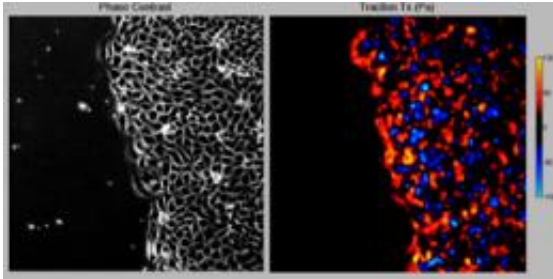


How growing cells move together

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The study showed how groups of cells fluctuate dramatically in space and in time. Courtesy Jeffrey Fredberg

(PhysOrg.com) -- Our cells are more than inert bags of proteins and genes whose complex signaling networks confound the world's most powerful computers. They also have a physical side whose brawny feats may guide our basic good health.

For the first time, researchers at Harvard School of Public Health (HSPH) have directly measured the physical forces at play when growing [cells](#) move together. The findings open up new avenues for exploring how the mechanical properties of cells sculpt new organs, shape full human beings, close a bleeding wound, form tumors, and propel metastasis.

Until now, most scientists figured that cells in growing tissue swarm ahead due to the pull of “leaders” at the edge, like a train engine pulling rail cars. Other plausible alternatives include all the cells motoring in

unison under their own power, like autos in rush hour traffic, or the dividing cells in the center pushing the growing mass further outward, like people shoving others out ahead of them to exit a crowded subway.

A study in [Nature Physics](#) rules out all three options. “Our paper showed that, among those three, it’s none of the above,” said senior author Jeffrey Fredberg, professor of [bioengineering](#) and physiology at HSPH.

Instead, the team found a more complex physical process at work. The forces come from cells crawling along a surface and from their bonds to neighboring cells. “It’s like a tug-of-war,” said first author Xavier Trepát, who led the project as a postdoctoral fellow. “Each cell is pulling on the one next to it, while exerting forces on the ground.”

The leading cells are like the people anchoring the end of the rope in a tug-of-war match. Starting with the mild pull of the leading cells, each cell further inward transmits and adds to the drag so that tension increases further inside the pack, much like a rope's tension is highest in the middle. “Why cells like to be under tension is not yet clear,” said Trepát, now a Ramón y Cajal Investigator at the Institut de Bioenginyeria de Catalunya and the Universitat de Barcelona in Spain.

Within that global state of tension, the researchers found surprising pockets of higher or lower tension. “The thing that catches the eye is the fluctuation in space and time,” Fredberg said. “On average, if you squint, it’s a tug-of-war with everyone pulling away from the center. In a more detailed view, it’s chaos, with some cells pulling in the wrong direction, certain cells where forces are huge, and other cells with nothing. But it’s not totally random. There is a certain order to the chaos.”

The data come from a combination of experimental and theoretical advances. Researchers in Fredberg’s lab have developed a handful of nanotechnologies to measure forces in individual cells. For this paper,

Trepat and his colleagues grew kidney epithelial cells in a lab dish for 24 hours. The colony grew outward in all directions on the surface of a gel containing a grid of tiny fluorescent beads.

Like footprints in the sand, each cell left a tiny impression from the surface traction force as it moved ahead. Using a microscope, the team tracked thousands of tiny displacements in the gel by monitoring the moving beads underlying the creeping cells. Most of the effort went into the analysis and software to analyze the data, including a new set of algorithms ultimately based on Newton's laws of motion from HSPH co-author Jim Butler, senior lecturer on physiology.

The authors hope this technique will help scientists bridge the knowledge gap between biochemistry and physics of cells, allowing them to link genes, transcription factors, and protein networks to the motion of cells.

“This paper measures for the first time the traction forces produced by a whole moving culture of cells, during the process of collective cell movements,” said Nir Gov, a theoretical physicist at The Weizmann Institute of Science in Israel, who was not involved in the study. “The implications of these observations is that cells are able to respond to the mechanical and chemical signals from their neighbors, so that their local traction forces are synchronized to produce collective motion. How exactly this synchronization is achieved will now have to be further explored.”

Fredberg hopes the finding will also help biologists better appreciate mechanical properties of cells as a conserved core process likely with redundant and robust features. Said Fredberg, “Cells are not immune from the laws of physics.”

More information: [www.nature.com/nphys/journal/v ...
6/abs/nphys1269.html](http://www.nature.com/nphys/journal/v.../6/abs/nphys1269.html)

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