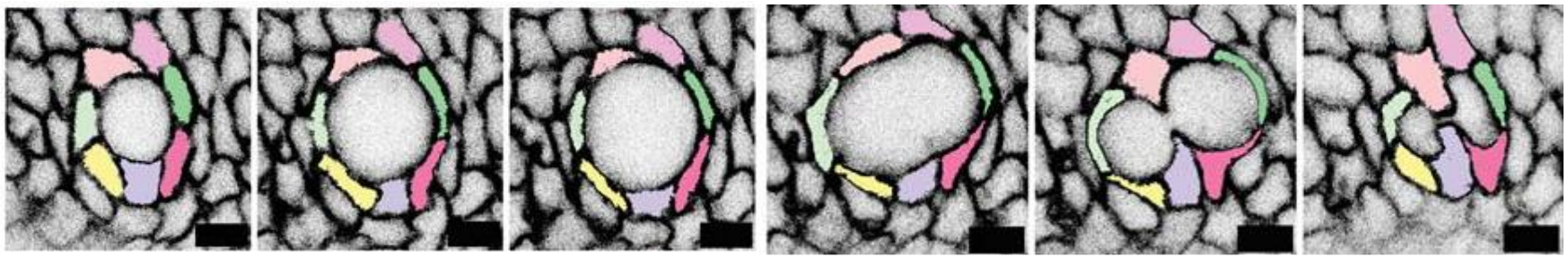
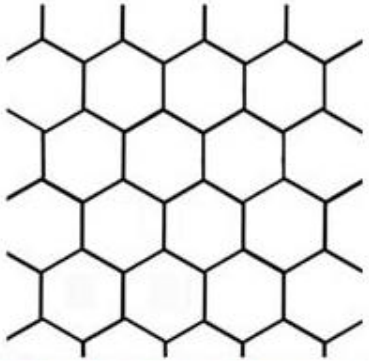
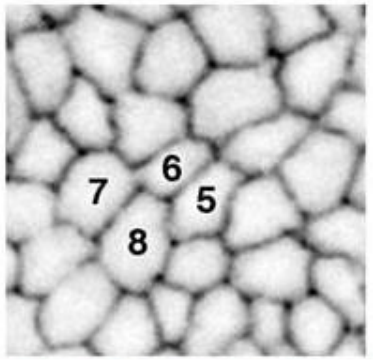
The emergence of geometric order in proliferating epithelial cells : a Markov chain approach



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History

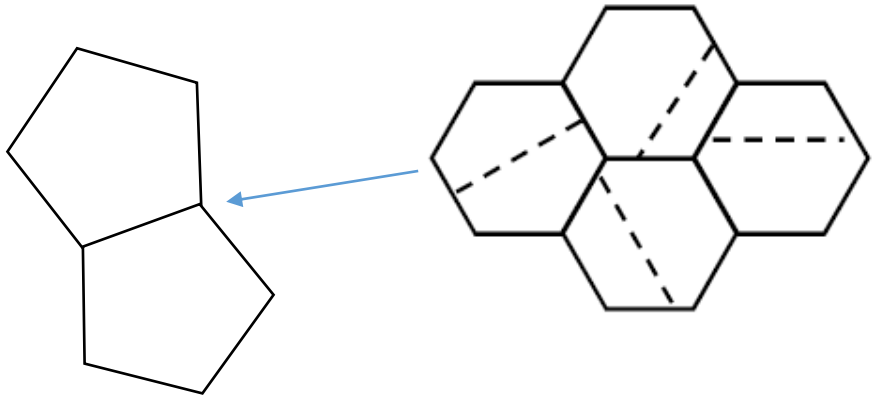




- From sponges to humans, the organization of cells into epithelial sheets is an essential feature of animal design.
- Historically, the ‘cobblestone’ topology of monolayer epithelia has been presumed to reflect optimal cell packing.
- Many biological and non-biological systems do indeed form predictable geometric arrays due to a tendency either to minimize surface energy or maximize space filling.
- Prominent examples include insect retinal cells, non-proliferating epithelia, honeycombs, compressed soap bubbles, and even coins pushed together on a tabletop.
- In contrast with these systems, proliferating epithelia rarely exhibit a honeycomb pattern
- discrete Markov model validated by time-lapse microscopy and clonal analysis to demonstrate that the distribution of polygonal cell types in epithelia is not a result of cell packing, but rather a direct mathematical consequence of cell proliferation.

