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# Theoretical perspectives on rapid evolutionary change

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## 2.1 Introduction

Rapid evolutionary change is a common outcome of strong phenotypic selection—from exposure to unusual temperatures to attack by unfamiliar parasites to growth on new food resources—organisms evolve rapidly under challenging circumstances as long as the requisite genetic variation is present. As recounted throughout this book, revolutionary changes in sequencing technology and bioinformatics have allowed biologists to develop a detailed understanding of the genetic basis of rapid evolutionary change from a variety of case studies, from antibiotic resistance to evolutionary responses to sexual conflict.

This chapter explores the theoretical implications of strong selection. Much of basic evolutionary theory assumes weak selection acting on a gene; here we will ask when and to what extent strong selection would alter our theoretical predictions. To begin, we must address the issue that strong selection at the phenotypic level need not generate strong selection at the genic level. We then explore the implications of selection when it is strong at the genic level.

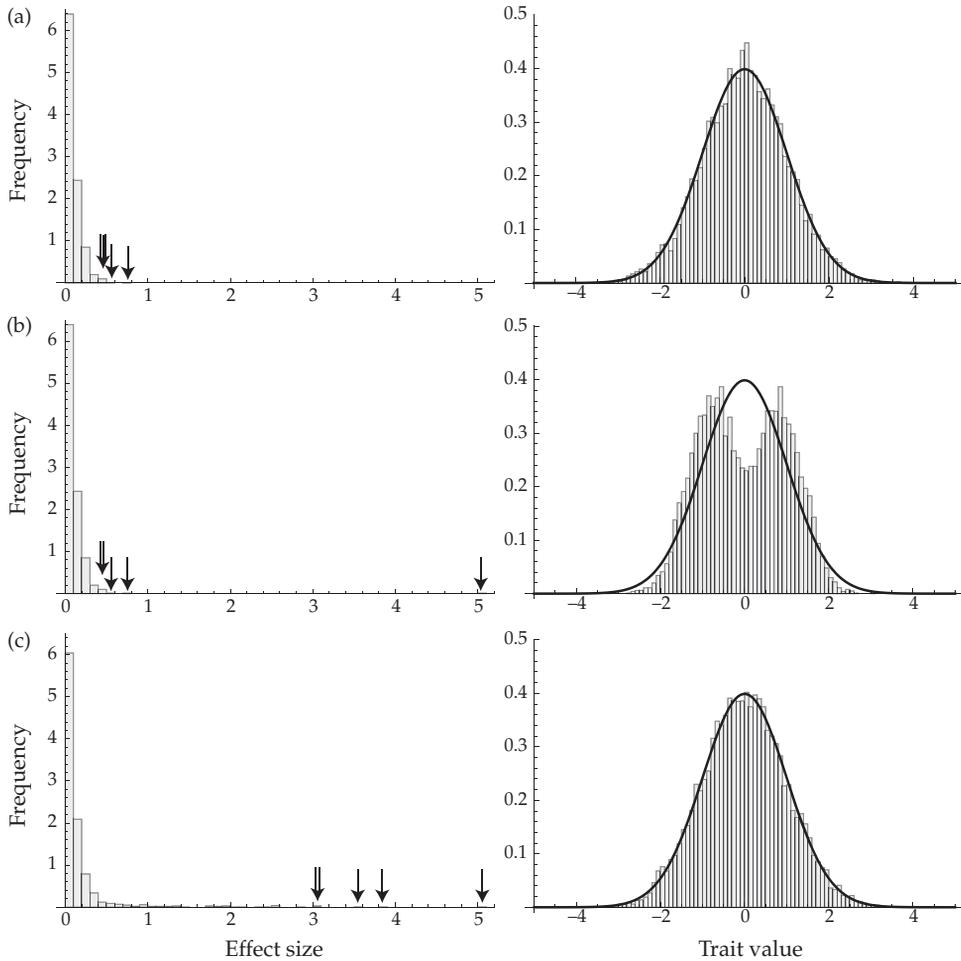
## 2.2 When is strong selection strong?

