Mathematical Model of Epithelial Tissue: linking patterns of cellular division with tissue topology

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Abstract

Experimental observations reveal the striking identity of topological patterns formed by cells in various epithelial tissues: on apical (and basal) sides of epithelial tissue cells form polygons, and histograms of cell-edges distributions are practically identical for all inspected tissues. Since tissues form and grow as a result of cellular proliferation it is reasonable to assume that topology of cellular divisions underpins the topology of entire tissue. A few mathematical models have been reported which derive tissue topology from cellular division patterns. However, none of them have succeeded in reproducing experimental observations. Here, we report a new model which is represented by master equations and overcomes shortcoming of previous models. Particularly, based on simulations which we have performed using vertex model we concluded that the probability of cellular division should increase exponentially with the number of cell edges. This assumption turned to be critical for successful reproduction of experimental data.

Some Information

- The regulation of cellular division is one of the most important mechanisms that drive the development of living organisms.
- Many serious diseases such as cancer in epithelial tissue can happen as a result of abnormal divisions.
- The distributions of cell shape depend heavily on the pattern of proliferation but are independent of initial conditions.
- Cells in epithelial sheets and proliferating epithelia, often have approximately polygonal (different shapes) cross-sections (in 2D).
- A useful way to characterize this "tissue topology", cells have well-defined sided, is to build a histogram of CNN (Cell's number of neighbours).

number of edges per).

The most important previous models

The most important previous models that studied the cell-edges distributions:

1-Gibson's Model (GPNP Model).

The primary assumptions of the GPNP model are:

1. Complete absence of 3-sided cells.
2. The division leaves, at least, two mother nodes on each side of the divisional line (otherwise it is random).
3. Cells divide synchronously with discrete generations.

The results

GPNP model show very good agreement with the biological data except with one significant shortcomings representing by absent of 3% - 4% in the experimental observation for 4-sided cells [1].

2- Newman's Modification (SCWN modification) Models.

In these models, they pursued two improvements by re-examining assumptions 1 and 2 in the GPNP model[2].

SCWN models try to solve not only the problem of the absence of 4-sided cells but also to deal with the random process of distributing the edges of a mother between its daughters to be statistically more unbiased.

First SCWN Model:

This model allows three-sided cells.

Second SCWN Model:

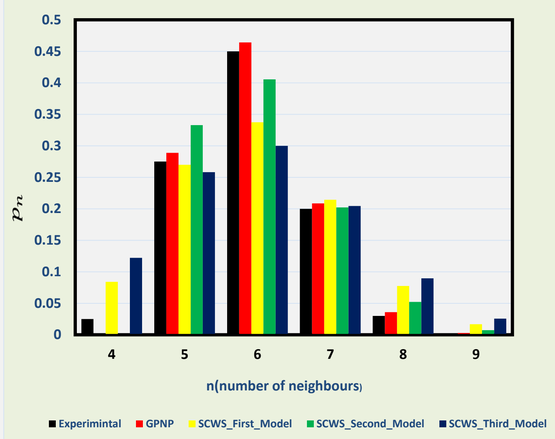
In this model, the nodes have been distributed purely random with the absence of three-sided cells.

Third SCWN Model:

In this model, the nodes have been distributed purely random with allowing three-sided cells.

The results :

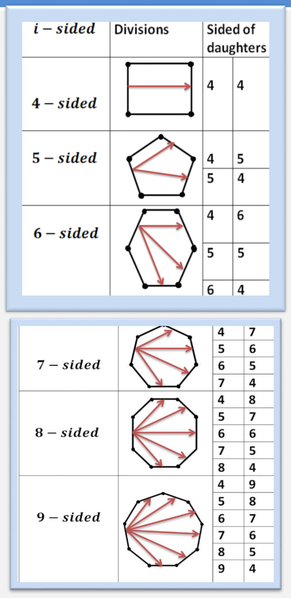
These models have also failed to be compatible with the biological data for Drosophila wing epithelium.



AAHV Model(Our Model)

In this model, we assume that

1. **The divisions are asynchronous.**
2. **A complete absence of cells with less than four neighbours.**
3. **Irrespective of junction rearrangements, the cell division is the only processes of development of the epithelial sheet.**
4. **N is the number of the cells, N_i (i=4,5…,9) is the number of cells with i edges, $p_i=\frac{N_i}{N}$, and t is the time.**



Basic form(BF)

$$\frac{dp_i}{dt} \cong \alpha\left[\frac{dN_i}{dN} - p_i\right], \text{where } \alpha = \frac{dN}{Ndt} \qquad (1)$$

The Cleavage pattern term in the BF(CPT)

The only term that will be changed in BF according to the different types of the pattern is $\frac{dN_i}{dN}$.

