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The role of epistasis in the increase in the additive genetic variance after population bottlenecks

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Summary

The effect of population bottlenecks on the additive variance generated by two neutral independent epistatic loci has been studied theoretically. Three kinds of epistasis were considered: (1) additive × additive, (2) multiple dominant genotype favoured, and (3) Dobzhansky–Muller type. The additive variance in an infinitely large panmictic population (ancestral variance) was compared with its expected value at equilibrium, after t consecutive bottlenecks of equal size N (derived variance). Formulae were derived in terms of allele frequencies and effects at each locus and the corresponding epistatic effects. An increase in the additive variance after bottlenecks will occur only if its ancestral value is minimal or very small. This has been detected only for: (1) intermediate ancestral allele frequencies at both loci; (2) extreme ancestral allele frequencies at one or both loci. The magnitude of the excess was inversely related to N and t. With dominance gene action, enhanced additive variance after bottlenecks implies a rise in the genotypic frequency of homozygous deleterious recessives, resulting in inbreeding depression. Considering multiple loci, simultaneous segregation of unfavourable alleles at intermediate frequencies, or of favourable recessives at low frequencies, cannot easily be conceived of unless there is strong genotype–environment interaction. With this possible exception, it is unlikely that the rate of evolution may be accelerated after population bottlenecks, in spite of occasional increments of the derived additive variance over its ancestral value.

1. Introduction

Theoretically, it has been shown that the additive genetic variance generated by loci showing dominance and/or epistasis can increase over its previous level following population bottlenecks, as a fraction of the ancestral non-additive variance can be 'converted' to derived additive variance (Robertson, 1952; Goodnight, 1987, 1988; Cockerham & Tachida, 1988; Tachida & Cockerham, 1989; Willis & Orr, 1993; Whitlock *et al*., 1993; Cheverud & Routman, 1996).

This phenomenon has often been invoked in the discussion of the consequences of very influential evolutionary models, and has been considered an additional benefit of genetic drift facilitating, rather than hindering, evolutionary innovation. Thus, in Wright's (1931) 'shifting-balance' theory of evolution, a transient increase in the additive variance in small demes may enhance the chance of a peak shift, by flattening the adaptive surface. In models of founder-effect speciation (Mayr, 1963; Carson, 1968; Templeton, 1980), an increase in the additive variance after population bottlenecks may result in a larger rate of genetic change leading to reproductive isolation and speciation. Nevertheless, the evolutionary significance of the phenomenon has generally been taken for granted rather than critically analysed (but see Coyne *et al*., 1997).

Experimentally, enhanced additive variance after bottlenecks has been observed for fitness-components traits in *Drosophila melanogaster* (López-Fanjul & Villaverde, 1989; García *et al*., 1994) and *Tribolium castaneum* (Fernández *et al*., 1995; Ruano *et al*., 1996; Wade *et al*., 1996), and was invariably accompanied by strong inbreeding depression, indicating directional dominance. Thus, these results were explained primarily by dominance, irrespective of possible epistasis of the loci involved, as the experimental design did not

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allow a separate study of epistatic effects. It is not clear, however, whether inbreeding depression can be counteracted by increased additive variance and, therefore, the impact of the latter on the outcome of natural selection is uncertain.

In this paper, we have theoretically investigated the effect of successive population bottlenecks on the mean and the additive variance generated by two-loci systems. Among the three epistatic models considered, two are immediate extensions of classical models, where epistasis has been imposed on systems showing either additive or dominance action at the single locus level (additive × additive epistasis or multiple dominant genotype favoured, respectively). In the present context, the multiple dominant epistatic model has not been previously studied. It is, however, an important case, as dominance at the single locus level has commonly been found and, for a broad range of dominance coefficients, this type of gene action has been shown to be a sufficient condition for increases in additive variance following bottlenecks (Robertson, 1952; Willis & Orr, 1993). The third model is the epistatic situation, originally proposed by Dobzhansky (1937) and Muller (1942), which has recently been considered in models of founder-effect speciation (Gavrilets & Hastings, 1996). Our approach follows that of Robertson (1952), where the expected values of the derived mean and additive variance, after consecutive bottlenecks of size N, are obtained from the expressions giving the corresponding ancestral values in an infinite population at equilibrium and the moments of the allele frequency distribution in populations of size N with binomial sampling. For additive × additive epistasis, this procedure allows a formulation of the dynamics of the process in terms of the ancestral additive and non-additive components of the genetic variance, identical to that resulting from measurements of co-ancestry and drift (Tachida & Cockerham, 1989, and references therein). For all models, explicit equations in terms of specific epistatic effects and allele frequencies were obtained, thus providing further insight into the necessary conditions for the conversion of non-additive to additive variance that have not been examined directly in previous studies.

2. The model

We consider the variation due to segregation at two neutral independent loci (A and B) at Hardy–Weinberg equilibrium. At each locus there are two alleles, with frequencies p_1 ($q_1 = 1-p_1$) and p_2 ($q_2 = 1-p_2$) at locus A and B, respectively.

The additive variance in an infinitely large panmictic population (ancestral variance V_A) is compared to its expected value at equilibrium, after t consecutive bottlenecks of N randomly sampled parents each (derived variance V^*_{At}). For any set of genotypes considered (Table 1), the average effect of gene substitution at each locus (α and β, respectively) can be obtained from the corresponding marginal genotypic values (Crow & Kimura, 1970, p. 125), and V_A is given by

$$V_A = 2\alpha^2 p_1 q_1 + 2\beta^2 p_2 q_2.$$

We can also compute the rate of divergence between lines $V(M_t)$, all of them independently started from the ancestral population and subsequently maintained with equal effective size N in each of t consecutive generations. For each genetic model in Table 1, that can be accomplished by taking variances $V(M)$ in the corresponding expression giving the ancestral population mean M. In parallel, the change in the population mean is given by $\Delta M_t = M^*_t - M$, where M^*_t is the expected value of M after t bottlenecks.

In general, equations for M, V_A and $V(M)$ are polynomial functions of p_i^k ($i = 1, 2$; $k =$ 1–4). Expressions for M^*_t, V^*_A and $V(M_t)$ can readily be obtained by substituting p_i^k in M, V_A and $V(M)$ by the exact kth moment of the allelic frequency distribution with binomial sampling, given by Crow & Kimura (1970, p. 335).

Table 1. *Genotypic values for different two-loci epistatic systems*

	A_1A_1	A_1A_2	A_2A_2
(*a*) *Additive × additive epistasis* ($k, s > 0$)			
B_1B_1	$1+k$	$1-s/4$	$1-s/2-k$
B_1B_2	$1-s/4$	$1-s/2$	$1-3s/4$
B_2B_2	$1-s/2-k$	$1-3s/4$	$1-s+k$
(*b*) *Multiple dominant genotype favoured* ($k, s > 0$)			
B_1B_1	1	1	$1-s$
B_1B_2	1	1	$1-s$
B_2B_2	$1-s$	$1-s$	$1-ks$
(*c*) *Dobzhansky–Muller epistasis* ($h, k, m, n, s > 0$; $h, m \leqslant k$, $n \leqslant 1$)			
B_1B_1	1	$1-hs$	$1-ns$
B_1B_2	$1-ms$	$1-s$	$1-hs$
B_2B_2	$1-ks$	$1-ms$	1

3. Analytical results

(i) *Additive × additive epistasis*

The genotypic values of Crow & Kimura's (1970, p. 79) two-locus model have been used (Table 1*a*), where $s/4$ is the additive effect and k measures the strength of epistasis ($k, s > 0$). After scaling ($k = hs/4$), the average effects of gene substitution at each locus are

$$\alpha = k[1 + h(1-2q_2)]/h$$

and

$$\beta = k[1 + h(1-2q_1)]/h,$$

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and the ancestral additive variance V_A is given by

$$V_A = 2k^2[(1+h)^2(p_1q_1+p_2q_2) - 8h^2p_1q_1p_2q_2 - 4h(p_1+p_2)q_1q_2]/h^2.$$

The ancestral additive × additive variance V_{AA} can be obtained by subtracting the additive variance from the total genotypic variance, yielding

$$V_{AA} = 4k^2p_1q_1p_2q_2.$$

To obtain the derived additive variance V^*_{At} after t consecutive bottlenecks of equal size N, we substitute p_i and p_iq_i in V_A by their respective expected values p_i and $p_iq_i\lambda_2^t$, where $\lambda_2 = 1-1/2N$, giving

$$V^*_{At} = 2k^2\lambda_2^t[(1+h)^2(p_1q_1+p_2q_2) - 8h^2\lambda_2^tp_1q_1p_2q_2 - 4h(p_1+p_2)q_1q_2]/h^2.$$

After some rearrangement, we obtain

$$V^*_{At} = \lambda_2^tV_A + 4\lambda_2^t(1-\lambda_2^t)V_{AA},$$

in agreement with previous results (Cockerham & Tachida, 1988; Goodnight, 1988; Whitlock *et al.*, 1993). Alternatively,

$$V^*_{At} - V_A = (1-\lambda_2^t)(4\lambda_2^tV_{AA} - V_A). \quad (1)$$

From (1), the condition $V^*_{At} > V_A$ can be expressed as $V_{AA} > V_A/4\lambda_2^t$, as found by Goodnight (1988). As V_{AA} will generally be much smaller than V_A, the former condition is less likely to hold in those populations reiteratively subjected to severe bottlenecks. For instance, for $t = 1$, the condition is $V_{AA} > 0{\cdot}33\,V_A(N = 2)$ or $V_{AA} > 0{\cdot}26\,V_A(N = 10)$ but, for $t = 4$, $V_{AA} > 0{\cdot}78\,V_A(N = 2)$ or $V_{AA} > 0{\cdot}31\,V_A(N = 10)$. Equation (1) also shows that, for $V^*_{At} > V_A$, V^*_{At} initially increases with λ_2^t, until a maximum is reached for $\lambda_2^t = (V_A+4V_{AA})/8V_{AA}$. This indicates a direct relationship between the effective population size and the number of generations needed to attain the maximum value of V^*_{At}. Obviously, V^*_{At} will ultimately vanish when fixation is reached.

