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COMMENTARY

Evolution of Epistasis: Small Populations Go Their Separate Ways

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Much of the enduring appeal of evolutionary theory lies in the complex, and often surprising, dynamics that can be produced by varying apparently simple evolutionary parameters such as selection coefficients, mutation rates, and population sizes. And while it may have once been possible to view the predictions of theoretical models as mathematical curiosities, the parameters that describe populations are as diverse as the populations themselves, so that it seems increasingly clear that for almost every theoretically possible phenomenon there is some evolving system—whether RNA viruses, or endosymbiotic bacteria—where the evolutionary parameters combine in just the right way to turn the theoretical into the actual.

In the current issue of JME, Sydykova et al. (2020) explore another surprising theoretical interaction of this type, where decreasing the fitness of genotypes that harbor multiple deleterious mutations can sometimes increase the long-term fitness of the population. As a consequence, they show that when epistasis is allowed to evolve there are actually two qualitatively different ways of maximizing fitness. The first way is to increase mutational robustness, so that the effects of combining multiple deleterious mutations are as benign as possible. However, the second way is to distort the fitness landscape in the opposite direction, so that multiple mutations combine in a manner that is as deleterious as possible. In this second case, fitness is high because natural selection is strong enough to restrict populations to the most highly fit genotypes, a phenomenon known as "drift robustness" because populations are protected from the deleterious effects of genetic drift (LaBar and Adami 2017).

To understand these results, it is helpful to first consider a simple thought experiment. If we have a population evolving on some specific fitness landscape, is it possible to increase the long-term fitness of a population by decreasing the fitness of an individual genotype or subset of genotypes? For the simplest case of an infinite asexual population, the answer is no (Hermisson et al. 2002). In that case, no matter what the structure of the fitness landscape, the long-term fitness of the population changes monotonically with the fitnesses of the individual genotypes, so that increasing the fitness of a genotype always increases the long-term fitness of the population and decreasing the fitness of a genotype always decreases the long-term fitness.

However, in finite populations this result no longer holds, an observation that Sydykova et al. show has important implications for our understanding of how epistasis evolves. In particular, Sydykova et al. study a simple model of a fitness landscape that has a tunable degree of epistasis given by the parameter q (Fig. 1). The fitness landscape is single-peaked with a wild-type genotype whose fitness is optimal and which is in turn surrounded by less fit single mutants. The parameter q then determines how these single mutations interact when combined, with larger values of q resulting in multiple mutants being less and less fit. Thus, the fitness landscape goes from having a high degree of buffering due to strong positive epistasis for q near 0, but becomes increasingly sharply peaked for larger values of q.

While increasing q can only decrease the fitness of individual genotypes, Sydykova et al. show that the fitness of the population at mutation-selection-drift balance displays surprisingly complex behavior as a function of q. In particular, they observe that as q increases the long-term fitness of the population initially decreases as one would expect because the fitness effects of having multiple mutations is becoming increasingly severe. However, at a sufficiently high degree of epistasis, this trend reverses so that adding additional epistasis causes the long-term fitness of the population to increase again, often increasing back to nearly the maximal fitness.

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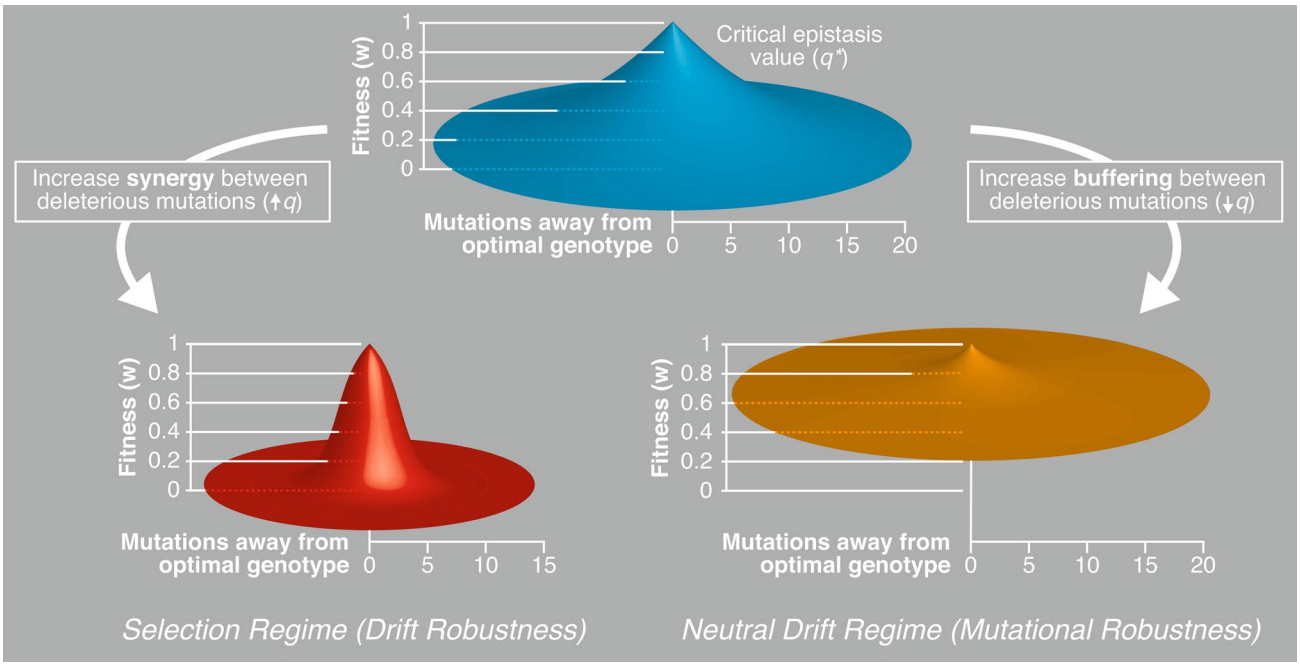

