no way to confine this molecule within cell walls experimentally, "observing" this behavior was possible only through computational modeling, says **Tal Danino**, graduate student in the UCSD Department of Bioengineering and lead author of the study.

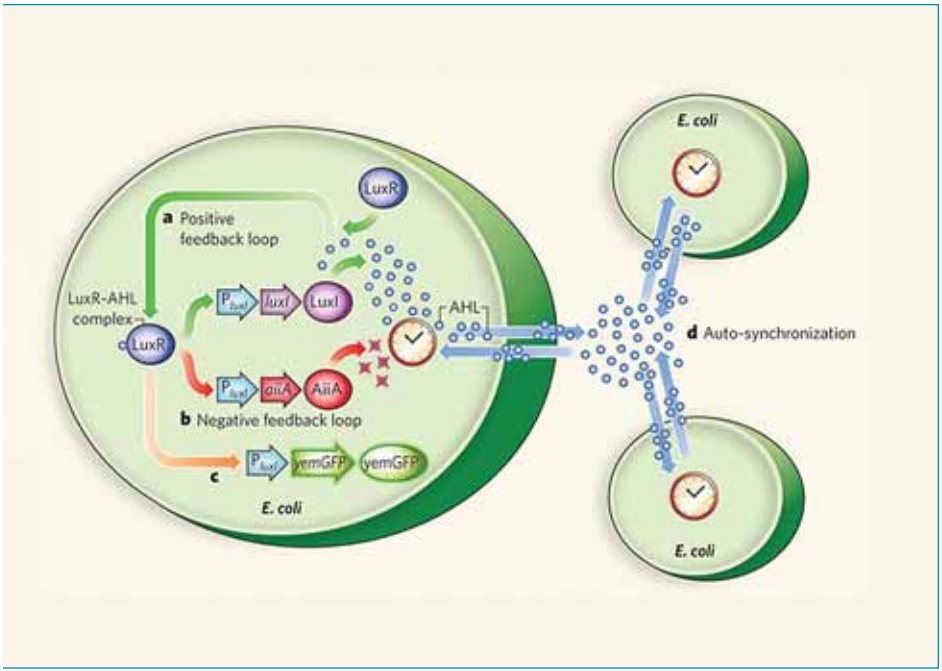
Computation is indeed a valuable tool for understanding gene networks, Hasty says. "We learned about time delay in gene regulatory networks, how signals propagate through colonies, and how interactions come together to synchronize behavior between cells." And with essentially only two genes at the heart of the synchronization mechanism, the system is a great demonstration of how small systems can generate very complex behavior. "It showed that you don't need a lot of genes in a network to get very interesting and rich dynamics, where all kinds of spectacular things can happen," he says.

"The complexity of the system is astonishing," says **Martin Fussenegger, PhD**, professor of biosystems science and engineering at the Swiss Federal Institute of Technology Zurich in Basel, Switzerland, who wrote an accompanying perspective on the study. Not only is the timing mechanism radically different from that of the central pacemaker in the brain, which uses one-way synchronization to control cellular clocks in remote tissue, but the cells manage to stay synchronized even while in constant motion and dividing every 20 minutes.

The bacteria can also be programmed to change their synchronized blinking rate in response to environmental triggers. This ability could lead to applications such as super-sensitive bacterial sensors that would flash more quickly in the presence of environmental contaminants, says **James Anderson, PhD**, program director for the Center for Bioinformatics and Computational Biology at the National Institute of General Medical Sciences within the National Institutes of Health.

But the immediate use of the work is more basic, Anderson points out. These researchers created computational models of the synchronization to drive both *in silico* and *in vitro* experiments of the synthetic biology, which in turn help refine the computational models even further. "What the synthetic biologists are doing now is helping us understand how the natural traits actually work at the same time that they're creating synthetic ones."

