Since Alexander Fleming discovered in 1928 that a substance secreted by a mold could kill bacteria, we have become used to the ease of administering cocktails of antibiotics to fight bacterial infections. However, the use and misuse of antibiotics in human medicine and livestock farming over many decades has had the serious side effect of selecting for bacteria that survive drug attack: many bacterial strains have emerged that are resistant to antibiotics, most famously the multi-drug-resistant *Staphylococcus aureus* strain, the source of *Staph* infections, that represents a major threat to hospital patients. The pool of effective antibiotics is running out, and finding new strategies to prevent the rapid evolution of drug resistance has become a pressing challenge for global health.

Now, two independent theoretical studies, one published in *Physical Review Letters* by Philip Greulich at the University of Edinburgh, UK, and colleagues [1], and the other by Rutger Hermsen at the Center for Theoretical Biological Physics, San Diego, and colleagues in *Proceedings of the National Academy of Sciences* [2], address how the evolution of drug resistance can be profoundly influenced by how drugs are distributed in biological tissues. Once administered, drugs do not spread evenly throughout the human body, which is compartmentalized and composed of tissues that have different affinity for retaining the drugs. The new research suggests that variations in drug concentrations may play an important role in selecting bacterial strains that are able to survive exposure to antibiotics.

The rapid evolution of drug resistance is an impressive demonstration of the efficiency of bacterial adaptation. Bacterial populations are large and cells are able to replicate rapidly (sometimes in minutes) and to exchange genetic material. These are ideal conditions for Darwinian evolution to act: slight changes, or mutations, in the genomes arise by chance from one bacterial generation to the next. While most of these changes are deleterious, some, such as resistance to an antibiotic substance, may confer an advantage to bacteria living in human tissues, allowing the population of resistant mutant strains to rapidly increase. As a consequence, unless a bacterial infection is completely wiped out by a large dose of antibiotics, drug resistant strains emerge.

Yet when a mix of antibiotics is administered, the buildup of drug resistance requires multiple mutations and becomes harder to explain [3]; in this case, the bacterial population should be driven to extinction, unless a resistant multimutant arises. This, however, becomes prohibitively unlikely for just a handful of required mutations. Why then does drug resistance evolve so readily?

The work of Greulich *et al.* and Hermsen *et al.* could solve this puzzle because it demonstrates that spatial variations in drug concentrations allow for a gradual selection of drug resistant mutants. Heterogeneities in drug concentrations have been previously recognized as a potential driver of drug resistance [4, 5], as was demonstrated in a recent microfluidic experiment [6]. Yet quantitative models have been lacking so far. The new theoretical studies fill this gap and help identify parameters that may be key to controlling drug resistance evolution.

In a gradient of drug concentration, resistance can evolve following the stepwise dynamics illustrated in Fig. 1. Initially, only a small population of wild-type (i.e., nonmutant) cells can be sustained in the regions where drug concentration is low. The growth of bacteria in this suitable habitat is balanced by the death of bacteria that move by chance into less hospitable regions of higher drug concentration. During this continual population turnover, a mutant will eventually appear that is slightly more resistant than the wild type. This mutant will then be able to endure higher drug concentration and move up the concentration gradient. Thereby the mutant population can overgrow the wild type and reach a steady-state distribution that covers a slightly larger region than
tat heterogeneity [7], in which the bacterial population is an analogy to ecological models characterized by habitat evolution only if resistance strictly increases in each step of the mutational path leading from the original wild type to the resistant mutant. By this mechanism, the bacterial population can plausibly penetrate the concentration gradient and efficiently develop any number of mutations provided that each mutation increases resistance. The two research groups consider how this Darwinian selection process can work in two different regimes. Greulich et al. assume a relatively smooth gradient in drug concentration, and analyze the resulting dynamics in a spatially continuous one-dimensional framework [4]. Their analysis leads to predictions for the drug resistance buildup time depending on few control parameters, such as bacterial densities, the steepness of the concentration gradient, mutation rates, and diffusion coefficients. The authors demonstrate that heterogeneities indeed enable a stepwise buildup of antibiotic resistance. Recent advances in the theory of wavelike expansion of populations may help develop a unified model that captures both mechanisms [8, 9].

Experiments in microfluidic devices along the lines of Ref. [6] or in petri dishes [10] may now be devised to test the basic trends predicted by the two new studies. Further theoretical work is needed to take into account more than one spatial dimension, realistic heterogeneities in drug concentrations, or the specific mutational pathways leading to resistance. Yet the simplicity of these two models, based on only few assumptions, makes them quite general and an excellent starting point for quantifying and understanding the development of drug resistance in a broad set of systems, including populations of cancerous cells developing resistance against chemotherapeutic agents.

References


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