Investigations of a Tissue Growth Model:

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
- Previous Research
- Proposal
- Mathematical Model
- Computational Model
- Results
- Conclusion

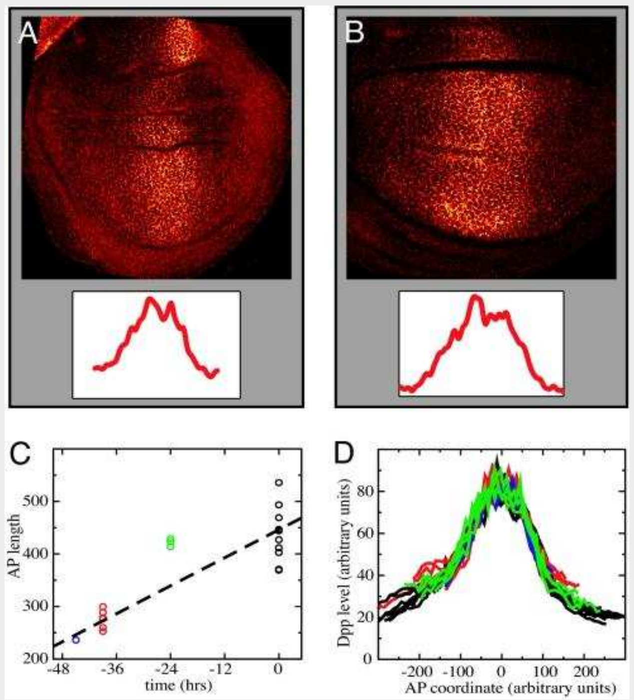
Problem

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

- To understand tissue growth and arrest within a non-uniform gradient distribution

Previous Research

- Day and Lawrence (2000) [2]
  - concluded cell growth was directly proportional to the length of the Dpp “strip”



- Lecuit and Brook (1996) [1]
    - concluded that cell growth was independent of a cells' positional value, but dependent on Dpp concentration
- Hufnagel and Teleman (2006) [3]
    - concluded that the length of the Dpp strip was independent of wing imaginal disc size
    - cell growth was regulated by mechanical stress within the tissue, driven by the morphogen gradient

Proposal

- Simulate the tissue growth model proposed by Hufnagel and Teleman
  - Comparing Cell Growth vs Time
  - Disk size as a function of growth parameters
- To investigate the role of pressure sensitivity on the growth of the cells

The Model: A Qualitative Description

-Hufnagel's Assumptions-

- All cells have the same size and same shape (hexagonal)
- Daughter cells immediately grow to their full size
- Pressure is caused by growth rate difference
- Pressure causes deformation
- Cells behave like a solid rather than a fluid, thus the deformation is very small (0.1%)

The Model: A Mathematical Description

- Definition of Morphogen Gradient:

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

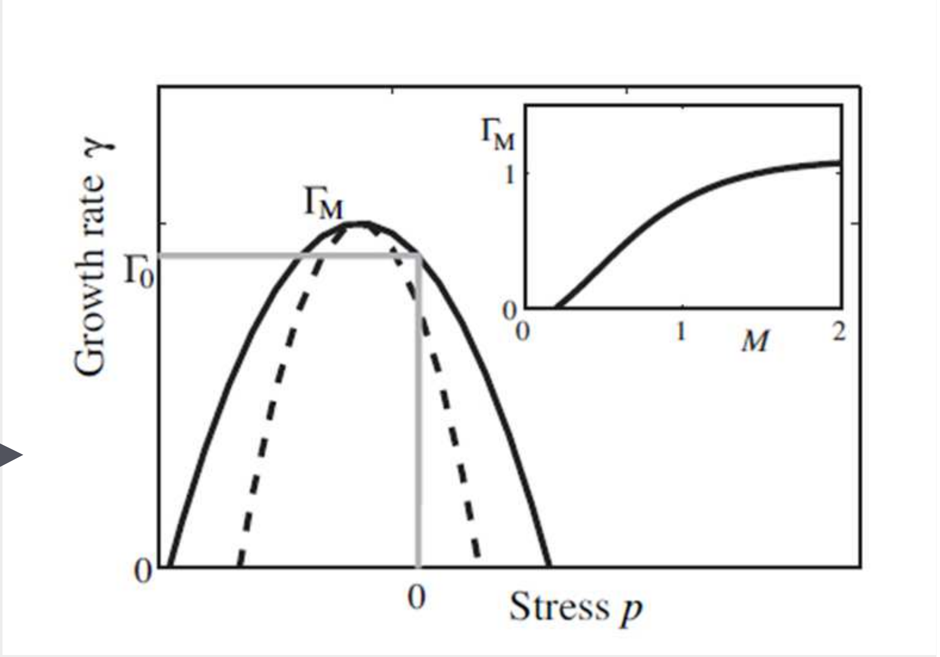
  - r - morphogen concentration
  - m - morphogen amplitude
  - λ - characteristic length scale

