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# Lethals in subdivided populations

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**Summary**

The fate of lethal alleles in populations is of interest in evolutionary and conservation biology for several reasons. For instance, lethals may contribute substantially to inbreeding depression. The frequency of lethal alleles depends on population size, but it is not clear how it is affected by population structure. By analysing the case of the infinite island model by numerical approaches and analytical approximations it is shown that, like population size, population structure affects the fate of lethal alleles if dominance levels are low. Inbreeding depression caused by such alleles is also affected by the population structure, whereas the mutation load is only weakly affected. Heterosis also depends on population structure, but it always remains low, of the order of the mutation rate or less. These patterns are compared with those caused by mildly deleterious mutations to give a general picture of the effect of population structure on inbreeding depression, heterosis, and the mutation load.

## 1. Introduction

The genetic basis of inbreeding depression is of major importance for evolutionary and conservation biology. It is widely accepted that partially recessive deleterious alleles contribute the major portion of inbreeding depression (Charlesworth & Charlesworth, 1987, 1999). These mutations can be divided into two classes (Simmons & Crow, 1977; Crow, 1993): mildly deleterious partially recessive mutations, and highly recessive lethal ones. Although less abundant, the latter class probably causes as much inbreeding depression as detrimentals (Simmons & Crow, 1977; Charlesworth & Charlesworth, 1987).

The pattern of inbreeding depression in natural populations must depend strongly on the kind of deleterious mutations involved. For instance, population structure differentially affects the fate of these two types of alleles. Weakly deleterious and moderately recessive alleles may be fixed in small populations (Kimura *et al.*, 1963) or in strongly subdivided populations (Whitlock *et al.*, 2000). However, if they are highly recessive they can be purged by drift in small populations, provided that drift does not overwhelm selection (Glémin, 2003). In moderately subdivided populations they can also be partially purged if they are highly recessive (Whitlock, 2002; Roze & Rousset, 2004). Nei (1968) showed that the frequency of lethal alleles is virtually insensitive to population size, except if they are fully recessive, in which case their frequency is much lower in small than in large populations (see also Wright, 1937). He also argued that in infinite subdivided populations the deterministic equilibrium should be reached, regardless of how recessive the alleles are, provided that the product of the local population size by the migration rate, $Nm$, i.e. the number of migrants, is large. However, Hedrick (2002) recently showed numerically that the frequency of lethal alleles with low but non-zero dominance coefficients, compatible with experimental estimates ($h = 1$–$3\%$; Simmons & Crow, 1977), does depend on the population size. This suggests that subdivision should also affect the fate of highly recessive lethal alleles, but it is not clear how fast the deterministic equilibrium is reached as $Nm$ increases.

Recently, several theoretical approaches have been used to investigate inbreeding depression, heterosis

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and the mutation load in subdivided populations (Whitlock *et al*., 2000; Theodorou & Couvet, 2002; Glémin *et al*., 2003; Roze & Rousset, 2004). However, none of these studies explicitly focused on highly recessive lethals alleles, mainly because they violate the assumptions of the methods used (except the one by Theodorou & Couvet, 2002). For instance, the moment method developed by Glémin *et al*. (2003) is inappropriate for highly recessive alleles as it assumes that selection mainly occurs against heterozygotes. Roze & Rousset (2003) developed a general method for deriving diffusion approximations in subdivided populations and applied it to deleterious alleles causing inbreeding depression (Roze & Rousset, 2004). However, they assumed weak selection to ensure that coalescence occurs within demes before selection modifies the allele frequencies. This method is thus also inappropriate for lethal alleles.

Here, we analyse the infinite island model for lethal alleles. Some analytical approximations are given and checked against accurate numerical computations. We investigate how population structure can affect the fate of lethal alleles for various dominance levels, and the magnitude of the resulting inbreeding depression, heterosis and mutation load.

## 2. Mean and variance of lethal allele frequency

### (i) *General background*

Consider a single locus with two alleles: a wild-type and a mutant deleterious allele. The fitness of the genotypes with 0, 1 or 2 deleterious alleles are 1, $1-hs$, and $1-s$, respectively. As this study focuses on lethal alleles, it is assumed that $s$ is close to 1 and $h$ close to 0. Mutation occurs from the wild-type to the lethal allele at rate $u$, and at rate $v$ in the reverse direction. Consider an infinite island model with symmetric migration occurring at rate $m$. All the demes have the same size $N$. At equilibrium, the probability density function of the frequency of the deleterious allele within a deme is given by Wright's formula (Wright, 1937):

$$\Phi(x) = C(1-x)^{4N(v+m(1-\bar{x}))-1} x^{4N(u+m\bar{x})-1} \times (1-2hsx-s(1-2h)x^2)^{2N}, \quad (1a)$$

$$\Phi(x) \approx C(1-x)^{4N(v+m(1-\bar{x}))-1} x^{4N(u+m\bar{x})-1} \times e^{-4Nhsx-2N(1-2h)sx^2}, \quad (1b)$$

where $C$ is a constant such that $\int_0^1 \Phi(x)dx = 1$, and $\bar{x}$ is the equilibrium mean frequency of the deleterious frequency and is implicitly given by:

$$\bar{x} = \int_0^1 x\Phi(x)dx. \quad (2)$$

It is worth noting that in Wright's equation infinitesimal changes in allele frequencies due to selection, migration and mutation are assumed to be small enough to neglect the interaction among them. When $m$ tends towards 1 the use of Wright's equation can be problematic (see below). In general, equation (2) has no analytical solution. It can be solved numerically by iteration: starting from an arbitrary $\bar{x}$ introduced in $\Phi$, a new $\bar{x}$ is computed from (2), which is itself introduced in $\Phi$ at the next step. This procedure is iterated until convergence (see for example Whitlock *et al*., 2000). The frequency of a lethal allele in the infinite island model was thus investigated numerically using the function NIntegrate of the Mathematica software (Wolfram, 1996). For low values of $Nu$ and $Nm$, $\Phi$ diverges in $x=0$ (and in $x=1$ for weak selection). In this case, integration techniques given by Kimura *et al*. (1963) were used. Knowing $\bar{x}$, second and higher moments can then be easily computed. In what follows, some approximations for the mean and variance of the allele frequency are also given.

### (ii) *Low migration approximation*

Several approximations can be made. First, the frequency of the lethal allele will remain small over most conditions, such that $x \ll 1$ and $\bar{x} \ll 1$. The first part of equation (1b), $(1-x)^{4N(v+m(1-\bar{x}))-1}$, can thus be approximated by 1 as in Nei (1968). However, this will be valid only for $Nm \ll 1$ which is much more restrictive than the condition $Nv \ll 1$ for a single population. A better approximation is given by:

$$(1-x)^{4N(v+m(1-\bar{x}))-1} \approx e^{-(4Nm-1)x} \approx e^{-4Nmx}.$$

Thus we can write:

$$\Phi(x) = Cx^{A-1}e^{-Bx-Sx^2}$$

where $A = 4N(u+m\bar{x})$, $B = 4N(hs+m)$ and $S = 2N(1-2h)s$.