Alternatively, $V^*_{At} > V_A$ can be written as

$$4hq_1q_2[p_1+p_2+2(1+\lambda_2^t)hp_1p_2] > (1+h)^2(p_1q_1+p_2q_2).$$

For equal allele frequencies at each locus ($p_1 = p_2 = 1/2$), the above condition reduces to $h^2 > 1/\lambda_2^t$ or $k > (1/\sqrt{\lambda_2^t})(s/4)$, showing again the inverse relationship between the magnitude of the epistatic effect k (relative to the additive effect $s/4$) and the number and severity of the bottlenecks. In this particular case, the condition implies that the epistatic effect must always be larger than the additive effect.

After t bottlenecks of size N, the derived additive × additive variance V^*_{AAt} is given by

$$V^*_{AAt} = 4k^2\lambda_2^{2t}p_1q_1p_2q_2 = \lambda_2^{2t}V_{AA}.$$

Therefore, V^*_{AAt} decreases by λ_2^2 per generation until it reaches zero. From (1), it follows that any excess of V^*_{At} over its ancestral value V_A can come only from the corresponding reduction of V^*_{AAt} – hence, the expression of non-additive variance being *converted* to additive variance (Goodnight, 1988). The temporal change of the ratio of the additive variance to the additive × additive variance is given by

$$V^*_{At}/V^*_{AAt} = (1/\lambda_2^t)V_A/V_{AA} + 4(1-\lambda_2^t)/\lambda_2^t.$$

From the genotypic values in Table 1 *a*, the ancestral population mean M is given by

$$M = 1+k+2k[2hq_1q_2 - (1+h)(q_1+q_2)]/h. \quad (2)$$

Taking variances in this expression, we have

$$V(M) = 4k^2\{V(q_1)[2hq_2-(1+h)]^2 + V(q_2)[2hq_1-(1+h)]^2 + 4h^2V(q_1)V(q_2)\}/h^2.$$

To obtain the between-line variance $V(M_t)$ after t successive bottlenecks of equal size N, we substitute $V(q_i)$ in $V(M)$ by its expected value $p_iq_i(1-\lambda_2^t)$. After some rearrangement, we obtain

$$V(M_t) = 2(1-\lambda_2^t)V_A + 4(1-\lambda_2^t)^2V_{AA},$$

in agreement with Goodnight (1987). Thus, $V(M_t)$ monotonically increases with time until a final value $2V_A+4V_{AA}$ is attained asymptotically. However, the number of generations needed to obtain a fixed value of $V(M_t)$ is inversely related to the bottleneck size.

Obviously, the previous equations can also be expressed in terms of the inbreeding coefficient after t generations ($F_t = 1-\lambda_2^t$) and, therefore, they can also be applied when bottleneck sizes are not constant from generation to generation.

The derived mean M^*_t after t bottlenecks is obtained by taking expectations in (2). It follows that $M^*_t = M$, a well-known result indicating that, with additive × additive epistasis, the population mean does not change with inbreeding (Crow & Kimura, 1970, p. 80).

With no additive × additive epistasis ($\alpha = \beta = s/4$, $k = 0$) the system reduces to a two-loci additive model. In this case, it is well known (Wright, 1951) that $V^*_{At} = \lambda_2^tV_A$, i.e. the additive variance always declines after bottlenecks by a fraction λ_2 per generation, regardless of allele frequencies. In parallel, $V(M_t) = 2(1-\lambda_2^t)V_A$, showing that the between-line variance continuously increases after bottlenecks, until a maximum value $2V_A$ is reached at fixation.

(ii) *Multiple dominant genotype favoured*

Genotypic values are given in Table 1 *b*. The average effects of gene substitution at each locus are

$$\alpha = sq_1[1+(k-2)q_2^2]$$

and

$$\beta = sq_2[1+(k-2)q_1^2].$$

Thus, the dominance effect s becomes a scale factor and k specifies the kind of epistasis involved ($0 < k <$

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2, diminishing epistasis; $k > 2$, reinforcing epistasis). For $k = 2$, the system reduces to a two-loci recessive model with no epistasis. In this situation, Robertson (1952) showed that the additive variance due to segregation of rare recessives will increase after consecutive bottlenecks, reaching a maximum when λ_2^t is close to 0·5.

The ancestral additive variance is given by

$$V_A = 2s^2[(p_1 q_1^3 + p_2 q_2^3) + 2(k-2)(p_1 q_1^3 q_2^2 + q_1^2 p_2 q_2^3) + (k-2)^2 (p_1 q_1^3 q_2^4 + q_1^4 p_2 q_2^3)].$$

To obtain the derived additive variance V_{At}^* after t bottlenecks of size N, we substitute q_i^2, $p_i q_i^3$ and q_i^4 by their respective expected values (Crow & Kimura, 1970):

$$q_i(1-p_i\lambda_2^t),$$

$$p_i q_i\left\{\lambda_2^t\frac{(3N-2)}{(10N-6)}+\lambda_3^t\left(q_i-\frac{1}{2}\right)-\lambda_4^t\left[p_i q_i-\frac{(2N-1)}{(10N-6)}\right]\right\}$$

and

$$q_i - p_i q_i\left\{\left[\lambda_2^t\frac{(18N-11)}{(10N-6)}\right]+2\lambda_3^t\left(q_i-\frac{1}{2}\right)-\lambda_4^t\left[p_i q_i-\frac{(2N-1)}{(10N-6)}\right]\right\},$$

where $\lambda_2 = 1-1/2N$, $\lambda_3 = \lambda_2(1-2/2N)$ and $\lambda_4 = \lambda_3(1-3/2N)$ are the roots of the transition matrix for the allele frequency moments.

As indicated, expressions for V_{At}^* can easily be obtained but the inequality $V_{At}^* > V_A$ becomes analytically intractable, even in the simple case of a single bottleneck and equal frequencies at both loci. Of course, numerical solutions for any combination of allele frequencies can be computed from the formulae.

In parallel, the dominance V_D, additive × additive V_{AA}, additive × dominance V_{AD} and dominance × dominance V_{DD} ancestral components of variance are given by

$$V_D = 4(d_1^2 p_1^2 q_1^2 + d_2^2 p_2^2 q_2^2) = \alpha^2 p_1^2 + \beta^2 p_2^2,$$

where $d_1 = -s[1+(k-2)q_2^2]/2 = -\alpha/2q_1$ and $d_2 = -s[1+(k-2)q_1^2]/2 = -\beta/2q_2$, and

$$V_{AA} = 4s^2(k-2)^2 p_1 q_1^3 p_2 q_2^3,$$

$$V_{AD} = 2s^2(k-2)^2 p_1 q_1^2 p_2 q_2^2 (q_1 p_2 + p_1 q_2)$$

and

$$V_{DD} = s^2(k-2)^2 p_1^2 q_1^2 p_2^2 q_2^2.$$

Thus, expressions for V_{Dt}^*, V_{AAt}^*, V_{ADt}^* and V_{DDt}^* can also be derived by substituting p_i^k by its expected value, but they can only be managed numerically.

From the genotypic values in Table 1 *b*, the ancestral population mean is given by

$$M = 1 - s(q_1^2 + q_2^2) - s(k-2) q_1^2 q_2^2. \quad (3)$$

Taking variances in this expression, we have

$$V(M) = s^2\{V(q_1^2)[1+(k-2)E(q_2^2)]^2 + V(q_2^2)[1+(k-2)E(q_1^2)]^2 + (k-2)^2 V(q_1^2) V(q_2^2)\}.$$

The between-line variance $V(M_t)$ after t consecutive bottlenecks can be obtained by substituting $V(q_i^2)$ in $V(M)$ by its expected value $E(q_i^4) - [E(q_i^2)]^2$, both frequency moments given by Crow & Kimura (1970) (see above).

The equation for $V(M)$ shows that $V(M_t)$ in the absence of epistasis ($k = 2$) is always smaller than with reinforcing epistasis ($k > 2$). For diminishing epistasis ($0 < k < 2$), this condition holds only for small values of q_1 and q_2.

Taking expectations in (3), we obtain the change in mean after t bottlenecks:

$$\Delta M_t = -s(1-\lambda_2^t)[p_1 q_1 + p_2 q_2 + (k-2) q_1 q_2 (1 - q_1 q_2) - (k-2) p_1 q_1 p_2 q_2 \lambda_2^t],$$

where the coefficient of the quadratic term λ_2^{2t} is equal to the dominance × dominance standard deviation, as indicated by Crow & Kimura (1970, p. 80).

