

Bottleneck Effect on Genetic Variance: A Theoretical Investigation of the Role of Dominance

Jinliang Wang,* Armando Caballero,† Peter D. Keightley* and William G. Hill*

*Institute of Cell, Animal and Population Biology, University of Edinburgh, Edinburgh EH9 3JT, Scotland and †Departamento de Bioquímica, Genética e Inmunología, Facultad de Ciencias, Universidad de Vigo, 36200 Vigo, Spain

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ABSTRACT

The phenomenon that the genetic variance of fitness components increase following a bottleneck or inbreeding is supported by a growing number of experiments and is explained theoretically by either dominance or epistasis. In this article, diffusion approximations under the infinite sites model are used to quantify the effect of dominance, using data on viability in *Drosophila melanogaster*. The model is based on mutation parameters from mutation accumulation experiments involving balancer chromosomes (set I) or inbred lines (set II). In essence, set I assumes many mutations of small effect, whereas set II assumes fewer mutations of large effect. Compared to empirical estimates from large outbred populations, set I predicts reasonable genetic variances but too low mean viability. In contrast, set II predicts a reasonable mean viability but a low genetic variance. Both sets of parameters predict the changes in mean viability (depression), additive variance, between-line variance and heritability following bottlenecks generally compatible with empirical results, and these changes are mainly caused by lethals and deleterious mutants of large effect. This article suggests that dominance is the main cause for increased genetic variances for fitness components and fitness-related traits after bottlenecks observed in various experiments.

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 F , the inbreeding coefficient of the population (Wright 1951). However, in recent years, several experiments have demonstrated that additive genetic variance and heritability of some quantitative traits within populations can actually increase following population bottlenecks. This phenomenon has been observed for morphometric traits (Bryant *et al.* 1986; Bryant and Meffert 1995, 1996) and behavioral traits (Meffert and Bryant 1992; Meffert 1995) in the house fly, and for fitness components in *Drosophila melanogaster* (López-Fanjul and Villaverde 1989; García *et al.* 1994) and *Tribolium castaneum* (Fernández *et al.* 1995). One explanation for the increased additive genetic variance following bottlenecks is dominance, the interaction between alleles within a locus. Robertson (1952) showed that when genetic variance is caused by rare recessive genes, inbreeding or bottlenecks can temporarily increase the additive variance. Willis and Orr (1993) examined the effect of the degree of dominance on the expected additive variance following a bottleneck

and found that a broad range of dominance coefficients could cause an increase in additive variance. Another explanation is epistasis, the interaction among loci. Theoretical work has shown that genetic drift during a bottleneck can “convert” additive \times additive variance (Goodnight 1988; Whitlock *et al.* 1993) and other forms of epistatic variance (Cheverud and Routman 1996) into additive genetic variance. Thus, provided the proportion of epistatic variance in the ancestral population is high enough, a founder event may result in an increase in additive genetic variance.

It seems difficult to disentangle experimentally the causes of the increase in additive variance following bottlenecks, in particular to determine whether the increase is because of dominance, epistasis or both. Because of the widespread occurrence of inbreeding depression, which indicates directional dominance, rare recessive genes may be involved in the increase in variance for fitness components and related traits. Some authors concluded that their empirical results could be explained by the dominance model without the need for epistasis, although epistasis cannot be discounted (*e.g.*, García *et al.* 1994; Fernández *et al.* 1995), while others found that epistasis could provide reasonable fits to their data (*e.g.*, Bryant and Meffert 1995, 1996). The difficulty in distinguishing between dominance and epistasis as a source of the increase in variance after bottlenecks lies in the fact that the dominance coefficients, effects and frequencies of the genes underlying the quantitative traits, as well as the types of epistatic interaction between loci, are unknown.

