Divided media based simulations of tissue morphogenesis

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1. Introduction

Tissue morphogenesis is a key point remaining weakly understood in development biology. In particular, whatever the species considered (animals and vegetables), most of formed epithelial tissues show analogous cell polygonal distributions (Gibson 2009). Accordingly, one may wonder if there are invariant features governing this process. Among the numerous studies performed up today to answer this question, only few approaches including physical models have been developed (Graner et Glazier, 1993; Martinand-Mari et al., 2009). These models allow cellular reorganisation within tissues already formed but by considering only limited movements and without any growing cells, which does not exactly correspond to biological tissue morphogenesis.

Here, we propose in this communication an original biomechanical 2D-model based on divided media to explore the potential role of mechanics in epithelial morphogenesis. To do so, a cell is modelled as a set of repulsive grains surrounded by a network of tensed cables connected via "membrane-grains" (see Methods). Fundamental cellular mechanisms (i.e., growth, division and apoptosis) are then computed to simulate tissue development by following two distinct mechanisms: (i) accretion (additional deposit of cells) and (ii) proliferation (division with or without apoptosis). The obtained numerical tissues show final geometrical characteristics similar to those experimentally observed, i.e. with the same distributions of cell polygonal shapes.

This approach may then be useful to investigate the role of cell mechanical behaviour and of forces interacting between cells.

2. Methods

The proposed model is based on the physics of divided media (Radjai et Dubois, 2011) and is managed by direct contact for both the cytoplasm grains (in black) and the membrane elements, i.e. tight cables and grains (in green) connecting them (Fig. 1).

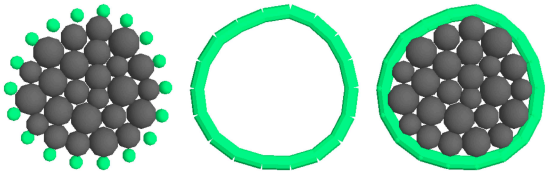

Figure 1: The basal cell of the model

For each grain of the model, the equation of dynamics is solved by using molecular dynamics and a 4th order Runge-Kutta method. The mechanical equilibrium hence results from the balance between contact repulsive forces between elements (grains and cables) and tension supported by the cables.

Two types of substrate geometry are considered: a sphere (to mimic epithelia covering *Ciona Intestinalis* eggs), corresponding to "periodic boundary conditions", and a plane (mimicking epithelia on (i) circular and (ii) square culture boxes or (iii) infinite planar substrates). For spherical substrates, accretion and proliferation are simulated whereas for planar ones only proliferative scenario is performed (Table 1).

Substrate geometry	Boundary condition	Scenario	Proliferation Rate
spherical	periodic	accretion and proliferation	0 or 1/3 or 1/5
plane	circular or square or without	proliferation	0 or 1/3 or 1/5

Table 1: Potential study cases

Each scenario begins by taking into account the same initial state: 15 cells are randomly positioned on the substrate.

Then, in the accretion scenario, the sphere and the cells grow while new small cells arrive. Three rates of tissue formation (i.e., the rate of arrival of new cells, the rates of cell growth and of spherical egg growth, taken all together) are considered. A reference rate is empirically defined to obtain the same final number of cells on the egg (~ 60) and a polygonal cell distribution close to those observed for *Ciona intestinalis*. Then, a two-times slower and a two-times faster rates are defined and used to study the influence of the formation rate.

In the proliferative scenario, the cells growth and afterwards divide and/or die. The ratio between the number of apoptosis and of mitoses defines the "proliferation rate" (chosen as 0, 1/5 or 1/3; Table 1).

At the end of the simulations (i.e., when the surface is totally covered), the number of neighbours of each cell (corresponding to the cell polygonal shape) is counted.

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3. Results and Discussion

Part of the distributions of polygonal classes numerically obtained is plotted in the same graph (Fig. 2). Some experimental data are also reported for comparison.

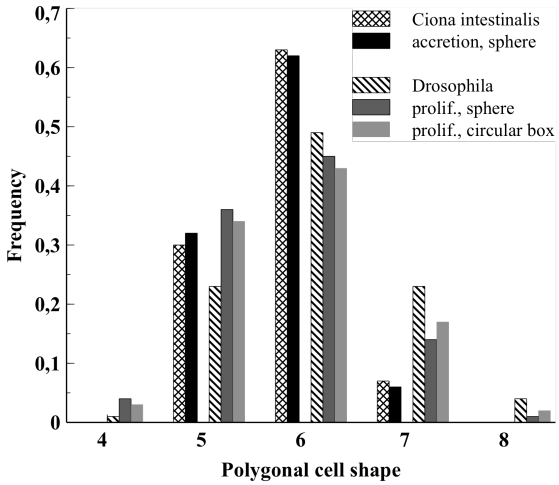

Figure 2: Distribution of cell polygonal shapes

First, all the simulation results appear close to the experimental observations. This may indicate that the balance between inner compressive forces and peripheral tensions at the cell scale, combined with repulsive interactions between cells, could play a major role in tissue formation. At the opposite, both the substrate geometry and the boundary conditions seem to not significantly influence cell geometry, which was difficulty foreseeable.

Concerning the accretion scenario, it appears that the number of hexagonal cells and the standard deviation of the polygonal distributions decrease slightly when reducing the tissue formation rate. This denotes that a slower development speed could permit the cells to better fill the free spaces during their reorganization and growth, resulting in a more stable cell organization in tissue morphogenesis.

Otherwise, the numbers of hexagonal cells obtained for the accretion scenario are always higher than those resulting from the proliferative scenario. This effect is in good accordance with experimental data (Azzag, 2011). It may be related to the plausible disruptive role of cell division in tissue reorganization, as already reported (Gibson et al., 2006).

Furthermore, when considering the proliferation scenario, the obtained numerical distributions seem to get closer to experimental observations when the proliferation rate increases. In parallel, the corresponding standard deviations also decrease while this rate heightens. Accordingly, apoptosis may play a crucial regulating role in tissue morphogenesis by counterbalancing the plausible disruptive effect of cell division.

4. Conclusions

In spite of the oversimplification of the presented cell model (i.e., 2D, global inner compression balanced by peripheral tension, no cytoskeleton, etc.), the implementation of main fundamental mechanisms in the simulation (i.e., cell division and apoptosis) by using the physics of dived media leads to numerical tissue organizations, mimicking those experimentally observed. Besides, this approach allows studying the role of cell mechanics and of cell-cell interactions. In particular, the proposed model is able to determine a geometrical order of accretion-tissues closer to the theoretically optimal Euler's distribution than for proliferation-tissues, as experimentally observed. Moreover, the simulation results are in good accordance with the already reported disruptive impact of cell division while predicting a possible fundamental regulating effect of apoptosis in tissue morphogenesis.
Overall, this promising approach, based on an original cell-tissue modelling, may allow new useful architectural descriptions and mechanical analysis of cell and tissue evolution in epithelial morphogenesis.

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