

# Patterns of Inbreeding Depression and Architecture of the Load in Subdivided Populations

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## ABSTRACT

Inbreeding depression is a general phenomenon that is due mainly to recessive deleterious mutations, the so-called mutation load. It has been much studied theoretically. However, until very recently, population structure has not been taken into account, even though it can be an important factor in the evolution of populations. Population subdivision modifies the dynamics of deleterious mutations because the outcome of selection depends on processes both within populations (selection and drift) and between populations (migration). Here, we present a general model that permits us to gain insight into patterns of inbreeding depression, heterosis, and the load in subdivided populations. We show that they can be interpreted with reference to single-population theory, using an appropriate local effective population size that integrates the effects of drift, selection, and migration. We term this the “effective population size of selection” ( $N_e^s$ ). For the infinite island model, for example, it is equal to  $N_e^s = N(1 + m/hs)$ , where  $N$  is the local population size,  $m$  the migration rate, and  $h$  and  $s$  the dominance and selection coefficients of deleterious mutation. Our results have implications for the estimation and interpretation of inbreeding depression in subdivided populations, especially regarding conservation issues. We also discuss the possible effects of migration and subdivision on the evolution of mating systems.

**I**NBREEDING depression, the decline of fitness of inbred individuals relative to outbred ones, is a general phenomenon observed in many species (CHARLESWORTH and CHARLESWORTH 1987) and for a long time (DARWIN 1876). It has been much studied theoretically (LANDE and SCHEMSKE 1985; CHARLESWORTH *et al.* 1990b; BATAILLON and KIRKPATRICK 2000) and experimentally (SCHEMSKE and LANDE 1985; HUSBAND and SCHEMSKE 1996) because it is supposed to play a key role in the evolution of mating systems and to challenge the viability of small populations. The genetic basis of inbreeding depression has been extensively investigated and it is now recognized that it is due mainly to deleterious and partially recessive mutations, even if polymorphism maintained by balancing selection may also play a role (CHARLESWORTH and CHARLESWORTH 1999). The mutation load is often defined as the decline of mean fitness due to mutation accumulation relative to an ideal population free of mutation (CROW 1970). In very large populations, the mutation load depends only on the genomic mutation rate (often referred to as  $U$ ; HALDANE 1937), while the magnitude of inbreeding depression depends on  $U$  and on the levels of dominance of the

mutations (CHARLESWORTH and CHARLESWORTH 1987). Fully recessive mutations are maintained in higher frequencies than partially recessive ones and thus cause greater declines in fitness under consanguineous matings. Inbreeding depression can be easily estimated by comparing the performances of progenies produced by outcrosses *vs.* consanguineous crosses. On the contrary, one cannot estimate the load directly because the ideal reference population does not exist. A better knowledge of the load and inbreeding depression can be obtained by characterizing the properties of deleterious mutations (mutation rates, level of dominance, and deleterious effect) and different methods have been proposed to estimate them (for review, see DENG and FU 1998; BATAILLON 2000a). One method relies upon mutation accumulation experiments (MUKAI *et al.* 1972), whereas the others use measures of inbreeding depression or some equivalent (CHARLESWORTH *et al.* 1990a; DENG and LYNCH 1996; DENG 1998).

In methods using measures of inbreeding depression, the underlying models neglect two potentially important factors: population size and population structure. Nevertheless, population size and genetic drift may have a huge impact on the expected inbreeding depression due to deleterious mutations. Moreover, drift has opposite effects on the load and inbreeding depression: the load is higher in small populations than in large ones (KIMURA *et al.* 1963) while the reverse pattern is expected

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for inbreeding depression (BATAILLON and KIRKPATRICK 2000). Population subdivision introduces two additional complications for studying the effects of deleterious mutations. First, the outcome of selection is dependent on process both within populations (selection and drift) and between populations (migration). Second, crosses and their fitness can be defined at different scales and the choice of a reference is thus crucial, as already pointed out by WALLER (1993) and KELLER and WALLER (2002).

Some experimental studies have attempted to estimate inbreeding depression and/or heterosis in subdivided populations. Heterosis can be defined as the excess in mean fitness of individuals produced by crosses between demes relative to mean fitness of individuals produced by outcrosses within deme. Some studies have addressed population levels and hierarchical measures of inbreeding depression (OUBORG and VAN TREUREN 1994; CARR and DUDASH 1995; BYERS 1998; RICHARDS 2000; SHERIDAN and KAROWE 2000) while others have conducted only global analysis (SACCHERI *et al.* 1998; VAN OOSTERHOUT *et al.* 2000). In both types of studies, inbreeding depression and the mutation load are often not clearly distinguished. Indeed, until very recently, the lack of theoretical predictions on the expected patterns of inbreeding depression, heterosis, and the load in subdivided populations was patent. Selection in subdivided populations has already been investigated (MARRYAMA 1972a,b,c; NAGYLAKI 1989). However, to our knowledge, only two recent studies have focused on the patterns of inbreeding depression in subdivided population. THEODOROU and COUVET (2002) have used numerical computations to study specifically the joint effect of selfing and population subdivision on the evolution of inbreeding depression. WHITLOCK (2002) has developed an analytical method for large metapopulations and weak selection, addressing the outcome of selection and its prediction using neutral  $F_{ST}$ .

Here, we present a general method to study the pattern of inbreeding depression, heterosis, and mutation load expected for a broad range of population structure. We have adapted a two-locus diffusion method, developed by OHTA and KIMURA (1969, 1971), to a one-locus treatment in multideme systems. We obtain analytical results in the case of strong selection that naturally lead to the definition of a new effective population size, which integrates the effects of selection, drift, and migration. The pattern of inbreeding depression, heterosis, and the load can be comprehensively interpreted with reference to single-population theory, using this effective population size. Our results suggest a way to define and estimate inbreeding depression and the load in subdivided populations. We also discuss the implications of our results for the evolution of mating systems and conservation issues.

## MODELS AND RESULTS

### General presentation

We consider a single locus with two alleles in a metapopulation of  $K$  demes, each composed of  $N$  diploid individuals, connected by migration. Individuals successively experience mutation and reproduction in each local deme. After zygotic migration, selection occurs within each local deme, followed by density regulation. The contribution of each deme to the next generation is constant and independent of the mean fitness of the deme. The wild-type allele,  $A$ , mutates at rate  $\mu$  to a partially recessive, deleterious allele,  $a$ . The reverse mutation occurs at rate  $\nu$  with  $\nu \ll \mu$ . The relative fitnesses of the  $AA$ ,  $Aa$ , and  $aa$  genotypes are 1,  $1 - hs$ , and  $1 - s$ , respectively, where  $s$  is the selection coefficient and  $h$  the dominance coefficient. For simplicity, we analyze only the case where  $h$  and  $s$  are identical across all demes. We first consider random mating in each deme. For a deleterious mutation segregating at frequency  $x_i$  in the  $i$ th deme, we can define the mean fitness of individuals produced by the different types of crosses. The mean fitness among individuals produced by outcrossing, in the  $i$ th deme,  $W_i^O$ , is equivalent to the mean fitness of the deme assuming random mating,  $W_i^{\text{within}}$ :

$$W_i^{\text{within}} \equiv W_i^O = 1 - 2hsx_i(1 - x_i) - sx_i^2. \quad (1a)$$

The mean fitness among individuals produced by selfing in this deme is

$$W_i^S = 1 - hsx_i(1 - x_i) - \frac{s}{2}(x_i^2 + x_i). \quad (1b)$$

Finally, we can define the mean fitness of individuals produced by crosses between parents coming from different demes,  $i$  and  $j$ :

$$W_{ij}^{\text{between}} = 1 - hs(x_i + x_j) - s(1 - 2h)x_ix_j. \quad (1c)$$

In deme  $i$ , we define inbreeding depression,  $\delta_i$ , as the decline in mean fitness of selfed individuals relative to outcrossed individuals within the deme (CHARLESWORTH and CHARLESWORTH 1987), and the genetic load,  $L_i$ , as the decline in the mean fitness of the deme relative to the optimal genotype ( $AA$ ; CROW and KIMURA 1970):

$$\delta_i(x_i) \equiv 1 - \frac{W_i^S}{W_i^O} = \frac{s(1 - 2h)x_i(1 - x_i)}{2(1 - 2hsx_i(1 - x_i) - sx_i^2)} \quad (2a)$$

$$L_i(x_i) \equiv 1 - W_i^{\text{within}} = 2hsx_i(1 - x_i) + sx_i^2. \quad (2b)$$

We define the heterosis,  $H_{ij}$ , between two demes  $i$  and  $j$  as the excess in mean fitness of individuals produced by outcrosses between demes relative to mean fitness of individuals produced by outcrosses within the demes. We also define between-deme inbreeding depression,  $\gamma_{ij}$ , as the decline in mean fitness of selfed individuals relative to outcrossed individuals between demes.

$$H_{ij}(x_i, x_j) \equiv 1 - \frac{1}{2} \frac{W_i^O + W_j^O}{W_{ij}^{\text{between}}} = \frac{s(1-2h)(x_i - x_j)^2}{2(1 - hs(x_i + x_j) - s(1-2h)x_i x_j)} \quad (2c)$$

$$\gamma_{ij}(x_i, x_j) \equiv 1 - \frac{1}{2} \frac{W_i^S + W_j^S}{W_{ij}^{\text{between}}} = \frac{s(1-2h)(x_i + x_j + x_i^2 + x_j^2 - 4x_i x_j)}{4(1 - hs(x_i + x_j) - s(1-2h)x_i x_j)}. \quad (2d)$$

To obtain expected values for our load and inbreeding depression parameters ( $L$ ,  $\delta$ ,  $H$ ,  $\gamma$ ), we have to compute the expectation of the four quantities previously defined over  $\Phi(x_1, \dots, x_K)$ , the probability distribution of the deleterious allele frequency over the  $K$  demes of the metapopulation. One can use Wright's distribution (see WRIGHT 1969) or the extensions given by MARUYAMA (1972b) for stepping-stone models. However, because these distributions are implicitly defined, only numerical results can be obtained. WHITLOCK *et al.* (2000) followed this approach to investigate the magnitude of heterosis and drift load for the infinite island model. Here, we develop analytical approximations for the patterns of inbreeding depression in subdivided populations. If we are able to satisfactorily approximate  $\delta$ ,  $L$ ,  $H$ , and  $\gamma$  by polynomial functions of degree  $p$ , their expectations over  $\Phi$  will depend only on the  $p$  first moments of  $\Phi$ . Practically, the two first moments are sufficient: the load is a quadratic function of  $x_i$  and good approximations of  $\delta_i$ ,  $H_{ij}$ , and  $\gamma_{ij}$  are obtained, assuming that  $W_i^{\text{within}}$  and  $W_{ij}^{\text{between}}$  in the denominators of Equations 2a, 2c, and 2d, respectively, are nearly equal to 1, which is the case if  $x_i \ll 1$  (strong selection) but also if  $s \ll 1$  (weak selection). So the mean inbreeding depression, heterosis, and load can be approximated by

$$E_{\Phi}[\delta_i] \approx \frac{1}{2}s(1-2h)(E_{\Phi}[x_i] - E_{\Phi}[x_i^2]) \quad \text{for } i = 1, \dots, K \quad (3a)$$

$$E_{\Phi}[L_i] = 2hsE_{\Phi}[x_i] + (1-2h)sE_{\Phi}[x_i^2] \quad \text{for } i = 1, \dots, K \quad (3b)$$

$$E_{\Phi}[H_{ij}] = \frac{1}{2}s(1-2h)(E_{\Phi}[x_i^2] + E_{\Phi}[x_j^2] - 2E_{\Phi}[x_i x_j]) \quad \text{for } i \neq j \quad (3c)$$

$$E_{\Phi}[\gamma_{ij}] = \frac{1}{4}s(1-2h)(E_{\Phi}[x_i] + E_{\Phi}[x_j] + E_{\Phi}[x_i^2] + E_{\Phi}[x_j^2] - 4E_{\Phi}[x_i x_j]) \quad \text{for } i \neq j \quad (3d)$$

where  $E_{\Phi}$  denotes expectation with respect to the  $\Phi$  distribution.