Corresponding author: Jinliang Wang, Institute of Cell, Animal and Population Biology, Ashworth Lab, University of Edinburgh, West Mains Road, Edinburgh EH9 3JT, Scotland.
E-mail: jinliang.wang@ed.ac.uk

The accumulation of information on mutation rates and mutant effect distributions for polygenic variation, mainly viability in *D. melanogaster*, makes it possible to investigate theoretically the importance of dominance in determining the redistribution of genetic variance with inbreeding. The mutation parameter estimates come from experiments on spontaneous and induced mutations (*e.g.*, Simmons and Crow 1977), on the segregating variation in natural populations (*e.g.*, Mukai *et al.* 1972) and on mutations accumulated in inbred lines (Fernández and López-Fanjul 1996; García-Dorado 1997). Using these mutation parameters in the diffusion approximations under the infinite sites model (Kimura 1969), we can obtain the equilibrium distribution of frequencies of genes of various effects and dominance coefficients in a large population at mutation-selection balance, and predict the changes in genetic variances, heritability and inbreeding depression following bottlenecks or inbreeding. Since we assume no epistasis, these predicted changes result solely from dominance. By comparing predictions from the present model with observations from experiments, we hope to know to what extent the observed results can be accounted for by dominance alone. We will also investigate the proportional contributions of different genes with different classes of additive and dominance effect to the observed increase in genetic variance following bottlenecks. Since most empirical information on mutation and changes in genetic variance following bottlenecks is concerned with viability in *Drosophila*, we will use this trait as an example throughout this article (although we will also consider viability in *Tribolium*). The results and conclusions from this study are, however, applicable to other fitness components and fitness-related traits in various species provided their genetic architectures are similar to that of viability in *Drosophila*.

MODEL

Diffusion approximations: We use Kimura's (1969) diffusion approximations under the infinite sites model to obtain the equilibrium frequency distribution (and thus genetic variances and other properties) of a mutant with a specific effect and dominance coefficient in a large population at mutation-selection balance. The bottleneck or inbreeding effect on this distribution can be evaluated directly by binomial sampling.

Let the frequencies of the wild-type allele (*A*) and the mutant allele (*a*) at a given locus affecting viability be $1 - x$ and x , respectively, and the genotypic frequencies of *AA*, *Aa*, and *aa* be $(1 - x)^2$, $2x(1 - x)$, and x^2 , respectively. If the effect and dominance coefficients of the mutant are s and h , respectively, then the relative fitnesses of the three genotypes are 1, $1 - hs$, and $1 - s$, respectively, where $s > 0$ (unconditional harmful mutation). A population of N monoecious individuals, with an effective size N_e and random mating, is assumed. If

mutants at different loci act independently, the stationary distribution of allele frequency under mutation-selection balance is (Kimura 1969)

$$\phi(x) = \frac{4N_e\lambda[1 - u(x)]}{x(1 - x)G(x)}, \quad (1)$$

where λ is the haploid genome mutation rate, x is the frequency of mutants segregating in the equilibrium population [$1/(2N) \leq x \leq 1 - 1/(2N)$], $G(x) = \exp[2N_e s x(x + 2h - 2hx)]$, and the fixation probability of a mutant with initial frequency x is

$$u(x) = \frac{\int_0^x G(z) dz}{\int_0^1 G(z) dz}. \quad (2)$$

$\phi(x) dx$ gives the expected number of loci at which the mutant frequency is in the range $x \sim x + dx$ in the equilibrium population. Integration of the product of (1) and a given arbitrary function $f(x)$,

$$I_f = \int_{1/(2N)}^{1-1/(2N)} f(x)\phi(x) dx, \quad (3)$$

gives the expectation of this function. The following are calculated using the above equations.

Additive variance (V_A) and dominance variance (V_D) are calculated using $f(x) = 2x(1 - x)[1/2s + 1/2s(2h - 1)(1 - 2x)]^2$ and $f(x) = [x(1 - x)s(2h - 1)]^2$, respectively.

Number of segregating loci (L) is calculated as $L = \int_{1/(2N)}^{1-1/(2N)} \phi(x) dx$. We calculate the proportion of segregating loci of each class of mutants (classified according to the magnitude of their effects).

Average mutant frequency (\bar{x}) is calculated as $\bar{x} = (1/L) \int_{1/(2N)}^{1-1/(2N)} x\phi(x) dx$.