(iii) *Dobzhansky–Muller epistasis*

This genetic model (Table 1 *c*) is defined for h, k, m, n, $s > 0$, where h, $m \leqslant k$, $n \leqslant 1$. Thus, it generates an adaptive landscape with ridges connecting two peaks separated by a valley (Gavrilets, 1997).

The average effects of gene substitution at each locus are

$$\alpha = s[2(p_1 - q_1) p_2 q_2 - (p_2 - q_2)(m p_1 q_2 + h q_1 p_2) - (h p_2 - m q_2)(p_1 p_2 + q_1 q_2) - k p_1 q_2^2 + n q_1 p_2^2]$$

and

$$\beta = s[2 p_1 q_1 (p_2 - q_2) - (p_1 - q_1)(m p_1 q_2 + h q_1 p_2) - (h q_1 - m p_1)(p_1 p_2 + q_1 q_2) + k p_1^2 q_2 - n q_1^2 p_2].$$

For equal allele frequencies at each locus ($p_1 = p_2 = 1/2$),

$$\alpha = -\beta = s[2(h-m) + (n-k)]/8$$

and, when the two ridges are identical ($h = m, n = k$), the gene action becomes underdominant for both loci. Therefore, in this particular case, the ancestral genetic variance is totally non-additive.

Expressions for V_A and V_{At}^* can be obtained as indicated, allowing computation of numerical solutions for any combination of allele frequencies. However, they are analytically unmanageable.

From the genotypic values in Table 1 *c*, the ancestral population mean is given by

$$M = 1 - s[2(p_1 p_2 + q_1 q_2)(h q_1 p_2 + m p_1 q_2) + n q_1^2 p_2^2 + k p_1^2 q_2^2 + 4 p_1 q_1 p_2 q_2], \quad (4)$$

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and the between-line variance $V(M_t)$ after t bottlenecks can be obtained as indicated in the preceding sections.

Taking expectations in (4), the change in mean ΔM_t after t bottlenecks is given by

$$\Delta M_t = -s(1-\lambda_2^t)[(k-2m)p_1q_1+(n-2h)p_2q_2 - (2m-2h-k+n)p_1p_2(p_1-p_2) + (1+\lambda_2^t)(4m+4h-k-n+4)p_1q_1p_2q_2].$$

4. Numerical evaluation

For all possible combinations of allele frequencies at both loci, surfaces are represented giving the corresponding values of the following parameters: (1) ancestral mean M, (2) change of the mean after one bottleneck ΔM_1 ($N = 2$), (3) ancestral additive variance V_A, (4) ratio of derived to ancestral additive variances V_{A1}^*/V_A after one bottleneck ($N = 2$), (5) between-line variance $V(M_t)$ after one or ten bottlenecks ($N = 2$).

(i) *Additive × additive epistasis*

Only two representative cases are shown (Fig. 1), with weak ($s = 0{\cdot}1$, $k = 0{\cdot}025$, $h = 1$) or strong epistasis ($s = 0{\cdot}1$, $k = 1$, $h = 40$). An extreme case of the latter ($s = 0$) has been considered by Cheverud & Routman (1996).

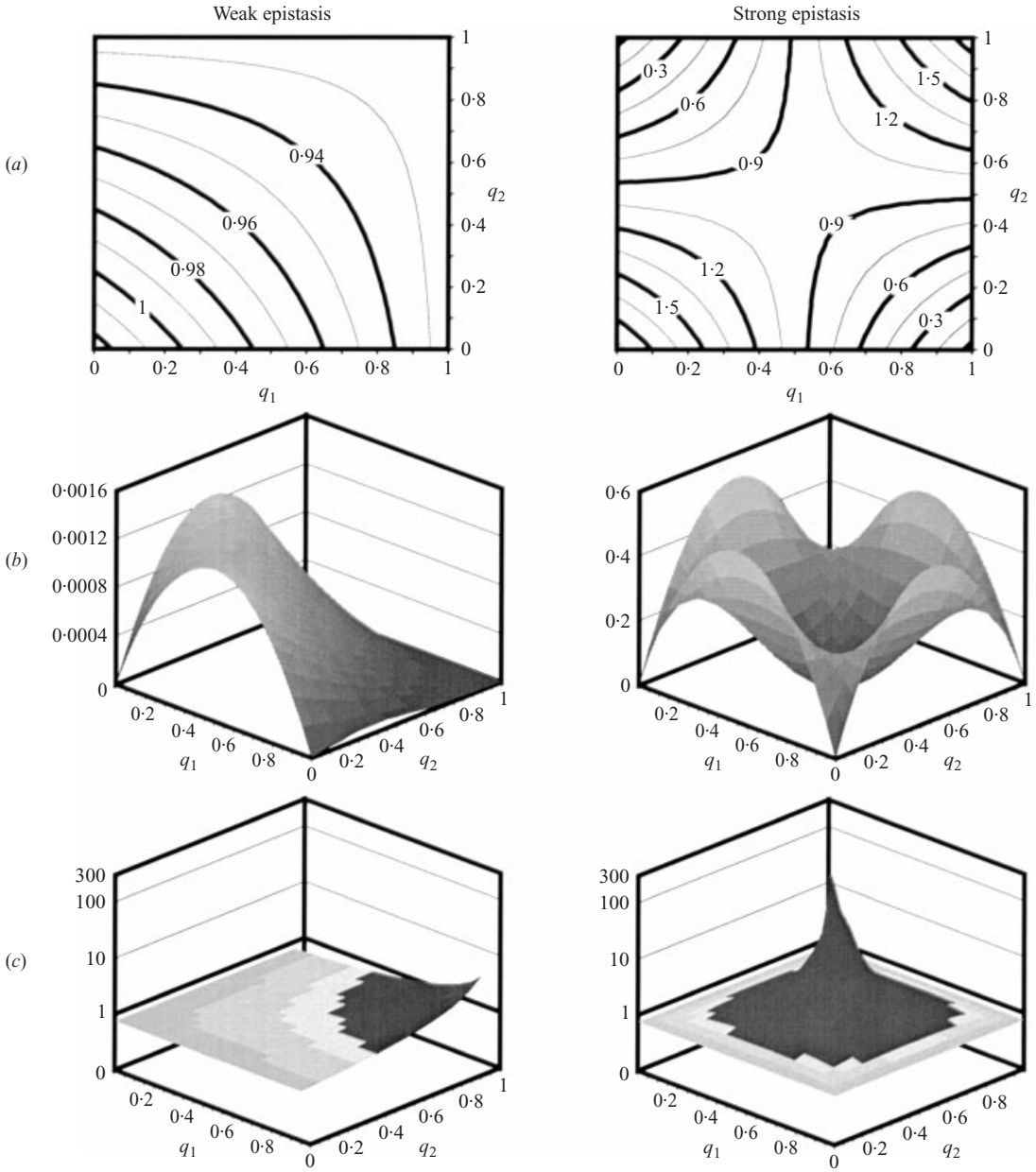

Fig. 1. Ancestral mean (*a*), ancestral additive variance (*b*) and ratio of derived to ancestral additive variances after one bottleneck (*c*, $N = 2$), plotted against two-locus allele frequencies, for weak or strong additive × additive epistasis (see text for further explanation). Darker zones in (*c*) correspond to variance ratios greater than one.

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For low k values, the surface representing the mean as a function of the allele frequencies (Fig. 1*a*) has a single peak at $q_1 = q_2 = 0$, the mean monotonically decreasing as the frequencies depart from those values. When larger values of k are considered, a second peak appears at $q_1 = q_2 = 1$ and intermediate frequencies at both loci determine a saddle.

The ancestral additive variance is plotted against two-locus allele frequencies in Fig. 1*b*. Differentiating the expression for V_A with respect to q_1 and q_2 and setting the two equations equal to zero, maxima and minima of the V_A surface are given by

$$p_1 q_1(q_1 - p_1)[(1+h)^2 - 8h^2 p_2 q_2 - 4hq_2] = p_2 q_2(q_2 - p_2)[(1+h)^2 - 8h^2 p_1 q_1 - 4hq_1].$$

It follows that four maxima, equal two by two, occur when one locus is fixed and the other segregates at equal frequencies. For small k values, those maxima corresponding to $q_1 = 0$, $q_2 = 1/2$ and $q_1 = 1/2$, $q_2 = 0$ are highest. As k increases, the four maxima become increasingly similar and the V_A surface approaches symmetry. The minimum V_A is obtained for equal frequencies at both loci ($p_1 = p_2, q_1 = q_2$), approaching $p_i = q_i = 1/2$ when k is large ($k \geqslant 1$). The latter is also the point of maximum V_{AA}.

After a bottleneck (Fig. 1*c*) the derived additive variance exceeds its ancestral value ($V_A^* > V_A$) only for those combinations of allele frequencies resulting in the smaller ancestral additive variances. Milder bottlenecks ($N > 2$, not shown) gave the same qualitative results, but the increase in the derived additive variance relative to the ancestral value was inversely related to the bottleneck size. With successive bottlenecks ($N = 2$), the shape of the surfaces giving V_{At}^*/V_A remains unchanged but the corresponding values of this ratio gradually decrease (not shown).

