Scientists show that bacteria can evolve a biological timer to survive antibiotic treatments

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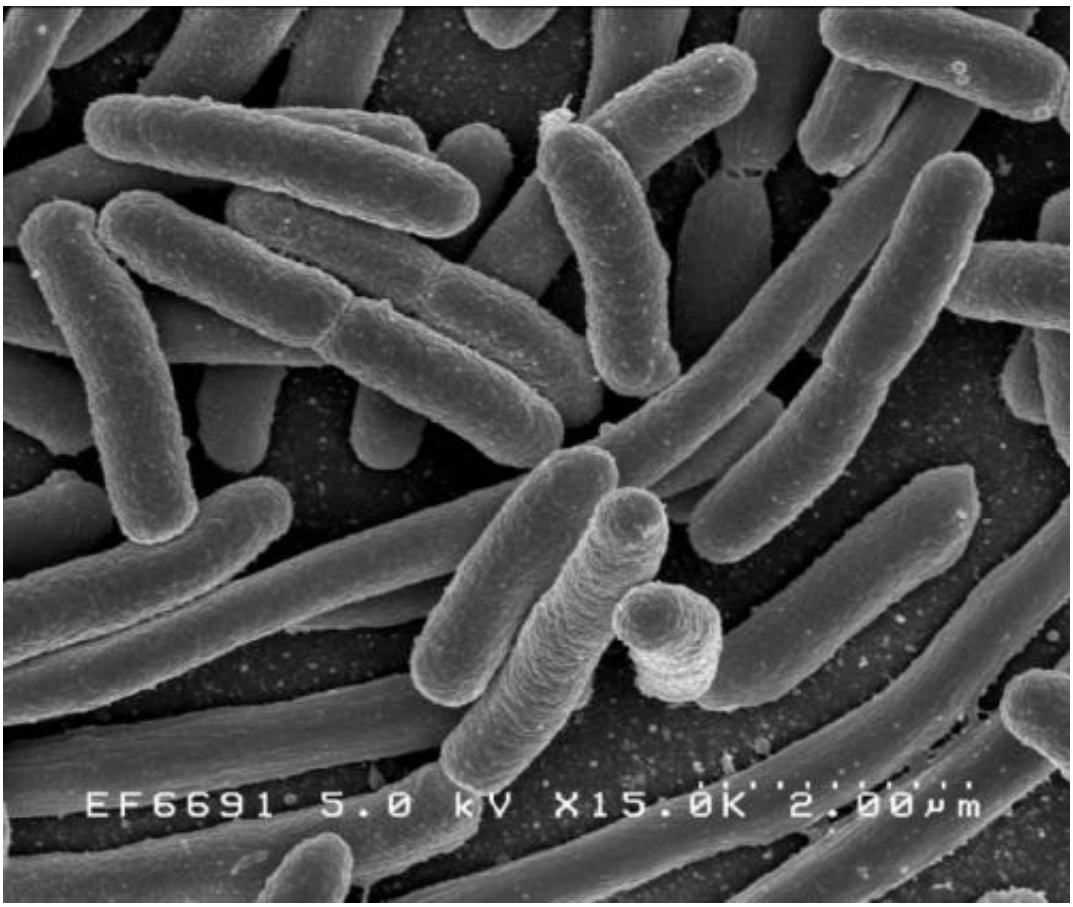

This is a scanning electron micrograph of *Escherichia coli* bacteria, for illustrative purposes. Credit: U.S. National Institutes of Health, public domain image

The ability of microorganisms to overcome antibiotic treatments is one of the top concerns of modern medicine. The effectiveness of many antibiotics has been reduced by bacteria's ability to rapidly evolve and develop strategies to resist antibiotics. Bacteria achieve this by specific mechanisms that are tailored to the molecular structure or function of a particular antibiotic. For example, bacteria would typically develop drug resistance by evolving a mutation that breaks down the drug.

Researchers at the Hebrew University of Jerusalem set out to determine if they could predict a different evolutionary process and follow it in real time. Using the quantitative approach of physicists, the team developed experimental tools to measure precisely the bacterial response to antibiotics, and developed a mathematical model of the process. The model led them to hypothesize that a daily three-hour dose would enable the bacteria to predict delivery of the drug, and go dormant for that period in order to survive.

The research was led by Prof. Nathalie Balaban at the Racah Institute of Physics in the Hebrew University's Faculty of Science, working with colleagues at the Racah Institute, the Hebrew University's Sudarsky Center for Computational Biology, and the Broad Institute of Harvard and MIT. The research paper, "Optimization of lag time underlies tolerance in bacterial populations evolved under intermittent antibiotic exposure," appears in the June 25 edition of the journal *Nature*.

To test their hypothesis, the researchers delivered antibiotics to bacterial populations in the lab for precisely three hours each day. After only ten days they were able to observe the bacteria using a new survival tactic. When exposed to these repeated cycles of antibiotic treatments, the bacteria evolved an adaptation to the duration of the antibiotic stress by remaining dormant for the treatment period.

The results demonstrated that bacteria can evolve within days. Most

significantly, it showed for the first time that bacteria can develop a biological timer to survive under antibiotic exposure.

To further test their hypothesis, the researchers delivered antibiotics for different periods, exposing three different bacteria populations to repeated daily antibiotic exposures lasting 3, 5, or 8 hours. Remarkably, each of the populations adapted by prolonging their dormant stage to match the exposure duration.

With this new understanding of how bacterial populations evolve survival strategies against antibiotics, scientists could develop new approaches for slowing the evolution of antibiotic resistance.

Now that they have identified the mutation responsible for the biological timer, the researchers want to gather clinical data to see if a similar timed response to antibiotics is active in people, allowing bacteria to render less effective the antibiotics people take on a fixed schedule. If this is discovered to be the case, it may explain the failure of antibiotic treatments observed in several diseases. In the future, it may help doctors to recommend different treatment schedules. It could also lead to the development and greater use of drugs that can maintain constant levels in the body.

According to the researchers, the study demonstrates that quantitative approaches from Physics can be used to address fundamental as well as clinically relevant issues in Biology.

More information: Optimization of lag time underlies antibiotic tolerance in evolved bacterial populations, *Nature* (2014) DOI: 10.1038/nature13469