### Analytical results for the case of strong selection ( $Nhs \gg 1$ )

**Ohta-Kimura equation for subdivided populations:** To compute the first two moments of  $\Phi$ , we adapted the method developed by OHTA and KIMURA (1969, 1971) to study the linkage disequilibrium in two-locus models under mutation-drift equilibrium (see also Appendix 3 of KIMURA and OHTA 1971 for details). This method has been used for two-locus problems in different situations (*e.g.*, see PETRY 1983; NORDBORG *et al.* 1996), but, to our knowledge, this is the first time that it has been adapted to model subdivided populations.

According to diffusion theory, for each deme, we need

to write the following infinitesimal terms: the mean change of allele frequency,  $M_{\delta x_i}$ , the variance of the change of allele frequency,  $V_{\delta x_i}$ , and the covariance of the change of allele frequency in a pair of demes,  $W_{\delta x_i, \delta x_j}$ .  $M_{\delta x_i}$  reflects mutation, migration, and selection:

$$M_{\delta x_i} = \Delta_{\text{mut}}(x_i) + \Delta_{\text{mig}}(x_i) + \Delta_{\text{sel}}(x_i) \quad \text{for } i = 1, \dots, K. \quad (4a)$$

Here, we assume that changes in allele frequency between generations are small enough to neglect interaction terms between these elementary processes. Further,

$$V_{\delta x_i} = \frac{x_i(1-x_i)}{2N_i} \quad \text{for } i = 1, \dots, K \quad (4b)$$

and

$$W_{\delta x_i, \delta x_j} = 0 \quad \text{for } i \neq j. \quad (4c)$$

According to OHTA and KIMURA (1969, 1971), for any  $f(x_1, \dots, x_K)$ , a function of the deleterious allele frequencies in each deme, we have

$$\begin{aligned} \frac{dE_{\Phi}[f(x_1, \dots, x_K)]}{dt} = E_{\Phi} \left[ \sum_{i=1}^K M_{\delta x_i} \frac{\partial f(x_1, \dots, x_K)}{\partial x_i} \right. \\ \left. + \frac{1}{2} \sum_{i=1}^K V_{\delta x_i} \frac{\partial^2 f(x_1, \dots, x_K)}{\partial x_i^2} \right. \\ \left. + 2 \sum_{i=1}^K \sum_{j>i} W_{\delta x_i, \delta x_j} \frac{\partial^2 f(x_1, \dots, x_K)}{\partial x_i \partial x_j} \right]. \end{aligned} \quad (5)$$

Equation 5 corrects some typographical errors in OHTA and KIMURA (1971). We consider only the case where the left-hand term is zero, which corresponds to the stationary distribution  $\Phi$ . However, using tedious algebra manipulations, temporal dynamics of the moments can be computed. When  $M_{\delta x_i}$  is linear in  $x_i$ , we can compute  $E_{\Phi}[x_i]$ ,  $E_{\Phi}[x_i^2]$ , and  $E_{\Phi}[x_i x_j]$  by choosing appropriate  $f$  functions, one for each moment. Thus we have to solve a system of  $2K + K(K-1)/2$  equations, which give the  $K$  moments  $E_{\Phi}[x_i]$ , the  $K$  moments  $E_{\Phi}[x_i^2]$ , and the  $K(K-1)/2$  moments  $E_{\Phi}[x_i x_j]$ . Because of the linearity of  $M_{\delta x_i}$ , all moments of interest can be computed for arbitrary population structure, because the system to be solved is linear with respect to all moments. However, we consider only simple population structures where all demes have the same properties (*i.e.*, equal  $N$ ,  $m$ ,  $h$ , and  $s$ ), which greatly reduces the number of moments to compute. Note that, if  $M_{\delta x_i}$  is not linear in  $x_i$ , the moment equations form an infinite linear system and heuristic arguments must be used to close and solve it.

**Assumptions for solving the system:**  $\Delta_{\text{mut}}(x_i)$  and  $\Delta_{\text{mig}}(x_i)$  are linear terms but not  $\Delta_{\text{sel}}(x_i)$ . To satisfy the linearity condition on  $M_{\delta x_i}$ , we linearized the selection term in 0 ( $x_i \ll 1$ ) following ROBERTSON (1970) and BATAILLON and KIRKPATRICK (2000):  $\Delta_{\text{sel}}(x_i) = -hsx_i$ . This is equivalent to assuming that selection acts only against heterozygotes. This assumes that deleterious alleles are not too

recessive ( $h > 0$ ) and maintained in low frequencies; so it is also assumed that  $\mu \ll hs$ . This approximation is thus valuable only if local drift is not too strong. In a single population these conditions correspond about to  $Nhs > 5$  (BATAILLON and KIRKPATRICK 2000). With low migration rates, the analytical results are thus valid for population sizes of the order of 100 at least. If migration overwhelms local drift (high migration rates), we might expect that  $x_i$  will be in low frequency in all demes such that the  $Nhs$  limit can be lower. Accuracy of the approximation is now tested further against numerical or simulation results.

**The Kisland model:** *Computation of the moments:* We consider  $K$  panmictic demes of size  $N$ , connected by migration at a rate  $m$ . The infinitesimal diffusion terms are given by Equations 4a–4c with (4a) becoming

$$M_{\delta x_i} = -hsx_i + \mu(1 - x_i) - mx_i + \frac{m}{K-1} \sum_{j \neq i} x_j \quad \text{for } i = 1, \dots, K. \tag{6}$$

The reverse mutation,  $\nu$ , is neglected.

For the function  $f(x_1, \dots, x_K) = x_i$ , Equation 5 implies, for the stationary distribution,

$$E_{\Phi}[M_{\delta x_i}] = \mu - (hs + \mu + m)E_{\Phi}[x_i] + \frac{m}{K-1} \sum_{j \neq i} E_{\Phi}[x_j] = 0. \tag{7}$$

Considering the symmetry of the model, all the  $E_{\Phi}[x_i]$  are found to be equal and we drop the subscript  $i$  and refer to them as  $E_{\Phi}[x]$ . Equation 7 can be simplified:

$$E_{\Phi}[x] = \frac{\mu}{hs} + O(\mu^2). \tag{8}$$

Note that such linear approximation neglects the effect of drift and subdivision on the mean frequency of  $x$ .

For the function  $f(x_1, \dots, x_K) = x_i^2$ , Equation 5 implies

$$\begin{aligned} E_{\Phi}[2x_i M_{\delta x_i} + V_{\delta x_i}] &= 2(\mu + \frac{1}{4N})E_{\Phi}[x_i] \\ &\quad - 2(hs + \mu + m + \frac{1}{4N})E_{\Phi}[x_i^2] \\ &\quad + \frac{2m}{K-1} \sum_{j \neq i} E_{\Phi}[x_i x_j] = 0. \end{aligned} \tag{9a}$$

For the function  $f(x_1, \dots, x_K) = x_i x_j$ , Equation 5 implies

$$\begin{aligned} E_{\Phi}[x_i M_{\delta x_j} + x_j M_{\delta x_i} + 2W_{\delta x_i \delta x_j}] &= \mu(E_{\Phi}[x_i] + E_{\Phi}[x_j]) \\ &\quad + \frac{m}{K-1}(E_{\Phi}[x_i^2] + E_{\Phi}[x_j^2]) \\ &\quad - 2(hs + \mu + m)E_{\Phi}[x_i x_j] \\ &\quad - \frac{m}{K-1} \sum_{k \neq i, k \neq j} (E_{\Phi}[x_i x_k] + E_{\Phi}[x_j x_k]) = 0. \end{aligned} \tag{9b}$$

Considering the symmetry of the model, all the  $E_{\Phi}[x_i^2]$

are found to be equal and denoted  $E_{\Phi}[x^2]$ . All the  $E_{\Phi}[x_i x_j]$  are also found to be equal and denoted  $E_{\Phi}[xx']$ . Equations 9a and 9b can then be reduced to the following system:

$$\begin{bmatrix} -2(\mu + \frac{1}{4N}\frac{\mu}{hs}) \\ -\frac{2\mu^2}{hs} \end{bmatrix} = \begin{bmatrix} -2(hs + \mu + m + \frac{1}{4N}) & 2m \\ \frac{2m}{K-1} & -2(hs + \mu + \frac{m}{K-1}) \end{bmatrix} \begin{bmatrix} E_{\Phi}[x^2] \\ E_{\Phi}[xx'] \end{bmatrix} \tag{9c}$$

Solving the system gives the second-order moments:

$$\begin{aligned} E_{\Phi}[x^2] &= \mu \left[ hs \left( 1 + 4Nm \frac{Khs}{m + (K-1)hs} + 4Nhs \frac{(K-1)hs}{m + (K-1)hs} \right) \right] \\ &\quad + O(\mu^2) \end{aligned} \tag{10a}$$

$$\begin{aligned} E_{\Phi}[xx'] &= \mu \left[ hs \left( 1 + 4Nm \frac{Khs}{m + (K-1)hs} + 4Nhs \frac{(K-1)hs}{m + (K-1)hs} \right) \right] \\ &\quad \times \frac{m}{m + (K-1)hs} + O(\mu^2). \end{aligned} \tag{10b}$$

Taking the limit of (10a) and (10b) for  $K$  going to infinity gives the value for the infinite island model:

$$E_{\Phi}[x^2] = \frac{\mu}{hs(1 + 4Nm + 4Nhs)} + O(\mu^2) \tag{11a}$$

$$E_{\Phi}[xx'] = O(\mu^2). \tag{11b}$$

We can also compute the moments of the distribution of deleterious allele frequencies over the whole metapopulation,  $\Psi$ . The frequency,  $y$ , of the deleterious allele in the whole metapopulation is  $y \equiv 1/K \sum_{i=1}^K x_i$ , implying

$$E_{\Psi}[y] = \frac{1}{K} \sum_{i=1}^K E_{\Phi}[x_i] \tag{12a}$$

and

$$E_{\Psi}[y^2] = \frac{1}{K^2} \left( \sum_{i=1}^K E_{\Phi}[x_i] + 2 \sum_{i=1}^K \sum_{j>i} E_{\Phi}[x_i x_j] \right). \tag{12b}$$

Using Equations 8, 10a, and 10b, we obtain

$$E_{\Psi}[y] = \frac{\mu}{hs} + O(\mu^2) \tag{13a}$$

and

$$\begin{aligned} E_{\Psi}[y^2] &= \mu \left[ hs \left( 1 + 4Nm \frac{Khs}{m + (K-1)hs} + 4Nhs \frac{(K-1)hs}{m + (K-1)hs} \right) \right] \\ &\quad \times \frac{Km + (K-1)hs}{(m + (K-1)hs)} + O(\mu^2). \end{aligned} \tag{13b}$$

Taking the limit for  $K$  going to infinity gives the value for the infinite island model and leads to  $E_{\Psi}[y^2] = O(\mu^2)$ . In the infinite island model, the distribution over the whole metapopulation is, as expected, a Dirac's  $\delta$  distribution at the point  $\mu/hs$ .

