

Metabolic reactions: Less is more in single-celled organisms

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All single-celled organisms are not alike. Or are they? A Northwestern University study has found a surprising similarity among four quite different organisms. The simplest organism, a bacterium called *H. pylori*, uses the same number of biochemical reactions (around 300) as yeast, the largest, most complex organism of the group, when optimizing growth.

The other surprising finding is that to optimize, or efficiently perform, metabolic tasks, such as growing fast or converting sugars to ethanol, the organisms tend to use only a small fraction of the biochemical reactions available to them in the metabolic network. Less efficient, or suboptimal, behavior tends to use a much larger number of reactions.

The results contribute a new understanding of the interplay between metabolic network activity and biological function and indicate there is a general behavior that is common to diverse organisms.

The research was led by Adilson E. Motter, assistant professor of physics and astronomy in Northwestern's Weinberg College of Arts and Sciences; the study will be published Friday, Dec. 5, by the journal *PLoS Computational Biology*, an open-access, online journal published by the Public Library of Science.

Motter's collaborators and co-authors of the paper, titled "Spontaneous Reaction Silencing in Metabolic Optimization," are Takashi Nishikawa, formerly a visiting scholar at Northwestern, now of Clarkson University,

and Natali Gulbahce, of Northeastern University and the Dana Farber Cancer Institute.

Little is known about what the individual parts of the cell do in relation to the whole organism. These new findings -- that many of the parts, or chemical reactions, are shut down spontaneously for the cell to perform optimally -- provide an area of focus to scientists who want to control cell behavior by manipulating one or more biochemical reactions.

The knowledge may help researchers genetically engineer cells or treat sick cells. Yeast, for example, is used to produce ethanol, so to increase production the research indicates how shutting down some of the cell's biochemical reactions could force the cell to produce ethanol more efficiently. The identification of drug targets and the development of new therapies also often require manipulating molecular reactions to produce a desirable outcome.

"Each organism is a very versatile chemical factory," said Motter, who is also a member of the Northwestern Institute on Complex Systems. "It is clear that inactivating some reactions can force other reactions to be active. We want to better understand the cell's spontaneous shutdown of parts so we can induce it ourselves."

The research team also found that when a cell is perturbed (when there is a change in the nutrients available or a gene is shut down), the number of biochemical reactions it uses increases immediately, putting it in a sub-optimal state. The cell seems lost for a while, but then it adapts to the new conditions. The number of reactions decreases, and the cell returns to an optimal state.

"A reaction becomes inactive and triggers a cascade that makes other reactions inactive until you have several hundreds or even thousands of inactive reactions," said Motter. "This is the network analogue of

sculpting: in order for the desired behavior to manifest itself, specific parts of the systems have to be suppressed. In this analogy, the expression of a whole-cell objective would not be possible were it not for the pattern shaped by the absent or inactive parts in the bulk of the cellular network."

"Why do organisms have reactions they don't use? Presumably so they have the flexibility to adapt to different conditions. One optimization situation will engage a certain set of reactions, while another situation will require a different set. It remains to be demonstrated, however, whether different conditions alone can justify the presence of all available reactions. The fact that this question is yet to be answered makes the entire problem even more attractive," Motter said.

Motter and his team used computational results to re-interpret and explain specific recent experimental results. First they gathered extensive experimental information on the metabolic networks of four different single-celled organisms: three bacteria (*H. pylori*, *S. aureus* and *E. coli*) and yeast (*S. cerevisiae*). Then the researchers built general quantitative models of the organisms that allowed them to predict cellular behavior. With those models, the researchers conducted mathematical analyses and computer experiments, simulating the organism and its metabolic function under optimal and non-optimal conditions.

They observed that for all four organisms in a typical non-optimal state, all utilizable reactions in the metabolic network, with a few exceptions, were active. In contrast, when the four organisms were growing at their optimal rate, each of them spontaneously silenced a large number of metabolic reactions. The number of active reactions, around 300, was the same for all four, despite differences in the size and complexity of each organism's genome and metabolic network. And the number stayed around 300 for a variety of quite different optimization scenarios.

"Mathematical abstraction of the problem suggests that spontaneous shutdown may not be limited to metabolic networks," said Nishikawa, who led the mathematical part of the effort. "What appears to be essential for this phenomenon is that a complex network that is under constraints and locally in balance is 'trying' to optimize its function. There are other important systems, like transportation networks, where the same type of analyses could be useful."

Source: Northwestern University

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