The mean contribution to viability of a mutant with frequency x , effect s and dominance coefficient h is $1 - 2hsx(1 - x) - sx^2$. Assuming the multiplicative model, the mean viability caused by all segregating loci is

$$\bar{v} = \left[\frac{1}{L} \int_{1/(2N)}^{1-1/(2N)} [1 - 2hsx(1 - x) - sx^2]\phi(x) dx \right]^L. \quad (4)$$

We assume that a number of lines of size N_F are drawn at random from the equilibrium population. After one or more generations of reproduction at size N_F , each line expands immediately to a large size with random mating so that no subsequent inbreeding or genetic drift exists and the population is restored to Hardy-Weinberg and linkage equilibrium. The genetic variances and other properties of the enlarged populations can be evaluated in two ways, yielding the same results.

First, genetic variances can be calculated by the corresponding equations from Crow and Kimura (1970, pp. 343) as $f(x)$ in (3). However, mean viability, the number of segregating loci, and the average mutant frequency

cannot be calculated without knowing the redistribution of mutant frequency after bottlenecks.

Second, binomial sampling is utilized to obtain the redistribution of mutant frequencies after bottlenecks. If the number of copies of a particular mutant is n in the bottlenecked line of size N_F , then its frequency is $n/(2N_F)$ with probability

$$\phi_F\left(\frac{n}{2N_F}\right) = \binom{2N_F}{n} \int_{1/(2N)}^{1-1/(2N)} x^n (1-x)^{2N_F-n} \phi(x) dx. \quad (5)$$

In the enlarged population after bottlenecks, the gene frequency distribution remains the same as the bottlenecked population, $\phi_F(x)$. This is true if we consider only a few generations after bottlenecks, so that new mutations are few and can be ignored. Substituting this new gene frequency distribution instead of $\phi(x)$ in (3), we can obtain all the parameters for populations after bottlenecks.

Inbreeding depression is measured as $D = (\bar{v}_0 - \bar{v}_F)/(\bar{v}_0 F)$, where \bar{v}_0 and \bar{v}_F are the mean viability in the equilibrium population and in populations after bottlenecks with inbreeding coefficient F . Therefore, D signifies the decrease in mean viability per 1% increase in inbreeding coefficient, expressed as a percentage of the mean viability in large outbred populations.

Throughout this article, symbols with subscripts 0 and F always refer to populations before and after the bottleneck event, respectively; symbols without subscripts 0 and F may refer to both.

Mutation parameters: Information on rates, effects, and dominance coefficients of polygenic mutations is available mainly from three kinds of experiments, and two completely different sets of mutation parameters are obtained.

The first set of parameters is primarily from Mukai *et al.* (1972). By using balancer chromosomes with visible markers and exploiting the lack of recombination in males, Mukai and co-workers could accumulate mutations on intact second chromosomes of *D. melanogaster*. They obtained an estimate of the haploid mutation rate (λ) for viability in *Drosophila* of about 0.4 from these experiments. Subsequent work by Ohnishi (1977) on the same species with the same method gave an estimate of λ of 0.15. These estimates exclude lethal mutations that occur at a much lower rate than the above. From the observed inbreeding depression of outbreeding populations of three *Drosophila* species, Lynch *et al.* (1995) obtained an estimate of $\lambda = 1.13$. This estimate is in agreement with the above estimates because it also considers lethal mutations and half of the inbreeding depression is expected to come from lethals. However, it is assumed that mutation-selection balance is the only force maintaining genetic variation. More recent indirect estimates from naturally selfing plants in natural populations, again assuming mutation-selection balance, yield similar results (Charlesworth *et al.* 1990; Johnston and Schoen 1995).

Mukai (1969) also found that the average dominance coefficient (\bar{h}) of newly arisen mutations is about 0.36 by using assays of chromosomal heterozygotes. Information on the relative fitness of inbred and outbred populations gives a similar estimate of \bar{h} (0.39; Lynch *et al.* 1995).

An upper-bound estimate of the composite parameter $2(1 - \bar{h})\bar{s}$ from the above spontaneous mutation accumulation experiments is about 0.039, which yields an average mutant effect $\bar{s} \leq 0.03$ with $\bar{h} = 0.36$. Using maximum likelihood assuming a gamma distribution of mutant effects, Keightley (1994) obtained upper bound estimates of \bar{s} from reanalyses of Mukai *et al.*'s (1972) data and of Ohnishi's (1974) data, which are 0.034 and 0.020, respectively. These bounds correspond to upper 95% confidence limits.

