

# Selection, Load and Inbreeding Depression in a Large Metapopulation

Michael C. Whitlock<sup>1</sup>

*Department of Zoology, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada*

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## ABSTRACT

The subdivision of a species into local populations causes its response to selection to change, even if selection is uniform across space. Population structure increases the frequency of homozygotes and therefore makes selection on homozygous effects more effective. However, population subdivision can increase the probability of competition among relatives, which may reduce the efficacy of selection. As a result, the response to selection can be either increased or decreased in a subdivided population relative to an undivided one, depending on the dominance coefficient  $F_{ST}$  and whether selection is hard or soft. Realistic levels of population structure tend to reduce the mean frequency of deleterious alleles. The mutation load tends to be decreased in a subdivided population for recessive alleles, as does the expected inbreeding depression. The magnitude of the effects of population subdivision tends to be greatest in species with hard selection rather than soft selection. Population structure can play an important role in determining the mean fitness of populations at equilibrium between mutation and selection.

THE subdivision of species into local populations has been much studied, typically from the point of view of the differentiation of neutral allele frequencies or the adaptation of these demes to locally divergent conditions (FELSENSTEIN 1976; HEDRICK *et al.* 1976; HEDRICK 1986; BARTON 2001). Yet most loci must be under some selection, and arguably most selection must be largely independent of local conditions, because deleterious, loss-of-function mutations at most loci are likely to decrease fitness over a broad range of circumstances. For these classes of uniformly selected mutations, however, we have little population genetic theory appropriate for subdivided populations.

The subdivision of a species into spatially isolated populations affects the outcome of selection in several ways. Population structure engenders nonrandom mating, because organisms are more likely to mate with nearby individuals than those far away. This results in an excess of homozygotes relative to that expected under random mating. If an uncommon allele is less than completely dominant to a common allele, then this excess of homozygotes will allow a greater response to selection at this locus. More generally, with any deviation from additive gene action, the marginal effects of alleles will change as a function of their likelihood of expression as homozygotes. The effects of inbreeding within a population on the response to selection have been extensively studied (WRIGHT 1942; OHTA and COCKERHAM 1974; LANDE and SCHEMSKE 1985; CHARLESWORTH and CHARLESWORTH 1987; CABALLERO and HILL 1992; POLLAK and

SABRAN 1992; POLLAK 1995), but population structure introduces new complications. In particular, if alleles are clustered in space and if the absolute success of individuals depends on some locally limited resource, then the success of one individual will disproportionately affect the reproductive success of other individuals carrying similar alleles. Another way of saying this is that the genetic variance within a population tends to be reduced by local drift, such that the response to selection is lowered. Thus with population structure, the response to selection may be increased by the greater expression of homozygotes but decreased by the effects of local drift and local competition. BARTON and WHITLOCK (1997) briefly discussed the effects of population subdivision with soft selection on a locus with additive effects and found that the effects of population structure were relatively minor in this case. Here this model is extended to include arbitrary dominance and a broader range of population structures and modes of selection. Simple expressions for the response to selection, mutation load, and the inbreeding depression in structured populations are found. Population structure can have a large effect on these important quantities.

## CHANGE IN ALLELE FREQUENCY BY SELECTION

**Definitions and moments of the gene frequency distribution among populations:** Consider the case of a locus with two alleles, one fit and one somewhat deleterious. The frequencies of these alleles within deme  $i$  are given by  $p_i$  and  $q_i$ , respectively. For diploid individuals, the relative fitnesses of the three possible genotypes are given by 1,  $1 + hs$ , and  $1 + s$ , respectively. Assume for now that there is random mating within each deme such

<sup>1</sup>Address for correspondence: Department of Zoology, University of British Columbia, 6270 University Blvd., Vancouver, BC V6T 1Z4, Canada. E-mail: whitlock@zoology.ubc.ca

that the genotypes are present in local Hardy-Weinberg proportions. In this case, the local mean relative fitness is given by  $\bar{w}_i = 1 + 2hs\bar{p}_i q_i + s\bar{q}_i^2$ .

The overall change in the allele frequency of the metapopulation depends on the relationship between the mean fitness of a local population and its contribution to the next generation. Two extreme possibilities are typically considered: soft and hard selection (WALLACE 1968). With soft selection, each deme contributes to the next generation independently of its mean relative fitness, whereas with hard selection, its contribution is proportional to its mean relative fitness. It is possible to scale between these two extremes; we can scale the relationship between the genetic makeup of a deme and its contribution to the next generation by a linear function with slope  $b$ . Define  $N_i$  as the size of deme  $i$ ,  $N_{\text{tot}} = \sum N_i$ , and  $\bar{\bar{w}} = \sum \bar{w}_i N_i / N_{\text{tot}}$  as the mean fitness of all demes. If  $\psi_i = N_i / N_{\text{tot}}$  and  $\psi'_i$  are the proportions of all individuals in the current and following generations, respectively, contributed by deme  $i$ , we can write

$$\psi'_i = C_i \psi_i \left( 1 - b \left( 1 - \frac{\bar{w}_i}{\bar{\bar{w}}} \right) \right), \quad (1)$$

where  $C_i$  is genotype independent and reflects differences in the success of demes due to effects extrinsic to this locus, such as variation in the quality of the local environment or selection at other loci. Throughout this article, we assume that  $C$  is not correlated with  $\bar{w}$  or  $\psi$ , which means that the expected value of  $\psi'_i$  is  $w_i(1 - b(1 - \bar{w}_i/\bar{\bar{w}}))$  for all  $i$ . For simplicity of presentation, then, all subsequent equations of global change in allele frequency are given as expectations over the distribution of  $C$ , without explicit subsequent statement of this assumption.

Note that  $\psi'_i$  is defined as the contribution of deme  $i$  in this generation to the total number of individuals in the next generation. These individuals could still be in  $i$  or in any other deme. If  $b = 0$ , then we have soft selection, and all demes contribute to the next generation independently of their genetic fitness. In contrast,  $b = 1$  corresponds to hard selection, and the contribution of each deme is in proportion to its mean fitness.

The mean relative fitness of all individuals in the population can be calculated as

$$\bar{\bar{w}} = \sum_i \psi_i \bar{w}_i = 1 + s(2h\bar{q} + (1 - 2h)E[q^2]), \quad (2)$$

where  $\bar{q}$  is the mean across demes of  $q$  and the expectations are taken weighted by  $\psi$  (e.g.,  $\bar{q} = \sum \psi_i q_i$ , etc.). If we define  $F_{\text{ST}} = V[q] / \bar{p}\bar{q}$ , where  $V[q]$  is the variance among demes in allele frequencies, weighted by  $\psi$ , we can find the mean value of  $q^2$  across demes:

$$E[q^2] = V[q] + \bar{q}^2 = \bar{q}(F_{\text{ST}} + (1 - F_{\text{ST}})\bar{q}). \quad (3)$$

Note that this definition of  $F_{\text{ST}}$  as weighted by population size can differ from that often calculated by some definitions. With Equation 3, we can find

$$\bar{\bar{w}} = 1 + s\bar{q}(2h + (1 - 2h)(F_{\text{ST}}\bar{p} + \bar{q})). \quad (4)$$

