Individual Variation in Inbreeding Depression: 
The Roles of Inbreeding History and Mutation

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ABSTRACT

We use mutation-selection recursion models to evaluate the relative contributions of mutation and inbreeding history to variation among individuals in inbreeding depression and the ability of experiments to detect associations between individual inbreeding depression and mating system genotypes within populations. Poisson mutation to deleterious additive or recessive alleles generally produces far more variation among individuals in inbreeding depression than variation in history of inbreeding, regardless of selfing rate. Moreover, variation in inbreeding depression can be higher in a completely outcrossing or selfing population than in a mixed-mating population. In an initially random mating population, the spread of a dominant selfing modifier with no pleiotropic effects on male outcross success causes a measurable increase in inbreeding depression variation if its selfing rate is large and inbreeding depression is caused by recessive lethals. This increase is observable during a short period as the modifier spreads rapidly to fixation. If the modifier alters selfing rate only slightly, it fails to spread or causes no measurable increase in inbreeding depression variance. These results suggest that genetic associations between mating loci and inbreeding depression loci could be difficult to demonstrate within populations and observable only transiently during rapid evolution to a substantially new selfing rate.

Natural selection can favor the evolution of self-fertilization in hermaphroditic plants and animals for several reasons, including reproductive assurance, local adaptation, and conservation of energetic resources (reviewed in Jarne and Charlesworth 1993). Fisher (1941) showed that a semidominant allele causing complete selfing but no loss in male outcross success or other fitness components has a 50% transmission advantage at low frequency and always spreads to fixation while leaving the mean population fitness unchanged. However, the reduced fitness of inbred individuals has long been recognized as a powerful selective force opposing the evolution of self-fertilization (Darwin 1876; Charlesworth and Charlesworth 1987). For example, Lloyd (1979) showed that the fate of a selfing allele depends on the relative fitness of a selfed zygote or the "inbred fitness": if selfing competes equally with outcrossing and is accomplished at a negligible cost in terms of male gametes, then the selfing allele is lost if the inbred fitness is <0.5 and spreads to fixation otherwise, leaving only complete selfing or complete outcrossing as evolutionarily stable endpoints. This threshold in inbred fitness is moved upward in the presence of biparental inbreeding (Uyenoyama 1986) or lowered male outcross success in selfers (Nagylaki 1976).

A drawback of Lloyd's and similar models is the assumption that the inbred fitness is an invariant parameter of a population. Lande and Schemske (1985) were the first to describe an explicit model of the joint evolution of selfing rate and inbreeding depression (defined as one minus the inbred fitness) within a population and found that a selfing mutation of large effect can create an evolutionary dynamic not predicted in previous studies. They argued that a rare allele causing complete selfing will eventually spread to fixation in an infinite population, regardless of inbreeding depression, if inbreeding depression is caused by partially recessive deleterious alleles maintained by mutation-selection balance. In such a population, some of the selfing lineages within an otherwise outcrossing population will become "purified" of most of their inbreeding depression because of their history of inbreeding. These selfing lineages will therefore be able to increase in frequency because their mean fitness will eventually exceed that of the outcrossing lineages, even though inbreeding depression may be substantial in the population as a whole. Holsinger (1988) verified this process in a simulation model, and Charlesworth et al. (1990) showed that even modifiers causing less than complete selfing can sometimes increase despite inbreeding depression in excess of 0.5. More recently, Uyenoyama and Waller (1991a,c) have presented further analytical treatment of these and related results, including the acceleration of this differential purging caused by genetic linkage between a mating system locus and an inbreeding depression locus. These models included two-locus dynamics that assumed that the selfing rate always equaled the proportional loss of male outcross success.
Common to each of these studies is the observation that, in a population with intermediate selfing rate, individuals will vary in their history of inbreeding and the more highly inbred individuals will carry fewer deleterious alleles. Because these individuals will also tend to carry fewer alleles favoring outcrossing, these outcrossing alleles will become statistically associated with the deleterious alleles still present in the more outcrossed individuals. This association, manifested as selection in favor of the selfing alleles, is not accounted for in Lloyd’s (1979) models.

Some workers have argued that this differential “purging” is sufficiently strong, even in the absence of any genetic linkage, to render the net inbreeding depression of a population virtually irrelevant as an agent in the evolution of mating systems. For example, the mean population inbreeding depression “is not appropriate for addressing evolutionary questions” (Campbell 1986, p. 239) and “is not a meaningful concept in its own right” (Campbell 1986, p. 232), or simply “doesn’t matter” (Holsinger, 1988). Instead, they have suggested that a more informative measure is the inbreeding depression of individual maternal parents, defined as one minus the mean fitness ratio of a self from that individual to a random outcross onto that individual. For example, Uenoyama et al. (1994) pose an empirical question they consider of paramount importance: “does the level of inbreeding depression differ among families that show different rates of self-fertilization?”

Variation among individuals in inbreeding depression is clearly a potential indicator of their variation in inbreeding history (whether or not an individual’s inbreeding history is under genetic control) and hence also of their variation in degree of purging. Variance in inbreeding depression among individuals may thus be an important indicator of those genetic associations hypothesized to control the outcome of evolution at mating system loci. Indeed, when variation among individuals in inbreeding depression is found in experimental studies, it is often attributed to variation in the history of inbreeding. For example, Ågren and Schemske (1993), in their study of the primarily selfing plants Begonia hirsuta and B. semiovata, found large variation among maternal plants in the fitness effects of inbreeding and hypothesized that such variation “is expected if plants differ in the number of recessive deleterious alleles that they carry, which in turn, should be influenced by their history of inbreeding.” This perception arises because it is well known that inbreeding depression in a population as a whole can be caused only by genes with some form of dominance (Crow and Kimura 1970) and it is natural to assume that the genetic causes of inbreeding depression at the individual level are the same as those at the population level.

For variation in inbreeding depression to be thus informative, however, the component due to variation in inbreeding history must be distinguishable from components caused by other factors. A potentially important other factor is simply random variation among individuals in the number of loci containing deleterious alleles, caused by a Poisson distribution in the number of new mutations per generation, regardless of the magnitude and dominance of the mutational effects (see Charlesworth et al. 1990, 1991).