In Keightley's reanalyses, the gamma distribution,

$$g(s) = (\beta/\bar{s})^\beta s^{\beta-1} e^{-\beta s/\bar{s}}/\Gamma(\beta), \quad (6)$$

was used to describe the mutant effects, where $\Gamma(\cdot)$ is the gamma function and β is the shape parameter. When $\beta = 1$, it reduces to the exponential distribution. As $\beta \rightarrow 0$, the distribution becomes increasingly leptokurtic, while as $\beta \rightarrow \infty$, all mutants tend to have the same effect. The upper bound estimates of β estimated from the data of Mukai *et al.* (1972) and Ohnishi (1974) are about 1.6 and 0.3, respectively (Keightley 1994), again corresponding to upper 95% confidence limits.

Direct information on the distribution of the dominance coefficient is scarce. Biochemical arguments suggest an inverse relationship between the effect and the degree of dominance of mutants, genes of large effect tending to be recessive and genes of small effect tending to be additive (Kacser and Burns 1981). Mutation accumulation experiments also provide evidence that mutants with large effect usually show degrees of dominance closer to recessivity than those with small effects (Simmons and Crow 1977). A review of the data from several mutation accumulation experiments suggested that mutants of small effects can have any degree of dominance between completely dominant and completely recessive but as mutant effects increase, there is a tendency toward recessivity (Caballero and Keightley 1994). They used the exponential function, e^{-ks} (where k is a constant), to define the upper limit of the dominance coefficient of a mutant with effect s , and the dominance coefficient of the mutant is a random value drawn from the uniform distribution such that

$$h < e^{-ks}. \quad (7)$$

The predictions from this model fit well with empirical observations although there are ascertainment problems for mutants with very small effects. In this study we use this model and the constant k is determined so that for a given distribution of s , the average dominance coefficient is \bar{h} . For example, if s follows the exponential

distribution with average value $\bar{s} = 0.03$, $k = 13$ yields $\bar{h} = 0.36$.

The second set of mutation parameters comes from an induced mutagenesis experiment in *D. melanogaster* (Keightley and Ohnishi 1998), a long-term mutation accumulation experiment with full-sib lines of *D. melanogaster* (Fernández and López-Fanjul 1996), and from further reanalyses of the data from the mutation accumulation experiments of Mukai *et al.* (1972) and Ohnishi (1977). In these reanalyses, models with discontinuous distributions of mutation effects were assumed, or the balancer chromosomes were assumed not to be genetically stable (Keightley 1996; García-Dorado 1997), and these models were found to fit the data significantly better than the continuous distribution model analyzed by Keightley (1994). Keightley (1996) and Keightley and Ohnishi (1998) used maximum likelihood to estimate genome-wide mutation rates and distribution parameters for EMS-induced mutations in *Drosophila*. By using the lethal mutation rate as a standard, corresponding spontaneous mutation rates were inferred. The calculations assumed that the mutation spectra for EMS-induced and spontaneous mutations are the same. For competitive viability relative to a *Cy* chromosome, a minimum estimate of λ (corresponding to a lower 95% confidence limit) was ~ 0.006 , an upper limit for \bar{s} was ~ 0.3 , and an upper limit for β was ~ 3 . However, the fit to the data improved as λ increased and \bar{s} and β decreased. For example, with $\beta = 0.5$, the estimate for λ is ~ 0.02 and \bar{s} is ~ 0.1 . For egg-to-adult viability, corresponding estimates with $\beta = 0.5$ are $\lambda = 0.04$ and $\bar{s} = 0.13$ (Keightley and Ohnishi 1998). García-Dorado (1997) analyzed data on egg-to-adult viability from a spontaneous mutation accumulation experiment in *Drosophila* involving the maintenance of replicated isogenic lines by full-sib mating for more than 100 generations. Point estimates of $\lambda = 0.015$, $\bar{s} = 0.058$, and $\beta = 3$ were obtained. These estimates of λ and \bar{s} must be viewed as minimum and maximum estimates, respectively, as mutants with extremely small viability effects may not be fitted in the model. Furthermore, mutations with large fitness effects will tend to be selectively eliminated from lines maintained by full-sib mating, in contrast to mutation accumulation in chromosomes maintained against balancers, in which case only mutations with large effects in heterozygotes will be selectively eliminated. However, these estimates imply a much lower rate of decline in fitness caused by the accumulation of mildly detrimental mutations than do the experiments of Mukai *et al.* (1972). This is also supported by mutation accumulation experiments in *Caenorhabditis elegans* (Keightley and Caballero 1997), in *Drosophila* and mouse (Caballero and Keightley 1998), and in *Escherichia coli* (Kibota and Lynch 1996). No estimate of the average dominance coefficient of mutants is available from these experi-

ments. We use the average dominance coefficient from the first set of parameters in this article.