The mean frequency can be computed according to equation (2). However, as $\Phi(x)$ vanishes very quickly as $x$ tends to infinity, one can integrate $\Phi$ over 0 to infinity instead of 1 (see Nei, 1968). This leads to the implicit formula to the mean frequency of the lethal allele:

$$E[x] = \bar{x} = \frac{\sqrt{S}\Gamma\left[\frac{1+A}{2}\right]F\left[\frac{1+A}{2},\frac{1}{2},\frac{B^2}{4S}\right] - B\Gamma[1+A]F\left[1+\frac{A}{2},\frac{3}{2},\frac{B^2}{4S}\right]}{S\Gamma\left[\frac{A}{2}\right]F\left[\frac{A}{2},\frac{1}{2},\frac{B^2}{4S}\right] - B\sqrt{S}\Gamma\left[1+\frac{A}{2}\right]F\left[\frac{1+A}{2},\frac{3}{2},\frac{B^2}{4S}\right]} \quad (3)$$

where $\Gamma$ is the Gamma function and $F$ is Kummer's confluent hypergeometric function (Abramowitz & Stegun, 1970). Equation (3) cannot be solved analytically. For $A \ll 1$, however, Taylor expansion of

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equation (3) in $A$ leads to a tractable linear equation in $\bar{x}$:

$$E[x]=\frac{A}{2\sqrt{S}}e^{\frac{B^2}{4S}}Erfc\left[\frac{B}{2\sqrt{S}}\right] \tag{4}$$

where *Erfc* denotes the complementary error function (Abramowitz & Stegun, 1970).

The solution of equation (4) is:

$$E[x]=U\left(\frac{2e^{-\frac{B^2}{4S}}\sqrt{S}}{\sqrt{\pi}Erfc\left[\frac{B}{2\sqrt{S}}\right]}-M\right)^{-1} \tag{5}$$

with $U=4Nu$ and $M=4Nm$.

For $h=0$, equation (5) is a good approximation only for $Nm$ less than about 30. However for $h>0$, equation (5) is very accurate even for higher migration rates and population sizes. We can give a simpler expression: recalling that $Z=\frac{B}{2\sqrt{S}}=2\sqrt{\frac{N}{s}(hs+m)}$ will be small for low migration rates and very recessive alleles, and using $e^{-Z^2}\approx 1$ and $Erfc[Z]\approx 1-\frac{2Z}{\sqrt{\pi}}$ for $Z$ close to 0, we get:

$$E[x]=\frac{2\pi Nu}{\sqrt{2\pi Ns}+4Nhs-2Nm(\pi-2)}. \tag{6}$$

For low migration, the Taylor expansion of (6) in $m$ also gives accurate results and does not diverge when the denominator approaches 0:

$$E[x]=\frac{2\pi Nu}{\sqrt{2\pi N(1-2h)s}+4Nhs}+4Nm\frac{\pi(\pi-2)Nu}{\left(\sqrt{2\pi N(1-2h)s}+4Nhs\right)^2}. \tag{7}$$

For $h=0$ this takes the following simple form:

$$E[x]=u\sqrt{\frac{2N\pi}{s}}+m\frac{2N(\pi-2)u}{s}. \tag{8}$$

For $m=0$, this corresponds to the classic approximation for single populations (Wright, 1937; Nei, 1968). Then the second moment can easily be computed, using the Taylor expansion in $A$ and the value of $\bar{x}$ given by equation (5):

$$E[x^2]=\frac{U\left(1-e^{\frac{B^2}{4S}}\sqrt{\pi}\frac{B}{2\sqrt{S}}Erfc\left[\frac{B}{2\sqrt{S}}\right]\right)}{2S-e^{\frac{B^2}{4S}}\sqrt{\pi}\sqrt{S}Erfc\left[\frac{B}{2\sqrt{S}}\right]}. \tag{9}$$

Equation (9) gives good results even for high migration but simpler accurate formulae were not found. For $h=0$, equation (9) becomes simply:

$$E_\Phi[x^2]=\frac{\mu}{s}. \tag{10}$$

The second moment is thus independent of $m$ and $N$. This result was also found by Nei (1968) for a single population, but it also holds in the infinite island model.

(iii) *Approximations using the moment method*

Equations (5) and (9) are generally accurate even for high migration rates, but we can try to find simpler approximations. Glémin *et al.* (2003) developed a method to compute the moments of $\Phi$ in a subdivided population, based on work of Ohta & Kimura (1969, 1971). The method is briefly summarized here (for details see Glémin *et al.*, 2003 and the Appendix). The rationale is to obtain a set of linear equations as functions of the moments of the distribution $\Phi$. Let $M_{\delta x_i}$ be the infinitesimal mean change of allele frequency in deme $i$, $V_{\delta x_i}$ its variance and $W_{\delta x_i \delta x_j}$ the covariance of the change between demes $i$ and $j$. For the K-island model, these terms are given by:

$$M_{\delta x_i}\approx u(1-x_i)-hsx_i-s(1-3h)x_i^2+s(1-2h)x_i^3-mx_i+\frac{m}{K-1}\sum_{j\neq i}x_j, \tag{11a}$$

$$V_{\delta x_i}=\frac{x_i(1-x_i)}{2N}, \tag{11b}$$

$$W_{\delta x_i \delta x_j}=0. \tag{11c}$$

In equation (11a) back mutations ($v$) are neglected and it is assumed that the mean fitness of the population is close to 1. As in Wright's equation, interaction terms between migration and selection are neglected. Let $\Phi(x_1, \ldots, x_n)$ be the probability density function of the deleterious allele in the $n$ demes of the population.

For any function $f(x_1, \ldots, x_n)$, Ohta & Kimura (1969, 1971) showed that:

$$\frac{dE[f]}{dt}=E\left[\sum_{i=1}^{n}M_{\delta x_i}\frac{\partial f}{\partial x_i}+\frac{1}{2}\sum_{i=1}^{n}V_{\delta x_i}\frac{\partial^2 f}{\partial x_i^2}+2\sum_{i=1}^{n}\sum_{j>i}W_{\delta x_i \delta x_j}\frac{\partial^2 f}{\partial x_i \partial x_j}\right]. \tag{12}$$

At equilibrium, $\frac{dE[f]}{dt}=0$. By choosing appropriate $f$ functions, expressions can be obtained for each moment. However, this method leads to an infinite system of equations. To close the system, Glémin *et al.* (2003) linearized the selection term in equation (11a). Biologically, this means that selection acts only against heterozygotes, which is obviously not the case for highly recessive alleles. Another way to close the system is to assume that, up to a given order, moments vanish. Assuming an infinite number of demes greatly simplifies the problem as all the