Growth Rate Model

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

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

Growth rate Vs Pressure



Computational Model - Considerations

- All cells have same size and shape (square)
- Daughter cells immediately grow to full size
- The daughter cells push other cells to the nearest empty space
- Tissue perimeter (to calculate area) is modeled by a “bounding box”

Computational Model - Construction

- Each turn go through all the grid to find empty space and cells
- Calculate each cell’s morphogen concentration and local pressure based on its position
- Calculate each cell’s possibility based on its morphogen concentration and local pressure

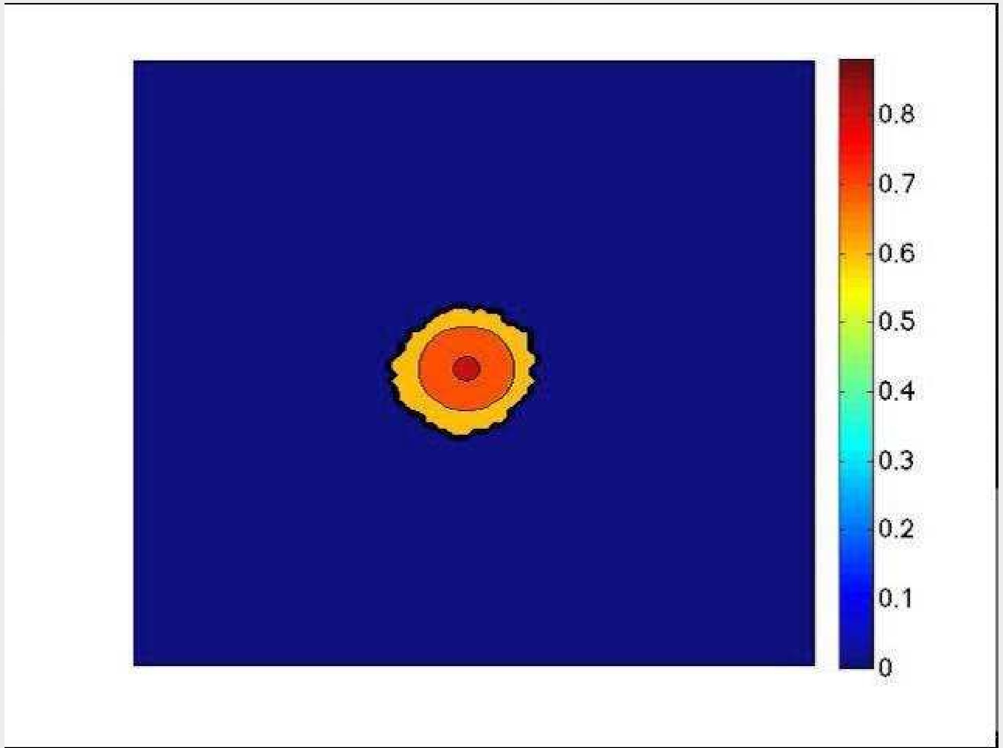
Computational Model - Construction

- Use a random number generator to determine whether the cell split or not
- If a cell splits, the daughter cell immediately grow to full size, and push a cell to the nearest empty spot
- Calculate the total number of cells to find the tissue size and total growth rate.