In summary, we use two sets of parameters for deleterious mutations in this study, considering the possible range of each parameter. The parameters are listed in Table 1.

The above mutation parameters refer to deleterious mutants. In fact the distribution of mutation effects is bimodal, with a unique class of lethal mutants occurring at a rate of approximately 0.015 per haploid genome (Crow 1993). Mutants are classified as homozygous lethal if they have a viability of less than 10% (Simmons and Crow 1977). The average dominance coefficient of lethals is about 0.03 (Crow 1993). In this study we consider both detrimental and lethals, and the effect of a lethal mutant is assumed to be uniformly distributed between 0.9 and 1.0. The lethal mutation parameters used in this study are also listed in Table 1.

Simulations: Numerical results were obtained using the above equations and mutation parameters by stochastic simulations. One mutant with a given s and h was sampled from the distributions defined by (6) and (7) (for a lethal mutant, s is uniformly distributed between 0.9 and 1.0 and $h = 0.03$). The equilibrium distribution (1) was computed and the mean viability and genetic variances in equilibrium populations and the population after bottlenecks from the mutant were then calculated. This process was repeated for 10^5 deleterious mutants and 10^3 lethals for each combination of mutation parameters. Arithmetic (geometric) mean genetic variances (viabilities) from deleterious mutants and from lethals were obtained separately, and their sum (product) gave the final output. Numerical integration was undertaken by Simpson's rule with 1000 to 100,000 intervals depending on the combinations of mutation parameters. The number of replicates (mutants) and the number of integration intervals were chosen to ensure convergence of the simulation results.

RESULTS

Using a given combination of mutation parameters for lethals and detrimental listed in Table 1, we can obtain the genetic architecture of a large population at mutation-selection balance by the diffusion method. We then impose bottlenecks on the population and examine the redistribution of genetic variances and mean viability (inbreeding depression) and the nature of these changes.

Mean viability and genetic variances in equilibrium populations: Predicted mean viability, genetic variances and heritability in large ($N_e = 10^4$) populations at mutation-selection balance for the two sets of mutation parameters are compared with the empirical observations in the upper panel of Table 2. The deleterious mutation parameter combinations used in the predictions are $\lambda = 0.4$, $\bar{s} = 0.03$, $\bar{h} = 0.36$, $\beta = 1$ from set I and $\lambda = 0.03$,

TABLE 1
Mutation parameters

Mutations	λ	\bar{s}	\bar{h}	β	h
Deleterious					
Set I	0.2–0.5	0.01–0.05	0.36	0.5–2.0	Exponential
Set II	0.005–0.050	0.10–0.30	0.36	2.0– ∞	Exponential
Lethal	0.015	0.9–1.0	0.03	—	\bar{h}

$\bar{s} = 0.15$, $\bar{h} = 0.36$, $\beta = 3$ from set II, both giving a mutational variance of about 0.0004 which is similar to that from Mukai *et al.* (1972). The same lethal mutation parameters ($\lambda = 0.015$, $\bar{h} = 0.03$) are used in both predictions.