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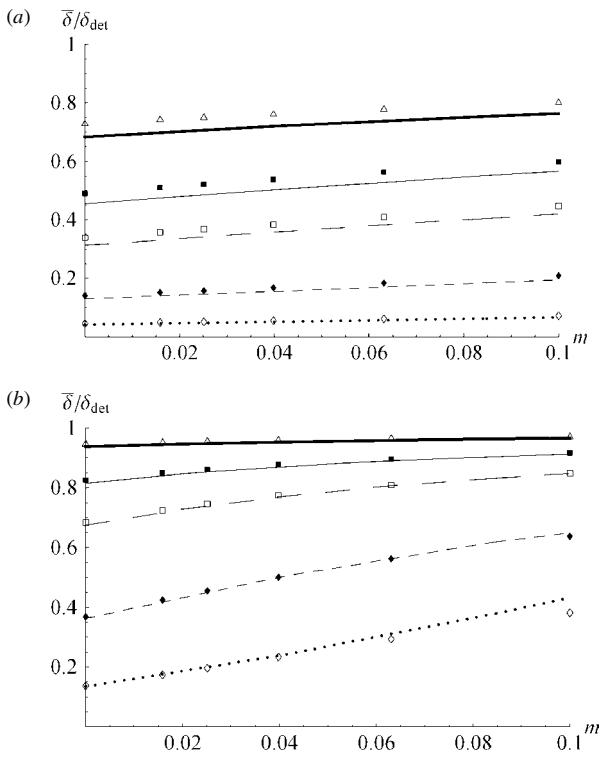


Fig. 1. Mean within-deme inbreeding depression relative to the deterministic expectation as a function of the migration rate, $m$. Dots correspond to numerical integrations and lines to approximations using equation (15a) with $E[x]$ given by equation (5) and $E[x^2]$ given by equation (9), respectively. Using (A4a) and (A4b) gives similar but slightly less accurate results. For $h=0$, equation (16a) is also very accurate, whereas for $h>0$ equation (17a) is less accurate, unless $h$, $N$ and $m$ are not too small (see main text). Parameters used are: $s=1$; $u=10^{-5}$; $v=10^{-7}$; $N=30$ (*a*) or $N=300$ (*b*); $h=0$ (open diamonds and dotted line), $h=0{\cdot}01$ (black diamonds and short-dashed line), $h=0{\cdot}03$ (open squares and long-dashed line), $h=0{\cdot}05$ (black squares and thin unbroken line) or $h=0{\cdot}1$ (open triangles and bold unbroken line).

moments of the form $E[x_i^n\, x_j^p\, x_k^q \ldots]$ can be neglected, and only moments of the form $E[x^n]$ must be computed. Details of the computation are given in the Appendix. Numerically, we found that the mean frequency is a decreasing function of $N$ and $m$ (see Fig. 1), the behaviour of which is well captured by keeping an even number of moments. For mildly deleterious alleles, $\bar{x}$ depends non-monotonically on $N$ and $m$ (see for example figure 1 in Roze & Rousset, 2004), which is better captured by keeping an odd number of moments. However, we have no proof of the general validity of these patterns.

By keeping the two first moments only, the following approximation is obtained:

$$E[x]=\frac{u(1+4Nm+4Nhs)}{s(1+(4Nm-2)h+4Nh^2s)}, \tag{13a}$$

$$E[x^2]=\frac{u}{s(1+(4Nm-2)h+4Nh^2s)}. \tag{13b}$$

For the first moment, the approximation is good if $Nm$ is not too small, except for $h=0$ when $E[x]$ increases linearly with $m$ which is valid only for low $Nm$. The second moment approximation is better than the first one, even for $h=0$ for which we again find $E[x^2]=u/s$. Using the four first moments improves the approximations, and even captures the fact that $E[x^2]$ is not exactly constant for $h=0$. For the first moment, this approximation is also poor for $h=0$. The equations are quite long and are given in Appendix 1.

(iv) *Summary*

Table 1 gives several numerical results to check the accuracy of the approximations for the two first moments. We can see that the case $m=1$ does not match well the deterministic expectations, especially for small $N$ and $h$ values. That can be explained because interaction terms between migration and selection are neglected in Wright's equation. This implies that local drift and selection interact before migration occurs. This artefact allows local 'purging by drift' (Glémin, 2003), even with full migration. This discrepancy is thus important for small population sizes and low dominance coefficients (see Table 1). This effect can be compared with the one (which is not an artefact) obtained by Roze & Rousset (2004) because they allow self-fertilization to occur at rate $1/N$.

For $h=0$, the different approximations are accurate only for low $Nm$. However, for $h>0$ the range of validity of the approximation is much wider. The low migration approximations of equations (5) and (9) are still valid for high migration rates. As in Glémin *et al.* (2003), approximations using the moment method are better for high $Nm$ and when alleles are not too recessive. However, the accuracy is good for a much wider set of parameters than previous approximations.

The frequencies of lethal alleles decrease with both decreasing migration rate and decreased population size. Even for moderately recessive alleles ($h=0{\cdot}03-0{\cdot}1$) the deterministic frequency is reached only for high $Nm$. For moderate $h$ and $Nm$ value, the discrepancy can be very large. Like population size in a single population (Hedrick, 2002), population structure does matter, and using deterministic expectations without regard to population structure would be misleading. The second moment always increases with decreasing $N$ and $m$, but for $h=0$ it is almost insensitive to population size and migration rate. For large $Nm$, the second moment is simply given by $E[x^2]\approx\frac{u}{hs(1+4Nm+4Nhs)}\approx\frac{u}{hs(4Nm+4Nhs)}$ as found by Nei (1968) for lethals and by Glémin *et al.* (2003) for more general conditions ($Nhs\gg 1$).

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Table 1. *Accuracy of the different approximations for the two first moments of Φ, E[x] (× 10³) and E[x²] (× 10⁵), for (a) N = 30 and (b) N = 300; u = 10⁻⁵*

(*a*)

| | | E[$x$] | | | | | E[$x^2$] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $m$ | Num | Eq (5) | Eq (8) | Eq (13a) | Eq (A4a) | Num | Eq (9) | Eq (13b) | Eq (A4b) |
| $h=0$ | 0 | 0·149 | 0·137 | 0·137 | 0·010 | 0·010 | 1·135 | 1·000 | 1·000 | 1·017 |
| | 0·0001 | 0·149 | 0·137 | 0·137 | 0·010 | 0·010 | 1·134 | 1·000 | 1·000 | 1·017 |
| | 0·001 | 0·149 | 0·138 | 0·138 | 0·011 | 0·012 | 1·134 | 1·000 | 1·000 | 1·017 |
| | 0·01 | 0·156 | 0·144 | 0·144 | 0·022 | 0·030 | 1·128 | 1·000 | 1·000 | 1·023 |
| | 0·1 | 0·272 | 0·216 | 0·206 | 0·130 | 0·191 | 1·086 | 1·000 | 1·000 | 1·056 |
| | 1 | 1·103 | 1·220 | 0·822 | 1·210 | 1·249 | 1·016 | 1·000 | 1·000 | 1·016 |
| | deterministic | 3·162 | | | | | 1·000 | | | |
| $h=0·03$ | 0 | 0·118 | 0·110 | 0·111 | 0·044 | 0·062 | 0·800 | 0·712 | 0·954 | 0·929 |
| | 0·0001 | 0·118 | 0·110 | 0·112 | 0·044 | 0·062 | 0·799 | 0·712 | 0·954 | 0·928 |
| | 0·001 | 0·118 | 0·111 | 0·112 | 0·045 | 0·064 | 0·798 | 0·711 | 0·951 | 0·924 |
| | 0·01 | 0·122 | 0·114 | 0·116 | 0·054 | 0·075 | 0·781 | 0·701 | 0·923 | 0·888 |
| | 0·1 | 0·159 | 0·144 | 0·157 | 0·118 | 0·144 | 0·644 | 0·603 | 0·710 | 0·662 |
| | 1 | 0·268 | 0·267 | 0·563 | 0·268 | 0·270 | 0·219 | 0·213 | 0·215 | 0·214 |
| | deterministic | 0·330 | | | | | 0·011 | | | |
| $h=0·1$ | 0 | 0·076 | 0·072 | 0·078 | 0·065 | 0·073 | 0·389 | 0·354 | 0·500 | 0·422 |
| | 0·0001 | 0·076 | 0·072 | 0·078 | 0·065 | 0·073 | 0·388 | 0·354 | 0·500 | 0·422 |
| | 0·001 | 0·076 | 0·072 | 0·078 | 0·065 | 0·073 | 0·387 | 0·353 | 0·497 | 0·420 |
| | 0·01 | 0·076 | 0·073 | 0·080 | 0·067 | 0·074 | 0·374 | 0·343 | 0·472 | 0·400 |
| | 0·1 | 0·082 | 0·079 | 0·100 | 0·078 | 0·082 | 0·277 | 0·264 | 0·313 | 0·280 |
| | 1 | 0·095 | 0·094 | 0·297 | 0·095 | 0·095 | 0·072 | 0·071 | 0·071 | 0·071 |
| | deterministic | 0·100 | | | | | 0·001 | | | |

