On the Mechanism of Wing Size Determination in Fly Development

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Math 485: Mathematical Modeling
The University of Arizona

Outline

- Statement of the Problem
- Background
- Proposal
- Mathematical Model
- Results
- Future Analysis

Forming a fly: the imaginal disc

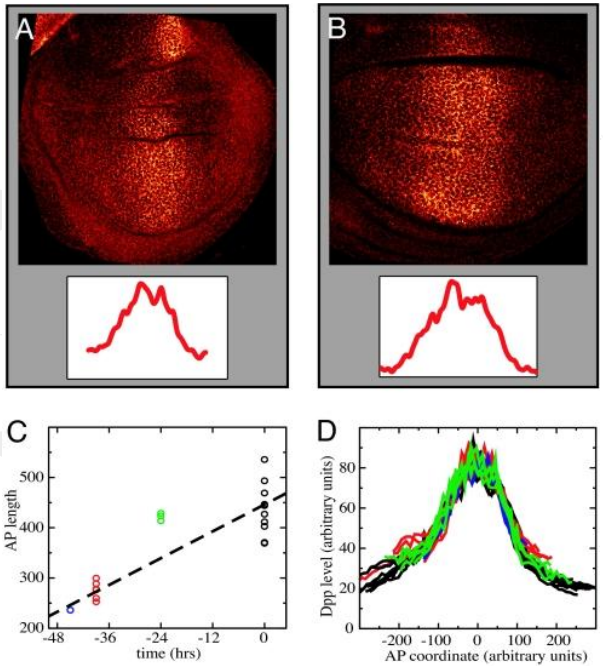
Problem

- Understanding the mechanism by which cells uniformly stop growing after a specific tissue has reached the appropriate size

- Understanding how there can be uniform growth although the gradient governing growth is not uniform

Other methods

- Day & Lawrence
  - Cells will/will not grow and divide depending on the steepness of the morphogen gradient [2]
- Positional Values
  - A value at cell birth based on where the cell is located relative to neighboring cells



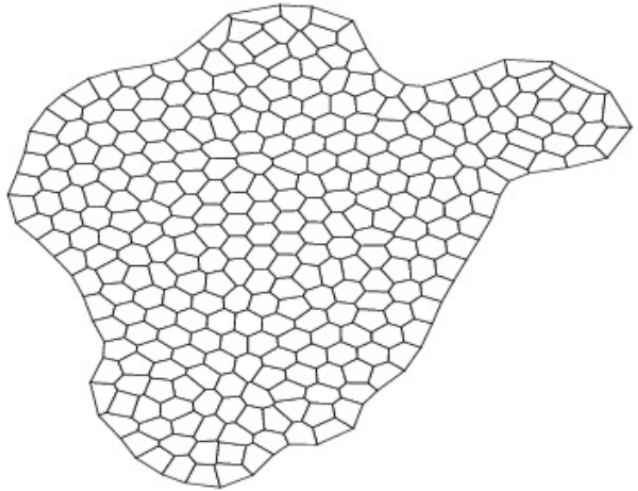
Proposal

- Cell growth is governed by the morphogen signal crossing a minimum threshold

- Tissues cease growth due to a negative feedback from mechanical stress on the cells

The Model

1. Assume a morphogen distribution, or gradient
2. Cells start off in mechanical equilibrium
3. Cell geometry
4. Cell division
5. The Cycle



The Model: A Mathematical Description

- Definition of Morphogen Gradient:

$$M(r) = me^{-r/\lambda}$$

r - morphogen concentration
m - morphogen amplitude
λ - characteristic length scale

- Definition of Mechanical Equilibrium:

$$E(r_i, \xi_\alpha) = \sum \text{(over } \alpha) \left[\rho_\alpha + a(V_\alpha - V_o)^2 \right.$$

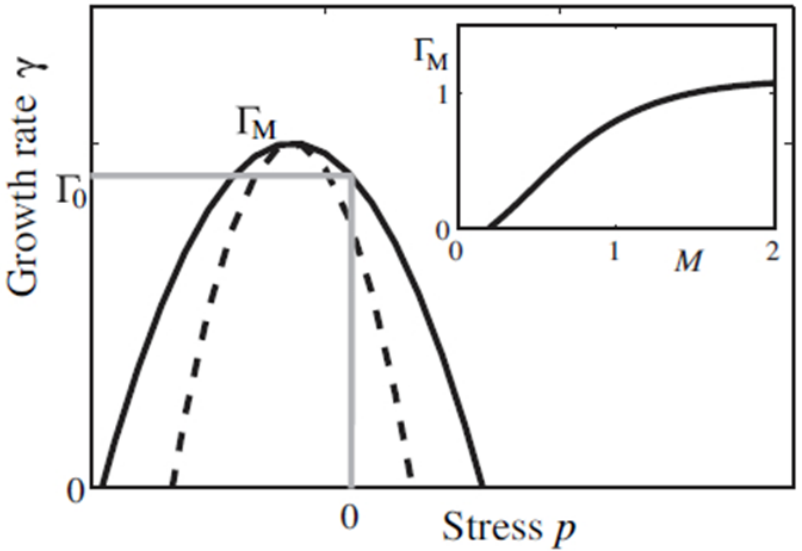
$$\left. + b \sum \text{(over } \beta = \upsilon(\alpha)) (\xi_\alpha - \xi_\beta)^2 + c(\xi_\alpha - 1)^2 \right]$$