Empirical estimates of egg-to-pupa viability and pupa-to-adult viability are in the range 0.80–0.92 and 0.85–0.88 (Tantawy and El-Helw 1970; Ehiobu *et al.* 1989; López-Fanjul and Villaverde 1989; García *et al.* 1994; Fernández and López-Fanjul 1996), respectively, the mean being 0.86 for both traits. Therefore, the mean empirical egg-to-adult viability is $0.86^2 = 0.74$, assuming a multiplicative model. However, the mean of 0.74 may be better considered as a lower limit rather than a true mean genotypic value, because we do not know if the “perfect” individual (with no mutations at all) would have a viability of exactly one. It is possible that there may be deaths caused, for example, by accidents of development. Compared to this value, it is clear that the first combination of mutation parameters gives a much lower predicted mean viability (Table 2). The important factor is the high mutation rate (0.4); other parameters have little effect in an equilibrium popula-

tion. The mean genotypic viability can be predicted approximately by $\bar{v}_0 = e^{-2\lambda}$ (Haldane 1937), where λ includes both deleterious and lethal mutations. Within the possible range of λ , set I always gives a much lower mean viability. Generally, the second set of mutation parameters gives a reasonable prediction of mean viability (0.88–0.96).

Mukai (1985) summarized estimates of genetic variances of viability for six natural populations of *Drosophila*. Extrapolating to the whole genome by multiplying the estimates for the second chromosome by 2.5, the additive and dominance variances are 0.0058–0.0505 and 0.0003–0.0030, respectively (Table 2). Compared with the empirical results, the predictions are just within the range of observations for the first set of mutation parameters but too small for the second set. Unlike mean viability that only depends on λ , all mutation parameters influence the equilibrium genetic variances.

If the environmental variance (V_E) for viability is known, we can also predict the heritability in equilibrium populations. The estimated V_E of Mackay *et al.* (1992) from the control lines of a *P*-element insertional mutagenesis experiment is about 0.07. Using this value

TABLE 2
Comparison between predicted and empirical results for mean viability, genetic variances and heritability in equilibrium populations (top) and their changes after a bottleneck of two individuals (bottom)

	Predicted from		Empirical observations	References ^a
	Set I	Set II		
\bar{v}_0	0.45	0.91	>0.74	1, 2, 4, 5, 8
V_{A0}	0.0059	0.0031	0.0058–0.0505	7
V_{D0}	0.0007	0.0001	0.0003–0.0030	7
h_0^2	0.09	0.05	0.03–0.16	3, 5, 8
D	1.55	0.53	0.50–0.82	4, 5, 6
V_{AF}/V_{A0}	9.4	13.1	1.6–14.9	3, 4, 5
h_F^2/h_0^2	3.7	5.8	2.5–13.3	3, 4, 5
$(V_{BF} - V_{B0})/V_{A0}$	4.0	5.5	0.7–3.9	3, 4, 5

The effective size of the parental population is 10^4 . Predictions in the second column are made using deleterious mutation parameters $\lambda = 0.4$, $\bar{s} = 0.03$, $\bar{h} = 0.36$, $\beta = 1$ from set I and predictions in the third column are made using deleterious mutation parameters $\lambda = 0.03$, $\bar{s} = 0.15$, $\bar{h} = 0.36$, $\beta = 3$ from set II. Lethal mutation parameters are $\lambda = 0.015$ and $\bar{h} = 0.03$ in both predictions.

^aThe references are (1) Ehiobu *et al.* (1989); (2) Fernández and López-Fanjul (1996); (3) Fernández *et al.* (1995); (4) García *et al.* (1994); (5) López-Fanjul and Villaverde (1989); (6) Mackay (1985); (7) Mukai (1985); (8) Tantawy and El-Helw (1970).

in combination with predictions of additive and dominance variances, we obtain the predicted equilibrium heritability (Table 2). The estimated heritability for egg-to-pupa viability of *Drosophila* in outbred populations is 0.1 from López-Fanjul and Villaverde (1989) and 0.29 from García *et al.* (1994). The average heritabilities of egg hatchability, larval viability, and pupal viability estimated from two laboratory populations, their cross, and a recently collected population of *Drosophila* are 0.09, 0.08, and 0.16, respectively (Tantawy and El-Helw 1970). The estimated heritabilities for early and late viability in *T. castaneum* are 0.03 and 0.08, respectively, from Fernández *et al.* (1995). The average of the above estimates is 0.12, or 0.09 if the extremely high estimate 0.29 is excluded. The predictions from both combinations of mutation parameters are in reasonable agreement with the empirical results.

Mean viability and genetic variances following bottlenecks: The predictions for the changes in mean viability (depression), genetic variances, and heritability after a bottleneck of two individuals ($F = 0.25$) using the two combinations of mutation parameters are compared to the empirical observations of Table 2 (bottom).