(*b*)

| | | E[$x$] | | | | | E[$x^2$] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | m | Num | Eq (5) | Eq (8) | Eq (13a) | Eq (A4a) | Num | Eq (9) | Eq (13b) | Eq (A4b) |
| $h=0$ | 0 | 0·441 | 0·434 | 0·434 | 0·010 | 0·010 | 1·038 | 1·000 | 1·000 | 1·002 |
| | 0·0001 | 0·441 | 0·435 | 0·435 | 0·011 | 0·012 | 1·038 | 1·000 | 1·000 | 1·002 |
| | 0·001 | 0·448 | 0·441 | 0·441 | 0·022 | 0·030 | 1·037 | 1·000 | 1·000 | 1·002 |
| | 0·01 | 0·517 | 0·506 | 0·503 | 0·130 | 0·207 | 1·051 | 1·000 | 1·000 | 1·008 |
| | 0·1 | 1·385 | 1·367 | 1·119 | 1·210 | 1·383 | 1·014 | 1·000 | 1·000 | 1·013 |
| | 1 | 2·779 | 12·020 | 7·284 | 12·010 | 12·050 | 1·001 | 1·000 | 1·000 | 1·002 |
| | deterministic | 3·162 | | | | | 1·000 | | | |
| $h=0·03$ | 0 | 0·228 | 0·226 | 0·241 | 0·183 | 0·214 | 0·355 | 0·343 | 0·495 | 0·400 |
| | 0·0001 | 0·229 | 0·226 | 0·242 | 0·183 | 0·214 | 0·355 | 0·343 | 0·494 | 0·399 |
| | 0·001 | 0·229 | 0·227 | 0·243 | 0·186 | 0·216 | 0·352 | 0·340 | 0·486 | 0·393 |
| | 0·01 | 0·237 | 0·235 | 0·263 | 0·206 | 0·231 | 0·324 | 0·314 | 0·420 | 0·345 |
| | 0·1 | 0·279 | 0·281 | 0·453 | 0·279 | 0·283 | 0·178 | 0·166 | 0·178 | 0·168 |
| | 1 | 0·322 | 0·325 | 2·358 | 0·325 | 0·325 | 0·036 | 0·026 | 0·026 | 0·026 |
| | deterministic | 0·330 | | | | | 0·011 | | | |
| $h=0·1$ | 0 | 0·095 | 0·094 | 0·119 | 0·095 | 0·095 | 0·072 | 0·071 | 0·078 | 0·072 |
| | 0·0001 | 0·095 | 0·094 | 0·119 | 0·095 | 0·095 | 0·072 | 0·071 | 0·078 | 0·072 |
| | 0·001 | 0·095 | 0·094 | 0·119 | 0·095 | 0·095 | 0·072 | 0·070 | 0·077 | 0·071 |
| | 0·01 | 0·095 | 0·095 | 0·124 | 0·095 | 0·095 | 0·067 | 0·065 | 0·071 | 0·066 |
| | 0·1 | 0·097 | 0·097 | 0·170 | 0·097 | 0·097 | 0·040 | 0·039 | 0·040 | 0·039 |
| | 1 | 0·099 | 0·099 | 0·630 | 0·099 | 0·099 | 0·009 | 0·008 | 0·008 | 0·008 |
| | deterministic | 0·100 | | | | | 0·001 | | | |

'Num' indicates numerical results by integration of Φ. Deterministic corresponds to an infinite single population. Approximations are labelled by their equation numbers.

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These results are based on the infinite island model. How robust are they when the number of demes, $n$, is finite? Roze & Rousset (2004) showed that for large $N$ and small $m$ the frequency of mildly deleterious alleles is roughly independent of the number of demes. Glémin *et al*. (2003) gave expressions for deleterious alleles not too recessive, which depend on $n$. However, the effect is weak unless a few demes are considered, say less than 10. The frequency of fully recessive lethals is very sensitive to the population size. If the total population size is small, $nN$, we expect that the frequency will be lower than in an infinite population even with complete migration. Generally, we also expect lower frequencies than predicted by previous equations. For partially recessive alleles, purging is less efficient such that the total population size and the number of demes should be less important.

## 3. Inbreeding depression, heterosis and the load

(i) *Expressions and approximations*

One can now turn to the consequences of these results for inbreeding depression, heterosis and the genetic load. Following Whitlock (2002), Glémin *et al*. (2003) and Roze & Rousset (2004), we can compute the load ($L$), the within-deme inbreeding depression ($\delta$), heterosis between demes ($H$) and the between-deme inbreeding depression ($\gamma$). Given $\Phi$, one can compute the mean inbreeding depression, load and heterosis by integrating over $\Phi$:

$$\bar{\delta} = \int_0^1 \delta(x)\Phi(x)dx, \tag{14a}$$

$$\bar{L} = \int_0^1 L(x)\Phi(x)dx, \tag{14b}$$

$$\bar{H} = \int_0^1 \int_0^1 H(x,y)\Phi(x)\Phi(y)dxdy, \tag{14c}$$

$$\bar{\gamma} = \int_0^1 \int_0^1 \gamma(x,y)\Phi(x)\Phi(y)dxdy \tag{14d}$$

where $x$ and $y$ are the frequencies of the lethal alleles in two different demes and:

$$\delta(x) = \frac{s(1-2h)x(1-x)}{2(1-2hsx(1-x)-sx^2)} \approx \frac{s(1-2h)}{2h}(x-x^2),$$

$$L(x) = 2hsx + (1-2h)sx^2,$$

$$H(x,y) = \frac{s(1-2h)(x-y)^2}{2(1-hs(x(1-y)+y(1-x))-sxy} \approx s(1-2h)(x-y)^2,$$

$$\gamma(x,y) = \frac{s(1-2h)(x+y+x^2+y^2-4xy)}{4(1-hs(x(1-y)+y(1-x))-sxy} \approx \frac{s(1-2h)}{4}(x+y+x^2+y^2-4xy).$$

