Work with power grids leads to cell biology discovery

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Gene therapy, in which a working gene is inserted into a cell to replace a faulty or absent gene, is a promising experimental technique for the prevention and treatment of disease.

Now a research team led by a Northwestern University physicist reports that a counterintuitive approach also holds promise. The targeted removal of genes -- the exact opposite of what a gene therapist would do -- can restore cellular function in cells with genetic defects, such as mutations.

Published online in the journal *Molecular Systems Biology*, the results have ramifications for medical research as well as for optimizing certain metabolic processes used in the production of biofuels, such as ethanol.

After gathering extensive experimental information on the metabolic networks of three different single-celled organisms, the researchers built a general quantitative model that can be used to control and restore biological function to cells impaired by a genetic defect or by other factors that compromise gene activity. Their network-based method does this by targeted deletion of genes, forcing the cell to either bypass the functions affected by the defective gene or to compensate for the lost function.

The research, led by Adilson E. Motter, assistant professor of physics and astronomy in Northwestern's Weinberg College of Arts and Sciences and the paper's lead author, grew out of Motter's earlier work on the U.S.

power grid -- another complex system that is very different from biological systems but also with many similarities.

After the 2003 Northeast blackout, where a sequence of failures in the power grid led to the largest outage in U.S. history, experts determined that the event could have been reduced or avoided by instigating small intentional blackouts in the system during the initial hours of instability.

“And the same could be valid in biology, where a defective gene may trigger a cascade of ‘failures’ along the cellular network,” said Motter, whose interest and expertise lie in complex systems and understanding how the structure and dynamics of a high-dimensional system, such as an intracellular network or a power grid, relate to its function.

“Our recent research shows that what is true in power networks is also true in biological networks. Inflicting a small amount of damage can control what otherwise would be much more significant damage.”

With the experimental information assembled, the researchers used their computer model to simulate the organism and its function. They started with a perfect cell and then, with a key gene deletion, damaged the cell so that it was unable to grow or had a significantly reduced growth rate.

Next, the researchers restored growth by deleting additional genes, which stimulated the cell to make a different choice and use different pathways. Interestingly, the cell’s recovery was stronger when more genes were deleted. They could even restore growth to non-growing mutant cells; the researchers dubbed this the “Lazarus effect.”

“Our research is based on optimizing the use of resources already available in the cell,” said Motter. “We are exploring existing reactions and genes in the cell that the cell would not use or use to a lesser degree under normal conditions. This is different from traditional gene therapy,

which is based on introducing new genes into the cell -- with its own advantages and problems because of that."

The team's use of predictive models is similar to how physicists use models, for example, to determine the position of the moon tomorrow at a specific time. Thanks to the recent wealth of available biological information, computational scientists now are beginning to develop quantitative models of biological systems that allow them to predict cellular behavior.

In one in silico experiment (via computer simulation) with E. coli, the researchers found that the deletion of one gene is lethal to the cell but when that same gene is removed along with other genes, it is not lethal. The gene, it turns out, is only essential in the presence of other genes. This touches the issue, says Motter, of whether organisms have an unconditional set of essential genes.

While Motter's team has not done actual laboratory experiments, they have used their computational results to re-interpret and explain specific recent experimental results. They have applied physics methods to solve a biological problem. Their method, for example, can identify the genes whose removal restores growth in gene-deficient mutants of E. coli and S. cerevisiae, a type of yeast.

"From a phylogenetic viewpoint, yeast is more similar to humans than E. coli," said Motter, a member of the Northwestern Institute on Complex Systems. "Of course, there is a distance between single-celled organisms and human cells, but our results should be seen as proof of principle. Many experimentalists are interested in our work, and part of this interest comes from its potential for disease treatment research. This work is a concrete application of complex networks to solve a real problem, and, as such, also requires substantial involvement of network theorists."

“Needless to say, this work is built on previous research and would not have been possible without the very significant contribution of my collaborators,” said Motter.

Source: Northwestern University