“Effective population size of selection”: Using the same approximation [linearization of  $\Delta_{sel}(x_i)$ ] BATAILLON and KIRKPATRICK (2000) have shown that, in a single large

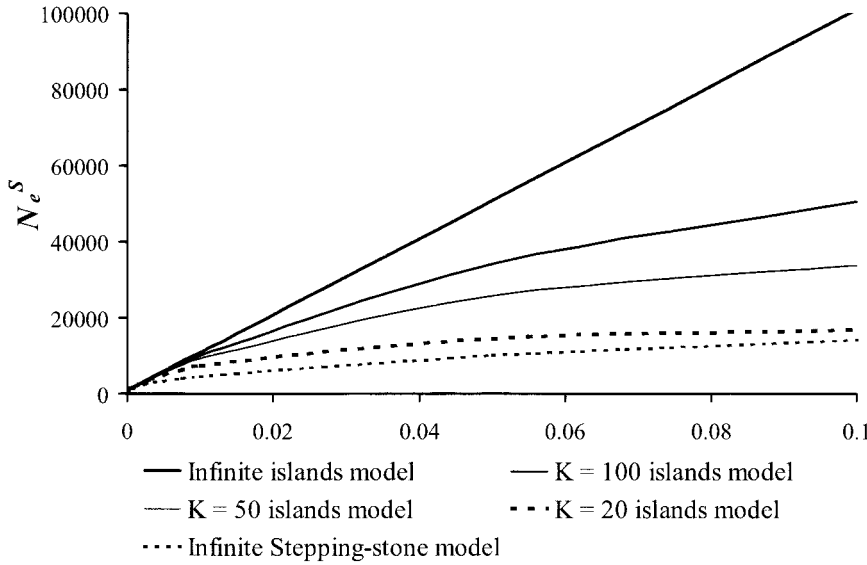


FIGURE 1.—Effective population size of selection as a function of migration rate for different population structures.  $N = 1000$ ,  $h = 0.2$ , and  $s = 0.05$ .

but finite population, the deleterious allele frequency follows a  $\beta$  distribution with mean  $\hat{x} = \mu/hs + O(\mu^2)$  and variance  $\sigma^2 = \mu/hs(1 + 4Nhs) + O(\mu^2)$ . Comparing this result to Equations 8 and 11a, we note that each local deme under the infinite island model is equivalent to a single population under this model, with a new local effective population size. We chose to call this parameter “effective population size of selection.” Extracting  $N$  from the expression for  $\sigma^2$ , we can generally define this parameter:

$$N_e^s \equiv \frac{1}{4hs} \left( \frac{\mu}{\sigma^2 hs} - 1 \right) = \frac{1}{4hs} \left( \frac{\mu}{V_\Phi[x] hs} - 1 \right). \quad (14)$$

$N_e^s$  is defined as the population size of a single population where the two first moments of the distribution of the deleterious allele frequency would be the same as in a local deme of the whole population. However, using such effective size also provides good approximations for higher moments (see Table 2 for skewness and kurtosis with  $Nhs = 30$  and  $Nhs = 3$ ).

For the  $K$ -island model,

$$N_e^s = N \frac{Km + (K - 1)hs}{m + (K - 1)hs}, \quad (15a)$$

and for  $K$  tending to infinity,

$$N_e^s = N \left( 1 + \frac{m}{hs} \right). \quad (15b)$$

Equations 15a and 15b show that migration increases the local effective population size (see Figure 1) and this increase is more important for recessive and weakly deleterious mutations, which are the mutations that are the most difficult to purge in a single population.

$F_{ST}^s$  at the selected locus: An index of population structure, denoted here  $F_{ST}^s$  to distinguish it from the neutral

$F_{ST}$ , can be defined for the selected locus as the ratio of the among-deme variance over the total variance of allele frequency,

$$F_{ST}^s = \frac{E_\Phi[x^2] - E_\Phi[xx']}{K/(K - 1)E_\Phi[x] - 1/(K - 1)E_\Phi[x^2] - E_\Phi[xx']} \quad (16a)$$

(WRIGHT 1969), which reduces to

$$F_{ST}^s = \frac{E_\Phi[x^2] - E_\Phi[x]^2}{E_\Phi[x](1 - E_\Phi[x])} \quad (16b)$$

for the infinite island model (see APPENDIX A).

Using (8), (10a), and (10b), we find for the  $K$ -island model

$$F_{ST}^s = \frac{1}{1 + 4Nm(K/(K - 1))^2 + 4NhsK/(K - 1)} + O(\mu^2) \quad (17a)$$

and for the infinite island model

$$F_{ST}^s = \frac{1}{1 + 4Nm + 4Nhs} + O(\mu^2). \quad (17b)$$

This means that, for strong selection,  $F_{ST}^s$  at a selected locus is much smaller than  $F_{ST}$  at a neutral locus. As expected, strong and uniform selection limits population differentiation. Selection prevents the local fixation of deleterious alleles and increases the effective migration rate of wild-type alleles such that differentiation between demes declines. For weak selection, the results obtained are quite robust and Equations 17a and 17b are still valid. Indeed, as  $s$  tends toward 0, we recover the expected value for a neutral  $F_{ST}$  (see Figure 2 and WHITLOCK 2002).

Average inbreeding depression, genetic load, and heterosis: Using Equations 3a–3d, the expressions for the first-

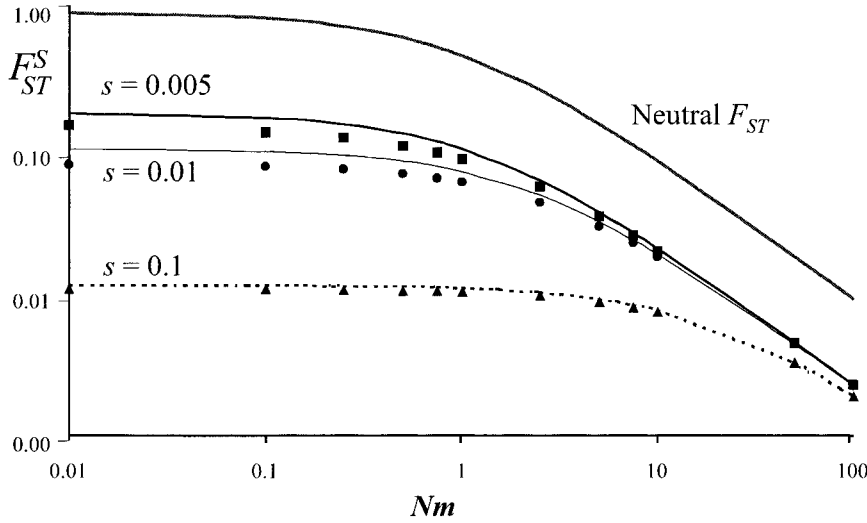


FIGURE 2.— $F_{ST}^S$  at the selected locus in the infinite island model as a function of the number of migrants ( $Nm$ ), for different coefficients of selection. Curves correspond to Equation 17b and symbols to numerical results given by integration of Wright's equation for the infinite island model (see APPENDIX C). Neutral  $F_{ST}$  is also given.  $N = 1000$ ,  $h = 0.2$ ,  $\mu = 10^{-6}$ , and  $\nu = 10^{-7}$ .

and second-order moments and the expressions for the  $F_{ST}^S$ , we can now compute the average local inbreeding depression and genetic load and the average heterosis and inbreeding depression between two demes.

Inbreeding depression is given by

$$E_{\Phi}[\delta] \approx \delta_{TOT}(1 - F_{ST}^S), \quad (18)$$

where

$$\delta_{TOT} = \frac{\mu(1 - 2h)}{2h} \times \left( 1 - 1 / \left( 1 + 4Nm \frac{Khs}{m + (K - 1)hs} + 4Nhs \frac{(K - 1)hs}{m + (K - 1)hs} \right) \frac{Km + (K - 1)hs}{(m + (K - 1)hs)} \right) + O(\mu^2).$$

$\delta_{TOT}$  is the average inbreeding depression over the whole metapopulation considered as a single unit, *i.e.*, the inbreeding depression averaged over the  $\Psi$  distribution. It reduces to  $\delta_{TOT} = \mu(1 - 2h)/2h + O(\mu^2)$  in the infinite island model, which corresponds to the deterministic inbreeding depression (CHARLESWORTH and CHARLESWORTH 1987).

In the same way, we can compute the average load,

$$E_{\Phi}[L] \approx L_{TOT} + 2\delta_{DET}F_{ST}^S, \quad (19)$$

where

$$L_{TOT} = 2\mu + \frac{\mu(1 - 2h)}{2h} \frac{1 + Km/((K - 1)hs)}{K(1 + m/((K - 1)hs) + 4NmK/(K - 1) + 4Nhs)} + O(\mu^2).$$

$L_{TOT}$  is the average load over the whole metapopulation computed over the  $\Psi$  distribution. It reduces to  $L_{TOT} = 2\mu + O(\mu^2)$  in the infinite island model, which corresponds to the deterministic load (HALDANE 1937).

Heterosis is given by

$$E_{\Phi}[H] \approx \frac{2K}{K - 1} \delta_{TOT} F_{ST}^S \quad (20)$$

and inbreeding depression between demes by

$$E_{\Phi}[\gamma] \approx \delta_{TOT} \left( 1 + \frac{K + 1}{K - 1} F_{ST}^S \right). \quad (21)$$

These derivations show that population subdivision has opposite effects on inbreeding depression within and between demes. It decreases local inbreeding depression, compared to an infinite population, whereas it increases between-deme inbreeding depression. As expected, heterosis also increases with subdivision. According to the expression of  $F_{ST}^S$ , within-deme inbreeding depression is smaller and between-deme inbreeding depression and heterosis are correspondingly higher, as migration, population size, and selection coefficient are smaller (see Figure 3 for the infinite island model and Figure 4 for  $K = 10$ ).

Results for the load are slightly inaccurate because we have neglected the mild purging effect that occurs in finite but not too small populations under weak subdivision when  $h < 1/3$  (see S. GLÉMIN, unpublished results; and WHITLOCK 2002). This purging effect has only weak quantitative consequences on Equation 19 but some qualitative consequences under  $h < 1/3$ . For  $h > 1/3$ , Equation 19 is quite accurate (see Figures 4 and 5). For  $h < 1/3$ , the load decreases with weak subdivision before increasing when subdivision is more important (see also WHITLOCK 2002). However, these variations are weak relative to the strong increase of the load in small populations (KIMURA *et al.* 1963).