r_i - vertices of cell
ξ_α - cell height
ρ_α - cell perimeter
V_α - cell volume
$V_\alpha = A_\alpha \xi_\alpha$
A_α - cell area (determined by r_i)

a - deviations of V_α from V_o
b - imposes a penalty on the variation of ξ_α between adjacent cells
c - controls deviations of ξ_α from unstressed value

$$\gamma(r,t) = \Gamma\big(M(r,t), p(r,t)\big)$$

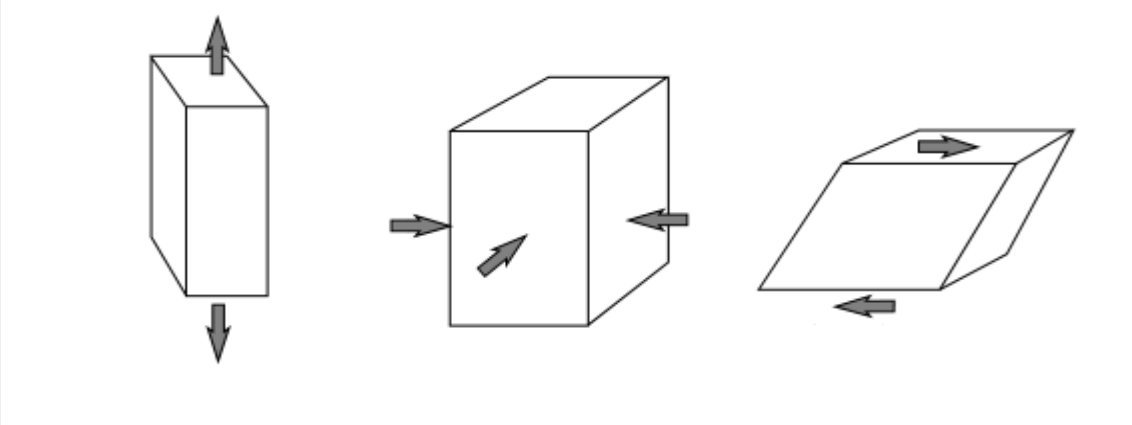
Local growth rate at position r and time t	Morphogen concentration	Local uniaxial compression stress



Elastic strain energy

The strain energy stored in an elastic material upon deformation.

Depend on displacement of all direction and transverse strains.



By determine the minimal elastic strain energy, we can find the relation between pressure and time.

$$H = \int d^2r[\frac{\mu}{2}\left(\Delta u_{ab} - \frac{\delta_{ab}}{2}\Delta u_{cc}\right)^2 + \frac{K}{2}(\Delta u_{cc} - \Delta t\gamma)^2 + \frac{w^2}{2}(\partial_a \Delta\xi)^2 + \frac{\beta}{2}\Delta\xi(\Delta u_{cc} - \Delta t\gamma) + \frac{K_\xi}{2}\Delta\xi^2]$$

Elastic strain energy	Energy caused by displacement of a tissue patch	Energy caused by displacement of a tissue patch	Energy caused by change of height	Energy caused by change in transverse strain	Energy caused by change in transverse strain

$$-w^2\nabla^2\xi\,(r,t) + \xi\,(r,t) = \alpha p(\mathrm{r,t})$$

The layer height $\xi(r,t)$ is proportional to the local stress

$$\gamma = \Gamma(\xi, M) = \Gamma M\,(M)[1 - q(\xi - \xi_0)\text{^}2\,]$$

$\xi(r,t)$ can not vary too rapidly with position and has a characteristic length w, below which its variation is suppressed

Result

I. Morphogen distribution is independent of disk size but depends on the parameters of morphogen production and spreading.

II. When disk boundary reaches the stress threshold the arrest of cell proliferation throughout the disk is induced by mechanical stress in the tissue.

Future Analysis:

- To simulate the model using a finite elements method coded in C and implemented in MATLAB
- To generalize a more realistic dual morphogen gradient
- To extend the model to a 3D structure

References

[1] Hufnagel L, Teleman A, Rouault H, Cohen S, Shraiman B (2007) On the mechanism of wing size determination in fly development. Proc Natl Acad Sci U S A 104: 3835–3840.

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[4] Lecuit T, Brook WJ, Ng M, Calleja M, Sun H, Cohen SM. Nature. 1996;381: 387–393

[5] Garcia-Bellido AC, Garcia-Bellido A. Int J Dev Biol. 1998;42:353–362.