The emergence of geometric order in proliferating metazoan epithelia.

by Gibson *et al.* *Nature*, 2006

Computational Biology and Bioinformatics Seminar

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ETH Zurich

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Introduction

Motivation

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

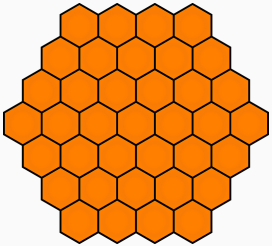
Gibson *et al* [**?**]

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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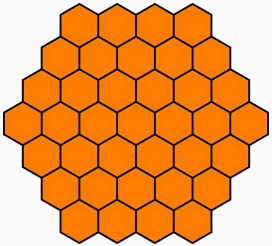

How is the geometry of *growing* epithelial cells organized and how can it be explained?

Emergent behaviour

$\rightarrow$ requires understanding emergent behaviours

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Emergent behaviour

It is the behaviour of a system that can *only* be explained by examination of a system's **parts** *and* their **relationships**.

Model Assumptions

Post-mitotic relationship between two daughter cells

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

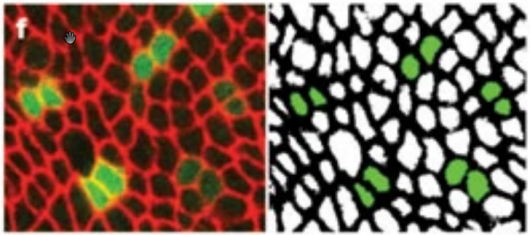

Figure 1: Daugher-cell relationship.

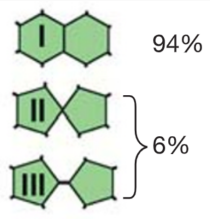

Figure 2: Observed post-mitotic relationship between daughter cells.

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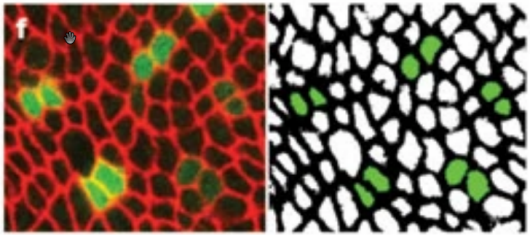

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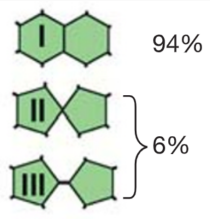
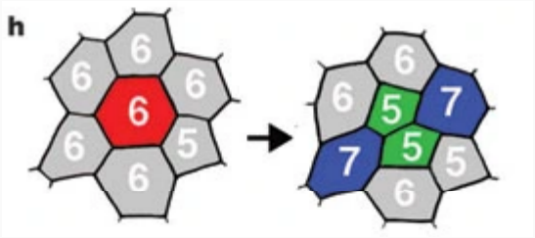


Figure 2: Observed post-mitotic relationship between daughter cells.

$\rightarrow$ required to model relationships between cells

Typical topology changes of a dividing cell

Figure 3: Topology changes during cell division



A Discrete Markov Model for Proliferating Epithelia

Markov models

A Markov chain is a discrete stochastic process with the Markov property:

$$P(X_t|X_{t-1}, \ldots, X_1) = P(X_t|X_{t-1})$$

where X_t is the time-dependent r.v. describing the state of the system at time t.

It is determined by a probability transition matrix P and an initial probability distribution.

Applying a discrete Markov model to growing epithelkiia

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P_{ij}	the probability 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.

Transition matrices

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

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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

Predicting the equilibrium E from $T = PS$

The Perron-Frobenius theorem guarantees that a Markov chain will converge to a unique equilibrium E which is the principal eigenvector of the transition matrix $T = PS$.

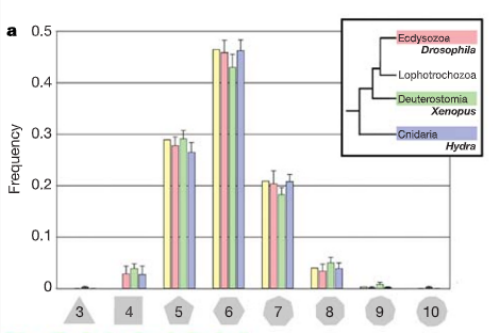

Figure 4: Distribution of the predicted and observed polygons (yellow: predicted equilibirum)

Robust equilibrium topology

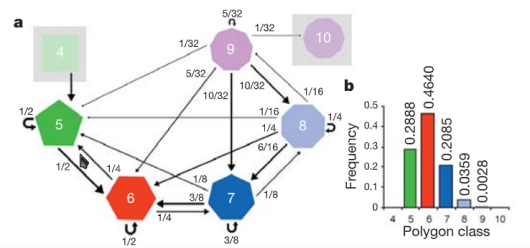

Figure 5: Discrete state dynamics

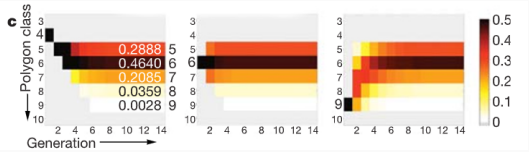

Figure 6: Figure showing the same attained equilibirum, no matter the initial conditions