**The infinite island model with nonrandom mating:**

With nonrandom mating, we need more general expressions for inbreeding depression, the genetic load, and heterosis as a function of the moments of the probability distribution of deleterious allele frequency. The various mean fitnesses of interest can be expressed as functions of the deleterious allele frequency and fixation index  $F_{IS}$  (CABALLERO and HILL 1992). We assume that all demes have the same  $F_{IS}$ . Within the  $i$ th deme,

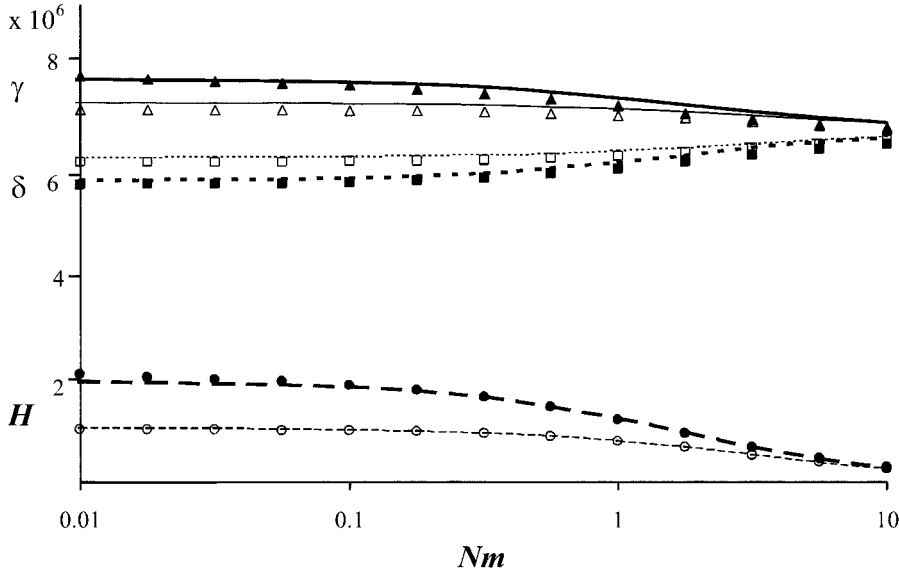


FIGURE 3.—Inbreeding depression within ( $\delta$ ) and between ( $\gamma$ ) demes and heterosis ( $H$ ) in the infinite island model as a function of the number of migrants ( $Nm$ ). Curves correspond to Equation 18 for within-deme inbreeding depression, to Equation 20 for heterosis, and to Equation 21 for between-deme inbreeding depression. Symbols correspond to numerical results given by integration of Wright's equation for the infinite island model (see APPENDIX C).  $N = 1000$ ,  $h = 0.3$ ,  $\mu = 10^{-5}$ , and  $\nu = 10^{-6}$ . Thick curves and solid symbols correspond to  $s = 0.05$ . Thin curves and open symbols correspond to  $s = 0.1$ .

$$W_i^{\text{within}} = 1 - 2hs(1 - F_{\text{IS}})x_i(1 - x_i) - s(x_i^2 + F_{\text{IS}}x_i(1 - x_i)) \quad (22a)$$

$$W_i^{\text{O}} = 1 - 2hsx_i(1 - x_i) - sx_i^2 \quad (22b)$$

$$W_i^{\text{S}} = 1 - hs(1 - F_{\text{IS}})x_i(1 - x_i) - s(x_i^2 + \frac{(1 + F_{\text{IS}})}{2}x_i(1 - x_i)). \quad (22c)$$

With nonrandom mating, the mean fitness of the population is different from the mean fitness of outcrossed individuals. The mean fitness of individuals produced by crossing between parents of two different demes,  $i$  and  $j$ , is the same as in the previous case. The four quantities previously defined are now given by the following expressions:

$$\delta_i(x_i) \equiv 1 - \frac{W_i^{\text{S}}}{W_i^{\text{O}}} \approx \frac{1}{2}s(1 + F_{\text{IS}})(1 - 2h)(E[x_i] - E[x_i^2]) \quad (23a)$$

$$L_i(x_i) \equiv 1 - W_i^{\text{within}} = (F_{\text{IS}} + 2h - 2hF_{\text{IS}})sE[x_i] + (1 - F_{\text{IS}})(1 - 2h)sE[x_i^2] \quad (23b)$$

$$H(x_i, x_j) \equiv 1 - \frac{1}{2} \frac{W_i^{\text{O}} + W_j^{\text{O}}}{W_{ij}^{\text{between}}}$$

$$\approx \frac{1}{2}s(1 - 2h)(E[x_i^2] + E[x_j^2] - 2E[x_i x_j]) \quad (23c)$$

$$\begin{aligned} \gamma(x_i, x_j) &\equiv 1 - \frac{1}{2} \frac{W_i^{\text{S}} + W_j^{\text{S}}}{W_{ij}^{\text{between}}} \\ &\approx \frac{1}{4}s(1 - 2h)((1 + F_{\text{IS}})(E[x_i] + E[x_j]) \\ &\quad + (1 - F_{\text{IS}})(E[x_i^2] + E[x_j^2]) - 4E[x_i x_j]). \end{aligned} \quad (23d)$$

*Computation of the moments:* Following CABALLERO and HILL (1992) and BATAILLON and KIRKPATRICK (2000) with the addition of migration, the infinitesimal diffusion terms are obtained from Equations 6, 4b, and 4c by changing  $h$  to  $h_F = (h + F_{\text{IS}} - hF_{\text{IS}})$  and  $N$  to  $N_e = N/(1 + F_{\text{IS}})$ . Here, the linearization of the selection term is equivalent to assuming that selection acts only on heterozygotes produced by random mating and against homozygotes produced by nonrandom mating.

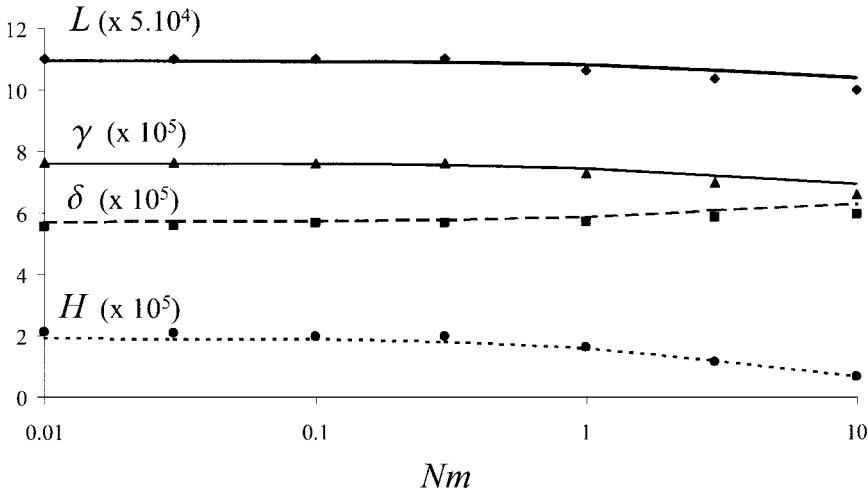


FIGURE 4.—Inbreeding depression within ( $\delta$ ) and between ( $\gamma$ ) demes, heterosis ( $H$ ), and the load ( $L$ ) in the finite island model ( $K = 10$ ) as a function of the number of migrants ( $Nm$ ). Curves correspond to Equation 18 for within-deme inbreeding depression, to Equation 19 for the load, to Equation 20 for heterosis, and to Equation 21 for between-deme inbreeding depression. Symbols represent results of stochastic simulations.  $N = 100$ ,  $h = 0.3$ ,  $s = 0.05$ ,  $\mu = 10^{-4}$ , and  $\nu = 10^{-5}$ .

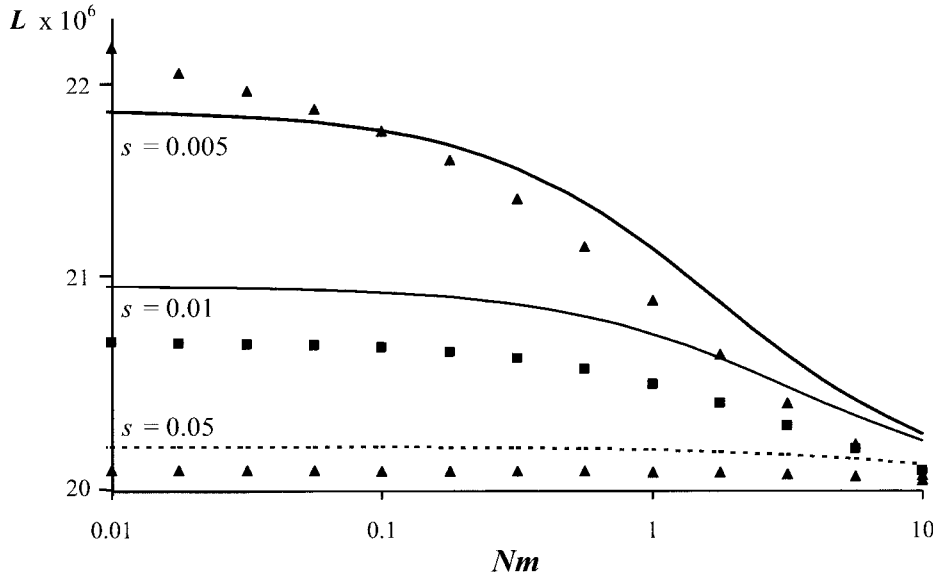


FIGURE 5.—The mutation load in the infinite island model as a function of the number of migrants ( $Nm$ ). Curves correspond to Equation 19. Symbols correspond to numerical results given by integration of Wright's equation for the infinite island model (see APPENDIX C).  $N = 1000$ ,  $h = 0.3$ ,  $\mu = 10^{-5}$ , and  $\nu = 10^{-6}$ .

Using Equation 5 for the same appropriate  $f$  functions and considering the symmetrical properties of the island model, we can compute the first- and second-order moments of  $\Phi$  in the case of nonrandom mating. All moments are found to be the same as in the panmictic case (see Equations 8, 10a, and 10b), after replacement of  $h$  by  $h_f$  and  $N$  by  $N_e = N/(1 + F_{IS})$ .

*Effective population size of selection and selected  $F_{ST}^S$ :* As previously defined, we can compute the effective population size of selection and  $F_{ST}^S$  for the selected locus. The results are the same as in the case of random mating, replacing  $N$  by  $N_e$  and  $h$  by  $h_f$ . Contrary to a neutral locus, inbreeding decreases  $F_{ST}^S$ . Inbreeding enhances genetic drift (the effective size is divided by two for complete inbreeding) but also increases the apparent dominance coefficient  $h_f$ . As a result, inbreeding leads to more efficient selection, which in turn limits population differentiation. Similarly, inbreeding decreases the effective size of selection but unmasks deleterious alleles in homozygotes. The second process overwhelms the first one. As a result, selection is more efficient with inbreeding in subdivided populations, just as in infinite ones.

*Average inbreeding depression, genetic load, and heterosis:* Using Equations 23a–23d and the expressions for the first- and second-order moments, we can now compute the average local inbreeding depression and genetic load and the average heterosis and inbreeding depression between two demes. For inbreeding depression, Equation 13 is still valid using the appropriate  $F_{ST}^S$  and  $\delta_{TOT} = \mu(1 - 2h)(1 + F_{IS})/2(h + F_{IS} - hF_{IS})$ .

The expression for the load is different from (18),

$$E_{\Phi}[L] \approx L_{TOT} + 2 \frac{1 - F_{IS}}{1 + F_{IS}} \delta_{TOT} F_{ST}^S, \quad (24)$$

where

$$L_{TOT} = \frac{\mu(2h + F_{IS} - 2hF_{IS})}{(h + F_{IS} - hF_{IS})}.$$

Inbreeding depression between demes and heterosis are now given by

$$E_{\Phi}[H] \approx \frac{2}{1 + F_{IS}} \delta_{TOT} F_{ST}^S \quad (25)$$

$$E_{\Phi}[\gamma] \approx \delta_{TOT} \left(1 + \frac{1 - F_{IS}}{1 + F_{IS}} F_{ST}^S\right). \quad (26)$$

Inbreeding due to nonrandom mating ( $F_{IS}$ ) decreases both inbreeding depression and the load (as in an infinite population). It also decreases heterosis and inbreeding depression between demes (see Figure 6). With high levels of inbreeding, the effect of migration on the load and inbreeding depression (within and between demes) is very weak (see Figure 6A for inbreeding depression). The effect of migration on heterosis is more important, even with inbreeding (see Figure 6B). For weak selection, equivalent results have been obtained independently with numerical methods by THEODOROU and COUVET (2002) for inbreeding depression and the load. However, they found that for high inbreeding levels, migration has also very little effect on heterosis.

