Device allows scientists to control gene activity across generations of cells

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Just as cells inherit genes, they also inherit a set of instructions that tell genes when to become active, in which tissues and to what extent. Now, Rockefeller University researchers have built a device that, by allowing scientists to turn genes on and off in actively multiplying budding yeast cells, will help them figure out more precisely than before how genes and proteins interact with one another and how these interactions drive cellular functions.

“A slight disturbance in the abundance of a single protein can affect the functioning of a cell dramatically,” says Gilles Charvin, a postdoc who works with both Eric Siggia, head of the Laboratory of Theoretical Condensed Matter Physics, and Frederick Cross, head of the Laboratory of Yeast Molecular Genetics. “So, we wanted to devise a way to supply a single cell with a controlled pulse of protein at any time and then see how the cell would respond,” he says.

Although scientists have had the tools to track single cells and measure the protein levels within them, the new device allows scientists to track them for a longer period of time while not only monitoring but also controlling the activity of genes. The precision with which the device can track single cells also allows scientists to construct pedigrees, making it possible to compare gene activity from one cell to the next.

The device relies on electrovalves to control a flow of media, which travels through a tube and then diffuses across a porous membrane to reach the budding yeast cells. The cells are clamped between this

membrane and a soft material, which forces them to bud horizontally without damage.

“That was the major design hurdle,” says Charvin. “To create a device in which cells don’t move, so that you can track hundreds of single cells for a long time — about eight rounds of cell division — which typically lasts 12 hours.”

In order to induce the activity of a gene, the researchers used inducer molecules that diffuse through the cell membrane and control DNA segments called promoters. The molecule’s presence silences the promoter, which silences the expression of the gene; the molecule’s absence, on the other hand, activates the promoter, which activates the gene to crank up the molecule’s production.

By exploiting this principle, the scientists showed that they could successfully turn specific genes on and off by controlling the flow of an inducer molecule called methionine. They observed that pulses as short as 10 minutes led to changes in protein levels that could be measured.

The group used this device to study the cell cycle by putting a gene that must be expressed for cells to divide under the control of the methionine promoter, and showed that budding yeast cells would stop and start dividing in perfect synchrony with alternating pulses of media that did and didn’t contain methionine. “Like slaves, the cells relied on the external pulse we gave them to figure out what to do next,” says Charvin. “We thought this was a pretty striking illustration of the capabilities of this device.”

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