New and Notable

Being Squeezed into the Right Place within the Egg Shell

Karen Alim*
School of Engineering and Applied Sciences and Kavli Institute for Bionano Science and Technology, Harvard University, Cambridge, Massachusetts

The development of an organism is a fascinating showdown of biology's might, where just a single fertilized cell gives rise to all cells that together build the multifaceted parts of an organism. An elaborate biological machinery of proteins and metabolites works together to specify individual cell positions and cell identities. How could the simple rules of physics assist the dynamics of development? The physical forces that minimize surface tension have proven to be very successful in determining cell position within tissues (1). Cell shape and arrangement (2) and cell sorting (3) result from the balance of surface forces generated from cell properties such as cell contractility and cell-cell adhesion. In this issue, Struntz et al. (4) show that the forces arising from elastic repulsion between cells account for the cell positions during the first cycles of embryogenesis of the nematode (roundworm), *Caenorhabditis elegans*.

The development of nematodes is characterized by cells acquiring their unique identity at an early stage. In fact, the entire cell lineage is invariant between different eggs and fully documented for *C. elegans* (5). Cells acquire their different identities by the unequal distribution of some factors during asymmetric cell division. In early embryogenesis, cell identity is also specified by a cell's interaction with its immediate neighboring cells. Therefore, the positions of cells within the egg shell are important in defining cell identity and ensuring successful development. How does the embryo achieve a robust and reliable positioning of cells?

Struntz et al. (4) use gentle yet fast, three-dimensional fluorescence microscopy by employing selective plane illumination microscopy to trace the trajectories of individual cell nuclei during early embryogenesis. Variation of the nuclei positions between individual eggs is observed to be <2 μm within a 50-μm-long egg. Cell nucleus position is therefore found to be a very reliable and robust readout of cell positioning. Observed nuclei trajectories are fully accounted for within a physical model describing three-dimensional nuclei trajectories as stochastic relaxation dynamics driven by repulsive forces between neighboring cells and the cells and the egg shell. In the picture of the model, the cells act like soft spheres with the center of the nucleus at the center of the sphere. Being squeezed together into an egg shell, the deformation of theses soft spheres causes an elastic repulsion that forces the nuclei and thus the cells to relax into their positions (see Fig. 1). With every cell division, one big sphere is divided into two smaller ones and all spheres rearrange to make most use of the limited space provided within the egg shell. The sphere's centers, i.e., the nuclei, diffuse to positions where repulsive forces are minimal. The model employs measured cell division times, orientation of the division axes, and cell division asymmetry, and allows the observation of deviations from normal trajectories when these input parameters are modified in the simulation.

The authors find that the nuclei positions are robust regarding the exact timing of cell divisions as long as the sequence of cell divisions is kept in order. In contrast, changes in the orientation of cell division axes are found to result in very different nuclei trajectories. The orientation of cell division axes therefore needs tight control. In *C. elegans*' first cell division, mechanical forces have been identified to control the orientation of the cell division axis and the asymmetry of the division (6). It would be fascinating to find out how physical forces and the resulting cell shapes are correlated with division axes' orientation at later stages. At large numbers of cells (>12), the repulsive forces alone are found to be insufficient to reliably determine cell nuclei position. At this stage, the packing problem becomes mathematically difficult and may have multiple equally good solutions, so guidance by biological signaling is needed for direction. The work by Struntz et al. (4) provides a fascinating physical framework that can, in future, be complemented with the observation and perturbation of biological factors to study how biochemical signaling and mechanical forces are intertwined to coordinate development.

During the last decade, surface forces have been found to assist in multiple processes during the

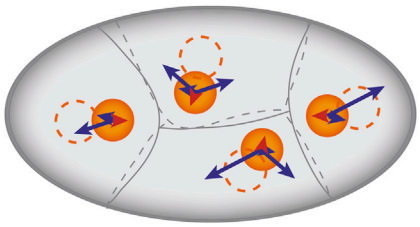

FIGURE 1 Two-dimensional sketch illustrating the repulsive forces rearranging cell nuclei (*orange*) after the cell divisions that gave rise to the four-cell stage. (*Solid circles*) Position of nuclei shortly after division; (*dashed circles*) position after relaxation. Within the physical model, nuclei position is determined as the center of soft spheres, representing the elastic properties of cells. Upon being squeezed into the egg shell, spheres are deformed and repulsive forces arise both between neighboring cells (*blue*) and between cells and the egg shell (*red*). (*Solid* and *dashed gray lines*) Initial and final cell-cell boundaries not determined within the model. To see this figure in color, go online.

Submitted August 23, 2013, and accepted for publication September 4, 2013.

*Correspondence: kalim@seas.harvard.edu

Editor: Jeffrey Fredberg.

0006-3495/13/10/1735/2 $2.00

http://dx.doi.org/10.1016/j.bpj.2013.09.016

development of organisms (7). Struntz et al. (4) now show that the elastic forces of mutual repulsion between cells are enough to explain the robust positioning of cells during the early stages of *C. elegans* embryogenesis. This is an elegant example of simplicity in the midst of the bewildering complexity of development.

The author acknowledges funding by the Human Frontiers Science Program and the Deutsche Akademie der Naturforscher Leopoldina.

REFERENCES

1. Lecuit, T., and P. -F. Lenne. 2007. Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis. *Nat. Rev. Mol. Cell Biol.* 8:633–644.
2. Hayashi, T., and R. W. Carthew. 2004. Surface mechanics mediate pattern formation in the developing retina. *Nature*. 431:647–652.
3. Foty, R. A., and M. S. Steinberg. 2005. The differential adhesion hypothesis: a direct evaluation. *Dev. Biol.* 278:255–263.
4. Struntz, P., R. Fickentscher, and M. Weiss. 2013. Mechanical cues in the early embryogenesis of *Caenorhabditis elegans*. *Biophys. J.* 105:1805–1811.
5. Sulston, J. E., E. Schierenberg, …, J. N. Thomson. 1983. The embryonic cell lineage of the nematode *Caenorhabditis elegans*. *Dev. Biol.* 100:64–119.
6. Grill, S. W., P. Gönczy, …, A. A. Hyman. 2001. Polarity controls forces governing asymmetric spindle positioning in the *Caenorhabditis elegans* embryo. *Nature*. 409: 630–633.
7. Wozniak, M. A., and C. S. Chen. 2009. Mechanotransduction in development: a growing role for contractility. *Nat. Rev. Mol. Cell Biol.* 10:34–43.