**The unidimensional stepping-stone model:** We now consider a circular stepping-stone model with  $K$  panmictic demes of size  $N$ , with  $K = 2p$  or  $K = 2p + 1$ . We assume only local and equal migration between two adjacent demes. We now need to compute  $p + 2$  moments:  $E_{\Phi}[x]$ ,  $E_{\Phi}[x^2]$ , as in the previous cases and the second-order interdeme moments,  $E_{\Phi}[x_i x_{i+k}]$  for a pair of demes separated by  $k$  steps, which depend on the distance between demes. All the moments between two demes at distance  $k$  are equal and we denote them  $E_{\Phi}[xx_k]$ . We



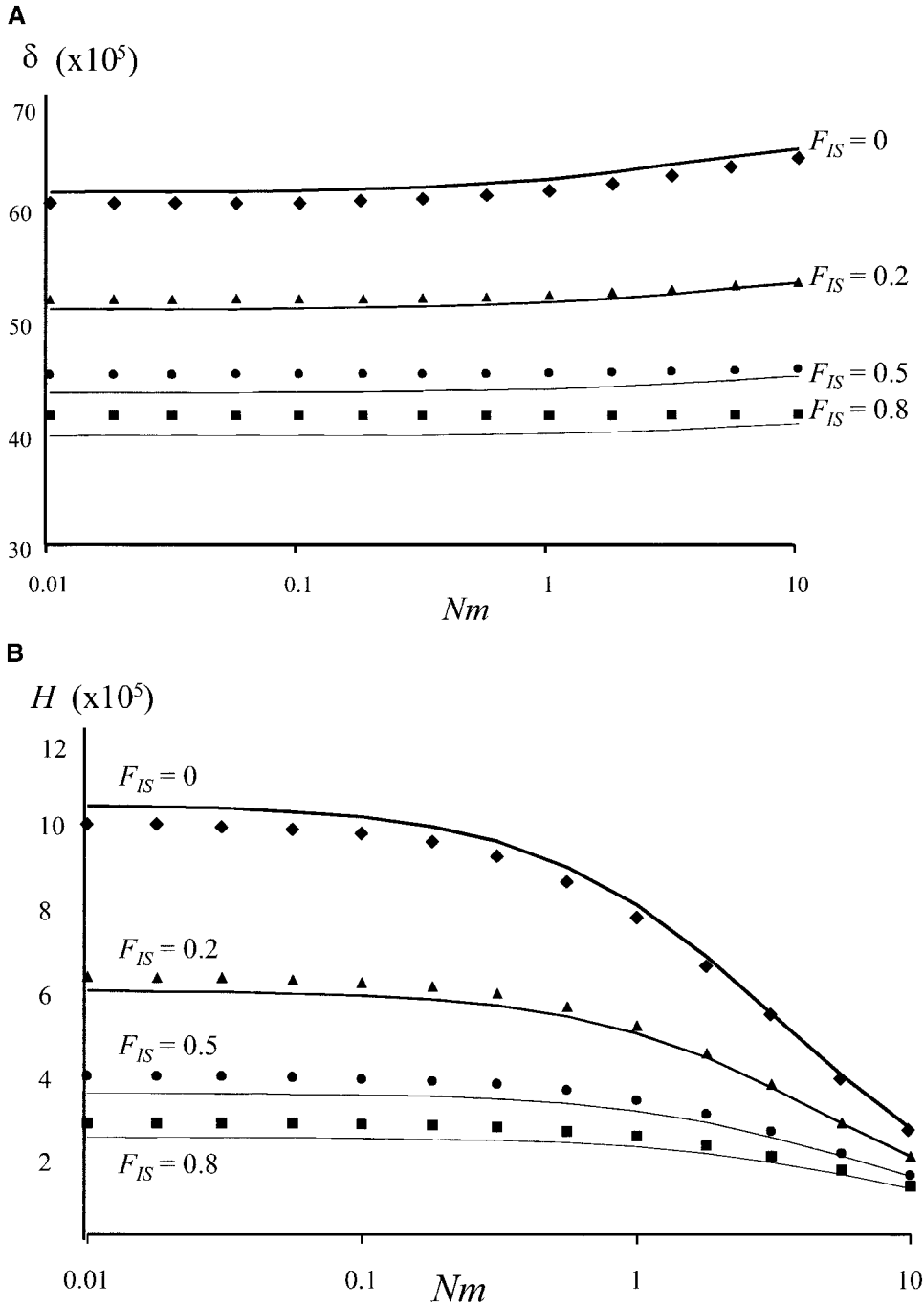


FIGURE 6.—Within-deme inbreeding depression (A) and heterosis (B) in the infinite island model as a function of the number of migrants for different  $F_{IS}$  values. Curves correspond to Equation 16 for inbreeding depression with appropriate  $\delta_{TOT}$  and  $F_{ST}^S$  and to Equation 25 for heterosis. Symbols correspond to numerical results given by integration of Wright's equation for the infinite island model (see APPENDIX C).  $N = 100$ ,  $h = 0.3$ ,  $s = 0.1$ ,  $\mu = 10^{-4}$ , and  $\nu = 10^{-6}$ .

then use  $p + 2$  different  $f$  functions to solve the system (see APPENDIX B). Here, we give the results for the infinite unidimensional stepping-stone model ( $K \rightarrow \infty$ ):

$$E_{\Phi}[x] = \frac{\mu}{hs} + O(\mu^2) \quad (27a)$$

$$E_{\Phi}[x^2] = \frac{\mu}{hs(1 + 4Nhs\sqrt{(1 + 2m/hs)})} + O(\mu^2) \quad (27b)$$

$$E_{\Phi}[xx_k] = \frac{\mu}{hs(1 + 4Nhs\sqrt{(1 + 2m/hs)})} \rho^k + O(\mu^2) \quad (27c)$$

with  $\rho = (m/(m + hs + \sqrt{hs(2m + hs)}))$  representing the correlation coefficient of deleterious allele frequencies between two adjacent demes. This result is numerically consistent with the one found by MARUYAMA (1972c) for finite linear stepping stones (see Equation 12 in MARUYAMA 1972c with the number of demes tending to infinity).

We can also compute

$$N_e^S = N\sqrt{(1 + 2m/hs)} \quad (28)$$

and

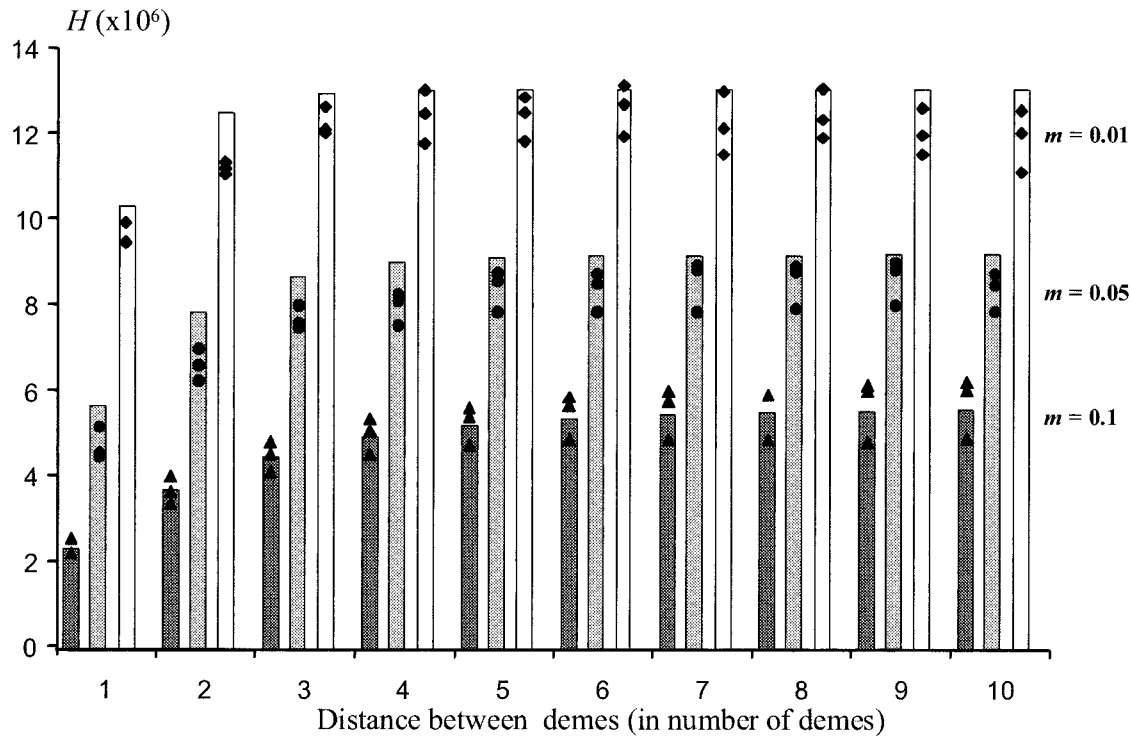


FIGURE 7.—Heterosis as a function of the distance between demes in the stepping-stone model. Bars correspond to theoretical predictions given by Equation 30. Symbols represent results of stochastic simulations with  $K = 20$  demes.  $N = 100$ ,  $h = 0.3$ ,  $s = 0.05$ ,  $\mu = 10^{-4}$ , and  $\nu = 10^{-6}$ .

$$F_{ST}^S = \frac{1}{1 + 4Nhs\sqrt{(1 + 2m/hs)}}. \quad (29)$$

For inbreeding depression and mutation load, Equations 18 and 19 still hold, and we can compute the heterosis and inbreeding depression between two demes at distance  $k$ :

$$E_{\Phi}[H_k] \approx 2\delta_{TOT}F_{ST}^S(1 - \rho^k) \quad (30)$$

$$E_{\Phi}[\gamma_k] \approx \delta_{TOT}(1 + F_{ST}^S(1 - \rho^k)). \quad (31)$$

These equations clearly show that heterosis and between-deme inbreeding depression increase with distance as expected (see Figure 7 for heterosis). If  $m$  is small,  $\rho \approx m/2hs$ , so maximum heterosis ( $2\delta_{TOT}F_{ST}^S$ ) and inbreeding depression between demes ( $\delta_{TOT}(1 + F_{ST}^S)$ ) are reached for nearby demes.