The mean viability is decreased by the bottleneck event. Compared to empirical observations (Table 2), the predicted inbreeding depression is reasonable for the second combination of mutation parameters, but is too large for the first combination of mutation parameters.

The predicted changes in additive variance (V_A), dominance variance (V_D), within-line genotypic variance (V_C), and between-line genotypic variance (V_B) with inbreeding coefficient (F) are shown in Figure 1. The pattern of the redistribution of genetic variances with inbreeding is generally similar to that shown by Robertson (1952) for completely recessive rare genes. V_A and V_D increase initially with inbreeding, reaching a maximum when F is a little under 0.5, and decrease gradually to zero with F approaching one. V_B increases slowly with initial inbreeding until F is about 0.5; thereafter it increases almost linearly. One implication for selection in a subdivided population is that, when genetic variance is mainly determined by rare recessive genes, within-line selection in the initial period should be effective, while in the later period, between-line selection should become more and more effective. The reason that different sets and combinations of deleterious mutation parameters in conjunction with lethal mutations give similar patterns of the redistribution of genetic variance with inbreeding is, as will be shown later, that lethal mutations determine most of the changes in variance with inbreeding, though they are not important in large outbred equilibrium populations.

In what follows we will compare the above predictions of genetic variances after a bottleneck of two individuals with empirical observations in *D. melanogaster* (López-Fanjul and Villaverde 1989; García *et al.* 1994) and

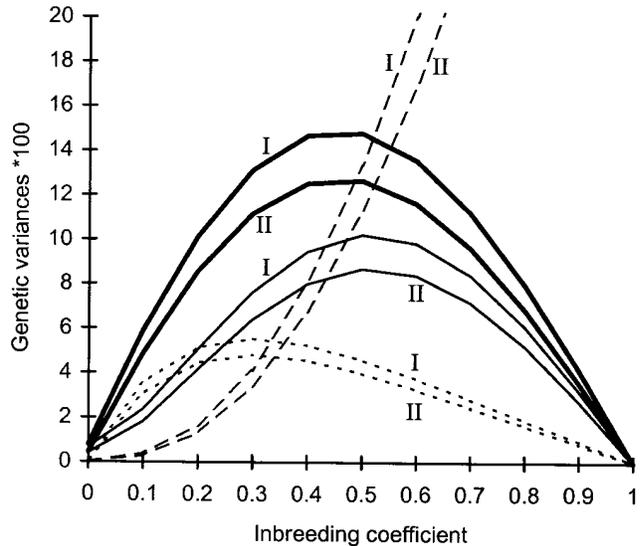


Figure 1.—The changes in additive variance (thin lines), dominance variance (dotted lines), within-line genotypic variance (thick lines), and between-line genotypic variance (dashed lines) with inbreeding. Lines denoted by I are produced using the deleterious mutation parameter combination $\lambda = 0.4$, $\bar{s} = 0.03$, $\bar{h} = 0.36$, $\beta = 1$ from set I and lines denoted by II are produced using the deleterious mutation parameter combination $\lambda = 0.03$, $\bar{s} = 0.15$, $\bar{h} = 0.36$, $\beta = 3$ from set II. All predictions are made with lethal mutation parameters $\lambda = 0.015$, $\bar{h} = 0.03$, and the effective size of the ancestral population $N_e = 10^4$.

T. castaneum (Fernández *et al.* 1995). The empirical genetic variances for *Drosophila* were calculated from arcsine-transformed percentage survival data, while the predicted variances were calculated using untransformed data. This difference is, however, irrelevant if we are interested in the relative changes in genetic variance following bottlenecks. After a bottleneck of two individuals, V_A is predicted to increase (compared with the equilibrium value in the ancestral large population) by 9.4 and 13.1 times from the first and second combination of mutation parameters, respectively (see Figure 1 and Table 2). The corresponding empirical values are 1.6 (García *et al.* 1994) and 5.0 (López-Fanjul and Villaverde 1989) for egg-to-pupa viability in *Drosophila*, and 14.9 and 8.3 for early and late viability, respectively, in *T. castaneum* (Fernández *et al.* 1995). The increase in V_A observed in García *et al.*'s (1994) experiment is much lower than the predictions. This may be because of purging selection in the experiment, which tends to increase the mean and decrease the additive variance in inbred lines. García *et al.* (1994) observed that the percentage of surviving lines was 50–60% when $F = 0.25$ – 0.5 and was only 20% when $F = 0.73$, indicating strong purging selection. In the present theoretical model, however, we do not consider purging selection. Comparisons across inbreeding experiments are difficult to make because inbred lines usually have a very small size, and sampling and genetic drift may play an

