The emergence of geometric order in proliferating metazoan epithelia.

by Gibson *et al* – Computational Biology and Bioinformatics Seminar

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April 25, 2020

ETH Zurich

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Introduction

Motivation

'The organisation of cells into epithelial sheets is an essential feature of animal design.'

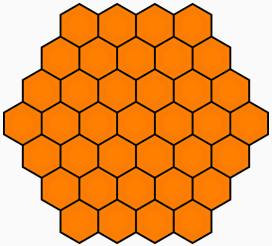
Gibson *et al* [2]

Context

Predictable geometries arise when *minimising surface energy* or *maximising space filling* in biological and non-biological structures:

Examples

- *Drosophila Melanogaster*'s retinal cells
- Honeycombs
- Coins on tabletops



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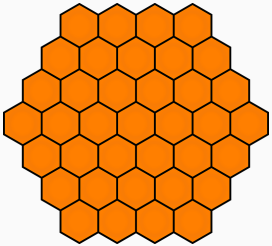

How is the geometry of *growing* epithelial cells organized and how can it be explained?

Geometry of *growing* epithelial cells

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Time-lapse movies collected revealed the following findings:

- Initially polygonal prophase cells rounded up and divided
- Cell-neighbour relationships were stably maintained throughout the cell cycle
- The topology of the divided cells is invariant over time.

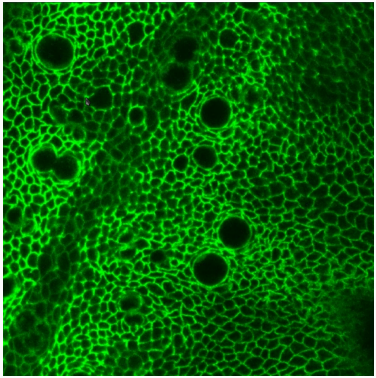

Figure 1: General hexagon-dominated topology of growing epithelial in *Drosophila Melanogaster*.

Model Assumptions

Post-mitotic relationship between two daughter cells

Stochastically marked cell lineages with GFP revealed stable post-mitotic patterns.

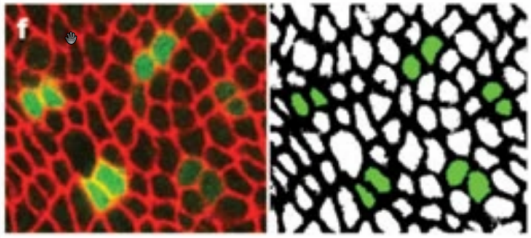

Figure 2: Daugher-cell relationship.

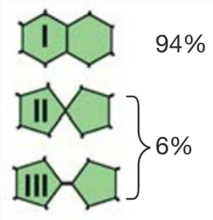

Figure 3: Observed post-mitotic relationship between daughter cells.

A Discrete Markov Model for Proliferating Epithelia

A discrete Markov model to model stochastic cell proliferation

s	state of the cell as its number of sides, where $s > 3$.
p_s	the relative frequency of s-sided cells in the population
$\mathbf{p}^{(t)}$	the infinite row vector $\mathbf{p}^{(t)} = [p_4, p_5, p6, \ldots]$ state of the population at generation t.
$\mathbf{p}^{(t+1)} = \mathbf{p}^{(t)}PS$	the state dynamics, where P and S are the probabilistic transition matrices.
P_{ij}	the probabilty that an i sided cell divides to produce a j-sided daughter cell.
S_{ij}	the probability of an i-sided cell will gain sides from dividing neighbour cells divisions to become j-sided.

Derivation of Markov state dynamics - transition matrix P

- P_{ij}: the probabilty that an i sided cell divides to produce a j-sided daughter cell.
- K_t: the number of junctions distributed to one daughter cell on division at generation t. $s_{t-1} - K_t$ are left for the other.

