

Modelling the impact of drift and population subdivision on inbreeding depression and heterosis

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ABSTRACT

We investigated theoretically the effects of drift and migration on the amount of inbreeding depression and heterosis caused by partially recessive deleterious mutations at a single locus. The analysis shows how inbreeding depression is expected to decrease as the population size becomes smaller and or the rate of inbreeding increases. In contrast, the amount of hybrid vigor expected following crosses between isolated finite populations increases with genetic drift. As expected, connections between populations increase the amount of inbreeding depression and reduce heterosis. Interestingly, our analysis shows how the population size and the level of gene flow determine which kind of mutations will contribute to inbreeding depression and heterosis.

INTRODUCTION

Inbreeding depression, the reduced genetic value of offspring from matings between relatives compared to offspring from random matings within the same population is routinely observed in both breeding programs and natural populations. A related phenomenon, known as hybrid vigor or heterosis arises among populations: mean phenotypes of progeny from crosses between populations often perform substantially better than the average of the parents (Falconer, 1981; Lynch and Walch, 1998). Inbreeding depression and hybrid vigor are generally viewed as two opposite facets of a same genetic mechanism. Two main theories were early proposed to account for these two phenomena. These are the overdominance and partial dominance hypothesis. Most research into this question provides support for the second hypothesis, *i.e.* that most inbreeding depression is caused by the expression of deleterious and partially recessive mutations in homozygous individuals. Conversely, hybrid

vigor arises because crosses between differentiated populations result in a net masking of the deleterious effects of these mutations in hybrids.

Both inbreeding depression and heterosis are important in relation to many basic issues in evolutionary biology as well as on a number of practical issues in agriculture and conservation biology. For example, the prediction and exploitation of heterosis are today the mainsprings of modern breeding. Second, conservation of domesticated and endangered natural populations must take into account the possible effects of either mating between relatives within population or cross-fertilization between populations. Finally, inbreeding depression is thought to be a prominent evolutionary factor shaping mating systems in plants (Darwin, 1876; Lande and Schemske, 1985; Charlesworth and Charlesworth, 1987) as well as behavioral mechanisms for avoiding mating with close relatives in animals (Thornhill, 1993). Consequently, there have been numerous theoretical studies quantifying the expected amount of standing inbreeding depression in natural populations under several genetic models and mating systems. However, most models of inbreeding depression assume that populations are of infinite size. Now, both breeders and conservation biologists mostly deal with populations of finite (and often small) size that may sometimes be connected from one another through (either artificial or spontaneous) gene flow (See however, Charlesworth *et al.*, 1992; Ronfort and Couvet, 1995; Bataillon and Kirkpatrick, 2000).

In this article we present results obtained by developing a model for inbreeding depression and heterosis that takes into account the effect of drift and population subdivision. We consider the partial dominance hypothesis only as its importance has generally been supported by empirical studies. We start by a quick review of the basic model underlying the prediction of inbreeding depression in a large infinite population. We then show how this simple model can be extended when drift or migration (or both) are involved.

MODEL AND RESULTS

General assumptions

We consider a single diploid locus. Each generation, mutation occurs from the wild type allele A to the deleterious allele a at a rate μ ; back mutation from a to A occurs at a rate ν . The relative fitnesses of the three genotypes AA , Aa and aa are denoted as 1, $1-hs$, $1-s$ respectively. s measures the selection against homozygotes for the deleterious allele ($s > 0$) and h the dominance of the deleterious allele ($h = 0.5$ implies additivity). We will assume that the deleterious allele is partially recessive, i.e. $0 < h < 0.5$. The frequency of the deleterious allele in the population is denoted x . Then, assuming that f defined as the proportional excess of homozygotes caused by inbreeding, measures the inbreeding rate in the population, the frequency of genotypes AA , Aa and aa are $(1-x)^2 + x(1-x)f$, $2x(1-x)(1-f)$ and $x^2 + x(1-x)f$ respectively.