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Cell division



Cell division results in two new vertices and three new sides per cell.

Findings

- On the basis of in vivo analysis of mitotic cell junction dynamics in Drosophila they mathematically predict the convergence of epithelial topology to a fixed equilibrium distribution of cellular polygons.
- This distribution is empirically confirmed in tissue samples from vertebrate, arthropod and cnidarian organisms, suggesting that a similar proliferation-dependent cell pattern underlies pattern formation and morphogenesis throughout the metazoa.

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Method

- The state of a cell, s, as its number of sides where s > 3.
- Will derive the probabilistic transition matrices P and S.
- The relative frequency of s-sided cells in the population was defined as p_s, and the state of the population at generation t as an infinite row vector $p(t) = [p_4, p_5, p_6, p_7, p_8, \ldots]$
- The state dynamics is described by $p(t+1) = SPp(t)$
  where P and S are probabilistic transition matrices

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Matrix P:

- P_{ij}: is the probability 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, leaving $S_{t-1} - K_t$ for the other.
- Assumption: each daughter receives at least two junctions from the parent, leaving $S_{t-1} - 4$ junctions to be distributed among the daughters.(no triangular cells are observed empirically)
- The distribution of these remaining junctions as balls thrown into one of two bins (daughters) with equal probability.

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Binomial distribution

- Thus, the number of additional parental junctions received by the first daughter is $K_t - 2$, a binomial random variable with parameters $n = S_{t-1} - 4, p = 1/2$
- Finally, each daughter also gains two new junctions as a result of the newly created interface.
- Therefore, the probability of transition from an i-sided cell to a j-sided daughter is

$$P_{ij} = \Pr[K_t + 2 = j | S_{t-1} = i] = comb(i-4, j-4)/2^{(i-4)}$$

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$$\begin{pmatrix} 1 & 1/2 & 1/4 & 1/8 & 1/16 & \cdots \\ 0 & 1/2 & 1/2 & 3/8 & 1/4 & \cdots \\ 0 & 0 & 1/4 & 3/8 & 3/8 & \cdots \\ 0 & 0 & 0 & 1/8 & 1/4 & \cdots \\ 0 & 0 & 0 & 0 & 1/16 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix}$$

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Shift Matrix S:

- accounts the effect of neighbor cell divisions on the polygon class of a given cell
- the entries, S_{ij}, represent the probability that an i-sided cell will gain sides from dividing neighbours to become j-sided.
- On mitosis, a cell adds one side to each of two neighbouring cells.

$$\begin{pmatrix} 0 & 0 & 0 & 0 & \cdots \\ 1 & 0 & 0 & 0 & \cdots \\ 0 & 1 & 0 & 0 & \cdots \\ 0 & 0 & 1 & 0 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix}$$

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Steady State

- classes: {4} is transient and {5, 6,…}is recurrent.
- Matrix SP is truncated to form a finite-dimensional mXm matrix ~ P.
- if m > 15, then $2^{1-m} < 1 \times 10^{-4}$. Approximating the elements of the truncated matrix ~ P to four decimal places yields a stochastic matrix of dimension m X m; the transition matrix for a finite Markov chain model for proliferating epithelial cells.
- The finite Markov chain applied to the set {5,6,7, …,10}is positive recurrent.
- Thus, there exists a unique stationary probability distribution. The approximate stationary probability distribution for cells up to 10 sides

  (0.2888, 0.4640, 0.2085, 0.0359, 0.0027, 0.0001)

With expected value = 6

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Validation:

