

The effect of linkage disequilibrium and deviation from Hardy–Weinberg proportions on the changes in genetic variance with bottlenecks

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A growing body of experimental work has shown that the additive genetic variance of fitness components can increase following a founder event or a bottleneck of population size. This is usually explained theoretically by the conversion of dominance variance and/or epistatic variance to additive variance following bottlenecks. The present analysis considers the effects of deviation from Hardy–Weinberg proportions (DHW) and linkage disequilibrium (LD) caused by bottlenecks. It is shown that DHW may also cause an increase in the additive variance for rare recessive genes, the largest increase arising with completely recessive genes of low initial frequency in intermediate-sized populations. LD among nonadditive loci results in a large increase in genotypic variance and also a small increase in additive variance. Even for the case of no linkage among the loci and linkage equilibrium in the ancestral population, severe bottlenecks result in a significant increase in genotypic variance as a result of LD among dominant loci. More restrictive conditions (many linked loci with large dominance coefficients and rare recessive genes), however, are required for LD to cause an evident increase in the additive variance. The effects of LD on genetic variances enhance with an increase in number of loci and dominance coefficients and with a decrease in recombination fractions, bottleneck sizes and initial recessive gene frequencies. Although the effects of LD on genetic variance decline gradually in the flush population, they may persist for some generations, especially when there is high linkage among the relevant loci.

Keywords: dominance, founder events, genetic variance, linkage disequilibrium, population bottlenecks.

Introduction

Although it is well established experimentally and theoretically that a population bottleneck reduces gene diversity and genetic heterozygosity (Crow & Kimura, 1970), its effect on genetic variance is complex. When the genetic variation underlying a quantitative trait is controlled by genes that act additively within and between loci, the additive genetic variance within a population following a bottleneck event or inbreeding is expected to decrease by a proportion of F (inbreeding coefficient of the population) (Wright, 1951). However, when there is dominance (Robertson, 1952; Willis & Orr, 1993) or

epistasis (Cockerham & Tachida, 1988; Goodnight, 1988; Whitlock *et al.*, 1993; Cheverud & Routman, 1996), the additive variance may actually increase with bottlenecks. The latter theoretical predictions are now supported by a growing number of experiments, e.g. in morphometric traits (Bryant *et al.*, 1986; Bryant & Meffert, 1993) and behavioural traits (Meffert & Bryant, 1992; Meffert, 1995) in the house fly, and in fitness components in *Drosophila melanogaster* (López-Fanjul & Villaverde, 1989; García *et al.*, 1994) and *Tribolium castaneum* (Fernández *et al.*, 1995; Wade *et al.*, 1996).

In this paper, we show that linkage disequilibrium (LD), which is the correlation of frequencies of genes at different loci, induced by random sampling during bottlenecks may cause a significant increase

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in genotypic variance and also a small increase in additive variance. The genetic conditions for changes in genotypic variance because of LD are less restrictive, and any degree of dominance (except pure additive) will cause an increased genotypic variance after bottlenecks. When the number of rare recessive genes at linked segregating loci involved in a quantitative trait is large, the increase in additive variance during bottlenecks caused by LD is also substantial.

A bottleneck event not only changes gene frequencies and induces correlations of gene frequencies among loci (LD) but also causes gene frequency correlations within loci (deviation in genotypic frequencies from Hardy–Weinberg proportions, denoted DHW), which also have an influence on genetic variance. For a population expanded to a very large size after a bottleneck (that is, in the flush phase) as considered by Willis & Orr (1993) theoretically and Bryant *et al.* (1986) in experiments, no DHW is present. However, for populations of small to moderate sizes such as the subdivided population under selection in the experiment by García *et al.* (1994), DHW is produced by sampling and exerts its influence on genetic variance. DHW and its effect on genetic variance are especially important when, in a subdivided population structure, within- and between-subpopulation selections are utilized to increase selection response (Madalena & Hill, 1972; López-Fanjul & Villaverde, 1989; García *et al.*, 1994). In this paper, we show that DHW may cause a large increase in additive variance arising from rare recessive genes and a small decrease in additive variance caused by additive genes or genes of small dominance coefficient. Somewhat surprisingly, the additive variance in populations as large as 1000 individuals may also be increased substantially by DHW for rare recessive genes.

Independent loci model

In this part, as did Robertson (1952) and Willis & Orr (1993), we assume that there is no LD and that genes at different loci act independently (no epistasis). We consider a single locus with two alleles, *A* and *a*, at which the three genotypes, *AA*, *Aa* and *aa* have genotypic values *a*, *d* and $-a$, respectively. The results for a single locus can be extended straightforwardly to include many loci.

Assume that from an infinite outbred ancestral source population of a monoecious species, a large number of lines are formed and maintained with constant and equal size of *N* individuals in each generation. If the frequency of allele *A* in a particu-

lar line of generation *t* is *p*, the mean and variance of *p* among lines are

$$E(p) = \bar{p}, \quad V(p) = \bar{p}(1-\bar{p})[1-(1-1/2N)^t], \quad (1)$$

where *E* denotes expectation and \bar{p} is the initial frequency of allele *A* in the ancestral population. Because *N* is small, the random process will not only result in fluctuations of gene frequency (genetic drift), but also cause departures of genotypic frequencies from Hardy–Weinberg proportions within lines. Given the observed gene frequency *p* in a line of generation *t*, the theoretical genotypic frequencies from the Hardy–Weinberg law are $D_e = p^2$, $H_e = 2p(1-p)$ and $R_e = (1-p)^2$. The observed genotypic frequencies (denoted as *D*, *H* and *R*) are generally different from the above theoretical predictions, but have expectations $E(D) = p^2 + fp(1-p)$, $E(H) = 2p(1-p)(1-f)$ and $E(R) = (1-p)^2 + fp(1-p)$, where *f* measures the DHW and is predicted to be $f = -1/(2N-1)$ for monoecious species (Kimura & Crow, 1963) and $f = -3/2N$ (*N* is the number of individuals, half in each sex) for dioecious species (Wang, 1996). The observed frequencies, genotypic values, additive values and dominance deviations of the three genotypes are listed in Table 1, where $g = (D-R)a + Hd$ is the population mean and α_1 and α_2 are the average effects of alleles *A* and *a*, respectively.