Summarizing, increases of the additive variance following consecutive bottlenecks can be only expected if the ancestral additive variance is low and the ancestral mean is small (weak epistasis) or intermediate (strong epistasis) corresponding, respectively, to extreme or intermediate frequencies at both loci.

(ii) *Multiple dominant genotype favoured*

Again, only two representative cases are shown (Fig. 2), for diminishing ($s = 0{\cdot}1$, $k = 0{\cdot}1$) or reinforcing ($s = 0{\cdot}1$, $k = 3$) epistasis.

The surface giving the level of the ancestral mean for each combination of allele frequencies is shown in Fig. 2*a*. For diminishing epistasis, this surface is of the saddle type, the mean being highest for $q_1 = q_2 = 0$ and $q_1 = q_2 = 1$, and lowest for $q_1 = 1$, $q_2 = 0$ and $q_1 = 0$, $q_2 = 1$. With reinforcing epistasis, the surface has a single peak at $q_1 = q_2 = 0$. The changes in mean value after a single bottleneck are also represented in surface form in Fig. 2*b*. With reinforcing epistasis, a reduction in the mean was observed for all combinations of allele frequencies. On the other hand, an unrealistic enhancement of the mean was detected in the special case of diminishing epistasis and large frequencies of the recessive alleles at both loci, since the values of the $A_1A_2B_2B_2$ and $A_2A_2B_1B_2$ genotypes are smaller than that of the $A_2A_2B_2B_2$ homozygote. After successive bottlenecks ($N = 2$), the shape of the surfaces giving ΔM_t remained unaltered, but the magnitude of the changes was larger (not shown).

The ancestral additive variance is plotted against two-locus allele frequencies in Fig. 2*c*. Maxima and minima of this V_A surface are given by the expression

$$p_1 q_1^4(q_1 - 3p_1)[1 + (k-2)q_2^2] = p_2 q_2^4(q_2 - 3p_2)[1 + (k-2)q_1^2],$$

indicating that there are four local maxima, equal two by two, when one locus is fixed and the other segregates at a frequency $q = 3/4$. Those maxima for $q_1 = 0$, $q_2 = 3/4$ and $q_1 = 3/4$, $q_2 = 0$ are highest with diminishing epistasis and lowest with reinforcing epistasis. With reinforcing epistasis, there is an additional maximum at $q_1 = q_2 = 3/4$, which exceeds all local maxima. Minima exist only for diminishing epistasis at $q_1 = q_2 = 3/4$. Thus, the V_A surface has three 'folds' of low variance, corresponding to zones of highest and lowest means, ascending to a peak (reinforcing epistasis) or converging in a valley (diminishing epistasis). The non-additive ancestral variance is always maximum at $q_1 = q_2 = 3/4$, irrespective of the value of k.

After a bottleneck (Fig. 2*d*), the derived variance exceeds the ancestral one ($V_A^* > V_A$) only for those combinations of allele frequencies resulting in small values of V_A (folds and valley). At those frequencies, milder bottlenecks ($N > 2$, not shown) also resulted in larger additive variances, but the increment was smaller as the size of the bottleneck increased. The shape of the surfaces giving the value of V_{At}^*/V_A after successive bottlenecks ($N = 2$) did not change, but the variance ratio diminished as the number of bottlenecks increased (not shown).

In the case of two non-epistatic recessive loci (Robertson, 1952), the results (not shown) are very similar to those obtained for multiple dominant genotype favoured with reinforcing epistasis, but the increase in the variance after a bottleneck was smaller. Summarizing, an increase in the additive variance after bottlenecks can be attained only at the expense of a rise in the genotypic frequencies of homozygous recessives, thus lowering the population mean.

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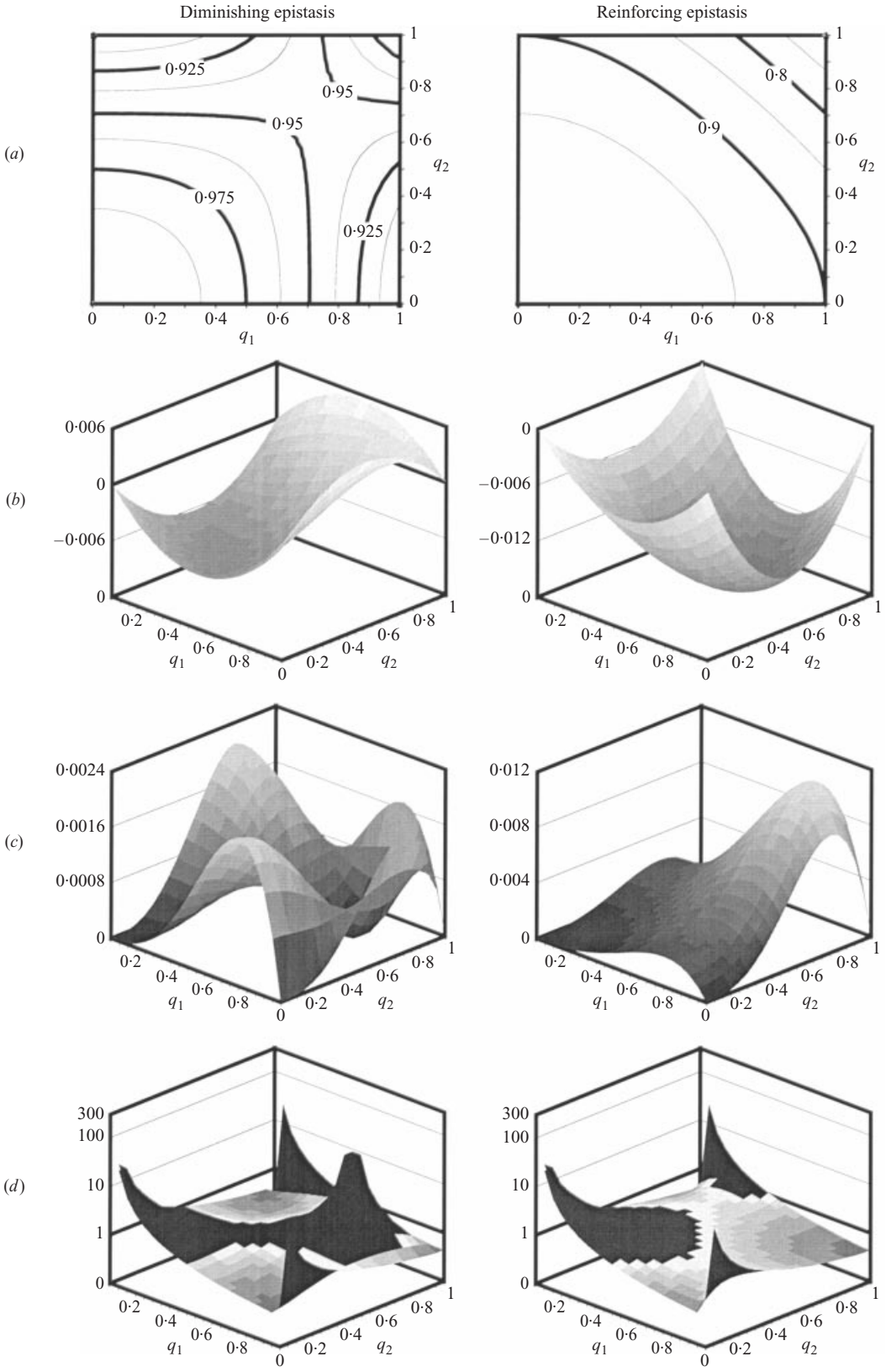

Fig. 2. Ancestral mean (*a*), change of the mean after one bottleneck (*b*, $N = 2$), ancestral additive variance (*c*) and ratio of derived to ancestral additive variances after one bottleneck (*d*, $N = 2$), plotted against two-locus allele frequencies, for multiple dominant genotype favoured reinforcing or diminishing epistasis (see text for further explanation). Darker zones in (*d*) correspond to variance ratios greater than one.

