Ecological Determinants of Mutation Load and Inbreeding Depression in Subdivided Populations

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ABSTRACT: Population structure can dramatically alter mutation load, but the magnitude and direction of this effect depend on whether selection is soft or hard. The abstract nature of previous load models obscured the importance of ecological details in determining the softness of selection. Under the more ecologically explicit model used here, I show that genes related to intrinsic growth rate tend to experience hard selection whereas those genes affecting competitive ability experience softer selection. Although resource limitation determines the strength of selection on competitive ability, it only affects the softness of selection, and thus the load, of mutations with pleiotropic effects on intrinsic growth rate. While competition is typically considered necessary for soft selection, the model shows that interspecific competition hardens selection and can thereby lead to reduced load. Finally, genetic variation in the consumption rates of individuals who die before reproduction can cause supersoft selection, resulting in large increases in load. The same conditions that increase mutation load also increase inbreeding depression.

Keywords: mutation load, population structure, competition, hard and soft selection.

Introduction

The vast majority of mutations affecting fitness are deleterious (Keightley and Lynch 2003). The presence of these alleles reduces the average genetic quality of individuals below what would be expected in the absence of deleterious mutation. This reduction is known as the mutation load (Muller 1950; Crow and Kimura 1970). According to classic theory (Haldane 1937), this load can be quite large if the genome-wide rate of deleterious mutation is not too small ($U > 0.1$). Evidence is mounting that mutation rates are sufficiently high in many multicellular eukaryotes (Baer et al. 2007) that the predicted loads are considerable.

Haldane's (1937) study of the balance between selection and mutation laid the framework for mutation load theory. His model produced the classic result that the reduction in mean fitness due to recurrent mutation at a single locus depends only on that gene's mutation rate, that is, a load of $L = 2\mu$. This remarkable result is appealing because it does not depend on the details of how the mutant allele affects fitness.

Along with several other key assumptions (e.g., infinite population size, no epistasis), Haldane (1937) assumed that populations were completely panmictic. In reality, most populations are subdivided to some extent, with organisms interacting and mating locally rather than globally. Population structure results in an excess of homozygotes at the metapopulation level because of the tendency of individuals to mate locally. This increase in homozygosity can increase the variance in fitness, allowing selection to operate more efficiently and resulting in a reduction in mutation load (Crow and Kimura 1970; Agrawal and Chasnov 2001). This homozygosity effect is particularly potent when deleterious alleles are partially recessive, as indicated by empirical data (Garcia-Dorado and Caballero 2000; Peters et al. 2003; Phadnis and Fry 2005; Shaw and Chang 2006). For example, assuming that mutations are partially recessive ($h = 0.1$) and assuming a genome-wide mutation rate of $U = 1$, a weakly subdivided population ($F_{ST} = 0.05$) is predicted to be ~40% more fit than an unstructured population (Agrawal and Chasnov 2001).

However, the circumstances that give rise to genetic population structure may also alter how selection operates. Individuals may tend to compete mostly at a local scale rather than a global scale. When an individual's fitness depends on its own genetic quality relative to the local average, selection is described as soft (Wallace 1975; Whitlock 2002). When an individual's fitness depends on its own genetic quality relative to the global average, selection is described as hard. If individuals not only mate locally but also compete locally, then individuals tend to compete with others of similar genetic quality. Under these conditions, deleterious alleles can be sheltered from selection because individuals carrying a deleterious allele tend to

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compete against other individuals also carrying a deleterious allele rather than against wild-type individuals (Whitlock 2002). I refer to this as the soft-selection effect of population structure.

Whitlock (2002) investigated these two effects of population structure on mutation load. In his model, the fitness of an individual of genotype i from deme j can be represented as

$$W_{ij} = (1 - b)\frac{\omega_i}{\omega_{\cdot j}} + b\frac{\omega_i}{\omega_{\cdot\cdot}}, \quad (1)$$

where ω_i is the genetic quality of an individual of genotype i (e.g., $\omega_{AA} = 1$, $\omega_{Aa} = 1 - hs$, and $\omega_{aa} = 1 - s$), $\omega_{\cdot j}$ is the average genetic quality of deme j, and $\omega_{\cdot\cdot}$ is the global average (across all individuals in all demes). The parameter b represents the hardness of selection. When $b = 0$, selection is completely soft, whereas selection is completely hard when $b = 1$. When the model is parameterized in this fashion, Whitlock's (2002) fitness function explicitly acknowledges that hard selection and soft selection are points on a continuum; competition may be partly local and partly global.

The terms used above require some clarification because they have not always been used consistently in the literature. The fitness of an individual represents the number of offspring it contributes to the next generation of the metapopulation. Genetic quality is a latent variable that is positively correlated to fitness. The relationship between quality and fitness is simple when we consider individuals within the same deme; an individual with higher genetic quality always has higher fitness than does one with low genetic quality. However, when we consider the entire metapopulation, the distinction between these terms is necessary because the precise nature of the quality/fitness relationship depends on the hardness of selection.

With pure hard selection ($b = 1$), fitness is directly proportional to genetic quality. An individual's fitness depends on its genotype and is independent of the genetic quality of those in its local deme. If we consider the fitnesses of entire demes, hard selection implies that demes vary in their contribution to the next generation. Demes containing mostly individuals of high genetic quality have higher average fitness than do demes containing mostly low-quality individuals.

With pure soft selection ($b = 0$), the fitness of an individual depends on its genetic quality relative to the average quality in the deme. There is no fitness advantage to being of high quality if high-quality individuals are surrounded by other high-quality individuals but low-quality individuals are surrounded by other low-quality individuals. The average fitness of individuals within a deme is independent of the genetic composition of that deme when selection is completely soft. Demes full of low-quality individuals contribute as much to the next generation as do demes full of high-quality individuals.

Whitlock (2002) showed that when selection is hard ($b = 1$), population subdivision reduces mutation load because of the efficiency of selection on homozygotes (i.e., the homozygosity effect). However, as selection becomes softer, the load increases with subdivision because deleterious alleles are sheltered from selection (i.e., the soft-selection effect). Using a different modeling approach, Roze and Rousset (2004) also observed these opposing effects of population structure on load when selection was soft; on the one hand, selection is more efficient because of elevated homozygosity, but on the other, it is less efficient because of local competition among similar genotypes (see also Glémin et al. 2003; Theodorou and Couvet 2006). The relative importance of these competing effects is mediated by dominance, with the benefits of increased homozygosity being greatest when h is low.