In our model, after fixing the first side of the cleavage plane, the second side can be chosen in one of three ways: equal probabilities, binomial, and equal split cleavage patterns. The matrix form can be used to constitute the cleavage pattern term (CPT) for these types and as follows:

$$\frac{dN_i}{dN} = M_i + K_i \qquad (i = 4,5, \dots 9) \qquad (2)$$

where the term M_i is dependent on the type of pattern and this will be described later when we in detail explain these different types.

$$K_i = -2p_i(1-p_i) - 2p_i^2 + 2p_{i-1}(1-p_{i-1}) + 2p_{i-1}^2, (i = 4,5, \dots 9) \qquad (3)$$

where K_i has relation to the neighbours of mitotic cells. The first term in (3) occurs, in case one of the two mitotic cell's neighbours, that will get an extra edge as a result of the division, have (i) sides and the other neighbour have a different number of sides. The second term in (3) occurs, in case the both of mitotic cell's neighbours, that will get an extra edge as a result of the division, have (i) sides. The third and fourth terms can be explained in a similar way with replacing (i) by $(i-1)$. Now, since we assumed that cells with less than 4 sides and cells with greater than 9 sides have been neglected in our model, therefore the terms (3, 4) and the terms (1,2) in the equation (3) have been cancelled in the case of K_4 and in the case of K_9 respectively.

- **Equal probability cleavage pattern (EP-CP)**

In this case, M_i can be represented as

$$M_i = 2\sum_{j=i}^{9} \frac{1}{j-3} p_j - p_i, \quad (i = 4,5,..,9) \qquad (4)$$

- **Binomial cleavage pattern (B-CP)**

In this case, M_i can be given as:

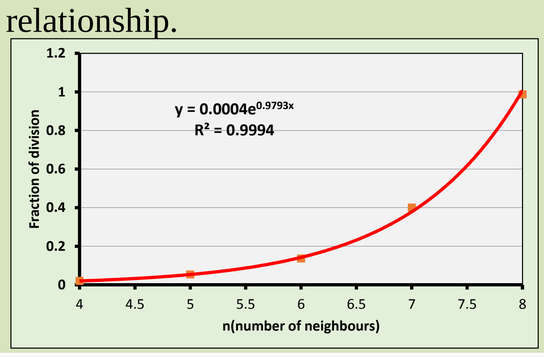
$$M_i = 2\sum_{j=i}^{9} \binom{j-4}{i-4} \frac{1}{2^{j-4}} p_j - p_i, (i = 4,5,..,9), \qquad (5)$$

- **The Equal Split Cleavage Pattern (EP-CP)**

In this case, M_i can be described as :

$$M_i = \begin{cases} 2p_{2i-4} + p_{2i-3} - p_i & if\ i = 4 \\ p_{2i-5} + 2p_{2i-4} + p_{2i-3} - p_i & if\ 4 < i < 7, \\ p_{2i-5} - p_i & if\ i = 7 \\ -p_i & if\ i > 7 \end{cases} \qquad (6)$$

The results that have been observed from the simulations data indicate that the division fraction of a cell is depending on the number of its edges. The following graph shows this relationship.



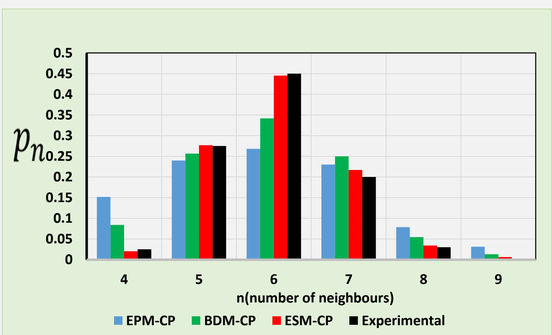
The modification models: (EPM-CP),(BM-CP), and (ESM-CP)

To reformulate the cleavage pattern term (CPT) for the models (EP-CP), (B-CP), and (ES-CP), the equations (4),(5), and (6) are multiplied by the values of σ_i for all i (σ_i denote the fraction of a division for $i-sided$ cells), hence the equation (2) for each of the new model can be described as

$$\frac{dN_i}{dN} = \sigma_i M_i + K_i, \qquad (i = 4,5, \dots 9), \qquad (7),$$

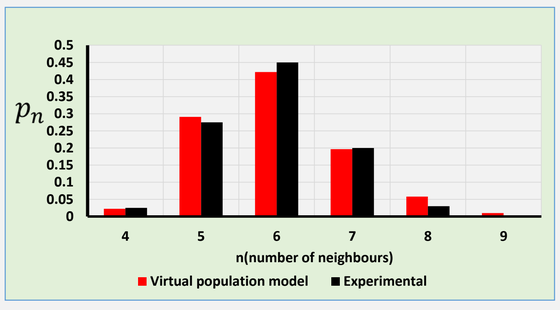
The Results:

This histogram illustrates that the distribution of cell-edges that obtained from ESM-CP (red) is a very good agreement with the experimental data (Black) and to some extend the distribution of cell-edges that obtained from BDM-CP (green) has also a good agreement with the biological observations.



The Virtual population model:

To construct this model, we start each step by choosing , using the equal split mechanism, a certain cell randomly to be a divided mother cell, then we select randomly two another cells to be its neighbours for adding to each of them An extra edge. The process is continuing many times and then the result have been represented as a histogram. The outcomes show a very good agreement with the experimental observations. In order to build this model we used the software Matlab2015.



Future Plane

1-Study topological characteristics of tissue, particularly the distribution of number of edges per cell in a tissue undergoing cellular mixing (i.e. plastic deformations).

2-Analysis mechanical properties of heterogeneous tissue.

acknowledgements

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References

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[2] S. A. sandersius, M. C., C. J. Weijer, and T. J. Newman (2011). Correlating cell behavior with tissue topology in embryonic epithelia. PLoS ONE 6, e18081.

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