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NEWS AND COMMENTARY

Mutation load under spatial variation

Variation in selective intensity over space alters classic mutation load predictions

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The constant input of new deleterious alleles via mutation makes individuals less fit, on average, than they would be otherwise. This so-called 'mutation load' has been studied by evolutionary geneticists for more than 75 years. A theoretical study by Roze (2012) reported in this issue of *Heredity* adds an important new dimension to this classic body of theory by examining how spatial variation in selection alters the mutation load. In contrast to the canonical theory in which selection is (surprisingly) unimportant to load, Roze describes how several aspects of the ecology of selection can influence how metapopulations are affected by deleterious mutations.

In a classic paper, Haldane (1937) calculated the equilibrium frequency of deleterious alleles at a single locus at the balance between mutation pressure and selection. Further, he calculated the average reduction in fitness relative to the ideal (mutation-free) genotype due to the presence of these deleterious alleles. Under some simplifying assumptions, including independent gene effects and no linkage disequilibrium, he was able to extend his single-locus results to consider fitness genome-wide. Under these conditions, equilibrium mean fitness relative to the ideal genotype is $E[W]=e^{-2U}$ where U is the haploid genome-wide deleterious mutation rate.

This classic result is remarkable in two respects. First, it shows the mutation load, $L=1-E[W]=1-e^{-2U}$, can be quite large. For example, if there is, on average, one new mutation per diploid genome per generation, $2U=1$, then individuals are $L=63\%$ less fit than a mutant-free genotype, according to Haldane. With modern sequencing technologies, our ability to estimate U has been advanced considerably. Recent studies show that many multicellular organisms have deleterious mutation rates that are on the order of $2U=1$ (Baer *et al.*, 2007; Keightley, 2012), suggesting that such taxa may suffer from high mutation loads.

The second noteworthy feature of Haldane's load result is that equilibrium mean fitness is independent of s, the strength of selection against a deleterious mutation. This is because increasing s has two opposing effects—decreasing the equilibrium frequency of deleterious alleles but increasing the per-copy effect on mean fitness—that cancel out so there is no net effect of selection on load, at least under Haldane's assumptions.

Implicit in Haldane's model is the assumption that selection is constant over space but it is likely that the strength of selection against most deleterious alleles varies over space (that is, an allele may be strongly deleterious in some habitats but only weakly deleterious in others). As Roze's analysis confirmed, such changes in s across habitats are unimportant if those changes are not strongly correlated across loci. However, Roze found that spatial variation becomes considerably more interesting if most genes are affected similarly by the environment, that is, if most genes experience stronger selection in the same habitat as one another.

When some habitats are more strongly selective, in general, than other habitats, Roze found mean fitness could be considerably higher than predicted under Haldane's result. This occurs for two reasons, one of which can occur even if there is complete mixing between habitats each generation. When selection strength varies over space, deleterious alleles are more common in the strongly selective habitats than one would expect if this was the only habitat type. Consequently, individuals in this habitat are less fit than expected under Haldane's result. However, in weakly selective habitats, deleterious alleles are rarer than expected so that individuals are more fit than expected. The non-linear relationship between mutation frequency and fitness guarantees that the increase in fitness of weakly selective habitats will outweigh the decrease in fitness of strongly selective habitats.

The effect of spatial variation is even stronger when there is limited migration between habitats. The difference in selection strength between habitats, combined with limited migration, allows positive linkage disequilibrium to build up across the genome. Weakly selective habitats contain genomes with an excess of deleterious alleles, whereas strongly selective habitats contain genomes with fewer than expected deleterious alleles. When migration occurs between habitats, there is an asymmetry in the impact of the migrants. Good genotypes migrating into weakly selective habitats enjoy a selective advantage over residents, which lasts for multiple generations, as recombination assimilates the migrant genome. In contrast, heavily loaded genotypes moving into strongly selective habitats are rapidly eliminated. This represents an example of the general result that mutation load is reduced if the number of deleterious alleles eliminated per selective death is increased (King, 1966; Kondrashov and Crow, 1988).

The results described above apply to the situation where selection is 'soft', meaning that each habitat contributes to the next generation in proportion to its abundance

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in the landscape. Roze also considered the case where selection is ‘hard’, meaning that each habitat contributes to the next generation in proportion to its mean fitness. In contrast to soft selection, mutation load can be considerably higher than the canonical prediction with hard selection. In Roze’s hard-selection model, the harsh conditions of strongly selective habitats mean that these habitats make a disproportionately small contribution to the next generation. Consequently, the effective average selection is more like that in the weakly selective demes, allowing deleterious alleles to reach relatively high frequencies so that mean fitness in strongly selective habitats can become very low. This result is closely related to earlier work in which persistence in marginal habitats is prevented because mutational decay of habitat-specific alleles is only weakly opposed by selection elsewhere in the species range (Kawecki, 1995; Kawecki et al., 1997).

Roze’s model shows that spatial variation in selection can be very important but only if some habitats are more strongly selective across the genome. Consistent with this requirement, a number of experiments have found significant differences in the average strength of selection between environments (Agrawal and Whitlock, 2010). However, we lack a general understanding on why some environments are more selective than others. Counter to common intuition, variation in mean selection strength is not easily explained by differences in ‘stressfulness’ among environments (Martin and Lenormand, 2006). Differences in density dependency is a promising hypothesis (Agrawal and Whitlock, 2010) but remains to be properly tested.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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