The approximations for $\delta(x)$, $H(x, y)$ and $\gamma(x, y)$ hold for weak selection and for $x \ll 1$ or $y \ll 1$ which applies under strong selection. Using these approximate terms, the mean inbreeding depression as the mean load can be expressed in terms of the two first moments of $\Phi$ (see for example Bataillon & Kirkpatrick, 2000; Glémin *et al*., 2003):

$$\bar{\delta} \approx \frac{s(1-2h)}{2}(E[x]-E[x^2]), \tag{15a}$$

$$\bar{L} = 2hsE[x] + (1-2h)sE[x^2], \tag{15b}$$

$$\bar{H} \approx s(1-2h)(E[x^2]-E[x]^2), \tag{15c}$$

$$\bar{\gamma} \approx \frac{s(1-2h)}{2}(E[x]+E[x^2]-2E[x]^2). \tag{15d}$$

Equations (15c) and (15d) come from the fact that $E[x] = E[y]$ and $E[xy] = E[x]E[y] = E[x]^2$ in the infinite island model. Numerical integration of equations (14c) and (14d) is somewhat problematic because of the double integral sum, such that equations (15c) and (15d) will be preferred.

Approximate analytical expressions can then be given using the expressions for the first and second moments. For $h = 0$, using expressions (8) and (10) in equations (15), and neglecting the terms in $u^2$, we get:

$$\bar{\delta} = \frac{u}{2}(\sqrt{2\pi Ns} + 2(\pi-2)Nm - 1), \tag{16a}$$

$$\bar{L} = u, \tag{16b}$$

$$\bar{H} = u, \tag{16c}$$

$$\bar{\gamma} = \frac{u}{2}(\sqrt{2\pi Ns} + 2(\pi-2)Nm + 1). \tag{16d}$$

For $h > 0$, using equations (13a) and (13b) leads to:

$$\bar{\delta} = \frac{2Nu(1-2h)(m+hs)}{1+(4Nm-2)h+4Nh^2s}, \tag{17a}$$

$$\bar{L} = \frac{u(1+8Nhm+8Nh^2s)}{1+(4Nm-2)h+4Nh^2s}, \tag{17b}$$

$$\bar{H} = \frac{u(1-2h)}{1+(4Nm-2)h+4Nh^2s}, \tag{17c}$$

$$\bar{\gamma} = \frac{u(1-2h)(1+2N(m+hs))}{1+(4Nm-2)h+4Nh^2s}. \tag{17d}$$

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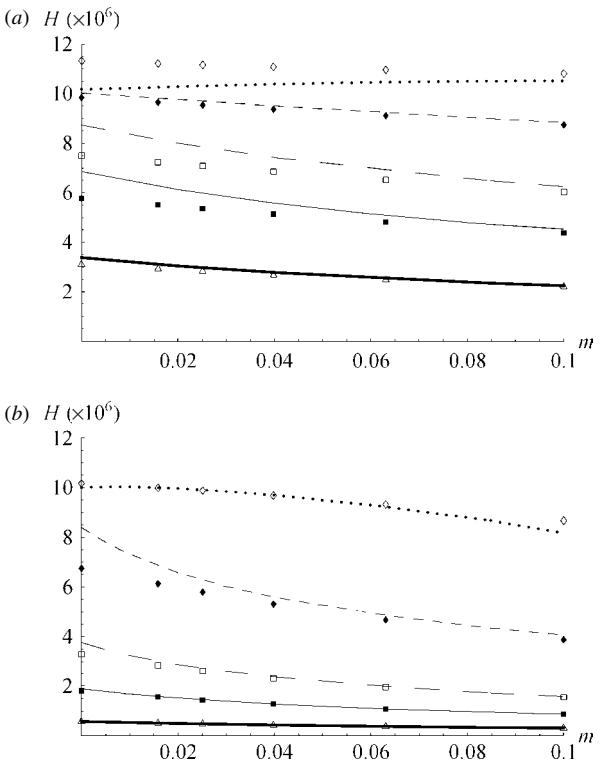


Fig. 2. Mean heterosis between populations (absolute value) as a function of the migration rate, $m$. Dots correspond to numerical integrations and lines to approximations using equation (15c) with $E[x]$ given by equation (A4a) and $E[x^2]$ given by equation (A4b), respectively. Terms in $u^2$ are neglected, except for $h=0$, which improves the approximation. Equations (16c) and (17c) are less accurate for $N=30$, but give good results for $N=300$. Using equations (5) and (9) gives similar but slightly less accurate results. Parameters used are: $s=1$; $u=10^{-5}$; $v=10^{-7}$; $N=30$ (*a*) or $N=300$ (*b*); $h=0$ (open diamonds and dotted line), $h=0{\cdot}01$ (black diamonds and short-dashed line), $h=0{\cdot}03$ (open squares and long-dashed line), $h=0{\cdot}05$ (black squares and thin unbroken line) or $h=0{\cdot}1$ (open triangles and bold unbroken line).

Equations (16) can be used for $m<0{\cdot}1$ and equations (17) are quite good for population sizes not too small, about $N>50$, and mutations not too recessive, about $h>0{\cdot}05$. More accurate expressions can be obtained using equations (5) and (9) or (A4a) and (A4b) given in the Appendix, but the expressions are quite long and not given here.

The within-deme inbreeding depression depends on $N$ and $m$, even for moderately recessive alleles ($h=0{\cdot}05-0{\cdot}1$) and can be much smaller than in an infinite single population (Fig. 1). The load, however, is almost insensitive to the population structure. For $h=0$, equation (17b) collapses to (16b), such that the load is independent of both the population size and the migration rate. For low $h>0$, the load takes value between $u/(1-2h)$ and $2u$. Heterosis is always low, $H<u$, but depends on the population size and the population structure (Fig. 2). When $h=0$, $H$ does depends on $m$ and $N$, contrary to what equation (16c) predicts, which thus gives the upper limit. Finally, because heterosis is low, between-deme inbreeding depression is very close to within-deme inbreeding depression.

### (ii) *Comparison with mildly deleterious alleles*

Consideration of the present results and those from previous studies (Theodorou & Couvet, 2002; Whitlock, 2002; Glémin *et al*., 2003; Roze & Rousset, 2004) gives a general picture of the effect of population structure on inbreeding depression, heterosis and the load caused by the whole range of deleterious mutations. Some examples are given in Fig. 3, in which results for mildly deleterious and lethal alleles are compared.

