norms/social capital*
U7 Knowledge of SES/mental models*
U8 Importance of resource*

*Subset of variables found to be associated with self-organization.

Ostrom, "A General Framework for Analyzing Sustainability of Social-Ecological Systems." *Science* (2009)

Recommended readings

- “Physical Biology of the Cell” (2nd ed. 2012)
- K. Kaneko, “Life” (Springer)
- Newman & Forgas, “Biological physics of developing embryo”

- 鈴木理、「分子生物学の誕生」（秀潤社, 1996）
- 人体の不思議　（講談社の動く図鑑）
  http://zukan-move.kodansha.co.jp/pc/contents/human.html