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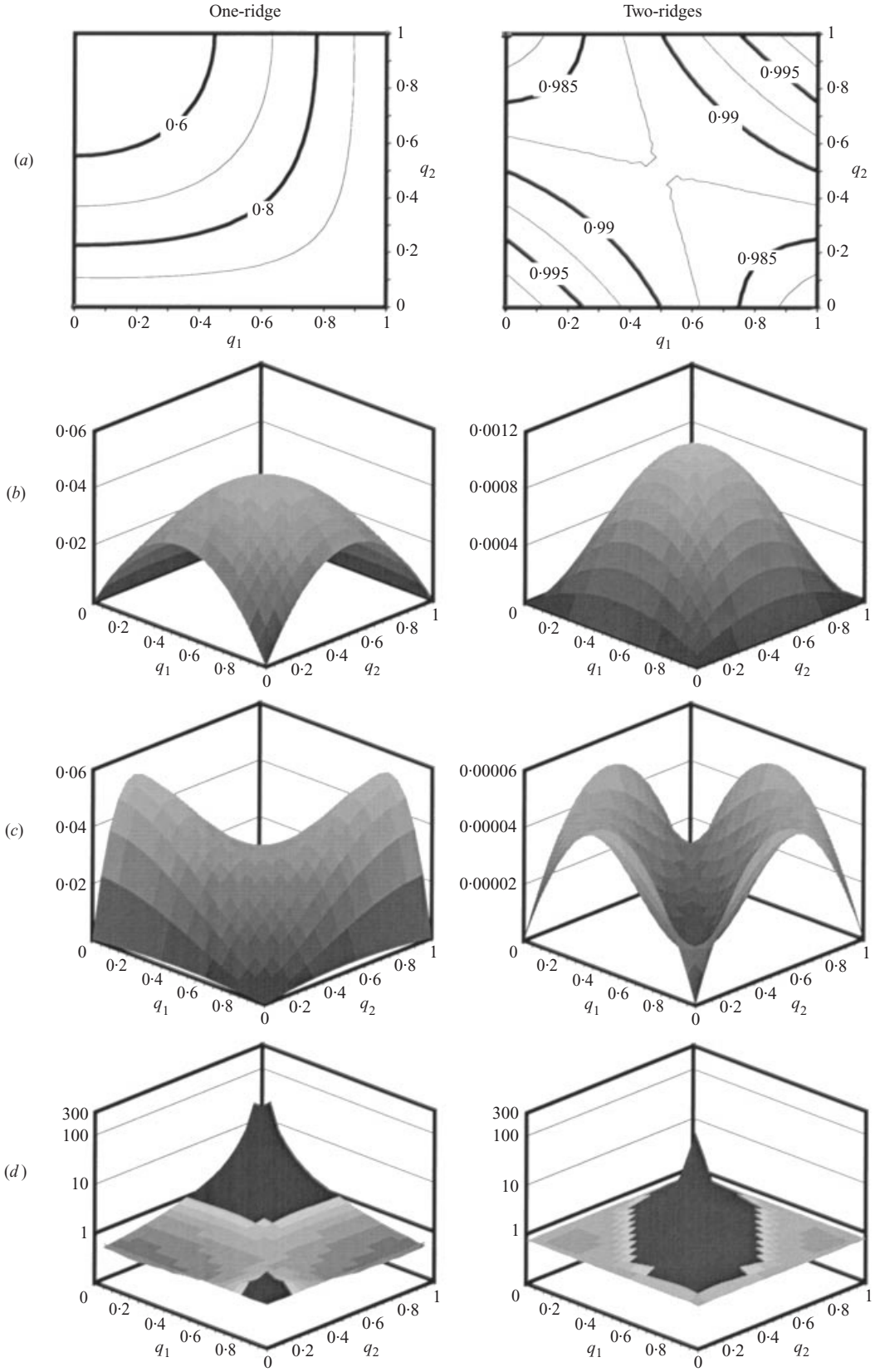

Fig. 3. Ancestral mean (*a*), change of the mean after one bottleneck (*b*, $N = 2$), ancestral additive variance (*c*) and ratio of derived to ancestral additive variances after one bottleneck (*d*, $N = 2$), plotted against two-locus allele frequencies, for one-ridge or two-ridges Dobzhansky–Muller epistasis (see text for further explanation). Darker zones in (*d*) correspond to variance ratios greater than one.

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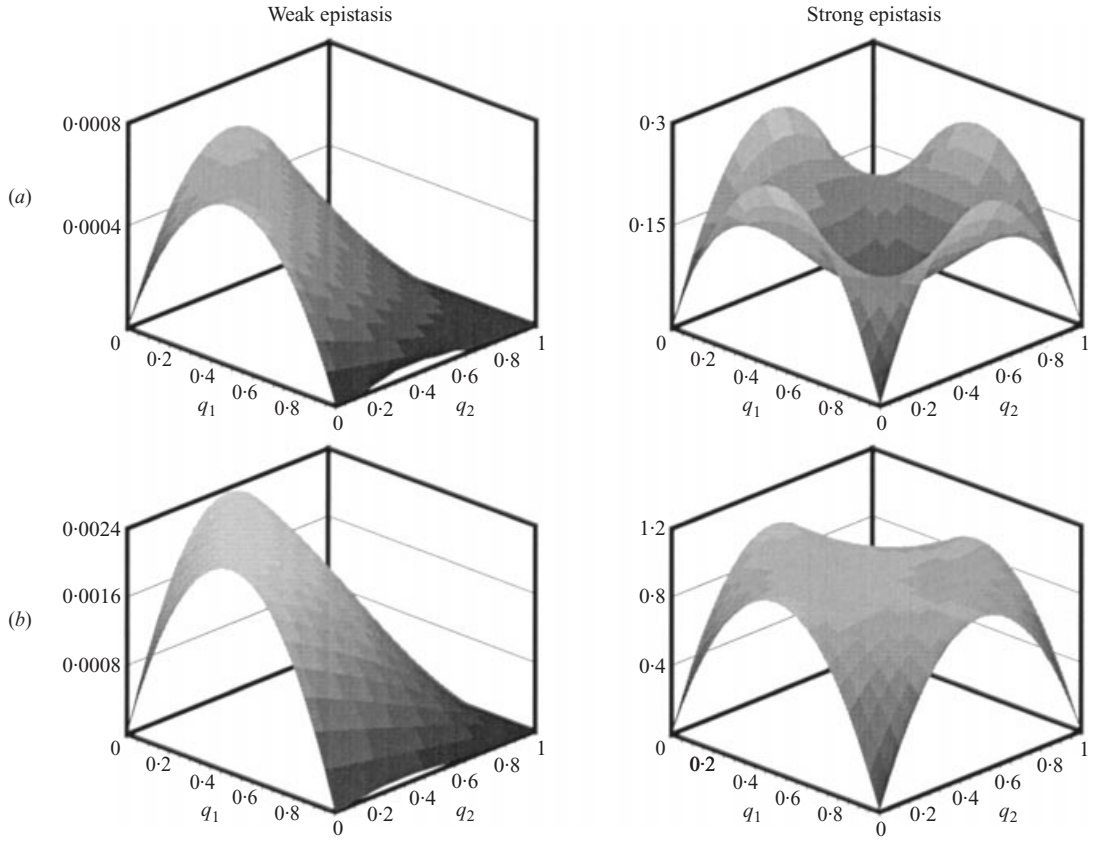

Fig. 4. Between-line variance after one (*a*) or ten (*b*) bottlenecks ($N = 2$), plotted against two-locus allele frequencies, for weak or strong additive × additive epistasis (see text for further explanation).

(iii) *Dobzhansky–Muller epistasis*

Two representative examples (Gavrilets, 1997) are shown (Fig. 3) corresponding to one ridge ($s = 0{\cdot}5$, $h = n = 1$, $m = 0{\cdot}02$, $k = 0{\cdot}04$) or two ridges ($s = 0{\cdot}02$, $h = m = 0{\cdot}5$, $k = n = 1$) connecting the two peaks of the ancestral mean surface (Fig. 3*a*). After bottlenecks, the population mean always increases, since the genotypic value of the double heterozygote is lowest. Only the surface representing the changes in the mean after a single bottleneck is shown (Fig. 3*b*). The surfaces corresponding to successive bottlenecks ($N = 2$) had the same shape but the magnitude of the change increased with bottleneck number (not shown).

The ancestral additive variance (Fig. 3*c*) shows four local maxima, equal two by two, when only one locus segregates. Their values and the corresponding gene frequencies depend on the type of gene action at the segregating locus (given by the values of the h/n and m/k ratios). In the one-ridge case considered ($h = n$, $k = 2m$) single gene action is additive in two instances ($p_1 = 1$ or $p_2 = 0$) and recessive in the other two ($p_1 = 0$ or $p_2 = 1$), and the corresponding maxima additive variances are larger with recessive action (at $q_1 = 0$, $q_2 = 1/4$ and $q_1 = 3/4$, $q_2 = 1$) than with additive action (at $q_1 = 1$, $q_2 = 1/2$ and $q_1 = 1/2$, $q_2 = 0$). In the two-ridge case studied ($h = m$, $n = k$) the gene action at the segregating locus is always additive and the gene effects are equal in all instances. Therefore, the four local maxima (at $p_i = q_i = 1/2$) are also equal. In parallel, intermediate gene frequencies at both loci correspond to minimum additive variance (two ridges) or to a saddle of the additive variance surface (one ridge).

The derived additive variance after a bottleneck (Fig. 3*d*) exceeded the ancestral value only at intermediate (two ridges) or extreme (one ridge) frequencies. In those situations, the ancestral additive variance is very small and the ancestral non-additive variance is maximum. After successive bottlenecks ($N = 2$), a similar outcome was obtained but for a much restricted set of allele frequencies (not shown).

