Quantitative approaches provide new perspective on development of antibiotic resistance

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Using quantitative models of bacterial growth, a team of UC San Diego biophysicists has discovered the bizarre way by which antibiotic resistance allows bacteria to multiply in the presence of antibiotics, a growing health problem in hospitals and nursing homes across the United States.

Two months ago, the Centers for Disease Control and Prevention issued a sobering report estimating that antibiotic-resistant bacteria last year caused more than two million illnesses and approximately 23,000 deaths in the United States. Treating these infections, the report said, added $20 billion last year to our already overburdened health care system.

Many approaches are now being employed by public health officials to limit the spread of antibiotic resistance in bacteria—such as limiting the use of antibiotics in livestock, controlling prescriptions of antibiotics and developing new drugs against bacteria already resistant to conventional drug treatments. But understanding how bacteria grow and evolve drug resistance could also help stop its spread by allowing scientists to target the process of evolution itself.

"Understanding how bacteria harboring antibiotic resistance grow in the presence of antibiotics is critical for predicting the spread and evolution of drug resistance," the UC San Diego scientists say in an article published in the November 29 issue of the journal *Science*.

In their study, the researchers found that the expression of antibiotic resistance genes in strains of the model bacterium *E. coli* depends on a complex relationship between the bacterial colony's growth status and the effectiveness of the resistance mechanism.

"In the course of developing complete resistance to a drug, a strain of bacteria often first acquires a mechanism with very limited efficacy," says Terry Hwa, a professor of physics and biology who headed the research effort. "While much effort has been spent elucidating individually how a drug inhibits bacterial growth and how a resistance mechanism neutralizes the action of a drug, little is known previously about how the two play off of each other during the critical phase where drug resistance evolves towards full strength."

According to Hwa, the interaction between drug and drug-resistance is complex because the degree of drug resistance expressed in a bacterium depends on its state of growth, which in turn depends on the efficacy of drug, with the latter depending on the expression of drug resistance itself. For a class of common drugs, the researchers realized that this chain of circular relations acted effectively to promote the efficacy of drug resistance for an intermediate range of drug doses.

The use of predictive quantitative models was instrumental in guiding the researchers to formulate critical experiments to dissect this complexity. In their experiments, *E. coli* cells possessing varying degrees of resistance to an antibiotic were grown in carefully controlled environments kept at different drug doses in "microfluidic" devices—which permitted the researchers to manipulate tiny amounts of fluid and allowed them to continuously observe the individual cells. Hwa and his team found a range of drug doses for which genetically identical bacterial cells exhibited drastically different behaviors: while a substantial fraction of cells stopped growing despite carrying the resistance gene, other cells continued to grow at a high rate. This

phenomenon, called "growth bistability," occurred as quantitatively predicted by the researchers' mathematical models, in terms of both the dependence on the drug dose, which is set by the environment, and on the degree of drug resistance a strain possesses, which is set by the genetic makeup of the strain and is subject to change during evolution.

"Exposing this behavior generates insight into the evolution of drug resistance," says Hwa. "With this model we can chart how resistance is picked up and evaluate quantitatively the efficacy of a drug." However, this model has only been established for one class of drugs and one class of drug-resistance mechanisms. Hwa believes it is important to establish such predictive models for all the common drugs in pathogenic bacterial species.

"My hope," he adds, "is to get the message out to drug companies and hospitals that there is an informative, quantitative way to look at the action of a drug on bacteria and at the consequences of using a drug on bacteria as they try to pick up resistance, and that this approach can be incorporated in both the design and evaluation of drug efficacy in clinically relevant settings."

Hwa says the principle of interaction between drug and drug-resistance is important to understand not only for the evolution of antibiotics, but also for the emergence of drug resistance in other diseases. A prominent example is the rapid emergence of cancer lines resistant to drug treatment, which underlies most failures in cancer drug therapies. While there are obviously numerous differences between the evolution of drug resistance in bacteria and in cancer, Hwa noted that the connection between the two was sufficient to motivate the Physical Science-Oncology program of the National Cancer Institute to co-sponsor this study.

More information: "The Innate Growth Bistability and Fitness

Landscapes of Antibiotic-Resistant Bacteria" *Science*, 2013.

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