Cells exercise suboptimal strategy to survive

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Rice University researchers Amina Qutub and Andre Schultz are studying how greed and fear can keep a cell's performance suboptimal for its own good. The research has implications for the control of metabolic pathways to treat disease. Credit: Jeff Fitlow/Rice University

There are few times in life when one should aim for suboptimal performance, but new research at Rice University suggests scientists who

study metabolism and its role in evolution should look for signs of just that.

A study published this month in the journal *BMC Systems Biology* details a computational method called corsoFBA. FBA stands for flux balance analysis and the program predicts internal cell flux—the rate at which cells process and store energy—at what researchers call suboptimal growth.

The ultimate goal of the study is to discover how organisms, including humans, adapt to changing environments, including the body's response during exercise.

The method allows researchers to model how metabolic pathways, chains of chemical reactions in the cells of all living beings, will react in the presence or absence of certain conditions, like the availability of oxygen or the acidity of the environment. It does so by measuring how a cell spends its fixed energetic resources—its protein cost—to preserve flux in more than one pathway.

The work springs from the mind and talents of a Rice graduate student who spent years training his body for absolutely optimal performance. André Schultz is a former member of the Brazilian national swim team who trained alongside Olympic legend Michael Phelps at the University of Michigan. As an undergraduate there, he divided his time between competitive swimming and academics, particularly his love for mathematics.

At Rice, where he is a student of bioengineer and co-author Amina Qutub, Schultz turned his attention to biophysics, specifically mathematical models of metabolic pathways.

As an elite swimmer, Schultz trained at high altitude to maximize his

endurance by calling upon his own metabolic pathways to make adjustments. In an oxygen-depleted environment, athletes who train between 6,000 and 7,000 feet above sea level can temporarily increase their red blood cell count and alter muscle metabolism in ways that benefit their performance closer to sea level.

One focus of the Qutub lab at Rice's BioScience Research Collaborative is the study of hypoxia, or oxygen starvation, and its effect on biological systems. The lab studies molecular signaling pathways through computer models and experiments to see how they impact the body's response to oxygen and how the pathways can be manipulated. The goals are to treat stroke and neurodegenerative diseases, stop cancer progression—and learn how organisms adapt to their environments.

Standard computer models like flux balance analysis, developed in the 1980s, look at a metabolic pathway's optimal performance, but Schultz said they don't show the whole picture.

"Flux balance analysis is geared for optimization, and it works really well with microorganisms, which is where most of this analysis has been applied," he said. "When you simulate the growth of bacteria—E. coli, for example—it's safe to assume that bacteria are trying to grow as much as possible.

"But if you look at a muscle, its cells are not always trying to move as much as they can," Schultz said. "You're not always using maximal force. So the ability to see what a system is doing at suboptimal levels is beneficial."

Metabolism can take many routes to turn sugars into energy-storing adenosine triphosphate or prompt the production of particular catalytic compounds. Schultz said discussions among researchers, including University of California at San Diego Professor Bernhard Palsson, a

pioneer in the field of whole genome wide metabolic reconstruction who mentored him during a visit to Rice earlier this year, have led to the belief that two factors—greed and fear—can keep a cell's performance suboptimal for its own good. But no study has sought to quantify suboptimal signaling, he said.

"When bacteria are greedy, they want to grow and multiply, but conditions might change at some point, and they might have to adapt," he said. "So they invest protein cost and leave some flux through alternate pathways in case, for example, the pH suddenly changes and they're in an acid or base environment, or they had to switch from glucose to acetate (to produce energy).

"This fear part puts them on guard and takes away from greed," he said.

Qutub suspects organisms hedge their bets as a matter of course. Learning the secrets of alternate molecular pathways could provide clues about how to use them to patients' advantage, she said.

"Our question is, How does the hypoxia response pathway interact with metabolism in a way that allows animals to adapt at the tissue and whole-body level? The answer for mammalian systems is that cells don't optimize these pathways to achieve the maximal growth possible, with the possible exception of cancer cells," Qutub said.

One immediate goal is to use Schultz's model to predict how humans adapt to high- and low-altitude hypoxia. "First, we'll be testing on deer mice that have adapted to two extreme environments: the Colorado mountains and Death Valley," she said.

Schultz has traveled with the lab's collaborators, Jay Storz at the University of Nebraska-Lincoln and Zac Cheviron at the University of Illinois, to gather mice from low and high altitudes to study how they

have successfully adapted to their environments—as he once did.

While the proof-of-principal study focuses on flux in single-cell bacteria, the lab's ongoing work will extend analysis to muscle, liver and fat tissue in mammals. "We chose these tissues because they're particularly important during exercise," Qutub said.

More information: *BMC Systems Biology* , www.biomedcentral.com/1752-0509/9/18/abstract

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