With the elegant way in which it transitions between soft and hard selection, Whitlock's (2002) model highlights the importance of the scale of selection (local vs. global). However, in this and other recent models of load in structured populations (Agrawal and Chasnov 2001; Glémin et al. 2003; Roze and Rousset 2004; Theodorou and Couvet 2006), the form of selection (hard or soft) is assumed rather than developed from an ecologically motivated model of selection.

While this type of approach does not affect the validity of the resulting theoretical analyses, it can be misleading with respect to how we think about selection. For example, one might wrongly infer from previous models that ecological circumstances determine the hardness of selection in a way that affects all genes similarly. Local density regulation is often cited as the reason for soft selection (Wade 1985; Roze and Rousset 2004). Local density regulation seems to imply that one deme cannot be more fit than another. This suggests that one can increase fitness only by being better than others within one's own deme; genetic quality relative to individuals in other demes appears irrelevant (i.e., soft selection). Because density regulation occurs at the organism level rather than at the gene level, it is tempting to think that density regulation must have a similar effect on the softness of selection for all genes (but see Ravigné et al. 2004). However, density regulation is an ecological concept, not a selective one, and local density regulation does not preclude hard selection. The relationship between density regulation and the softness of selection can depend on a number of factors, including the relative timing of selection and density regulation in the life cycle (Kelly 1992, 1994*a*; Ravigné et al. 2004). For example, consider a population of toad tadpoles developing in series of small ponds. Because of limited resources

within each pond, selection against a mutation that reduces foraging rate may be under soft selection; that is, the strength of selection against such a mutation depends on the local frequency of these mutants. However, a mutation that affects proper limb development during metamorphosis will be under hard selection because such a mutation is deleterious regardless of the frequency of others from the same pond sharing this affliction.

Using a simple but more ecologically motivated model of mutation load, I show that mutations affecting different types of traits can experience different hardnesses of selection. Moreover, even traits mediating local competition can be subject to hard selection, depending on the ecological circumstances.

Model and Results

An Ecologically Motivated Model of Selection

Although the details differ, the model I present below is conceptually similar to that used by Clarke (1973*a*, 1973*b*) in his ecologically explicit model of mutation load and its effect on demography in panmictic populations. However, my model is not intended to describe demographic changes. I implicitly assume that the population is at equilibrium with respect to population size and that this does not change in any significant way as we consider the small fitness effects due to mutation load at a single locus. Although the model incorporates more ecological concepts than do most other load models, there is still a high level of abstraction; as such, the model is intended to provide only heuristic insights on how ecological factors affect load.

Within each deme, there is a limited amount of food, and individuals compete for these resources. The fitness of an individual depends on (i) the amount of resources it is able to obtain and (ii) the efficiency with which it is able to convert those resources into offspring.

The amount of resources acquired by an individual depends on the abundance, a, of resources in the deme and the number, n, of individuals competing for these resources. For simplicity, I assume that demes do not vary in resource abundance or population size (i.e., a and n are constants). In addition, the success of an individual in obtaining contested resources depends on its acquisition ability relative to the average acquisition ability of others in its deme. An individual's acquisition ability, A, is determined by traits such as foraging ability and consumption rate. On the basis of these ideas, a very simple model of competition would predict that the total amount of resources acquired by an individual of genotype i in deme j is $T_{ij} = aA_i/nA_j^*$, where A_i is the acquisition ability of individual i and A_j^* is the average acquisition ability of individuals in deme j (for a similar model of resource competition, see Peck and Waxman 2000).

Under the simplistic model proposed above, an individual can obtain an infinite amount of resources if resources are unlimited ($a \to \infty$). This is unrealistic because organisms cannot continually increase their resource acquisition without bounds, even when resources are superabundant. Rather, organisms often show saturating functional responses to resource abundance (Holling 1959; Gross et al. 1993; Krebs 1994). Numerous functions could be used to depict resource acquisition as a saturating function of relative acquisition ability. Following the tradition in ecological theory, I use Holling's (1959) disc equation (Type II functional response) so that the total amount of resources acquired by an individual is

$$T_{ij} = \frac{aA_i/nA_j^*}{1 + aA_i/nA_j^*}. \tag{2}$$

This function has two desirable properties that are illustrated in figure 1. First, the total amount of resources acquired by an individual, T, is a saturating function of resource abundance, a. Second, the relative difference in the total amount of resources acquired (T) between two individuals that differ in acquisition ability (A) declines with resource abundance. When resources are very abundant, competition is expected to be less intense, so individuals with reduced acquisition ability should be at less of a disadvantage. Several alternative approaches to modeling competition (not shown) that shared this latter feature yielded results qualitatively similar to those presented below.

Competition can be both intra- and interspecific. A fraction, f, of the n individuals are members of the focal species, and the remaining fraction $(1 - f)$ are interspecific competitors. Thus, the average acquisition ability of individuals in deme j, A_j^*, is given by

$$A_j^* = fA_{\cdot j} + (1 - f)\alpha, \tag{3}$$

where $A_{\cdot j}$ is the average acquisition ability of individuals of the focal species in deme j and α is the acquisition ability of the competitor species. I assume no variation among demes in the frequency or quality of interspecific competitors (i.e., f and α are constants).

The efficiency with which an individual of genotype i is able to convert its acquired resources into reproductive output is given by R_i. This parameter is determined by traits such as digestive efficiency, basal metabolic rate, intrinsic mortality rate, and so on. In this model, R is the sole determinant of fitness when resources are unlimited and thus can be thought of as related to intrinsic growth rate, r, in the classic Lotka-Voltera models. (The param-