—By Regina Nuzzo, PhD

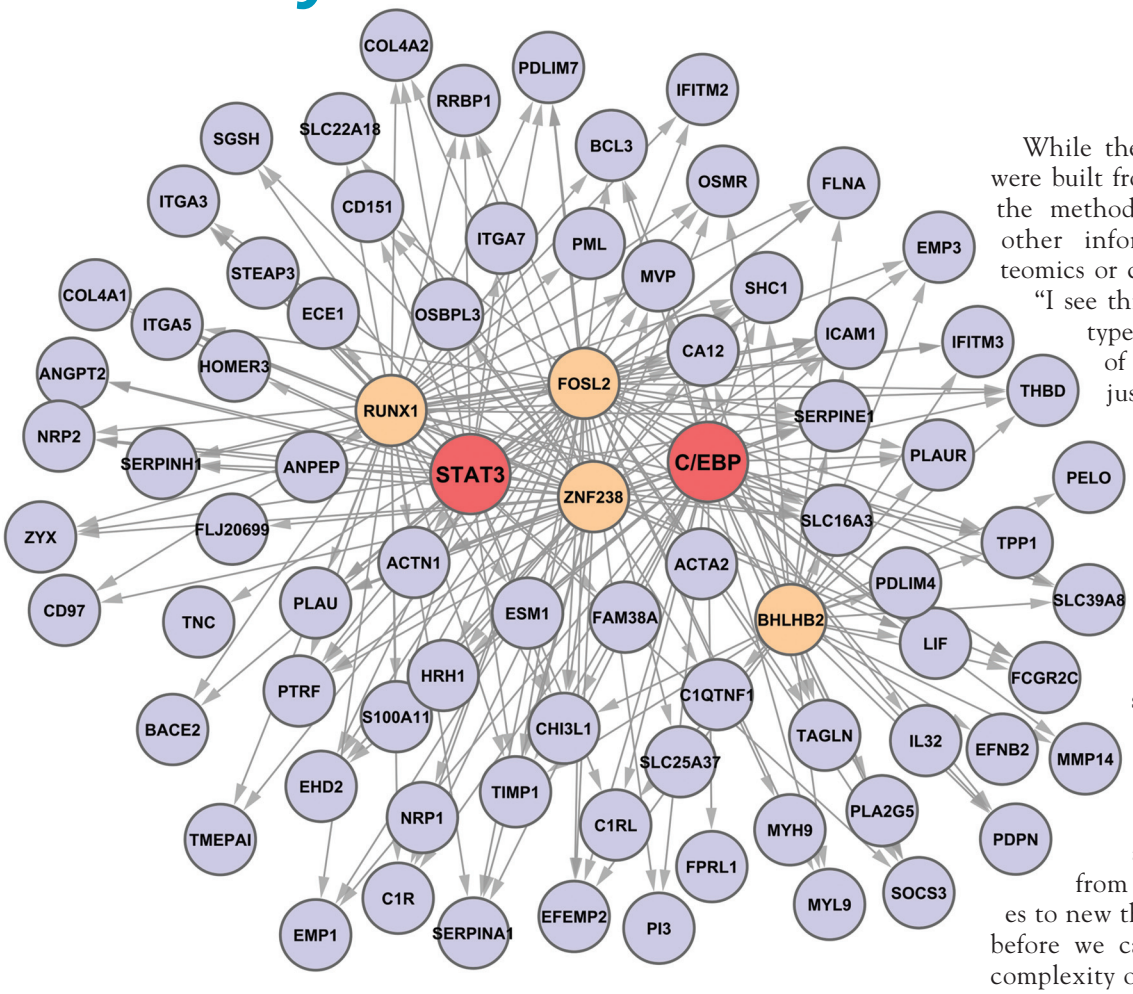


A team at UCSD built a network of genes and proteins in* E. coli *that acts as a molecular clock and can be synchronized across cells. A positive-feedback loop (a) triggers expression of a quorum-sensing gene that produces AHL, an intercellular communication molecule. At the same time, a negative-feedback loop (b) triggers a protein that degrades AHL and a green fluorescent protein (c) makes the waves of activity visible. The dynamic interactions of the positive- and negative-feedback loops produce regular pulses of AHL (d), which act as the metronome in the molecular clock. Since all the cells simultaneously send and receive AHL, they adjust and synchronize their clocks with each other. The result: coordinated fluorescent flashes. Reprinted by permission from MacMillan Publishers, Ltd: from Fussenegger, M, Synchronized Bacterial Clocks,* Nature *463, 301-302 (2010).