Computational Model - Construction

- Go through the grids again to find the edge of the tissue and determine the bounding box's perimeter
- Repeat the above steps until time reaches timemax

Results: Tissue Growth Model code generated and executed in MATLAB



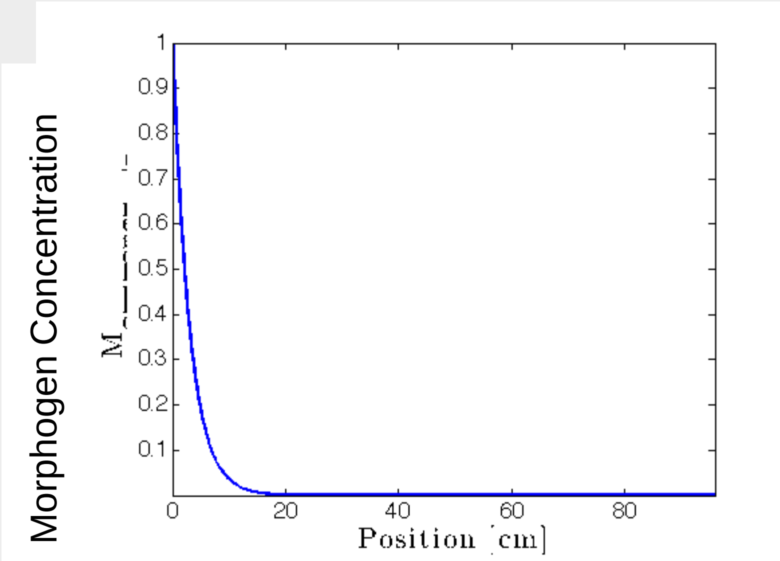
Results: Cell Growth and Its Relation to Morphogen Concentration and Gradient

- Cell growth caused by morphogen is determined by the exponential function:

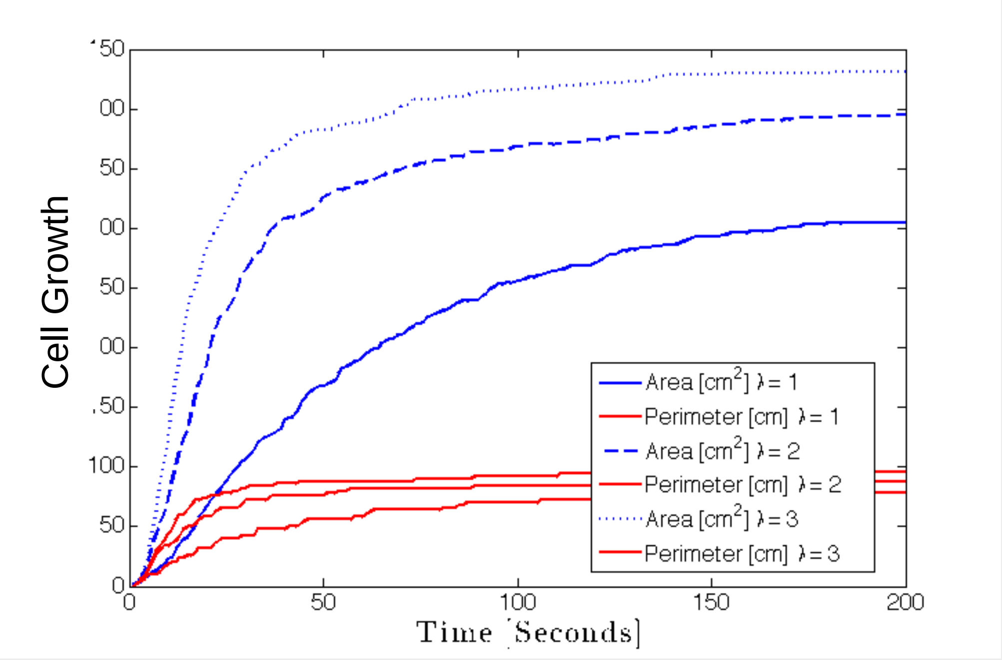
$$e^{-d/\lambda}$$

  - morphogen threshold =0.01
  - λ = characteristic length scale

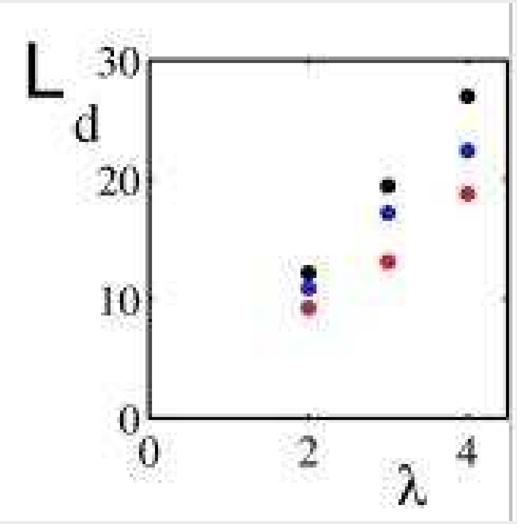
(in this case, λ = 2)