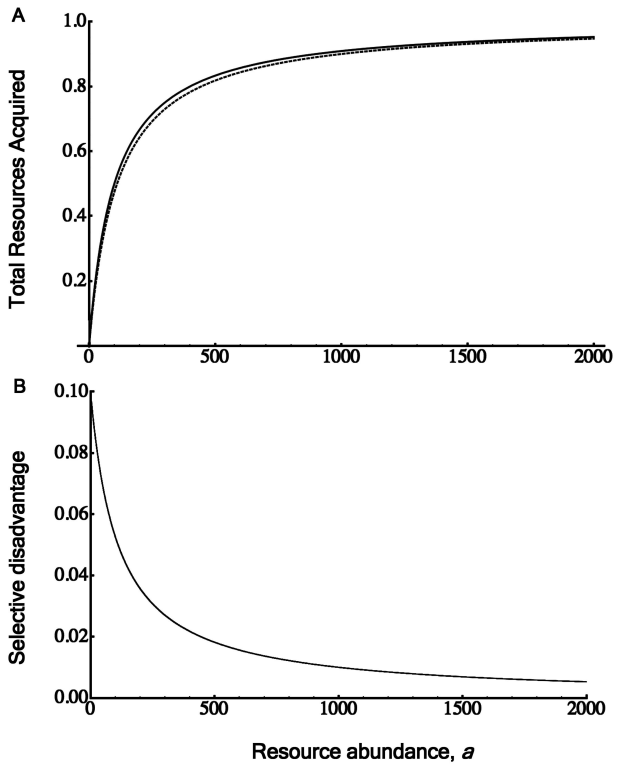

Figure 1: Acquisition ability and resource abundance. *A*, Total resources acquired by wild-type individual (*solid curve*) and an individual homozygous for a mutation reducing acquisition ability (*dashed curve*) as a function of the amount of resources present within a deme. These values were calculated using equation (2) with $q = 10^{-3}$, $h_A = 0.1$, $s_A = 0.1$, $f = 1$, and $n = 100$. *B*, Selective disadvantage of the mutant relative to the wild type with respect to resources acquired. The selective disadvantage of reduced acquisition ability declines when resources are more abundant.

eters r and R are not identical for several reasons, including that one is used for a continuous time model and the other for discrete time; also, one is used for numerical increases and the other for fitness.) Considering both the total amount of resources acquired and the efficiency with which these resources are used, the fitness of individual i in deme j is given by $W_{ij} = T_{ij}R_i$.

Change in Mutant Frequency due to Selection

Below I calculate the equilibrium frequency of mutations at mutation-selection balance. A Mathematica file containing these results is available as a zip file in the online edition of the *American Naturalist*. Consider mutation occurring at a single locus in the focal species; M alleles mutate to m at rate μ. The R and A values for each genotype are $R_{MM} = A_{MM} = 1$, $R_{Mm} = 1 - h_R s_R$, $A_{Mm} = 1 - h_A s_A$, $R_{mm} = 1 - s_R$, and $A_{mm} = 1 - s_A$. For generality, I have allowed the mutation to affect both the growth rate (R) and the acquisition ability (A) traits, but it is easy to consider a gene that affects only one of these traits by setting either s_R or s_A to 0.

The covariance of allele frequency and relative fitness completely quantifies the change in allele frequency due to selection (Price 1970; Frank 1998). In this model, the fitness of a genotype depends on the genotypic composition of its deme whenever there is competition for resources. Thus, it becomes useful to decompose the total covariance into the covariances within and among demes (Price 1972; Wade 1985):

$$\Delta q_s = C(q, w) = \mathrm{E}\left(C_j\left(q_{ij}, \frac{W_{ij}}{W_{\cdot j}}\right)\right) + C\left(q_{\cdot j}, \frac{W_{\cdot j}}{W_{\cdot\cdot}}\right), \quad (4)$$

where q_{ij} is the frequency of the m allele in individuals of genotype i in deme j (e.g., $q_{MM,j} = 0$, $q_{Mm,j} = 1/2$, $q_{mm,j} = 1$ for all j), $q_{\cdot j}$ is the frequency of m in deme j, $W_{\cdot j}$ is the average fitness of individuals in deme j, $W_{\cdot\cdot}$ is the mean fitness in the entire metapopulation, and $C_j(q_{ij}, W_{ij}/W_{\cdot j})$ is the covariance within deme j of an individual's allele frequency with its fitness relative to others in its deme (this term represents the change in the frequency of m within deme j due to selection). We need to take the average value of this covariance over all demes to obtain the average change due to selection within demes. The term $C(q_{\cdot j}, W_{\cdot j}/W_{\cdot\cdot})$ is the covariance of a deme's allele frequency with its contribution to the next generation; this term quantifies selection arising from variance in fitness among demes (i.e., selection among demes).

To calculate these covariances, I use the identity $C(x, y) = \mathrm{E}(xy) - \mathrm{E}(x)\mathrm{E}(y)$. It is often necessary to take averages across demes of functions involving within-deme allele frequency (e.g., $W_{\cdot j}$ is a function of $q_{\cdot j}$). To calculate such averages, I use a third-order Taylor series approximation around the metapopulation mean allele frequency, $q_{\cdot\cdot}$:

$$\mathrm{E}(F(q_{\cdot j})) \approx F(q_{\cdot\cdot}) + \frac{1}{2}V(q_{\cdot j})\frac{\partial^2 F(q)}{\partial q^2}\bigg|_{q=q_{\cdot\cdot}} + \frac{1}{6}S(q_{\cdot j})\frac{\partial^3 F(q)}{\partial q^3}\bigg|_{q=q_{\cdot\cdot}}, \quad (5)$$

where $V(q_{\cdot j})$ is the variance in allele frequency among demes and $S(q_{\cdot j})$ is the third central moment of the distribution of demic allele frequencies. This approximation works well when there is a large number of demes and the deviations in demic allele frequencies are not too large;

the latter condition is easily satisfied at mutation-selection balance, provided there is some gene flow. Following Whitlock (2002), I use $F_{ST} = V(q_{\cdot j})/q_{\cdot\cdot}(1 - q_{\cdot\cdot})$ and $\gamma_{ST} = S(q_{\cdot j})/q_{\cdot\cdot}(1 - q_{\cdot\cdot})(1 - 2q_{\cdot\cdot})$ as standardized measures of among-deme variance and skewness in allele frequency, respectively.

If we assume s_R, s_A, $q_{\cdot\cdot} \ll 1$, the change due to selection within demes is

$$\Delta q_{s,\text{within}} = \mathrm{E}\left(C_j\left(q_{ij}, \frac{W_{ij}}{W_{\cdot j}}\right)\right)$$

$$= -q_{\cdot\cdot}\left(H_{1,R}s_R + \frac{nA'}{a + nA'}H_{1,A}s_A\right), \qquad (6)$$

and the change due to selection among demes is

$$\Delta q_{s,\text{among}} = C\left(q_{\cdot j}, \frac{W_{\cdot j}}{W_{\cdot\cdot}}\right)$$

$$= -q_{\cdot\cdot}\left(H_{2,R}s_R + \frac{n(1-f)\alpha}{a + nA'}H_{2,A}s_A\right). \qquad (7)$$

The parameter $A' = f + (1 - f)\alpha$ can be interpreted as the leading-order approximation for the average acquisition ability across the metapopulation, accounting for both intra- and interspecific competitors.