The genotypic variance, V'_G , can easily be obtained from Table 1:

$$V'_G = a^2[4D + H - (2D + H)^2] + d^2H(1-H) - 2adH(2D + H - 1), \quad (2)$$

which reduces to $V'_G = 2p(1-p)[a + d(1-2p)]^2 + [2p(1-p)d]^2$ for the special case of Hardy–Weinberg equilibrium (HWE), as expected (Falconer & Mackay, 1996). The effect of DHW on genotypic variance can be obtained by taking the expectation of eqn (2) given gene frequency *p*, $E(V'_G | p)$. Omit-

Table 1 Frequencies, genotypic values, additive values, gene dosages and dominance deviations of the three genotypes

| Genotype | <i>AA</i> | <i>Aa</i> | <i>aa</i> |
|---------------------|-----------------------------------|---|-------------------------------------|
| Frequency | <i>D</i> | <i>H</i> | <i>R</i> |
| Genotypic value | <i>a</i> - <i>g</i> | <i>d</i> - <i>g</i> | - <i>a</i> - <i>g</i> |
| Additive value | $2\alpha_1$ | $\alpha_1 + \alpha_2$ | $2\alpha_2$ |
| Gene dosage | 2 | 1 | 0 |
| Dominance deviation | <i>a</i> - <i>g</i> - $2\alpha_1$ | <i>d</i> - <i>g</i> - $\alpha_1 - \alpha_2$ | - <i>a</i> - <i>g</i> - $2\alpha_2$ |

ting second-order terms of f , we obtain the approximate expression

$$E(V'_G | p) = 2p(1-p)[a + d(1-2p)]^2 + [2p(1-p)d]^2 + 2p(1-p)f[a^2 - d^2 + 4p(1-p)d^2 + 2(2p-1)ad]. \quad (3)$$

The first term on the right side of eqn (3) is the genotypic variance assuming HWE and the second term is the genotypic variance caused by DHW. Because $f < 0$, it is clear that DHW generally decreases the genotypic variance for rare recessive genes. The magnitude of the decrease depends on the dominance coefficient, gene frequency and line size. The additive variance, however, can be increased by DHW, as will be shown next.

From Table 1, we can derive the average effect of a gene substitution, α , in two ways. One is to regress genotypic value on gene dosage (the number of A alleles in the genotype, i.e. 2, 1 and 0 for genotypes AA , Aa and aa , respectively) and the regression coefficient is α by definition (Fisher, 1941; Falconer, 1985). The other way is to minimize the weighted average of the squared dominance deviations. By differentiating the resulting quadratic equation and equating to 0, we can obtain the least square estimates of α_1 and α_2 (Kempthorne, 1957; Crow & Kimura, 1970), and $\alpha = \alpha_1 - \alpha_2$ by definition. Both methods lead to the same expression,

$$\alpha = a - \frac{H(2D+H-1)}{4D+H-(2D+H)^2}d = a - \frac{H(2p-1)}{2(D+p-2p^2)}d. \quad (4)$$

For an infinite, regularly inbred population with genotypic frequencies $D = p^2 + Fp(1-p)$, $H = 2p(1-p)(1-F)$ and $R = (1-p)^2 + Fp(1-p)$ (F , inbreeding coefficient), eqn (4) reduces to $\alpha = a + d(1-2p)(1-F)/(1+F)$ which again reduces to $\alpha = a + d(1-2p)$ for random mating ($F = 0$) (Kempthorne, 1957; Crow & Kimura, 1970; Falconer, 1985). The parameters F and f defined above are clearly different. For regular systems of inbreeding, F is positive and therefore tends to enhance additive variance; whereas parameter f , the random deviation from HWE because of small population sizes, is small and negative, and may decrease or increase the additive variance depending on the initial gene frequencies, dominance coefficients and bottleneck line sizes (see below).

From eqn (4) we see that DHW has no influence on the average effect of the gene substitution for additive genes ($d = 0$) and has little influence for genes of intermediate frequency ($p \approx 0.5$).

From Table 1, the additive variance can be obtained as

$$V'_A = [4D + H - (2D + H)^2] \alpha^2, \quad (5)$$

which, when inserting eqn (4) and noting $2D + H = 2p$, reduces to

$$V'_A = 2(p - 2p^2 + D)a^2 - 2H(2p - 1)ad + \frac{H^2(2p - 1)^2}{2(p - 2p^2 + D)}d^2. \quad (6)$$

The effect of DHW on the additive variance can be obtained by taking the expectation of eqn (6) given gene frequency p , $E(V'_A | p)$. However, no simple expression is possible for $E(V'_A | p)$. For the special case of the additive model ($d = 0$), we have

$$E(V'_A | p) = E(V'_G | p) = 2p(1-p)(1+f)a^2. \quad (7)$$

Therefore DHW is expected to decrease the additive variance or genotypic variance (Bulmer, 1976) for additive genes by a proportion $f = -1/(2N-1)$ for monoecious species and $f = -3/(2N)$ for dioecious species. In Bulmer's (1976) simulation study of *Drosophila* and mouse populations, he predicted the genetic variance attributable to DHW to be $-E(V'_A)/(2N-1)$, whereas $-3E(V'_A)/2N$ should be used for the dioecious case. Indeed $-3E(V'_A)/2N$ gives predictions closer to both the *Drosophila* and mouse simulation results (Bulmer, 1976; Table 3).

Because it is not possible to get an explicit expression for $E(V'_A | p)$ with an arbitrary dominance coefficient, we use stochastic simulations to evaluate the effect of DHW on the additive variance. From an infinite ancestral population in HWE, N monoecious individuals are sampled to form a line of generation 0. In each successive generation, $2N$ genes at a diallelic locus are sampled randomly from the previous generation and are paired at random to form the N genotypes of the next generation. Using the observed genotypic frequency, we can obtain the gene frequencies and the expected genotypic frequencies from the Hardy-Weinberg law. The additive variance (V'_A) and additive variance assuming HWE ($V'_A | \text{HWE}$) can be calculated by eqn (6) using observed and expected genotypic frequencies, respectively. One thousand to one million replicates (depending on line size N and initial gene frequency) were run and the results for each generation were averaged to give the expected additive variance ($E(V'_A)$ and $E(V'_A | \text{HWE})$).

The simulation results, expressed as $E(V'_A)/E(V'_A | \text{HWE})$, are shown in Fig. 1 for various dominance coefficients with initial recessive gene frequency 0.01 and line size $N = 50$ over eight gener-

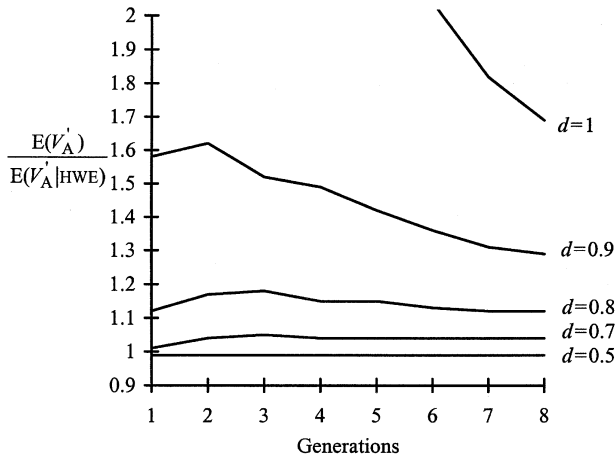


Fig. 1 The influence of the dominance coefficient on the effect of DHW on the additive variance ($E(V'_A)/E(V'_A | HWE)$) over generations. The line size is 50, initial recessive gene frequency 0.01, $a = 1$.