We also need the expected value of  $q^3$ ,

$$E[q^3] = \bar{q}^3(1 - 3F_{\text{ST}} + 2\gamma) + \bar{q}^2(3F_{\text{ST}} - 3\gamma) + \bar{q}\gamma, \quad (5)$$

where  $\gamma$  is a standardized measure of the skewness of allele frequencies among populations. This  $\gamma$  is approximately equal to the probability that three alleles chosen at random from the same deme are identical by descent. As such it is approximately equal to the three-allele descent measure  $\gamma$  of COCKERHAM (1971; see also WHITLOCK *et al.* 1993). In general, we do not have theory to determine the value of  $\gamma$  for a wide range of theoretical models (see TACHIDA and COCKERHAM 1987 and WHITLOCK *et al.* 1993 for some examples). For the neutral island model, however, it is easy to determine from Wright's distribution that  $\gamma = 2F_{\text{ST}}^2 / (1 + F_{\text{ST}})$ . In general, the deviation of  $\gamma$  from the neutral island model expectation will often be small. (See the APPENDIX.) We can use this deviation to define a new identity disequilibrium coefficient that will have useful properties,  $\eta \equiv 2F_{\text{ST}}^2 / (1 + F_{\text{ST}}) - \gamma$ . Therefore we can write  $E[q^3]$  as

$$E[q^3] \cong (\bar{q}^3(1 - F_{\text{ST}})^2 + \bar{q}^2(3F_{\text{ST}}(1 - F_{\text{ST}})) + 2\bar{q}F_{\text{ST}}^2) / (1 + F_{\text{ST}}) + \eta\bar{q}\bar{p}(\bar{q} - \bar{p}). \quad (6)$$

**Hard selection:** With hard selection, demes are represented in the next generation in proportion to their average fitness. If we assume, as we do for the rest of this article, that the nongenetic determinants of the contribution of a deme ( $C_i$ ) are not correlated with allele frequency, then the expected change due to selection in the overall allele frequency is given by

$$\Delta_s \bar{q} = \frac{E[q(q(1 + s) + (1 - q)(1 + hs))]}{\bar{\bar{w}}} - \bar{q} \cong s(\bar{q}h + E[q^2](1 - h)) + \bar{q}(1 - \bar{\bar{w}}), \quad (7)$$

where the approximation holds for  $s \ll 1$ . Using Equations 2 and 3 and assuming that  $F_{\text{ST}}$  does not change on average with  $\bar{p}$ , we can find

$$\Delta_s \bar{q}_{\text{hard}} \cong \bar{p}\bar{q} s \mathfrak{d}_{\text{hard}}, \quad (8)$$

where  $\mathfrak{d}_{\text{hard}} = F_{\text{ST}} + (1 - F_{\text{ST}})(h(1 - 2\bar{q}) + \bar{q})$ . Hard selection is always more effective in a structured population than in an undivided population because of the increased expression of homozygotes, as long as  $h < 1$ . With pure hard selection, however, there is no effect of local competition among relatives; thus the response to selection is not discounted by relatedness.

Pure hard selection corresponds exactly to the case of inbreeding within an undivided population, as treated previously (CABALLERO *et al.* 1991), with  $F_{\text{ST}}$  used in place of the inbreeding coefficient in these equations.

**Soft selection:** The allele frequency will change over

one generation within a population as a result of soft selection as

$$\Delta_i q_i = q_i \frac{p_i(1 + hs) + q_i(1 + s)}{\bar{w}_i} - q_i. \quad (9)$$

If  $s \ll 1$ , then Equation 9 is well approximated by

$$\Delta_i q_i \cong q_i(1 - q_i)s(h + q_i(1 - 2h)). \quad (10)$$

Thus the expected value of the change in allele frequency over all demes is

$$E[\Delta_i q_i] \cong s(\bar{q}h + E[q^2](1 - 3h) - E[q^3](1 - 2h)). \quad (11)$$

Using the expected values of  $q^2$  and  $q^3$  from Equations 3 and 6 above, we can find

$$\Delta_i \bar{q}_{\text{soft}} = E[\Delta_i q_i] \cong \bar{p} \bar{q} s \vartheta_{\text{soft}}, \quad (12)$$

where

$$\vartheta_{\text{soft}} = \frac{(1 - F_{\text{ST}})}{(1 + F_{\text{ST}})} (F_{\text{ST}} + (1 - F_{\text{ST}})(h(1 - 2\bar{q}) + \bar{q})) + \eta(1 - 2h)(1 - 2\bar{q}).$$

When  $\eta$  is small,  $\vartheta_{\text{soft}}$  is therefore approximately equal to  $(1 - r)\vartheta_{\text{hard}}$ , where  $r$  is the relatedness of individuals within a deme [ $r \cong 2F_{\text{ST}}/(1 + F_{\text{ST}})$ ]. With soft selection, the efficacy of selection is reduced by competition among close relatives [reflected in the  $(1 - r)$  term]. Nevertheless, selection is also made more efficient for many values of  $h$  by increased expression of homozygotes. For rare recessive alleles, selection is more effective in subdivided populations than in unstructured ones, even with soft selection.

**Generalizing the hard-soft dichotomy:** The overall change in allele frequency is

$$\Delta_i \bar{q} = \sum(q'_i \psi'_i - q_i \psi_i) = \sum(\Delta_i q_i \psi_i + q'_i \Delta \psi_i), \quad (13)$$

where  $\Delta \psi = \psi' - \psi$  is the change in the contribution of the deme to the next generation, which arises as a result of selection at this locus. Using Equation 1, we can then write

$$\Delta_i \bar{q} = (1 - b)\Delta_i q_{\text{soft}} + b\Delta_i q_{\text{hard}} \quad (14)$$

or

$$\Delta_i \bar{q} \cong \bar{p} \bar{q} s((1 - b)\vartheta_{\text{soft}} + b\vartheta_{\text{hard}}) \equiv \bar{p} \bar{q} s \vartheta. \quad (15)$$

For rare alleles such that  $\bar{q}$  is small relative to either  $h$  or  $F_{\text{ST}}$  and negligible identity disequilibrium, this last term is approximately

$$\vartheta \cong (1 - F_{\text{ST}} + 2bF_{\text{ST}})[F_{\text{ST}} + (1 - F_{\text{ST}})h]/(1 + F_{\text{ST}}).$$

**Limitations:** These approximations have made a few assumptions, and their easy use requires a few more assumptions. Relatively standard assumptions have been made about the strength of selection, in particular that  $|s| \ll 1$ . To use the assumption that the neutral expecta-

tion of  $F_{\text{ST}}$  is sufficient to describe the  $F_{\text{ST}}$  of selected loci, then it must also be true that  $|N_i s| < 1$ . However, for the deterministic equations given in this article to suffice, it must be the case that the allele is not nearly neutral at the species level; *i.e.*,  $|N_{\text{tot}} s| > 1$ . Together these assumptions will require that the number of demes in the species is not small. It is likely that the violation of the weak selection assumption will not cause a qualitative change in the conclusions below, but certainly there will be quantitative deviations from the predictions as selection gets strong.

Perhaps most importantly, it has been assumed that the strength of selection is equal everywhere. Clearly, there is an important class of mutations that will vary not only in the magnitude but also in the direction of selection in different subpopulations. This variability in what is locally adaptive will clearly change the expectations of mutation load and inbreeding depression from those derived later in this article. Relaxing these assumptions represents a major challenge for future work.