A rapid response to selection is possible by accumulating many small changes or a handful of larger ones. If variation is due to many alleles of weak effect, even very strong selection at the phenotypic level can result in weak selection at any one site. For example, if a trait were equally affected by 1000 single nucleotide polymorphisms (SNPs), selection could shift the value of the trait by 0.1

haldane (1/10th of a standard deviation) in a single generation (faster than most observed cases of natural selection; Hendry and Kinnison 1999), yet generate weak selection on any one SNP (e.g.  $s = 0.013$  assuming alleles at frequency 1/2, additive diploid selection, independent selective effects on each locus, no initial disequilibrium, and a heritability of 1/2). Indeed, in the infinitesimal limit, there is no appreciable selection or change in allele frequency at any one of the infinitely many loci underlying the trait (Crow and Kimura 1970; Bulmer 1971). Consequently, for strong selection at the phenotypic level to generate strong selection at the genic level requires that one or a few loci contribute disproportionately to the genetic variation present in a population.

Up until the late 1900s, many evolutionary biologists thought that major effect loci, while they underlie traits exhibiting Mendelian inheritance, would explain little of the response to selection on quantitative traits. Instead, it was widely regarded that quantitative traits evolved via slight changes in gene frequency at a great number of minor sites. To understand why this view was so commonplace and why it shifted, we must look back to the early days of population genetic theory.

In his groundbreaking reconciliation of Mendelian genetics and biometry, Ronald A. Fisher (1918) demonstrated that a normal distribution would emerge for a quantitative character influenced by numerous genetic, developmental, and environmental factors. Mathematically, this is the natural outcome of the central limit theorem: given a sufficiently large number of contributing factors, each of which is independent and identically distributed (or roughly so), the resulting distribution is

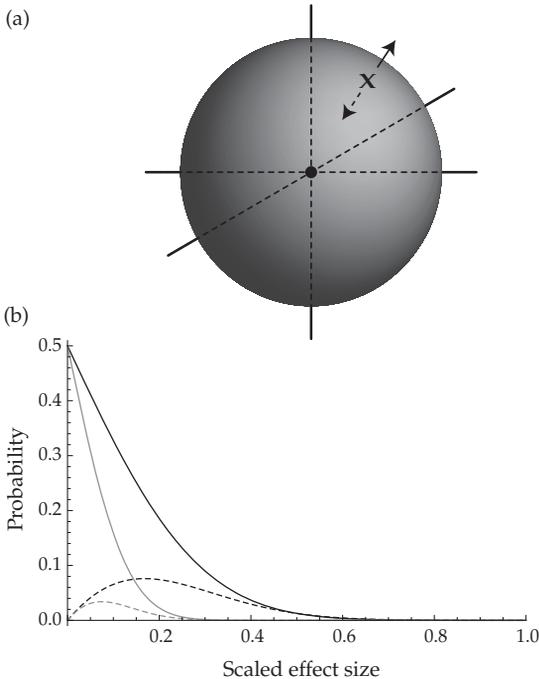


**Figure 2.1** Phenotypic distributions with major effect alleles. (a) 1000 loci affecting a trait were randomly assigned an allele with frequency drawn uniformly between 0 and 1 and effect size drawn from an exponential distribution (left panel). 10,000 individuals were then drawn from this population to obtain a phenotypic distribution, which was standardized to have a mean of 0 and a standard deviation of 1 (right panel; solid curve shows a normal distribution for comparison; panel assumes no environmental variation and no linkage disequilibrium). (b) Same as (a) but one allele was replaced with one having  $\sim 50$  times larger effect, resulting in a decidedly non-normal phenotypic distribution (right). (c) 1000 loci were redrawn from a long-tailed distribution (90% chance of being drawn from the same exponential as in (a) and a 10% chance of being drawn from a second exponential with a tenfold higher mean). Arrows show the five alleles with greatest effect.

normal (Fig. 2.1a). If a single gene contributes substantially to variation in a trait, however, the result will often be decidedly non-normal (Fig. 2.1b). Consequently, the widespread occurrence of normally distributed characters suggested that major effect alleles rarely contribute to variation in quantitative traits.