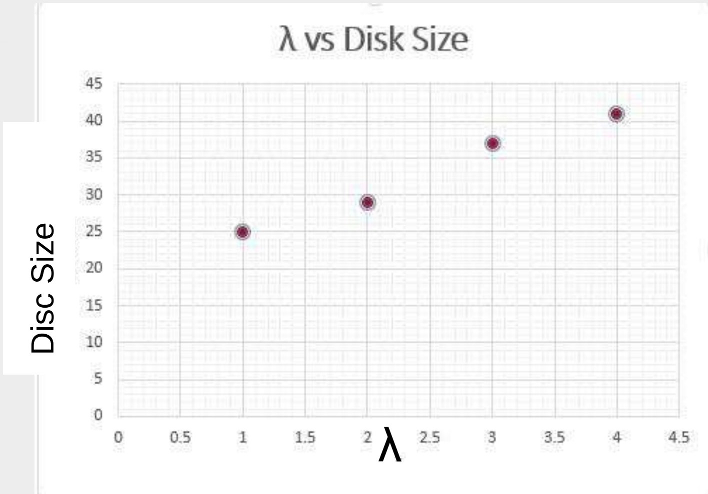
Results: Cell Growth is Proportional to Length of Dpp Strip



Results: Our Simulation is Quantitatively Similar to Hufnagel's Findings



Hufnagel's simulation



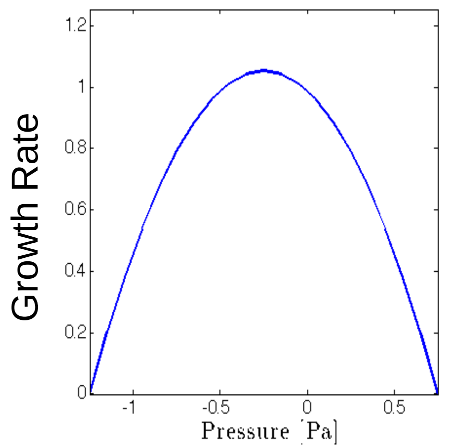
Our simulation

Results: Cell Growth and Its Relation to Mechanical Stress

- Cell growth caused by pressure is modeled by the quadratic:
  - -1.053*pressure(i,j)² - 0.527*pressure(i,j)+0.987
    - pressure is a function of the perimeter:

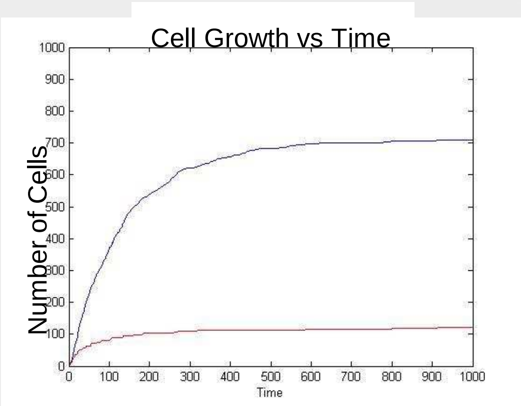
      pressure(i,j) = - (d - perimeter(dt)/2)/50

      (with p_min = -1.25 and p_max = 0.75)