#### MUTATION-SELECTION BALANCE

Now let us focus on deleterious mutations, such that  $s < 0$ . With weak mutation, the change in average deleterious allele frequency from one generation to another is given by

$$\Delta \bar{q} \cong \mu \bar{p} + \Delta_i \bar{q}, \quad (16)$$

where  $\mu$  is the mutation rate from the fit to less fit allele (see BARTON and WHITLOCK 1997). Thus at equilibrium, when the effects of mutation and selection are balanced, the frequency of the deleterious allele is on average approximately

$$\hat{q} \cong \frac{\mu(1 + F_{\text{ST}})}{-s(1 - (1 - 2b)F_{\text{ST}})(F_{\text{ST}} + (1 - F_{\text{ST}})h)} \quad (17)$$

(assuming that  $s^2$ ,  $\mu^2$ , and  $\hat{q}^2$  are all small). Thus for hard selection the equilibrium allele frequency is  $\mu/(-s(F_{\text{ST}} + (1 - F_{\text{ST}})h))$ , and for soft selection it is  $(1 - r)$  times that.

The frequency of a deleterious allele at equilibrium is likely to be much smaller in a subdivided population than in a panmictic population (see Figure 1). Selection is more effective in subdivided populations (*i.e.*,  $\hat{q}$  is lower) if

$$h < \frac{1 - F_{\text{ST}}(1 - 2b)}{3 - 2b - F_{\text{ST}}(1 - 2b)}. \quad (18)$$

With soft selection and low values of  $F_{\text{ST}}$ , this condition is  $\sim h < 1/3$ . With hard selection, for all values of  $F_{\text{ST}}$  (18) reduces to  $h < 1$ . Thus the frequency of deleterious mutations in a structured population is lower than for the same selection parameters in an undivided population for a broad range of dominance coefficients.

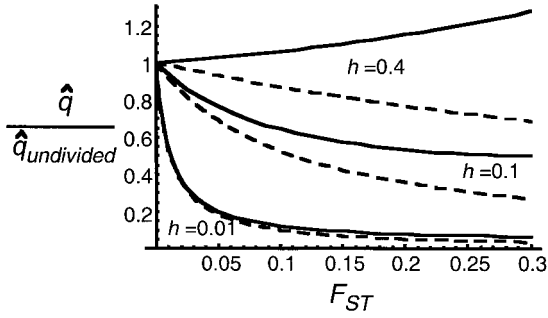


FIGURE 1.—The equilibrium value of the frequency of a deleterious allele can be substantially changed by population structure. Here the solid lines indicate pure soft selection, the dashed lines pure hard selection. With very recessive alleles, the equilibrium allele frequency is greatly reduced, relative to the case in an undivided population (where  $\hat{q} \cong -\mu/hs$ ). Parameter values used for these calculations were  $s = -0.1$ ,  $\mu = 10^{-6}$ , and the three lines correspond to  $h = 0.4, 0.1$ , and  $0.01$  from top to bottom.

MUTATION LOAD

The previous section has shown that under many circumstances, the frequency of deleterious alleles in subdivided populations is expected to be lower than in an undivided population. If alleles were taken at random from a subdivided species and crossed, the load calculated would likely be much smaller than that in an undivided population. It is more biologically relevant, however, to calculate the load in the context of the breeding system of the species, accounting for the nonrandom mating associated with population structure. In principle, the load can be increased in a subdivided population even if  $\hat{q}$  is lower, because of the increased expression of homozygotes. The load ( $L \equiv 1 - \bar{w}$ ) associated with a locus can be calculated using Equations 2 and 17, assuming that  $\hat{q}$ ,  $s$ , and  $\mu$  are all small, as

$$\begin{aligned}
 L &\cong \frac{(1 + F_{ST})(2h(1 - F_{ST}) + F_{ST})\mu}{(1 - (1 - 2b)F_{ST})(h(1 - F_{ST}) + F_{ST})} \\
 &= -(2h(1 - F_{ST}) + F_{ST})s\hat{q} \\
 &= \frac{\mu}{\bar{s}}(2h(1 - F_{ST}) + F_{ST}), \tag{19}
 \end{aligned}$$

which reduces to  $L = 2\mu$  as expected when  $F_{ST} = 0$ . The extent of the change in load can be dramatic, particularly with small values of  $h$  (see Figure 2). For hard selection, this reduces to the same result found (albeit with less approximation) by CROW and KIMURA (1970) for inbreeding.

Similar derivations as above find the load for a haploid population to be

$$L_{\text{haploid}} \cong \frac{\mu}{1 - (1 - b)F_{ST}}. \tag{20}$$

The haploid load thus is not changed by population subdivision with hard selection ( $L = \mu$ ), but with soft

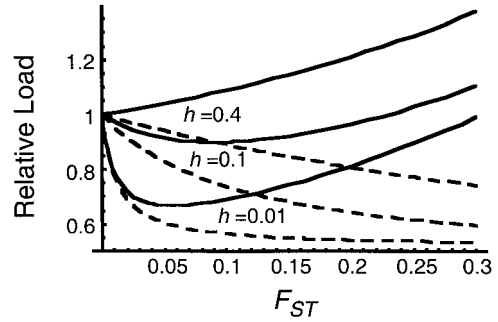


FIGURE 2.—The mutation load in a metapopulation relative to the load at a similar locus in an undivided population ( $\sim 2\mu$ ). For the values of  $F_{ST}$  likely to be found within species and relatively small values of the dominance coefficient  $h$ , the mutation load can be substantially reduced in a subdivided population. The solid lines show pure soft selection, while the dashed lines correspond to pure hard selection. Parameters for this example are  $s = -0.1$ ,  $\mu = 10^{-6}$ , and the three pairs of curves correspond to  $h = 0.4, 0.1$ , and  $0.01$  from top to bottom.

selection the load is increased by proportion  $1/(1 - F_{ST})$  with population structure.

Note that, as in most discussions of load, this definition of load does not predict the decline in the mean number of offspring per individual actually observed in a population, because under soft selection the mean number of offspring is assumed to be constant per deme, and even under hard selection the mean productivity is constant for the species. These calculations would give the mean deficit of the relative fecundity of individuals from this species in competition with an individual without deleterious alleles or a hypothetical sister species.

Also note that these calculations are derived from the equilibrium values in an infinitely large metapopulation. With finite metapopulations, there is a chance that deleterious alleles will fix in the population (and therefore contribute to drift load) or that deleterious alleles are lost. The mutation load due to segregating alleles in species with a relatively small number of individuals is likely to be different from the values given here.

INBREEDING DEPRESSION

For  $h < 1/2$  and  $s < 0$ , inbred individuals are likely to be less fit than relatively outbred individuals. This is because inbred individuals are more likely to express deleterious alleles as homozygotes than are outbreds. If organisms randomly chosen from a population are inbred such that their relative inbreeding coefficient is  $f$ , then their total inbreeding coefficient will be  $F_{\text{TOT}} \equiv 1 - ((1 - F_{ST})(1 - f))$ . The mean fitness of these inbred individuals is

$$\bar{w}_{\text{inbred}} = (1 - F_{\text{TOT}})(1 + 2\bar{p}\bar{q}hs + \bar{q}^2s) + F_{\text{TOT}}(1 + s\bar{q}). \tag{21}$$

The inbreeding depression,  $\delta$ , can be defined in several different ways, depending on the nature of the experiment (see JOHNSTON and SCHOEN 1994). One definition of inbreeding depression compares the reduction in fitness of experimentally inbred individuals relative to the average fitness of individuals mated randomly from individuals from the same deme; this definition would be appropriate for experiments that took samples from a single deme only. Let us call this  $\delta_1$ :

$$\delta_1 \equiv 1 - E\left[\frac{w_{\text{inbred}}}{w_{\text{outbred,within}}}\right]. \quad (22)$$

A second possible definition is that we might compare the average fitness of inbred individuals to the mean fitness of individuals outbred across all possible demes. In this case, the inbreeding depression (call it  $\delta_2$ ) would be given by

$$\delta_2 \equiv 1 - \frac{\bar{w}_{\text{inbred}}}{\bar{w}_{\text{outbred}}}, \quad (23)$$

where  $\bar{w}_{\text{outbred}}$  is the fitness of the experimentally outbred individuals.

