# Mechanical Feedback in the *Drosophila melanogaster* Embryo: Robustness and Intercellular Coordination


Michael C. Holcomb[1], Guo-Jie Jason Gao[2], Jeffrey H. Thomas[3], and Jerzy Blawzdziewicz[1,4]

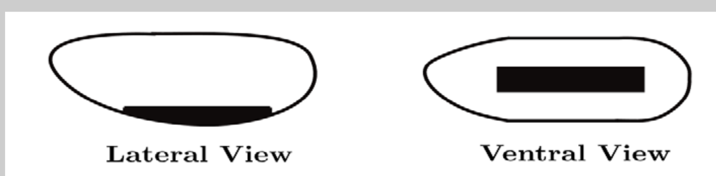
1) Department of Physics, TTU
2) Department of Mathematical and Systems Engineering, Shizudai
3) Department of Cell Biology and Biochemistry, TTUHSC
4) Department of Mechanical Engineering, TTU

Department of Physics

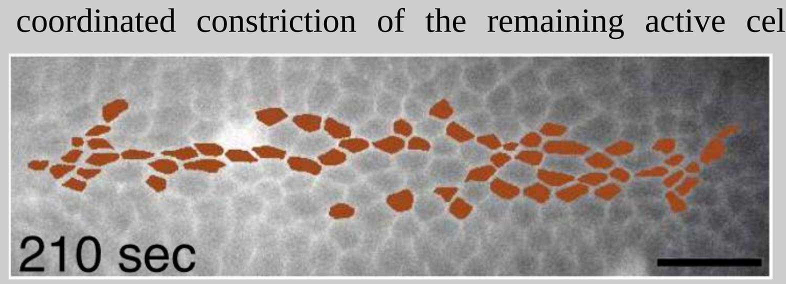

## Background

Tissues are a conglomeration of deformable, discrete objects (cells) that mechanically interact through direct contact and adhesion. Cells, however, are not merely passive, deformable objects. They are in fact subject to genetically prescribed active deformations that can give rise to large-scale cellular flows resulting in tissue-wide structural changes. One particularly striking example of such active cellular flows is the collection of regional cellular motions (morphogenetic movements) by which an embryo changes from a single layer of cells around a yolk center into a triple-layered structure (the process known as gastrulation). Gastrulation occurs in most animals; however, the applications of our modeling platform presented in these studies are motivated by specific features of gastrulation in the common fruit fly (*Drosophila melanogaster*).

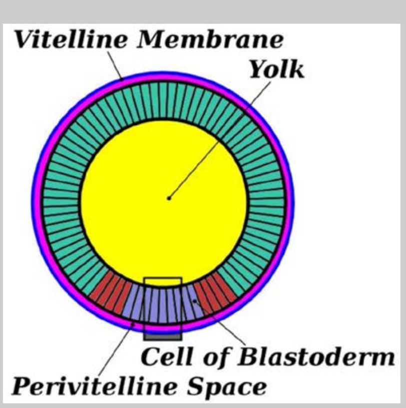
Gastrulation in *Drosophila* begins around 3 hours after fertilization and is completed through multiple morphogenetic movements which are driven by region-specific cell activities [1]. Ventral Furrow Formation (VFF) is the first morphogenetic movement of gastrulation and is initiated by the constriction of the outer (apical) faces of the cells on what will become the underside (ventral side) of the fruit fly. The constrictions produce negative spontaneous curvature of the active region of the cell monolayer, eventually leading to its invagination. This region of active cells is known as the mesoderm primordium and is composed of a band of cells on the ventral side of the embryo which take up approximately 80% of its length and 20% of its circumference [1], as is schematically depicted above.



