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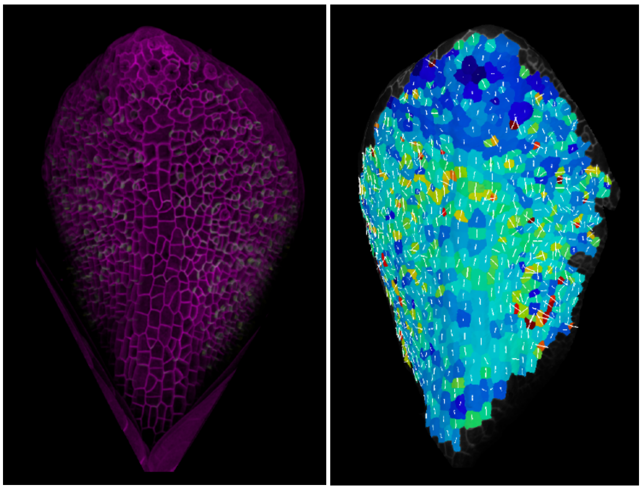
Think global, act local: How individuals influence their neighbors, and how the global neighborhood talks back to them



Images: Left, a young leaf where the outlines of all cells are in purple and green marks a "polarity protein" in stomatal stem cells. Right, a similar leaf after analysis with MorphograpX software that can compute how much and in which direction cells grow as a result of individual polarity and overall physical forces.

The behaviors of individuals can have far-reaching effects on the behavior of an entire community, and likewise, the way the community grows and develops shapes the life of individuals. We are used to thinking about these ideas in terms of human societies, but they are equally important in developing organs.

Every organ in our bodies—skin, liver, brain—is made of millions of individual cells that must work together for proper function. Getting to a functioning human, animal or plant from what was originally a single fertilized egg requires that cells become specialized for their different roles. Cells take on different shapes and *polarities* (differences between one part of the cell and another, like the axon and dendrite of a neuron or the tip of a hair growing from one surface) and these polarities have to be organized across the whole tissue. Think of the hairs on a cat that all point in the same direction to give the coat sleekness, and a preferred way to pet them!

During this process of forming organs when cells need to organize together, how do cells know what their neighbors are doing? Cells use a number of ways to communicate. They may send out chemical signals that their neighbors intercept by receptors on their surfaces, or cells may physically push or pull their neighbors.

Fueled by advances in nanotechnologies and computation, the study of how physical forces influence cell behavior, also called ***Mechanobiology*[1]*,*** has surged in power and popularity. Mechanobiology is important for understanding development, but also for understanding disease or injury. In a wound, for example, cells lose the push/pull information from their neighbors and use that as a signal to move and grow to repair the wound. In metastatic cancers, cells misinterpret or ignore what their neighbors are telling them and they grow and move to inappropriate places.

In organs as complex as a liver or brain, it is often hard to dissect the influence of mechanical force over other methods of communication. To make things simpler, researchers turn to cells they can grow in dishes, or to organs such as leaves where cells keep the same neighbors for long periods of time.

Stanford Scientists Martin Bringmann and Dominique Bergmann were interested in how cellular valves called stomata are organized in plant leaves. Stomata, whose name is the Greek word for *mouths,* are the dynamic openings that allow plants to breath in carbon dioxide and breath out oxygen and water vapor. Stomata are made by special "stomatal stem-cells". These stem cells, just like stem cells in muscles or skin, contain proteins that are polarized and when the cell divides, are inherited only by one of their daughters. Inheritance of a polarity protein will determine whether a cell continues dividing like a stem cell, or whether it will begin the process of differentiating into a mature functional stoma.

Bringmann and Bergmann wanted to know how stem cells knew where to put their polarity proteins while the leaf is rapidly growing and how this eventually leads to the optimal distribution of stomata throughout the leaf.

Although Bringmann noticed in his microscope images that many stomatal stem cells oriented their polarity proteins in the same direction, how or why they did that was a mystery. After presenting his initial results at the **Stanford**

BIO-X symposium on Mechanobiology[2], Bringmann realized that others on campus were seeing similar patterns in the animal cells they were studying. As a result of discussions in this emerging mechanobiology research community at Stanford, he designed and built a custom "leaf-stretch" device, which enabled him to test the effect of mechanical forces on the biased placement of polarized proteins.

Now these results are published in the journal *Current Biology*[3], and they describe how mechanical forces that result from friction between growing cells and stomatal stem cells guide the placement of polarized proteins. These proteins are important to determine the stem cell fate and therefore the placement of stomata.

These findings have opened new avenues of research at the intersection of growth and pattern in developing organs. They are also leading to a deeper understanding of leaf development, a field with increasing importance as we face the challenges of climate change.

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1: For more on Mechanobiology at Stanford University, see the new program from Chem-H
https://chemh.stanford.edu/mechanobio-postdoc

2: To hear a selection of talks on Mechanobiology
https://biox.stanford.edu/event/bio-x-symposium-%E2%80%93-mechanobiology-pushing-and-pulling-life-november-2014

3: Current Biology doi: http://dx.doi.org/10.1016/j.cub.2017.01.059