The H terms above arise because population subdivision affects how genetic variance in the phenotypes (R or A) is distributed within ($H_{1,x}$) and among ($H_{2,x}$) demes: $H_{1,x} = h_x(1 - F_{ST}) + (1 - 2h_x)(F_{ST} - \gamma_{ST})$ and $H_{2,x} = 2h_x(F_{ST} - \gamma_{ST}) + \gamma_{ST}$. For additive traits ($h_x = 1/2$), the H terms simplify to the classic coefficients of allelic variation within and among demes: $2 \times H_{1,x} = 1 - F_{ST}$ and $2 \times H_{2,x} = 2F_{ST}$ (Wright 1969; a factor of 2 occurs here because the opposing homozygotes differ by s_x phenotypic units in this model rather than $2s_x$). For nonadditive traits ($h_x \neq 1/2$), the distribution of genetic variance in phenotypes (but not genotypes) changes because the clustering of alleles in subpopulations results in an excess of homozygotes among demes.

Consideration of Factors Affecting the Softness of Selection

Before assessing how different parameters in the present model affect the hardness of selection, I first examine a simpler case. Analyzing Whitlock's (2002) model (eq. [1]) in a similar fashion gives $\Delta q_{s,\text{within}} = -q_{\cdot\cdot}H_1 s$ and $\Delta q_{s,\text{among}} = -q_{\cdot\cdot}bH_2 s$. The ratio of the selection response among demes to that within demes ($\Delta q_{s,\text{among}}/\Delta q_{s,\text{within}}$) contains information about the strengths of selection at the two levels, with each weighted according to the partitioning of genetic variance within and among demes. We can use $\pi = (\Delta q_{s,\text{among}}/H_2)/(\Delta q_{s,\text{within}}/H_1)$ to quantify the hardness of selection, as this measures the importance of selection among demes to selection within demes after removing coefficients arising from genetic partitioning. For Whitlock's (2002) model, $\pi = b$, indicating that increasing the value of b increases hardness of selection, as expected from how b was defined.

In the present model, for a mutation that affects intrinsic growth rate but not acquisition ability ($s_A = 0$), I find that $\pi_{R\,\text{only}} = 1$. This shows that, for this type of mutation, the hardness of selection is independent of resource abundance, a, or other parameters related to competition, f and α. More simply, such genes experience pure hard selection. This result is unsurprising; selection will not be soft on a mutation whose fitness effects are not influenced by competition.

For a mutation that affects acquisition ability, as it is modeled here, but not intrinsic growth rate ($s_R = 0$), I find that $\pi_{A\,\text{only}} = (1 - f)\alpha/(f + (1 - f)\alpha)$. It is clear that $\pi_{A\,\text{only}} < \pi_{R\,\text{only}}$, indicating that selection is softer on acquisition ability mutations than on resource-use efficiency mutations. However, even for acquisition ability mutations, the hardness of selection is independent of resource abundance, a. Of course, a affects the strength of selection of acquisition ability (e.g., these mutations are deleterious when resources are limiting but have no effect on fitness when resources are unlimited; fig. 1*B*). Because resource limitation similarly affects within- and among-deme selection, it does not affect the hardness of selection as measured by $\pi_{A\,\text{only}}$.

Though strong local competition is generally thought to make selection softer, this notion ignores interspecific competition. In fact, selection can be completely soft only in the absence of interspecific competition; that is, $\pi_{A\,\text{only}} = 0$ when $f = 1$ or $\alpha = 0$. Examination of $\pi_{A\,\text{only}}$ reveals that selection becomes harder as the strength of interspecific competition increases, either because heterospecifics make up a larger fraction of the pool of competitors ($\partial\pi_{A\,\text{only}}/\partial f < 0$) or because heterospecifics increase their competitive ability ($\partial\pi_{A\,\text{only}}/\partial\alpha > 0$).

Consider now a mutation that affects both traits. For simplicity, let $h_R = h_A$ and $s_A = \beta s_R$ so that β measures the phenotypic effect of the mutation on acquisition ability relative to its phenotypic effect on growth rate. As expected, selection is softer on mutations that have larger effects on acquisition ability ($\partial\pi_{R\&A}/\partial\beta < 0$). Although the degree of resource abundance, a, does not affect π for either of the nonpleiotropic mutations discussed above, resource abundance makes selection harder on pleiotropic mutations ($\partial\pi_{R\&A}/\partial a > 0$). When resources are unlimited, there is no selection on acquisition ability, so all of the selection experienced by the pleiotropic mutation is

through its effect on growth rate, and, as discussed above, selection on intrinsic growth rate is always hard. When resources are limited, a greater proportion of the total selection on the pleiotropic mutation is through its effect on acquisition ability, and this selection can be soft. Thus, resource limitation makes selection softer on a pleiotropic gene by increasing the selective importance of the mutation's effect on A, the trait that experiences soft selection.

Calculation of Mutation Load

Assuming that mutation is weak relative to selection (i.e., μ is $O(s^2)$), we can find the equilibrium frequency of the deleterious allele by solving $\Delta q_s + \mu = 0$, where $\Delta q_s = \Delta q_{s,\text{within}} + \Delta q_{s,\text{among}}$. Doing so for Whitlock's (2002) model using $\Delta q_{s,\text{within}} = -q_{..}H_1 s$ and $\Delta q_{s,\text{among}} = -q_{..}bH_2 s$ gives the same result reported in his equation (17) when the same assumptions are applied. For the present model, the equilibrium frequency of the deleterious allele is

$$\text{eq}q_{..} = \frac{\mu}{(H_{1,R} + H_{2,R})s_R + \left[\frac{A'n}{a + A'n}H_{1,A} + \frac{(1-f)n\alpha}{a + A'n}H_{2,A}\right]s_A}. \tag{8}$$

In a subdivided population, there are several ways in which one could conceivably quantify load. One measure of load is the selective disadvantage of the average individual in the actual metapopulation relative to that of a wild-type individual in that population:

$$L = \frac{\text{E}(W_{\text{wildtype in actual}}) - \text{E}(W_{\text{actual in actual}})}{\text{E}(W_{\text{actual in actual}})}, \tag{9}$$

where $\text{E}(W_{\text{wildtype in actual}})$ is the expected fitness of a wild-type individual when placed randomly within the actual metapopulation and $\text{E}(W_{\text{actual in actual}})$ is the average fitness of an individual from the actual metapopulation. In the results that follow, I assume that $\gamma_{\text{ST}} = 2F_{\text{ST}}^2/(1 - F_{\text{ST}})$, which is the level of skewness expected in the neutral island model (Whitlock 2002).