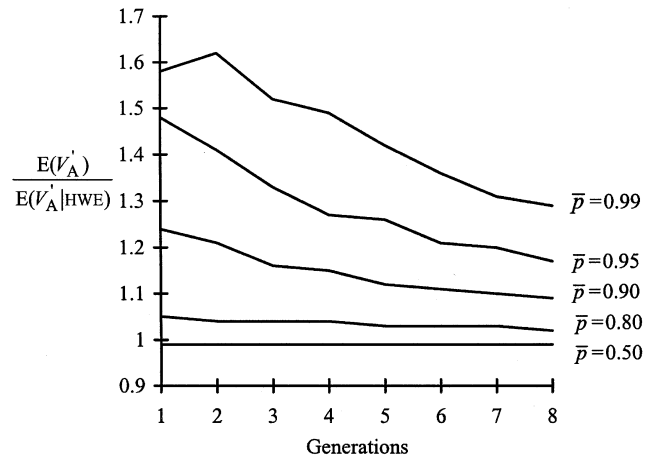


Fig. 2 The influence of initial gene frequency on the effect of DHW on the additive variance ($E(V'_A)/E(V'_A | HWE)$) over generations. The line size is 50, dominance coefficient $d = 0.9$, $a = 1$.

ations. For complete dominance, the increase in additive variance because of DHW is enormous initially ($E(V'_A)/E(V'_A | HWE) = 6$ in the first generation) and declines gradually to 1.7 in generation eight. As the dominance coefficient is decreased, the magnitude of effect of DHW on the additive variance decreases and the number of generations when the maximum effect is realized increases. The larger the dominance coefficient, the greater the effect of DHW on increasing the additive variance and also the greater the changes in the magnitude of the effect over generations. When $d < 0.6$ or so, the additive variance is always decreased by DHW, the proportional reduction predicted to be $1/(2N - 1)$ (or $E(V'_A)/E(V'_A | HWE) = 1 - 1/(2N - 1)$) approximately in any generation, similar to the additive model (Bulmer, 1976).

The influence of the initial recessive gene frequency on $E(V'_A)/E(V'_A | HWE)$ is depicted in Fig. 2 with $N = 50$, $d = 0.9$ over eight generations. It is clear that the rarer the initial recessive gene, the greater is the increase in additive variance caused by DHW in bottlenecked lines. For common recessive genes ($\bar{q} = 1 - \bar{p} \approx 0.5$), the additive variance is decreased by a constant proportion of $1/(2N - 1)$ by DHW, irrespective of the dominance coefficient and the number of generations, because the dominance coefficient has little effect on the additive variance when $\bar{q} \approx 0.5$ (see eqn (6)). When the initial recessive gene frequency is high (say $\bar{q} > 0.7$), the additive variance is also increased by DHW; but the magnitude of the increase is small and constant over generations (data not shown).

The effect of line size on the changes in $E(V'_A)/E(V'_A | HWE)$ is shown in Fig. 3, with initial recessive gene frequency = 0.01, $a = 1$ and $d = 0.9$. DHW shows the largest effect on increasing additive variance with intermediate line size ($N = 20 - 500$), most evident in the first few generations of bottlenecking. When the line size is small ($N < 5$), the additive variance is actually decreased by DHW in initial generations. When the line size is large ($N = 1000 - 5000$), there is a small increase in additive variance which is nearly constant over genera-

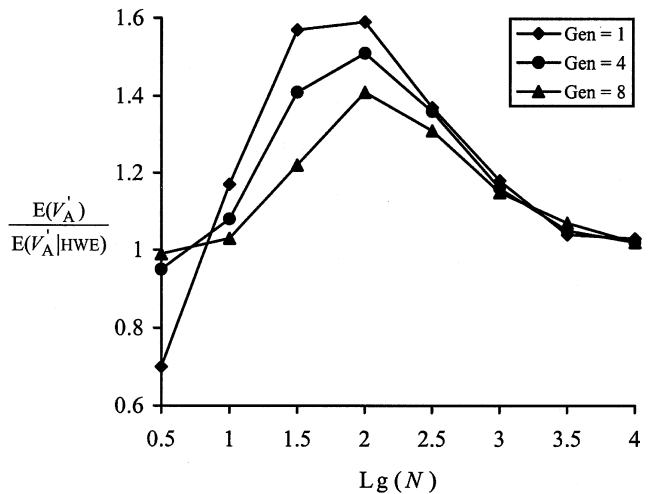


Fig. 3 The influence of line size (in common logarithm) on the effect of DHW on the additive variance ($E(V'_A)/E(V'_A | HWE)$) in generations one, four and eight. The initial recessive gene frequency is 0.01, dominance coefficient $d = 0.9$, $a = 1$.

tions. For very large lines ($N > 10000$), the DHW is small and its effect on the additive variance is negligible.

The reason for the increase in V_A because of DHW is similar to that for the increased V_A caused by genetic drift in gene frequency (Robertson, 1952; Willis & Orr, 1993; Falconer & Mackay, 1996). Consider the simple case of a completely recessive gene with a small initial frequency q . Because the dominant homozygote and heterozygote have the same genotypic value and the recessive homozygote is very rare, V_A is determined mainly by the recessive homozygote frequency (R). Among a large number of replicate lines of size N , the average observed frequency of recessive homozygotes will be decreased by a proportion of $f q (1 - q)$ by DHW. Therefore, if we use the average genotypic frequencies of replicate lines to calculate V_A , there will always be a decrease in V_A caused by DHW, irrespective of the gene action (dominance coefficient). Now, however, consider the genotypic frequencies and additive variance of each line. Because of DHW, R (and thus V_A) may be increased, decreased or not changed in the specific line. The proportion of V_A -increased lines is generally small (because $f < 0$). However, the average increase in V_A in these V_A -increased lines is very high, whereas the average decrease in V_A in those V_A -decreased lines is rather small. Thus, averaging the V_A over all lines, there is still an increase in V_A . The smaller the line size, the greater the average increase in V_A in V_A -increased lines, whereas the average decrease in V_A in V_A -decreased lines is always small and changes little with line sizes. The proportion of lines with increased V_A , however, declines with decreasing line sizes; the smaller the line size, the smaller is the proportion of V_A -increased lines. Therefore, the two counteracting factors result in the greatest increase in V_A caused by DHW in intermediate-sized lines. If the line size is very small, the proportion of V_A -increased lines is minute. If the line size is very large, DHW is small and the average increase in V_A in V_A -increased lines is negligible. In both cases no evident increase in V_A as a result of DHW is expected.