In large and moderately subdivided populations, the mutation load is weakly sensitive to the kind of mutations involved. In small and strongly subdivided populations, slightly deleterious mutations create a large drift load while strongly deleterious alleles, like lethals, still cause a low mutation load, of the order of the mutation rate. The mutation load is also weakly sensitive to the level of dominance (but see Whitlock, 2002; Roze & Rousset, 2004). By contrast, inbreeding depression depends on the dominance levels and the magnitude of the deleterious effects of mutations for a wider range of population structure. The more deleterious and the more recessive the mutations are, the higher the inbreeding depression is. In addition, the dependence on the selection coefficient is stronger for more recessive mutations (compare $h=0{\cdot}01$ and $h=0{\cdot}3$ in Fig. 3, and see also table 1 in Roze & Rousset, 2004). Finally, like inbreeding depression, heterosis depends both on $h$ and on $s$. In small and isolated populations, weakly deleterious mutations of intermediate effect contribute the most to heterosis (see Whitlock *et al*., 2000). Lethals cause the highest heterosis in large and moderately subdivided populations. However, in such conditions the effect is small, of the order of the mutation rate.

## 4. Discussion

### (i) *Distribution of lethal alleles in subdivided populations*

It has long been recognized that fully recessive lethals alleles have much lower equilibrium frequencies in small than in large populations (Wright, 1937; Nei, 1968). Recently, Hedrick (2002) showed that population size also affects alleles with low dominance levels, typically within the range of available estimates: $h=0{\cdot}01$ to $0{\cdot}03$ (Simmons & Crow, 1977; Charlesworth & Charlesworth, 1999). The present results show that, for the same set of parameters, population structure may also strongly affect lethal

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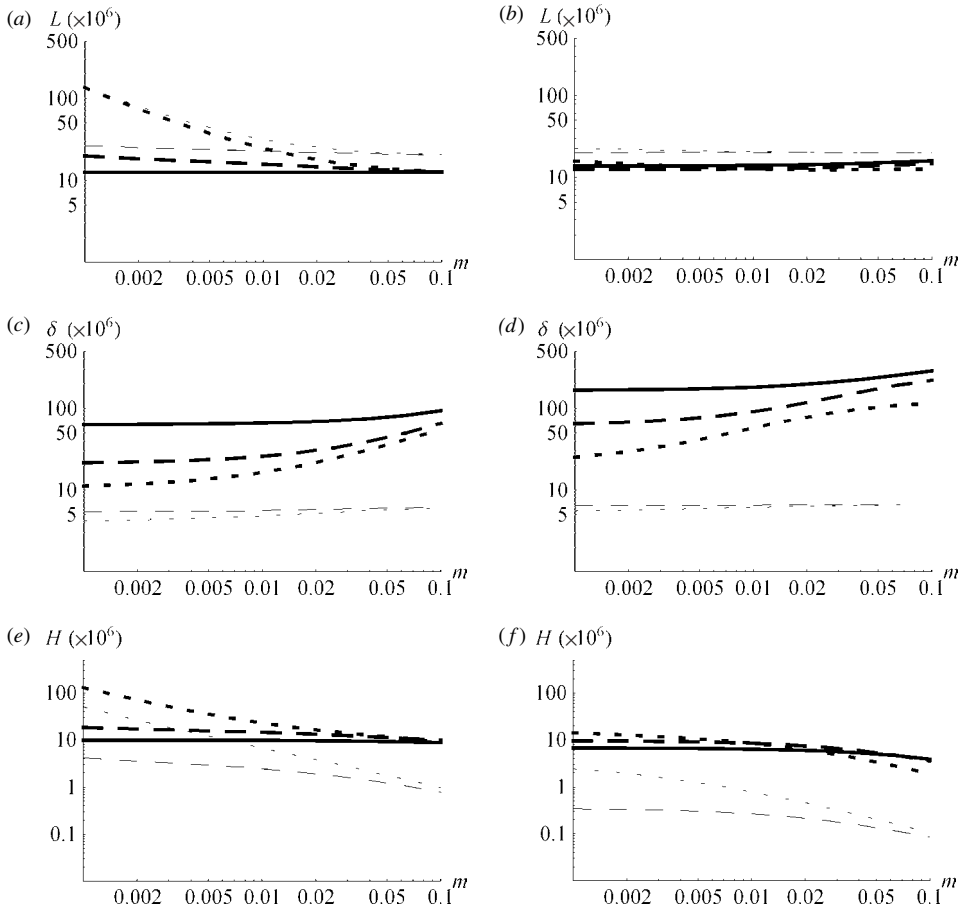


Fig. 3. Mean mutation load ($a, b$), within-deme inbreeding depression ($c, d$), and heterosis ($e, f$) caused by lethal and mildly deleterious alleles, as a function of the migration rate. Results have been obtained by numerical integration of equation (2). Parameters used are: $u=10^{-5}$; $v=10^{-7}$; $N=30$ ($a, c, e$) or $N=300$ ($b, d, f$). Plain unbroken line: $h=0{\cdot}01$ and $s=1$. Dashed bold line: $h=0{\cdot}01$ and $s=0{\cdot}1$. Dotted bold line: $h=0{\cdot}01$ and $s=0{\cdot}01$. Thin dashed line: $h=0{\cdot}3$ and $s=0{\cdot}1$. Thin dotted line: $h=0{\cdot}3$ and $s=0{\cdot}01$.

allele frequencies. For example, for $N=100$, $m=0{\cdot}01$ and $h=0{\cdot}03$, the frequency is half that expected in a single large population; for $h=0{\cdot}01$, it would be one-quarter. For a given $Nm$ value, the frequency of lethal alleles also decreases with deme size. Populations subdivided into numerous small subpopulations should have low standing variation for lethals. Population structure ceases to affect lethal frequencies for dominance levels higher than about $h=0{\cdot}1$, much higher than the available estimates. High numbers of lethals are thus expected in very large and weakly subdivided populations, as was found in some coniferous trees (Remington & O'Malley, 2000) or in bivalve species (Launey & Hedgecock, 2001). However, high mutation rates towards lethal alleles may also explain such results, at least in coniferous trees (Remington & O'Malley, 2000).

For partially selfing species, population structure should have much less impact. Indeed, partial selfing helps purge highly recessive alleles with large fitness effect, such that the expected frequency of lethals should be low irrespective of the population structure. Noting that partial selfing increases the effective dominance coefficient according to $h_e=h+F_{IS}-hF_{IS}\approx F_{IS}$ (Caballero & Hill, 1992), an $F_{IS}$ of about $0{\cdot}1$ would be sufficient to remove the effect of the population structure. For a recessive lethal, $F_{IS}\approx\frac{\sigma}{2+\sigma}$ where $\sigma$ is the selfing rate (Lande & Schemske, 1985; Glémin, 2003); so above a selfing rate of about 20% population structure should not affect the fate of lethal alleles.