With these simple definitions and using the approximation for  $\hat{q}$  in (17), the approximate value of  $\delta_1$  can be found. To approximate the value of an expectation of a ratio, we can use the formula derived in LYNCH and WALSH (1998, Appendix 1), which requires the variance of the denominator and the covariance of the numerator and denominator. These covariance terms require the expectation of  $q^4$ , which is unknown in most cases but can be found as above for the neutral island model from Wright's distribution (details not shown). After some algebra, the mean inbreeding depression can be found to be approximately

$$\delta_1 \approx -s f(1 - F_{ST})(1 - 2h)\hat{q} \quad (24)$$

(assuming  $s \ll 1$ ). Putting in the value of  $\hat{q}$  from above, the inbreeding depression for a given  $f$  is therefore changed in subdivided populations relative to undivided populations such that

$$\delta_{\text{structured}} \approx \frac{(1 - F_{ST}^2)h}{(1 - (1 - 2b)F_{ST})(F_{ST} + (1 - F_{ST})h)} \delta_{\text{unstructured}}. \quad (25)$$

The inbreeding depression due to a locus is thus lower in structured populations than undivided populations if

$$h < \frac{(1 - (1 - 2b)F_{ST})}{2(1 - b)(1 - F_{ST})}, \quad (26)$$

which for biologically relevant values of  $F_{ST}$  is true for all  $h$  ( $h < 1/2$ ) that give inbreeding depression. See Figure 3A.

When inbreeding depression is calculated using the mean fitness of experimentally inbred individuals relative to the mean fitness of individuals experimentally outcrossed randomly across the metapopulation, the mean fitness of inbred individuals is as above, and the mean fitness of these outbred individuals is  $1 + 2\bar{p}qhs +$

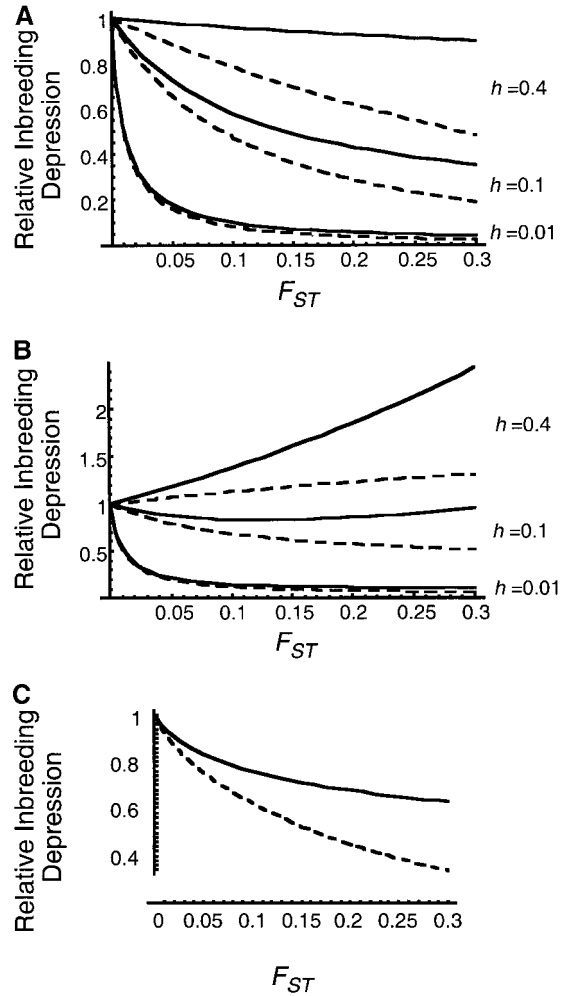


FIGURE 3.—The inbreeding depression expected in a subdivided population, expressed as a ratio of the inbreeding depression expected in an undivided species with the same genetic parameters. (A) The inbreeding depression, measuring the fitness of inbred individuals relative to other members of the same local populations ( $\delta_1$ ), can be much reduced by population structure if  $h$  is small. As in other figures, the parameters used to calculate these graphs were  $s = -0.1$ ,  $\mu = 10^{-6}$ , and the three pairs of curves correspond to  $h = 0.4, 0.1$ , and  $0.01$  from top to bottom. The solid lines show pure soft selection, while the dashed lines correspond to pure hard selection. (B) When inbred individuals are compared to individuals that are experimentally outbred to randomly chosen members of the whole metapopulation, the inbreeding depression ( $\delta_2$ ) can be much reduced by population structure or much increased, depending on  $F_{ST}$  and  $h$ . (C) Since the distribution of  $h$  is largely unknown, a first guess of the overall effect of population structure is made by assuming that  $h$  is uniformly distributed between 0 and 0.5. The relative inbreeding depression ( $\delta_1$ ) can still be substantially reduced by population structure.

$\bar{q}^2$ s. At mutation-selection balance, the inbreeding depression defined in this way is then approximately

$$\delta_2 \approx \frac{\mu(1 + F_{ST})F_{\text{TOT}}(1 - 2h)}{(1 - (1 - 2b)F_{ST})(F_{ST} + (1 - F_{ST})h)}. \quad (27)$$

By this standard, inbreeding depression will be lower

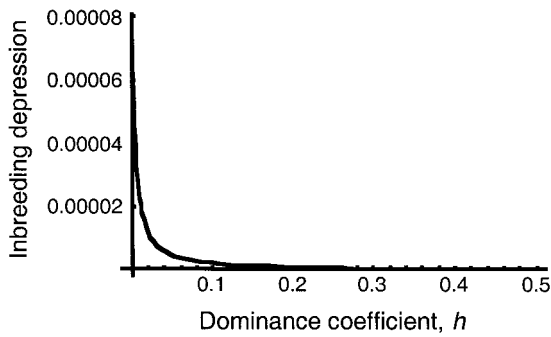


FIGURE 4.—The expected inbreeding depression due to a locus at mutation-selection balance, as a function of the dominance coefficient  $h$ . These values are calculated for an undivided population, with  $s = -0.1$  and  $\mu = 10^{-6}$ . Inbreeding depression is dramatically larger for values of  $h$  approaching zero.

in structured populations only for small values of  $h$ . See Figure 3B. This is important though, because loci with small values of  $h$  are responsible for a disproportionate fraction of inbreeding depression. Inbreeding depression is expected to be trivial for values of  $h$  near  $1/2$ , so most inbreeding depression due to recessive alleles is likely due to the subset of mutations that have small values of  $h$  (see Figure 4). It is exactly in this range in which population structure has the strongest effect (see Figure 3, A and B). If, as a starting guess, new mutations had a uniform distribution of  $h$  between 0 and  $1/2$ , then the reduction in inbreeding depression due to population structure can be dramatic (Figure 3C).

