Measuring the forces of wound healing

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In many biological systems, cells work collaboratively toward a final goal. Wound healing is one such system where multiple cells collectively act to produce a force to reduce an opening in a tissue. We use the fruit fly as a model system to study wound healing for many reasons, but perhaps most importantly since it has cellular and molecular processes that are highly conserved when compared to humans and since fly proteins are very similar to human proteins. This allows us to transfer what we can learn from the fly back to humans.

During a stage in the fruit fly's embryonic development, the epidermis undergoes a process where two flanking tissues are brought together by the aid of two other force producing tissues. The first, the purse string, is a supracellular cable-like structure that is found along the edge of the two flanking tissues. The second tissue, the *amnioserosa*, is in between the two flanking tissues, which produces a measurable tension through the collabor-ation of multiple cells. Understanding the dynamics of these cellular processes is an open question in the field.

The first step consists of imaging the dorsal closure process under a powerful microscope. Atypical image is shown here:

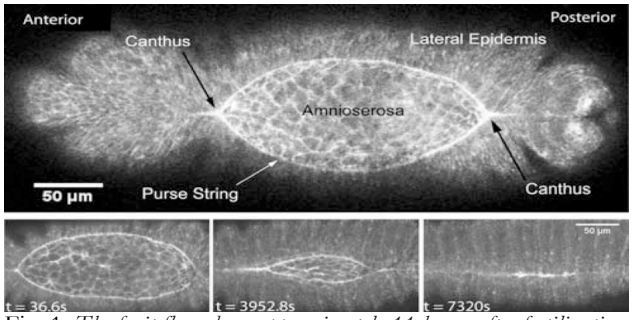

Fig. 1: *The fruit fly embryo approximately 11 hours after fertilization during a stage called dorsal closure (top). The images are captured by genetically altering the fruit fly so that a green fluorescent protein from a jellyfish is attached to the protein of study. The bottom three panels of this image show the tissues over the time course of two hours.*

Image Segmentation

We follow the *amnioserosa* tissue in the image above by tracking its constituent cells throughout all of closure. This involves tackling a problem in computer vision where an image is broken up so that individual pixels are grouped together and assigned to their respective cells. We do this by implementing an active contour method, which is applied to each cell in the image. This segmentation process provides the boundary of a cell for each time an image is captured in a microscope coordinate system. The cell area is calculated by splitting a cell into multiple small triangles and summing over their areas.

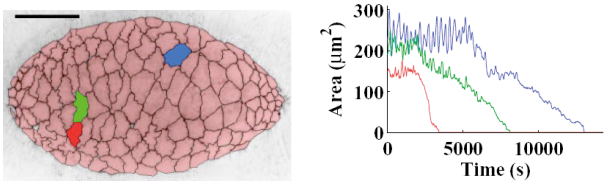

Fig. 2: *The plot on the right shows the color coded time courses of the area of three representative cells shown in the initial segmented image shown in the left panel. Although the area time courses vary in detail, they exhibit common trends, which we analyze in our force model.*

Dynamical Modeling

Patterns begin to emerge after repeated observation of the kinematics of *amnioserosa* cells. These patterns allow us to construct a model that makes predictions for the internal force production of a cell. By applying the constraints of the biological system to our mathematical model we, in turn, have experimentally measurable checkpoints for our model. In particular, we can test the assumption of a low Reynolds constraint. Under this assumption, the inertial terms are negligible compared to the viscous damping. This leaves the visco-elastic forces as well as the internal active contractile forces as drivers of the cell shape changes.

$$\rho\ddot{A} = \sum Forces$$
$$\rho\ddot{A} = F_{el} + F_{vis} + F_{int}$$
$$\rho\overset{0}{\ddot{A}} \approx F_{el} + F_{vis} + F_{int}$$

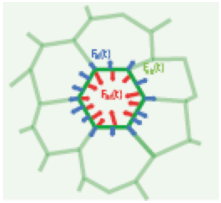

Fig. 3: *Dynamical force equations (left) and force diagram for a single cell (right).*

Conclusion

The combination of experimental and analytical methods enabled us to systematically investigate cell oscillations and cell delamination. Our dynamic modeling efforts allow us to attribute particular observable kinematics to processes that are driven by active cellular force production that, in turn, allows us to speculate on the force producing mechanisms.