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- Because no triangular cells are observed, each daughter receives at least two junctions, leaving $s_t - 4$ junctions to be distributed among the daughters with equal probability.
- So, the number of junctions received by the first daughter is $K_t - 2 \sim \mathcal{B}(n = s_{t-1}, p = \frac{1}{2})$.

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- Therefore, the unnormalized entries of P are the coefficients of Pascal's triangle:

$$P = \begin{array}{c} \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ \vdots \end{array} \begin{array}{c} \begin{array}{cccccc} 4 & 5 & 6 & 7 & 8 & 9 & \dots \end{array} \\ \begin{pmatrix} 1 & & & & & & \\ 1 & 1 & & & & & \\ 1 & 2 & 1 & & & & \\ 1 & 3 & 3 & 1 & & & \\ 1 & 4 & 6 & 4 & 1 & & \\ 1 & 5 & 10 & 10 & 5 & 1 & \\ & & & & & & \ddots \end{pmatrix} \end{array}$$

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- On average the number of sides gained per cell is $\frac{2N}{2N} = 1$. That is, a cell will gain 1 side every cycle on average.
- Thus, $S_{ij} = 1$ if $j = i+!$ and 0 otherwise.

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 & & & & 0 & 1 & \\
 & & & & & 0 & 1 \\
 & & & & & & \ddots
\end{pmatrix}
\end{array}
$$

Predicting the equilibrium E from $T = PS$

The Perron-Frobenius theorem guarantees that a Markov chain will converge to a unique equilibrium $\mathbf{p}*$ where $\mathbf{p}*$ is the principal eigenvector of the transition matrix T.

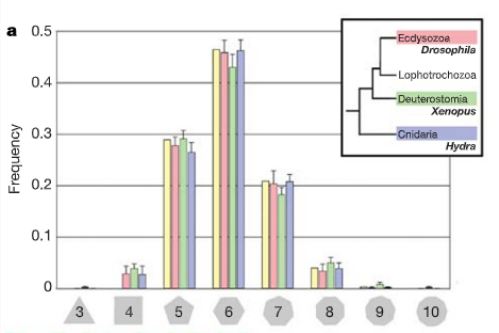

Figure 4: Distribution of the predicted and observed polygons

Robust equilibrium topology

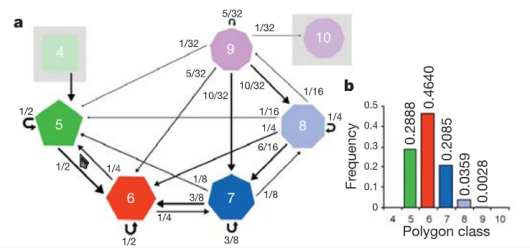

Figure 5: Discrete state dynamics

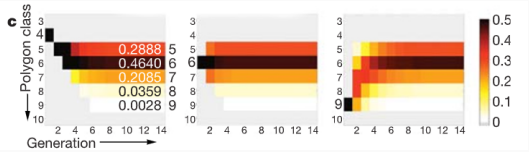

Figure 6: Figure showing the same attained equilibirum, no matter the initial conditions

Additional insights on mitotic cells

As seen in the construction of S, the average mitotic cell gains approximately one side, and daughter cells have one less side. Experimental evidence confirms this:

Non-mitotic cells	(5.94 ± 0.06)
Mitotic cells	(6.99 ± 0.07)

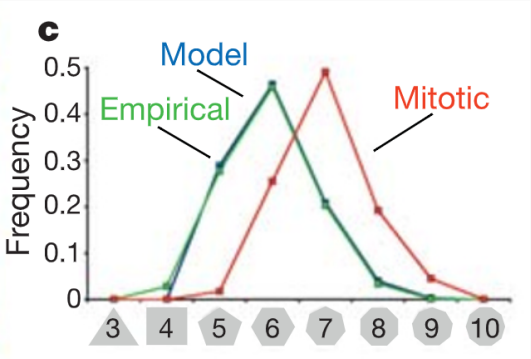

Figure 7: Polygon distributions of mitotic cells vs. non-mitotic cells

Polygon distribution of mitotic cells in non-proliferating tissues

The polygon distribution of proliferating cells in a non-proliferating tissue is not the same as that in proliferating tissue. This is demonstrated by forcing mitosis (using a proten named *string*, abbreviated *stg*) in some cells in quiescent tissue.

