Balance between growth and adaptability shapes microbial success, evolution

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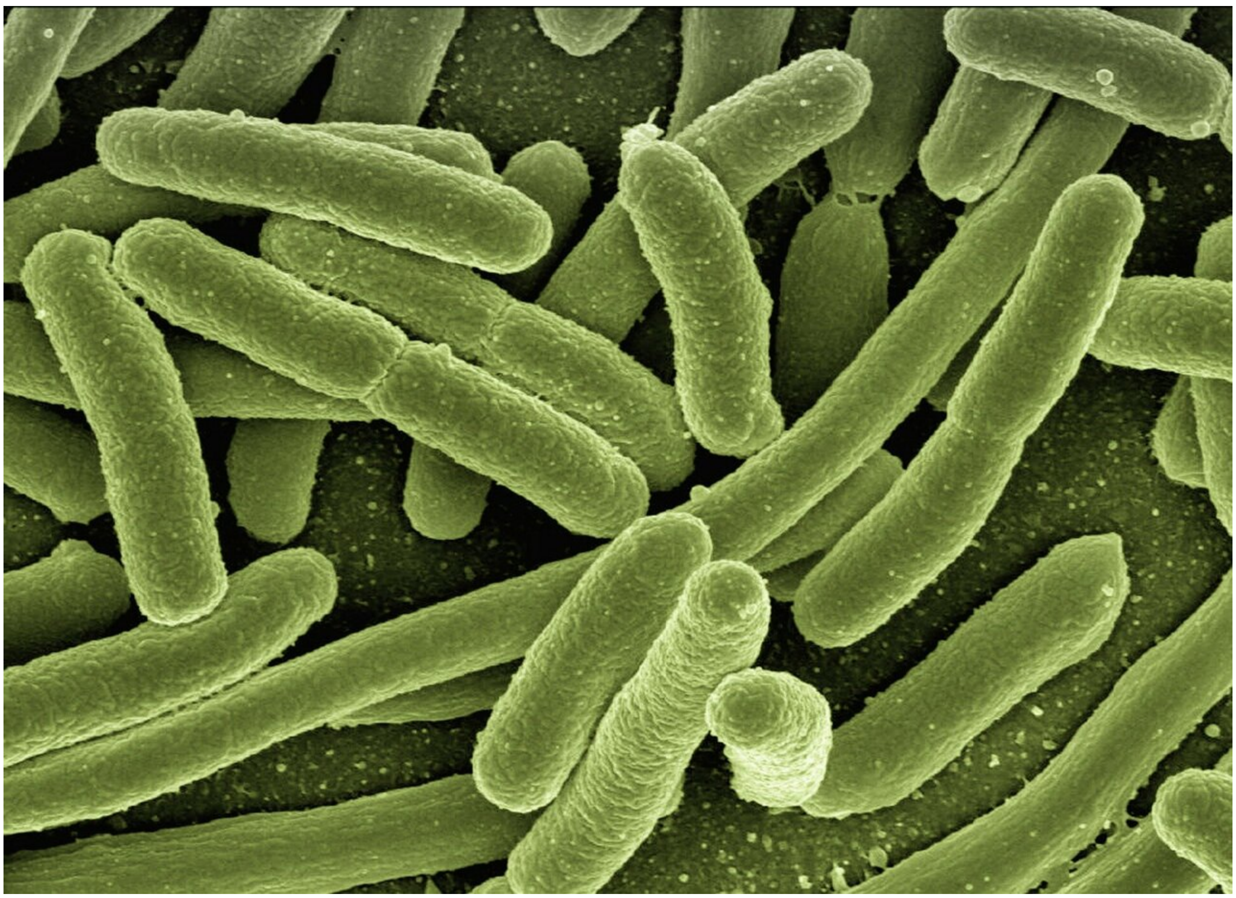

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One of the foremost challenges in biology is the quest to uncover the underlying rules that determine how biological organisms behave in different situations. Even seemingly simple questions, such as why bacteria grow at a certain rate and why there is a tremendous variation in growth rate across species in different environments, have remained unclear.

A new study published in *Nature* in July by scientists from Harvard Medical School, ETH Zurich and the University of California, San Diego now sheds light on these long-standing mysteries.

Their findings reveal that the success and evolution of microbes in different ecosystems are shaped by a fundamental trade-off between two traits: rate of growth under constant environments and the ability to adapt to changing environments.

The researchers found that bacteria growing exceptionally fast struggled as environmental conditions changed, experiencing lag time in which they were unable to grow for many hours and only eventually adapted. In comparison, when the same bacteria grew slowly, they quickly adapted to changing conditions.