OVERDOMINANCE

With overdominance, heterozygotes are the most fit genotypes; therefore overdominance is another potential cause of inbreeding depression. Similar equations to those above can be derived to predict the evolution of overdominant loci in structured populations. With the fitness of each of the three genotypes defined as  $1 - s:1:1 - t$ , the mean fitness of a deme with allele frequencies  $p$  and  $q = 1 - p$  is  $\bar{w} = 1 - (sp^2 + tq^2)$ . Similarly, the expected overall mean fitness is given by  $\bar{\bar{w}} = 1 - (sE[p^2] + tE[q^2])$ . The expected change in  $q$  within a deme, assuming that mutation is weak relative to selection, is given by

$$\Delta_s q \equiv q' - q = q \frac{p + q(1 - t)}{\bar{w}} - q. \tag{28}$$

Taking the expectation of (28) assuming  $s, t \ll 1$  and using Equations 3 and 5, we get the change in allele frequency per generation with hard selection,

$$\begin{aligned} \Delta_s \bar{q} &= \frac{E[q(1 + tq)]}{\bar{\bar{w}}} - \bar{q} \\ &\cong tE[q^2] + \bar{q}(1 - \bar{\bar{w}}). \end{aligned} \tag{29}$$

Therefore

$$\Delta_s \bar{q}_{\text{hard}} = \bar{p}\bar{q}\bar{\xi}_{\text{hard}}, \tag{30}$$

where  $\bar{\xi}_{\text{hard}} = s(\bar{p} + F_{\text{ST}}\bar{q}) - t(F_{\text{ST}}\bar{p} + \bar{q})$ . With soft selection,

$$\Delta_s \bar{q}_{\text{soft}} = E[\Delta_s q] \cong \bar{p}\bar{q}\bar{\xi}_{\text{soft}}, \tag{31}$$

where  $\bar{\xi}_{\text{soft}} = (1 - r)\bar{\xi}_{\text{hard}} + (\bar{q} - \bar{p})(s + t)\eta$  and the approximation holds for  $s, t \ll 1$ , as above. Again, hard selection leads to larger average changes per generation in allele frequencies than does soft selection. To combine the soft-hard dichotomy,  $\Delta_s \bar{q} = \bar{p}\bar{q}((1 - b)\bar{\xi}_{\text{soft}} + b\bar{\xi}_{\text{hard}})$ .

Solving for an equilibrium and assuming small  $\eta$ , we can find the mean allele frequency

$$\hat{q} \cong \frac{s - tF_{\text{ST}}}{(s + t)(1 - F_{\text{ST}})}, \tag{32}$$

except in cases when this quantity is  $<0$  or  $>1$ , in which case the equilibrium is at 0 or 1, respectively. This condition implies that intermediate equilibria that are stable with random mating do not exist with population structure. This parallels results for inbreeding within populations, where fewer overdominant polymorphisms are stable (WORKMAN and JAIN 1966). The equilibrium allele frequency turns out to be independent of  $b$  if  $\eta$  is small; therefore it is indifferent to hard or soft selection.

Calculating the segregation load,  $L = 1 - \bar{\bar{w}}$ , gives

$$L = \frac{(1 + F_{\text{ST}})st}{s + t}, \tag{33}$$

which reduces to the segregation load in a panmictic population when  $F_{\text{ST}} = 0$  (CROW 1958). Therefore the segregation load is  $(1 + F_{\text{ST}})$  times as great in a subdivided population as in an undivided one, as expected by the increased number of homozygotes.

The inbreeding depression expected due to a locus with overdominant selection in a structured population can be calculated as above assuming  $\eta, s, t \ll 1$ , giving for  $\delta_1$  and  $\delta_2$ , respectively,

$$\delta_1 = f\hat{p}\hat{q}(1 - F_{\text{ST}})(s + t) \tag{34}$$

and

$$\delta_2 = F_{\text{TOT}}\hat{p}\hat{q}(s + t). \tag{35}$$

Therefore the inbreeding depression in subdivided populations due to overdominance is expected to be

$$\delta_{\text{subdivided}} = \frac{(s - tF_{\text{ST}})(t - sF_{\text{ST}})}{(1 - F_{\text{ST}})st} \delta_{\text{undivided}}, \tag{36}$$

for inbreeding depression measure 1 or approximately  $(1 - F_{\text{ST}})$  as large as in an undivided population for values of  $s \approx t$ . The equivalent ratio for  $\delta_2$  is the same, multiplied times  $F_{\text{TOT}}/f$ . Thus, for either of the most likely causes of inbreeding depression, overdominance or segregating deleterious recessive alleles, the inbreeding depression is expected to be somewhat lower in a subdivided population than in an undivided population with the same genetic parameters. However, the inbreeding depression due to deleterious recessives should be

much more reduced than that due to overdominance. The exception to this prediction is if there are many overdominant loci with very asymmetric homozygote fitnesses ( $s \neq t$ ), such that the internal equilibrium is lost with nonrandom mating and inbreeding depression due to the locus goes to zero.

### FINDING THE $F_{ST}$ OF SELECTED LOCI

The preceding calculations are useful only if we know the value of  $F_{ST}$  for selected loci. In general this is a difficult task, but for weak purifying selection the  $F_{ST}$  of loci that are under uniform selection may be closely approximated by the  $F_{ST}$  of a neutral locus under the same population structure. This can be quantified under Wright's island model, using Wright's distribution of allele frequencies among populations (WRIGHT 1937a,b). Assuming mutation to be weak relative to migration, we can find  $E[q^2]$  as

$$E[q^2] = \int_0^1 Cq^2 q^{4Nm\bar{q}-1} (1 - q)^{4Nm(1-\bar{q})-1} \bar{W}^{2N}, \quad (37)$$

where  $C$  is a constant of integration. If we assume that  $S \equiv -4Ns \ll 1$  (remembering that this  $N$  refers to the size of a local deme, not the species as a whole), then (37) can be solved analytically. Calculating  $F_{ST}$  and assuming that  $\bar{q}$  is small, we then get

$$F_{ST} \cong F_{ST,neutral}(1 - \sigma), \quad (38)$$

where  $F_{ST,neutral} = 1/(1 + 4Nm)$  and

$$\sigma = S \frac{3 + 8hNm}{(2 + 4Nm)(3 + 4Nm)}. \quad (39)$$

Thus for the assumed parameter range  $S \ll 1$ , the discrepancy between neutral and selected loci for  $F_{ST}$  will be negligible in the island model. The magnitude of this discrepancy can be seen in Figure 5 for a variety of examples. Numerical calculations show that even when  $S > 1$ , the neutral  $F_{ST}$  well predicts the  $F_{ST}$  for selected loci if  $|s| < m$  (Figure 5).

Similar calculations with overdominance show that if  $Ns, Nt \ll 1$ , then  $F_{ST}$  of selected loci will be closely approximated by a neutral  $F_{ST}$  if  $s, t < m$ . Here the assumption of uniform selection has been quite important. With balancing selection, locally variable selection, or frequency-dependent selection, or even relatively weak selection may potentially cause  $F_{ST}$  to deviate from its neutral expectation.

