Simulating Human Metabolism to Find New Diets to New Drugs

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Bioengineering researchers at UC San Diego have painstakingly assembled a virtual human metabolic network that will give researchers a new way to hunt for better treatments for hundreds of human metabolic disorders, from diabetes to high levels of cholesterol in the blood. This first-of-its-kind metabolic network builds on the sequencing of the human genome and contains more than 3,300 known human biochemical transformations that have been documented during 50 years of research worldwide.

UC San Diego researchers, from left, Monica L. Mo, Scott A. Becker, Neema Jamshidi, Ines Thiele, and bioengineering professor Bernhard Palsson used strict quality control criteria accepted by the scientific community to assemble the human metabolic network piece by metabolic piece during more than a year of intense work.

In a report in the *Proceedings of the National Academy of Sciences* (*PNAS*) made available on the journal's website on Jan. 29, the UCSD researchers led by Bernhard Ø Palsson, a professor of bioengineering in the Jacobs School of Engineering, unveiled the BiGG (biochemically, genetically, and genomically structured) database as the end product of this phase of the research project.

Each person's metabolism, which represents the conversion of food sources into energy and the assembly of molecules, is determined by genetics, environment, and nutrition. In a demonstration of the power and flexibility of the BiGG database, the UCSD researchers conducted 288 simulations, including the synthesis of testosterone and estrogen, as well as the metabolism of dietary fat. In every case, the behavior of the model matched the published performance of human cells in defined conditions.

Researchers can use the computationally based database to quickly discover the effects on a given cell type of changing the performance of any of the 3,300 known human metabolic reactions operating in that cell. The tool is designed to help scientists explore hundreds of human disorders in the metabolism of amino acids, carbohydrates, lipids, minerals, and other molecules. It also is intended to be used in the future to study metabolic variations between people as a way to individually tailor diet for weight control.

Studying the metabolism of cholesterol is another potential application. Cholesterol is a lipid that is incorporated into all cell membranes. An estimated 105 million adults in the United States have total blood cholesterol values of 200 milligrams per deciliter (mg/dl) and higher, and of these about 36.6 million have levels of 240 mg/dl or more, according to the American Heart Association. Such high cholesterol levels are associated with an elevated risk of heart disease.

More than two dozen biochemical reactions in human cells are needed to make cholesterol. Cholesterol-lowering drugs called statins affect just one of those reactions, reducing the synthesis of cholesterol as if they were pinching a garden hose, slowing the flow of cholesterol through it. However, metabolic pathways are actually labyrinths of interconnected garden hoses with complicated flow patterns.

"Pinching off one part of the labyrinth can have a good effect, but it can also have unexpected consequences, or even no effect because of redundancy built into metabolic systems," Palsson said. "The new tool we've created

allows scientists to tinker with a virtual metabolic system in ways that were, until now, impossible, and to test the modeling predictions in real cells."

Each type of cell in the human body utilizes only a fraction of all 3,300 metabolic reactions, and scientists can create *in silico* any type of cell, from a heart cell to a red blood cell, with its particular complement of metabolic enzymes, and adjust their genetic or other properties to compute the cell's behavior.

"We can analyze abnormal metabolism at the root cause of diseases such as hemolytic anemia, which can result from a deficiency in metabolic reactions," said Neema Jamshidi, an MD/Ph. D. student at UCSD and co-author of the paper. "We can study both the causes and consequences of this and other diseases, which may lead to novel insights about how new drugs might be designed to treat them."

After tabulating all reliable metabolic information about human cells, the team employed mathematical tools traditionally used in signal processing and operations research to identify a cell's most influential metabolic components in key metabolic states. "This approach confirmed in a mathematically rigorous way what cell biologists already understand to be true: cells use compartmentalization to coordinate their metabolism," Jamshidi said. "Our technique provides scientists with a new way to investigate the role of compartmentalization in metabolism."

The reconstructed metabolic network is based on the human genome sequence. Palsson's team of six researchers manually analyzed 1,500 key books, review papers, and legacy scientific reports published over the past 50 years. The team used strict quality control criteria accepted by the scientific community to assemble the network piece by metabolic piece during more than a year of intense work.

"This accomplishment was made possible by the Human Genome Project, and its scope and utility will grow over time," Palsson said. Some parts of human metabolism require additional research, and that information, when obtained, will be added to the model as part of the project's next phase.

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