"Bacteria cannot simultaneously excel at growing fast and at switching quickly between conditions when the environment suddenly changes," said study lead author Markus Basan, assistant professor of systems biology in the Blavatnik Institute at HMS.

The results may explain why microbes such as E. coli grow at vastly different rates in different environments, often much more slowly than would be expected, the authors said.

"As an analogy, one can think of a person training to become an elite long-distance runner and also an elite weight lifter at the same time," Basan added. "The weight of the muscle mass required to excel at weightlifting will undoubtedly hamper the ability of energy efficient long-distance running, at least to some degree. This is what constitutes a trade-off."

Strikingly, this effect was not specific to a few isolated conditions. In E. Coli, the team found that this trade-off is conserved across dozens of growth conditions, involving different nutrients and changing environments. They also observed the same trade-off in different microbial species separated by millions of years of evolution, including single-celled eukaryotes, all described by the same mathematical equation.

The team's experiments suggest the observed universality of the trade-off between growth and adaptability is because it emerges directly from metabolic mechanisms that are fundamental to life on earth.

Sisyphean task

The element carbon is a primary component of much of the material that makes up every living cell, such as proteins. Through diet, animals can acquire preformed building blocks like amino acids that comprise proteins. Bacteria, on the other hand, are able to convert a single source of carbon, such as a sugar, into all carbon-based building blocks using biochemistry.

However, the metabolic reactions that bacteria use to convert different sugars into biomolecules can move in opposing directions. For example, when E. coli breaks down glucose, the bacteria's carbon source of choice, they produce a molecule called acetate, which is its primary fermentation product. Under certain conditions, such as when glucose runs dry, the opposite reaction can occur, and acetate can be used for growth.

Therefore, when a preferred carbon source like glucose is depleted, bacteria must transition from one reaction direction to the opposite direction. This can wreak havoc on its metabolism, especially if the bacteria were growing quickly before the transition.

To support high growth rates, bacteria must contain a large number of enzymes that facilitate reactions in one direction. As a result, if the environment changes suddenly, only a small number of enzymes are present that can facilitate reactions in the new, correct direction. Even worse, the bacteria still contain a large number of enzymes running the reaction in the wrong direction, which actually burns energy.

"This leaves the cell trapped in a terrible situation, where most of its own enzymes are suddenly working in the wrong direction, preventing the enzymes operating in the correct direction from being produced," Basan said. "It resembles the task of Sisyphus, where despite a lot of effort the metabolites are just not getting anywhere."

After uncovering this underlying problem, the researchers were able to formulate a theoretical model that precisely captures the mathematical relationship of the trade-off between the rate of growth and the rate of adaptability. The model also made a number of precise quantitative predictions of genetic changes that affect the trade-off, which were validated experimentally.

The trade-off uncovered in this study potentially explains why microbes grow at different rates in different environments, sometimes much more slowly than expected based on other experimental evidence such as protein composition, Basan said.

Slower-than-expected growth was thought to be due to poor-quality nutrients, but the new findings suggest that it may instead arise because some nutrients signal unstable, highly fluctuating ecological environments to the microbe, where a more careful growth strategy is advantageous.

This is illustrated by a number of simple mutations in the E. coli genome that allow for much faster growth in specific conditions but also cause deficiency in adaptability.

"The study illustrates how hard-wired trade-offs between competing objectives may have shaped microbial evolution and the phenotypes that we see in different bacterial species today," Basan said. "Understanding such trade-offs gives us a rare glimpse into the complex ecological choices made by different bacterial species and helps us model these choices in a quantitative and predictive way."

The trade-off between fast growth and adaptability uncovered in this work, may help to understand the interactions in complex microbial communities like in the microbiota.

"Such trade-offs can give rise to the coexistence of bacteria with different strategies in the same ecological niche," Basan said.

Because central metabolism is highly conserved between species from bacteria to humans, a better understanding of central metabolism and its intrinsic limitations may help to understand complex human diseases.

Mathematical models that can quantitatively predict the behavior of complex biological systems like one developed in this work can also have practical relevance for synthetic biology and bioengineering applications, the authors said.

"Hopefully, quantitative and predictive models can someday transform the process for building things in biology from tedious trial and error to something more like a modern engineering discipline," Basan said. "For example, it's pretty useful for engineers to be able to calculate that something like the Golden Gate Bridge is not going to collapse, without needing build it first to try it out."

More information: Markus Basan et al. A universal trade-off between growth and lag in fluctuating environments, *Nature* (2020). DOI: 10.1038/s41586-020-2505-4

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