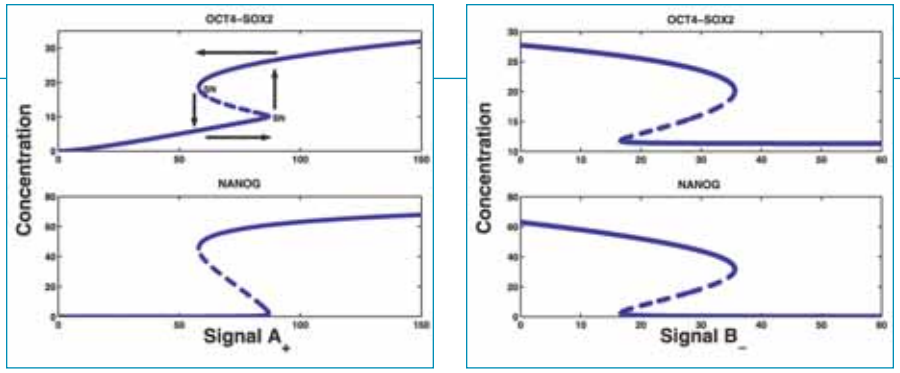


A+ represents hypothetical factors that activate OCT4 and SOX2. In response to increasing that signal, the OCT4-SOX2 dimer and NANOG switch from all off to all on. B- represents factors that repress NANOG, which has the effect of turning the switch off. Courtesy of Carsten Peterson.

Cambridge, Massachusetts. She thinks other components must function with the trio of proteins. However, she says, the work "provides a testable model to explain how OCT4, SOX2 and NANOG may contribute to these seemingly opposing activities."

The heart of the model—explaining how stem cells reconcile their dual identities—is vital, says Boyer. "If you are ever going to realize the therapeutic potential of these cells, you really need to find the key for understanding how embryonic stem cells balance their ability to self-renew or differentiate."

—Ewen M. Callaway

Connecting the (Microarray) Dots from Drug to Disease

Normal cells, diseased cells and cells on drugs share a common language: They all produce their own patterns of gene expression. And the patterns can be compared in useful ways—given a disease in which a certain set of genes are up- and down-regulated, one would like to find a drug that specifically counteracts those changes. A powerful new web-based tool allows researchers to draw just such connections. Researchers from all around the world can use the tool, called the Connectivity Map, to identify potential new drugs for a variety of diseases, and potential new uses for existing drugs.

"The objective is to connect diseases with the genes that underlie them and the drugs that treat them," says **Justin Lamb, PhD**, a senior scientist at the Broad Institute of Harvard and MIT. He and his colleagues described their work in the September 29, 2006, issue of *Science*.

The advent of DNA microarrays more than a decade ago made the Connectivity Map possible by allowing scientists to study thousands of genes all at once. Lamb and his colleagues used microarrays to determine which genes were turned up or down in cells treated with 164 different biologically active compounds (mostly drugs). They also gathered together previously published gene expression data for various diseases, including obesity, Alzheimer's Disease, and various types of cancer. Using pattern-recognition software the team developed, any researcher around the world can query the database at http://www.broad.mit.edu/cmap to identify drugs or diseases with patterns that are either the same as or opposite to a particular gene signature of interest.

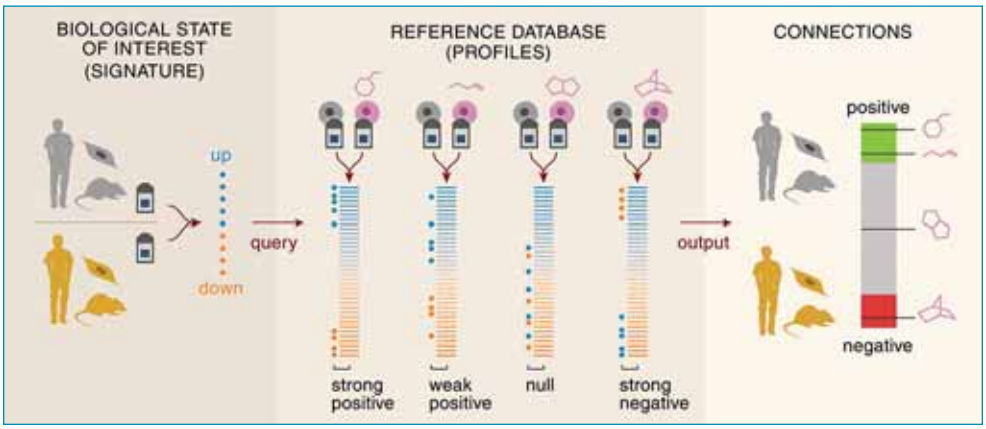
The most exciting use of this approach is in suggesting potential drug therapies for real diseases, Lamb says. In one of the team's initial tests, gene signatures exposed a possible new treatment for children with drug-resistant acute lymphoblastic leukemia. The researchers also have used the database to seek novel treatments for obesity and Alzheimer's disease.

The Connectivity Map also can unveil how drugs work on a molecular scale, says Lamb. For instance, similar genomic patterns in the database pointed to a connection between a compound called gedunin and a class of well-understood drugs. This implies gedunin might operate in a similar fashion to disrupt hormone signals in cancerous cells.

Having completed the Connectivity Map's pilot stage, the team intends to expand to cover all drugs approved by the Food and Drug Administration. One limitation is that it is restricted to specific cells in a petri dish, which neglects other interactions that occur in a human body, says **Eric Schadt, PhD**, senior scientific director of Rosetta Inpharmatics in Seattle. Still, Schadt says, "It's a great piece of work. It's a great tool, and it will be well-used."

"The whole field is on fire with these large-scale experiments," Schadt adds. "It's the only way you can uncover these networks that drive diseases. I think it's right on the money."

—Marcus Woo □



The Connectivity Map lets users compare the gene expression signature of any cell state of interest (left) with a reference database of profiles from cultured human cells treated with various drugs. Pattern-matching algorithms score each reference profile for the direction and strength of enrichment with the query signature to produce a "connectivity score." Here the columns for the first and second drug treatments show a positive connection to the state of interest; the third has no relationship to it; and the fourth has a negative connection. From: The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease, by Lamb, et al.,* Science *2006 Sep 29;313(5795):1929-35. Reprinted with permission from AAAS. http://www.sciencemag.org/cgi/content/full/313/5795/1929