**Robustness and generalization of the analytical results:** The results above are not valid for weak selection. Indeed, because of genetic drift, the frequency of a deleterious allele can be high (near 1), so we cannot linearize  $\Delta_{sel}(x_i)$  around  $x_i = 0$ ; *i.e.*, selection against homozygotes  $aa$  cannot be neglected. However, we can extend qualitatively our theory to more general sets of parameters. The weakness of our approximations is that drift and subdivision do not affect the mean frequency of the deleterious allele, which is always  $\mu/hf_s$ . However, the variance of the frequency of the deleterious allele, which leads to the definition of the effective size of

selection, is much better predicted by the theory (see Table 1). Consequently, as we have already said, the expression for  $F_{ST}^S$  is quite robust (see Figure 2) and remains a useful qualitative index of the level of population differentiation at the selected locus. Because heterosis depends on the variance of allele frequency but not on the mean (see Equation 3c), our approximations for heterosis are also quite robust under weak selection. Approximations are less robust for inbreeding depression and the load because they depend on both the mean and variance of allele frequency (see Equations 3a and 3b). In a single population, inbreeding depression and the load show clear patterns as a function of the population size (KIMURA *et al.* 1963; BATAILLON and KIRKPATRICK 2000). Mutations of large effects ( $Ns \gg 1$ ) segregate at low frequencies and cause most of the inbreeding depression (BATAILLON 2000b; see S. GLÉMIN, unpublished results, for more precise conditions). Weak mutations ( $Ns < 1$ ) are maintained in high frequency and tend to be fixed in the population and cause drift load (for example, see WHITLOCK *et al.* 2000). The drift load is much higher than the load due to segregating mutations. Moreover, these mutations also cause most of the heterosis (WHITLOCK *et al.* 2000). We predict that the same patterns are expected in a metapopulation with the population size corresponding to the appropriate effective size of selection. To test this heuristic prediction, we computed Wright's equation for a single

TABLE 1  
Variance of the deleterious allele frequency in the infinite islands model

$m$	Neutral $F_{ST}$	$F_{IS} = 0$											
		$s = 0.05$		$s = 0.01$		$s = 0.005$		$s = 0.05$		$s = 0.01$		$s = 0.005$	
		Numerical	Theory	Numerical	Theory	Numerical	Theory	Numerical	Theory	Numerical	Theory	Numerical	Theory
0.00001	0.96	11.2	10.9	258.9	255.6	1062.8	933.1	6.4	6.1	160.7	144.8	724.3	543.3
0.00003	0.89	11.2	10.9	257.2	253.9	1014.2	921.7	6.4	6.1	159.8	144.1	682.3	538.6
0.0001	0.71	11.1	10.9	252.1	248.8	958.6	887.7	6.4	6.1	157.2	142.0	644.7	524.5
0.0003	0.44	11.0	10.7	237.4	233.7	843.8	794.8	6.3	6.0	149.6	135.9	572.6	484.2
0.001	0.20	10.5	10.3	201.2	196.1	632.8	597.2	6.1	5.9	130.2	119.6	438.5	389.6
0.003	0.07	9.4	9.1	137.8	130.0	372.8	334.3	5.6	5.4	93.7	86.7	266.5	240.8
0.01	0.02	7.0	6.6	72.8	62.9	181.8	139.8	4.4	4.2	51.9	46.4	130.1	109.1
		$F_{IS} = 0.5$											
0.00001	0.96	3.7	3.5	97.8	83.8	482.6	317.4	2.3	2.2	62.3	52.2	334.1	198.9
0.00003	0.89	3.7	3.5	97.4	83.5	445.5	315.5	2.3	2.2	62.1	52.1	299.8	198.1
0.0001	0.71	3.7	3.5	96.2	82.7	420.6	309.8	2.3	2.2	61.5	51.7	281.9	195.5
0.0003	0.44	3.7	3.5	92.6	80.2	379.3	292.8	2.3	2.2	59.8	50.6	258.0	187.7
0.001	0.20	3.6	3.4	83.0	73.3	300.7	249.5	2.2	2.1	55.0	47.4	212.1	166.8
0.003	0.07	3.4	3.2	63.4	57.5	191.9	170.0	2.1	2.0	44.3	39.5	143.1	123.3
0.01	0.02	2.8	2.7	37.5	34.2	96.7	84.7	1.9	1.8	28.2	25.8	75.8	67.5

Variance of the deleterious allele frequency is given  $\times 10^{-6}$ ,  $N = 1000$ ,  $h = 0.3$ ,  $\mu = 10^{-5}$ , and  $\nu = 10^{-7}$ . Accuracy of the theory is checked against numerical values given by integration of Wright's equation (see APPENDIX C).

**TABLE 2**  
**Accuracy of the effective size of selection ( $N_e^s$ ) to predict the distribution of deleterious allele frequency**

$Nm$ :		0.1	0.3	1	3	10
Neutral $F_{ST}$ :		0.71	0.44	0.20	0.07	0.02
$h = 0.3, s = 0.1 (Nhs = 30)$						
$E[x]$	Numerical	3.34E-05	3.34E-05	3.34E-05	3.34E-05	3.33E-05
	$N_e^s$	3.34E-05	3.34E-05	3.34E-05	3.33E-05	3.33E-05
$V[x]$	Numerical	2.73E-07	2.71E-07	2.65E-07	2.50E-07	2.06E-07
	$N_e^s$	2.73E-07	2.71E-07	2.65E-07	2.49E-07	2.06E-07
Sk [ $x$ ]	Numerical	31.00	30.90	30.57	29.67	27.06
	$N_e^s$	31.00	30.90	30.56	29.66	27.04
Kurt [ $x$ ]	Numerical	1429.67	1420.76	1390.47	1310.85	1093.12
	$N_e^s$	1429.63	1420.64	1390.07	1309.81	1090.59
$h = 0.3, s = 0.01 (Nhs = 3)$						
$E[x]$	Numerical	3.31E-04	3.31E-04	3.30E-04	3.30E-04	3.31E-04
	$N_e^s$	3.31E-04	3.30E-04	3.30E-04	3.30E-04	3.31E-04
$V[x]$	Numerical	2.4E-05	2.3E-05	1.9E-05	1.3E-05	6.2E-06
	$N_e^s$	2.4E-05	2.3E-05	1.9E-05	1.3E-05	6.2E-06
Sk [ $x$ ]	Numerical	28.05	27.30	25.15	21.08	14.78
	$N_e^s$	28.14	27.31	25.13	20.99	14.68
Kurt [ $x$ ]	Numerical	1120.64	1062.50	905.98	645.13	324.31
	$N_e^s$	1137.81	1069.39	906.58	639.98	319.77
$h = 0.05, s = 0.005 (Nhs = 0.25)$						
$E[x]$	Numerical	0.00126	0.00132	0.00154	0.00202	0.00281
	$N_e^s$	0.00135	0.00153	0.00193	0.00247	0.00305
$V[x]$	Numerical	0.00023	0.00022	0.00018	0.00013	6.5E-05
	$N_e^s$	0.00021	0.00018	0.00013	9E-05	4.7E-05
Sk [ $x$ ]	Numerical	19.26	17.96	14.80	10.21	5.57
	$N_e^s$	19.60	14.06	9.79	6.46	3.93
Kurt [ $x$ ]	Numerical	479.92	419.16	291.98	147.05	48.11
	$N_e^s$	548.01	257.09	127.51	57.97	23.76
$h = 0.05, s = 0.0005 (Nhs = 0.025)$						
$E[x]$	Numerical	0.01365	0.01076	0.01236	0.01712	0.02257
	$N_e^s$	0.07956	0.01278	0.0171	0.02133	0.02459
$V[x]$	Numerical	0.0082	0.00411	0.00225	0.00126	0.00053
	$N_e^s$	0.06101	0.00205	0.00123	0.00068	0.00028
Sk [ $x$ ]	Numerical	8.28	8.57	6.37	3.78	1.95
	$N_e^s$	3.63	5.71	3.25	1.94	1.06
Kurt [ $x$ ]	Numerical	76.38	88.48	54.77	22.56	8.44
	$N_e^s$	13.44	46.36	16.24	7.57	4.30

First moments of the distribution are computed using Wright's equation for the infinite islands model (Numerical) and using  $N_e^s$  in Wright's equation for a single population.  $N = 1000$ ,  $\mu = 10^{-6}$ ,  $\nu = 10^{-7}$ . Details of the computation are given in APPENDIX C. Sk, skewness; Kurt, kurtosis.

population, changing the population size by the effective size of selection, and tested it against numerical computations of Wright's equation for the infinite island model (see APPENDIX C).

Qualitative patterns of the load due to segregating mutations are well predicted by  $N_e^s$  (see Table 2). In particular, using  $N_e^s$  instead of  $N$  in Wright's equation accounts for the weak purging effect that affects the mean frequency of deleterious alleles, which we previously neglected. Higher moments of the distribution are also quite well predicted (see skewness and kurtosis in Table

2). However, for low migration rates and weak selection, migration increases the local effective size more than predicted by  $N_e^s$ . Because of this limitation, the effective size of selection must be used with caution for weak selection and further investigations are needed.

## DISCUSSION

**Heuristic value of the theory and limitations of the model:** In this study, we adapted a diffusion method to provide general and analytical results to understand the

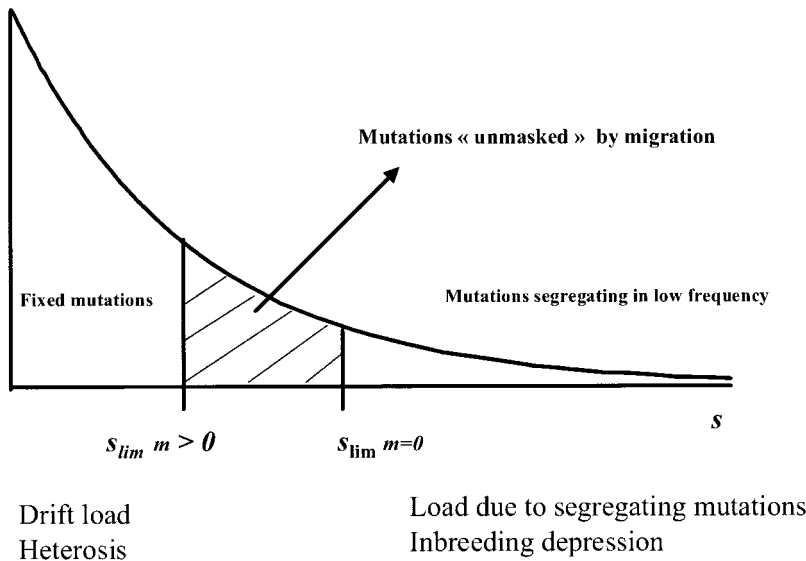


FIGURE 8.—Distribution of deleterious effects of mutations and their consequences. Leptokurtic distribution of selection coefficients is represented (see, for example, KEIGHTLEY 1994). In a single isolated population ( $m = 0$ ), mutations with effect  $s > s_{lim}$  ( $s_{lim}$  of the order of  $5/N$ ; for example, see BATAILLON and KIRKPATRICK 2000) segregate in low frequency at approximated mutation-selection equilibrium. These mutations cause inbreeding depression if revealed by consanguineous matings. Mutations with effect  $s < s_{lim}$  are fixed and cause drift load and heterosis (WHITLOCK *et al.* 2000) but no inbreeding depression (BATAILLON and KIRKPATRICK 2000). Migration among populations greatly reduces  $s_{lim}$  and thus “unmasked” locally fixed mutations.

effects of population subdivision on patterns of inbreeding depression, heterosis, and the load due to partially recessive deleterious mutations. Because this method leads to linear equations with respect to the moments of the distribution of allele frequency, any kind of subdivision can be studied. The more general and heuristic result we obtained is that one can use an index of effective size of selection to interpret the effect of subdivision by reference to single-population theory. Accurate analytical results are obtained for strong selection. Our effective size of selection is still a useful index for a wider range of situations in which our analytical results may be less accurate. In a single population, deleterious alleles for which  $Ns \gg 1$  segregate in low frequency while those for which  $Ns < 1$  can be nearly fixed. In a local deme of a subdivided population, qualitative predictions can be easily made using the same dichotomy but replacing  $N$  by  $N_e^s$ . Compared to a single isolated population, the main effect of migration is thus to increase the local effective size and consequently to increase the proportion of mutations that can be efficiently eliminated ( $1/N_e^s < 1/N$ , see Figure 8). Furthermore, this condition is conservative because migration helps purge the drift load more efficiently than predicted by  $N_e^s$ . The use of our effective size of selection also offers a synthetic way of comparing the effect of different population structures (see Figure 1). In the island model, for a large number of demes, the effective size of selection increases linearly with migration. A few migrants can boost the effective size. However, if the number of demes is small, the effect of migration on the effective size of selection is limited ( $N_e^s < N_e K$ ). If there is isolation by distance, the effect of migration is less important. Local migration does not greatly increase the effective size because the distributions of deleterious allelic frequencies in neighboring demes are correlated. This agrees with MARUYAMA (1972c), who showed that, in a

stepping-stone model, local drift may carry a deleterious gene to high frequency even if the whole metapopulation size is high. So, local migration and migration in a small island metapopulation (small  $K$ ) do not increase the efficacy of selection much. Similar results were obtained using stochastic simulations by HIGGINS and LYNCH (2001), who showed that mutational meltdown can be important in small metapopulations or under local migration.