(iv) *Between-line variance after bottlenecks*

For each type of epistasis considered, the surfaces giving the ancestral additive variance (Figs. 1*b*, 2*c*, 3*c*) and the between-line variance after one bottleneck (Figs. 4*a*, 5*a*, 6*a*) have the same shape but, in all cases, the values of the latter were, approximately, one-half those of the former. Thus, at low levels of inbreeding, the between-line variance with epistasis behaves similarly to that with pure additive gene action as, at that stage, the contribution of the ancestral non-

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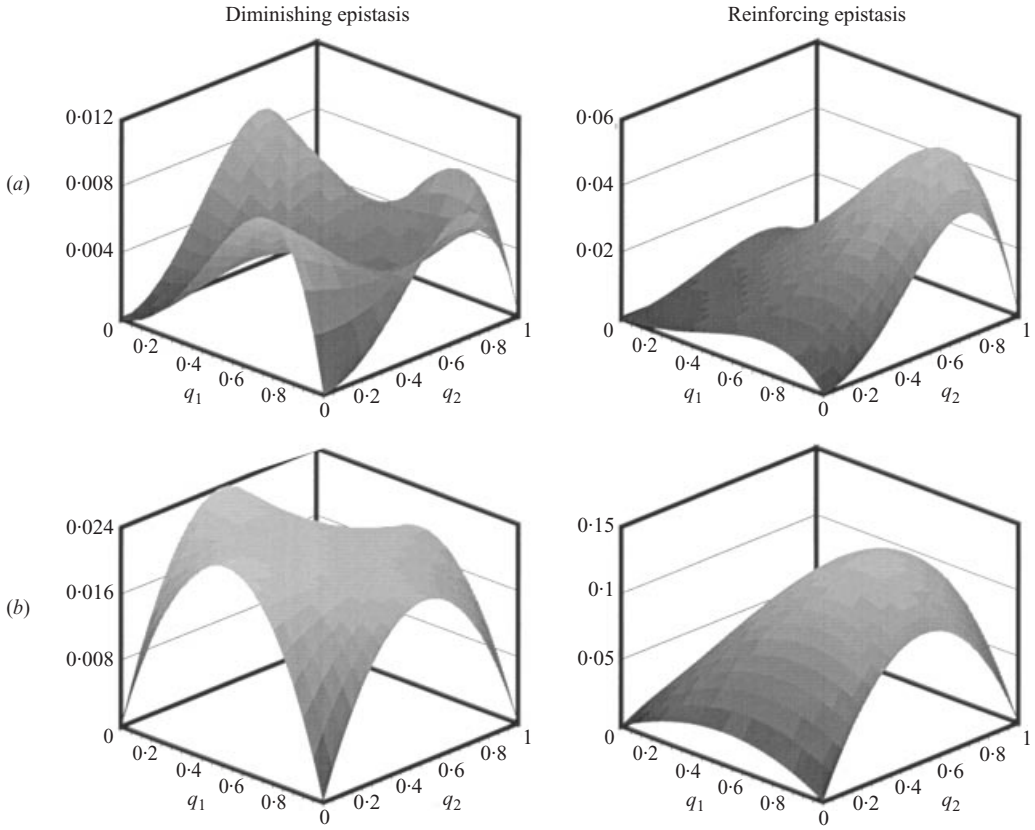

Fig. 5. Between-line variance after one (*a*) or ten (*b*) bottlenecks ($N = 2$), plotted against two-locus allele frequencies, for multiple dominant genotype favoured reinforcing or diminishing epistasis (see text for further explanation).

additive variance to the between-line variance is always small.

With weak additive × additive or reinforcing (multiple dominant favoured) epistasis, the ancestral additive variance surface has no minimum and the shape of the between-line variance surface does not appreciably change after successive bottlenecks. With additive × additive epistasis, the between-line variance after 10 bottlenecks (Fig. 4*b*) was very close to the additive expectation, since the epistatic variance was always small relative to the additive variance and, therefore, its contribution to the between-line variance $[4(1-\lambda_2^t)\,V_{AA}]$ was negligible. With reinforcing epistasis, the dynamics of the process is much slower than expected with additive gene action and, after 10 bottlenecks, the between-line variance was approximately equal to the ancestral additive variance (Fig. 5*b*).

With strong additive × additive, diminishing (multiple dominant favoured) and Dobzhansky–Muller (two ridges) epistasis, intermediate frequencies at both loci determine both minimum additive and maximum non-additive ancestral variances. Thus, the contribution of non-additive variance to the between-line variance may be large. After two or three bottlenecks ($N = 2$, not shown), the most important change of the between-line variance surface was the conversion of the initial minimum at intermediate frequencies to a level top. Thereafter, the shape of the between-line surface did not change much (Figs. 4*b*, 5*b*, 6*b*).

5. Discussion

Of the countless ways in which epistasis can be modelled, we have concentrated on two immediate extensions of previous work by adding epistasis to systems showing either additive or complete recessive action at the single locus level. In these cases, we have found that an increase in the additive variance after population bottlenecks will occur only if its ancestral value is either minimal or very small. In both instances, the difference between the additive and non-additive ancestral components of variance is large and, therefore, the potential for conversion of the second to the first is also large. The following conclusions apply to populations subjected to a single bottleneck of any size, albeit the excess of the derived additive variance over its ancestral value decreases as the bottleneck size increases. They also apply to successive bottlenecks of equal size, but the rate of increase of the derived additive variance declines with the number of bottlenecks until a maximum value is reached, subsequently decreasing to zero.

An excess of the derived additive variance over its

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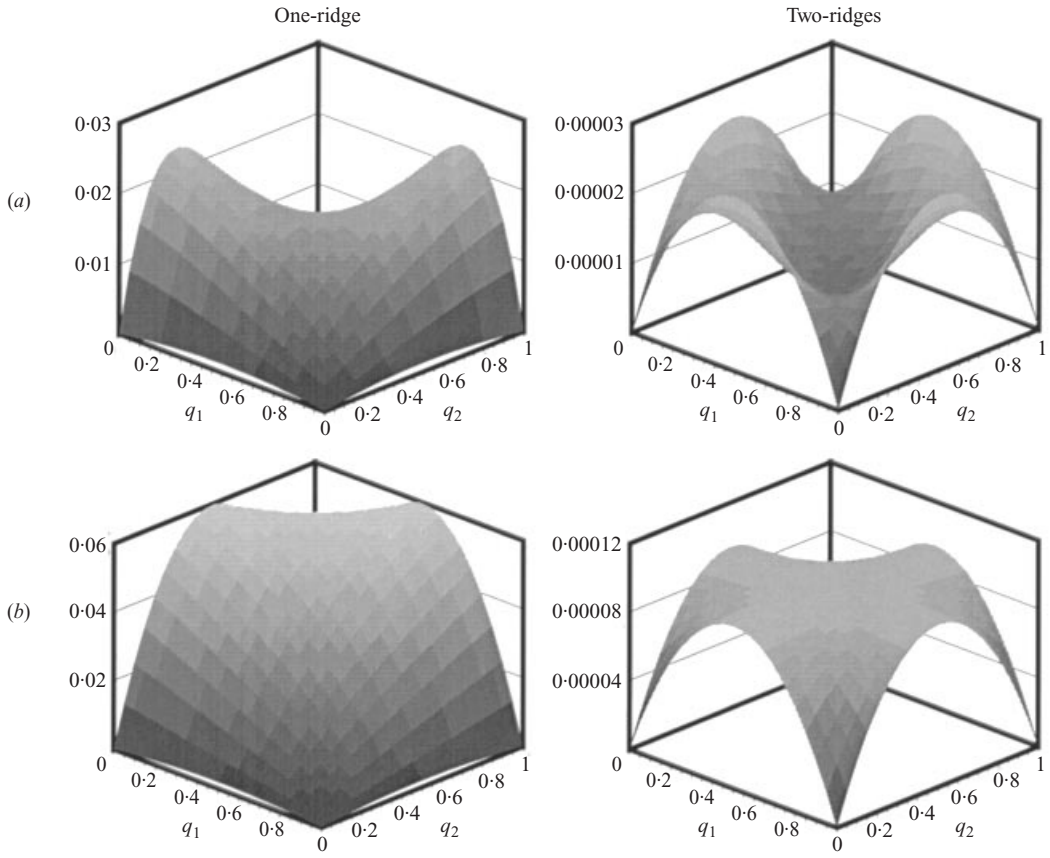

Fig. 6. Between-line variance after one (*a*) or ten (*b*) bottlenecks ($N = 2$), plotted against two-locus allele frequencies, for one-ridge or two-ridges Dobzhansky–Muller epistasis (see text for further explanation).

ancestral value has been only detected in two situations, sharply differing in their corresponding degree of genic heterozygosity. With strong additive × additive, diminishing (multiple dominant favoured) and Dobzhansky–Muller (two ridges) epistasis, that excess occurs for intermediate frequencies at both loci, determining: (1) a valley of the ancestral mean surface, (2) minimum ancestral additive variance, (3) maximum ancestral non-additive variance. On the other hand, with weak additive × additive and reinforcing (multiple dominant favoured) epistasis, the ancestral mean surface has a single peak and the ancestral additive variance surface shows no minimum. In this situation, the derived additive variance exceeds its ancestral value only when alleles of negative effects segregate with high frequency at both loci (additive × additive epistasis) or for recessives segregating with low frequencies at both loci or with low frequency at one locus and high frequency at the other. In practice, this latter case is equivalent to that of a single dominant locus, as the corresponding epistatic components of variance will be much smaller than the dominance component.

Strictly, our analysis assumes neutrality, but the conclusions can be qualitatively extended to fitness. In this case, it is difficult to conceive of a situation in which the frequencies of deleterious alleles are intermediate (additive × additive epistasis), unless large genotype–environment interaction implies a reversal of the sign of the allelic effects, converting harmful alleles to beneficial ones. Moreover, for recessive alleles at low frequencies, the enhancement of additive variance after bottlenecks will always be penalized by a large inbreeding depression, excepting the case of favourable recessives. In practice, however, simultaneous segregation of low-frequency favourable recessives at a number of loci is improbable excepting, again, with strong genotype–environment interaction. On the other hand, the main feature of Dobzhansky–Muller epistatic models is an adaptive lanscape where peaks are connected by ridges, making it unnecessary to cross adaptive valleys. Nevertheless, we have shown that the derived additive variance will be larger than its ancestral value only for those gene frequencies determining the valley but not the ridges. Therefore, bottlenecks will not make the chance of a peak shift greater. Summarizing, for the epistatic models studied, occasional increases in the derived additive variance can be observed. However, it is unlikely that the rate of evolution may be accelerated after population bottlenecks, unless unrealistic parameter values are assumed.