Fig. 1 Two routes to adaptation in small populations. For small asexual populations, Sydykova et al. (2020) show both analytically and by way of simulation that intermediate values of epistasis (q) are not evolutionarily stable. An unstable fixed point exists below which selection will favor decreasing q leading to mutational robustness and above which selection will favor increasing q leading to drift robustness

Why does this phenomenon occur? To answer this question, Sydykova et al. start by modeling this system in the weak mutation limit where it is possible to derive analytical expressions for the form of the mutation-selection-drift equilibrium. The key intuition is that at low q selection is too weak to confine the population to the peak, and thus the population often contains genotypes with multiple mutations. On the other hand, for high q the most deleterious mutations are so unfit that they are effectively removed from the landscape, and so these low fitness values no longer contribute to the long-term average. Sydykova et al. show that the minimal long-term fitness occurs at a critical value of epistasis q^* that represents the crossover point between these two regimes and derive an analytical approximation for this critical value. An interesting feature of this analysis is the important role played by the geometry of sequence space. In particular, even though natural selection exponentially enriches for fit genotypes, the geometry of sequence space means that there are exponentially more unfit sequences far from the wild-type than there are fit sequences close to it, resulting in an entropic pull towards the less fit sequences, with the critical value of q^* occurring at the point where these two forces are of equal strength.

While the above results were derived using analytical arguments, Sydykova et al. confirmed their results through stochastic simulations and also investigated the dynamics of finite polymorphic populations with higher mutation rates, showing that qualitatively similar phenomena occur in this regime as well.

Finally, the authors considered the implications of their analysis for the evolution of epistasis by simulating evolution under a modifier model where the parameter q itself could evolve. These simulations showed that populations evolved in one of two ways, depending on the initial amount of epistasis. Populations that started with a value of q below a critical threshold further decreased q, resulting in a state with high mutational robustness. However, populations starting with a high value of q maintained this drift robust state, as predicted.

While the evolution of mutational robustness has already been observed in several experimental systems including viruses (e.g., Montville et al. 2005; Sanjuán et al. 2007) and individual proteins (e.g., Bloom et al. 2007), whether drift robustness will evolve in an experimental system is unclear. As Sydykova et al. describe, the evolution of drift robustness requires that the initial epistasis be above the critical value of q^*, and even then, q may stabilize rather than increase.

Where then would one look for examples of drift robustness in nature? Sydykova et al. offer the trypanosome *T. bruci* as an example. The mitochondrial genome of *T. bruci* contains overlapping open reading frames that are resolved by mRNA editing. Because the number of overlapping genes should correlate with the degree of synergistic epistasis among deleterious mutations, the authors predict that

experimental evolution of strains that differ in the number of overlapping genes could provide a test of their theory. A similar experimental design could be constructed using more tractable experimental systems such as the "refactored" T7 and øX174 bacteriophage that have been have been engineered to resolve overlapping open reading frames (Chan et al. 2005; Jaschke et al. 2012). Nevertheless, an experimental test of the ability of populations to evolve and maintain drift robustness will be challenging.

From a naive point of view, the complex and non-monotonic relationship between the deleteriousness of multiple mutants and the fitness of a population may appear unusual. However, non-monotonic relationships of this type are a common consequence of deleterious mutations. For example, the rate of fitness decline in Muller's ratchet and lethal mutagenesis is maximized for mutations of intermediate size (Gabriel et al. 1993; Lande 1994), and the long-term substitution rate and level of standing variation are both maximized when moderately deleterious alleles are favored by mutational biases (Lawrie et al. 2011; McVean and Charlesworth 1999). From a broader perspective, deleterious mutations with intermediate fitness effects often have the greatest impact because mutations that are too deleterious are effectively removed from the population and mutations too close to neutrality essentially function as additional neutral mutations.

Sydykova et al.'s work also provides another striking example of the range of exotic dynamical behaviors that occur in finite populations. Broadly speaking, our population-genetic understanding of the interaction between natural selection, mutation, and genetic drift is deepest for problems that can be addressed using diffusion theory, such as the classical one-locus biallelic case studied by Fisher and Wright. But the field has slowly been accumulating examples of behaviors that cannot be well-understood using classical diffusion models such as clonal interference (Desai and Fisher 2007; Gerrish and Lenski 1998), stochastic tunneling (Iwasa et al. 2004; Weissman et al. 2009), and various phenomena involving the evolution of mutational robustness (Wilke et al. 2001), including unexplained patterns of populations shifting from one robust region of genotypic space to another (Forster et al. 2006). The work by Sydykova et al., in conjunction with other recent literature on drift robustness (LaBar and Adami 2017) adds another basic phenomenon to the list, and suggests that whether a population evolves towards mutational or drift robustness may depend on specific details of fitness landscape structure.

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