A positive-feedback system ensures that cells divide

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(PhysOrg.com) -- In the life of every cell, there's a point of no return. Once it enters the cell cycle and passes a checkpoint known as "Start," a cell will follow the steps it needs to divide — no matter what changes might occur in its environment. Now, in research appearing in the July 17 issue of *Nature*, scientists at Rockefeller University show that a positive-feedback system ensures that a cell that has made the decision to divide finishes what it has started.

Part of the decision process includes activating more than 200 genes simultaneously, a formidable problem considering the noisy environment of the cell. "Given how difficult it is for a cell to activate just one gene, activating 200 at the same time seems like a very difficult task," says Jan Skotheim, a postdoc who collaborated on the research with Frederick Cross, head of the Laboratory of Yeast Molecular Genetics, and Eric Siggia, head of the Laboratory of Theoretical Condensed Matter Physics. "And the way the cell solves this challenge is through positive feedback. It keeps all these events in sync."

Positive-feedback mechanisms allow cells to adapt to changes in their environment rapidly and efficiently. In the case of cell division, the key is a pair of molecules called Cln1 and Cln2, part of a family of proteins known as G1 cyclins. Skotheim and his colleagues, including graduate student Stefano Di Talia, show that when budding yeast (Saccharomyces cerevisiae) cells sense that they are big enough to divide, they synthesize an activator molecule that triggers a positive feedback system in which Cln1 and Cln2 advance their own expression.

“So what happens is that the very rapid ramp-up of the G1 cyclins during Start lead to all those target genes getting fired synchronously,” says Skotheim. “It’s a function of positive feedback that hasn’t been thought of before: synchrony and coherence.”

For the genes to be fired synchronously, a protein called Whi5 must be exported from the nucleus, and kept out until the two daughter cells are born. During Start, which lasts approximately three minutes, Cln1, Cln2 and the activator molecule all collaborate to kick out Whi5. Once out, Cln1 and Cln2 must continue to advance their own expression in order to keep Whi5 out. Then, the moment the two daughter cells separate, the G1 cyclins are inactivated, Whi5 enters back into the nucleus and the complex detaches. In previous work, the team showed that the export of Whi5 is the molecular event that signals Start. Now they show that a positive-feedback mechanism is what drives it.

In the past, when scientists tested the possibility that positive feedback could be behind cell division, the results always came out negative. But Skotheim took a different approach from that of his predecessors. Instead of averaging the results across many cells, he looked at data from individual cells, an approach that minimizes data loss.

Working with two strains of single-celled budding yeast, only one of which had Cln1 and Cln2, the researchers observed that most cells without the two molecules had less predictable divisions. They took longer to start dividing, and when they finally passed Start, the time it took them to complete the process varied considerably. Some cells, in fact, didn’t bud at all.

“By looking at averages, previous attempts to find a potential positive-feedback loop had obscured what was going on,” explains Skotheim. “By studying single cells, we regained the lost information and found the opposite of what others had found: that positive feedback drives and

coordinates a cell's commitment to divide."

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