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For a broad range of dominance coefficients, population bottlenecks have been shown to increase the contribution of individual loci to the additive variance (Robertson, 1952; Willis & Orr, 1993). Thus, a relevant part of our analysis is that comparing the behaviour of dominant loci with and without epistasis. Our results clearly show that, for those systems implying dominance at the single locus level, additional epistasis will not greatly affect the value of the derived additive variance over single locus expectations, as those combinations of allele frequencies resulting in derived additive variance larger than its ancestral value, also result in small epistatic variances. This is an important point, as deleterious recessive alleles have commonly been found but experimental evidence for epistasis remains elusive (see below). Therefore, dominance can be considered as the primary cause of an increase in the ancestral additive variance after bottlenecks.

For additive gene action within and between loci, the between-line variance after a bottleneck ($N = 2$) is equal to $V_A/2$. This prediction holds approximately both for simple dominance and for the epistatic models considered. The reason for this is that only small fractions of the non-additive components of variance contribute to the between-line variance, those components being generally smaller than the additive component. Thus, one can safely make the generalization that, at low levels of inbreeding, the behaviour of the between-line variance of a trait will not be greatly affected by the type of gene action of the loci involved. That approximation also holds after several bottlenecks, excepting the cases of strong additive × additive, diminishing (multiple dominant favoured) and Dobzhansky–Muller epistasis, with both loci initially segregating at intermediate frequencies. Only in the latter situations does the between-line variance strongly depart from non-epistatic loci predictions.

The behaviour of the additive variance after bottlenecks has also been studied by Cheverud & Routman (1996) for specific two-loci models in which genotypic values equal the epistasis values ('physiological epistasis'), concluding that the derived additive variance will always exceed the ancestral variance after one or several bottlenecks. Nevertheless, these models are very restrictive, implying: (1) minimum ancestral additive variance with intermediate frequencies at both loci, (2) maximum ancestral additive variance when one locus is fixed, (3) underdominance (overdominance) at one or both loci considered, with additive × dominance or dominance × dominance epistasis, respectively. Moreover, Cheverud & Routman (1996) considered only the special case of an ancestral population segregating with intermediate frequencies at both loci, i.e. the case of maximum potential for conversion of non-additive to additive variance. These restrictions have a marked influence on the dynamics of the additive variance in bottleneck populations. As we have shown, their conclusion of the additive variance invariably increasing after bottlenecks cannot be extended to non-intermediate ancestral allelic frequencies or to other, simpler epistatic models (weak additive × additive or reinforcing epistasis) with intermediate frequencies.

Some of our models imply an enhancement of the mean with inbreeding (diminishing epistasis, for high-frequency recessives; Dobzhansky–Muller epistasis, for all allele frequencies). Dobzhansky–Muller epistatic models were originally proposed in the study of the evolution of reproductive isolation. In this context, their validity is an open question that can only be established empirically. Recently, that type of gene action has been claimed to be a general property of multidimensional adaptive landscapes (Gravilets & Gravner, 1997). However, this generality is questionable, since the model implies an enhancement of the population mean with inbreeding. After a single bottleneck ($N = 2$), this is also the case for Cheverud & Routman (1996) models (additive × dominance epistasis, for $q_1 > 1/2$; dominance × dominance epistasis, for extreme frequencies at any one locus). That undesirable property makes those models unrealistic, since it contradicts the general observation of fitness-related traits being subjected to inbreeding depression.

The case of additive × additive epistasis has been studied by Goodnight (1987, 1988) in terms of coancestry measures and ancestral components of the genetic variance. For independent loci, we have obtained the same results. In our model, alternative formulae were found in terms of genotypic effects and allelic frequencies, thus providing further insight into the problem. Starting from an ancestral population at linkage equilibrium, Goodnight was able to show that recombination does not affect the contribution of the ancestral additive variance to either the derived additive variance or the between-line variance. However, large recombination rates increase the contribution of the ancestral epistatic variance to the derived additive variance, but decrease it to the between-line variance. After a single bottleneck ($N = 2$), those effects are small and, therefore, it is unlikely that linkage can qualitatively affect our results. In a similar analysis, Tachida & Cokerham (1989) also reached the same conclusion. Nevertheless, the effect of linkage disequilibrium on the additive variance after multiple bottlenecks has not been analysed. The case of rare non-epistatic recessives has been considered by Wang *et al.* (1998*a*). They have shown that linkage disequilibrium can lead only to a small transient increase in the derived additive variance, above that expected from drift alone. Deviation from Hardy–Weinberg proportions, however, can result in a substantial increment in the derived additive variance, but this effect vanishes completely once the

population is expanded. In parallel, the between-line variance due to non-epistatic recessives is not affected by linkage disequilibrium generated by sampling if there is no disequilibrium in the base population (Avery & Hill, 1979).

So far, this discussion has been limited to investigating the consequences of population bottlenecks on the mean and additive variance generated by two-loci epistatic systems. An extension of these results to the whole set of loci determining the additive variance of a quantitative trait will, in principle, require a complete specification of genotypic effects and allelic frequencies, as the contribution of loci with the same type of gene action to the difference between the ancestral and the derived additive variances can even be of different sign, depending on their respective allele frequencies. Generalization into multilocus systems can only be made if individual loci show the same type of gene action and segregate with similar frequencies. Only in this situation do our theoretical results provide a framework within which some experimental data can be interpreted. The following discussion will be restricted to *Drosophila melanogaster*, where detailed genetic information on pertinent traits is available.

At one extreme of the spectrum, we have traits such as abdominal or sternopleural bristle number. In natural populations, much of the genetic variance of these characters has been shown to be contributed by a small number of loci segregating at intermediate frequencies, with quasi-neutral effects on fitness and considerable, nearly additive effects on bristle number (Robertson, 1967; Gallego & López-Fanjul, 1983). Recent data on spontaneous mutations have confirmed that those with an effect on bristles smaller than one-half phenotypic standard deviation of the trait are predominantly additive and quasi-neutral (Santiago *et al*., 1992; López & López-Fanjul, 1993). Furthermore, if deleterious mutations affecting those traits occur at low rate, as suggested by recent analyses (García-Dorado, 1997; García-Dorado *et al*., 1998), quasi-neutral additive alleles can be found segregating at intermediate frequencies in natural populations, contributing a large fraction of the total variance. Evidence for epistasis is ambiguous. No epistatic effects between pairs of mutations affecting abdominal bristle number were found by Caballero *et al*. (1991) and Merchante *et al*. (1995). Epistatic effects were found in a single third chromosome extracted from a line previously selected for sternopleural bristle number (Shrimpton & Robertson, 1988). However, those effects were small relative to the additive variance of the base population. The discrepancy may be taken as an indication of epistatic effects not being large. For abdominal bristle number, the effect of three consecutive bottlenecks ($N = 2$) has been studied in a highly replicated experiment (López-Fanjul *et al*., 1989). With additive × additive epistasis, an increase in the additive variance following bottlenecks can be expected only if $V_{AA} > V_A/4\lambda_2^t$, i.e. $V_{AA} > 0{\cdot}59V_A$ in our case ($\lambda_2 = 3/4$, $t = 3$). This inequality is unlikely to hold as it implies strong epistatic effects. In agreement with previous information on the genetic architecture of the trait, no inbreeding depression was detected and the between-line and within-line additive variance (estimated from the response to divergent artificial selection) very closely approached the expectations under the pure additive model.

At the other end of the spectrum we consider viability, accounting for about one-third of total fitness effects (Sved, 1971). Recent information indicates that most mutations affecting viability show a large homozygous disadvantage (García-Dorado, 1997; García-Dorado *et al*., 1998). Therefore, in natural populations, much of the genetic variance of the trait should be due to partially (or totally) recessive deleterious alleles segregating at low frequencies. However, the additive variance has been shown to be much larger than the dominance component (Mukai, 1985). This conforms with an average dominance coefficient of newly arisen mutations (excluding lethals) of about 0·36 (Mukai, 1969). Again, evidence of epistasis for viability is inconclusive. Comparing individuals homozygous and heterozygous for entire second and third chromosomes extracted from recently collected populations, Temin *et al*. (1969) found no interactions, Kosuda (1971) detected a small but significant interaction, and a larger but just significant interaction was reported by Seager & Ayala (1982). Synergistic effects of viability mutations have been described but were not large (Mukai, 1969; Simmons & Crow, 1977). Furthermore, synergism may be an artifact caused by instability of transposable element copy number leading to a non-linear increase in the mutation rate (Keightley, 1996). The effects of one or several bottlenecks ($N = 2$) have been studied by López-Fanjul & Villaverde (1989) and García *et al*. (1994). The ancestral mean viability was depressed by about 0·7% per 1% increase in inbreeding coefficient, indicating strong directional dominance of some of the loci involved. The additive variance after a bottleneck (estimated from the response to upward artificial selection) significantly increased above the ancestral value by a factor of about 3·3. However, as indicated by our analysis, the between-line variance could not be statistically discerned from the expectation under pure additive gene action. In natural populations of *Tribolium* similar results were obtained (Fernández *et al*., 1995; Wade *et al*., 1996). The response to artificial selection to increase viability in lines previously subjected or not to a single bottleneck ($N = 2$) has been studied by García *et al*. (1994). Equal short-term response and selection limits were obtained in both cases, indicating that the excess of additive

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variance following the bottleneck only compensated the strong inbreeding depression incurred. Using mutational information, Wang *et al*. (1998*b*) have been able to show that the inbreeding depression and the increase in additive variance of viability following a bottleneck can be mainly ascribed to lethals and partially recessive mutations of large deleterious effect.