For a mutation that affects only intrinsic growth rate and not acquisition ability ($s_A = 0$), the load is

$$L_{R\text{only}} = \mu\left[1 + \frac{(1 - F_{\text{ST}})h_R}{F_{\text{ST}} + (1 - F_{\text{ST}})h_R}\right]. \tag{10a}$$

Population structure increases homozygosity, contributing to an increase in the efficiency of selection and potentially reducing load. This homozygosity effect of population structure is captured by the fraction in the brackets; increasing the value of F_{ST} in this term reduces the magnitude of load. This term depends on dominance, reflecting the fact that the increase in phenotypic variation exposed via excess homozygosity is greatest for rare recessive mutations. As discussed above, intrinsic growth rate mutations always experience hard selection. For such mutations, the homozygosity effect is the only consequence of population subdivision, and thus population structure always reduces the load. Note that this result collapses to the classic result of $L = 2\mu$ when there is no subdivision ($F_{\text{ST}} = 0$); this is also true for the other types of mutations discussed below. At the other extreme ($F_{\text{ST}} = 1$), the load is $L = \mu$, indicating that the the maximal reduction in load due to the homozygosity effect is 50%. This reduction occurs because in highly inbred populations, each selective death removes two deleterious alleles rather than just one (Kondrashov and Crow 1988; Whitlock 2002).

For a mutation that affects only acquisition ability and not intrinsic growth rate ($s_R = 0$), the load is

$$L_{A\text{only}} = \mu\left[1 + \frac{(1 - F_{\text{ST}})h_A}{F_{\text{ST}} + (1 - F_{\text{ST}})h_A}\right] \times \left\{\frac{(1 + F_{\text{ST}})[f + (1 - f)\alpha]}{(1 - F_{\text{ST}})f + (1 + F_{\text{ST}})(1 - f)\alpha}\right\}. \tag{10b}$$

In addition to the homozygosity effect (given by the first term in brackets), acquisition ability mutations experience a second consequence of population structure; local competition reduces the efficiency of selection, potentially causing an increase in load. This soft-selection effect is captured by the second term in brackets in equation (10b); increasing the value of F_{ST} in this term increases its magnitude, thus increasing load. By examining derivatives of this term in equation (10b) with respect to f and α, it can be seen that interspecific competition reduces the magnitude of this term and thus reduces the load. This is consistent with the earlier claim that interspecific competition tends to harden selection and that hard selection reduces load. When competition is completely intraspecific ($f = 1$ or $\alpha = 0$), equation (10b) gives the same load predicted by Whitlock's (2002) model for pure soft selection. When competition is mostly interspecific ($f \to 0$), equation (10b) gives the same load predicted by Whitlock's (2002) model for pure hard selection. When these two extremes are compared, the load is greater by a factor of $(1 + F_{\text{ST}})/(1 - F_{\text{ST}})$ when competition is mostly intraspecific rather than interspecific. This amounts to an ~10% increase in load for $F_{\text{ST}} = 0.05$.

For a pleiotropic mutation with $h_R = h_A = h$ and $s_A = \beta s_R$, the load is

$$L_{R\&A} = \mu\left[1 + \frac{(1 - F_{ST})h}{F_{ST} + (1 - F_{ST})h}\right] \tag{10c}$$

$$\times \left(\frac{(1 + F_{ST})[a + A'n(1 + \beta)]}{(1 + F_{ST})\{a + n[A' + (1 - f)\alpha\beta]\} + (1 - F_{ST})fn\beta}\right).$$

This result is very similar to that in equation (10b), though the soft-selection term is different, owing to the fact that the mutation affects two traits, only one of which is related to local competition for resources. Examination of the term in parentheses in equation (10c) confirms two additional points with respect to soft selection on pleiotropic mutations. First, the derivative of this term with respect to β is positive, indicating that mutations with a large effect on A relative to R cause the most load. A pleiotropic mutation is subject to selection through its effect on both intrinsic growth rate and acquisition ability. Because only the latter trait can experience soft selection, the softness of selection experienced by the pleiotropic mutation depends on the extent to which the total selection on the mutation is due to its effect on A. Thus, mutations with a larger phenotypic effect on A (i.e., larger β) experience softer selection and contribute more load. Second, the derivative of the soft-selection term with respect to a is negative, indicating that resource abundance reduces the load from pleiotropic mutations. This result is somewhat surprising, given that resource abundance does not affect the load due to mutations that exclusively affect acquisition ability (eq. [10b]). However, this result makes more sense when we recall that increasing a reduces the strength of selection on acquisition ability even though it does not affect the softness of selection on this trait. For a pleiotropic mutation, increasing the abundance of resources reduces the softness of selection by reducing the proportion of the total selection on these alleles that is due to their effect on acquisition ability.

Inbreeding Depression

Compared to mutation load, inbreeding depression is a more empirically tractable measure of the presence of deleterious mutations. Following Whitlock's (2002) δ_1 measure, I calculate inbreeding depression as the reduction in fitness of experimentally inbred individuals relative to individuals randomly mated to others from the same deme:

$$\delta = 1 - \mathrm{E}\left(\frac{\overline{W}_{\text{inbred}}}{\overline{W}_{\text{outbred}}}\right), \tag{11a}$$

where the expectation is taken over all demes. It can be shown this is equal to

$$\delta \overset{\text{eq}}{=} q_{..}(1 - F_{ST})\phi\left[(1 - 2h_R)s_R + (1 - 2h_A)\frac{A'n}{a + A'n}s_A\right], \tag{11b}$$

where ϕ is the level of experimental inbreeding.

Substituting in the equilibrium mutation frequency from equation (8), I find a set of results for inbreeding depression similar to those for load (see data file for details). Neither resource abundance nor the strength of interspecific competition affects the amount of inbreeding depression from a mutation that affects only intrinsic growth rate. However, interspecific competition reduces the inbreeding depression from a recessive mutation that affects only acquisition ability; resource abundance has no effect. For a recessive pleiotropic mutation, inbreeding depression is greatest if the mutation's effect on acquisition ability is large and/or if resources are limited. These results indicate that inbreeding depression increases under those conditions that make selection softer. This matches Whitlock's (2002) result that inbreeding depression is greatest under soft selection.

Wasted Resources and Supersoft Selection

The model used above implicitly assumes that all resources consumed by the focal species contribute to the productivity of the deme. This is unrealistic because some individuals will consume resources and die before contributing to the next generation. Nicholson (1954*b*, 1957) discussed this ecological phenomenon at length, arguing that in some situations a substantial amount of resources is effectively wasted on juveniles who die before reaching maturity.