In his 1930 book, Fisher introduced a second argument against major effect alleles. He argued

by metaphor that mutations were akin to random turns of the focus knobs of a microscope. If the image was slightly out of focus, a large random turn to a knob would be unlikely to bring the image closer in focus. A small turn in either direction, however, would have a 50:50 chance of sharpening the image. Geometrically, with  $n$  knobs, the degree of focus can be represented as a point on an  $n$ -dimensional sphere, whose center represents



**Figure 2.2** Fisher's geometric model. (a) Shown is an imaginary three-dimensional trait space, where the current population lies at a point,  $x$ , on the surface of a sphere, whose centre represents the optimal trait combination (black circle). All trait combinations that are equally distant from the optimum (on the sphere's surface) have the same fitness. Mutations pointing out of the sphere are thus disadvantageous (solid arrow), while mutations pointing inward are beneficial (dashed arrow). (b) Fisher (1930) approximated the probability (solid curves) that a mutation pointing in a random direction would be beneficial given a particular effect size ( $x$ -axis) in  $n$ -dimensional trait space (black:  $n = 20$ ; grey:  $n = 100$ ), where the scaled effect size of a mutation is its magnitude times  $\sqrt{n}/d$  for a sphere of diameter  $d$ . Kimura (1983) noted, however, that only a fraction of these (roughly proportional to the effect size) would survive loss while rare (dashed curves), shifting the modes of the curves toward larger effect mutations.

the optimal focus. By analogy, we can imagine an organism positioned on a sphere some distance from its optimum in  $n$ -dimensional trait space (Fig. 2.2a). The beauty of this metaphor is that it can be used to determine the probability that a mutation, randomly pointing in any direction, falls inside the sphere and so is advantageous (Fig. 2.2b). Fisher noted that this probability falls sharply as mutations increase in their effect size. This argument bolstered the view that small-effect mutations would contribute to the bulk of evolutionary change.

The opposing view, that large-effect mutations matter, has gained prominence in recent decades, with a combination of theoretical and empirical support. Building on Fisher's microscope metaphor, Kimura (1983) pointed out that small-effect mutations, even if more numerous, are more likely to be lost by random genetic drift while rare. Consequently, the distribution of mutations that are both beneficial and survive loss while rare is shifted, with a mode no longer at zero (Fig. 2.2b). Orr (1998) further showed that if we consider not just the first step, but a series of steps toward the optimum, the largest step taken need not be the first step and so is slightly larger, on average, than the first step. A number of other theoretical studies also predict that large-effect mutations contribute substantially more often to adaptation than one would expect based on the frequency of such mutations. These include models that consider the fitness distribution of all possible sequences reachable by single mutations (Gillespie 1984; Orr, 2002; Joyce et al. 2008), that track a changing optimum (Otto and Jones 2000; Griswold and Whitlock 2003), that account for migration swamping small-effect mutations (Griswold 2006; Yeaman and Whitlock 2011), and that incorporate clonal interference in asexual populations (Rozen et al. 2002).

Returning to the argument that quantitative characters are typically normally distributed, it turns out that the central limit theorem is remarkably robust; even if factors are drawn from a distribution with a long tail, such that large-effect alleles are reasonably common, a normal distribution still emerges with enough underlying factors. In Fig. 2.1a, for example, we drew factors from an exponential distribution, the tail of which included two major alleles whose effects were 5.9 and 7.9 times larger than the average. If allele effects are drawn from even more long-tailed distributions, the resulting genotypic distribution may still appear normal, despite the presence of major effect alleles (as in Fig. 2.1c, where the two largest alleles have effects 21.0 and 27.5 times the average). Thus, the observation of a normal phenotypic distribution does not exclude the possibility of large-effect alleles, and such alleles could rise rapidly in frequency in response to strong phenotypic selection. The question is fundamentally an empirical one: how often

do major alleles underlie variation in quantitative traits?

