

## Researchers Map Circuitry Of Yeast Genes Using Technique That Could Be Applied To Humans

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Researchers at UCSD have invented a technique that organizes the genetic information contained in the 16 chromosomes of the yeast *Saccharomyces cerevisiae* into a wiring diagram resembling an electronic circuit board. An analogous diagram of the human genome, when developed, is expected to help in the discovery of the genetic basis of many diseases.

In a paper published in the May issue of *Nature Biotechnology*, professor Trey Ideker and graduate student Ryan Kelley reported that their new approach allowed them to predict new functions for 343 yeast proteins based on their positions in the new wiring diagram. "Beyond deciphering the circuitry of a yeast cell, our analytical approach can be applied in humans to find what years of research using other methods have failed thus far to uncover: combinations of genes that are the true culprits in many diseases," said Ideker, a professor in the Jacobs School of Engineering's Department of Bioengineering.

Ideker and Kelley designed their technique to take advantage of an expanding library of interactions of yeast genes. Discovering such interactions has been made possible by a new type of automated experiment in which yeast strains with one harmless mutation are mated with an array of other strains, each carrying a different harmless mutation. The experiments are designed to find double-mutant daughter cells that fail to grow. Such fatal genetic interactions in yeast are thought to mimic the underlying basis of human diseases in which combinations of mutated genes, rather than mutations of single genes, are at fault.

Geneticists have traditionally studied yeast because it grows rapidly and each stage of its cell cycle is easy to visualize. Scientists have also found many homologs of yeast genes in all eukaryotes, ranging from the worm and fruit fly, to humans. To date, roughly 30 percent of mutated genes implicated in human disease have yeast homologs, a finding that leads researchers to believe that mutated pairs of genes that cause the death of yeast cells could have disease-causing homologs in human cells.

The UCSD researchers made use of several libraries of scientific information about yeast, such as the known physical assemblages of proteins, protein-DNA complexes, and metabolic networks involved in a variety of cellular processes.

Ideker and Kelley pieced together their yeast circuit board based on more than 4,800 cases in which a lethal effect was caused by two mutations together, called synthetic lethal interactions. "We took the classical approaches that have been used to analyze synthetic lethal interactions, but we created a method to automatically categorize these interactions," said Kelley. "We then took this automatic categorization scheme to determine the wiring diagram for yeast."

The UCSD researchers plan to refine their circuit diagram of yeast as more synthetic lethal interactions become known. Their eventual goal is to use the approximately 200,000 potential synthetic lethal interactions and other information about the physical interactions of yeast proteins to generate a computer model of a living yeast cell.

Ideker believes that the eventual wiring diagram of human cells will be similar to that of yeast; however a newly developed technology is needed to verify his theory. "You can't probe human cells as easily as we can yeast, but RNAi [RNA interference] lets you target pairs or triplets of genes," said Ideker. "This approach in humans, patterned on yeast experiments, could eventually lead to more sophisticated drugs and gene therapies based on taking down not single genes, but combinations of genes that cause disease."

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