Even variation at an entirely additive locus, in which the phenotype of the heterozygote is midway between the phenotypes of the homozygotes, will contribute to the inbreeding depression of an individual, even though the contribution of that locus to the mean population inbreeding depression is zero. To see this, assume for simplicity that fitness is determined by a single additive locus segregating for several alleles. At this locus, the average fitness of a genotype’s selfed progeny is simply the expected fitness of that genotype. The average fitness for that same genotype’s randomly outcrossed progeny is the average of that genotype’s expected fitness and the populational outcross mean. Genotypes with expected fitness greater than the mean outcross fitness in the population will therefore have a negative inbreeding depression, whereas genotypes with fitness lower than the outcross mean will have a positive inbreeding depression. For these reasons, the simple existence of genetic variation in any phenotype will cause variation in inbreeding depression, even if alleles act additively within loci and the mean inbreeding depression of the population in that phenotype is zero (refer to Table 1 for a general summary).

This theoretical article addresses three main questions. First, how much variation in inbreeding depression should exist in completely outcrossing or selfing populations? Second, how much variation in inbreeding depression is caused by random variation in inbreeding history versus mutation? Finally, are associations between mating system genotypes and inbreeding depression likely to be detectable experimentally?

We first calculate the distribution of inbreeding depression among individuals in an infinite population, genetically uniform for selfing rate and at mutation-selection equilibrium for deleterious recessive alleles. Surprisingly, we find in most cases that random genetic variation is the primary cause of inbreeding depression variation and the contribution of variation in family history of inbreeding is trivial in comparison and therefore not likely to be empirically detectable. We then show that genetic variation in alleles that act additively within loci can greatly increase the individual variation in inbreeding depression and obscure any relationship between the number of deleterious recessive alleles contained in an individual and its inbreeding depression.

Second, we allow a dominant allele that increases the selfing rate (but leaves male fertility unaltered) to spread through an initially outcrossing population at mutation-selection equilibrium while monitoring its ef-
factors on viability and individual variation in inbreeding depression. We find that if the modifier causes only a small increase in the selfing rate, its effect on the inbreeding depression variance is practically unmeasurable. If the allele causes a large increase in selfing rate, its effect can be greater but is transient because the allele spreads rapidly to fixation. If inbreeding depression is caused by a moderate mutation rate to alleles of small effect, the selfing allele causes very little increase in inbreeding depression variance regardless of its effect. Surprisingly, the small increase observed is due to an increase in inbreeding depression of the more inbred selfing genotype, due in turn to both lower viability of its selfed offspring and higher viability of its outcrossed.

MATERIALS AND METHODS

We construct two mutation-selection equilibrium models that share several simplifying assumptions. Mutations are assumed to be unconditionally deleterious and to occur at a fixed rate \( U \) per diploid genome per sexual generation. We denote the selection coefficient and dominance of a mutant allele \( a \), respectively, as \( s \) and \( h \), so that the viability of genotypes \( AA, Aa, \) and \( aa \) are, respectively, \( 1, 1 - h, \) and \( 1 - s \). To facilitate comparisons to previous work (CAMPBELL 1986; HOLSINGER 1988; CHARLESWORTH et al. 1990), we assume that mating system loci segregate independently of inbreeding depression loci, that selfing causes no change in total fecundity or the probability that an ovule will be fertilized, and that selfers experience no loss in male outcross success. The last assumption may apply in most angiosperm species that are highly or fully outcrossing and whose pollen-ovule ratios are on the order of 1000 (CRUDEN 1977). In plants, the selfing mutations we envision include those causing reduced stigma-anther separation within a flower (see GANDERS et al. 1985; RICK et al. 1979), increased temporal proximity of pollen presentation and stigma receptivity (see SCOEN 1982), or weakening of the self-incompatibility reaction. Our assumption of no simultaneous effect of selfing on ovule fertilization rate strictly excludes mutations causing delayed selfing of ovules not yet fertilized at the end of the period of stigma receptivity. Our separate analyses of these mutations, however, has shown that their effects on inbreeding depression variation differ little from the results reported here. Our assumption of no pleiotropic effect reducing male outcross success excludes mutations causing self-fertilization within a permanently closed flower whose pollen is inaccessible ("cleistogamy") or mutations causing lowered floral attractiveness. We currently are extending our studies to include modifiers with pleiotropic effects on male outcross success and have found that a positive effect of the selfing allele on male outcross success reduces the associations between the mating system locus and inbreeding depression loci, whereas a negative effect increases such associations.

We report results for dominant selfing alleles only, for ease of comparison with previous studies (e.g., CHARLESWORTH et al. 1990), and because the greatest associations between mating system loci and inbreeding depression loci occur under strong initial selection against the selfing genotype. Because recessive modifiers eventually increase more slowly, such selection greatly increases the probability that a recessive modifier will be lost to drift in a finite population (the same is true if these modifiers reduce male outcross success). We have replicated the results reported here, however, in the case of semidominant selfing modifiers (as analyzed in HOLSINGER 1988), whose effects on the inbreeding depression distribution differ only slightly from those of dominant modifiers.

Viability is assumed to combine multiplicatively across loci. Mating, mutation, and selection occur in that order in an annual species with discrete generations. We assume that net inbreeding depression in the population is caused by one of the two major classes of load alleles whose parameters have been empirically estimated in Drosophila melanogaster (MUKAI 1964, 1969; OHNISHI 1977). These studies yield minimum estimates of \( U \) for mildly deleterious mutations on the second chromosome pair from 0.01 to 0.4, and for the expression \( 1 - h \) from 0.090 to 0.061. In separate line-cross experiments, the mean dominance coefficient for new mutations was estimated to be \( h = 0.36 \) (MUKAI and YAMAZAKI 1968; MUKAI 1969; MUKAI et al. 1972). This yields estimates of maximum \( s \) ranging from 0.047 to 0.095. This is our class of partially recessive mildly detrimental mutations for which we assume \( s = 0.05, h = 0.35, \) and \( U = 1.0-5.0, \) summed over all chromosomes.