The above explanation is examined in Fig. 4 with $q = 0.01$, $a = 1$ and $d = 0.9$. The proportion ($\times 500$) of V_A -increased (caused by DHW) lines increases, and the average additive variance in these increased lines relative to the average additive variance of all lines ($E(V'_{A+})/E(V'_A | \text{HWE})$) decreases with line sizes. In Fig. 4 we do not consider the proportion of V_A -decreased (caused by DHW) lines and the contribution of these lines to the average additive

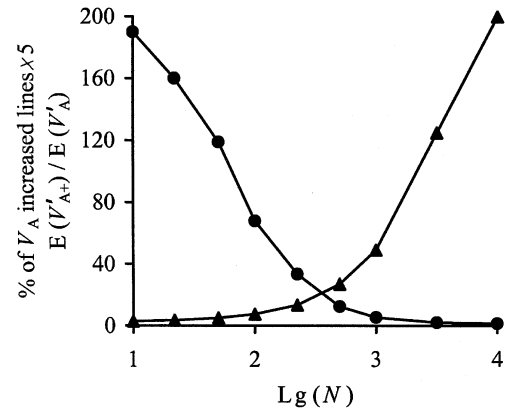


Fig. 4 The percentage ($\times 5$) of additive variance increased lines because of DHW (\blacktriangle) and the average increase of the additive variance of these lines relative to that of all lines ($E(V'_{A+})/E(V'_A | \text{HWE})$), (\bullet) with a single bottleneck of various sizes (in common logarithm). The initial recessive gene frequency is 0.01, dominance coefficient $d = 0.9$, $a = 1$.

variance. This is because the average decrease in V_A caused by DHW is rather small. Therefore, lines of intermediate sizes with moderate proportions of V_A -increased lines and medium values of $E(V'_{A+})/E(V'_A | \text{HWE})$ result in the greatest increase in additive variance attributable to DHW.

In summary, the largest increase in V_A because of DHW occurs in the initial generations for rare recessive genes and intermediate-sized lines. When either the recessive gene is common or the dominance coefficient is small, the behaviour of V_A because of DHW is similar to that of the pure additive model. An increase in V_A implies a potentially higher selection response. Therefore, for a trait whose genetic variation is determined mainly by many loci with rare recessive alleles of deleterious effects, as is believed for viability in *Drosophila* (Crow, 1993), an improved selection response is expected in small populations both from genetic drift in gene frequency (Robertson, 1952) and from DHW.

For rare recessive genes, the additive variance in bottlenecked lines is increased both by genetic drift (changes in gene frequency) and DHW (changes in genotypic frequency, so that we can call it 'genotypic drift'). The relative importance of the two causes depends on the size of the bottleneck and its duration as well as the dominance coefficient and initial gene frequency. Generally, genetic drift is more important than DHW when F is not too small; but in some cases, DHW may result in a greater increase than genetic drift in the additive variance.

For example, with $N = 50$, $a = 1$, $d = 0.9$ and $\bar{q} = 0.01$, the additive variance is increased by 110% (133%) in generation 1 (2) by DHW, calculated as $[(E(V'_A) - E(V'_A | \text{HWE})) / V_A] \times 100\%$ where V_A is the additive variance in the ancestral large population; whereas the corresponding value is 70% (111%) by genetic drift, calculated as $[(E(V'_A | \text{HWE}) - V_A) / V_A] \times 100\%$. The DHW considered above is caused by sampling alone, which results in a decrease in the expected recessive homozygote

frequency ($f < 0$). For partially inbreeding populations, there will be an increase in the expected recessive homozygote frequency ($f > 0$) and the magnitude of the increase in additive variance because of DHW will be further increased.

The above results are on genetic variances within lines during bottlenecks. If the population expands to a large size, then there is no DHW in the expanded population and only the effect of gene frequency drift during the bottleneck persists.

Linkage disequilibrium model

Linkage disequilibrium (LD), which may come from sampling in small populations and declines slowly when linkage is tight, can have a substantial effect on the genetic variances of quantitative traits that are determined by many loci. We extend Avery & Hill's (1979) model to consider the effect of a bottleneck on genetic variance. For simplicity, we assume linkage equilibrium in the ancestral population.

Assume that in each generation, the N individuals in a line generate a potential infinite number of progeny, from which N individuals are sampled to form the next generation. The sampling gives DHW when N is small. The genotypic variance within the infinite progeny group is given by Avery & Hill (1979),

$$V_G^* = \sum_{i=1}^n [2\alpha_i^2 p_i (1-p_i) + 4d_i^2 p_i^2 (1-p_i)^2] + 2 \sum_{i=1}^n \sum_{j>i}^n (2\alpha_i \alpha_j D_{ij} + 4d_i d_j D_{ij}^2), \tag{8}$$

where p_i , a_i and d_i are the dominant gene frequency and the genotypic values of dominant homozygote and heterozygote at locus i , $\alpha_i = a_i + d_i(1-2p_i)$ is the average effect of a gene substitution at the i th locus when there is no LD and DHW, D_{ij} is the LD between loci i and j in the infinite progeny group, $\sum_i \sum_{j>i}^n$ denotes summation over all values of i and j between loci 1 and n with i less than j . V_G^* has two components, the contribution from individual loci (denoted as $V'_{G(i)}$) and the contribution from pairs of loci because of LD (denoted as $V'_{G(p)}$). For a single locus $V'_{G(i)}$ reduces to eqn (2) for the infinite progeny group under HWE.

The expectation of V_G^* from eqn (8),

$$E(V_G^*) = E(V'_{G(i)}) + E(V'_{G(p)}), \tag{9}$$

gives the average genotypic variance within the infinite progeny group. Expanding $V'_{G(p)}$ yields

$$E(V'_{G(p)}) = 4 \sum_{i=1}^n \sum_{j>i}^n \{a_i a_j E(D_{ij}) + a_j d_i E[(1-2p_i)D_{ij}] + a_i d_j E[(1-2p_j)D_{ij}] + d_i d_j E[(1-2p_i)(1-2p_j)D_{ij}] + 2d_i d_j E(D_{ij})^2\}. \tag{10}$$

For a parental population in linkage equilibrium, Serant & Villard (1972) showed that $E(D_{ij}) = E((1-2p_i)D_{ij}) = 0$, so eqn (10) reduces to

$$E(V'_{G(p)}) = 4 \sum_{i=1}^n \sum_{j>i}^n \{d_i d_j E[(1-2p_i)(1-2p_j)D_{ij}] + 2d_i d_j E(D_{ij})^2\}. \tag{11}$$