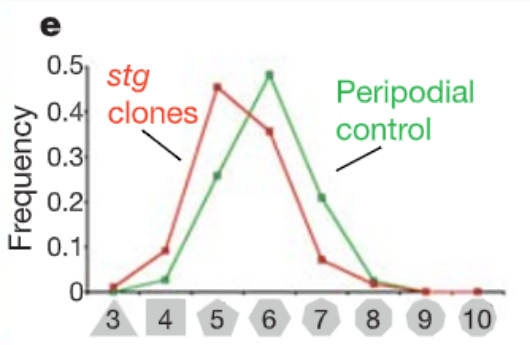

Figure 8: Distribution of polygons in non-proliferating titsue

→ Differential proliferation influences cell shape and morphogenesis (not modelled here).

Subsequent work

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Work on 3D structures:

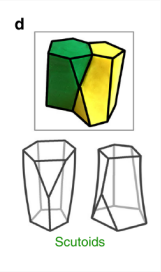

Figure 9: The scutoid has been discovered as a solution to 3D cell packing.[3]

Work on dynamics

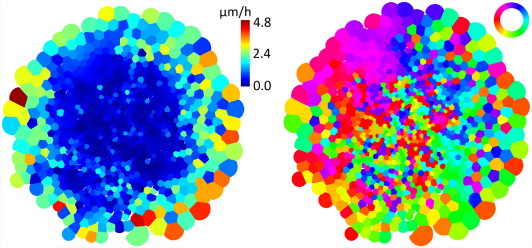

Figure 10: Modelling and prediction of speed and direction of proliferating epithelia. [1]

Take home messages

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1. shows how epithelial topology can be irregular, but **not random**.

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4. shows an **emergent mechanism** by which epithelia accomodate **rapid proliferation** while maintaining **structural integrity**.

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1. shows how epithelial topology can be irregular, but **not random**.
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3. predicts the **overall distribution** of polygonal cell types
4. shows an **emergent mechanism** by which epithelia accomodate **rapid proliferation** while maintaining **structural integrity**.
5. Provides a **framework** for investigating other models for **cell division** such as **cleavage plane** choices or **aberrant cell division**.

Questions?

Backup slides - Assumptions of the recurrence system

From the aforementioned observations observations we make the following assumptions about the mathematical modelling of cell epithelia:

- Cells are polygons with a minimum of four sides
- Cells do not resort
- Mitotic siblings retain a common common junctional interface
- Cells have asynchronous but uniform cell cycle times
- Cleavage places cut a side rather than a vertex of the mother polygon
- Mitotic cleavage orientation randomly distributes existing tricellular junctions to both daughter cells.

Recurrence system

Figure 11: Topology changes during cell division

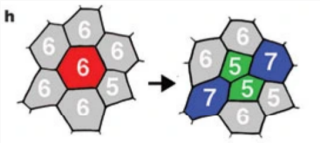

Table 1: Cell features, topological equivalence and evolution at division t

Cell feature	Graph equivalent	Evolution at division t
Tricellular junction	Vertex, v_t	$v_t = v_{t-1} + 2f_t$
Cell side	Edge, e_t	$e_t = e_{t-1} + 3f_{t-1}$
Apical cell surface	Face, f_t	$e_t = e_{t-1} + 3f_{t-1}$

So we can construct the following system:

$$s_t = \frac{2(e_t + 3f_{t-1})}{2f_{t-1}} = \frac{s_{t-1}}{2} + 3$$

which exponentially converges to 6 provided the initial condition:

$$s_t = 6 + 2^{-t}(s_0 - 6)$$

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