Modeling of Epithelial Sheet Deformation Under External Force Applied by a Migrating Cell

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Introduction: One of the important determinants of cell migratory ability is mechanics of its surrounding. Immune and cancer cells often migrate along or through epithelial sheets, as also seen in *Drosophila* embryo – an experimental model of barrier crossing by cells[1,2] (Fig.1). ***Epithelial tissue*** is a layer of tightly attached cells with differential mechanical properties on top (apical), bottom (basal) and adhered (lateral) sides[3]. We simulate how ***tensions*** of epithelial cells domains influence the ***deformability*** of the whole sheet and, thus, the speed of migrating cells[4].

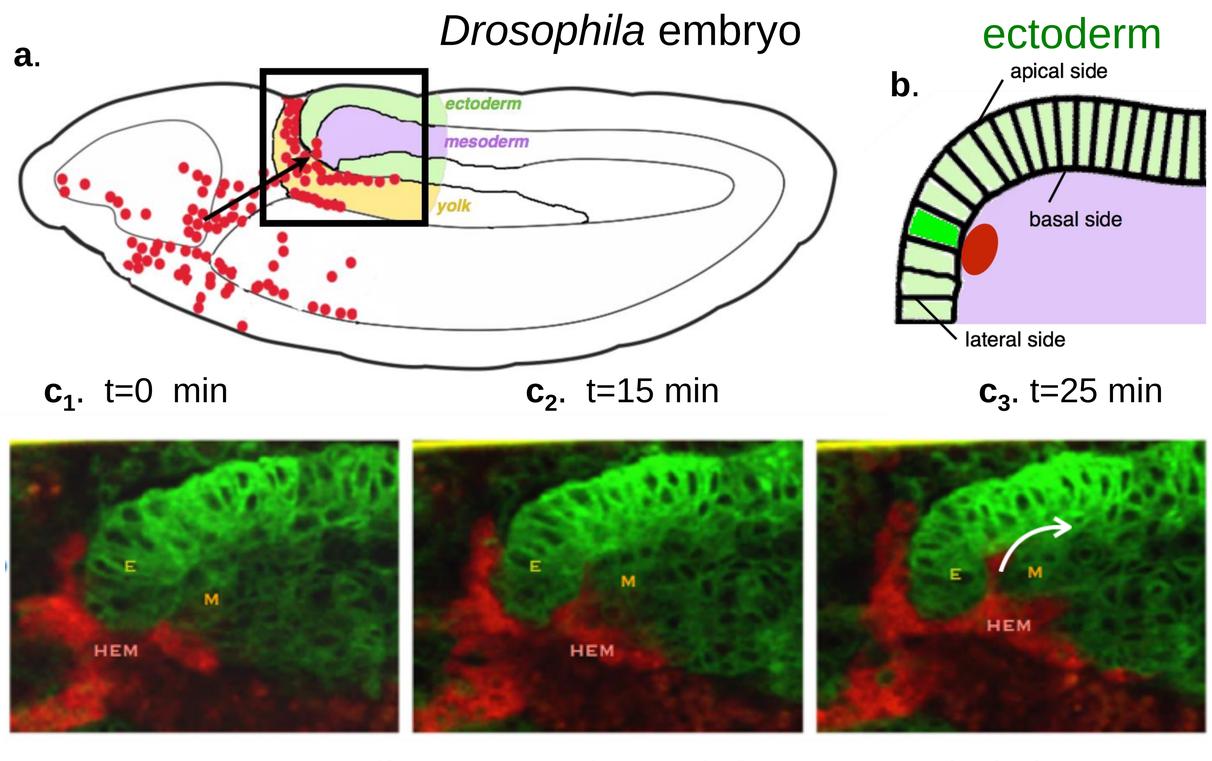


Figure 1. Immune cells (HEM, red) are deforming epithelial tissue (green) during migration between E(ectoderm) and M(mesoderm)

