Modeling Cell Polarization and Intercalation During Fruit Fly Development

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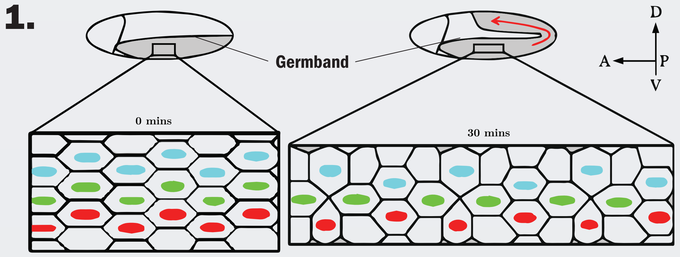
Introduction

During development of the fruit fly embryo, a collection of cells known as the germband approximately doubles in length along the head-to-tail (AP) axis and narrows in width along the front-to-back (DV) axis. Surprisingly, this occurs without external forces pulling on the tissue. The primary driving force for convergent extension arise internally within the cell through a process called cell intercalation. Cell intercalation is regulated by two main components, (1) biochemical signals at the cellular level and (2) mechanical forces and deformation.

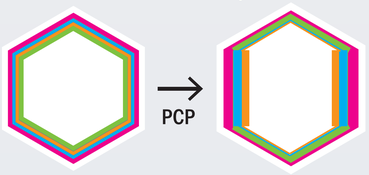
Germband Extension

1.



Germband extension is primarily driven by cell intercalation.
Planar cell polarity is a necessary precursor for cell intercalation.

2. Planar Cell Polarity (PCP):
Non-uniform distribution of proteins in a cell



Shroom Rok Bazooka Myosin

Shroom polarity on the vertical edges act as an upstream trigger for Rok polarity. Rok polarity in turn produces polarity in myosin. Rok inhibits Baz and Baz supresses myosin. This results in accumulation of Rok and Myosin on vertical edges and Baz on the shoulders.

The interplay between PCP and mechanical forces leads to cell intercalation:
Rearrangement of cells causes elongation along AP axis and narrowing along DV axis

3. Cell Intercalation: A Process Whereby Cells Move By Exchanging Neighbours

4 Cells: T1 Swap

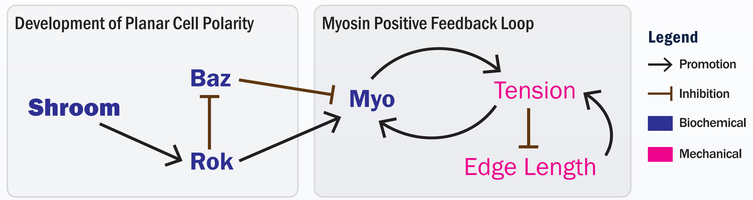
>5 Cells: Rosette Formation & Resolution

Both components of cell intercalation have been examined separately in prior experiments by biologists, yet, the connection between them remains elusive.

To help elucidate the underlying biological mechanisms of cell intercalation, we use mathematics to develop a differential equation model that describes the interaction between biochemical signals and mechanical forces:

- 2D vertex-based model with 733 coupled differential equations (ODEs). Each cell is represented as a hexagon with six vertices and six edges.
- Elastic cell edges carry four biochemical signals: Myosin, Rok, Baz and Shroom.
- Differential equations describe the motion of the vertices and the dynamics of four protein signals.
- The system is investigated by solving the ODEs numerically using a computer program developed in Python and MATLAB.

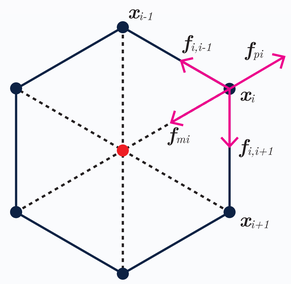
Biochemical Model



Myosin (Myo) Dynamics	Rho-Kinase (Rok) Dynamics	Bazooka (Baz) Dynamics
$\frac{dm}{dt} = k_1 R + k_2 mB - k^- m$ $k^- = k_3 e^{-k_4 f_{ij}}$ 1. Promotion of myosin by Rok 2. Suppression of myosin by Baz 3. Load-dependent association rate of myosin: as tension increases, dissociation decreases and myosin increases. (Positive Feedback Loop)	$\frac{dR}{dt} = q_R - k_r e^{-S} R$ 1. Source term for Rok 2. Dissociation rate of Rok Represents the polarizing effect of Shroom on Rok (as Shroom increases, Rok dissociation decreases)	$\frac{dB}{dt} = q_b - k_b RB$ 1. Source term for Baz 2. Dissociation rate of Baz Represents the effects of Rok inhibiting Baz

