EXPERIMENTAL EVOLUTION

Life on the frontline reveals constraints

The existence of trade-offs between traits under selection is a fundamental concept in evolutionary biology. Analysis of a densely sampled collection of adaptive mutations in yeast reveals that no single mutation can allow it to overcome detected trade-offs between key traits under selection.

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The concept of trade-offs — that improvement in one aspect comes at the expense of another — is a common thread across the fields of economics, engineering and biology. A classic biological example is *r/K* selection theory proposed by MacArthur and Wilson to explain why some organisms reproduce rapidly, while others are long-lived[1]. Trade-offs feature prominently in evolutionary biology because they constrain adaptation of traits that are negatively correlated due to physiological limitations (for example, the size and number of eggs per clutch). However, detecting trade-offs is difficult, as negative correlations can arise for non-physiological reasons (for example, adaptation in different environments). Further, trade-offs can be obscured by studying organisms that are far from the optimum for traits under consideration. Writing in *Nature Ecology & Evolution*, Li et al.[2] report trade-offs between traits involved in glucose metabolism in the yeast *Saccharomyces cerevisiae*. Sampling an unprecedented number of single adaptive mutations allows the authors to circumvent both issues in detecting trade-offs. Crucially, they demonstrate that no single mutation allows yeast to overcome these trade-offs, suggesting that evolution is indeed constrained, at least over short timescales.

Li et al. measured fermentation, respiration and stationary-phase survival, key traits associated with yeast's ability to tolerate variation in glucose availability. Fermentation allows rapid energy production when glucose is abundant. Respiration is more efficient, producing more energy per unit of glucose at the expense of speed. Stationary phase is yeast's 'starvation mode', where in the absence of nutrients it shuts off both fermentation and respiration and instead relies on storage carbohydrates[3]. To select for a diverse collection of mutations, they evolved yeast populations under different conditions that favoured each trait. The effect of each mutation on each trait was then measured by growing each mutant under all selection conditions. This revealed that respiration is negatively correlated with both fermentation and stationary-phase survival, but that no negative association occurs between fermentation and stationary-phase survival.

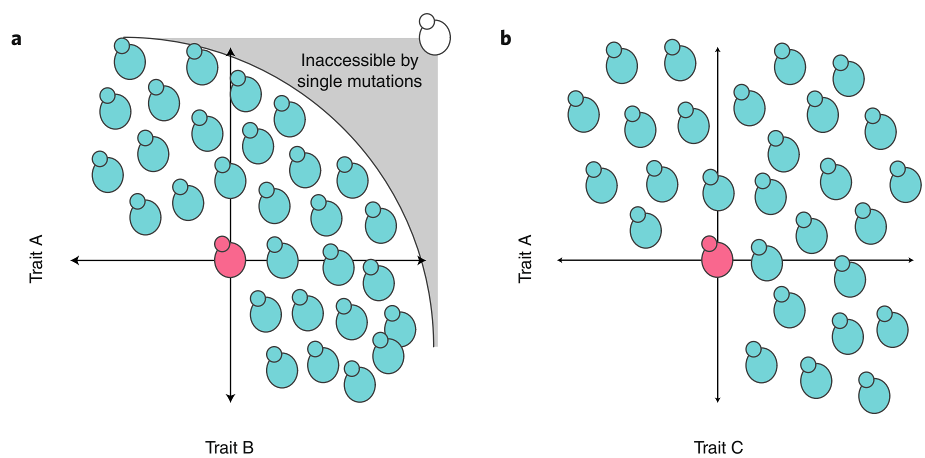

Fig. 1 | Trade-offs between traits in yeast. Detecting trade-offs can be difficult if the ancestral yeast (pink) does not possess the optimal state for each trait (white). **a**, Sampling a sufficient number of mutant offspring with trait variation arising through spontaneous mutations (blue) can be used to delineate a Pareto front in trait space (grey), which reveals the trade-off. Optimal values for each trait cannot be achieved through a single mutation. **b**, Absence of a detectable trade-off can result because no trade-off actually exists, the ancestor is far from optimal in either trait value and insufficient offspring are sampled, or trade-offs with an additional unmeasured trait constrains the measured traits.

To demonstrate the existence of trade-offs, the authors employ a concept originally from economics and engineering on the optimal allocation of resources to a process, so-called 'Pareto optimality'. A strategy is Pareto optimal if any change in allocation to improve one aspect of performance results in a decreased performance of another aspect. Consider a manufacturing process, where the goal is to maximize profit. Product quality, manufacturing rate and cost of production are aspects to be optimized, but no strategy can optimize all three — as the adage goes, 'good, fast or cheap: pick two'. Following this example, a 'Pareto front' defines the set of possible optimal strategies: in this example, good and fast (but not cheap), good and cheap (but not fast) or fast and cheap (but not good).

Applied to evolutionary biology, a Pareto front describes the set of genotypes where spontaneous mutations can improve one trait under selection only at the expense of another[4]. Consequently, it defines the region of trait space that is accessible to evolution through single mutational events (Fig. 1). The dense sampling of mutations in this work is what enables Li et al. to demonstrate the existence of Pareto fronts. This is crucial because the ancestor itself lies behind the Pareto front — indeed, many single mutations improved more than one trait, as has been observed in other studies[5,6]. The authors point out that sampling too few mutations prevents characterization of the front, which may explain why Pareto fronts have not been delineated in previous studies. Working from the predicted fitness benefit of a mutation that could optimize multiple traits, the authors predict that no single mutation would allow the ancestor to optimize respiration at the same time as either fermentation or stationary-phase survival. Short-term evolution in the ancestral yeast is therefore constrained to increasing either respiration or fermentation, but not both simultaneously.

Showing that Pareto fronts can be characterized has positive implications for our ability to predetermine phenotypes that can be achieved through single-point mutations. This is especially relevant for yeast and other microbes used in bioprocess manufacturing, such as brewing, that primarily develop strains through random mutagenesis because of regulations — and consumer preferences — surrounding genetically modified organisms[7]. More broadly, it has important implications for the ability to predict how organisms will evolve in response to changing environmental conditions. A prime example of this is adaptation to climate change, where global temperature and carbon dioxide concentrations are expected to change in concert with other aspects of the environment. Altering the number of traits simultaneously under selection has been shown to dramatically influence the ability of organisms to adapt to simulated climate change[8].

The main limitation of this study, as the authors point out, is that it follows only short-term evolution, meaning that the inaccessible region of trait space may only be inaccessible to the ancestral yeast. Acquiring multiple mutations sequentially may allow access to previously inaccessible regions of trait space[9]. Other sources of genetic variation may also allow yeast to overcome such constraints, such as horizontal acquisition of genes through hybridization or other processes — a habit in which yeasts and other microbes regularly partake[10]. Ultimately, whether Pareto fronts result from single mutations having limited pleiotropic effects on multiple traits or from persistent physiological constraints remains to be determined. However, a similar trade-off between fermentation and respiration was recently found for *Escherichia coli*, suggesting that the relationship may be founded on the biochemical constraints of ATP production[11]. Future work investigating longer-term evolution involving multiple genetic substitutions, as well as other forms of genetic change, is needed to make this determination. Nevertheless, the approach developed by Li et al. provides a framework from which these questions can be addressed. ❐

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Published online: 14 October 2019
https://doi.org/10.1038/s41559-019-1010-3

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Competing interests

The author declares no competing interests.