Empirically, two forms of data have provided evidence that large-effect alleles can contribute to phenotypic differences in quantitative traits. First, studies searching for quantitative trait loci (QTL) typically find some genomic regions that have a major effect on the phenotype. For example, among the QTL studies summarized by Lynch and Walsh (1998, supplementary table available online), the maximum QTL accounted for an average of 21.6% of the phenotypic variance across 201 different trait and species combinations (SE = 1.0%, range 2–86%). Granted, the effect sizes are somewhat overestimated due to the 'Beavis effect' (Beavis 1994), and many smaller QTL are typically found as well (average minimum QTL:  $7.0 \pm 0.47\%$  of the phenotypic variance; average number of QTL:  $6.1 \pm 0.3$ ). Moreover, many small-effect QTL certainly remain undetected. Indeed, in the earlier mentioned studies, the total percentage of phenotypic variation explained by all of the detected QTL was only  $42.7\% \pm 1.5\%$ , on average. Furthermore, even those major QTL detected might be comprised of linked loci of smaller effect (e.g. Perez and Wu 1995). More powerful QTL studies based on genome-wide SNPs have revealed hundreds of potential underlying factors, but even then only a handful are often responsible for the bulk of the variation. For example, in a recent genomic analysis of trait variation in *Drosophila melanogaster*, 6–10 SNPs accounted for 65–90% of the genetic variation in all three traits considered (Mackay et al. 2012).

Overall, it is not uncommon to find one or more QTL contributing a substantial fraction of the phenotypic variation in a quantitative trait, substantial enough that we can expect strong selection at the phenotypic level to translate into strong selection at the genetic level. This is an essential issue if we are to have any hope of observing signs of past selection from sequence data. If numerous very small-effect loci underlie a phenotypic trait, selection on the phenotype might lead to only small shifts in allele frequency, occurring so slowly over time that recombination would destroy the signals of selection. Nevertheless, as Roff (2003) cautions, we should not throw out the baby with the bathwater: the major-effect loci often co-occur with

enough small-effect loci that the Gaussian assumption underlying quantitative genetic theory is reasonable, and genetic variation may remain roughly constant even as the major-effect alleles spread, especially in the presence of new mutations (Turelli and Barton 1994; Barton and Keightley 2002).

A second type of evidence for large-effect alleles has come from genomic scans revealing signs of selection at a number of sites. For example, Sabeti et al. (2007) report finding ~300 candidate regions showing longer than expected haplotypes in a cross-population analysis of human genomes (XP-EHH: cross-population extended haplotype homozygosity). Several of these sites are implicated in disease resistance, diet (e.g. lactose tolerance), or skin and hair variation. Very weak selection would not generate such extended haplotypes, because recombination would have time to break down the extended haplotype during the slow spread of a weakly favored allele. A plethora of such genomic scans have now been published (Akey (2009) reviews 21 genome-wide scans), based on a variety of different metrics, including allele frequency distributions, linkage disequilibria (including extended haplotype methods), and population differentiation (e.g. studies based on  $F_{st}$ ). Regardless of the metric, however, weak selection at a single site is almost certain to remain undetected. Indeed, it has been estimated that selection on a site must be stronger than  $\sim 100/N_e$ , where  $N_e$  represents the effective population size, for there to be a reasonable chance of detection (Akey 2009). Of course, humans might be a poor species in which to study selective differences among populations (except for the obvious reason of self-interest) because we are all so closely related, with recent common ancestry within Africa and a relatively small effective population size. Genomic scans in non-human species promise to provide fascinating information about the prevalence and nature of major effect alleles.

### 2.3 Does strong selection differ in kind from weak selection?

Strong selection obviously differs in degree from weak selection, but does it ever differ in kind? Does it ever lead to dramatically different evolution-

any outcomes than weak selection? Theoreticians often resort to assuming weak selection in order to obtain analytical solutions; if selection is strong, do the results differ in any substantial way? As we review here, the answer to this set of questions is mixed, depending on the phenomenon being modeled. Often, the expected outcome of evolution under strong selection exhibits only minor quantitative discrepancies from what we would predict by increasing the strength of selection in weak selection approximations. In other cases, however, predictions are fundamentally different when selection is strong rather than weak.