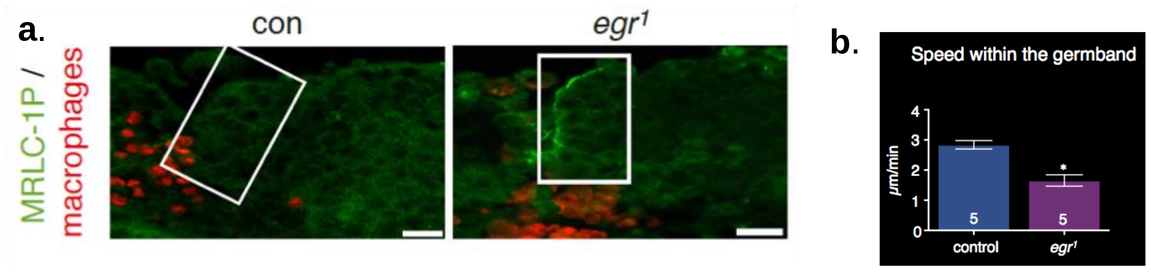


Figure 2. Increase in *apical* tension **(a)** of ectoderm in *egr*[1] mutant impedes cell migration speed on the *basal* side of ectoderm (along the white arrow in Fig.1c$_3$)**(b)** (from ref. [4]). ***How can it work?***

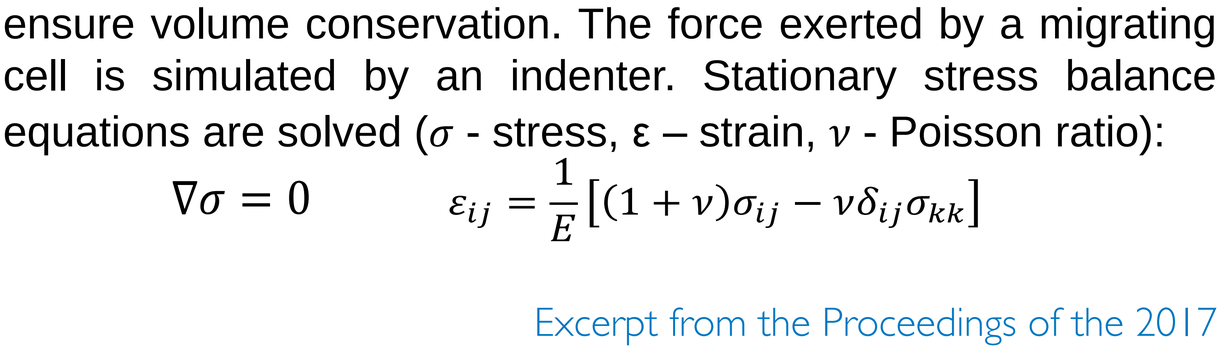
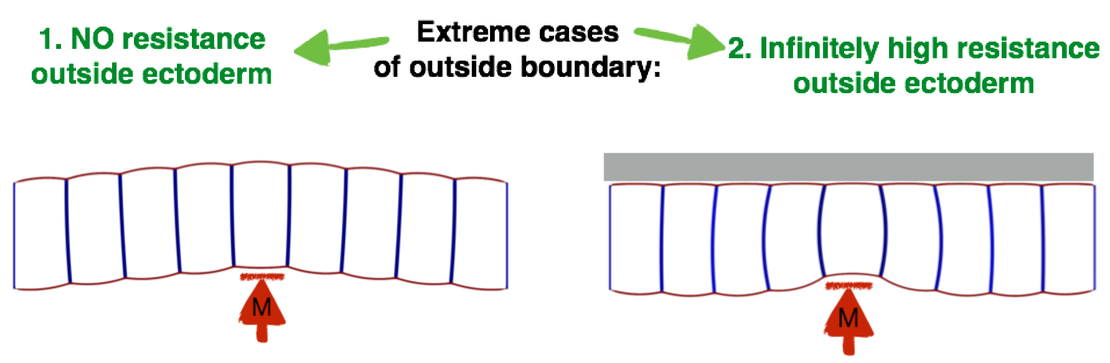


Figure 3. Model geometry. Each cell is a "liquid drop" with interfacial surface tensions & filled with incompressible fluid.

