Physics strategy tested as solution for antibiotic resistance

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A Virginia Tech biologist proposes to use a physics strategy called resonant activation to nudge dormant bacteria cells into a stage where they will be sensitive to antibiotics.

In medicine, resonance means the sound the doctor hears when he or she thumps your chest. In physics, resonance is a periodic force or an oscillation whose frequency is close to that of a natural system's frequency. Sound waves are an example of a natural system that can be altered with resonant activation.

Jianhua Xing, an assistant professor of biological sciences at Virginia Tech who has studied more than a smattering of physics, was considering the problem of antibiotic resistance when he remembered a physics paper on resonant activation that he had read as a student.

One strategy bacterial colonies use to survive antibiotics is to create a few persister cells. Because these cells are dormant or grow very slowly, they can dodge an antibiotic attack that requires active cell wall growth to be effective. Persister cells convert to normally growing cells at a random and slow rate so that there are always a few that remain dormant until the antibiotics are gone. Extending antibiotic treatment can be a dangerous strategy because of severe side effects, such as liver damage.

Persister cells have multiple steady states, with fluctuations in the numbers of proteins as they transition to a normal cell. Xing viewed this fluctuation during synthesis and degradation of proteins as a potential

target for resonant activation. Instead of a sound wave or electronic signal, the perturbing signal would be repetitive antibiotic treatment.

Xing's student, Yan Fu, a second year graduate student in the Interdisciplinary Program of Genetics, Bioinformatics, and Computational Biology at Virginia Tech; and another student, Meng Zhu of the School of Computing at Clemson University, created a computer simulation to compare different strategies of periodic antibiotics cued to protein fluctuations in persister cells. Their finding that resonant activation - fluctuating antibiotic treatments - accelerates bacteria colony sterilization was published in the journal *Physical Biology* in March 2010 ("Resonant activation: a strategy against bacterial persistence," Fu, Zhu, and Xin.).

Xing acknowledges that that the computer simulation simplified the problem by neglecting further complication due to mutation, but said he believes the concept has applications for cancer treatment. "On and off dosing with chemicals could be as effective as or more effective than long-term dosage. You need to stop and let the body recover, then resume," he said.

He is particularly interested in conducting experiments to see if resonant activation could increase the efficiency of inducing a normal (somatic) cell into an undifferentiated or stem cell.

"Bacteria mutate quickly, but there could be applications for cancer or stem cell conversion, where mutation is slower or not an issue," Xing said.

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