To begin, consider one of the core equations in evolutionary biology, which describes the change in frequency,  $p(t)$ , of an allele  $A$  over time  $t$ . To keep things simple, we consider a haploid population subject to discrete and non-overlapping generations, where allele  $A$  causes its carriers to have fitness is  $1 + s$  times that of an alternate allele,  $a$ . After one generation of selection, the  $A$  allele changes in frequency to:

$$p(t+1) = \frac{(1+s)p(t)}{(1+s)p(t) + (1-p(t))} \quad (2.1)$$

(see Otto and Day (2007) for derivations of the results presented in this chapter). This equation can be solved exactly for any strength of selection to give the allele frequency in any future generation:

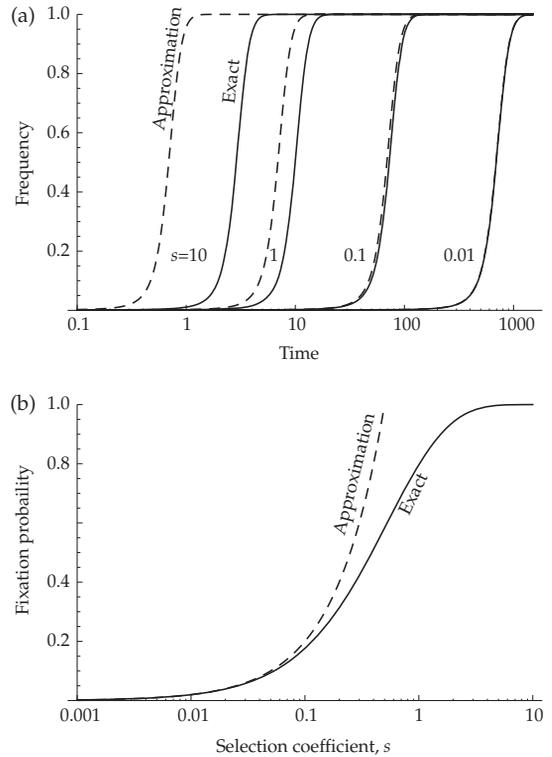
$$p(t) = \frac{(1+s)^t p(0)}{(1+s)^t p(0) + (1-p(0))}. \quad (2.2)$$

In most models of evolutionary change, where additional complications are incorporated (e.g. dominance or frequency dependence), an exact solution is not possible. Theoreticians then often invoke a weak-selection approximation, for example, replacing the recursion equation (2.1) with the analogous differential equation:

$$\frac{dp}{dt} = s p(t) (1 - p(t)). \quad (2.3)$$

A wider array of differential equations can be solved, which is why a weak-selection approximation is often invoked. For example, the solution to equation (2.3) is:

$$p(t) = \frac{e^{st} p(0)}{e^{st} p(0) + (1 - p(0))}. \quad (2.4)$$



**Figure 2.3** Weak versus strong selection. (a) The frequency of a beneficial allele with relative fitness  $1 + s$  is shown over time in a haploid population, starting at frequency 0.001. The exact frequency in a haploid population (equation 2.2; solid) predicts a slower response to selection than the weak selection approximation (equation 2.4; dashed). (b) The exact fixation probability of a beneficial allele in an infinitely large population (equation 2.6; solid) is lower than the weak selection approximation,  $2s$  (equation 2.7; dashed).

While different in form from equation (2.2), the qualitative behavior is very similar (Fig. 2.3a), and visible differences in the speed of the trajectories only appear for  $s$  greater than about 0.1. For example, the time to spread from any initial frequency to any final frequency is 4.7% faster under the approximation (2.4) than with the exact solution (2.2) when  $s = 0.1$ . Even then, the trajectories remain S-shaped and differ solely in timing. Only if we needed precise predictions about the timing of the spread of a favorable allele would strong selection violate the weak-selection approximation (2.4).