Reverse-Engineering Transcriptional Networks

A cell may change states several times in its lifetime—from a stem cell to a specialized cell, for example, or from a normal cell to a cancerous one. Each time this happens, a veritable army of genes must be raised to do the tasks needed by the new cell type. Now, researchers have successfully used computational approaches to identify the "master regulators" that, like generals, control the transformation of benign brain cells into the malignancies that cause high grade glioma, one of the most aggressive forms of brain cancer. The computational findings were then confirmed experimentally.

The work, which was published in *Nature* in February 2010, demonstrates the value that can come from reverse engineering molecular interaction networks for specific cell types. Coauthor **Andrea Califano, PhD**, professor of bioinformatics at Columbia University and director of the Center for the Multiscale Analysis of Genetic Networks (MAGNet), hopes to apply these methods to other questions of cellular transformation and development, particularly those relevant to dis-



This transcriptional network of high-grade glioma cells shows the two master regulators in red and other significant transcription factors in orange. Together, these transcription factors control about 80 percent of an HGG tumor's signature. Image courtesy of Columbia University, Califano Lab. Reprinted with permission from MacMillan Publishers, Ltd.: Carro, M.S., et al., The transcriptional network for mesenchymal transformation of brain tumours,* Nature *463, 318-325 (21 January 2010).

ease states such as cancer. "We can now ask what are the genes that control an arbitrary transformation," he says.

For a healthy cell to become the beginnings of a high-grade glioma (HGG) tumor, it needs to express a large number of genes that otherwise would never be activated. To find the key genes that produce that altered gene expression state, Califano's team first mapped out the regulatory logic of the most aggressive type of HGG cells using an information theory algorithm called ARACNE. The method can reconstruct regulatory networks from gene expression profiles of particular cell populations, even pruning out indirect interactions to determine which genes directly control others. Next, the researchers looked for genes in this network that were part of the tumor's signature – those that are highly expressed in HGG cells but not in normal brain cells. A handful of transcription factors emerged that together control about 80 percent of the characteristic genes. Two in particular, STAT3 and C/EBP, appeared to hierarchically control the others, even though they are expressed at levels so small they do not appear in the signature.

Further experiments, done with brain tumor experimentalist **Antonio Iavarone, MD**, verified the model, showing that activating the two genes simultaneously in neural cells causes the shift to a tumor-like cell. Likewise, silencing the genes together eliminated the malignant phenotype.

While the networks in this study were built from gene expression data, the method could also work with other information, such as proteomics or chromatin structure data. "I see this work as being a prototype of the power of this type of approach, but it's really just the beginning," says **Howard Fine, MD**, chief of the Neuro-Oncology branch at the National Cancer Institute.

Fine is also hopeful that the results of this work could lead to glioma treatments. "They've identified one small module within this very complex signaling network that is a cancer cell," he says. "This says to us, we might be able to translate findings from these kinds of approaches to new therapies for patients well before we can fully understand the complexity of the tumor cell."

— By Beth Skwarecki

Research Reproducibility from MSWord

A particular mashup of data and tools produces the unique results found in each computational biology publication. Now, researchers have developed a model system that gives readers—especially those lacking programming skills—the tools, data, and parameters they'd need to reproduce those results. Dubbed a "reproducible research system" (RRS), it lets the reader replicate original computational research directly from a Microsoft Word document.

"This effort was meant to show that the technology exists to make research reproducible by the non-programming user," says **Jill Mesirov, PhD**, director of computational biology and bioinformatics at the Broad Institute of the Massachusetts Institute of Technology. The work was described in a policy forum in *Science* in January 2010.