

ANTIBIOTIC RESISTANCE

Evolution without trade-offs

Artificial selection for antibiotic resistance in microorganisms 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.

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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 trade-offs, 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. Writing in *Nature Ecology & 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 trade-off 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 Wilson² 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). The 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 Pianka³) but envisioned trade-offs between adaptations that favour r versus K . Although 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 and co-workers¹ 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 use 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 (Fig. 1). There is an rK trade-up at low glucose concentrations, meaning that some microorganisms 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 *Escherichia coli* that vary in the number of rRNA 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. The 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 threefold) 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 balance⁶. 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

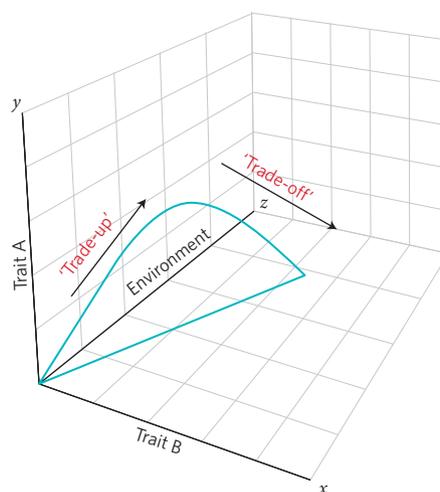


Figure 1 | The superorganism phenomenon across environments. Trade-ups and trade-offs between life-history traits occur across conditions due to G×E interactions. Reding-Roman *et al.* show that in the case of antibiotic-resistant *E. coli*, the relationship between r (Trait A) and K (Trait B) varies with glucose concentration (the environment, z -axis) in the medium.

and Woodruff⁷ 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. Vorburger⁸ 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 trade-off between the acquisition of resources and their allocation. Sgro and Hoffman⁹ review more

than 20 papers that show G×E (genotype–environment) 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 G×E interactions that suggest that genotypes are adapted to different features of the environment. Condition-dependent costs have been described in many other contexts (for example, refs ^{9,10}) and convey the general message that seeing trade-offs 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. □

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Competing interests

The authors declare no competing financial interests.