The genomic rate of mutation to lethal alleles in D. melanogaster has been estimated as 0.02 and is due to roughly 5000 loci producing lethal mutations at a per-locus rate of about \( 2 \times 10^{-6} \) (SIMMONS and CROW 1977). The flowering plant Arabidopsis thaliana has been estimated to contain roughly the same number of embryonic lethal-producing loci (JÜRGENS et al. 1991). In D. melanogaster, the harmonic mean dominance of lethal alleles is approximately \( h = 0.02 \) (SIMMONS and CROW 1977). This is our class of lethal highly recessive alleles for which we assume \( s = 0.95, h = 0.02, \) and \( U = 0.02-1.0. \) In

### TABLE 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype mean</th>
<th>Outcrossed progeny mean</th>
<th>Genotype inbreeding depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_A )</td>
<td>( y + x )</td>
<td>( y + px )</td>
<td>( 1 - \frac{y + x}{y + px} )</td>
</tr>
<tr>
<td>( A_a )</td>
<td>( y )</td>
<td>( \frac{2y + x(2p - 1)}{2} )</td>
<td>( 1 - \frac{2y}{2y + x(2p - 1)} )</td>
</tr>
<tr>
<td>( a_a )</td>
<td>( y - x )</td>
<td>( y - x(1 - p) )</td>
<td>( 1 - \frac{y - x}{y - x(1 - p)} )</td>
</tr>
</tbody>
</table>

The range of phenotypes is \( 2x \) and the frequency of the \( A \) allele in the population is \( p \). Notice that since \( 0 < p < 1 \), the inbreeding depression for \( A_A \) individuals is always negative, whereas that of \( A_a \) individuals is always positive. Inbreeding depression of the heterozygote is zero only if \( p = 0.5 \), and positive or negative if \( p \) is, respectively, \( > \) or \( < 0.5 \).
some runs we also postulate an additional class of additive mutations \((h = 0.5)\), which do not generate a net inbreeding depression in a population. For these alleles, we assume \(s = 0.05\) and \(U = 1.0 - 2.0\). Because plants lack a separate germ line and hence may often have higher per generation mutation rates than Drosophila, values of \(U\) greater than those measured for Drosophila were sometimes used. Values for additive mutations are speculative because of the lack of any empirical measures. However, the low recessivity of the average mild mutation in Drosophila could in principle be the result of a mixture of additive and recessive alleles.

**Kondrashov model:** We analyze the effects of variation among individuals in their history of inbreeding, which causes identity disequilibrium among loci (Haldane 1949; Weir and Cockerham 1975), by expanding on techniques originated by Kondrashov. For technical details, see Kondrashov (1985) and Charlesworth et al. (1990). This model assumes no variation in \(s\) and \(h\) among an infinite number of unlinked loci at which deleterious mutations occur. We generate a joint discrete probability distribution each generation: the frequency of individuals in the population containing \(n_1\) and \(n_2\) loci heterozygous and homozygous, respectively, for the deleterious allele, for all combinations of \(n_1\) and \(n_2\), each from zero to infinity. This is referred to as the load distribution, and any given \(n_1\) and \(n_2\) is referred to as the load class, which has a unique frequency at each stage in the life cycle each generation. At the start of each run, all individuals have zero mutations (i.e., the frequency of load class 0.0 is unity). Mutations are added each zygotic generation according to the Poisson probability distribution, selection is then allowed to occur, and binomial probabilities are calculated from the load distribution in the surviving parents to compute the load distribution in the zygotes the next generation. Outcrossed zygotes are assumed to contain no homozygous loci, and added mutations are assumed to occur only at loci not already containing a mutation in any individual in the population. Mutations are thus allowed to accumulate each generation until their frequency reaches a plateau at mutation-selection equilibrium, at which the load distribution is thereafter unchanging. Where no variation at a mating system locus occurs, we assume constant population selfing rate caused by any distribution of selfing rates among individuals.

Mean inbreeding depression in the population is defined as \(\delta = 1 - w_1/w_0\), where \(w_1\) and \(w_0\) are the population mean viabilities of selfs and outcrosses. Note that this definition uses the ratio of mean viabilities rather than the mean ratio across load classes. These two quantities will generally be close but not identical, and only the former is reported here. We iterate these equations until equilibrium is reached and then calculate the inbreeding depression for each load class with non-zero frequency among adults. This is done by calculating the load probability distribution and viability in selfed and outcrossed zygotes from adults in each load class. We then obtain the inbreeding depression probability distribution as the frequency of load class \((n_1, n_2)\) in adults for the unique inbreeding depression produced by that load class.

We report the ratio of variance to mean in number of loci \(n_1\) heterozygous for a deleterious allele as a measure of the importance of identity disequilibrium. If the population is random mating or completely inbred, then \(n_1\) will be Poisson distributed, with mean equal to variance. If the population is partially selfing and partially outcrossing, the variance in \(n_1\) will exceed the mean because some individuals will be highly homozygous (due to several generations of selfing) and others will be the product of random mating. Identity disequilibrium then produces a deviation from Poisson, which then causes the increased variation in individual inbreeding depression.

The same arguments apply to \(n_2\), the number of loci at which an individual is homozygous for a deleterious allele.

To uncover the effect of identity disequilibrium on the inbreeding depression distribution, we construct this distribution for two populations. The first is calculated from the equilibrium load distribution unaltered and the second from an artificial load distribution generated by the Poisson distribution with the same mean numbers of heterozygous and homozygous loci per individual as in the first. The difference between the two inbreeding depression distributions thus is due entirely to the identity disequilibrium present in the population at equilibrium.

To analyze the effect of a dominant allele \(M\), producing a selfing rate \(r'\) in genotypes \(MM\) and \(Mm\) at the mating system locus (at which genotype \(mm\) has selfing rate \(r\)), we calculate the load distribution separately for the three genotypes at this locus. The \(M\) allele is introduced as a heterozygote of frequency 0.001 into a uniform \(mm\) population at mutation-selection equilibrium. The load distribution of \(Mm\) at introduction is assumed equal to that of the \(mm\) genotype at equilibrium, which means that the frequency of \(Mm\) individuals within every load class is 0.001 at introduction. Although this assumption cannot be true in reality (because only one \(Mm\) individual exists at introduction), it is useful because any other load distribution would constitute an arbitrary genotypic association between the load loci and the \(M\) locus. In this study we are interested only in associations that develop after introduction, as a result of selection and the mating system.