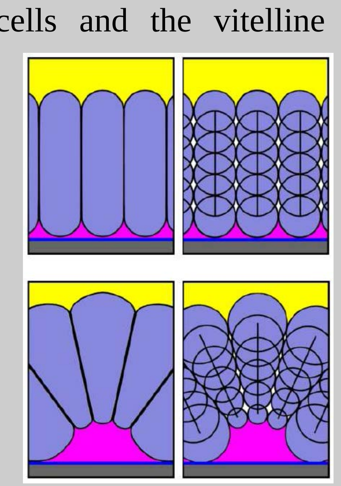

During the initial constriction phase, approximately 40% of the cells gradually constrict in a seemingly random order. Furrow formation is subsequently completed with a rapid, coordinated constriction of the remaining active cells (fast phase) [2]. A close inspection of the distribution of constricted cells prior to the fast phase reveals the presence of chain-like arrangements called *cellular constriction chains*, as shown to the left.

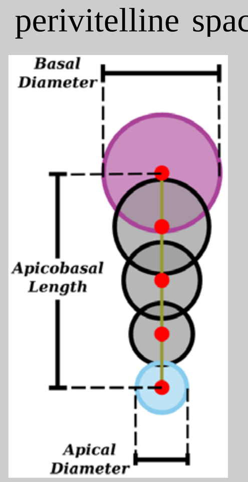



## Methods: Multiple Force Center Model (MFC)




The cross section of the embryo consists of four distinct areas: blastoderm, vitelline membrane, yolk, and perivitelline space. Each cell of the blastoderm is represented as a collection of spherically symmetric force centers that are uniformly distributed along a straight line. Neighboring cells interact via repulsive and attractive spring potentials that mimic elastic and adherent cell interactions. In addition to the nearest-neighbor cell interactions, there are also short-range repulsive forces between the cells and the vitelline membrane and between nonadjacent cells which come into contact during the furrow formation. The model also includes the pressure exerted on the cells by the yolk sac and fluid in the perivitelline space. Since the relaxation of elastic intercellular forces occurs on a time scale much shorter than the characteristic time of morphogenetic movements [3] (seconds versus minutes), the evolution of the system is quasistatic (i.e., for a given cell conformation the system is in mechanical equilibrium). The results shown were obtained by introducing prescribed changes to the radii of the force centers where the rate of change is modulated by the stress experienced by each individual cell, respectively. Quasistatic evolution is achieved via overdamped dynamics.

