Peer Community In
Evolutionary Biology

What doesn't kill us makes us stronger: can Fisher's Geometric model predict antibiotic resistance evolution?

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doi: 10.24072/pci.evolbiol.100028

Open Access

Cite as: Fragata I and Bank C. 2017. What doesn't kill us makes us stronger: can Fisher's Geometric model predict antibiotic resistance evolution? *Peer Community in Evolutionary Biology*. 100028. doi: 10.24072/pci.evolbiol.100028

A recommendation of

Harmand N, Gallet R, Jabbour-Zahab R, Martin G and Lenormand T. 2017. Fisher's geometrical model and the mutational patterns of antibiotic resistance across dose gradients. ***Evolution*** 71: 23-37. doi: 10.1111/evo.13111

Published: 2 August 2017

The increasing number of reported cases of antibiotic resistance is one of today's major public health concerns. Dealing with this threat involves understanding what drives the evolution of antibiotic resistance and investigating whether we can predict (and subsequently avoid or circumvent) it [1]. One of the most illustrative and common models of adaptation (and, hence, resistance evolution) is Fisher's Geometric Model (FGM). The original model maps phenotypes to fitness, meaning that each point in the fitness landscape corresponds to a phenotype rather than a genotype. However, it has been shown that when mutations are numerous enough, FGM can also describe adaptive walks in genotype space [2]. Nevertheless, limitations have been highlighted, particularly when trying to study complex scenarios such as antibiotic resistance evolution [3].

Harmand *et al.* [4] incorporated three extensions to the FGM, which allowed them to match the mutational patterns of antibiotic resistance that they obtained from a screen across a gradient of drug concentrations. The implemented extensions took into account that: 1) only a subset of mutations may contribute

to traits under selection, reflecting that not all regions in the genome affect the ability to resist antibiotics; 2) mutations that confer a fitness increase in one environment may not reflect a similar increase in others, if the selective constraints are different; and 3) different antibiotic concentrations may either constrain the maximum fitness that populations can reach (changing the height of the fitness peak) or change the rate of fitness increase with each mutation (changing the width/slope of the peak).

Traditionally, most empirical fitness landscape studies have focused on a subset of mutations obtained after laboratory evolution in specific conditions [5, 6]. The results obtained in Harmand *et al.* [4] indicate a potential shortcoming of studying these small fitness landscapes: rather than having a constrained evolutionary path to a resistant phenotype, as previously observed, their results suggest that antibiotic resistance can be the product of mutations in different regions of the genome. Returning to the fitness landscape perspective, this indicates that there are many alternative paths that can lead to the evolution of antibiotic resistance. This comparison points at a difficult challenge when aiming at developing a predictive framework for evolution: real-time experiments may indicate that evolution is likely to take similar and predictable paths because the strongest and most frequent mutations dictate the outcome, whereas systematic screens of mutants potentially indicate several paths, that may, however, not be relevant in nature. Only a combination of different experimental approaches with motivated theory as presented in Harmand *et al.* [4] will allow for a better understanding of where in this continuum evolution is taking place in nature, and to which degree we are able to interfere with it in order to slow down adaptation.

Reference

[1] Palmer AC, and Kishony R. 2013. Understanding, predicting and manipulating the genotypic evolution of antibiotic resistance. Nature Review Genetics 14: 243—248. doi: 10.1038/nrg3351

[2] Tenaillon O. 2014. The utility of Fisher's geometric model in evolutionary genetics. Annual Review of Ecology, Evolution and Systematics 45:179—201. doi: 10.1146/annurev-ecolsys-120213-091846

[3] Blanquart F and Bataillon T. 2016. Epistasis and the structure of fitness landscapes: are experimental fitness landscapes compatible with Fisher's geometric model? Genetics 203: 847—862. doi: 10.1534/genetics.115.182691

[4] Harmand N, Gallet R, Jabbour-Zahab R, Martin G and Lenormand T. 2017. Fisher's geometrical model and the mutational patterns of antibiotic resistance across dose gradients. Evolution 71: 23—37. doi: 10.1111/evo.13111

[5] de Visser, J. A. G. M., and J. Krug. 2014. Empirical fitness landscapes and the predictability of evolution. Nature 15: 480—490. doi: 10.1038/nrg3744

[6] Palmer AC, Toprak E, Baym M, Kim S, Veres A, Bershtein S and Kishony R. 2015. Delayed commitment to evolutionary fate in antibiotic resistance fitness landscapes. Nature Communications 6:1-8. doi: 10.1038/ncomms8385