As in other models (WHITLOCK *et al.* 2000; THEODOROU and COUVET 2002; WHITLOCK 2002), our predictions hold for one locus. Extrapolation for total fitness, which is of interest for the evolution of mating systems and conservation issues, must assume independence among loci. Under drift and subdivision this can be misleading because linkage disequilibrium can lessen the efficiency of selection (HILL and ROBERTSON 1966). Under the assumptions we used (strong selection,  $Nhs \gg 1$ ), we expected that such associations should develop only between tightly linked loci. However, if there is a wide distribution of deleterious effects of alleles, interferences between weakly and strongly selected loci are more likely to happen (STEPHAN *et al.* 1999). Multilocus extension of such models is thus needed to answer to these questions.

**The genetic basis of inbreeding depression and heterosis in subdivided populations:** Inbreeding depression and heterosis are often seen as two aspects of the same genetic process. However, we show here that their genetic basis can be quite different. Inbreeding depression is primarily due to mutations with strong effect (for which  $F_{ST}^s$  is low, see Equation 18) whereas heterosis is due to mutations of weak effect (for which  $F_{ST}^s$  is high, see Equation 20). The level of gene flow and the local population size determine which kind of mutations will be the primary contributors to inbreeding depression and heterosis (see Figure 8). The limit between the two

classes of mutations should depend on the local effective population size. This analysis stresses important differences in the expected behavior of inbreeding depression and heterosis that can no longer be considered as two exact opposite sides of the same process.

Contrary to this interpretation, one can argue that it depends on the definition of heterosis, which differs from that generally given by plant breeders: “When inbred lines are crossed, the progeny show an increase of those characters that previously suffered a reduction from inbreeding. . . . The amount of heterosis is the difference between the crossbred and the inbred means” (FALCONER 1989, p. 254). Indeed, for completely autogamous populations, according to this definition, heterosis is the exact opposite of inbreeding depression. However, in all other cases, inbred lines have to be produced before outcrossing them. During recurrent selfing, purging of lethals and fixation of mildly deleterious alleles can occur. Consequently heterosis is not just the reverse of inbreeding depression that can be estimated in the base population. Each line can be viewed as a single isolated population and heterosis is well defined by the excess of mean fitness of individuals produced by outcrosses between demes (equaling lines) relative to mean fitness of individuals produced by outcrosses within demes (equaling mean fitness of a line).

**Consequences for the evolution of mating systems in subdivided populations:** Inbreeding depression is a key parameter in the evolution of mating system because it balances the “cost of outcrossing” (FISHER 1941; UYENOYAMA 1986). The majority of theoretical studies modeling the evolution of mating systems assumes single and large (infinite) populations (but see HOLSINGER 1986). Here, we show that drift and subdivision can modify the patterns of inbreeding depression and heterosis and should influence the direction of selection on the mating systems. In our analysis, the mating system does not evolve but it determines, jointly with the pattern of migration, the amount of inbreeding depression. In subdivided populations, two opposite pressures can influence the evolution of selfing. Increased subdivision, just as drift, leads to a decline of within-deme inbreeding depression, which reduces the advantage of outcrossing. However, subdivision also reduces the cost of outcrossing (UYENOYAMA 1986). Conversely, drift and subdivision also increase between-deme inbreeding depression, which may favor outcrossing with migrants. For weaker selection against deleterious alleles ( $Ns < 1$ ), THEODOROU and COUVET (2002) found similar patterns of inbreeding depression and heterosis. Taking account of both of these patterns and the cost of outcrossing, they suggest that mixed-mating systems should be stable for intermediate migration rates, especially with pollen migration (that is not assumed in our study). In this case, heterosis increases as the selfing rate increases (because selfing limits pollen migration). Advantage to migrants increases with selfing and can prevent the full invasion

of a modifier causing selfing. With a stochastic model of selection on selfing rates in a continuous structured population, RONFORT and COUVET (1995) also show that population structure should maintain intermediate selfing rates.

However, as already noted, our model and others (WHITLOCK *et al.* 2000; THEODOROU and COUVET 2002; WHITLOCK 2002) are basically single-locus models and associations between loci are not taken into account. To understand the real impact of population subdivision on the evolution of mating systems, such associations in subdivided populations should be modeled. Moreover, migration rates can also evolve in metapopulations in response to sib competition and to spatio-temporal variability in population sizes (*e.g.*, OLIVIERI and GOUYON 1997). Heterosis could also be another factor that selects for increasing migration rates (MORGAN 2002). However, the coevolution of mating system, inbreeding depression, and migration is still a challenging question.

**Implications for conservation biology:** The accumulation of deleterious mutations in small populations should increase the risk of extinction due to the process called “mutational meltdown” (LYNCH *et al.* 1995). A recent simulation study (HIGGINS and LYNCH 2001) has shown that this process can also occur in metapopulations. The increase in the risk of extinction is mainly due to the drift load. A simple conclusion of our analysis is that migration between populations efficiently purges the main part of the load, by converting the drift load into load due to segregating mutations; *i.e.*, more mutations can be selected against (see Figure 8). Moreover, long-distance migration purges the drift load more efficiently than local migration does (HIGGINS and LYNCH 2001); the effective size of selection is higher in the island model than in the stepping-stone one (see Figure 1). In our model, we neglect the fact that intermediate migration rates may favor the purging of recessive segregating alleles (see discussion above and WHITLOCK 2002). However, intermediate migration rates can reduce the load due to segregating mutations but increase the drift load (WHITLOCK *et al.* 2000). We thus think that for conservation of endangered populations, high connection among populations should be less risky and globally much better than maintaining intermediate migration rates. In addition, such optimal migration rates should be very difficult to estimate. Such a positive demographic effect of gene flow between populations, known as the “genetic rescue effect,” has been documented in metapopulations of *Silene* (RICHARDS 2000) and *Daphnia* (EBERT *et al.* 2002; HAAG *et al.* 2002). Advantages to migrants can increase the effective migration rates (see also INGVARSSON and WHITLOCK 2000) and protect some demes from extinction, especially small and isolated ones (RICHARDS 2000).

Other implications of our analysis include methodological considerations. The load would be an appropriate measure for estimating the impact of population

size and subdivision on the fitness of small populations. However, this quantity cannot be directly estimated. Experimental designs for the estimation of inbreeding depression have been proposed to address this question (CHARLESWORTH *et al.* 1990a; DENG and LYNCH 1996; DENG 1998). BATAILLON and KIRKPATRICK (2000) and others have already stressed that inbreeding depression is not a useful indication of the load in small populations. In subdivided populations this conclusion still holds. But our analysis shows that in subdivided populations, patterns of heterosis are similar to patterns of the load and may constitute a measure of the load more appropriate than inbreeding depression for conservation purposes. Moreover, mutations that cause the highest load also cause the highest heterosis but cause no inbreeding depression (BATAILLON 2000b). More precisely, heterosis can provide an indication of the local drift load (see also WHITLOCK *et al.* 2000), *i.e.*, the excess of load due to fixation of deleterious mutations in small populations compared to the load due to segregating mutations maintained in large ones. We thus propose that joint measures of inbreeding depression and heterosis provide a general picture of the architecture of the load in subdivided populations. The load due to segregating mutations could be estimated through inbreeding depression-based methods as already proposed (CHARLESWORTH *et al.* 1990a; DENG and LYNCH 1996; DENG 1998). However, the present study shows that corrections for population size and migration should be taken into account. Alternatively, the drift load could be estimated through the measurement of heterosis. A limitation of this method is that we need to assume no local adaptation. Consequently, an analysis of heterosis would probably underestimate the drift load.

Few data that compare inbreeding depression and heterosis among populations of different sizes or degrees of isolation exist. Often, mean performances of whole populations of different sizes are compared (ELDRIDGE *et al.* 1999; CASSEL *et al.* 2001). However, a positive correlation between population size (and thus global inbreeding level) and mean fitness is not evidence for inbreeding depression, as is sometimes claimed, but evidence of increasing load in small populations. A recent study on the plant *Silene alba* (RICHARDS 2000) is in good agreement with our predictions and clearly illustrates the distinction among inbreeding depression, heterosis, and the load. Germination rates were measured for sib crosses, outcrosses within and between sites, and two kinds of sites, central *vs.* isolated populations, were contrasted. Inbreeding depression was lower in isolated populations than in central ones ( $\sim 0.2$  *vs.* 0.5). On the contrary, heterosis was high in isolated populations ( $\sim 0.6$ ) but weak and nonsignificant in central populations ( $\sim 0.06$ ). Finally, germination rates for outcrosses within populations were higher in central than in isolated populations, which indicates a higher load in isolated populations. Estimation of the load through in-

breeding depression would lead to the reverse conclusion, that central populations suffer higher load than isolated ones. The comparison of inbreeding depression and heterosis shows that the architecture of the load differs between central and isolated populations. The load is weak and mainly due to segregating mutations in central populations whereas it is quite high and mainly due to fixed mutations in isolated populations. We thus suggest clearly distinguishing among inbreeding depression, heterosis, and the load in experimental studies, through the determination of the levels of population structure at which fitness-related traits are compared. This should allow easier comparison among studies and more complete analysis of the consequences of deleterious mutations in natural populations.

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APPENDIX A:  $F_{ST}^S$  AS A FUNCTION OF THE MOMENTS OF  $\Phi$ 

The total genetic variance of allele frequency over the whole metapopulation,  $\sigma_T^2$ , can be decomposed into the within-deme genetic variance,  $\sigma_W^2$ , and between-deme genetic variance,  $\sigma_B^2$ .  $F_{ST}^S$  can be defined as the ratio of the genetic variance between demes over the total genetic variance.

$$F_{ST}^S \equiv \frac{\sigma_B^2}{\sigma_T^2}. \quad (A1)$$

Expressions for variances are given by

$$\sigma_T^2 = \frac{1}{K} \sum_{i=1}^K x_i \left(1 - \frac{1}{K} \sum_{i=1}^K x_i\right) \quad (A2a)$$

$$\sigma_B^2 = \frac{1}{K} \sum_{i=1}^K \left(x_i - \frac{1}{K} \sum_{i=1}^K x_i\right)^2 \quad (A2b)$$

$$\sigma_W^2 = \frac{1}{K} \sum_{i=1}^K x_i (1 - x_i). \quad (A2c)$$

Taking the expectation of  $\sigma_T^2$ ,  $\sigma_B^2$ , and  $\sigma_W^2$  over the  $\Phi$  distribution, and considering the symmetry of the model, we obtain

$$\sigma_T^2 = E_\Phi[x] - \frac{1}{K} E_\Phi[x^2] - \frac{K-1}{K} E_\Phi[xx'] \quad (A3a)$$

$$\sigma_B^2 = E_\Phi[x^2] - \frac{1}{K} E_\Phi[x^2] - \frac{K-1}{K} E_\Phi[xx'] = \frac{K-1}{K} (E_\Phi[x^2] - E_\Phi[xx']) \quad (A3b)$$

$$\sigma_W^2 = E_\Phi[x] - E_\Phi[x^2]. \quad (A3c)$$

Using (A3a) and (A3b) in (A1), we obtain

$$F_{ST}^S = \frac{E_\Phi[x^2] - E_\Phi[xx']}{K/(K-1)E_\Phi[x] - 1/(K-1)E_\Phi[x^2] - E_\Phi[xx']}, \quad (A4)$$

which reduces to

$$F_{ST}^S = \frac{E_\Phi[x^2] - E_\Phi[x]^2}{E_\Phi[x](1 - E_\Phi[x])} \quad (A5)$$

for the infinite island model.