Using these genotype frequencies, it is possible to compute the expected fitness of individuals following either a self- (w_o) or a cross-fertilization (w_x) event. An expression for the mean inbreeding depression, defined as the decline in fitness in individuals produced by selfing relative to the fitness of outcrossed individuals ($\delta = 1 - w_o/w_x$, Charlesworth and Charlesworth, 1987) can then be found:

$$\delta = \frac{x(1-x)s(1-2h)(1+f)}{2[1-x(1-x)2hs-x^2s]} \quad (1)$$

To measure heterosis, at least two different populations must be considered. For simplicity, we will assume that the fitness of the three genotypes, the mutation rates (μ , ν) and the inbreeding rate (f) are constant with respect to populations. Then, if x_i denotes the frequency of the deleterious allele a in population i , we can compute the mean genetic value of individuals produced by crossing either two individuals from the same population (w_w) or from two different populations (w_b). The amount of heterosis can then be measured as the increase in mean fitness of hybrid relative to the pure-bred individuals, i.e. $w_b/w_w - 1$. This yields:

$$Het = \frac{(1-2h)s(x_1 - x_2)^2}{2[1-sh(x_1 + x_2) - s/2(1-2h)(x_1^2 + x_2^2)]} \quad (2)$$

The mutation-selection model (Ohta and Cockerham, 1974)

Assuming an infinite population size, Ohta and Cockerham (1974) have shown that the frequency of a deleterious allele at mutation-selection equilibrium is $\hat{x} = \mu/[s(h+f-hf)]$. Replacing x in equation (1) gives the expression of the amount of inbreeding depression expected for a single locus in an infinitely large population at mutation-selection equilibrium, i.e.:

$$\delta_\infty = \frac{\mu(1-2h)(1+f)}{2(h+f-hf)} \quad (3)$$

Examining equation (3) shows that the level of inbreeding depression depends on h , f , and μ but is independent of the deleterious effect of the mutation (s). The reason is that selection holds alleles that are more deleterious at lower frequencies. In contrast, deleterious mutations that are more recessive (low h value) are more efficiently masked in the heterozygous state. They thus generate more inbreeding depression (Crow, 1970). Expression (3) also shows that the average inbreeding depression is expected to decline as the rate of inbreeding goes up (f). This result illustrates a well-known phenomenon, the purging process: because inbreeding generates additional mutant homozygotes, it increases the efficiency of selection against deleterious alleles (two copies of the deleterious allele are eliminated with each selective death, Ohta and Cockerham, 1974). The decline of inbreeding depression then

simply follows from the reduced frequency of the mutant alleles. From equation (2), we found that no hybrid vigor is expected under our assumptions, i.e. similar mutation and selection regimes will lead to equal frequency of the deleterious alleles in different populations of large infinite size ($x_1 = x_2 = \hat{x}$).

Mutation-selection-drift model

In a finite population, there are fluctuations in gene frequency from generation to generation. Although predictions for such changes in an individual population are difficult to obtain mathematically, the average behavior of allele frequency at equilibrium between mutation, selection and drift in a large number of populations can be predicted using diffusion approximations. Mean values of linear function of the deleterious allele frequency can thus be computed (Kimura, 1963).

For sufficiently large populations ($N > 1/2s$), Bataillon and Kirkpatrick (2000) have shown that the distribution of the deleterious allele frequency can be approximated by a beta distribution with mean \hat{x} and variance σ^2 (σ^2 is a function of N , s , h , μ , ν and f , see Bataillon and Kirkpatrick for a complete derivation). Computing the second order Taylor expansion of equation (1) around $x=0$ and taking its expectation over the beta distribution then gives the average inbreeding depression expected in such a population (Bataillon and Kirkpatrick, 2000). Similarly, the second order Taylor expansion of equation (2) and its expectation over the beta distribution allow to find the average amount of heterosis expected between two populations. We will assume that both populations are of size N and submitted to similar selection and mutation regimes.

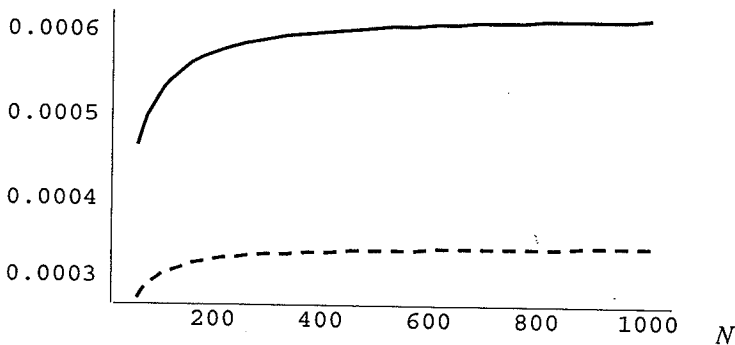


Figure 1. Inbreeding depression as a function of the population size and inbreeding coefficient. Full line : $f=0$; Dashed line: $f=0.2$. Mutation/selection parameters are: $\mu=0.0001$, $s=0.05$, $h=0.2$.