When this possibility is allowed for, the overall competitive pressure in deme j can be expressed as

$$A_j^{**} = f\left\{\sum_i F_{ij}[v_i A_i + (1 - v_i)D_i]\right\} + (1 - f)\alpha, \tag{12}$$

where F_{ij} is the frequency of genotype i in deme j and v_i is the probability that an individual of genotype i survives the resource acquisition phase of the life cycle (e.g., juvenile viability). Individuals of genotype i who die during the acquisition phase can be thought of as exerting only a fraction, D_i, of their full competitive force because they are expressing their acquisition ability for only a fraction of the competitive phase, after which they are dead. (Note

that eq. [12] collapses to eq. [3] when $v_i = 1$ for all genotypes.) The v and D values for *MM*, *Mm*, and *mm* individuals are $v_{MM} = v$, $v_{Mm} = v(1 - h_v s_v)$, $v_{mm} = v(1 - s_v)$, $D_{MM} = D$, $D_{Mm} = D(1 - h_D s_D)$, and $D_{mm} = D(1 - s_D)$. The variation in D values among genotypes can arise if, for example, mutants that die in the resource acquisition phase tend to die earlier than do wild-type individuals that also die during this phase. In this case, mutants that die remove fewer resources from the deme than do wild-type individuals that die.

Incorporating these new viability effects, the fitness of an individual of genotype i in deme j is

$$W_{ij} = R_i v_i \left(\frac{a A_i / n A_j^{**}}{1 + a A_i / n A_j^{**}} \right). \tag{13}$$

As before, R can still be thought of as the efficiency with which an individual is able to convert its acquired resources into fitness. However, v and R jointly determine fitness when resources are unlimited ($a \to \infty$); that is, intrinsic growth rate in this model is better described by Rv than by R alone. The term in parentheses is the same as equation (2) but with A_j^{**} replacing A_j^*.

For this model, the change due to selection within demes is

$$\begin{aligned} \Delta q_{s,\text{within}} &= \mathrm{E}\left(C_j \left(q_{ij}, \frac{W_{ij}}{W_{\cdot j}} \right) \right) \\ &= -q_{\cdot\cdot} \left(H_{1,R} s_R + H_{1,v} s_v + \frac{A'' n}{a + A'' n} H_{1,A} s_A \right), \end{aligned} \tag{14}$$

where $A'' = f[v + (1 - v)D] + \alpha(1 - f)$. The change due to selection among demes is

$$\begin{aligned} \Delta q_{s,\text{among}} &= C\left(q_{\cdot j}, \frac{W_{\cdot j}}{W_{\cdot\cdot}} \right) \\ &= -q_{\cdot\cdot} \left\{ H_{2,R} s_R + \frac{n(A'' - fv)}{a + A'' n} H_{2,A} s_A \right. \\ &\quad \left. + \frac{a + n[Df + \alpha(1 - f)]}{a + A'' n} H_{2,v} s_v - \frac{Dfn(1 - v)}{a + A'' n} H_{2,D} s_D \right\}. \end{aligned} \tag{15}$$

The key point of interest is that the final term in braces is negative whereas all the other terms are positive. With hard selection, the covariance between the genetic quality of the deme and its fitness is positive ($C(p_{\cdot j}, W_{\cdot j}/W_{\cdot\cdot}) > 0$). As selection becomes soft, this covariance declines, becoming 0 in pure soft-selection models (e.g., Whitlock's [2002] model with $b = 0$). However, equation (15) shows that 0 is not the lower limit for this covariance in this model. This covariance can be negative, resulting in supersoft selection, in which demes with more mutants have higher average fitness.

When all possible phenotypic effects are allowed for, the load is given by

$$L = \mu \frac{(a + A'' n)(H_{3,R} s_R + H_{3,v} s_v) + (A'' n) H_{3,A} s_A}{K_A s_A + K_R s_R + K_v s_v - K_D s_D}, \tag{16}$$

where

$$\begin{aligned} K_A &= n[A''(H_{1,A} + H_{2,A}) - H_{2,A} fv)], \\ K_R &= (a + A'' n)(H_{1,R} + H_{2,R}), \\ K_v &= a(H_{1,v} + H_{2,v}) \\ &\quad + n\{A'' H_{1,v} + [Df + \alpha(1 - f)] H_{2,v}\}, \\ K_D &= Dfn(1 - v) H_{2,D}, \\ H_{3,x} &= F_{\mathrm{ST}} + 2h_x(1 - F_{\mathrm{ST}}). \end{aligned}$$

We can use the result above to illustrate how the softness of selection affects load. In the following examples, I assume weak subdivision ($F_{\mathrm{ST}} = 0.05$), partial dominance ($h = 0.3$), and no interspecific competition ($f = 1$). First, consider a mutation experiencing pure hard selection ($v = 1$, $s_A = s_D = s_v = 0$). The load for such a mutation is $L_{\text{hard}} = 1.85\mu$. As expected, the load for a mutation under hard selection is lower than Haldane's (1937) prediction of 2μ for a panmicitic population. In contrast, for a mutation experiencing pure soft selection ($v = 1$, $s_D = s_R = s_v = 0$), the load is $L_{\text{soft}} = 2.05\mu$. Finally, for a mutation experiencing supersoft selection ($v = 0.5$, $D = 0.9$, $s_A = 0.01$, $s_D = 0.1$, $s_R = s_v = 0$), the load is $L_{\text{supersoft}} = 3.71\mu$. In this example, L_{soft} is 11% larger than L_{hard}, whereas $L_{\text{supersoft}}$ is 101% larger than L_{hard}. By allowing for supersoft selection, ecological circumstances can greatly increase the load beyond what is predicted by pure soft selection.

The potential for supersoft selection is greatest whenever a high fraction of resources is being wasted on the dead. This tends to occur when mortality during the resource acquisition phases is high (v is low) and when dying individuals tend to consume almost as many resources as survivors (D is high). Even when these conditions are met, supersoft selection can occur only when fewer resources are wasted on dying mutants than on dying wild-type individuals ($s_D > 0$). Figure 2 illustrates how these parameters affect the load by causing supersoft selection.