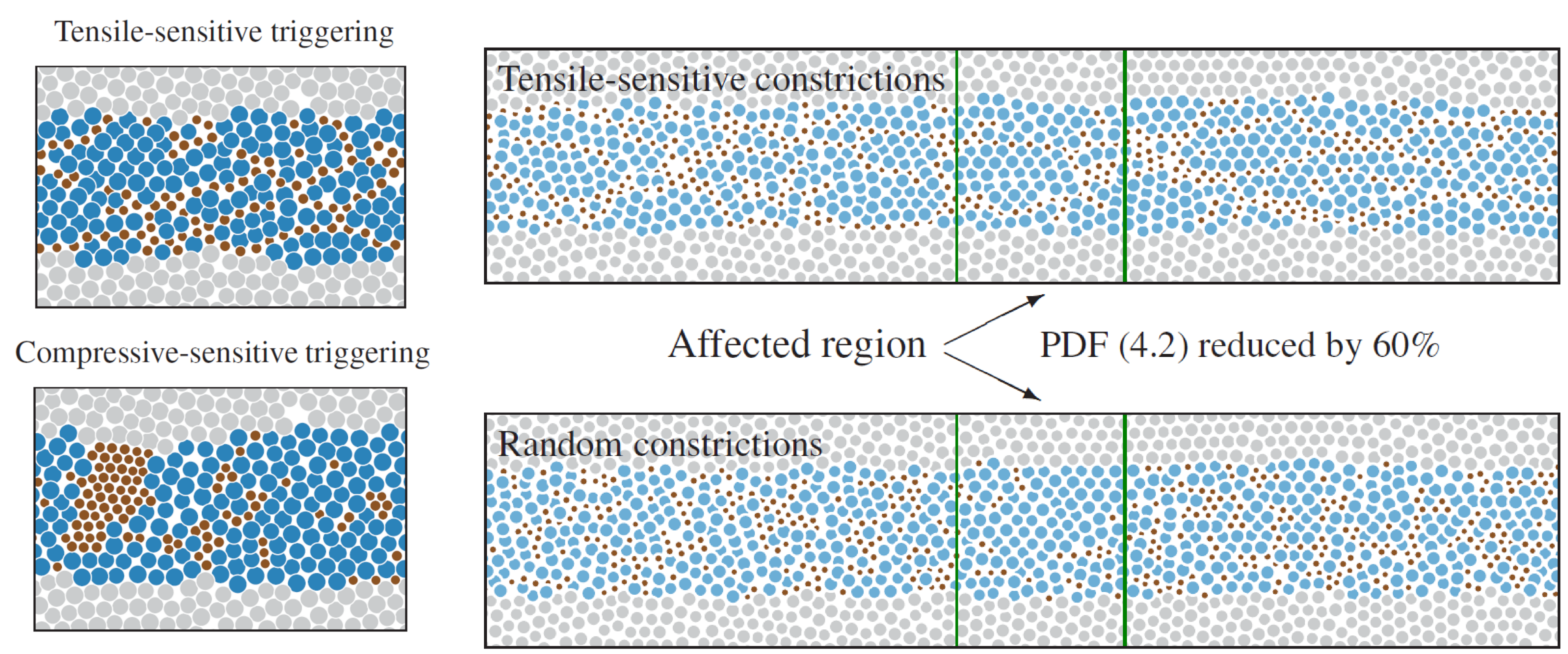


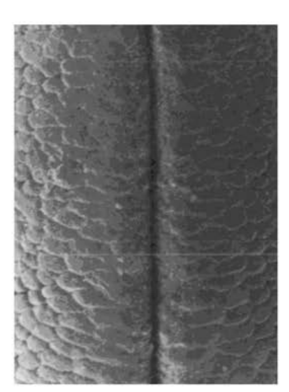


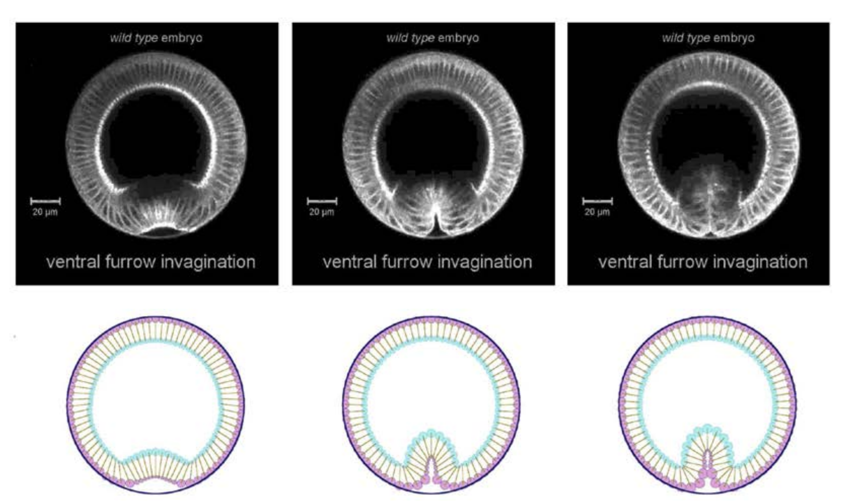


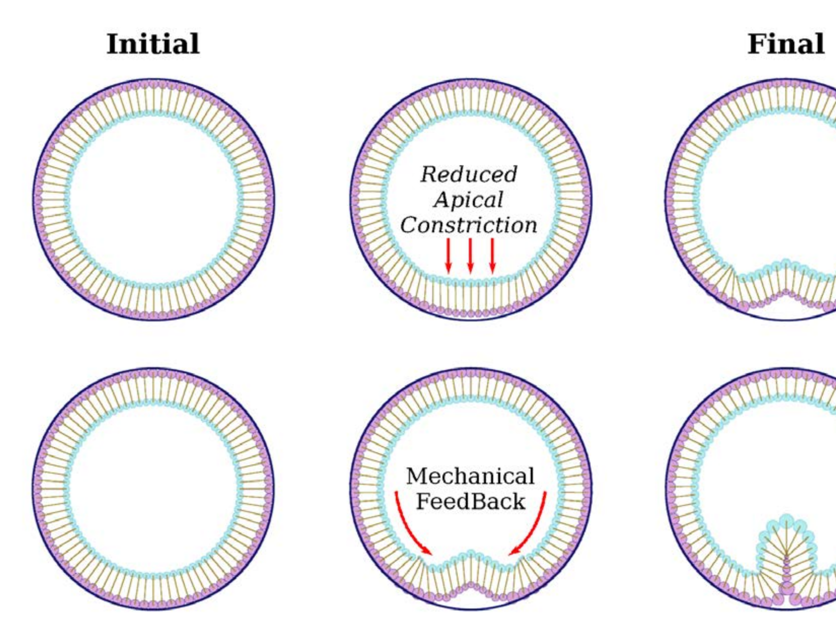
## Abstract

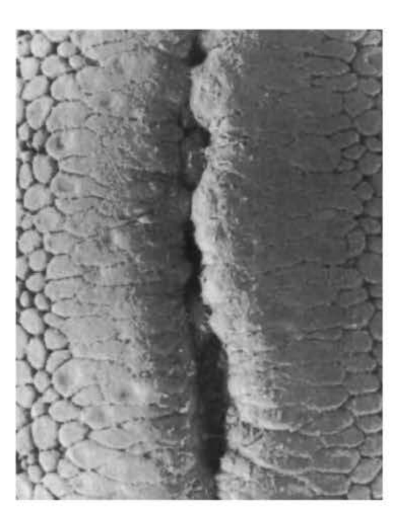
Successful embryonic development of any organism hinges on multiple morphogenetic processes working seamlessly in concert and requires both cellular coordination and the ability to continue development in spite of perturbations. We believe that this coordination and robustness are largely accomplished through intricate intercellular communication via mechanical stress fields and through associated feedback mechanisms. The importance of chemical signaling to biological development is undeniable; however, mechanical stress has been shown to play an important role in the sculpting of developing tissues. Systematic methods of studying the harmonization of cellular activities through mechanical stress and feedback within a tissue have yet to be developed. Motivated by the need for such methods, we introduce two novel modeling platforms which successfully capture different aspects of ventral furrow formation during the gastrulation of a Drosophila melanogaster embryo. Both modeling platforms represent cells as mechanically excitable objects which experience pairwise interactions; however, the first considers cells to be fully three dimensional, soft, non-spherical objects while the second hones in on the outer surface by simplifying cells into discs. Using both of these models we explore how mechanical feedback can facilitate the robustness of ventral furrow formation, the initiating morphogenetic process of gastrulation in the Drosophila embryo.