A second core equation in evolutionary theory concerns the fixation probability of an allele. Even beneficial alleles can be lost, by chance, after they

first arise, simply because their carriers fail to reproduce. In very large populations, Haldane (1927) argued that the probability that a newly arisen allele will ultimately be lost from the population must equal the probability that all  $j$  offspring carrying the allele are ultimately lost. Letting  $1 - P$  equal the probability of loss and assuming that the fate of each allele is independent, this logic results in the equation:

$$1 - P = \sum_j \text{prob}(j \text{ offspring}) (1 - P)^j, \quad (2.5)$$

where the sum is taken over the probability distribution of having  $j$  offspring. If this offspring distribution is Poisson with mean  $1 + s$  for individuals carrying the beneficial mutation, then the sum in equation (2.5) can be evaluated, leading to:

$$1 - P = e^{-(1+s)P}. \quad (2.6)$$

The fixation probability,  $P$ , is implicitly given by equation (2.6), but this is still a complicated equation to evaluate. Theoreticians often simplify such equations by assuming weak selection, obtaining answers that keep the leading order terms (e.g. of order  $s$ ) but drop terms of smaller order (e.g.  $s^2$  or smaller). In this case, such a 'Taylor series' approximation gives us the oft-cited probability of fixation for a beneficial allele:

$$P \approx 2s. \quad (2.7)$$

Fig. 2.3b shows that the weak-selection approximation (2.7) performs well for selection coefficients up to about 0.1 (the  $2s$  approximation then overestimates the fixation probability by 13.6%).

These considerations suggest that, roughly speaking, the boundary between weak and strong selection occurs at 0.1. This is a reasonable rule of thumb when it comes to theory considering only selection acting at a single locus. In general, however, what constitutes strong versus weak selection depends on the context. In reality, selection is never the only process acting on a population to affect allele frequencies. Thus, whether selection is strong is relative, depending on the magnitude of selection in comparison to the impact of other processes, such as drift, mutation, migration, and recombination.

Selection may be weak relative to 0.1, for example, but strong relative to random genetic drift. Selection overwhelms drift when the best predictor of the future distribution of allele frequencies is  $s$  rather than the population size,  $N$ . With respect to the fate of an allele, we say that selection is strong relative to drift when the fixation probability of an allele is predicted to be higher as a result of selection alone ( $\sim 2s$ ) than drift alone (fixation probability is  $1/(cN)$ , for an organism whose ploidy level is  $c$ ). For diploids ( $c = 2$ ), this leads to the oft-stated rule that selection overwhelms drift whenever  $2s \gg 1/(2N)$ , commonly written as  $\theta = 4Ns \gg 1$ .

Selection can be strong enough to overwhelm drift but not strong enough to overwhelm other processes, such as migration. Consider the simplest haploid case where an allele  $A$  is favored in a patch (with fitness 1 relative to the alternate allele with fitness  $1 - s$ ) but is reduced in frequency by migration from a source population (at rate  $m$ ). If selection is weak relative to migration ( $s < m$ ), the  $A$  allele fails to establish and the population in the patch remains locally maladapted. With stronger selection ( $s > m$ ), however, population differentiation can occur, with the  $A$  allele approaching a frequency of  $1 - m/s$  (Haldane (1930), who also considered diploidy and sex linkage; see also Yeaman and Otto (2011) for cases with bidirectional migration and drift). Empirically, these conditions are important because they indicate that population differentiation in the face of ongoing migration will typically not be comprised of small-effect alleles. Here, the strength of selection is critical; only alleles experiencing strong selection relative to migration are capable of being maintained and contributing to local adaptation in the face of gene flow (Griswold 2006; Yeaman and Whitlock 2011).

