Control of Stress-induced Morphogenesis of Epithelial Cells through Kinematic Constraints

ME251: Biomechanics

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Background

Growth and morphogenesis are dependent on the stresses experienced by the tissue/continuum body, the effect of growth on stress is accounted for in the continuum formulation by considering a fictitious intermediate deformation configuration caused by unconstrained growth, which is then expected to undergo a deformation (elastic) to satisfy compatibility constraints. Just as constrained growth induces stress, stress in the body can also induce growth/rearrangement, thus a coupling of both is needed to model these processes. Muñoz et al. [2010] developed the framework for stress-dependent morphogenesis, where they employed an empirical control law relating the active (growth) deformation gradient and passive gradient such that certain parts of the continuum body rearrange to feel desired levels of stress. They then specialized their framework for 1-D bar elements (truss elements) and showcased the ability of the model to predict invagination process in the *Drosophila melanogaster* embryo. With the help of the model they noted that the kinematic constraints (incompressibility of the yolk enclosed by the epithelial tissue, unilateral contact constraints imposed by the vitelline membrane surrounding the epithelial tissue) imposed on the body are essential. In the absence of such geometric restrictions, they observed that invagination is not realizable.

The local shape changes such as invagination are usually attributed to occur in response to apical constriction (differential contraction of myosin filaments present within the cell) and/or constrained expansion/contraction. Both are responsible for the change in the form of local shape that the tissue undergoes. Other popular forms of local shape change such as evagination or folding can also be observed in epithelial cells in response to appropriate biochemical and mechanical cues [Taber, 1995].

Objective

To understand the significance of mechanical constraints on the epithelial morphogenesis and question whether it would be possible to prescribe appropriate mechanical constraints to engineer particular forms of epithelial deformations at specific sites.

Hypothesis

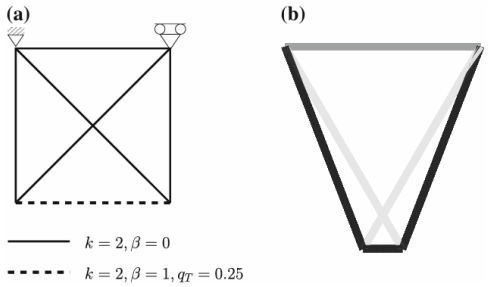
The form of local deformation the epithelial tissue undergoes during stress-induced morphogenesis can be controlled by appropriately modifying the kinematic constraints imposed on the tissue without need for external loads.

Methodology

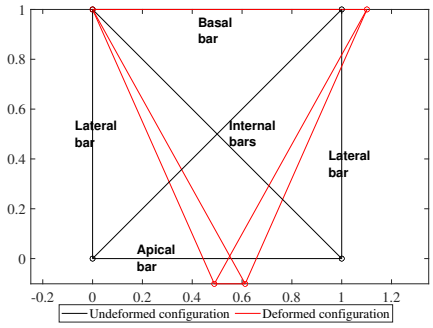
i. Implement a 2-D finite-element program incorporating the physics of stress-dependent morphogenesis prescribed in Muñoz et al. [2010].

ii. Benchmark the solver with the solution (for single cell deformation) obtained in Muñoz et al. [2010].

iii. Adapt the geometry described in Conte et al. [2009] for the embryo of the *Drosophila melanogaster* along with ad-hoc material parameters used in Muñoz et al. [2010] to investigate the hypothesis.



(a) Schematic of test involving apical constriction of an isolated epithelial cell (taken from Muñoz et al. [2010])



(b) Result obtained in this work

Figure 1: Benchmark tests (ratio of deformed and undeformed length of apical bar in Muñoz et al. [2010]=0.133, value calculated here=0.124)

Tests

The following equations[1] are solved for static equilibrium for each bar:

$$\frac{\partial}{\partial X_1}(ku' - ((u' - u'_g) + 0.5kG(u' - u'_g)^2)(1 + u'_g)) = ku''_g, \ \forall \ X_1 \in [0, L] \tag{1}$$

$$(ku' - ((u' - u'_g) + 0.5kG(u' - u'_g)^2)(1 + u'_g)) = \bar{\mathbf{q}}.\mathbf{E_1} + ku'_g, \ X_1 = \{0, L\} \tag{2}$$

$$G = \frac{\tau^* \theta \Delta t}{(1 + u'_g) + \tau^*(1 + u' - u'_g)\theta \Delta t} \tag{3}$$

$$\frac{\partial u'_g}{\partial t} = \tau^*(u' - u'_g) - q^*_T \quad \text{(Control law)} \tag{4}$$

The nonlinear differential equations are solved by spatially discretising them in their variational formulation, and the trapezoidal method is used to discretise them temporally. The programme is implemented in MATLAB.