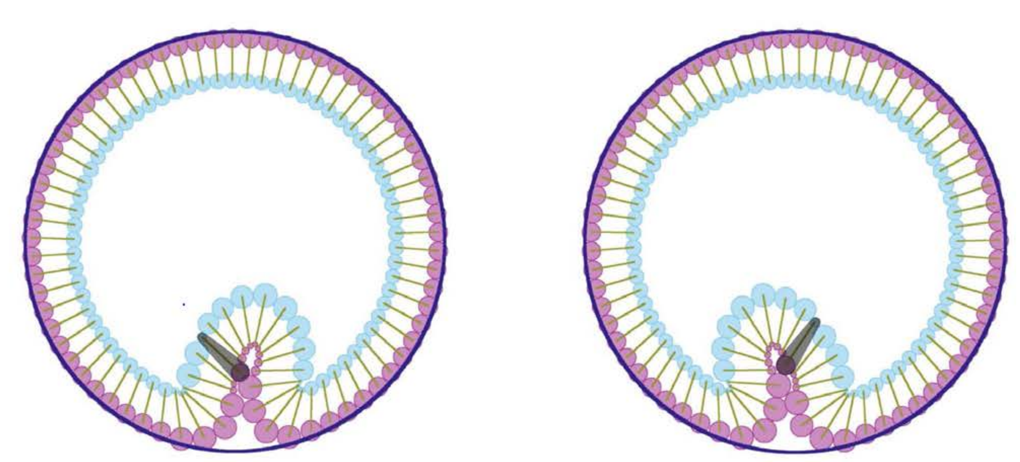





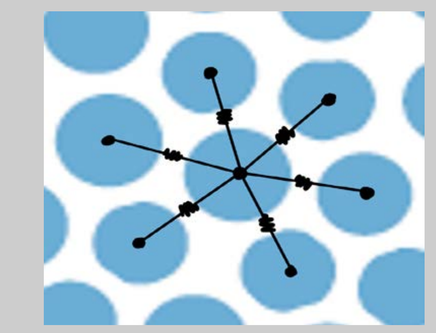


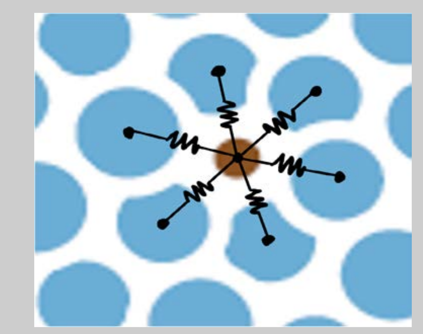
Live cross-sectional images are reprinted from Conte *et al.* [4]. Fixed SEM images are reprinted from Sweeton *et al.* [2].

## Methods: Active Granular Fluid Model (AGF)

Cells are represented as active disks that undergo stress guided stochastic constrictions and interact via finite-range repulsive forces and nearest-neighbor attraction. In the initial state and after each particle constriction step, the system is fully equilibrated, which makes the sequence of particle constriction steps quasistatic. Particle constrictions are performed by iteratively repeating the following procedure:

a) the system is fully equilibrated via energy minimization;
b) particle stress $\sigma(i)$ is evaluated for each particle $i$, as described below;
c) constriction probability $P(i)$ (per one step) is evaluated for each active (unconstricted) particle, according to the equation below;
d) diameters of the active particles are decreased with probability $P(i)$.





We characterize stress $\sigma(i)$ exerted on particle $i$ by adjacent particles using

$$\sigma(i) = -\sum_{j\neq i}\left(\frac{d_{ij}}{\epsilon}\right) f_{ij},$$

and evaluate the probability $P(i)$ of constriction of particle $i$ in a system from the expression

$$P(i) = \alpha\left(1 + \beta\sigma_i^p\right).$$

## Conclusion

Our MFC model of VFF successfully captures the intermediate profiles of the blastoderm that are observed in live wild-type *Drosophila* embryos. Our model shows that furrow malformations observed in mutant (*cta* or *fog*) embryos are likely the result of one, if not multiple, apical constriction failures. Further, using this model to study mechanical feedback effects shows that a mild pushing force, controlled by a positive feedback loop, can rescue VFF in an embryo with reduced apical constrictions. Direct measurement of mechanical feedback in tissues is experimentally difficult; however, the models presented here may provide fundamental insight into what mechanisms are possible.

The agreement between our AGF model predictions and constriction patterns observed in *Drosophila* provides evidence of the role of mechanical feedback in the early stage of morphogenesis examined here. It follows that mechanical feedback can be used to coordinate the development of system morphology. We show that the failure of *cellular constriction chains* to percolate across a constriction deficient region in the random constriction case can be recovered if the system is sensitive to tensile stresses. These results indicate that mechanical feedback is likely to significantly contribute to the robustness of developmental processes.

## References: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