To recalculate the genotype-specific load distribution each generation, we generate the load distribution in zygotes from each of the nine possible parental combinations at the \(M\) locus (three selfs and six outcrosses), add Poisson-distributed mutations as above, and incorporate the resulting mean zygotic viabilities into the population genetic recursion equations for the genotype frequencies at the locus. We report the mean inbreeding depression and its variance for each genotype at the adult stage \((MM, Mm, \text{and } mm)\) as the \(M\) allele spreads through the population and \(mm\) declines in frequency to 0.9, 0.8, and 0.1.

To investigate whether the strength of associations are affected by a stable mixed-mating polymorphism, we in some cases impose an arbitrary fecundity overdominance of 0.5 at the mating system locus. This creates an equilibrium mixture of mating types that differ in their selfing rate. We then construct the equilibrium inbreeding depression distribution for each genotype at the locus as described above. We then obtain the effect of variation at the mating system locus by comparing these distributions with that obtained in a separate population with selfing rate nonheritable and equal to the mean selfing rate in the polymorphic population. We generate the inbreeding depression distribution in this latter population with and without identity disequilibrium.

Any difference in the frequency of the \(M\) allele among load classes constitutes an "association" between the \(M\) locus and the load loci. Although there are in principle many ways to quantify such associations, we report only a potentially empirically measurable result of them: differences in viability inbreeding depression among genotypes at the \(M\) locus.

Results of the Kondrashov technique with fixed selfing rate were verified with the single-locus model (below) for selfing rates 0 and 1 and with Lande et al. (1994) for lethal alleles \((s = 1.0)\) and selfing rates in the full range. Equilibrium load parameters agreed with the single-locus model to within six significant digits for complete selfing and were almost equally close for complete outcrossing and \(h\) not close to zero. These minor differences are expected from the fact that no selection against completely recessive alleles can occur in the
KONDRAHOV model for a fully outcrossing population. Agreement was perfect with results of LANDE et al. (1994) in all comparisons. Results with two alleles segregating at the mating system locus were verified with CHARLESWORTH et al. (1990). Only minor discrepancies occurred, most likely because of a small methodological difference in their study (see RESULTS).

Single locus model: Because KONDRAHOV's method becomes computationally prohibitive for more than a single class of mutations and forces the assumption that the numbers of loci at which mutations occur are infinite for all classes, we use single-locus theory to find the mutation-selection equilibrium for two unequal groups of loci whose mutant alleles differ in selection coefficient and dominance. Because single-locus theory ignores identity disequilibrium, we analyze only the cases of complete outcrossing or selfing, for which identity disequilibrium is absent.

The inbreeding depression distribution is found by generating the distribution of number of loci heterozygous and homozygous in each of $10^{-5}$ individuals drawn from an infinite population. The total load of an individual is given by two random Poisson deviates, one for the heterozygous and the other for the homozygous load, for the two classes of mutant alleles. Mean number of heterozygous and homozygous loci (for input to the Poisson generator) are calculated as the product of the equilibrium heterozygote or homozygote frequency within a locus times the total number of loci at which the mutation occurs. Equilibrium frequencies are found for the case $r = 0$ by numerical extension of the zygotic equilibrium given by CROW and KIMURA (1970) to the adult stage. For the case $r = 1$, we generate the equilibrium with the singe-locus recursion equations presented in the APPENDIX. These are a generalization of the identity equilibrium model of LANDE et al. (1994) to handle mutations of arbitrary effect and make no assumptions about the proportions of load in the heterozygous and homozygous state. Inbreeding depression is then calculated directly for each of the $10^{-5}$ individuals.

RESULTS

Variation in inbreeding depression in completely outcrossing or selfing populations: Even in the absence of variation in inbreeding history, individuals could vary greatly in their inbreeding depression caused by all classes of mutations (Figure 1). Random variation was due to the assumption of a Poisson distribution of number of new mutations per generation, which resulted in a correlation between the variance and mean in number of mutations per individual at mutation-selection equilibrium. Self-fertilization increased both the proportion and the absolute number of mutant loci in the homozygous state, as well as the variance in these quantities. Hence, when a sufficiently large number of mutations could exist in the homozygous state (e.g., for mildly detrimental alleles), selfing tended to increase the variance in inbreeding depression (Figure 1b).

In contrast, when the potential number of homozygous loci was small (for recessive lethals) and inbreeding depression was moderate, selfing reduced the variance in inbreeding depression as it reduced the major heterozygous component of the load and its variance (Figure 1a). If a high mutation rate produced a high inbreeding depression, this effect was reversed. For example, if $U = 0.3$ to lethals, the mean and variance in inbreeding depression were 0.97 and 0.011 for $r = 0$ and 0.13 and 0.031 for $r = 1$. For any mutation rate higher than 0.15, inbreeding depression in an outcrossing population was high (>0.83) and had lower variance than in a selfing population. At $U = 0.15$, variances in inbreeding depression for $r = 0$ and 1 were nearly equal at 0.016 and 0.018 (with means 0.83 and 0.067).

The presence of purely additive mutations could produce large variation in inbreeding depression, even though these caused zero net inbreeding depression in the population. Individuals with a large number of mutations had a positive inbreeding depression because of the production of selfed offspring with low viability; individuals at the other extreme had negative inbreeding depression due to the production of selfed offspring with viability near 1 and outcrossed offspring with lower viability caused by expression of the mutations in the heterozygous state. Hence, any particular individual had nonzero inbreeding depression even though the total population viability of selfs was identical to that of outcrosses. Selfing had little effect on the variance in inbreeding depression due to additive mutations (Figure 1c).

The presence of additive mutations reduced the correlation between an individual's inbreeding depression and the number of recessive deleterious mutations contained in its genome (Figure 2). For example, in a completely selfing population, the coefficient of determination (the square of the correlation coefficient) dropped 82% when an additive load component was added to a lethal recessive complement of mutations and 21% when the additive component was added to a mildly detrimental partially recessive complement of mutations.

For any given number of recessive deleterious mutations in an individual, its inbreeding depression ranged widely (in some cases over 0.2 units) depending on the number of additive mutations it contained (Figure 2). This range could be increased indefinitely by increasing the genomic mutation rate to additive mutations (results not shown).

Variation in inbreeding depression in partially selfing populations with no variation at a mating system locus: In contrast to random genetic variation, identity disequilibrium for the most part had only a small effect on the inbreeding depression variance at a selfing rate of 0.5, which gave a near-maximum identity disequilibrium in all runs.