Benchmarking finite-element programme

Muñoz et al. [2010] reported results of single epithelial deformation subject to apical constriction, the same test is reproduced and results are reported in fig. 1.

Simulating local epithelial deformations

To simplify the problem, the constraint of incompressibility of each local epithelial cell and the yolk is ignored. Different boundary conditions were imposed to study how they can be potentially used to modify the pattern of local epithelial deformation. The employed geometry is described in figs. 2a and 2b, the light and dark grey regions in the former indicate ectoderm and mesoderm. The results are shown in figs. 2c to 2i.

Observations/Conclusion

Based on fig. 2, it is noted that the pattern of local epithelial deformation can be modified by just utilising apical constriction on the ventricular end of the epidermal tissue, along with appropriate kinematic constraints. Based on the simulation of different boundary conditions, it is observed that:

[1] θ, q^*_T, Δt refers to time integration parameter, desired state of stress, time step, k, G and τ^* can be regarded as material properties, other symbols have their usual notation and X_1 is in intermediate configuration.

i. Unless the constraints are carefully placed, the invagination of mesoderm will occur as it is the preferred form of deformation as apical constriction of mesoderm and contraction of lateral and internal cells in the ectoderm (which is observed to occur in nature and appropriate material properties were assigned to reflect it in Muñoz et al. [2010]) are most favored by this process, as can be observed in figs. 2c to 2e,

ii. Invagination of ectoderm cells instead of mesoderm cells too can be induced (but to a much smaller extent) as can be seen in fig. 2f.

iii. Purely localised evagination is much more challenging to realise. Here, we expect the deformation pattern to completely oppose the unconstrained deformation profile. It requires constraints both on the periphery and the interior (refer fig. 2h), and even the then observed deformation profile was not meaningful enough to suggest that evagination can be realized in the embryo which preferentially underoges invagination just by modifying the kinematic constraints.

iv. By relaxing the consrtaint offered by vitelline membrane at select location, the system folds instead of undergoing purely localized invagination as can be seen in figs. 2h and 2i. It is also possible to observe folding by placing constraints only on the interior surface.

The hypothesis could not be confirmed here as the evagination of cells was not realisable (to the desired extent) just by modifying kinematic constraints in the absence of external loads (which usually are responsible for inducing evagination Taber [1995]).

Limitations

The study had the following limitations:

i. The incompressibility constraint for each cell was ignored. By observing fig. 2e, we note that the dimensions of each cell are significantly altered at large deformation.

ii. The incompressibility of the internal constituents of the embryo was ignored as in all the cases reported here, the volume change of the interior domain was less than 3.2%, but nonetheless is consequential.

iii. Planar truss elements are allowed to overlap.

iv. Trapezoidal time stepping, along with the fixed point method used for solving the non-linear equation, is not as reliable compared to the Newton-Raphson method used in Muñoz et al. [2010], which introduces the error reported in the benchmark test.

v. Here, reasonable guesses for displacement conditions were placed, and it is assumed that they are realisable in practice. However, a more systematic ground-structure-based study considering all practically (or otherwise) realisable surface contact-based constraints along the exterior must be performed instead.

References

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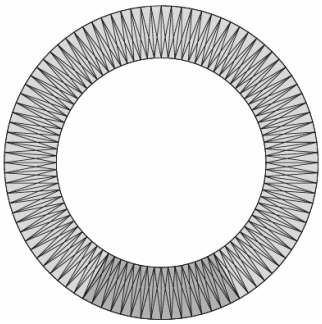
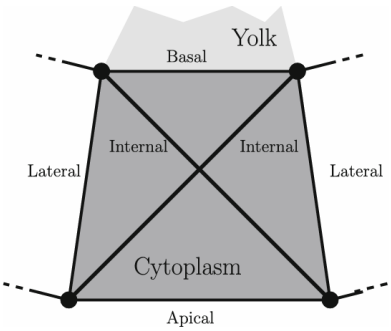
Muñoz Jose, Conte Vito, Miodownik M. Stress dependent morphogenesis: Continuum mechanics and system of trusses // Continuum Mechanics. 01 2010. 223–244.