Additional insights on mitotic cells

As seen in S, a mitotic cell gains on average 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)

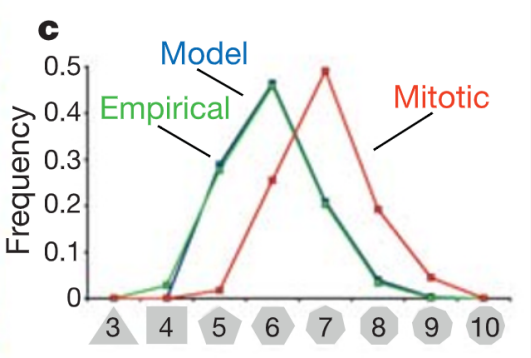

Figure 7: Polygon distributions of mitotic cells vs. non-mitotic cells

$\rightarrow$ cells accumulate sides until division.

Polygon distribution of mitotic cells in non-proliferating tissues

- The model does not apply to non-proliferating tissue
- Forcing mitosis using *string (stg)* in tissues does not replicate the proliferating tissue distribution.

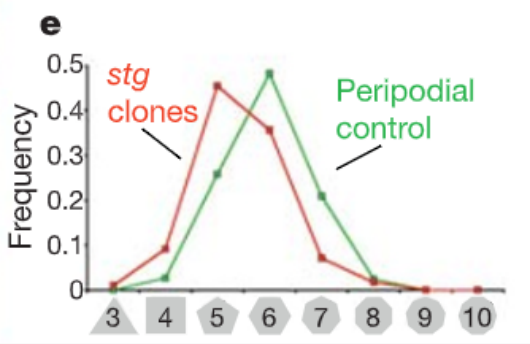

Figure 8: Distribution of polygons in non-proliferating tissue

→ Differential proliferation influences cell shape and morphogenesis.

Subsequent works

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→ additional work done to factor in biophysical aspects [**?**].

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Work on 3D structures

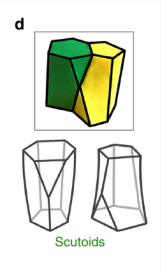

Figure 9: The scutoid has been discovered as a solution to 3D cell packing.[**?**]

Work on dynamics

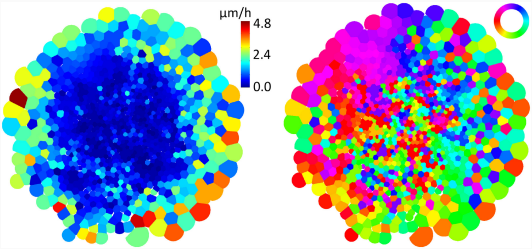

Figure 10: Modelling and prediction of speed and direction of proliferating epithelia. [**?**]

Conclusions

Take home messages

The proposed **discrete Markov chain**:

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

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The proposed **discrete Markov chain**:

1. shows how epithelial topology can be irregular, but **not random**.
2. **explains the predominantly hexagonal topology** of growing epithelia as well as the distribution of other polygons.
3. shows an **emergent mechanism** by which epithelia accomodate **rapid proliferation** while maintaining **structural integrity**.

Questions?

 https://github.com/pjhartout/CBB_Seminar

Geometry of *growing* epithelial cells

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.

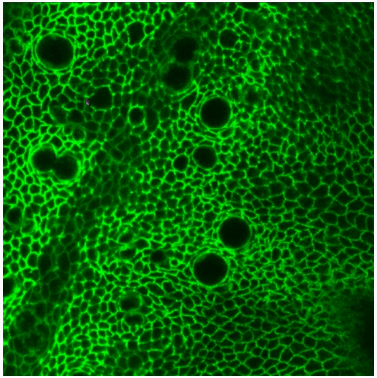

Figure 11: General hexagon-dominated topology of growing epithelial in *Drosophila Melanogaster*.

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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- As a result $P_{ij} = P(K_t + 2 = j | s_{t-1} = i) = \binom{i-4}{j-4} \cdot \frac{1}{2^{i-4}}$
- Therefore, the unnormalized entries of P are the coefficients of Pascal's triangle:

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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.

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- Assuming N cells in an epithelium, the number of cells after one round of divisions is $2N$
- 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 $j = i + 1$ and 0 otherwise.

$$
S = \begin{array}{c} \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ \vdots \end{array}
\begin{array}{c}
\begin{array}{cccccccc} 4 & 5 & 6 & 7 & 8 & 9 & \dots \end{array} \\
\begin{pmatrix}
0 & 1 & & & & & \\
 & 0 & 1 & & & & \\
 & & 0 & 1 & & & \\
 & & & 0 & 1 & & \\
 & & & & 0 & 1 & \\
 & & & & & 0 & 1 \\
 & & & & & & \ddots
\end{pmatrix}
\end{array}
$$

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

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:

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

References i