### (ii) *Consequences of lethals in subdivided populations*

The effect of population structure on inbreeding depression, heterosis and the mutation load are quite different. Despite purging, the load is weakly affected by the population structure. For fully recessive alleles, the load equals $u$ and is independent of the population structure. For $h>0$, it lies between $u/(1-2h)$ and $2u$. This relative independence of population structure can be explained because variance in allele frequency increases the load and compensates for the decreasing effect of the mean. On the contrary, within-deme

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Table 2. *Total inbreeding depression and heterosis due to lethals and detrimentals as a function of the migration rate*

| | | $U=0{\cdot}5$ | | $U=0{\cdot}1$ | |
|---|---|---|---|---|---|
| | Migration rate | Detrimentals | Lethals | Detrimentals | Lethals |
| Inbreeding depression | $m=0{\cdot}001$ | 0·237 | 0·231 | 0·053 | 0·231 |
| | $m=0{\cdot}01$ | 0·245 | 0·237 | 0·055 | 0·237 |
| | $m=0{\cdot}1$ | 0·267 | 0·293 | 0·060 | 0·293 |
| | deterministic | 0·283 | 0·539 | 0·064 | 0·539 |
| Heterosis | $m=0{\cdot}001$ | 0·187 | 0·037 | 0·041 | 0·037 |
| | $m=0{\cdot}01$ | 0·116 | 0·036 | 0·024 | 0·036 |
| | $m=0{\cdot}1$ | 0·039 | 0·030 | 0·008 | 0·030 |
| | deterministic | 0·000 | 0·000 | 0·000 | 0·000 |

A multiplicative effect of mutations on fitness is assumed. $U$ is the genomic detrimental mutation rate. For lethals, $U=0{\cdot}05$. $h=0{\cdot}03$ for lethals and $h=0{\cdot}3$ for detrimentals; $s=0{\cdot}1$ for detrimentals. $N=30$. Deterministic corresponds to an infinite single population.

inbreeding depression is greatly affected by the population structure (see Fig. 2). Both decreasing mean and increasing variance contribute to the decline of inbreeding depression in small and isolated populations. Depending on the population parameters and dominance coefficients, inbreeding depression can be reduced by up to fivefold relative to a single large population. As expected, heterosis is also affected by population structure because it depends on the variance of alleles frequencies between populations, which increases with increasing subdivision.

Lethals and detrimentals can contribute to inbreeding depression. This will depend on the magnitude of the genomic mutation rates towards these two gene categories. Mutation rates toward lethals may be one order of magnitude lower than mutation rates towards detrimentals (Drake *et al*., 1998), but other recent estimates in *Drosophila* suggest that it could be only one-half lower (Fry *et al*., 1999; Charlesworth *et al*., 2004). Despite these lower mutation rates, they could cause a substantial part of the within-deme inbreeding depression, mainly because they are believed to be more recessive (Charlesworth & Charlesworth, 1987). Table 2 shows the part of inbreeding depression and heterosis due to detrimentals and lethals respectively, assuming a simple model of multiplicative effect of mutations. Genomic mutation rate towards detrimentals is assumed to be 0·1 or 0·5, in the range of estimate found in *Drosophila* (Simmons & Crow, 1977; Charlesworth *et al*., 2004), the lower estimate being more probable. Genomics mutation rate towards lethals is assumed to be 0·05, giving one-tenth or one-half of the detrimental mutation rate. Dominance coefficients are $h=0{\cdot}03$ for lethals (Simmons & Crow, 1977) and $h=0{\cdot}3$ for detrimentals (for example Deng & Lynch, 1997; Dudash & Carr, 1998), and the selection coefficient for detrimentals is $s=0{\cdot}1$ (see review in Bataillon, 2000). Population structure may affect the genetic basis of inbreeding depression because mildly deleterious and partially recessive alleles are less affected by subdivision than almost fully recessive lethals. The part of inbreeding depression due to lethals greatly differs among species, from a minor (for instance in the monkey flower *Mimulus guttatus*: Willis, 1999) to a large contribution (for instance in some coniferous trees: Remington & O'Malley, 2000). Lethals and detrimentals can affect different life stages (Husband & Schemske, 1996), but, among other factors, population size and population structure could also explain such different patterns: high inbreeding depression mainly due to lethals in single large populations versus lower inbreeding depression contributed by both detrimentals and lethals in more subdivided populations.

The genetic basis of heterosis may also be sensitive to population structure (Table 2). In populations strongly subdivided in small demes, heterosis will be due mainly to weakly deleterious alleles (see Table 2 $U=0{\cdot}5$, Fig. 3e and Whitlock *et al*., 2000) because they individually cause higher heterosis and are more numerous. However, if detrimental mutation rates are not much higher than lethal mutation rates ($U=0{\cdot}1$ in Table 2), both can contribute equally. In large and weakly subdivided populations, mutations with large effect, including lethals, will contribute a substantial part of heterosis (Table 2, Fig. 3f). However, in such cases, the effect of lethal alleles on heterosis is one or two orders of magnitude lower than the effect on inbreeding depression (compare Fig. 3d and 3f). In those cases, the overall heterosis will be low and not easily detected in natural populations, unless mutation rates are very high.

### (iii) *Implications for conservation issues*

These results also have implications for conservation of endangered species. First, as Hedrick (2002)

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pointed out for small populations, species with a past history of strong population subdivision should have purged most of the load due to lethals. In such species, intentional inbreeding would be inefficient because any variation that can easily be purged will already have been removed. In addition, despite this purging process, the mutation load due to lethals is quite insensitive to population size and population structure, unlike the load due to slightly deleterious mutations (Kimura *et al*., 1963; Whitlock *et al*., 2000). Second, fragmentation of initially well connected populations will have short-term negative effects. The dynamics of purging after population fragmentation was not explicitly studied here; however, some general ideas can be given. For purging to occur, lethals must be expressed in homozygotes more frequently than in large undivided populations. During this phase a transient load will occur and may affect the population dynamics. This has been shown for a single bottlenecked population (Kirkpatrick & Jarne, 2000). The same reasoning should be valid for lethals in subdivided populations. Inferences on the detailed genetic basis of inbreeding depression should thus be helpful for characterizing the genetic risk that may threaten small and fragmented populations.

## Appendix 1

The general moments equations for the infinite island model are derived, extending the results of Glémin *et al*. (2003). Using equation (12) at equilibrium with the infinitesimal terms given by equations (11a,b,c) and appropriate $f$ functions, leads to linear equations with respect to the moment of the distribution of the deleterious allele frequency, $\Phi$. In the infinite island model, $E[x_i^m x_j^n x_k^p \ldots] = E[x_i]^m E[x_j]^n E[x_k]^p \ldots$, so that all these moments are in $o(u^{m+n+p+\ldots})$ and can be neglected. Because of the symmetry of the model, all moments of the form $E[x_i^n]$ are the same for any $i$, and denoted $E[x^n]$.