For lethal recessive mutations maintained by a genomic mutation rate of 0.02, the difference in the inbreeding depression distribution at $r = 0.5$ between populations with and without identity disequilibrium was too small to be visible in Figure 1d, and the variance fell negligibly. For a genomic mutation rate of 0.5, both total variance and the component due to identity disequilibrium (15%) were higher. This genomic muta-
Inbreeding depression distributions for different rates of self-fertilization. In a through c, the population is completely selfing or outcrossing; in d through f, the selfing rate is 0.5 and the distribution of inbreeding depression is presented with and without identity disequilibrium ("ID"). For clarity, histogram bars are not shown. Instead, the frequency of each class is plotted with a point representing the midpoint of the class. (a and d) Recessive lethals; (b and e) partially recessive mild detrimentals; (c and f) additive mild detrimentals. For lethal alleles (a and d) each point represents a discrete load class. For all other cases (b to f), each point represents a large number of pooled load classes. (a) For \( r = 0 \), mean and variance in inbreeding depression were 0.210 and 0.0412. Mean and variance in number of heterozygous loci per individual were both 1.03. For \( r = 1 \), mean and variance in inbreeding depression were 0.00929 and 0.00262. Mean and variance in number of heterozygous loci per individual were both 0.0385 and in number of homozygous loci per individual were both 0.000506. (b) For \( r = 0 \), mean and variance in inbreeding depression were 0.190 and 0.00577. Mean and variance in number of heterozygous loci per individual were both 56.1. For \( r = 1 \), mean and variance in inbreeding depression were 0.139 and 0.00757. Mean and variance in number of heterozygous loci per individual were both 1.93 and in number of homozygous loci per individual were both 9.17. (c) For \( r = 0 \), variance in inbreeding depression was 0.0118. Mean and variance in number of heterozygous loci per individual were both 78.0. For \( r = 1 \), variance in inbreeding depression was 0.0118. Mean and variance in number of heterozygous loci per individual were both 3.80 and in number of homozygous loci per individual 18.0. Mean inbreeding depression was zero in both cases. (d) With identity disequilibrium, the mean and variance in number of heterozygous loci per individual was 0.0786 and 0.0771 and...
Variance in inbreeding depression with and without identity disequilibrium was 0.00769 and 0.00679. Mean inbreeding depression was 0.160.

All four cases contained an additive class of mutations in which $s = 0.0123$ and 0.0121. Mean inbreeding depression was 0.

Inbreeding depression increased slightly with identity disequilibrium. This percentage approached zero as selfing rate approached 1.0.

For partially recessive mildly detrimental mutations maintained by $U = 1.0$, the variance in inbreeding depression increased slightly with identity disequilibrium and the proportion of total variance due to variation in inbreeding history was 0.13 (Figure 1c). For mild completely additive mutations and $U = 2.0$, the identity disequilibrium had no effect on inbreeding depression variance (Figure 1f).

**Variation at a mating system locus:** The small effect in number of homozygous loci per individual were both 0.000486. Variance in inbreeding depression with and without identity disequilibrium was 0.00470 and 0.00468. Mean inbreeding depression was 0.0179. (e) With identity disequilibrium, the mean and variance in number of heterozygous loci per individual was 26.5 and 170 and in number of homozygous loci 5.00 and 37.9. Variance in inbreeding depression with and without identity disequilibrium was 0.00769 and 0.00679. Mean inbreeding depression was 0.0160. (f) With identity disequilibrium, the mean and variance in number of heterozygous loci per individual was 59.7 and 433 and in number of homozygous loci 9.05 and 101. Variance in inbreeding depression with and without identity disequilibrium was 0.0123 and 0.0121. Mean inbreeding depression was 0.
of identity disequilibrium in these runs was not necessarily increased by the addition of genetic variation at a locus that controls selfing rate. In the absence of overdominance at the mating system locus, a dominant selfing allele (M) spread to fixation in an initially outcrossing population (uniformly mm) when the initial inbreeding depression was <0.5 or when the mutation caused a sufficiently large increase in selfing rate to compensate for the initial selection against the allele due to large inbreeding depression. A mutation causing complete selfing spread to fixation eventually regardless of the magnitude of inbreeding depression or of s, h, and U. These results are in agreement with previous authors (LANDE and SCHEMSKE 1985; CAMPBELL 1986; HOLSINGER 1988; CHARLESWORTH et al. 1990), except that in one case (see Table 3c) the time required for spread exceeded the span of observation in CHARLESWORTH et al. (1990), who then concluded that the allele failed to increase (Figure 6 in CHARLESWORTH et al. 1990).

Spread of the selfing allele caused variation in inbreeding depression among the three genotypes at the mating system locus but the magnitude and direction of this variation depended on the mutation rate, the dominance, and selection coefficient of the load alleles. In the absence of pleiotropic effects on male fertility, when the allele was introduced into an outcrossing population with low inbreeding depression caused by recessive, lethal alleles, load was purged rapidly and the selfing genotypes always had lower inbreeding depression than the outcrossing, due to higher viability of their selfed progeny (Figures 3 and 4, Table 2). If the inbreeding depression was caused by partially recessive mildly detrimental alleles, load was purged more slowly and the selfing homozygote tended to develop a higher inbreeding depression than the other two genotypes due to a higher viability of its outcrossed progeny and to a somewhat lower viability of its selfed progeny (Figure 5, Table 3a). Moreover, the total population inbreeding depression tended to increase immediately after introduction of the selfing allele (Figure 5).

For both types of mutation, both the rate of spread of the selfing allele and the magnitude of variation in inbreeding depression among the genotypes at the mating system locus decreased as the frequency of the M allele increased (Tables 2 and 3a).

For the partially recessive mildly detrimental case depicted in Figure 5 and Table 3a, the minimum sample size necessary to detect the difference in inbreeding depression between the two extreme genotypes, at mm frequency of 0.5, ranged from 70 families per genotype for r' = 1.0 in M– individuals to 900 families per genotype for r' = 0.1 in M– individuals, to reach a statistical power of 0.8, for a significance level of 0.05 in the absence of other sources of error, such as finite numbers of progeny assayed and environmental variation (ZAR 1984).