Another situation in which strong selection can behave qualitatively differently than weak selection is when the fitness surface is multi-peaked. The ability to traverse fitness valleys then depends critically on the strength of selection relative to other forces, especially the rate of recombination. For example, consider a population currently fixed for one gene combination ( $ab$ ) at two loci, where each single mutant is selected against (creating the 'fitness valley'), but where the double mutant ( $AB$ ) has highest fitness ( $W_{AB} > W_{ab}, > W_{Ab}, W_{aB}$ ). If selection is

weak relative to the recombination rate between the two loci,  $r$ , the fitness valley forms an insurmountable barrier, and the population remains fixed for  $ab$ . If selection is strong relative to recombination, such that  $W_{AB} (1 - r) > W_{ab}$  (or, in terms of selection coefficients,  $(s_{AB} - s_{ab}) / (1 + s_{AB}) > r$ ), then the favorable gene combination,  $AB$ , spreads (Bodmer and Felsenstein 1967). Thus, whether or not evolution is prevented from traversing a multi-peaked fitness surface depends on just how strong selection is, with strong selection being able to drive beneficial gene combinations through to fixation, despite the fact that these combinations are broken apart by recombination.

A related context in which the strength of selection matters involves hitchhiking of alleles linked to a site under selection. Maynard Smith and Haigh (1974) first tackled this question, assuming that a favorable allele spreads deterministically, having arisen on one particular genetic background. Considering a specific allele at a linked neutral site that initially co-occurs with the beneficial allele, they showed that hitchhiking in a haploid population causes a proportional reduction in the frequency of any other allele at this site by approximately:

$$\frac{r}{s} \log \left( \frac{1}{p_0} \right) \quad (2.7)$$

where  $r$  is the recombination rate between the selected and neutral site and  $p_0$  is the initial frequency of the selected allele in a haploid population ( $p_0 = 1/N$ ). This approximation assumes that selection is weak (again,  $s$  not much greater than 0.1) but greater than the recombination rate ( $r \ll s$ ). Importantly, equation (2.7) tells us that variation at linked neutral sites will be impacted whenever the recombination distance is small relative to the selection coefficient,  $s$ . Thus, what we might consider to be weak selection in an absolute sense ( $s \ll 0.1$ ) may still be strong selection when it comes to hitchhiking, as long as recombination rates are less than the selection coefficients. More sophisticated stochastic models have similarly shown that hitchhiking has a major impact on genetic variation and coalescence times only when selection is strong relative to recombination (Kaplan et al. 1989; Barton 1998). This is the underlying reason why genomic scans of selection based on unusual patterns of vari-

ation surrounding a site can only detect alleles of moderately strong effect.

Strong selection also affects the type of hitchhiking event that we should expect within a genomic region. The scenario considered by Maynard Smith and Haigh (1974) was of a beneficial allele that arose in only a single copy; the reduction in genetic variation at surrounding sites due to the spread of this allele is known as a 'hard selective sweep.' But if the environment changes and there are multiple copies of the beneficial allele when it first becomes favorable (i.e., there is standing genetic variation), then strong selection makes it more likely that more than one copy of the allele will survive loss while rare and contribute to adaptation (Hermisson and Pennings 2005). The co-fixation of distinct haplotypes bearing the favorable allele causes a so-called 'soft selective sweep.' Compared to hard selective sweeps, soft selective sweeps preserve more variation at neighboring sites, but they can also generate stronger patterns of linkage disequilibrium, extending further into surrounding regions, whenever the haplotypes are distantly related. Interestingly, one might also predict that strong selection would make it more likely to fix the same mutation if it recurred by chance after the sweep was underway, but the increased chance that such recurrent mutations would fix is almost entirely counterbalanced by the decreased amount of time taken until the sweep is over (Pennings and Hermisson 2006). Thus, strong selection has a large impact on how many alleles survive from the pool of standing genetic variation when the environment changes, but less impact on how many recurrent mutations get captured along the way.

A particularly negative consequence of hitchhiking with a favored allele is that less fit alleles at neighboring sites can rise in frequency and even fix (Barton 1995; Yu and Etheridge 2010; Hartfield and Otto 2011). Hitchhiking to fixation of deleterious alleles requires that selection for the favorable allele is even stronger relative to the recombination rate (compared to the case with one neutral and one selected site), because recombinant lineages that combine together the fittest alleles are especially likely to persist (Hartfield and Otto 2011). At the extreme of no recombination, deleterious alleles hitchhiking with favored alleles can cause a ratch-

eting decline in the fitness of an asexual lineage, which lacks recombination entirely, relative to a sexual population in the face of a changing environment, a decline that may eventually drive asexual lineages to extinction (Hadany and Feldman 2005).

