Scientists Find Cells Coordinate Gene Activity with FM Bursts

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(PhysOrg.com) -- How a cell achieves the coordinated control of a number of genes at the same time, a process that's necessary for it to regulate its own behavior and development, has long puzzled scientists.

Michael Elowitz, an assistant professor of biology and applied physics at the California Institute of Technology (Caltech), along with Long Cai, a postdoctoral research scholar at Caltech, and graduate student Chiraj Dalal, have discovered a surprising answer. Just as human engineers control devices ranging from dimmer switches to retrorockets using pulsed--or frequency modulated (FM)--signals, cells tune the expression of groups of genes using discrete bursts of activation.

Elowitz, who is also a Bren Scholar and an investigator with the Howard Hughes Medical Institute, and his colleagues discovered this process by combining mathematical and computational modeling with experiments on individual living cells. The scientists looked specifically at the molecular changes within simple baker's yeast (Saccharomyces cerevisiae) cells after exposure to excess calcium, which increases in concentration in cells in response to stressful conditions such as high salt levels, alkaline pH, and cell wall damage.

The scientists tracked that response using a protein called Crz1 labeled with a green fluorescent tag. Crz1 is stimulated in response to high calcium levels and activates genes that help protect the cell. The glowing of the fluorescent marker allowed Elowitz and colleagues to visualize the movement of Crz1 as it travelled within the cell from the cytoplasm into

the cell nucleus and out again into the cytoplasm. Using time-lapse microscopy, they created "movies" of that movement.

"This allowed us to discover that the localization of the Crz1 protein was randomly switching between nucleus and cytoplasm," says Elowitz. The researchers were able to see the Crz1 protein moving in a coherent fashion. "What's striking is that most of the Crz1 molecules jump in or out of the nucleus together. The typical length of time they stay in the nucleus is constant, but how often they all jump into the nucleus depends on the signal--in this case, calcium. Thus, you can say that calcium levels are 'encoded' in the frequency of these nuclear localization bursts."

Using mathematical modeling, the researchers were then able to determine that the burst-like movement most likely serves to coordinate gene expression. The process is similar to how a dimmer switch on household lights works. Such knobs control the fraction of time that current, which switches on and off rapidly, goes to the light fixture. Rotating the knob varies the relative amount of time that current is on or off, and the resulting intensity of the light is proportional to the fraction of time the switch is on. "The idea of controlling a system by flipping it between extreme 'on' and 'off' states at different rates, rather than fine-tuning it, is sometimes called 'bang bang' regulation," Elowitz says.

"Similarly, the amount of gene expression in the Crz1 system is proportional to the fraction of time that Crz1 is localized to the nucleus. Unlike the dimmer, it is the frequency--how often there are nuclear localization pulses--not the duration of these pulses, which the cell regulates. But in both cases, it is the fraction of time that the system is 'on' that is being controlled," Elowitz says.

One key point, he adds, "is that as the rate of these jumps changes, all genes are affected in the same way. One way of thinking about it is that each 'jump' activates all of the genes, albeit at different levels.

Therefore, the expression of each gene is individually proportional to the number or frequency of these jumps, and they are all proportional to each other as well."

The behavior of Crz1 is believed to control roughly 100 target genes. However, Elowitz and his colleagues suspect that frequency-modulated movement may be a common strategy for gene regulation. "Because the problem of coregulation of genes is very general, we suspect frequency modulation may be widespread across many genes, organisms, and cell types. We're now trying to determine how general this phenomenon is by looking at what other genes and cell types use this type of system," he says.

The paper, "Frequency-modulated nuclear localization bursts coordinate gene regulation," was published in the September 25 issue of the journal *Nature*. The work was supported by grants from the National Institutes of Health and the Packard Foundation.

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