When a mutant allele causing a sufficiently large increase in selfing rate (and no effect on male outcross success) was introduced into an outcrossing population with high inbreeding depression, it generally produced greater variation in inbreeding depression than the above cases, and the selfing homozygote had the lowest inbreeding depression throughout (Tables 2 and 3). Immediately after introduction, the selfing homozygote was selected against strongly, decreased to very low frequency, and was rapidly purged to low inbreeding depression, which even became initially negative if h was sufficiently large and the mean fitness close to zero (Table 3b). The selfing homozygote, however, had only
Variation in Inbreeding Depression

Figure 4.—Trajectory of inbreeding depression due to lethals and its components. Shown are inbreeding depression and frequency of genotype mm (a), mean self viability (b), and mean outcross viability (c) for the three genotypes at the mating system locus, as the selfing allele M spreads. See Table 2a, $r' = 1.0$, for means and variances in inbreeding depression at three sampling times.

a small effect on the overall inbreeding depression distribution during this initial purging process unless $h$ was large, especially for large $s$ (result not shown, see Table 3b). When its inbreeding depression had fallen to a sufficiently low level, the selfing homozygote then increased in frequency and gained in inbreeding depression. This gain occurred because its contribution through outcrossed male gametes increased, resulting in a greater frequency of the heterozygote because of fertilization of mm individuals by M sperm. This in turn resulted in the production of MM individuals (by selfing of Mm) with high mean inbreeding depression because of their short mean inbreeding history. In any case, the variation in inbreeding depression among the three genotypes was greatest when the M allele had the lowest frequency and hence was least likely to be empirically observed.

For the recessive lethal case depicted in Table 2b, in which the complete selfing allele was introduced to a population with high inbreeding depression, the minimum sample size necessary to detect the large difference in inbreeding depression between the two extreme genotypes, at $M$ frequency of 0.5, was five families per genotype. Note, however, that the allele failed to spread if it caused a selfing rate of 0.4 or lower, and the period during which the allele was at an intermediate frequency, and therefore visible, lasted only a few generations.

If both alleles $M$ and $m$ were maintained in a stable equilibrium by fecundity overdominance at the $M$ locus, the final distribution of inbreeding depression in the population as a whole was nearly the same as for a population without any variation at this locus, with or without identity equilibrium. In the case of partially recessive mildly detrimental mutations, the variance in inbreeding depression remained constant regardless of the presence of variation at the mating locus (Figure 3). Here, the mean inbreeding depression was again greatest for the selfing homozygote because its increased homozygous load outweighed its decreased heterozygous load.

DISCUSSION

Our purpose was to investigate the causes of variation in individual inbreeding depression as a way of determining the conditions under which different inbreeding histories are likely to result in measurable differences among individuals in inbreeding depression. We calculated the distribution of inbreeding depression among individuals due to deleterious alleles at mutation-selection equilibrium in an infinite hermaphroditic population and during approach to equilibrium as the population evolved a new rate of self-fertilization. Although in nearly all cases we confirmed predictions of previous studies regarding equilibrium inbreeding depression and conditions of spread of selfing alleles, we uncovered previously unexamined dynamics of the inbreeding depression distribution among individuals.

How much variation in inbreeding depression should exist in completely outcrossing or selfing populations? As shown in Table 1, “inbreeding depression” at the individual level merely reflects genetic variation for fitness among individuals, even if alleles act additively within loci and the population inbreeding depression is zero.

In our simulations, the existence of alleles with additive effects on viability reduced the correlation between the number of recessive deleterious alleles contained in an individual and its viability inbreeding depression by as much as 82%. We do not imply that a population’s additive component of load is measurable, rather that
Inbreeding depression is shown for the three mating system genotypes MM, Mm, and mm, as the frequency of mm decreases to 0.9, 0.5, and 0.1. (a) The dominant selfing allele M is introduced at equilibrium to a fully outcrossing population whose inbreeding depression is 0.210, causing self-fertilization at a rate ranging among runs from 0.05 to 1.0 in genotypes MM and Mm. The outcrossing genotype mm decreases at a rate indicated by the number of generations passed since introduction of M. (b) The dominant selfing allele M is introduced at equilibrium to a fully outcrossing population whose inbreeding depression is 0.692, causing self-fertilization at a rate ranging among runs from 0.4 to 1.0.

This component alone can cause substantial inbreeding depression in an individual. Thus, the causes of inbreeding depression in an individual and in the population as a whole can be fundamentally different.

In a population genetically uniform for the selfing rate, our results showed that complete selfing may or may not cause greater variance among individuals in inbreeding depression than random mating. If inbreeding depression was caused by a small number of lethal recessive alleles, a completely selfing population had the lowest variance in inbreeding depression because of the simple fact that the great majority of individuals were completely purged of these alleles. A completely outcrossing population, in contrast, had a higher variance due to greater mean and Poisson variance in number of loci heterozygous for the lethals. As the lethal mutation rate increased, however, this effect was reversed when over seven lethals accumulated per individual in an outcrossed population and both the viability of selfed progeny and the variance in inbreeding depression approached zero. The maximum variance in individual inbreeding depression, over 0.04, occurred in a completely outcrossing population in the presence of a small number of lethal alleles.

If moderate inbreeding depression was due to a large number of mildly detrimental partially recessive alleles, completely selfing populations had higher inbreeding depression variance because purging was ineffective and the genomic mutation rate was necessarily higher (to give the same inbreeding depression), allowing the greater genotypic variance to persist across generations. If inbreeding depression variation was caused by additive alleles, its variance was independent of the breeding system.

**How much variation in inbreeding depression is caused by random variation in inbreeding history?** Clearly, the random occurrence of deleterious mutations can cause large variation in inbreeding depression among individuals even in the complete absence of variation in inbreeding history. Empirical documentation
Variation in Inbreeding Depression

FIGURE 5.—Trajectory of inbreeding depression due to mild partially recessive detriments and its components. Same data shown as in Figure 4. See Table 3a, $r' = 1.0$, for means and variances in inbreeding depression at three sampling times.

of variance in inbreeding depression thus is by no means a sufficient indicator of differences among individuals in their inbreeding history. In partially selfing populations containing no variation at a mating system locus and undergoing a moderate rate of mutation to deleterious alleles, variation among individuals in history of inbreeding made only a small contribution (10–15%) to the total variance in inbreeding depression.