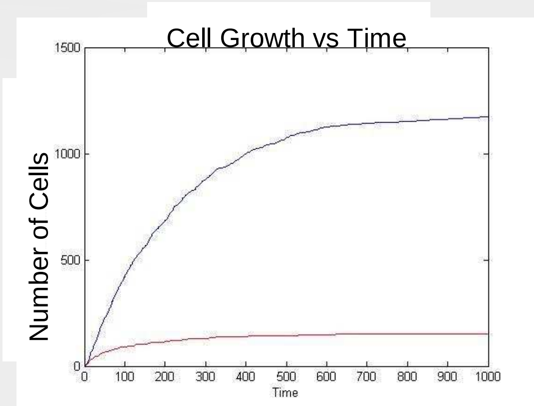


Results: Cell Growth and Its Relation to Mechanical Stress

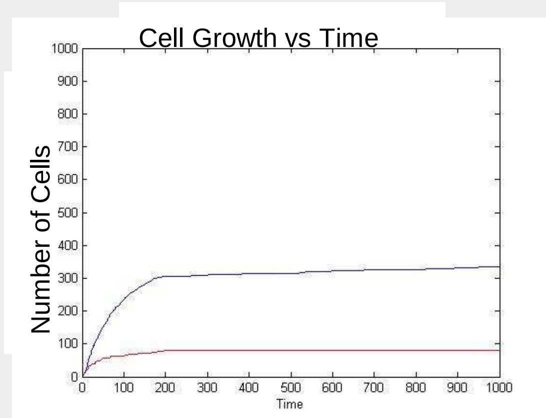
- Growth rate dependence on tensile pressure



Benchmark

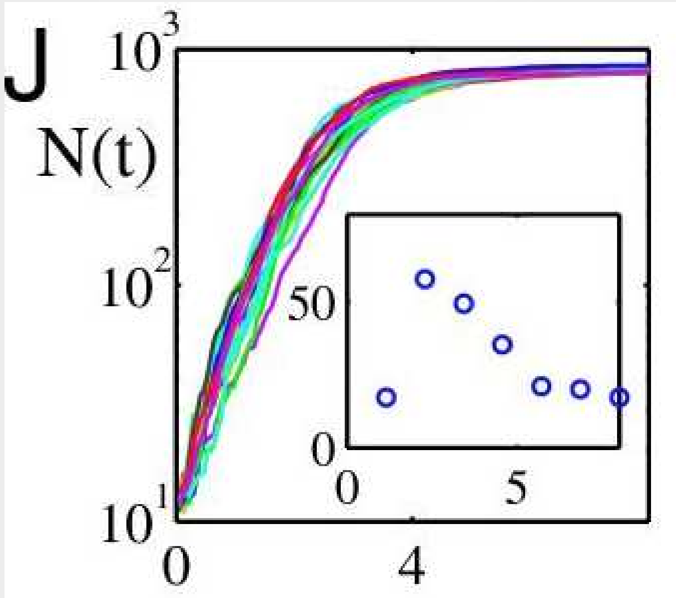


Insensitive group

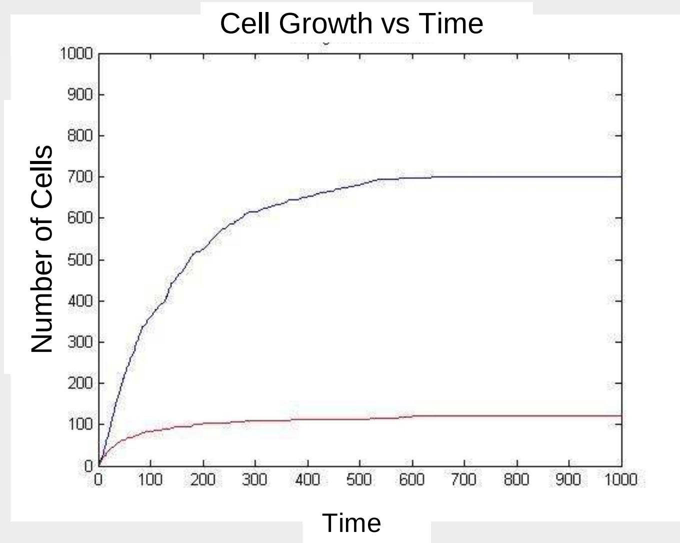


Sensitive group

Results: Our Simulation is Quantitatively Similar to Hufnagel's Findings



Hufnagel's simulation



Our simulation

Conclusion

- Hufnagel and his team:
  - Morphogen distribution is independent of disc size
  - When disc boundary reaches the stress threshold cell proliferation is ceased due to mechanical stress in the tissue
- Our model:
  - Cell geometry is generalized, and mechanical stress is simplified
  - Our results are quantitatively similar to the results found by Hufnagel and his team
  - Cellular growth is dependent on morphogen concentration and tensile pressure

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.

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

[3]Day SJ, Lawrence PA. Development (Cambridge, UK) 2000;127:2977–2987

[4] Tabata, T.. "Morphogens, their identification and regulation." *Development* 131.4 (2004): 703-712. Print.

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