In conclusion, an increase in additive variance after population bottlenecks could only facilitate the transition towards a higher peak of the adaptive surface in very specific situations, particularly those involving a strong genotype–environment interaction. For *Drosophila* viability, such interaction has been detected both in natural populations and for spontaneous mutations (Fernández & López-Fanjul, 1997 and references therein). The evolutionary relevance of this phenomenon, however, has not been explored in the present context.

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References

Avery, P. J. & Hill, W. G. (1979). Variance in quantitative traits due to linked dominant genes and variance in heterozygosity in small populations. *Genetics* **91**, 817–844.

Caballero, A., Toro, M. A. & López-Fanjul, C. (1991). The response to artificial selection from new mutations in *Drosophila melanogaster*. *Genetics* **128**, 89–102.

Carson, H. (1968). The population flush and its genetic consequences. In *Population Biology and Evolution* (ed. R. C. Lewontin), pp. 123–137. Syracuse, USA: Syracuse University Press.

Cheverud, J. M. & Routman, E. J. (1996). Epistasis as a source of increased additive genetic variance at population bottlenecks. *Evolution* **50**, 1042–1051.

Cockherham, C. & Tachida, H. (1988). Permanency of response to selection for quantitative characters in finite populations. *Proceedings of the National Academy of Sciences of the USA* **85**, 1563–1565.

Crow, J. F. & Kimura, M. (1970). *An Introduction to Population Genetics Theory*. New York: Harper and Row.

Coyne, J. A., Barton, N. H. & Turelli, M. (1997). Perspective: a critique of Sewall Wright's shifting balance theory of evolution. *Evolution* **51**, 643–671.

Dobzhansky, T. (1937). *Genetics and the Origin of Species*. New York: Columbia University Press.

Fernández, J. & López-Fanjul, C. (1997). Spontaneous mutational genotype–environment interaction for fitness-related traits in *Drosophila melanogaster*. *Evolution* **51**, 856–864.

Fernández, A., Toro, M. A. & López-Fanjul, C. (1995). The effect of inbreeding on the redistribution of genetic variance of fecundity and viability in *Tribolium castaneum*. *Heredity* **75**, 376–381.

Gallego, A. & López-Fanjul, C. (1983). The number of loci affecting a quantitative trait in *Drosophila melanogaster* revealed by artificial selection. *Genetical Research* **42**, 137–149.

García, N., López-Fanjul, C. & García-Dorado, A. (1994). The genetics of viability in *Drosophila melanogaster*: effects of inbreeding and artificial selection. *Evolution* **48**, 1277–1285.

García-Dorado, A. (1997). The rate and effects distribution of viability mutation in *Drosophila*: minimum distance estimation. *Evolution* **51**, 1130–1139.

García-Dorado, A., Monedero, J. L. & López-Fanjul, C. (1998). The mutation rate and the distribution of mutational effects of viability and fitness in *Drosophila melanogaster*. *Genetica* **102/103**, 255–265.

Gavrilets, S. (1997). Hybrid zones with Dobzhansky-type epistatic selection. *Evolution* **51**, 1027–1035.

Gavrilets, S. & Gravner, J. (1997). Percolation on the fitness hypercube and the evolution of reproductive isolation. *Journal of Theoretical Biology* **184**, 51–64.

Gavrilets, S. & Hastings, A. (1996). Founder effect speciation: a theoretical reassessment. *American Naturalist* **147**, 466–491.

Goodnight, C. (1987). On the effect of founder events on epistatic genetic variance. *Evolution* **41**, 80–91.

Goodnight, C. (1988). Epistasis and the effect of founder events on the additive genetic variance. *Evolution* **42**, 441–454.

Keightley, P. D. (1996). Nature of deleterious mutation load in *Drosophila*. *Genetics* **144**, 1993–1999.

Kosuda, K. (1971). Synergistic interaction between second and third chromosomes on viability of *Drosophila melanogaster*. *Japanese Journal of Genetics* **46**, 41–52.

López, M. A. & López-Fanjul, C. (1993). Spontaneous mutation for a quantitative trait in *Drosophila melanogaster*. II. Distribution of mutant effects on the trait and fitness. *Genetical Research* **61**, 117–126.

López-Fanjul, C. & Villaverde, A. (1989). Inbreeding increases genetic variance for viability in *Drosophila melanogaster*. *Evolution* **43**, 1800–1804.

López-Fanjul, C., Guerra, J. & García, A. (1989). Changes in the distribution of the genetic variance of a quantitative trait in small populations of *Drosophila melanogaster*. *Genetics*, *Selection*, *Evolution* **21**, 159–168.

Mayr, E. (1963). *Animal Species and Evolution*. Cambridge, USA: Harvard University Press.

Merchante, M., Caballero, A. & López-Fanjul, C. (1995). Response to selection from new mutation and effective size of partially inbred populations. II. Experiments with *Drosophila melanogaster*. *Genetical Research* **66**, 227–240.

Mukai, T. (1969). The genetic structure of natural populations of *Drosophila melanogaster*. VII. Synergistic interaction of spontaneous mutant polygenes controlling viability. *Genetics* **61**, 749–761.

Mukai, T. (1985). Experimental verification of the neutral theory. In *Population Genetics and Molecular Evolution* (ed. T. Ohta & K. I. Aoki), pp. 125–145. Berlin: Springer.

Muller, H. J. (1942). Isolating mechanisms, evolution and temperature. *Biological Symposia* **6**, 71–125.

Robertson, A. (1952). The effect of inbreeding on the variation due to recessive genes. *Genetics* **37**, 189–207.

Robertson, A. (1967). The nature of quantitative genetic variation. In *Heritage from Mendel* (ed. A. Brink), pp. 265–280. Madison, USA: University of Wisconsin Press.

Ruano, R. G., Silvela, L. S., López-Fanjul, C. & Toro, M. A. (1996). Changes in the additive variance of a fitness-related trait with inbreeding in *Tribolium castaneum*. *Journal of Animal Breeding and Genetics* **113**, 93–97.

Santiago, E., Albornoz, J., Domínguez, A., Toro, M. A. & López-Fanjul, C. (1992). The distribution of effects of spontaneous mutations on quantitative traits and fitness in *Drosophila melanogaster*. *Genetics* **132**, 771–781.

Seager, R. D. & Ayala, F. J. (1982). Chromosome interactions in *Drosophila melanogaster*. I. Viability studies. *Genetics* **102**, 467–483.

Shrimpton, A. E. & Robertson, A. (1988). The isolation of polygenic factors controlling bristle score in *Drosophila melanogaster*. I. Allocation of third chromosome sternopleural bristle effects to chromosome sections. *Genetics* **118**, 437–443.

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

Sved, J. A. (1971). An estimate of heterosis in *Drosophila melanogaster*. *Genetical Research* **18**, 97–105.

Tachida, H. & Cockerham, C. C. (1989). Effects of identity disequilibrium and linkage on quantitative variation in finite populations. *Genetical Research* **53**, 63–70.

Temin, R. G., Meyer, H. U., Dawson, P. S. & Crow, J. F. (1969). The influence of epistasis on homozygous depression in *Drosophila melanogaster*. *Genetics* **61**, 497–519.

Templeton, A. R. (1980). The theory of speciation via the founder principle. *Genetics* **94**, 1011–1038.

Wade, M. J., Shuster, S. M. & Stevens, L. (1996). Inbreeding: its effect on response to selection for pupal weight and the heritable variance in fitness in the flour beetle, *Tribolium castaneum*. *Evolution* **50**, 723–733.

Wang, J., Caballero, A. & Hill, W. G. (1988*a*). The effect of linkage disequilibrium and deviation from Hardy–Weinberg proportions on the changes in genetic variance with bottlenecking. *Heredity* **81**, 174–186.

Wang, J., Caballero, A., Keightley, P. D. & Hill, W. G. (1998*b*). Bottleneck effect on genetic variance: theoretical investigation of the role of dominance. *Genetics* **150**, 435–447.

Whitlock, M. C., Phillips, P. C. & Wade, M. J. (1993). Gene interaction affects the additive genetic variance in subdivided populations with migration and extinction. *Evolution* **47**, 1758–1769.

Willis, J. H. & Orr, H. A. (1993). Increased heritable variation following population bottlenecks: the role of dominance. *Evolution* **47**, 949–957.

Wright, S. (1931). Evolution in Mendelian populations. *Genetics* **16**, 97–159.

Wright, S. (1951). The genetical structure of populations. *Annals of Eugenics* **15**, 323–354.