### LOCAL INBREEDING

So far, we have assumed that each local population mates at random. When this restriction is lifted, the alleles within an individual can be correlated relative to other alleles in the deme, which is reflected in Wright's local inbreeding coefficient,  $F_{IS}$ . In this section results are derived that allow for this local inbreeding.

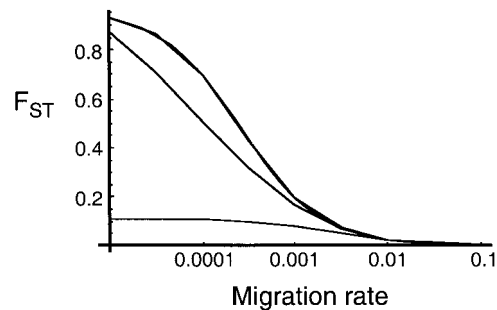


FIGURE 5.—The relationship between  $F_{ST}$  and selection in an island model. With Wright's distribution,  $F_{ST}$  can be calculated directly. The top curve on this graph is the value of  $F_{ST}$  as a function of migration rate for a neutral locus. Overlapping this line is a graph of the  $F_{ST}$  of a locus with two alleles, one of which is selected against with  $s = -0.001$ . In descending order, the other two lines have  $s = -0.01$  and  $-0.1$ , respectively. In all cases,  $N = 1000$  and  $h = 0.1$  with a forward mutation rate of  $10^{-5}$  and backward mutation of  $10^{-7}$ . The neutral  $F_{ST}$  predicts the  $F_{ST}$  of selected loci quite well as long as  $-Ns \leq 1$  or  $-s < m$ . Note that in the regions with the worst fit, the neutral  $F_{ST}$  is unreasonably large for conspecific populations.

With local inbreeding, each local population is not in Hardy-Weinberg proportions. The mean local fitness is then

$$\bar{w}_i = 1 + s[(1 - F_{IS})(2p_i q_i h + q_i^2) + F_{IS} q_i]. \quad (40)$$

Then the change in allele frequency among descendants of deme  $i$  is given by

$$\Delta q_i = \frac{q_i(F_{IS}(1 + s) + (1 - F_{IS})(q_i(1 + s) + p_i(1 + hs)))}{\bar{w}_i} - q_i. \quad (41)$$

Using the same formulas for the moments of the allele frequency distribution as above, we can get the expected change in mean allele frequency over the whole system,

$$\Delta \bar{q} = \bar{p} \bar{q} s \left( bh' + (1 - b) \left( \frac{1 - F_{ST}}{1 + F_{ST}} (h' + F_{IS} F_{ST}) + \eta(1 - 2h)(1 - 2\bar{q})(1 - F_{IS}) \right) \right), \quad (42)$$

where

$$h' = F_{IT} + (1 - F_{IT})(h + q - 2hq),$$

and

$$F_{IT} = 1 - (1 - F_{ST})(1 - F_{IS}),$$

as defined by Wright. Keep in mind that the addition of local inbreeding is likely to decrease the local effective population size and therefore increase the equilibrium value of  $F_{ST}$ , so the  $F_{ST}$  value in (42) is not constant with changing  $F_{IS}$ , all else being equal.

These equations match those from CABALLERO *et al.* (1991) and OHTA and COCKERHAM (1974) for the case of local inbreeding within an undivided population. With hard selection, the only effect of population struc-

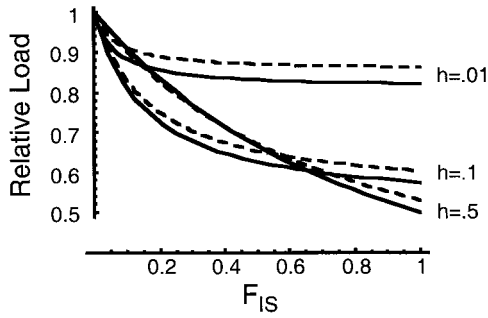


FIGURE 6.—The effect of  $F_{IS}$  on mutation load. In these examples, the  $F_{ST}$  is held constant at 0.05, ignoring the fact that for a constant demography,  $F_{ST}$  will be increased somewhat by increased  $F_{IS}$ , all else being equal. The  $y$ -axis is the load relative to the case of  $F_{IS} = 0$  (but unlike other graphs,  $F_{ST} = 0.05$ ). The solid lines correspond to soft selection, while the dashed lines plot hard selection. The mutation load can be substantially decreased by recurrent local inbreeding.

ture is a contribution of  $F_{ST}$  to the total inbreeding coefficient term. With soft selection, however,  $F_{ST}$  also affects the change in allele frequency by selection by affecting local competition, which is unlike the effects of  $F_{IS}$ .

For deleterious mutations ( $s < 0$ ) at an equilibrium between mutation and selection,  $\bar{q} \ll 1$ . Making this assumption, we can solve for the equilibrium frequency as above, and find

$$\hat{q} \cong \frac{\mu}{-s\vartheta}, \tag{43}$$

where

$$\begin{aligned} \vartheta = & b(F_{IT} + (1 - F_{IT})h) + (1 - b) \\ & \times \left( \frac{1 - F_{ST}}{1 + F_{ST}} (F_{IS}F_{ST} + F_{IT} + (1 - F_{IT})h) + \eta(1 - 2h)(1 - F_{IS}) \right). \end{aligned} \tag{44}$$

To find the mutation load, we want the mean fitness of the population given the mating system. In that case the mutational load is given by

$$L = 1 - \bar{w} = 1 - (1 + s[(1 - F_{IT})(2\bar{p}\bar{q}h + \bar{q}^2) + F_{IT}\bar{q}]). \tag{45}$$

Putting in the equilibrium allele frequency from above, we can find

$$L = \frac{\mu}{\vartheta}(1 - (1 - F_{IT})(1 - 2h)) \tag{46}$$

(to leading order in  $s$ ). Note that with population structure or local inbreeding, the load is a function of  $h$ , which does not drop out as in the random mating case. See Figure 6.

### DISCUSSION

**Efficiency of selection:** Many if not most species are to some extent subdivided into local populations, in

which individuals are more likely to breed and/or compete with nearby individuals, who are more likely to be related to each other than are randomly chosen members of the species. These simple facts change the way in which even the simplest selection acts to affect allele frequencies, mutation load, and the inbreeding depression that might result. With locally biased mating, the additive genetic variance within populations tends to be reduced for additive alleles but can be increased with rare recessive or overdominant alleles (ROBERTSON 1952; TACHIDA and COCKERHAM 1987, 1989; WHITLOCK *et al.* 1993; WILLIS and ORR 1993). Selection within populations therefore tends to be less effective in changing the frequencies of additively interacting alleles but can be more effective for rare recessive alleles. The genetic variance among populations and the total genetic variance in the species tend to increase with population structure, for the same overall allele frequency. Therefore, even with additively acting alleles, if populations are allowed to vary in their contribution to the next generation (as it would be in the case of hard selection), then a structured population will have more efficient response to selection than a panmictic one. The balance between these two effects—the change (up or down) in the response to selection within populations and the increase in efficiency of selection among populations—gives the overall effect of population structure on the change in allele frequency due to selection. Whether  $\Delta q$  is greater or less than expected in a panmictic population depends on whether individuals from different demes compete for resources (hard *vs.* soft selection), what the dominance relationships are between alleles, and the extent of genetic differentiation among populations.