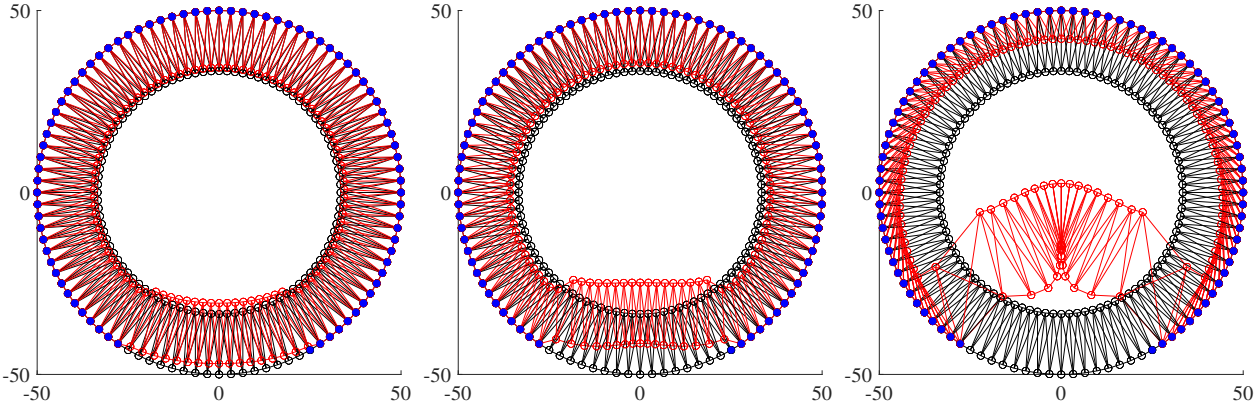
Taber Larry A. Biomechanics of Growth, Remodeling, and Morphogenesis // Applied Mechanics Reviews. 08 1995. 48, 8. 487–545.



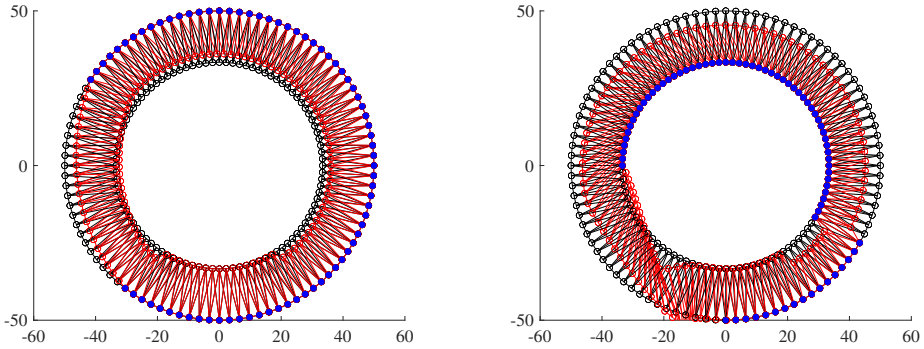
(a) Schematic of discretized geometry of epithelial tissue in the embryo of fruitfly (taken from Muñoz et al. [2010])



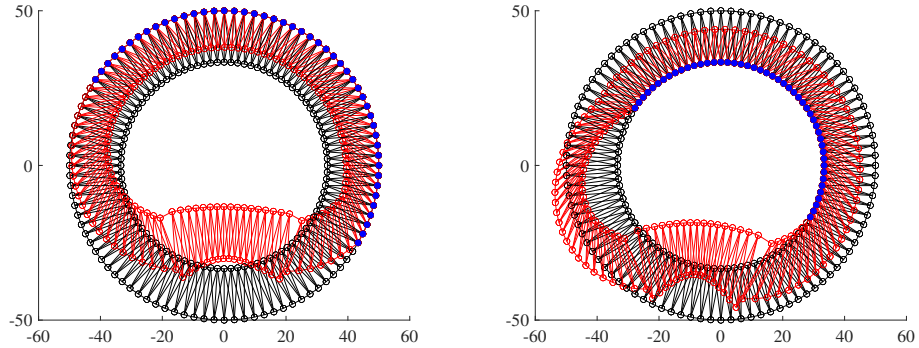
(b) Schematic depicting the different elements used to model the cytoskeleton of each cell (taken from Muñoz et al. [2010])



(c) Invagination (t=0.24 time units) (d) Invagination (t=0.26 time units) (e) Invagination (t=0.32 time units)



(f) Invagination-2(t=0.27 timeunit) (g) Evagination (t=0.31 time units)



(h) Folding-1 (t=0.30 time units) (i) Folding-2 (t=0.24 time units)

Figure 2: Simulating different forms of local epithelial deformation by only modifying the kinematic constraints; **Black** and **red** lines denote original and deformed configuration, respectively, **blue** markers denote constrained nodes.