For additive genes ($d = 0$), $E(V'_{G(p)}) = 0$ from eqn (11), which means that LD between additive genes does not contribute to the expected within-line genotypic variance if there is linkage equilibrium in the initial ancestral population (Bulmer, 1976). The two terms in eqn (11) can be calculated by the following recurrence equation (Avery & Hill, 1979, appendix):

$$\mathbf{Z}_t = \mathbf{TZ}_{t-1}, \tag{12}$$

where

$$\mathbf{Z}_t = \begin{pmatrix} \mathbf{E}(P_{ijt}) \\ \mathbf{E}(Q_{ijt}) \\ \mathbf{E}(D_{ijt}^2) \end{pmatrix} = \begin{pmatrix} \mathbf{E}[p_i(1-p_i)p_j(1-p_j)] \\ \mathbf{E}[(1-2p_i)(1-2p_j)D_{ijt}] \\ \mathbf{E}(D_{ijt}^2) \end{pmatrix}, \quad (13)$$

$$\mathbf{T} = \begin{pmatrix} (1-\frac{1}{2N})^2 & \frac{1}{2N}(1-\frac{1}{2N})^2 & 2(\frac{1}{2N})^2(1-\frac{1}{2N}) \\ 0 & (1-\frac{1}{N})^2(1-\frac{1}{2N}-c) & \frac{2}{N}(1-\frac{1}{N})(1-\frac{1}{2N}-c) \\ \frac{1}{2N}(1-\frac{1}{2N}-2c+2c^2) & \frac{1}{2N}(1-\frac{1}{2N})(1-\frac{1}{2N}-2c)+\frac{c^2}{2N} & (1-\frac{1}{2N}-2c)[(1-\frac{1}{2N})^2+(\frac{1}{2N})^2]+c^2 \end{pmatrix}, \quad (14)$$

in which c is the recombination fraction (between loci i and j). The initial value of \mathbf{Z} is $\mathbf{Z}_0^T = [p_i(1-p_i)p_j(1-p_j), 0, 0]$. Thus, using eqn (2) (assuming HWE, summing over loci and taking expectation), eqn (9) and eqns (11–14), we can predict the expected genotypic variance in the infinite progeny group in any generation.

The N individuals which are used to form the t th parental generation are a random sample of the infinite progeny group at generation t . Thus, in considering the expected genotypic variance among the N parents [$\mathbf{E}(V'_G)$], DHW resulting from sampling must be taken into consideration. Avery & Hill (1979) approximated V'_G as $(1-1/N)V_G^*$. From the independent loci model we know that the relationship between V'_G (with DHW) and V_G^* is complicated, depending not only on N but also on the gene frequency and dominance coefficient. However, because of the complexity involved with DHW that can not be tackled analytically, hereafter we always assume HWE and concentrate on the effect of LD on the genetic variance. This is roughly the case in an expanded population immediately after a bottleneck.

The above analyses are concerned with genotypic variance. Avery & Hill (1979) derived the variance between half-sib families, $\text{Var}(\text{HS})$. In a large population with no sampling or LD effects, $\text{Var}(\text{HS}) = (1/4)V_A$ (Falconer & Mackay, 1996). Thus we can approximate the additive variance as $V'_A = 4\text{Var}(\text{HS})$, using the equation for $\text{Var}(\text{HS})$ from Avery & Hill (1979),

$$V'_A = 2\lambda \sum_{i=1}^n \{p_i(1-p_i)[a_i + d_i(1-2p_i)\lambda]^2 + 2(\lambda/N)d_i^2p_i^2(1-p_i)^2\} + 4\lambda \sum_{i=1}^n \sum_{j>i}^n \{[a_i + d_i(1-2p_i)\lambda][a_j + d_j(1-2p_j)\lambda]D_{ij} + 2d_id_j(\lambda/N)D_{ij}^2\}, \quad (15)$$

where $\lambda = 1 - 1/N$. Similar to the derivation of the expected genotypic variance, we obtain from eqn (15) that

$$\mathbf{E}(V'_A) = \mathbf{E}(V'_{A(i)}) + \mathbf{E}(V'_{A(p)}), \quad (16)$$

where the expected additive variance attributable to single loci is

$$\mathbf{E}(V'_{A(i)}) = 2\lambda \sum_{i=1}^n \{(a_i + d_i\lambda)^2\mathbf{E}(p_i) - [a_i^2 + d_i\lambda(6a_i + 5d_i\lambda - 2d_i/N)]\mathbf{E}(p_i^2) + 4d_i\lambda(a_i + 2d_i\lambda - d_i/N)\mathbf{E}(p_i^3) - 2d_i^2\lambda(2\lambda - 1/N)\mathbf{E}(p_i^4)\} \quad (17)$$

and the expected additive variance attributable to pairs of loci is

$$\mathbf{E}(V'_{A(p)}) = 4\lambda^3 \sum_{i=1}^n \sum_{j>i}^n [d_id_j\mathbf{E}(Q_{ij})] + 8(\lambda^2/N) \sum_{i=1}^n \sum_{j>i}^n [d_id_j\mathbf{E}(D_{ij}^2)]. \quad (18)$$

Gene moments in eqn (17) [$\mathbf{E}(p_i^n)$, for $n = 1-4$] can be found in Crow & Kimura (1970, p. 335) and $\mathbf{E}(Q_{ij})$ and $\mathbf{E}(D_{ij}^2)$ can be calculated by recurrence eqns (12), (13), (14); so the effects of LD on the additive variance can be evaluated.

The effect of LD on genetic variances increases quickly as the number of loci increases as there are $\frac{1}{2}n(n-1)$ terms involving pairs of loci but only n for single loci. When the number of loci is large, LD has a large effect on the genotypic variance and a small but distinguishable effect on the additive variance. In Fig. 5, relative changes in genetic variances $[E(V'_G)/V_G, E(V'_A)/V_A]$ (where V_A and V_G are the additive and genotypic variances in the ancestral outbred population) and variances attributable to individual loci $[E(V'_{G(i)})/V_G, E(V'_{A(i)})/V_A]$ after a single bottleneck of four individuals are plotted against the number of loci. The difference between the two relative changes $[E(V'_G)/V_G - E(V'_{G(i)})/V_G, E(V'_A)/V_A - E(V'_{A(i)})/V_A]$ is the relative change in genetic variance attributable to pairs of loci $[E(V'_{G(p)})/V_G, E(V'_{A(p)})/V_A]$. The initial ancestral population is assumed to be in linkage and Hardy-Weinberg equilibrium; the effect ($a = 1$), dominance coefficient ($d = 0.9$) and the initial recessive gene frequency ($q = 0.1$) are the same for all loci; and the recombination fraction between the loci is assumed to be 0.3. It is clear that the larger the number of loci, the greater the contribution to genetic variances from pairs of loci. This is particularly obvious for the genotypic variance. The contribution of LD to the genotypic variance is mainly nonadditive; additive variance is less affected by bottlenecks because of