In a related fashion, alleles subject to strong selection because of their effect along one particular phenotypic axis can drag along stronger pleiotropic side consequences with respect to other traits. For example, consider an environmental change selecting for a particular trait, such as increased temperature tolerance. An allele that slightly increased heat tolerance but had numerous pleiotropic effects on other characters is more likely to have a net deleterious effect on fitness and fail to spread. By contrast, an allele that strongly increased heat tolerance, and experienced a strong selective advantage in doing so, is more likely to spread, despite disrupting other features. Otto (2004) estimated that the selective advantage of such favorable alleles would, on average, be halved by negative pleiotropic side-consequences. Because organisms having experienced strong selection in the past may have changed along multiple dimensions, it might be difficult to determine the precise trait(s) that was positively selected. We see this with domesticated corn, for example, where the *tb1* allele that differentiates corn from teosinte accounts for phenotypic differences in a large number of traits, including seed shattering, cob size, and apical dominance (Doebley et al. 1995), making it difficult to know which character(s) was most directly under selection.

We end with one final example where strong selection differs in kind from weak selection, involving the Red Queen explanation for sex and recombination. With strong selection acting on genes mediating interactions between hosts and parasites, gene combinations that have been favored in the recent past can be currently prevalent but disadvantageous, selecting for sex and recombination to break apart these combinations. Such a mismatch between which gene combinations are prevalent and which gene combinations are fittest only really occurs, however, if selection is strong relative to the forces breaking apart genetic associations, such as segregation, recombination, and mutation (Gandon and Otto 2007). With weak

selection, host–parasite cycles are relatively slow, allowing enough time for genetic associations to re-equilibrate and erasing previously favored gene combinations (Otto and Nuismer 2004). Thus, an important open empirical question facing the Red Queen hypothesis is how often strong selection acts on the genes mediating host–parasite interactions.

## 2.4 Concluding thoughts

Evolutionary biologists live fairly comfortably with using the terms ‘weak’ and ‘strong’ selection without strictly defining what we mean. The reason for this vagueness is that the dividing line between strong and weak depends so much on the context. When we are concerned with whether the change in allele frequency due to selection is overwhelmed by drift or by mutation, what counts as ‘strong’ selection may still be exceedingly weak (e.g.,  $2s \gg 1/(2N)$  or  $2s \gg \mu$  with mutation rate  $\mu$ ). In contrast, when we approximate complicated equations in terms of simpler functions of  $s$  (e.g. using a Taylor series, as in equation (2.7)), our standards shift; now, selection only starts to wreak havoc with our approximations once the strength rises above, approximately, 0.1 (essentially because terms involving  $s^2$  may no longer be small relative to terms involving only  $s$ ). Finally, the strength of selection can qualitatively impact the outcome of an evolutionary process when selection is opposed by other processes, such as migration of a disfavored allele or recombination breaking apart favorable gene combinations. In these contexts, what defines strong selection is, by necessity, relative (e.g. relative to  $m$  or to  $r$ ).

Finally, regardless of where we might place the dividing line between strong and weak selection at the genic level, the correspondence to strong and weak selection at the phenotypic level is fuzzy. Strong selection at the phenotypic level might generate only weak selection on the underlying loci, if there are many alleles of similar effect and/or substantial environmental variation contributing to the phenotypic variation. Conversely, relatively modest selection at the phenotypic level could cause strong selection at the genic level, if a few underlying loci contribute the bulk of phenotypic variation.

Although applying a more stringent and consistent definition for the term 'strong selection' might seem appealing, Aldous Huxley was almost certainly right when he cautioned that 'Consistency is contrary to nature, contrary to life. The only completely consistent people are dead.'

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