Computational Methods: Using the Structural Mechanics Module in COMSOL Multiphysics® we examine epithelial deformation under external force. Each epithelial cell is modeled in 2D as a thin shell (cell cortex) filled with incompressible fluid. The cell cortex is divided into 3 domains with distinct prestress along the surface, representing surface tension (σ_{a0}-apical, σ_{l0}-lateral and σ_{b0}-basal) and low elastic modulus (E). Pressure on the inner boundaries takes value to ensure volume conservation. The force exerted by a migrating cell is simulated by an indenter. Stationary stress balance equations are solved (σ - stress, ε – strain, ν - Poisson ratio):

$$\nabla\sigma = 0 \qquad \varepsilon_{ij} = \frac{1}{E}\left[(1+\nu)\sigma_{ij} - \nu\delta_{ij}\sigma_{kk}\right]$$

Results: Our model shows that similar shifts in tension of distinct cortex domains differently affect sheet deformability. If on apical side there is no external constraints then apical and basal tensions equally contribute to deformability (Fig.4). If epithelial sheet is not allowed to bend by resisting boundary, basal tension contributes mostly and apical tension doesn't considerably influence deformability (Fig.5). Model allows to find the value of outside resistance *in vivo* from experimentally measured tension ratios & cell shapes.



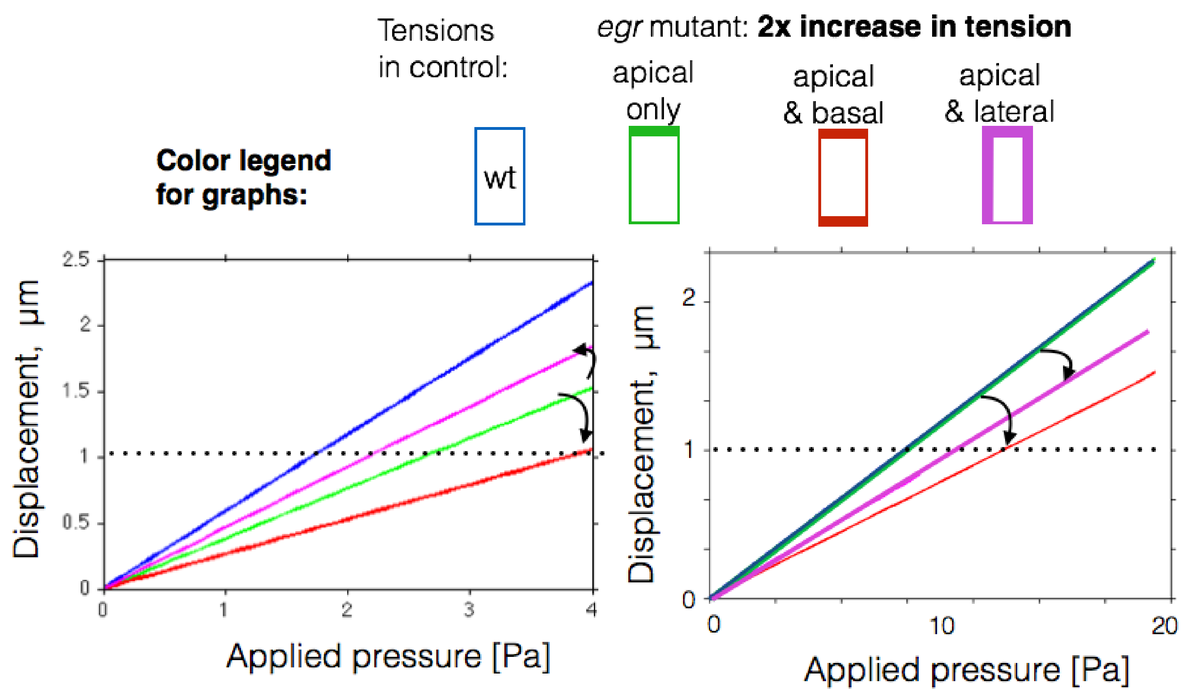


Figure 4. Apical tension contributes considerably to deformability, *if apical side can bend*. Lateral tension increase makes tissue *more deformable* in this case!

Figure 5. Apical tension contribution to deformability is negligeable, *if apical side can **not** bend.* Lateral tension increase makes tissue *less deformable* in this case.

Conclusions: *In vivo* higher epithelial tension on apical side impedes cell migration[4](Fig.2). Our model helps to evaluate how tensions of distinct epithelial domains are balanced to ensure robust mechanical events, such as cell translocation. This study contributes to cancer and immune cell invasion, as well as to *Drosophila* development research.

References:

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4. A. Ratheesh et al. The *Drosophila* TNF, Eiger, regulates tissue tension to facilitate macrophage tissue invasion during embryogenesis (in press)

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