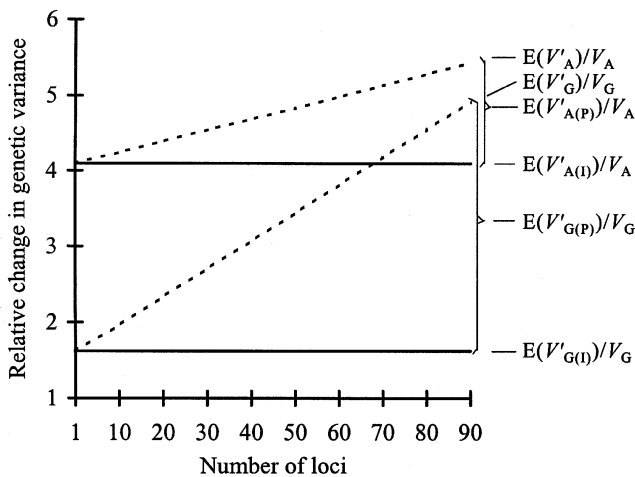


Fig. 5 The relative changes in expected genetic variances (dotted lines), expected genetic variances attributable to individual loci (continuous lines) and to pairs of loci (the difference between continuous and dotted lines) over the number of loci after a single bottleneck of four individuals. The same recombination fraction ($c = 0.3$) between loci and equal effect ($a = 1$), dominance coefficient ($d = 0.9$) and initial recessive gene frequency ($q = 0.1$) for all loci are assumed.

LD. Although the increase in the additive variance is larger than that in the genotypic variance after a bottleneck (Fig. 5), this is, however, mainly attributable to individual loci.

The contribution of LD to within-line variances is dependent on the dominance coefficients, as can be seen from eqns (11) and (18). If a locus is completely additive ($d = 0$), it does not affect genetic variances through LD with any of the other loci; and if all loci are additive, our model reduces to that of Bulmer (1976) and LD does not affect genetic variances. For a quantitative trait controlled by 30 loci with the same initial recessive gene frequency (0.1), equal effect ($a = 1$) and equal dominance coefficient, the changes in genetic variances relative to the ancestral population values after a single bottleneck of four individuals are plotted against the dominance coefficient in Fig. 6. The effect of LD on genetic variances increases with the increment in the dominance coefficient, especially for the genotypic variance and when the dominance coefficient is large, whereas the additive variance is little affected by LD.

LD is a statistical property of the population and its contribution to genetic variances after a bottleneck depends greatly on the initial gene frequencies.

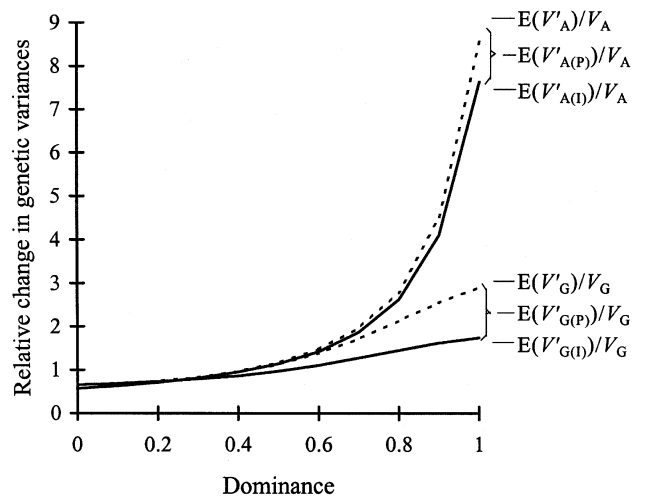


Fig. 6 Relative changes in expected genetic variances after a single bottleneck of four individuals over dominance coefficients. Thirty loci with equal effect ($a = 1$), dominance coefficient, initial recessive gene frequency (0.1) and recombination fraction between the loci ($c = 0.4$) are assumed. Relative changes in genetic variances $[E(V'_G)/V_G, E(V'_A)/V_A]$, in genetic variances attributable to individual loci $[E(V'_{G(i)})/V_G, E(V'_{A(i)})/V_A]$ and to pairs of loci $[E(V'_{G(p)})/V_G, E(V'_{A(p)})/V_A]$ are denoted by dotted lines, continuous lines and the difference between the two kinds of lines, respectively.

The absolute [$E(V'_{G(P)})$ and $E(V'_{A(P)})$] and relative [$E(V'_{G(P)})/V_G$ and $E(V'_{A(P)})/V_A$] changes in genetic variance attributable to LD caused by a single bottleneck over initial dominant gene frequencies are shown in Fig. 7. The bottleneck size is four and the quantitative trait is determined by 30 linked loci ($c = 0.4$) with the same effect ($a = 1$), dominance coefficient ($d = 0.9$) and initial gene frequency. It is clear that the rarer the recessive gene, the larger the contribution of LD to the relative increase in genetic variances. The absolute contributions of LD to genetic variances are, however, maximized with intermediate gene frequencies. Over the range of gene frequencies, LD contributes much more to the genotypic variance than to the additive variance. When the rare recessive gene frequency is 0.05, $E(V'_{G(P)})/V_G$, $E(V'_{A(P)})/V_A$, $E(V'_{G(I)})/V_G$ and $E(V'_{A(I)})/V_A$ are 0.97, 0.43, 2.57 and 7.94, respectively; 27% of the genotypic variance but only 5% of the additive variance is caused by LD.

Linkage augments the effect of LD on the genetic variance, in both magnitude and persistency. Figure 8 depicts the effect of linkage (recombination fraction c) on the genetic variances contributed by LD relative to the ancestral population variance [$E(V'_{G(P)})/V_G$, $E(V'_{A(P)})/V_A$] after a single bottleneck of four individuals, for a model of 30 loci with the same initial recessive gene frequency (0.1), effect

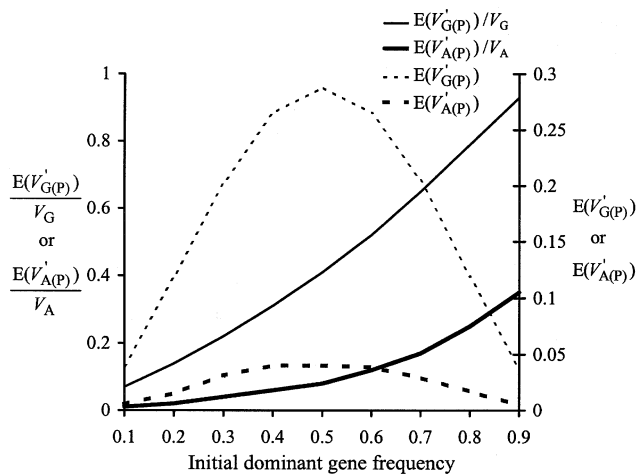


Fig. 7 The absolute and relative (to the ancestral population variances) changes of genetic variances attributable to pairs of loci over initial dominant gene frequencies. The line size is four, number of linked loci ($c = 0.4$) is 30 with equal effect ($a = 1$) and dominance coefficient ($d = 0.9$). The thin line denotes $E(V'_{G(P)})/V_G$, the thick line denotes $E(V'_{A(P)})/V_A$, the thin dotted line denotes $E(V'_{G(P)})$ and the thick dotted line denotes $E(V'_{A(P)})$.

