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Extension of the Apposed-Cortex Adhesion Model (ACAM) to simulate proliferative tissues

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1. Introduction

Epithelial tissue morphogenesis, essential for organ development and regeneration, is driven by a multifaceted interaction among cell behavior, proliferation, apoptosis, and adhesion with cell topology serving as a critical determinant. Building on the foundational work of Gibson et al. (2009), this research aims to enhance our understanding of tissue dynamics by simulating the intricate behaviors of proliferative tissues.

Incorporating insights from Chélin et al. (2013) and Azzag (2011) regarding cellular packing in proliferative epithelia, which encompasses both experimental and numerical work, we propose a new, general, and extensible numerical model capable of simulating proliferative tissue development. To do so, we have extended an existing 2D model by Bergmann et al. (2022), named the Apposed Cortex Adhesion Model (ACAM).

Herein, we present the first use case of this extension of the ACAM model and the benefits it could bring to further advancing our knowledge about tissue topology during proliferation.

2. Methods

2.1 ACAM: Brief overview

ACAM elucidates the mechanics of actomyosin dynamics and cell adhesion during epithelial tissue rearrangements, with inspiration from *in vivo* studies in the *Drosophila* germ-band. Diverging from traditional Cell Vertex Models, ACAM emphasizes the geometry of cell junctions, representing each cell in a tissue as a continuous viscoelastic rope-loop, thereby capturing the complex interactions between neighboring cells. These are intricately coupled by

explicit adhesion spring elements, which undergo turnover with a timescale named τ_{adh} , illustrating the dynamic nature of cell adhesion.

Central to the ACAM is the distinction between passive and active mechanics. Passive mechanics is depicted through these elastic adhesion bonds and the viscoelastic nature of the cell cortex, capable of resisting bending and extension. This is further detailed by incorporating cortical turnover time, i.e. τ_{cor} , reflecting the physiologically relevant timescale over which the cortex exhibits viscoelastic behavior. Active mechanics is introduced via morphoelastic theory, simulating the intrinsic stresses generated within tissues that drive the complex process of cell rearrangements.

2.2 Extension of the ACAM for diverse tissue simulations

Using Voronoi diagrams and Lloyd's algorithm, we generated uniform tissue structures, where circular cells within Voronoi regions adhere to and mimic their stencils, eventually adhering to each other for diverse natural tissue architectures. A deformable boundary was used for the tissue perimeter (Fig. 1A).

Cell cycle modelisation and simulation

The cell cycle is modeled in three distinct phases: growth, mitosis and apoptosis.

Growth: Cells can grow either by increasing internal pressure, cortex extension, or both, with growth simulated as an exponential function. This method allows for the dynamic representation of cell growth within the tissue context.

Mitosis: Modeled as a tension distributed across two points of a cell, creating a pinching movement. This “actin ring” tension increases exponentially until the pinched region is less than a certain threshold ratio named r_{ring} of the cell's largest diagonal, at which point the cell is topologically divided into two daughter cells. Various laws can be used to determine the division axis: perpendicular to the principal stress axis, parallel to it, random...

Apoptosis: Dying cells may shrink due to negative pressure or cortical shrinkage. Once a cell becomes sufficiently small, it is eliminated, and the space is filled by neighboring cells flowing in and adhering to one another.

