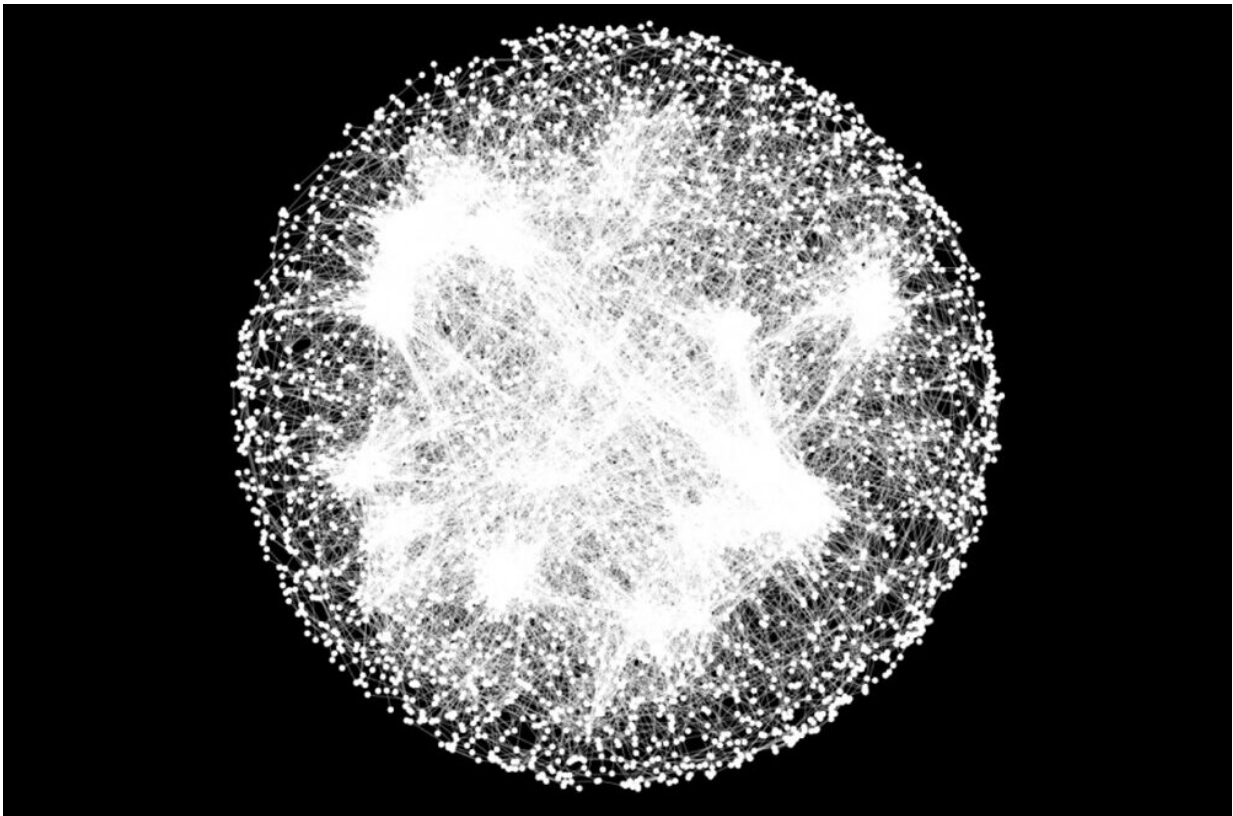


Cells are more resilient to environmental changes than previously thought

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The reference yeast genetic network stands strong in the face of environmental insults with the most of the wiring remaining in place in across various conditions. Credit: Michael Costanzo

Cells are more resilient to environmental perturbations than previously thought, Toronto researchers have found. The finding will enable

scientists to translate observations of the effects of drugs or mutations on cells grown in a lab setting as they seek to gain a better understanding of cellular function and to develop new diagnostics and treatments.

Writing in the journal *Science*, the group reported that the Baker's [yeast cells](#) employ the same network of gene interactions to coordinate [cell growth](#) in response to a wide range of different environments.

"We wanted to test in an unbiased way how the reference genetic network of a model cell changes in different environments," says study co-leader Brenda Andrews, University Professor at the Donnelly Centre for Cellular and Biomolecular Research at the University of Toronto.

"And we found that the network is highly resilient and remains broadly the same, which means that a single reference condition provides us with a nearly complete view of the molecular wiring of a cell."

Charles Boone, a professor of molecular genetics and interim director of the Donnelly Centre, and Chad Myers, a professor of computer science at the University of Minnesota-Twin Cities, were also senior authors on the paper.

The work builds on their previous research, published in a 2016 *Science* study, which established how all of yeast's ~6000 genes form a network of ~900,000 interactions. Yeast [cells](#) are similar to [human cells](#) but they are easier to study thanks to having smaller genomes and well-established techniques for genetic manipulations, which is why scientists have been using them as a research model to study the the molecular foundations of life.

As the only genome-wide map of genetic interactions for any cell, the global yeast genetic network is a unique reference resource. The connections between genes hold clues about their function, and they can

also reveal how mutations combine to produce cellular defects behind diseases. And, a robust reference map is also key for identifying the best genes to target therapeutically.

There was a concern, however, that genes might change their interacting partners depending on the cells' environment, which would complicate things because it would mean the molecular wiring is dynamic, like a moving target.

"Our reference map was constructed from data collected under standard laboratory conditions," says Michael Costanzo, a senior research associate in the Boone and Andrews labs and co-lead author on the paper.

"If you alter the conditions, maybe that would cause massive rewiring of the network."

Others have reported that the environment has the ability to rewire the connections within a select group of genes involved in a specific cellular process such as DNA repair, but its impact across the genome had not been assessed systematically.

Two genes are said to interact if cells lacking both genes grow better or worse than when either gene is missing on its own. The testing of all possible pairwise interactions that led to the creation of the reference map took over 15 years and cost tens of millions of dollars in research funding. Since it would have been impossible to replicate this tour de force under multiple conditions, the researchers selected a representative set of genes which span all major biological processes. In total, 30,000 genome-wide interactions were tested under 14 diverse environments, including an alternate food source, osmotic pressure, as well as various drugs.

The vast majority—more than 90 percent—of the interactions first identified in the reference map remained present across all the conditions. Only seven percent of the interactions were novel, meaning they were detected for the first time and only in some environments. These novel interactions typically occurred between genes involved in different cellular processes, showing that external stimuli have the power to forge more distant genetic connections.

"Our study tells us that reference maps are useful, but they also highlight that keeping your eyes open for some rare but new connections in modified conditions may lead us into completely new territory," says Andrews.

The team, including Professor Jason Moffat at the Centre, are now working to create the first human reference map—a huge task given the larger number of human [genes](#) (~20,000) and the 200 million possible interactions between them. But the researchers say that based on their yeast work they can be confident that the human map will equally capture the fundamental biology regardless of variables such as cell type or growth conditions.

"People have been concerned that there is too much variability between different human cell lines to make accurate predictions about the effects of drugs, for example," says Jing Hou, co-lead on the paper and Donnelly postdoctoral fellow who will soon be starting her own lab at the French National Centre for Scientific Research in Strasbourg.

"If we know that the global human network is stable, we can be confident about the interactions we see, and based on our yeast data across vastly [different environments](#) we expect that to be the case," she said.

More information: "Environmental robustness of the global yeast

genetic interaction network" *Science* (2021).
[science.sciencemag.org/cgi/doi ... 1126/science.abf8424](https://science.sciencemag.org/cgi/doi/10.1126/science.abf8424)

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