If inbreeding depression was caused by a small number of recessive lethal alleles, the small size of this contribution was due to near-purging of these alleles from the population under even partial selfing. Inbreeding depression caused by a large number of slightly detrimental partially recessive alleles, subject to less efficient purging, differed only moderately in inbred and outbred individuals. In populations with uniform selfing rate of 50%, for instance, half the individuals will have an inbreeding coefficient of zero, and the remaining individuals will have an inbreeding coefficient of $\geq 0.5$ because of one or more generations of selfing. If load is partially recessive and inbreeding depression is moderate, substantial purging will have occurred only in individuals with high inbreeding coefficient after several successive generations of selfing, but these are only a small fraction of the total population. Thus, even in a partially selfing population, variation in inbreeding depression among individuals cannot be equated to variation in history of inbreeding.

Increased mutation rate, however, reduced the degree of purging with partial selfing and increased the component of inbreeding depression variance due to inbreeding history. This component was still only 15% at a genomic mutation rate of 0.5 to lethals but increased to near 100% for higher rates, for which nearly all individuals had inbreeding depression of essentially one. However, this appears to occur only with large inbreeding depression caused by lethal recessives, in populations with selfing rates at or close to the threshold for purging (~0.5 for most parameter sets) (see LANDÉ et al. 1994). Although sufficiently large mutation rates to lethals have yet to be directly measured in plants or animals (see KIMURA 1983; KLEKOWSKI 1984; KLEKOWSKI and GODFREY, 1989; WILLIS 1992), some plant species may meet this condition (e.g., large long-lived perennials such as Pseudotsuga menziesii) (SORENSON 1969, 1973; see also LANDÉ et al. 1994). Few species, however, will meet both conditions of high mutation rate to lethals and selfing rate greater than the purging threshold but still substantially less than one. Thus, for populations with intermediate selfing rates, the conditions under which variation in inbreeding depression can be attributed to inbreeding history are stringent and probably rarely met.

Are associations between mating system genotypes and inbreeding depression likely to be detectable experimentally? Previous work has shown that as a selfing allele spreads in an outcrossing population, associations can develop immediately between genotypes at the mating system locus and at viability loci. In contrast, we found that such associations were usually not likely to be observable under experimental conditions. Moreover, in some biologically realistic cases, these associations were not strong enough to prevent the highly selfing homozygote from developing the highest inbreeding depression. Associations sufficiently strong to be observed were also sufficiently strong to propel the selfing allele to rapid fixation and hence were observable only briefly.

If inbreeding depression exceeded one-half then the modifier spread only if it caused almost complete self-fertilization in the cases examined in which the viability of outcrosses was substantially greater than zero. If the selfing rate of the modifier was much less than one, the genetic associations generated between the inbreeding
Trajectories of mean and variance in inbreeding depression due to mildly detrimental partially recessive mutations

<table>
<thead>
<tr>
<th>r'</th>
<th>Variable</th>
<th>0.9</th>
<th>0.5</th>
<th>0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm</td>
<td>Mm</td>
<td>MM</td>
<td>mm</td>
</tr>
<tr>
<td>0.1</td>
<td>Mean δ</td>
<td>0.19</td>
<td>0.191</td>
<td>0.223</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.006</td>
<td>0.006</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Generations</td>
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<td>227</td>
<td>331</td>
</tr>
<tr>
<td>1.0</td>
<td>Mean δ</td>
<td>0.192</td>
<td>0.197</td>
<td>0.246</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
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<td>0.009</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Generations</td>
<td>19</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td>0.2</td>
<td>Mean δ</td>
<td>0.621</td>
<td>0.458</td>
<td>-0.59</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.032</td>
<td>0.076</td>
<td>0.648</td>
</tr>
<tr>
<td></td>
<td>Generations</td>
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<td>46</td>
<td>88</td>
</tr>
<tr>
<td>1.0</td>
<td>Mean δ</td>
<td>0.801</td>
<td>0.637</td>
<td>0.16</td>
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<td>0.108</td>
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<tr>
<td></td>
<td>Generations</td>
<td>46</td>
<td>50</td>
<td>54</td>
</tr>
</tbody>
</table>

The dominant selfing allele M is introduced at equilibrium to an outcrossing population, r = 0 (a and b) or 0.2 (c), whose inbreeding depression is 0.190 (a), 0.617 (b), or 0.809 (c), causing self-fertilization at the rates indicated. Mean fitness of the initial outcross population in b was 0.0067. In b the selection coefficient was increased to s = 0.3 to conserve computing time by reducing the mean number of deleterious alleles per individual. Results as in Table 2.

depression loci and the mating system locus were too weak to cause spread of the selfing allele. This is because crossing between selfing and outcrossing genotypes randomizes their genetic backgrounds, decreasing the mean difference in viability of selfed progeny among the three genotypes, and decreasing the potential for selfing genotypes to undergo greater purging.

When the modifier spread, we always found differences in inbreeding depression between selfing and outcrossing genotypes. However, because variation was high within each genotype, these mean differences would be almost impossible to detect in an experiment of reasonable size (see above). Our estimates of family numbers needed are very optimistic, because we ignored sources of variation that would be inevitable in any inbreeding depression experiment, such as finite numbers of assayed progeny or of sires per outcrossed family, environmental variation in viability, and variation in recessivity among deleterious alleles at different loci (JOHNSTON and Schoen 1995). That sampling or environmental effects can be large in inbreeding depression experiments is suggested by the large and negative inbreeding depression occasionally observed in individuals (due to chance low performance of their outcrosses) (see Johnston and Schoen 1995), which has compelled some workers to express individual inbreeding depression using a mathematical function that constrains all negative values to the interval [−1, 0) (e.g., Ågren and Schemske 1993). Large negative inbreeding depression occurred in our models only under enormous, additive or near-additive load (see below). As long as the mean population viability was not near zero, individuals rarely had inbreeding depression below −0.1. The large variance in individual inbreeding depression reported in some studies might not persist after correcting for the expected contribution from sampling error within finite progeny arrays.