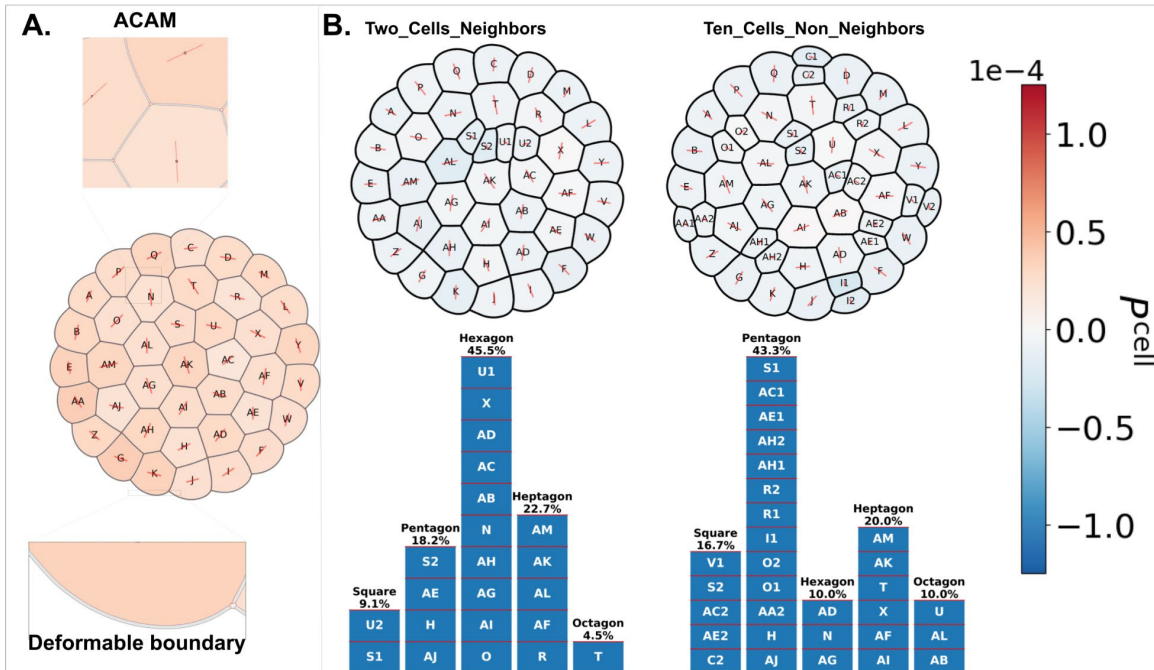


Figure 1: Comparative analysis of cellular division dynamics in epithelial tissue models. (A) Depicts the initial configuration using ACAM, delineating cellular structures within a deformable boundary framework. (B) Illustrates subsequent simulations: The division of two adjacent cells is shown on the left, while the division of ten dispersed cells is presented on the right. The corresponding histograms below each simulation provide tissue topology. The Color bar represents cell stress indices p_{cell} .

3. Results and discussion

Figure 1 juxtaposes two simulations of cell proliferation within an epithelial tissue model, starting from the same initial configuration: 20% of pentagons, 60% of hexagons and 20% of heptagons.

This comparative analysis reveals distinct tissue configurations when simulating the division of two neighboring cells versus ten non-neighbors. The histograms beneath each simulated tissue topology quantify changes in cell shape, while color bar provide a readout of cell stress, i.e. p_{cell} . Divisions conducted without a prior growth phase (G1) showed minimal changes in shape distribution for division counts below ten. However, as the number of mitoses reached 10 and 20, the distribution shifted towards a predominantly pentagon composition, representing 50% of the polygonal shapes (see Table 1).

Simultaneously, an increase in both lower-order shapes, such as triangles and squares, and higher-order polygons, like heptagons and octagons, was observed for all simulations.

Cell shape Distribution (%) by mitotic rate							
Mitotic rate	Triangle	Square	Pentagon	Hexagon	Heptagon	Octagon	9-gon
20*	0	8	45	27	10	10	0
10	0	17	43	10	20	10	0
10*	0	0	47	30	20	3	0
5	0	8	36	24	32	0	0
5*	0	12	20	36	24	8	0
3	0	9	26	35	22	8	0
3*	0	4	31	30	35	0	0
2	0	9	23	32	36	0	0
2*	0	9	18	45	23	5	0
1	0	0	24	57	19	0	0
0	0	0	20	60	20	0	0

* indicates that dividing cells are neighbors

Table 1: Cell shape distribution by mitotic rate in tissue lacking a prior growth (G1) phase. Stars indicate division of neighboring cells.

Differences between neighboring and non-neighboring cell divisions were slight, hinting that cell proximity might affect topology changes. However, the limited sample size (i.e. 40 initial cells) prevents drawing definitive conclusions. Moreover, divisions accompanied by growth further altered the tissue

topology, indicating that growth introduces additional perturbations (results not shown here).

Notably, neighbor exchanges during simulations were observed and influenced the final tissue topology, even with our initial model parameters. Future simulations with more cells are needed to better precisely determine the impact of these factors on tissue morphology.

4. Conclusions

These enhancements to the ACAM enable the simulation of complex tissue dynamics, covering cell growth, division, and apoptosis. With a rigorous method for tissue creation and cell cycle modeling, this expanded framework supports in-depth exploration of cellular behavior and tissue morphogenesis across various biological contexts. Moving forward, we aim to extend our research by simulating larger tissues with a greater number of cells and a diverse set of model parameters, to further understand the scalability and adaptability of the model to different biological scenarios. A 3D extension of present model is also currently in progress.

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Conflict of interest statement

The author declares that there are no conflicts of interest related to this research.

References

- Gibson, W. T., & Gibson, M. C. (2009). Cell topology, geometry, and morphogenesis in proliferating epithelia. *Current Topics in Developmental Biology*, doi:10.1016/s0070-2153(09)89004-2
- Chélin, Y., Averseng, J., Cañadas, P., & Maurin, B. (2013). Modèle granulaire de morphogénèse tissulaire. Retrieved from <https://hal.science/hal-00824090>
- Azzag, K. (2011). Origin of morphogenetic stability in metazoan epithelia (Doctoral thesis). Retrieved from <http://www.theses.fr/2011MON20112>
- Nestor-Bergmann, A., Blanchard, G. B., Hervieux, N., Fletcher, A. G., Etienne, J., & Sanson, B. (2022).

Adhesion-regulated junction slippage controls cell intercalation dynamics in an Apposed-Cortex Adhesion Model. *PLOS Computational Biology*. <https://doi.org/10.1371/journal.pcbi.1009812>

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