A pattern very similar to that shown for load in figure

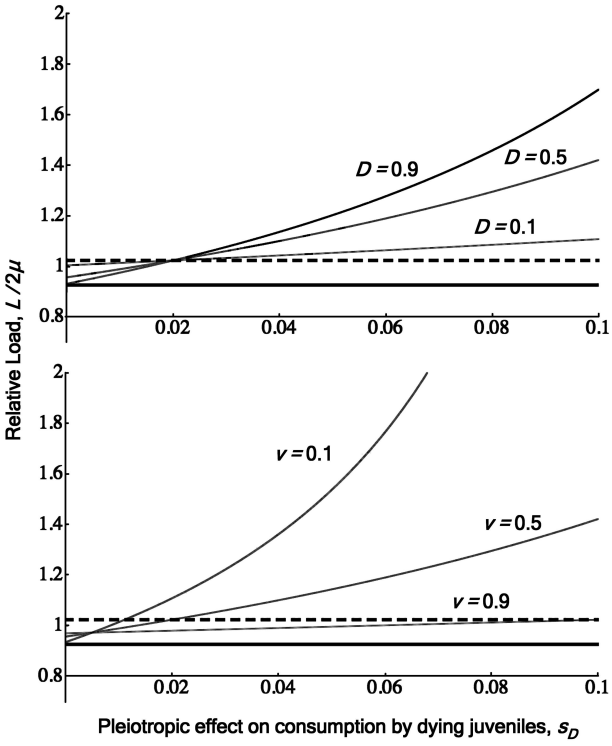

Figure 2: Mutation load of different types of mutations. The load is measured relative to the classic expectation of $L = 2\mu$. The relative load is shown for a mutation that has pleiotropic effects on juvenile mortality ($s_v = 0.01$) and the amount of resources consumed by juveniles that do not reach maturity (s_D on the horizontal axis). In the top panel, $v = 0.5$, and the three solid lines represent $D = 0.1$, 0.5, and 0.9. In the bottom panel, $D = 0.5$, and the three solid lines represent $v = 0.1$, 0.5, and 0.9. For both panels, the bold dashed line represents the load for a mutation experiencing pure soft selection ($L_{\text{soft}} = 2.05\mu$). The bold solid line represents the load for a mutation experiencing pure hard selection ($L_{\text{hard}} = 1.85\mu$). Other values: $F_{\text{ST}} = 0.05$, $h = 0.3$, and $f = v = 1$.

2 also occurs for inbreeding depression; inbreeding depression is greatly elevated by supersoft selection (see data file). Supersoft selection affects mutation load and inbreeding depression similarly for the simple reason that both metrics are linear functions of mutant allele frequency. With supersoft selection, deleterious alleles are maintained at elevated frequency, thus causing increased load and higher inbreeding depression. Nonetheless, it is of special interest that a trait that is seemingly unrelated to fitness (consumption rates of individuals who die before reproduction) has such a major impact on load and inbreeding depression.

Discussion

Population structure can substantially alter mutation load (Crow and Kimura 1970; Agrawal and Chasnov 2001; Glémin et al. 2003; Roze and Rousset 2004; Theodorou and Couvet 2006). However, the magnitude and even the direction of the change as a result of population structure depend on the softness of selection (Whitlock 2002), that is, the extent to which competition and selection occur locally versus globally.

The scale of competition is also important in the social-evolution literature (Boyd 1982; Taylor 1992; Wilson et al. 1992; Queller 1994; Frank 1998). In both contexts, local competition reduces the among-deme variance in fitness, thus increasing the relative importance of within-deme success. In the context of social evolution, altruism typically evolves through among-deme selection (Wade 1980), and thus a reduction in among-deme variance caused by local competition restricts the evolution of altruism. In the case of mutation load, the reduction in the among-deme component of variance reduces the total variance in fitness, making selection less efficient overall and increasing the load.

The purpose of the current model is not to repeat the well-established results of how subdivision affects load but rather to illustrate how ecological factors affect the softness of selection. Previous models have simply assumed a particular form of selection (hard or soft). When any justification has been provided at all, soft versus hard selection is said to be due to local versus global density regulation. This implies that the softness of selection is determined solely by extrinsic ecological factors that affect all genes uniformly (but see Ravigné et al. 2004).

When a more ecologically explicit model is used, it becomes clear that the softness of selection will vary among genes, depending on their phenotypic effects. Mutations affecting the efficiency of resource use (R) always experience hard selection, whereas selection can be soft on mutations affecting acquisition ability, at least as these traits are modeled here. Moreover, ecology interacts with phenotypic effects in some nonintuitive ways. For example, the degree of resource limitation does not affect the softness of selection on mutations that affect either the efficiency of resource use or acquisition ability. Yet for pleiotropic mutations, selection becomes softer (and the load higher) when resources are more limiting.

Why does softer selection result in a larger load? Deaths (or reproductive failures) that occur because of selective differences among genotypes are referred to as selective deaths. It is often said that mutation load depends on the number of mutations eliminated per selective death. More accurately, the model by Kondrashov and Crow (1988) shows that mutation load is an inverse function of the difference between the number of mutations per selective death and the mean number of mutations per survivor. When there is soft selection, deleterious alleles clustered within the same deme are sheltered from selection. Thus,

survivors in structured populations carry more deleterious alleles, on average, than they would in well-mixed populations. Consequently, there is a smaller difference in the mean number of mutations between survivors and nonsurvivors, resulting in a larger load under soft selection.

A seductive feature of Haldane's (1937) work was that the load depended only on mutation rate. One did not need to know the strength of selection on a mutation and certainly not the details of the mutation's phenotypic effects. As described above, the softness of selection depends on phenotypic effects. Unfortunately, this greatly complicates the data required to calculate the genome-wide load because it implies that one must know the distribution of phenotypic effects of new mutations.

Local competition is commonly invoked as the motivation for models assuming soft selection. Deleterious alleles can be sheltered from selection if mutants compete locally against other mutants rather than against wild-type individuals in other demes. However, the logical connection between local competition and the softness of selection holds only when competition is entirely intraspecific. In reality, competition between different species is common (Schoener 1983). When interspecific competitors are present, the local clustering of mutants no longer shelters these alleles from selection. Demes with mutants will produce fewer offspring of the focal species than will demes without mutants because the former will lose more resources to interspecific competitors. Thus, it can be said that interspecific competition effectively hardens selection against mutations that might otherwise experience soft selection. As a consequence, selection can be hard even when local competition is strong. Kelly (1994*b*) described a related phenomenon with respect to the effect of interspecific competition on the evolution of communal foraging.

One scenario in which the effects of interspecific competition may be of particular interest is with respect to sexual populations versus asexual populations. Obligately asexual organisms can be viewed as interspecific competitors to a focal sexual species. As shown here, the presence of interspecific competitors hardens selection, thus reducing load for the sexual species. (Note that asexual species cannot benefit from the homozygosity effect of subdivision, which is a consequence of local mating.) Thus, caution should be used in evaluating the models by Agrawal and Chasnov (2001) and Haag and Roze (2007) because both examined the loads of sexual and asexual populations in isolation from one another, ignoring how the presence of one species affects selection on the other.