## APPENDIX B: MOMENTS OF THE DISTRIBUTION OF DELETERIOUS ALLELE FREQUENCY IN THE STEPPING-STONE MODEL

We consider a circular stepping-stone model with  $K$  panmictic demes of size  $N$ , with  $K = 2p$  or  $K = 2p + 1$ . We assume local (and equal) migration between two adjacent demes. The diffusion terms are

$$M_{\delta x_1} = -hsx_1 + (1 - x_1)\mu - mx_1 + \frac{m}{2}(x_K + x_2)$$

$$M_{\delta x_i} = -hsx_i + (1 - x_i)\mu - mx_i + \frac{m}{2}(x_{i-1} + x_{i+1}) \quad \text{for } i = 2, \dots, K-1$$

$$M_{\delta x_K} = -hsx_K + (1 - x_K)\mu - mx_K + \frac{m}{2}(x_{K-1} + x_1)$$

$$V_{\delta x_i} = \frac{x_i(1 - x_i)}{2N} \quad \text{for } i = 1, \dots, K$$

$$W_{\delta x_i \delta x_j} = 0 \quad \text{for } i \neq j.$$

**First-order moments:** Using the function  $f(x_1, \dots, x_K) = x_i$ , Equation 5 implies

$$E_{\Phi}[-hsx_i + (1 - x_i)\mu - mx_i + \frac{m}{2}(x_{i-1} + x_{i+1})] = 0.$$

Under the symmetry of the model, all the  $E_{\Phi}[x_i]$  are equal and denoted  $E_{\Phi}[x]$ , giving

$$E_{\Phi}[x] = \frac{\mu}{hs} + O(\mu^2). \quad (\text{B1})$$

**Second-order moments:** Using the function  $f(x_1, \dots, x_k) = x_i^2$ , Equation 5 implies

$$E_{\Phi}\left[\left(2\mu + \frac{1}{2N}\right)x_i - 2\left(hs + \mu + m + \frac{1}{4N}\right)x_i^2 + m(x_{i-1} + x_{i+1})x_i\right] = 0.$$

Under the symmetry of the model,  $E_{\Phi}[x_i x_{i-1}] = E_{\Phi}[x_i x_{i+1}] = E_{\Phi}[xx_i]$  for any  $i$ , giving

$$2\left(hs + \mu + m + \frac{1}{4N}\right)E_{\Phi}[x^2] - 2mE_{\Phi}[xx_i] = \left(2\mu + \frac{1}{2N}\right)E_{\Phi}[x]. \quad (\text{B2})$$

Using the function  $f(x_1, \dots, x_k) = x_i x_{i+1}$ , Equation 5 implies

$$E_{\Phi}[\mu(x_{i+1} + x_i) - 2(hs + \mu + m)x_i x_{i+1} + \frac{m}{2}(x_{i-1} + x_{i+1})x_{i+1} + \frac{m}{2}(x_i + x_{i+2})x_i] = 0.$$

Using the same symmetry arguments,

$$2(hs + \mu + m)E_{\Phi}[xx_i] - mE_{\Phi}[x^2] - mE_{\Phi}[xx_2] = 2\mu E_{\Phi}[x]. \quad (\text{B3})$$

Let the function be  $f(x_1, \dots, x_k) = x_i x_{i+k}$  with  $1 < k < p$ . Equation 5 implies

$$E_{\Phi}[\mu(x_{i+k} + x_i) - 2(hs + \mu + m)x_i x_{i+k} + \frac{m}{2}(x_{i-1} + x_{i+1})x_{i+k} + \frac{m}{2}(x_{i+k-1} + x_{i+k+1})x_i] = 0.$$

Using the same symmetry arguments,

$$2(hs + \mu + m)E_{\Phi}[xx_k] - mE_{\Phi}[xx_{k-1}] - mE_{\Phi}[xx_{k+1}] = 2\mu E_{\Phi}[x]. \quad (\text{B4})$$

Finally, using the function  $f(x_1, \dots, x_k) = x_i x_{i+p}$ , Equation 5 implies

$$E_{\Phi}[\mu(x_{i+p} + x_i) - 2(hs + \mu + m)x_i x_{i+p} + \frac{m}{2}(x_{i-1} + x_{i+1})x_{i+p} + \frac{m}{2}(x_{i+p-1} + x_{i+p+1})x_i] = 0.$$

Under the symmetry of the model and noting that  $x_{i+p+1} = x_{i+p-1}$ ,

$$2(hs + \mu + m)E_{\Phi}[xx_p] - 2mE_{\Phi}[xx_{p-1}] = 2\mu E_{\Phi}[x]. \quad (\text{B5})$$

Writing  $A = 2(hs + \mu + m)$  and  $C = (2\mu + 1/2N)\mu/hs$  and neglecting  $\mu^2/hs$  terms in the left-hand side, we need to solve the following system:

$$\begin{bmatrix} C \\ 0 \\ \dots \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} A + 1/2N & -2m & 0 & \dots & \dots & \dots & \dots & \dots & 0 \\ -m & A & -m & 0 & \dots & \dots & \dots & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & \dots & \dots & \dots & \dots & 0 & -m & A & -m \\ 0 & \dots & \dots & \dots & \dots & \dots & 0 & -2m & A \end{bmatrix} \begin{bmatrix} E_{\Phi}[x^2] \\ E_{\Phi}[xx_1] \\ \dots \\ E_{\Phi}[xx_{p-1}] \\ E_{\Phi}[xx_p] \end{bmatrix}. \quad (\text{B6})$$

**System solving:** The system can be reduced to one general recurrent equation and two specific “boundary” conditions:

$$E_{\Phi}[x^2] = \frac{C + 2mE_{\Phi}[xx_1]}{A + 1/2N} \quad (\text{B7a})$$

$$-mE_{\Phi}[xx_{i-1}] + AE_{\Phi}[xx_i] - mE_{\Phi}[xx_{i+1}] = 0 \quad \text{for } i = 1, \dots, p-1 \quad (\text{B7b})$$

$$E_{\Phi}[xx_p] = \frac{2mE_{\Phi}[xx_{p-1}]}{A}. \quad (\text{B7c})$$

For  $i = 1, \dots, p - 1$ ,  $E_{\Phi}[xx_i] = a\lambda_1^i + b\lambda_2^i$ , where  $\lambda_1$  and  $\lambda_2$  are the roots of the characteristic equation  $m\lambda^2 - A\lambda + m = 0$ :

$$\lambda_1 = \frac{A - \sqrt{A^2 - 4m^2}}{2m} \quad \text{and} \quad \lambda_2 = \frac{A + \sqrt{A^2 - 4m^2}}{2m}.$$

To determine  $a$  and  $b$  we use Equation B7b for  $i = 1$  and  $i = p - 1$ , replacing  $E_{\Phi}[x^2]$  and  $E_{\Phi}[xx_p]$  by their expressions given by (B7a) and (B7c). We thus obtain two linear equations in  $a$  and  $b$ :

$$\begin{bmatrix} \frac{2CNm}{1 + 2AN} \\ 0 \end{bmatrix} = \begin{bmatrix} \lambda_1 \left( A - m \left( \frac{4Nm}{1 + 2AN} - \lambda_1 \right) \right) & \lambda_2 \left( A - m \left( \frac{4Nm}{1 + 2AN} - \lambda_2 \right) \right) \\ \frac{\lambda_1^{p-2}}{A} (Am - A^2\lambda_1 + 2m^2\lambda_1^2) & \frac{\lambda_2^{p-2}}{A} (Am - A^2\lambda_2 + 2m^2\lambda_2^2) \end{bmatrix} \begin{bmatrix} a \\ b \end{bmatrix}.$$

In the case of the infinite stepping-stone model,

$$a = \frac{2CNm}{\lambda_1(2A^2N + A(1 + 2Nm\lambda_1) - m(4Nm + \lambda_1))} \tag{B8a}$$

and

$$b = 0. \tag{B8b}$$

So we obtain

$$E_{\Phi}[x^2] = \frac{2C}{1 + 2\sqrt{A^2 - 4Nm^2}} \tag{B9a}$$

$$E_{\Phi}[xx_i] = \frac{2^{1-i}C(A - \sqrt{A^2 - 4m^2})^i}{m^i(1 + 2\sqrt{A^2 - Nm^2})}, \tag{B9b}$$

which give the following expressions, replacing  $A$  and  $C$  by their expression

$$E_{\Phi}[x^2] = \frac{\mu}{hs(1 + 4N\sqrt{hs(2m + hs)})} + O(\mu^2) \tag{B10}$$

$$E_{\Phi}[xx_i] = \frac{\mu}{hs(1 + 4N\sqrt{hs(2m + hs)})} \left( \frac{m + hs - \sqrt{hs(2m + hs)}}{m} \right)^i + O(\mu^2). \tag{B11}$$

APPENDIX C: NUMERICAL COMPUTATION OF WRIGHT'S EQUATION

For the infinite island model, we can compute numerical values of inbreeding depression, mutation load, and heterosis, using Wright's distribution for  $\Phi$ ,

$$\Phi(x) = C \frac{1}{V_{\delta x}} e^{f(2M_{\delta x}/V_{\delta x})} \tag{C1}$$

with

$$M_{\delta x} = \frac{x(1 - x)(1 - F_{IS})(1 - hs) + (x^2 + F_{IS}x(1 - x))(1 - s)}{W} + \mu(1 - x) - vx + m(x - \bar{x}) - x \tag{C2a}$$

$$V_{\delta x} = \frac{x(1 - x)}{2N_e}, \tag{C2b}$$

where  $\bar{x}$  is the average frequency of the deleterious allele over all the demes,  $C$  is a normalization constant such that  $\int_0^1 \Phi(x) dx = 1$ ,  $W = 1 - 2hs(1 - F_{IS})x(1 - x) - s(x^2 + F_{IS}x(1 - x))$ , and  $N_e = N/(1 + F_{IS})$ .

Equation (C1) can be numerically solved by iteration of the integration of  $\int_0^1 x\Phi(x) dx$  until  $\bar{x} = \int_0^1 x\Phi(x) dx$ . Then we take the expectations given by Equations 3a, 3b, and 3c over this distribution for inbreeding depression, the load, and heterosis. For the  $F_{ST}^S$ , we use Equation A5.

To test the usefulness of the effective size of selection, we also use Wright's equation for a single population, replacing  $N_e$  by  $N_e^S$ , with

$$M_{\delta x} = \frac{x(1-x)(1-F_{\text{is}})(1-hs) + (x^2 + F_{\text{is}}x(1-x))(1-s)}{W} + \mu(1-x) - \nu x - x \quad (\text{C3a})$$

$$V_{\delta x} = \frac{x(1-x)}{2N_c^s}. \quad (\text{C3b})$$

In both cases, direct calculations were done using the function `NIntegrate` of the mathematical software package *Mathematica* (WOLFRAM 1996).