For recessive alleles, the difference in response to selection can be substantial, even for relatively weak population structure. This difference is due largely to a change in the typical pattern of expression of the recessive alleles. With local mating, rare alleles are more likely to be expressed as homozygotes, and therefore the response to selection on recessive alleles will be in proportion to their homozygous effects rather than their weaker heterozygous effects. For hard selection, the change in the effects of selection and its consequences to load and inbreeding depression turn out to be exactly as would be expected from treating the nonrandom mating as a form of inbreeding (as in, for example, WORKMAN and JAIN 1966; CROW and KIMURA 1970; OHTA and COCKERHAM 1974; LANDE and SCHEMSKE 1985). With any soft selection, the resulting competition among relatives causes population structure to have unique effects.

**Genetic load:** Since HALDANE (1937) and MULLER (1950) proposed that the mean fitness of a population might be substantially reduced by “our load of mutations,” a great deal of argument has tried to resolve whether the rate of mutation to deleterious alleles is



sufficient to cause the mean fitness of populations to be dangerously low (CROW and KIMURA 1964; CROW 1993; LYNCH *et al.* 1999).

If the genomic mutation rate to deleterious alleles is represented by  $U$ , then the mutation load due to partially dominant, multiplicatively interacting deleterious mutations in a large panmictic population is expected to be  $1 - e^{-U}$  (CROW 1993). Thus if the genomic mutation rate approaches unity or higher (see EYRE-WALKER and KEIGHTLEY 1999; LYNCH *et al.* 1999), the mutation load could be quite large (*e.g.*, 63% for  $U = 1$ ; 93% for  $U = 2.7$ ). This has led to the exploration of various deviations from these basic assumptions, as this load is thought to be too large to be borne by many species. In particular, a great deal of attention has been paid to the idea that deleterious mutations might interact synergistically, so that the rate of loss of fitness increases as the number of mutations goes up. While it is true that synergistic epistasis can significantly reduce mutation load in theory (KIMURA and MARUYAMA 1966; KONDRASHOV and CROW 1988), there is little empirical support for the hypothesis that deleterious mutations interact in this way consistently (WHITLOCK and BOURGUET 2000 and references therein). Others suggest that load may be reduced by intraindividual selection (OTTO and ORIVE 1995) or sexual selection (WHITLOCK 2000). It may be that reproductive excess in resource-limited populations is sufficient to allow for substantial load without extinction (WALLACE 1991). It is also possible that for most organisms the genomic deleterious mutation rate is not so large (GARCÍA-DORADO *et al.* 1999). CROW and KIMURA (1970) showed that the expected load at equilibrium with inbreeding can be reduced. Added to these explanations now is the hypothesis that a substantial amount of the possible genetic load may be eliminated by population structure. New analyses and experiments show that new mutations tend to be recessive with a mean dominance coefficient in the area of 0.1–0.2 (HUGHES 1995; HOULE *et al.* 1997; GARCÍA-DORADO and CABALLERO 2000). In this range, the mutation load can be markedly reduced by even mild population structure, especially under hard selection.

A striking difference caused by population structure in the results for load is that the mutation load contributed by a locus is no longer independent of the genetic details of that locus. In particular, the dominance coefficient is now an important determinant of the mutation load, unlike the random mating case. Recessive alleles are likely to contribute less than codominant ones to the total mutation load.

The reduction in the overall frequency of deleterious recessive alleles and the expected decrease in the mutation load experienced by a subdivided population have much in common with the phenomenon of purging in bottlenecked or inbred populations. In bottlenecked or inbred populations, there can be a temporary reduction in the mutation load (BARRETT and CHARLESWORTH

1991; BYERS and WALLER 1999; WANG *et al.* 1999; BATAILLON and KIRKPATRICK 2000; KIRKPATRICK and JARNE 2000), although experimental results are mixed (BYERS and WALLER 1999; FOWLER and WHITLOCK 1999). These reductions in load are temporary, however, as mutation continues to increase load until it is returned to prebottleneck levels (KIRKPATRICK and JARNE 2000). In structured populations, however, purging is possible because of the increased expression of homozygous individuals, but the effect is not temporary because the populations continue to be somewhat interconnected. New variation is brought into each population by migration, so the purging does not stop as it does in inbred lines. [This effect is similar to the pattern observed by WANG (2000) with alternate outcrossing and full-sib mating.] The deleterious allele frequency is therefore allowed to reach a different equilibrium, with fewer deleterious alleles and potentially a lower mutation load than in an undivided population.

The maximum reduction in load is by a factor of one-half (with hard selection and nearly completely recessive alleles). This reflects the fact that in this case, most individuals that die a selective death are homozygotes, taking two deleterious alleles from the population for each selective death. Genetic load is a simple function of the number of individuals dying selective deaths and the number of deleterious alleles that die with them (KONDRASHOV and CROW 1988). If the number of alleles removed by each selective death could be doubled, then the genetic load is halved, as is almost the case in this example.

With overdominance and segregation load, however, the situation is reversed. Here the extra homozygosity caused by population structure results in a greater deviation from the maximum mean fitness, with an increase in load in proportion to  $F_{ST}$  (see Equation 33). This change in segregation load is surprisingly independent of whether the population experiences soft or hard selection. The relationship between load in subdivided and undivided populations is therefore likely to depend on whether mutation load or segregation load is more important.

It is important to note that the changes in genetic load that accompany population structure are not immediate. A previously undivided species that is suddenly subdivided will not change immediately to have a lower frequency of deleterious alleles, but it will quickly come to have a higher homozygosity. As a result, a newly formed metapopulation will be expected to have some inbreeding depression and a lower fitness than either an undivided species or a metapopulation at equilibrium. Therefore, for example, the fragmentation that results from human impact on the landscape is likely to have deleterious effects in the short to medium term.

**Inbreeding depression:** Inbreeding depression is likely due to a combination of the expression as homozygotes of rare recessive alleles maintained by mutation-

selection balance and a reduction in the number of overdominant heterozygous loci. These two patterns are called the dominance and overdominance models, respectively. With the dominance model, inbreeding not only reduces fitness but also allows the population to purge deleterious alleles to some extent, such that subsequent inbreeding may not display as much inbreeding depression (LANDE and SCHEMSKE 1985; BYERS and WALLER 1999; BATAILLON and KIRKPATRICK 2000; WANG 2000). Overdominance depends on the presence of two (or more) alleles in the population, and the equilibrium allele frequency maximizes fitness in a panmictic population. Therefore purging is not possible with overdominance, and inbreeding can only reduce fitness, both immediately and ultimately. Therefore experimental metapopulations with hard selection will be a useful way of discriminating between the dominance and overdominance models of inbreeding depression. An experiment that artificially created metapopulations with hard selection from a previously undivided species should, at equilibrium, show much reduced inbreeding depression if the dominance model is prevalent, but only slightly reduced inbreeding depression if the overdominance model is most important. (The caveat to this is that if much inbreeding depression is due to overdominant loci with very asymmetric homozygous effects, with population structure these loci can fix for the allele corresponding to the fitter homozygote and the associated inbreeding depression goes to zero.)

