New tool in the fight against tuberculosis

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University of Illinois Researcher Nathan Price has created an algorithm that successfully integrates the statistically derived transcriptional regulatory network with a biochemically derived metabolic network. The model, called probabilistic regulation of metabolism, enables researchers to perturb a given regulatory gene or metabolic process and see how that affects the entire network. Credit: Don Hamerman for the Institute for Genomic Biology / University of Illinois

Researchers at the Institute for Genomic Biology at the University of Illinois have developed a way to harness the prodigious quantities of both genomic and metabolic data being generated with high-throughput genomics and other techniques. They have developed an algorithm that automatically integrates both data sets. The model, called probabilistic regulation of metabolism (PROM), enables researchers to perturb a given regulatory gene or metabolic process and see how that affects the entire network.

"PROM provides a platform for studying the behavior of networks in a wide range of different conditions," says principal investigator Nathan Price, an associate professor of chemical and biomolecular engineering

at Illinois.

Using this model the researchers have created the first genome-scale, regulatory-metabolic network of Mycobacterium tuberculosis. Their results were published online by *PNAS* on September 27.

Using *E. Coli* as a benchmark, Price and graduate student Sriram Chandrasekaran showed that PROM was more accurate and comprehensive than the previous model for *E. Coli*, which had been done by hand and published in 2004.

After using *E. Coli* as a proof of principle, they targeted tuberculosis, a bacterium that has not been as thoroughly studied as *E. Coli*. Price and Chandrasekaran had less than half the amount of data then they had for *E. Coli* and were still able to create a model that predicted knockout phenotypes 95 percent of the time, says Price.

Price and Chandrasekaran built the algorithm using microarray data, transcription-factor interactions that regulate metabolic reactions, and knock-out phenotypes. The method is both accurate and fast. PROM may prove particularly helpful to tuberculosis researchers because, although when tuberculosis is growing it can be killed, the real challenge is to target the bacterium during its dormant or quiescent stage. PROM may enable researchers to identify and target the pathways keeping the cells alive during dormancy.

PROM also represents a major advance because it successfully integrates the statistically derived transcriptional regulatory network with a biochemically derived metabolic network.

"That is the new part," says Price. "People have created regulatory models and metabolic models. But there has been nothing before that could combine them in this automated fashion. It is difficult to get these

two to talk to each other in the right way."

Price and Chandrasekaran created an algorithm that makes use of probability. Earlier models used a Boolean or a binary approach, in which a gene is either on or off. PROM can account for a gene or enzyme that can also be part way on or part way off, so it acts more like a rheostat than a toggle switch.

"People were stuck here for a long time. That's why PROM is such a nice method. It's sort of Boolean but it's probabilistic Boolean. It does allow us to have a continuous variation," says Price.

"These models can guide genome-scale synthetic biology," he adds. "And understanding how the networks are put together lays the foundation for us to design genomes that encode for networks that behave in the way we want them to, such as engineering microbes to convert environmental toxins into biofuels, for example."

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