Mechanical Model

Forces Applied on a Vertex



1. Newton's Second Law of Motion

$$\eta \frac{d\mathbf{x}_i}{dt} = \sum \mathbf{f}_{ij} + \mathbf{f}_p + \mathbf{f}_m$$

2. Active and Passive Forces on an Edge

$$f_{ij} = \underbrace{\mu(l_{ij} - l_0)}_{\text{Passive Elasticity}} + \underbrace{\beta(m_{ij} - m^e)}_{\text{Active Tension due to Myosin}}$$

3. Pressure Force Resisting Change in Cell Volume

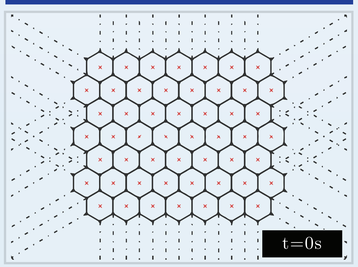
$$f_p = \alpha(A_0 - A)$$

4. Tension Towards Centroid Due To Medial Myosin

$$f_m = \beta A_m \sin^2\left(\frac{t\pi}{T} + \phi\right)$$

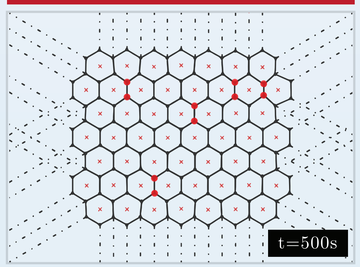
Simulation Rules

Initially, impose S=0.5 on all edges



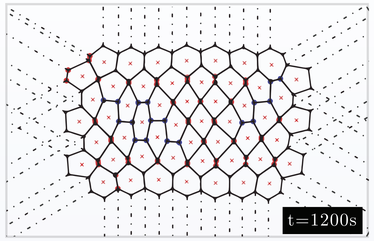
System undergoes gentle oscillations due to medial myosin until t=500s.

At *t*=500s, impose PCP on random edges

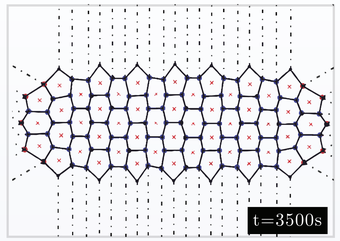


Select random vertical edges and impose S=1.0 on the vertical edges and S=0.625 on the surrounding shoulders.

Results

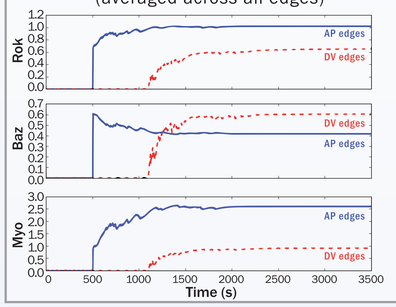


During the germband extension process.



Fully extended germband tissue.

Temporal Evolution of Protein Levels
(averaged across all edges)

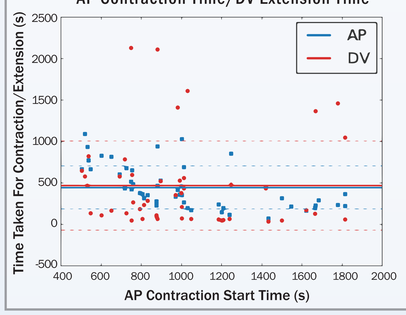


AP/DV Ratios

The magnitude of PCP can be quantified by the AP (vertical) to DV (horizontal) ratio of various proteins. We compare our model's predictions with literature values:

	Experiments	Model
Rok	1.5-1.9	**1.56**
Baz	0.48-0.50	**0.78**
Myo	~1.6	**2.78**

AP Contraction Time/DV Extension Time



Contraction/Extension Time

Experiments show that the duration of AP contraction is approximately 450-600s and the duration of DV extension approximately 360-600s. The durations in our model is in close agreement with literature values.

	Experiments	Model
AP (s)	450-600	**~250-500**
DV (s)	360-600	**~300-700**

The convergent-extension (CE) ratio is a measure of how much the germband elongated along the AP axis and narrowed along the DV axis. We examine the magnitude of convergent-extension by calculating the vertical-to-horizontal aspect ratio of the tissue at the start of the simulation divided by that ratio at the end (i.e.). In our model, the CE ratio is approximately 2.5. This is in close agreement with literature values of the CE ratio ranging from 2 to 2.5.

Conclusions

Our results show that the degree of PCP, timing of the structural changes and final amount of convergent-extension generated in our model are in close agreement with experimental data. Unlike prior vertex-based models in the literature, we do not postulate mechanical rules governing cell-cell interactions. Instead, we account for the underlying biochemistry and predict the mechanical outcomes.

Our research demonstrates how computational models, physics and mathematics can shed light on complex biological processes, which has important implications for the understanding of human development and the study of genetic diseases.