Population structure causes some inbreeding, due to the greater probability that individuals will mate with related individuals in the same deme. This may reduce inbreeding depression in two ways: first, because the fitness of standard "outbred" individuals may reasonably be measured relative to typical individuals in the species, which are themselves somewhat inbred; and second, by changing the allele frequencies of deleterious alleles in the species as a whole. The two measures of inbreeding depression discussed in this article include both of these effects (in the case of  $\delta_1$ ) or just the second (in the case of  $\delta_2$ ). The extent of change in inbreeding depression in metapopulations depends on exactly how it is measured.

The inbreeding associated with population structure allows purging of rare, recessive, deleterious alleles and therefore can reduce the inbreeding depression due to dominance but cannot much affect the inbreeding depression due to overdominance. With overdominance, there is a smaller reduction in inbreeding depression due solely to the fact that the mean fitness of outbred individuals is somewhat reduced, because of the deviation in subpopulations from the allele frequencies that give maximum mean fitness. The inbreeding depression in structured populations is expected to be lower than that in an undivided population, and it is much reduced for the inbreeding depression caused by rare, deleterious recessive alleles.

The extent of this reduction depends on the distribu-

tion of dominance coefficients among new mutations. Nearly recessive mutations are much affected by population structure, with great reductions in expected inbreeding depression expected even with relatively small values of  $F_{ST}$ . Mutations with higher values of  $h$  are less likely to be affected. There is very little information about some aspects of this important distribution. A simple theoretical observation may help. Alleles with dominance coefficients near  $\frac{1}{2}$  do not contribute much to inbreeding depression, even in a panmictic population, for the simple reason that the value of their heterozygotes is not much different from the mean of the homozygotes. As  $h$  approaches 0, inbreeding depression is much greater (see Figure 4). As a result, even if the spectrum of new mutations includes few that are nearly recessive, it is these that disproportionately cause inbreeding depression, and therefore the largest effect of population structure occurs for the dominance coefficients that are most important.

One difficulty remains, however. A substantial fraction of inbreeding depression is caused by alleles of very large effect (CHARLESWORTH and CHARLESWORTH 1987). Such strong selection falls outside the conditions assumed in this article. While the inbreeding depression due to these large mutations, which tend to be nearly recessive ( $\bar{h} \approx 0.02$ , SIMMONS and CROW 1977; CROW and SIMMONS 1983), is likely to be much reduced in metapopulations for the same reasons as with weak selection, the calculations with neutral  $F_{ST}$  will not give quantitative predictions for this class of alleles.

**Conclusions:** Spatial population structure has often been studied, both theoretically and empirically, reflecting to some extent its prevalence in natural systems. We have measurements of  $F_{ST}$  from a wide variety of species. Recently, the argument has been made that  $F_{ST}$  is not a good measure of the rate of dispersal, the reason for which  $F_{ST}$  is often studied (WHITLOCK and MCCAULEY 1999). This article, however, has shown the value of studying  $F_{ST}$  of even neutral loci and its power to predict interesting evolutionary processes.  $F_{ST}$ , as defined in this article, is an excellent description of the effects of spatial population structure on the response to weak selection.

The  $F_{ST}$  found to be most useful for these results differs, however, from its standard definition. The parameter needed gives equal weight to all individuals and does not necessarily weight populations equally. In this respect, it differs from other definitions in the literature. To simplify the mathematics, many theoretical models of  $F_{ST}$  assume equal population sizes at the point of measurement [*e.g.*, the island model (WRIGHT 1931), the stepping stone models (KIMURA and WEISS 1964), and the basic extinction-recolonization models (WHITLOCK and MCCAULEY 1990)]. These models will predict the  $F_{ST}$  required here, but more work is needed to define this weighting for other population structures. More importantly, current estimates of  $F_{ST}$  from data weight populations equally, independent of their size. For

many systems with variance in population size, empirical estimates of  $F_{ST}$  do not exactly match what is needed. Statistical work allowing the estimation of this weighted  $F_{ST}$  will therefore be very useful and straightforward.

Population structure allows an increase in homozygosity and competition among relatives, which both can change the dynamics of selection. As a result, the effects of selection can be weakened by local competition, but, perhaps more importantly on balance, selection can be intensified by the increase in genetic variance associated with greater homozygosity. As a result, equilibrium mutation load, inbreeding depression, and the rate of response to selection can be changed, often in a way beneficial to the fitness of the population.

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#### APPENDIX: $\gamma$ AND THE SKEWNESS OF THE ALLELE FREQUENCY DISTRIBUTION

Let us define  $\mu_3$  to be the skewness of  $q$  among populations. If we define a term  $\gamma = \mu_3 / (\bar{p}\bar{q}(\bar{p} - \bar{q}))$  as a standardized skewness of  $q$  (similar to the variance definition of  $F_{ST}$ ), we can see that

$$E[q^3] = \bar{q}\gamma + \bar{q}^2(3F_{ST} - 3\gamma) + \bar{q}^3(1 - 3F_{ST} + 2\gamma).$$

A similar equation results from a consideration of the probability of identity by descent of three alleles chosen from the same deme in a metapopulation. If  $\theta$  and  $\gamma'$  are the probabilities of identity by descent of two or three alleles (respectively) chosen from the same deme,

then the probability that three alleles from the same deme are identical in state for allele  $a$  is

$$\Pr[3 \text{ alleles}] \cong \bar{q}\gamma' + \bar{q}^2(3\theta - 3\gamma') + \bar{q}^3(1 - 3\theta + 2\gamma').$$

The approximation comes from assuming that the mean frequency of the  $a$  allele in the metapopulation is not much affected by the line of descent in any given local population, which will be true with recurrent mutation and a large number of demes. In that case,  $\theta$  is well approximated by  $F_{ST}$ , and  $\gamma'$  will be well approximated by the standardized skewness defined above.

We can calculate the value of  $\gamma$  in an island model. WRIGHT (1937a,b) determined the distribution of allele frequencies across populations for the neutral island model without mutation,

$$\Psi(q) = C(1 - q)^{4Nm(1-\bar{q})-1} q^{4Nm\bar{q}-1},$$

where  $\Psi(q)$  is the probability density of populations with allele frequency  $q$ ,  $\bar{q}$  is the mean allele frequency across all populations,  $Nm$  is the effective number of migrants into and out of each population, and  $C$  is a constant of integration such that  $\int_0^1 \Psi(q) dq = 1$ , so  $C = \Gamma[4Nm] / (\Gamma[4Nm\bar{q}]\Gamma[4Nm(1-\bar{q})])$ . The mean of this distribution [given by  $\int_0^1 q\Psi(q) dq$ ] does resolve to  $\bar{q}$ . We can confirm the variance among demes is as expected:

$$V(q) = E[q^2] - \bar{q}^2 = \int_0^1 q^2\Psi[q] dq - \bar{q}^2 = \frac{\bar{q}(1-\bar{q})}{4Nm+1}.$$

Similarly, we can find the expected value of  $q^3$ ,

$$E[q^3] = \int_0^1 q^3\Psi[q] dq = \frac{\bar{q}(1+2Nm\bar{q})(1+4Nm\bar{q})}{(1+2Nm)(1+4Nm)},$$

and the skewness ( $\mu_3$ ),

$$\mu_3 \equiv E[(q - \bar{q})^3] = \frac{\bar{q}(1-\bar{q})(1-2\bar{q})}{(1+2Nm)(1+4Nm)}.$$

Thus, for a neutral island model,

$$\gamma = \frac{1}{(1+2Nm)(1+4Nm)} = \frac{2F_{ST}^2}{(1-F_{ST})}.$$