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UCSD Bioengineers Develop First Genome-Scale Computational Model of Gene Regulation, Results Published in May 6 Issue of Nature

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It has taken more than 50 years to accumulate the current body of knowledge on Escherichia coli, a bacterium which is one of the best studied organisms in biology. Now, bioengineers at the University of California, San Diego have integrated this knowledge into the first genome-scale model of the gene regulatory system in E.coli. The computational model helps to define the rules governing cell function and quickly enabled an exponential increase in the understanding of the regulatory system in E. coli. Their work, which is published in the May 6, 2004 issue of *Nature*, represents a new way to systematically drive biological discovery.

"This research is evidence of how much more quickly biological discovery is going to progress now, given that we have high-throughput experimental tools for gathering large volumes of data, and the use of these tools can be guided by computer models," said Bernhard Palsson, professor of bioengineering at the UCSD Jacobs School of Engineering. Palsson co-authored the study with his UCSD bioengineering student Markus Covert, who is now a post-doctoral researcher at the California Institute of Technology.

"We have demonstrated that we can reverse-engineer a cellular regulatory system at the genome scale, and then use that model to systematically gain new knowledge about how the cell functions," said Palsson.

In 2000, Palsson completed an in silico (computational) model of E. coli metabolism that is now being used by scientists worldwide to design and interpret laboratory experiments as well as engineer strains for industrial purposes. In this more recent work, Covert modeled the regulatory network in E. coli representing how the cell responds to environmental cues and expresses genes involved in cellular metabolism. He scoured the scientific literature to reconstruct an E. coli model incorporating all known data about regulatory network components, their functions and their actions.

The UCSD model now includes a network for 1,010 genes, including 104 regulatory genes, whose products together with other molecules regulate the expression of 479 of the 906 genes known to be involved in metabolism.

The team conducted a series of experiments focused on E. coli's response to oxygen deprivation. They made predictions of cellular behavior through simulations with the in silico model. These predictions guided high-throughput data-gathering experiments using gene chip technology. In the laboratory, the team created strains of E. coli in which genes involved in oxygen regulation were deleted, and then subjected the strains to experiments both with and without oxygen. When the predicted outcomes did not match the experimental outcomes, the experimental data was used to update the in silico model.

Through this process, the team uncovered surprising new details about how E. coli responds to oxygen deprivation.

"We went into the experiments thinking that oxygen regulation is fairly well understood. But in one fell swoop, we identified 115 previously unknown regulatory mechanisms," said Covert. "For example, one interesting finding

was that in several cases when a protein that transcribes a gene is active, the expression level of that gene is actually reduced. We also identified new regulatory interactions for genes that no one previously had described, basically opening up a whole new research frontier in terms of characterizing regulatory networks in E. coli."

Another observation by the team was that E. coli's regulatory network is much more complex than might be expected for such a relatively simple single-cell microbe. And that, Covert says, means that lessons learned through the E. coli modeling process will help scientists model much more advanced organisms such as mice and even humans.

UCSD has filed a patent on the model and is negotiating a license agreement. Palsson's group at UCSD will continue to develop the E. coli model, and is also beginning to model the regulatory network in yeast, a single-cell organism more closely related to human cells. Meanwhile Covert at Caltech is focusing on signaling transduction pathways in the mouse.

In addition to Palsson and Covert, the other researchers involved in the study include Eric M. Knight, Jennifer L. Reed, and Markus J. Herrgard. Funding was provided through the National Institutes of Health.

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