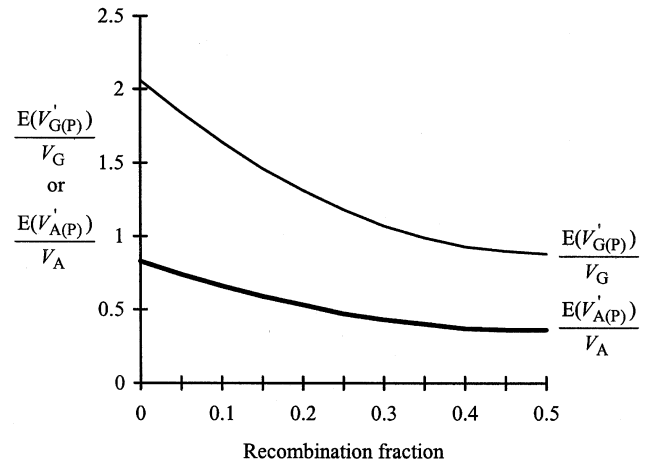


Fig. 8 The changes of genotypic variance (thin line) and additive variance (thick line) attributable to pairs of loci relative to the ancestral population variance [$E(V'_{G(P)})/V_G$, $E(V'_{A(P)})/V_A$] over recombination fractions after a single bottleneck of four individuals. The number of loci is 30 with equal effect ($a = 1$), dominance coefficient ($d = 0.9$) and initial gene frequency ($\bar{p} = 0.9$).

($a = 1$) and dominance coefficient ($d = 0.9$). With complete linkage ($c = 0$), the maximum value of $E(V'_{G(P)})/V_G$ is 2.06, 2.3 times the corresponding value for no linkage ($c = 0.5$). Even in the case of complete linkage ($c = 0$), the relative contribution of LD to the additive variance [$E(V'_{A(P)})/V_A$] is 0.83, only one-fifth of the corresponding value of individual loci.

Contrary to the effect of DHW, which disappears completely after the population expands to a very large size, LD and its effect on genetic variances persist for some generations after the expansion. In the expanded population, no new LD is produced and the remaining amount of LD diminishes at a rate of c in each generation (Falconer & Mackay, 1996). Some experiments have considered the genetic variance in the flush population after one or a series of bottlenecks (Bryant & Meffert, 1993; Meffert, 1995). From eqn (18) we see that in the expanded population only $E(Q_{ij})$ is affecting $E(V'_{A(P)})$. After a single bottleneck, we have $E(Q_{ij}) = 0$ from eqns (12), (13), (14). Thus if the population is expanded immediately after a single bottleneck, then LD has no effect on the additive variance in the flush population. After two generations of bottlenecks of $N = 2$, the changes in $E(V'_{A(P)})/V_A$ and $E(V'_{G(P)})/V_G$ of the expanded population over generations are shown in Fig. 9. The variables are 30 loci, $c = 0.1$, $\bar{p} = d = 0.9$ and $a = 1$.

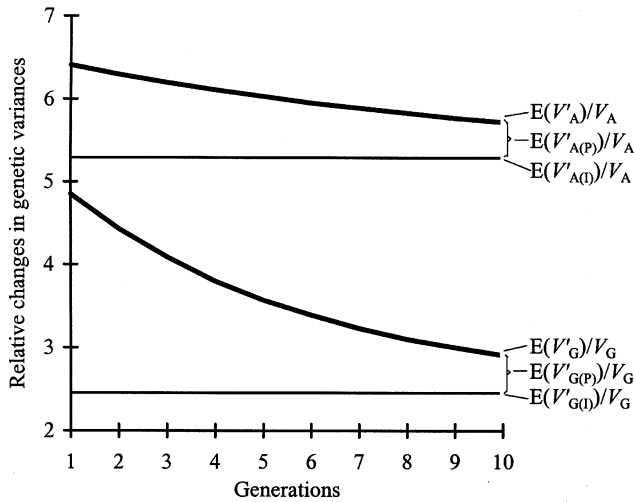


Fig. 9 Changes in the relative genetic variance [$E(V'_G)/V_G$, $E(V'_A)/V_A$, thick lines], genetic variance attributable to individual loci [$E(V'_{G(I)})/V_G$, $E(V'_{A(I)})/V_A$, thin lines] and to pairs of loci [$E(V'_{G(P)})/V_G$, $E(V'_{A(P)})/V_A$, the differences between thick and thin lines] over generations in an expanded population after two bottlenecks of two individuals. Thirty loci with equal initial gene frequency ($\bar{p} = 0.9$), effect ($a = 1$), dominance coefficient ($d = 0.9$) and recombination fraction ($c = 0.1$) are assumed.

Two or more continual generations of bottlenecks result in a small increase in the additive variance decaying in the flush population.

In the above, we assume that the recombination fraction is the same for any pair of loci whenever linkage is considered. Though the assumption is certainly not true, it makes the calculation simpler and still gives results qualitatively relevant. A more realistic linkage model would be that a certain number of loci are randomly distributed over a chromosome of a given length, with the recombination fraction between any pair of loci being determined by their distance apart. Calculations of genetic variances for each pair of loci can be made, and summing the results over all possible pairs of loci gives the total variances (Avery & Hill, 1979). However, the basic effect of linkage is to increase the magnitude and persistency of LD as shown above, no matter what kind of linkage model is used.

Discussion

A severe bottleneck has multiple genetic effects on the population genetic structure. It changes the gene frequency (genetic drift), increases the average level of homozygosity (inbreeding) and causes correla-

tions of gene frequencies within loci (DHW) and among loci (LD). For rare recessive genes, DHW may cause a substantial increase in the additive variance during bottlenecks. LD among dominant loci also leads to a small increase in the additive variance both during and after bottlenecks. These two factors, however, are unlikely to be the main cause for the huge jump in V_A with bottlenecks observed in empirical studies. In these, V_A is measured either in the expanded population (Bryant *et al.*, 1986) or in small inbred lines in comparison with outbred control lines of the same size (López-Fanjul & Villaverde, 1989; García *et al.*, 1994; Fernández *et al.*, 1995); in both cases DHW is irrelevant. Genetic drift of rare recessive genes (Robertson, 1952; Willis & Orr, 1993), epistasis (Goodnight, 1988; Whitlock *et al.*, 1993; Cheverud & Routman, 1996) or both may be the main cause for the observed bottleneck effect.