Figure 1 shows the effect of drift on inbreeding depression as computed following the above derivations (computations were done on the *Mathematica* software, version 3.0). As already shown and discussed in Bataillon and Kirkpatrick (2000), inbreeding depression

decreases as population size becomes smaller. For population sizes higher than about $5/hs$, the amount of inbreeding depression reaches its expected deterministic value. For smaller value of N , fluctuations in allele frequencies due to random drift progressively overwhelm the effect of selection. As a result, either the wild-type allele or the deleterious mutations may become fixed, reducing the chance of polymorphism in the population and hence the mean level of inbreeding depression. Figure 1 also shows that, as in the deterministic case ($N \rightarrow \infty$), inbreeding depression is a decreasing function of the rate of inbreeding. This means that the purging process still occurs in finite populations (as far as $N > 1/2hs$). This result contrasts with the well-known phenomenon that the mutation load increases with decreasing population sizes (Kimura *et al.*, 1963).

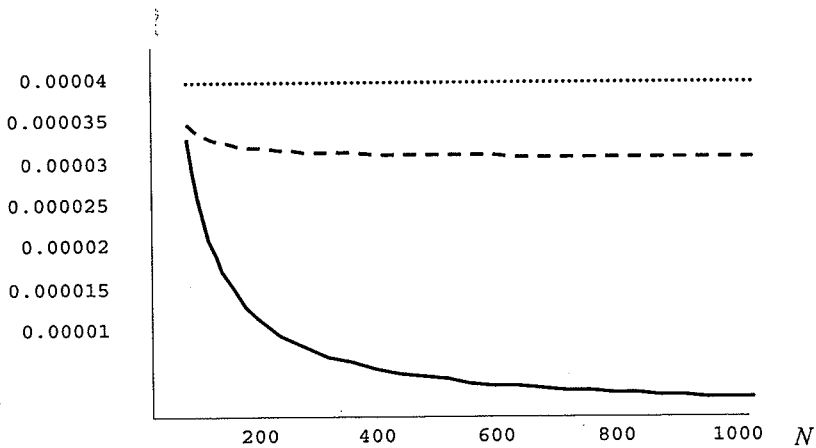


Figure 2. Hybrid vigor as a function of population size and inbreeding depression. Full line: $f=0$; Dashed line: $f=0.2$; dotted line: $f=1$ Mutation/selection parameters are: $\mu=0.0001$, $s=0.05$, $h=0.2$

As expected, the mean amount of heterosis expected in crosses among finite population shows the opposite behavior compared to inbreeding depression. Hybrid vigor always increases with drift (Fig. 2). In particular, a substantial heterosis is expected when the population number is lower than about $5/hs$. This result exemplifies how genetic drift might cause the frequencies of deleterious recessive alleles to vary among populations, resulting in a net masking of their effect in hybrids. Inbreeding also increases the expected amount of heterosis. For the selection regime assumed in figure 2, the amount of heterosis expected in a population of size N is always higher when the population is inbred. Opposite situations may however arise for highly recessive mutations (low h , data not shown).

Inter-connected populations

We wish to describe (1) the amount of inbreeding depression expected within population when this population is connected to another one through gene flow, and (2) the amount of heterosis expected in crosses between individuals from two populations that are

connected by some level of migration. To do so, we consider the infinite island model of population structure (Wright, 1951) : a infinite set of sub-populations, each consisting of N individuals that are submitted to similar mutation and selection regime (identical values for μ , ν , s , h). Populations have symmetric migration among them at rate m . Under this model, it is possible to use Wright's distribution of allele frequency at equilibrium between mutation, selection, migration and drift (Crow and Kimura, 1970). Just as in the preceding section, this distribution can be approximated by a beta distribution, with mean and variance that now also depend on the parameter m (Bataillon, 2000). Computing these moments shows that the distribution of allele frequency in a sub-population of size N , connected to a large number of other sub-populations by a rate of migration m is identical to the frequency distribution of an isolated population of size $N_e = N(1+m/hs)$. This result shows how gene flow may reduce fluctuations in allele frequency and thus increases the effective population size.