Using $f = x_i$, equation (12) becomes:

$$u-(u+hs)E[x]-s(1-3h)E[x^2]+s(1-2h)E[x^3]=0. \tag{A1}$$

Using $f = x_i^n$, $n>1$, equation (12) becomes:

$$n\left(u+\frac{n-1}{4N}\right)E[x^{n-1}]-n\left(u+hs+m+\frac{n-1}{4N}\right)E[x^n] -n(1-3h)sE[x^{n+1}]+n(1-2h)sE[x^{n+2}]=0. \tag{A2}$$

This procedure leads to an infinite system of linear equations that must be closed by neglecting the moments up to a given order. For the $n$ first moments, using matrix notations, the vector of moments at equilibrium, $\mathbf{M}=\{E[x],\ E[x^2],\ \ldots,\ E[x^n]\}$ is the solution of:

$$\mathbf{U}=\mathbf{PM} \tag{A3}$$

where:

$$\mathbf{U}=\{-u,\ 0,\ \ldots,\ 0\}$$

and

$$\mathbf{P}=\begin{bmatrix} u+hs & s(1-3h) & s(1-2h) & 0 & . & . & . & . \\ -2\left(u+\frac{1}{4N}\right) & 2\left(u+hs+m+\frac{1}{4N}\right) & 2(1-3h)s & 2(1-2h)s & 0 & . & . & . \\ . & . & . & . & . & . & . & . \\ . & 0 & -k\left(u+\frac{k-1}{4N}\right) & k\left(u+hs+m+\frac{k-1}{4N}\right) & k(1-3h)s & k(1-2h)s & 0 & . \\ . & . & . & . & . & . & . & . \\ . & . & . & 0 & -n\left(u+\frac{n-1}{4N}\right) & n\left(u+hs+m+\frac{n-1}{4N}\right) & n(1-3h)s & n(1-2h)s \end{bmatrix}$$

For example, keeping the four first moments gives the following results:

$$E[x]=u\frac{3+N(22m+(6-8h)s)+8N^2(6m+(5-9h)s)(m+hs)+32N^3(m+hs)^3}{6Ns(m+(1-2h)^2s)+8N^2s(m+3hm+6(1-2h)hs)(m+hs)+32N^3hs(m+hs)^3}, \tag{A4a}$$

$$E[x^2]=u\frac{3+N(10m+(6-8h)s)+8N^2(m+hs)^2}{6Ns(m+(1-2h)^2s)+8N^2s(m+3hm+6(1-2h)hs)(m+hs)+32N^3hs(m+hs)^3}, \tag{A4b}$$

These expressions can then be used in equations (15a) and (15b) to compute the mean inbreeding depression and the mean load, respectively.

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## References

Abramowitz, M. & Stegun, I. A. (1970). *Handbook of Mathematical Functions*. New York: Dover.

Bataillon, T. (2000). Estimation of spontaneous genome-wide mutation rate parameters: wither beneficial mutations? *Heredity* **84**, 497–501.

Bataillon, T. & Kirkpatrick, M. (2000). Inbreeding depression due to mildly deleterious mutations in finite populations: size does matter. *Genetical Research* **75**, 75–81.

Caballero, A. & Hill, W. G. (1992). Effects of partial inbreeding on fixation rates and variation of mutant genes. *Genetics* **131**, 493–507.

Charlesworth, B. & Charlesworth, D. (1999). The genetic basis of inbreeding depression. *Genetical Research* **74**, 329–340.

Charlesworth, B., Borthwick, H., Bartolome, C. & Pignatelli, P. (2004). Estimates of the genomic mutation rate for detrimental alleles in *Drosophila melanogaster*. *Genetics* **167**, 815–826.

Charlesworth, D. & Charlesworth, B. (1987). Inbreeding depression and its evolutionary consequences. *Annual Review of Ecology and Systematics* **18**, 237–268.

Crow, J. F. (1993). Mutation, mean fitness, and genetic load. In *Oxford Surveys in Evolutionary Biology*, vol. 9 (ed. D. Futuyma & J. Antonovics), pp. 3–42. Oxford: Oxford University Press.

Deng, H.-W. & Lynch, M. (1997) Inbreeding depression and inferred deleterious-mutation parameters in *Daphnia*. *Genetics* **147**, 147–155.

Dudash, M. R. & Carr, D. E. (1998). Genetics underlying inbreeding depression in *Mimulus* with contrasting mating systems. *Nature* **393**, 682–684.

Drake, J. W., Charlesworth, B., Charlesworth, D. & Crow, J. F. (1998). Rates of spontaneous mutation. *Genetics* **148**, 1667–1686.

Fry, J. D., Keightley, P. D., Heinsohn, S. L. & Nuzhdin, S. V. (1999). New estimates of the rates and effects of mildly deleterious mutation in *Drosophila melanogaster*. *Proceedings of the National Academy of Sciences of the USA* **96**, 574–579.

Glémin, S. (2003). How are deleterious mutations purged? Drift versus nonrandom mating. *Evolution* **57**, 2678–2687.

Glémin, S., Ronfort, J. & Bataillon, T. (2003). Patterns of inbreeding depression and architecture of the load in subdivided populations. *Genetics* **165**, 2193–2212.

Hedrick, P. W. (2002). Lethals in finite populations. *Evolution* **56**, 654–657.

Husband, B. C. & Schemske, D. W. (1996). Evolution of the magnitude and timing of inbreeding depression in plants. *Evolution* **50**, 54–70.

Kimura, M., Maruyama, T. & Crow, J. F. (1963). The mutation load in small populations. *Genetics* **48**, 1303–1312.

Kirkpatrick, M. & Jarne, P. (2000). The effect of a bottleneck on inbreeding depression and the genetic load. *The American Naturalist* **155**, 154–167.

Lande, R. & Schemske, D. W. (1985). The evolution of self-fertilization and inbreeding depression in plants. I. Genetic models. *Evolution* **39**, 24–40.

Launey, S. & Hedgecock, D. (2001). High genetic load in the Pacific Oyster *Crassostrea gigas*. *Genetics* **159**, 225–265.

Nei, M. (1968). The frequency distribution of lethal chromosomes in finite populations. *Proceedings of the National Academy of Sciences of the USA* **60**, 517–524.

Ohta, T. & Kimura, M. (1969). Linkage disequilibrium at steady state determined by random genetic drift and recurrent mutation. *Genetics* **63**, 229–238.

Ohta, T. & Kimura, M. (1971). Linkage disequilibrium between two segregating nucleotide sites under the steady flux of mutations in a finite population. *Genetics* **68**, 57–580.

Remington, D. L. & O'Malley, D. M. (2000). Whole genome characterization of embryonic stage inbreeding depression in a selfed loblolly pine family. *Genetics* **155**, 337–348.

Roze, D. & Rousset, F. (2003). Selection and drift in subdivided populations: a straightforward method for deriving diffusion approximations and applications involving dominance, selfing and local extinctions. *Genetics* **165**, 2153–2166.

Roze, D. & Rousset, F. (2004). Joint effects of self-fertilization and population structure on mutation load, inbreeding depression and heterosis. *Genetics* **167**, 100–1015.

Simmons, M. & Crow, J. F. (1977). Mutations affecting fitness in *Drosophila* populations. *Annual Review of Genetics* **11**, 49–78.

Theodorou, K. & Couvet, D. (2002). Inbreeding depression and heterosis in a subdivided population: influence of the mating system. *Genetical Research* **80**, 107–116.

Whitlock, M. C. (2002). Selection, load, and inbreeding depression in a large metapopulation. *Genetics* **160**, 119–1202.

Whitlock, M. C., Ingvarsson, P. K. & Hatfield, T. (2000). Local drift load and the heterosis of interconnected populations. *Heredity* **84**, 452–457.

Willis, J. H. (1999). The role of genes of large effect on inbreeding depression in *Mimulus guttatus*. *Evolution* **53**, 1648–1691.

Wolfram, S. (1996). *The Mathematica Book*. Cambridge: Cambridge University Press.

Wright, S. (1937). The distribution of gene frequencies in populations. *Proceedings of the National Academy of Sciences of the of the USA* **23**, 307–320.