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Genetic constraints on adaptive evolution in principle and in practice[1]

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Geneticists have long recognized that pairs of mutations often produce surprising effects on the organism, given their effects in isolation. Such mutational interactions are called epistasis. Importantly, epistasis among mutations influencing an organism's survival or reproductive success can constrain the temporal order in which mutations will be favored by natural selection. After exploring these theoretical considerations more fully, we will demonstrate substantial epistatic constraint on the evolution of an enzyme that confers bacterial antibiotic resistance. Such epistatically induced constraints turn out to be rather common in enzyme evolution, and we will briefly discuss recent work that seeks to explicate its mechanistic basis using methods of molecular and structural biology. Finally we observe that the epistatic interaction between two mutations itself often varies with genetic context, implying the existence of higher-order interactions. We present a computational framework for assessing magnitude of epistatic interactions of all orders, and show that non-negligible epistatic interactions of all orders are common in a diverse set of biological systems.

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