Figure 3 shows the expected behavior of inbreeding depression and heterosis as a function of the migration rate. As expected, the amount of hybrid vigor between connected populations decreases as migration increases. In contrast, inbreeding depression increases because migration re-injects some polymorphism at loci that would have been fixed otherwise. An interesting result however is that hybrids between populations interconnected by low to moderate levels of migration can have large positive heterosis, especially if the populations are small in size.

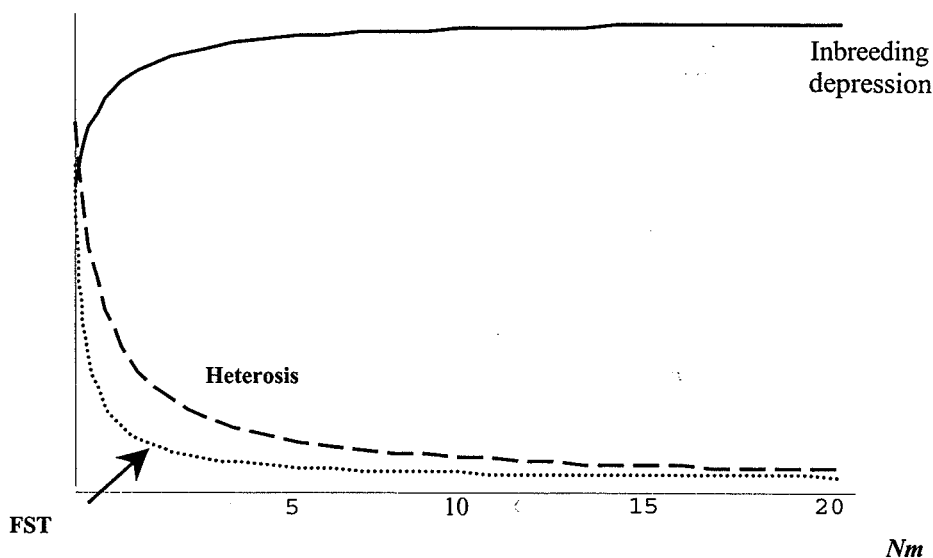


Figure 3. Heterosis and inbreeding depression as a function of the migration rate (Nm). Mutation/selection parameters are: $\mu=0.0001$, $s=0.05$, $h=0.2$; $N=50$.

DISCUSSION

It is well known that genetic drift reduces the polymorphism within population and increases the among populations variance in gene frequencies. Our analysis shows how this first effect reduces the mean amount of inbreeding depression expected in finite populations, while the second increases heterosis. Crow (1948) commented on this possible impact of genetic drift on hybrid vigor, however this mechanism was not mathematically examined at that time (see however the recent work of Whitlock *et al.*, 2000).

As already shown (Kimura *et al.*, 1963), the mutation-selection-drift model shows how population size determines a threshold value for the selection coefficient (s_{lim}) below which the effect of genetic drift overwhelmed the effect of selection. As a result, mutations with lower effect than s_{lim} are likely to be fixed and thus do not contribute to inbreeding depression (Bataillon and Kirkpatrick, 2000). As shown here, these mutations of small effects will however contribute to the amount of heterosis expected in crosses between plants from different populations. When the population size decreases, s_{lim} increases so that the range of mutations contributing to inbreeding depression (respectively heterosis) decreases (respectively increases).

Information on population size is thus of interest. It is common for the effective size to be an order of magnitude smaller than the census populations size, as a result of variance in reproductive success and fluctuation in population size over time (Frankham, 1995). For most species, effective population sizes may be 10^3 or smaller (Schoen and Brown, 1991). The amount of inbreeding depression due to mutations of small effect in large populations is thus likely to be eliminated by drift in small populations.

As expected, gene flow, by increasing the effective population size, has an inverse effect on both inbreeding depression and heterosis. Its effect however depends on the ratio between m and hs , i.e. the effect of migration is maximal for highly recessive mutations of small effect.

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