Solving 1960s genetics mystery could clear obstacles for synthetic biologists

August 30 2012

The threads of an evolutionary mystery that dates to the birth of molecular biology are beginning to unravel, thanks to a new investigation by computational bioengineers at Rice University and the University of Texas MD Anderson Cancer Center.

In new research published online this week in *PLOS* Computational Biology, Rice's Oleg Igoshin and MD Anderson's Christian Ray offer a possible explanation for the existence of jointly controlled clusters of genes called operons, which are found in bacterial chromosomes but not in those of higher order organisms like humans.

The new study harkens to one of the earliest 20th-century discoveries in molecular biology, and it could help clear 21st-century hurdles for synthetic biologists.

In the early 1960s, just as scientists were discovering how cells transcribed information from DNA to create the necessary proteins for life, French scientists Jacques Monod and François Jacob found that the bacterium Escherichia coli used three specialized genes to create the proteins it needed to break down and digest lactose. They also found that these three metabolic genes were switched on and off together from a single control point.

Monod and Jacob had discovered the first operon, a set of multiple genes that are controlled as one. It marked the first time that scientists had identified a gene regulatory network, and it earned them a share of the

1965 Nobel Prize in Physiology or Medicine. Monod and Jacob's lac operon turned out to be the first of many bacterial operons. But by the late 1960s, it was clear that operons weren't the biological norm. None have ever been found in humans, for instance, and very few have been identified in multicellular organisms.

"There's never been a definitive explanation for why nature would preferentially select for operons in prokaryotes but not in eukaryotes," said Igoshin, associate professor of bioengineering at Rice. "In addition, we do not know how genes get grouped into operons. Why, for example, are some interacting genes selected to be in one operon while others are not?"

Igoshin and Ray are computational bioengineers who apply mathematics and computational bioinformatics to study cell signaling and other biochemical processes. Ray, a former Rice postdoctoral research associate in Igoshin's research group, is now in the Department of Systems Biology at MD Anderson. Ray and Igoshin began investigating operons in late 2009 to determine whether their evolution might have been influenced by the "noisy" nature of biochemical signals that regulate bacterial gene transcription.

"When a cell is responding to its environment, it can use regulators to control gene expression, but the amount of control that the cell has is limited by the number of molecules like messenger RNAs, which mediate protein production," Ray said. "So, in bacteria, the number of copies of a protein expressed by a gene can vary widely, say from 50 one hour to 100 the next. And this happens even when conditions outside the cell have not changed."

Igoshin and Ray knew that these random fluctuations were less of an issue for eukaryotic cells, which have larger volumes and more copies of messenger RNA and proteins. So they hypothesized that operons play a

role in helping bacteria deal with these "noisy" conditions.

To test their idea, they developed a series of mathematical models of gene networks that could be run on a computer rather than on cell cultures, as well as statistical tests that could be performed using the information accumulated in bioinformatic databases.

Their mathematical models of gene networks covered six different types of protein-protein interactions. For each interaction type, they compared how operons affected noise in networks encoded by the member genes. For three of the six networks, operons worked to suppress noise. For the other three, they worked to increase noise. The findings from the simulations therefore suggested that operons could reduce the detrimental effects of noisy signals in some gene regulatory networks, but not others.

To further test the idea, Igoshin and Ray examined the operon organization of the E. coli genome. They found operons were frequent when the type of interaction that they encoded worked to suppress noise. When the encoded interaction did not suppress noise, operons were infrequent.

"Operons that emerged in the course of evolution in E. coli are consistent with selection for noise suppression and selection against noise amplification," Igoshin said.

The study also suggested why specific genes might be found in a specific operon.

"Certain genes perform much better when they're controlled as a unit, particularly if they produce co-ingredients that are required in proportional amounts," Ray said. "In the simulations, when these were split up and put onto separate operons, the inherent noise in the control

signals would create a situation where the cell had way too much or too little of one co-product. In some cases, this is just inefficient, but in others the buildups could be toxic."

Ray and Igoshin said the study has implications for synthetic biologists who are trying to imbue cells with new biological functions not found in nature.

"For example, if you need to take multiple enzymes from different species and put them into a bacterium—something that was done recently to produce a low-cost anti-malaria drug—it might be easier to take them separately and put them into different parts of the chromosome," Igoshin said. "What this new finding shows is that there may be a cost for that in terms of overall fitness of the organism. Nature sometimes groups things together, particularly in cases where one of the enzymes makes or consumes toxic intermediates, and synthetic biologists would do well to pay attention to these types of interactions as they prepare their designs."

More information: www.ploscompbiol.org/article/i … journal.pcbi.1002672

Provided by Rice University