The load under pure soft selection is larger than the load under pure hard selection by a factor of $(1 + F_{ST})/(1 - F_{ST})$, which is about 10% for $F_{ST} = 0.05$. However, pure soft selection is not the softest form of selection. Selection can be supersoft, and when it is, the load can be much larger (fig. 2). Attempts to measure the softness of selection on mutations in *Drosophila melanogaster* suggest that supersoft selection may be common (Laffafian et al., forthcoming).

Supersoft selection can occur because of juvenile mortality. When juveniles die, the resources they have previously consumed are partially or completely lost from the resource pool. If mutants that die as juveniles die earlier than do wild-type individuals that die as juveniles, fewer resources will be wasted on dead juvenile mutants than on dying juvenile wild types. In demes with only wild-type individuals, a large fraction of the total resources may be wasted on juveniles who almost reach maturity but fail to do so. In contrast, a deme with a high fraction of mutants may experience a slightly higher rate of juvenile mortality (if mutants have lower viability), but if mutants tend to die when they are very young, the dead will leave a bounty of unused resources for the survivors. This advantage to demes with mutant individuals allows the deleterious allele to persist at higher frequencies than it otherwise would.

The connection to the social-evolution literature is particularly strong for those genes that experience supersoft selection. As for altruism (Wade 1980), genes that experience supersoft selection are selected positively at the among-deme level but negatively within demes. In models of altruism, the focus is on cases in which among-deme selection outweighs within-deme selection, resulting in a net benefit to the altruistic allele. In the case of load, no net benefit is required since the allele is maintained through mutation. The deleterious allele is maintained at a higher frequency in a subdivided population than it would be in an unstructured population because its negative individual-level affects are partially offset by positive among-deme selection. Whereas a relatively small fraction of genes may be able to produce the type of cooperative behaviors that we typically associate with altruism, a much wider set of mutations are likely to cause early juvenile mortality and, thus, potentially experience supersoft selection.

Since Nicholson's (1954*a*, 1954*b*) classic studies of population growth in blowflies, ecologists have known that increased mortality can, in some cases, result in larger population sizes. This seemingly paradoxical phenomenon has been observed in several other experiments and in many ecological models and, recently, has been termed the hydra effect (see review by Abrams [2009]). While supersoft selection is conceptually related to the hydra effect, these two phenomena are not the same. The hydra effect is a strictly ecological concept, whereas supersoft selection refers to the differential fitnesses of genotypes in a metapopulation context. Specifically, supersoft selection occurs

when the total selection against a deleterious allele is reduced because individual-level costs are partially offset by the higher productivity of demes enriched for the allele. Because this implies that demes with higher mortality have elevated productivity, supersoft selection seems more likely to occur under those conditions that also cause hydra effects. As described by Abrams (2009), hydra effects can occur via several different mechanisms, and it is plausible that supersoft selection could arise in ways other than the early juvenile mortality mechanism proposed here.

In principle, the types of mutations that experience supersoft selection could be favored by selection if group-level advantages outweigh individual-level disadvantages. This is mathematically equivalent to the classic "evolution of altruism" scenario. I have not considered this possibility in the model; mutations were assumed to be net deleterious, as this seems more likely. The beneficial-mutation scenario would require small individual-level disadvantages and large group-level benefits, as well as strong population structure, to realize those benefits. Phenotypically, the best chance for being beneficial would be if the mutation only slightly increased juvenile mortality but induced juvenile mortality at a much younger stage whenever it happened in mutants.

Though it remains a challenge to accurately measure the standing genetic variance in fitness and quantify its sources, deleterious mutation is likely an important factor (Charlesworth and Hughes 1999). Because of soft selection, and especially supersoft selection, deleterious alleles can be maintained at higher frequencies in subdivided populations relative to unstructured populations. Ultimately, this means that deleterious alleles can make a substantially greater contribution to the maintenance of genetic variance for fitness traits (Santos 1997; Whitlock 2002) than predicted from classic mutation models assuming panmixis (Mukai et al. 1974; Charlesworth 1987).

Although motivated by classic ecological theory, the models I used here are simplistic and would not be suited for some types of ecological scenarios. Nonetheless, several of the key points are intuitively sensible and thus are likely to hold over a fairly wide range of ecologies. At the very least, the model demonstrates that ecological details matter for mutation load, a subject typically regarded as a purely genetical one. This serves as yet another example of the need to better integrate ecological and evolutionary concepts.

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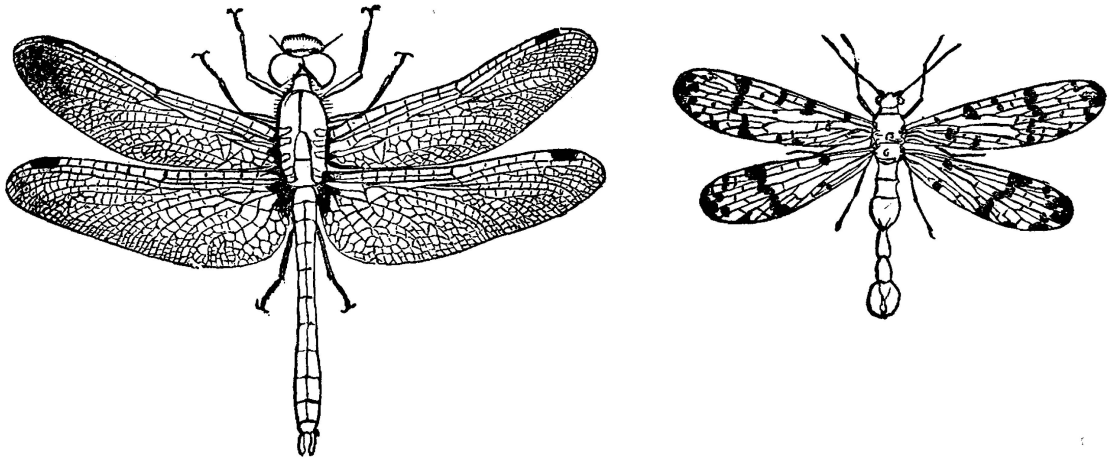

"Among other beneficial insects belonging to the Neuroptera is the immense family of Libellulidae, or Dragon-flies, of which *Diplax berenice* Drury (*left*) is a fine representative. The Forceps-tail, or *Panorpa P. rufescens* (*right*) is found in bushy fields and shrubbery. They prey on smaller insects, and the males are armed at the extremity of the body with an enormous forceps-like apparatus." From "Natural History Calendar" by A. S. Packard (*American Naturalist*, 1867, 1:277–279).