

Antibiotic Resistance: Evolution without trade-offs?

David Reznick, Department of Biology, University of California, Riverside, 92521, USA

Kayla King, Department of Zoology, University of Oxford, South Parks Road, Oxford, OX1 3PS, UK

Artificial selection for antibiotic resistance in microbes reveals why and how expected evolutionary trade-offs between population growth rate and population carrying capacity are not observed in resource-limited environments, with 'trade-ups' occurring instead.

Compromise is a rare commodity in contemporary politics, but it has the status of law in some areas of biology. One such area is the theory of life history evolution, which traditionally assumes compromise, or tradeoffs, among competing resource investments in growth, reproduction and maintenance. A compelling challenge to such assumed compromise is the empirical observation of apparent superorganisms that seem to have more of everything in comparison with their ancestors or other members of their species. In this issue of *Nature Ecology and Evolution*, Reding-Roman *et al.* [1] present us with another superorganism, this time in an experimentally evolved antibiotic-resistant bacterium. Their selection lines sustain higher population growth rates and attain higher carrying capacities than control lines. In doing so, they defy the anticipated tradeoff between intrinsic population growth rate and carrying capacity assumed in the theory of r- and K-selection, an early representative of life history theory.

Robert MacArthur and Edward Wilson [2] coined r- and K-selection as one of the first general concepts of life history evolution at a time when the dominant question in ecology was "what determines the abundance and distribution of organisms?" The answer had resolved into the competing proposals of density-dependent versus density-independent population regulation. MacArthur and Wilson envisioned organisms adapting to density-independent regulation by evolving a capacity for rapid increase in population size (r-selection) to replenish their numbers after a crash. Density-dependent regulation instead selected for organisms to persist in the face of intense intraspecific competition (K-selection). "r" represents the intrinsic rate of population increase and "K" the carrying capacity in the logistic equation for population growth. They did not detail how such alternative adaptations evolved (done later by Pianka [3]) but envisioned tradeoffs between adaptations that favour r versus K. While r- and K-selection has faded as a general explanation for life history evolution, we still observe that life histories often fall along a fast-slow axis of variation [4,5], suggesting that some compromise is logical. Reding-Roman *et al.*'s [1] superbug defies this expectation because it evolved resistance to the antibiotic doxycycline while simultaneously evolving a higher population growth rate and carrying capacity. The authors refer to this relationship as an rK 'trade-up', as opposed to trade-off. The selection lines retained these advantages over the ancestor even after the antibiotic was removed, suggesting no cost of resistance.

Reding-Roman *et al.* [1] first develop a model that weds two equations describing microbial population dynamics - one that predicts K and one that predicts r - to develop an equation to explore the functional relationship between r and K. The shape of the resulting function is parabolic in response to glucose concentration. There is an rK trade up at low glucose concentrations, meaning that some microbes are unconditionally superior, but a trade off between r and K at high

glucose concentrations. They then show this parabolic relationship within strains of a eukaryotic, clinical pathogen (*Candida glabrata*) and *E. coli* that vary in the number of r-RNA operons. A similar pattern of variation emerges among strains of bacteria. The authors then created an 'uberbug' by experimentally selecting *E. coli* under 'normal' concentrations of doxycycline antibiotic. *r* and *K* of these antibiotic-resistant lineages are positively correlated, even in the absence of antibiotics. These evolved lines reveal costs to high *r* and high *K* that could exist in a within-host environment. Antibiotic-resistant pathogens lost a prophage associated with stress resistance and have a vastly increased lag time (by over 3-fold) between the inoculation of a culture and the onset of population growth. Are these costs big enough to prevent the rise of the uberbug? First, less stress resistance might make pathogens more vulnerable to host immune responses. Second, the difference in lag times might give non-resistant clones a competitive edge in a mixed infection in the absence of antibiotics. Whether higher *r* and *K* life-history traits associated with doxycycline resistance evolve and are maintained in patients, despite these scenarios, requires investigation.

The superorganism phenomenon has reared its head in other species and contexts. If higher fitness can evolve without cost, then such genotypes should fix and we should not see sustained genetic variation of this sort in natural populations, save for certain forms of mutation-selection balance [6]. Despite the seeming impossibility of such variation, the list of occurrences is growing, so we should consider why. Genotype by environment interactions represent a possible general explanation. Superorganisms may be super in some environments, but inferior in others. Tessier and Woodruff [7] present such an example with the characterization of species/clones of microcrustacea that are unconditionally superior when food is abundant. When food is scarce, seemingly inferior species/clones become superior because they have a lower cost of acquisition. Vorburger [8] discovered naturally occurring clones of aphids with seemingly unconditionally superior attributes. While the super clones were also the most common, the inferior clones were sufficiently abundant for mutation-selection balance to be an implausible explanation for their presence. Host plant specialization is a common phenomenon in aphids, so the apparently inferior clones may instead be specialized for life on different host plants.

Both examples invoke a tradeoff between the acquisition of resources and their allocation. Sgro and Hoffman [9] review more than 20 papers that show GxE interactions for fitness that suggest similar niche diversification on temperature, resource quality, population density, shade and rainfall. Common to all is the presence of genetic variation and GxE interactions that suggest that genotypes are adapted to different features of the environment. Condition-dependent costs have been described in many other contexts [e.g., 9,10] and convey the general message that seeing tradeoffs might require envisioning them in multiple dimensions. From this perspective, we gain an understanding of the interdependencies among different biological functions. In the case of antibiotic resistance, such multidimensionality will be cold comfort if, in the context of our bodies, the uberbug can prevail. (966 words)

Literature Cited

1. Reding-Roman, C., et al., *Reconciling tradeoff theories and antibiotic-resistant genotypes that evolve to quickly grow to high densities*. Nature Ecology Evolution, 2017.
2. MacArthur, R.H. and E.O. Wilson, *The Theory of Island Biogeography*. 1967, Princeton, NJ: Princeton University Press.
3. Pianka, E.R., *r- and K-selection*. American Naturalist, 1970. **104**: p. 592-597.

4. Hamel, S., et al., *Cohort variation in individual body mass dissipates with age in large herbivores*. Ecological Monographs, 2016. **86**(4): p. 517-543.
5. Hille, S.M. and C.B. Cooper, *Elevational trends in life histories: revising the pace-of-life framework*. Biological Reviews, 2015. **90**(1): p. 204-213.
6. Charlesworth, B., *Optimization models, quantitative genetics, and mutation*. Evolution, 1990. **44**: p. 520-538.
7. Tessier, A.J. and P. Woodruff, *Trading off the ability to exploit rich versus poor food quality*. Ecology Letters, 2002. **5**(5): p. 685-692.
8. Vorburger, C., *Positive genetic correlations among major life-history traits related to ecological success in the aphid *Myzus persicae**. Evolution, 2005. **59**(5): p. 1006-1015.
9. Sgro, C.M. and A.A. Hoffmann, *Genetic correlations, tradeoffs and environmental variation*. Heredity, 2004. **93**(3): p. 241-248.
10. Messina, F.J. and J.D. Fry, *Environment-dependent reversal of a life history trade-off in the seed beetle *Callosobruchus maculatus**. Journal of Evolutionary Biology, 2003. **16**(3): p. 501-509.