We found two situations where variation among modifier genotypes in inbreeding depression was potentially detectable in a reasonably sized experiment: when inbreeding depression was caused by highly recessive alleles or by partially recessive alleles maintained by mutation rates so high as to reduce the viability of outcrossed progeny to near zero. If the equilibrium viability of the outcrossed population was substantially greater than zero, the variance in inbreeding depression generated by spread of the allele was unmeasurably small unless inbreeding depression was caused by highly recessive
lethal alleles and the selfing allele caused an increase in selfing rate greater than ~20%. This minimum rate of selfing was necessary again to prevent breakdown of the genetic associations. However, the greater the increase in selfing rate caused by the mutant allele, the faster it spread through the population: fixation occurred in tens of generations if the selfing rate of the mutant was 40% or more.

On the other hand, if inbreeding depression was again caused by partially recessive alleles but maintained by a moderate mutation rate, the dominant selfing allele created only moderate variation in inbreeding depression. Surprisingly, this was due to a higher inbreeding depression in the selfing homozygote. This occurred because this genotype produced selfed seed progeny of slightly lower viability (due to their higher inbreeding coefficient relative to selfed progeny of outcrossed parents) and outcrossed seed progeny of slightly higher viability (due to somewhat greater purging of the selfing genotype) than those of the other two genotypes. Thus, a standing distribution developed again in which selfing homozygotes on average had only moderate inbreeding coefficient and were only moderately purged due to recovery of new load each generation by their outcrossed male gametes. Only small quantitative changes in these results occurred when the polymorphism was maintained by fecundity overdominance at the mating system locus.

Previous studies have shown or suggested that selfing genotypes will exhibit greater inbreeding depression in the presence of sufficiently large heterozygote advantage at viability loci (e.g., UenoYama and Waller 1990b). Our last-described results show that this relationship can also occur where inbreeding depression is due to purely recessive mutational load and if a large component of that load is expressed in heterozygotes. Thus, greater inbreeding depression in more inbred individuals does not constitute evidence that overdominance is the cause of inbreeding depression.

Another practical difficulty arises from the fact that in partially selfing populations, associations will develop between inbreeding depression loci and loci that are entirely selectively neutral and have no effect on the selfing rate (OhTa and Cockerham 1974; Charlesworth 1991). These associations will lead to differences in inbreeding depression among genotypes at the neutral locus. The rare homozygote will generally have the lowest inbreeding depression, because it will be produced by selfing events more than the other genotypes and will therefore become more purged of deleterious alleles. The rare neutral allele will nevertheless fail to spread, because the heterozygote carries greater load as a result of being produced more by outcrossing than the other genotypes. Hence, lower inbreeding depression in a rare homozygote does not necessarily indicate true selection for the rare allele. These differences, however, are likely to be even less pronounced than among genotypes differing in selfing rate.

This study suggests guidelines for empiricists seeking to document selectively important genetic associations by observing differences among individuals in inbreeding depression. First, differences will be greatest in populations where genotypes at the mating locus are most reproductively isolated from each other. Isolation will occur if some genotypes produce very few outcrossed progeny, through either female or male function. Second, differences will be greatest in genotypes that differ greatly in their selfing rate. If mating modifiers have only small quantitative effects, their individual influence on the inbreeding depression distribution will be nearly impossible to observe. In principle, the combined action of a large number of modifiers of small effect can produce large variation in selfing rate. However, the contribution of such quantitative genetic variation to natural variation in selfing rate is poorly known (but see Domée 1981) and environmental effects can be extreme (e.g., Harding et al. 1974). Third, loci producing highly recessive deleterious mutations are likely to develop the strongest associations with mating loci. Lethal mutations are usually highly recessive (Simmons and Crow 1977) and expressed early in development (e.g., plant seed set and germination) (see Husband and Schemske 1995). Therefore, empirical studies should focus on populations exhibiting large genetically controlled variation in rate of self-fertilization and on the earliest observable stages in the life cycle.

Finally, we emphasize that we do not claim here that associations between selfing rate and inbreeding depression due to differential purging do not occur in nature. Lowered inbreeding depression in early fitness components has been demonstrated for highly selfing species and highly selfing populations within a single species (Husband and Schemske 1995). Our results show, rather, that such associations will be difficult to observe and quantify within a single population and their evolutionary importance relative to other fitness differences within the population will be therefore difficult to assess.

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APPENDIX

Single-locus recursion model. At a given locus, denote the frequency of the homozygous dominant, heterozygous, and homozygous recessive genotypes in adults D, 2H, and R. For fixed secondary selfing rate r*, the frequencies at this locus in the pre-mutation zygote population are

\[ D^* = r^* (L + H/2) + (1 - r^*) (1 - H - R)^2, \]

\[ H^* = r^* H/2 + (1 - r^*) (H + R) (1 - H - R), \]

\[ R^* = 1 - 2H^* - D^*. \]  

(A1)

If mutation occurs at the rate \( \mu \), with back mutation negligible, then the postmutation zygotic frequencies are

\[ D^{**} = (1 - \mu)^2 D^*, \]

\[ H^{**} = (1 - \mu) H^* + \mu (1 - \mu) D^*, \]

\[ R^{**} = 1 - 2H^{**} - D^{**}. \]  

(A2)
After selection, the frequencies in adults are

\[
D' = \frac{D^{**}}{\bar{w}},
\]
\[
H' = \frac{(1 - hs)H^{**}}{\bar{w}},
\]
\[
R' = \frac{(1 - s)R^{**}}{\bar{w}},
\]

(A3)

where \(s\) and \(h\) are the selection coefficient and dominance of the mutant allele and \(\bar{w}\) is the mean viability, equal to \(D^{**} + (1 - hs)2H^{**} + (1 - s)R^{**}\).

Mean inbreeding depression in adults is calculated assuming that all mutant alleles within a group of loci have the same selection coefficient and dominance, so that total viability is equal to the viability at a given locus, taken to the \(n\)th power, where \(n\) is the number of loci at which the mutants occur. The viability of an outcross and self is then found by deriving \(\bar{w}\), respectively, for \(r^* = 0\) and \(r^* = 1\), giving

\[
w_s = \left[\frac{(20 + H)h - D - H^2}{2}\right]s^2 - (2Dh + H)s + \left(\frac{1}{2}\right)s + 1\right]^n. 
\]

(A4)

and

\[
w_s = \left[\frac{(20 + H)h - D - H^2}{2}\right]s^2 - (2Dh + H)s + \left(\frac{1}{2}\right)s + 1\right]^n, 
\]

(A5)

where \(q\) is the adult frequency of the mutant allele at a locus, equal to \(H + R\).