There are similarities in the patterns of the effects of genetic drift, epistasis, LD and DHW on the additive variance. The smaller the bottleneck size, the larger the effects of the first three factors; the maximum effects are attained at an intermediate inbreeding coefficient. The effects of genetic drift, LD and DHW on additive variance depend critically on the interaction within loci (dominance) and increase with the increase in the dominance coefficient and the decrease in initial recessive gene frequency. However, there are also some differences among the effects of the four factors. For genetic drift in gene frequency or DHW to cause an increase in the additive variance, the initial recessive gene frequency needs to be small and the dominance coefficient large, and the line size needs to be small for genetic drift or intermediate for DHW. For the case of epistasis, there has to be a large proportion of additive \times additive variance present in the ancestral population. The genetic conditions for an increase in the genotypic variance are less restricted for the LD model; any degree (except pure additive) at a number of loci will suffice. However, the conditions for LD to result in an apparent increase in the additive variance are rather restrictive: a large number of rare recessive genes in close linkage are required. The amount of increase in variance induced from epistasis declines with decreasing values of the recombination fraction (Goodnight, 1988; Whitlock *et al.*, 1993), which is in contrast to the LD model shown in this article.

The behaviour of the changes in genetic variance in the flush population after bottlenecks is quite different for the four models. For the genetic drift

model, the increased variance during bottlenecks is completely kept in the flush population. For the epistasis model, most of the increased variance is maintained in the enlarged population (Goodnight, 1988; Whitlock *et al.*, 1993; Cheverud & Routman, 1996). The present analysis shows that the additive variance from DHW will be completely lost once the population is expanded and that the increased genetic variance from LD during bottlenecks will disappear gradually over generations in the flush population. The time required to attain the linkage equilibrium (thus complete loss of increased variance because of LD) depends on the recombination fraction and the amount of disequilibrium accumulated before the flush phase. Thus, testing the changes in variance over time in the flush population may provide a way to distinguish the four possible factors. As pointed out by Whitlock & Fowler (1996), however, even with a gradual decrease in the amount of variance, it is still impossible to attribute the effects to LD unambiguously, because other evolutionary forces, such as stabilizing selection, may also cause a reduction in variance.

Because of the widespread occurrence of inbreeding depression which indicates directional dominance for fitness components and other quantitative traits (Simmons & Crow, 1977; Charlesworth & Charlesworth, 1987), rare recessive genes may be involved in the increase in variance with bottlenecking. Some authors could explain their observed results by the dominance model, without the need of epistasis (López-Fanjul & Villaverde, 1989; García *et al.*, 1994; Fernández *et al.*, 1995). *Drosophila* experiments (reviewed by Crow, 1993) indicate the existence of two main classes of mutations affecting viability: lethal and deleterious mutations. Most mutations are not lethal and the average dominance coefficient of these deleterious mutations is 0.36, a consensus value from various experiments (Lynch *et al.*, 1995). If all the loci have the same average dominance coefficient (0.36), then an increase in variance is not possible from dominance as a result of gene frequency drift (Willis & Orr, 1993) or DHW (the present study) at single loci but is possible from pairs of loci because of LD. However, it is generally accepted that coefficients of dominance are negatively correlated with mutant effects; mutants of small effect tend to be additive whereas mutants of large effect tend to be recessive, as empirically deduced (e.g. Caballero & Keightley, 1994). Owing to their harmful effects, mutants tend to be rare in populations under mutation–selection balance. From the above deduction, we think that

the increased genetic variance of fitness components after bottlenecks may be caused mainly by genetic drift of gene frequencies at a few loci with large effects, large dominance coefficients and small initial recessive gene frequencies, and may also be caused to a less extent by LD among a large number of loci with small effects and dominance coefficients. LD plays an even more important role for species such as *Drosophila* and the housefly, which have a small number of chromosomes with no crossing-over in males. For populations during bottlenecks of intermediate sizes, DHW may also cause a substantial increase in the additive variance.

Epistasis plays a critical role in various theories about speciation and evolution via founder events and bottlenecks. However, compared with dominance, the evidence for epistasis affecting quantitative traits is scarce (Barker, 1979; Barton & Turelli, 1989), although the theoretical likelihood of epistasis is high for fitness components under stabilizing selection (Robertson, 1955; Wright, 1977). When epistatic interactions are found, they are often not large relative to the additive genetic variance (Kearsey & Kojima, 1967; Shrimpton & Robertson, 1988; Paterson *et al.*, 1990). Recently, significant epistatic interactions among QTL loci affecting bristle number in *Drosophila melanogaster* were observed (Long *et al.*, 1995) and a substantial epistatic variance component was found for morphometric traits in the housefly (Bryant & Meffert, 1995, 1996). However, information for epistasis is still scarce in general. It is also difficult to measure the additive \times additive variance in the ancestral population, as is required for the epistatic model of Goodnight (1988) or Whitlock *et al.* (1993). Cheverud & Routman's (1996) epistatic model does not need the measurement of epistatic variance, but it requires genotypes to be measured at quantitative loci, which may be possible only for a very limited number of QTL with large effect. Thus the effect of epistasis on genetic variance after bottlenecks has still to be investigated.

In the present study, we have considered DHW *during* bottlenecks. DHW and its effect on the additive variance during bottlenecks are important when there is selection, either natural selection caused by inbreeding depression or artificial selection carried out experimentally (e.g. García *et al.*, 1994). It is shown that for rare recessive genes DHW results in the maximum increase in additive variance in intermediate-sized lines; and for the special case of additive genes ($d = 0$), our results reduce to that derived by Bulmer (1976). The effect of DHW does not

accumulate over generations, and it disappears completely once the population is expanded to a very large size. We have considered DHW only from sampling, assuming random mating, but the results can readily be extended to nonrandom mating, such as partially selfing, populations. For partially inbreeding populations, DHW is increased (see Wang, 1996 for quantification) and thus its effect on genetic variances is augmented. DHW and its effect on genetic variances are also important in the situation where a population is kept constant in size but the mating strategy changes from random mating to nonrandom mating.

Some of the assumptions made in our analysis could be relaxed without altering qualitatively the conclusions reached. The results are readily extended to dioecious species, nonrandom mating and other more complicated situations (such as variable distributions of family size) if an appropriate effective size rather than actual size is used. An important assumption is that no natural or artificial selection exists either within or between lines. Because inbreeding depression is observed universally, some degree of natural selection is inevitable. Nevertheless, most of our results should have qualitative relevance, particularly if the traits are determined by many genes of small effect which change little in frequency as a result of selection. The present results are also applicable to genes which are effectively neutral, because their fates are mainly determined by genetic drift as long as the bottlenecks are severe enough, even though they may cause inbreeding depression. Another important assumption made is that there is no epistasis. Under this assumption, there is a linear decrease in mean performance with inbreeding coefficient because of dominance. Wright (1977) has reviewed much of the plant and animal literature on inbreeding effects and, although exceptions do exist, the simple dominance model seems to give a reasonable fit to much of the data. Many recent experiments on inbreeding (as cited in this article) yield similar results.

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