important role in these experiments (Lynch 1988). Though following the same experimental design and using the same species, the absolute value of the estimated V_A from López-Fanjul and Villaverde (1989) is substantially smaller, and the relative increase of V_A following bottlenecks ($F = 0.25$) is much larger than those from García *et al.* (1994). Our predictions are in reasonable agreement with the empirical results of López-Fanjul and Villaverde (1989) and Fernández *et al.* (1995).

Using the estimated $V_E = 0.07$ of Mackay *et al.* (1992) and assuming that it is not changed by the bottleneck event, we can predict the changes in heritability following bottlenecks. After a bottleneck of two individuals, the predicted heritability is increased by 3.7 and 5.8 times from the first and second combination of parameters, respectively (Table 2). The corresponding empirical values (Table 2) are 2.5 times (García *et al.* 1994) and 4.0 times (López-Fanjul and Villaverde 1989) for egg-to-pupa viability in *Drosophila* and 13.3 and 5 times for early and late viability in *T. castaneum* (Fernández *et al.* 1995). Our theoretical predictions using both sets of mutation parameters are generally compatible with these empirical observations.

In the experiments, between-line variances are greater than zero at $F = 0$, due to sampling and environmental errors. If we are interested in the relative changes in between-line variance with inbreeding, then the sampling errors and different scaling in these experiments can be reasonably accounted for by using the quantity $B = (V_{BF} - V_{B0}) / V_{A0}$ (Fernández *et al.* 1995), where V_{BF} and V_{B0} are between-line variances in inbred lines and outbred lines, respectively, and V_{A0} is the additive variance in outbred lines. After one generation of full-sib mating, values of B are predicted to be 4.0 and 5.5 using the first and the second combination of mutation parameters, respectively (Table 2). The corresponding estimates of B are 0.7 (García *et al.* 1994) and 2.0 (López-Fanjul and Villaverde 1989) for egg-to-pupa viability in *Drosophila* and 3.9 and 3.0 for early and late viability in *T. castaneum* (Fernández *et al.* 1995). Again the predictions are compatible with observations in general, except that the estimate from García *et al.* (1994) is much lower, possibly due to purging selection. From the additive model, $V_{BF} = 2FV_{A0}$ (Wright 1951), resulting in a B value of 0.5 after one generation of full-sib mating. This value is close to García *et al.*'s result but is much smaller than the observations in other experiments.

Nature of redistribution in genetic variances after bottlenecks: Following Caballero and Keightley (1994), we analyzed the contributions of different classes of mutants (classified according to their magnitude of homozygous effect) to the equilibrium genetic variances and to the changes of variance with inbreeding. By comparing the distribution of frequencies of mutants in different classes and their relative contribu-

tions to genetic variances before and after bottlenecks, we can obtain an understanding of the nature of changes in genetic variance.

Numerical results for the average mutant frequency at segregating loci (\bar{x}), average dominance coefficient (\bar{h}), percentage of mutants generated per generation (M), percentage of segregating loci (L), relative contributions (in percentage) to additive (V_A) and dominance (V_D) variances, and mean viability (\bar{v}) for each class of mutants in equilibrium populations are shown in the upper panel of Table 3. The overall mean viability is the product of the viability caused by each class of mutants. The results are obtained using deleterious mutation parameters $\lambda = 0.4$, $\bar{s} = 0.03$, $\bar{h} = 0.36$, $\beta = 1$ and lethal mutation parameters $\lambda = 0.015$ and $\bar{h} = 0.03$, with effective size $N_e = 10^4$.

Table 3 (top) shows that mutants of small effect ($N_e s < 100$) have a much higher average frequency than those of large effect. Though roughly a similar number of deleterious mutants in each class occurs per generation, mutants of large effect tend to be lost, and thus the majority of segregating loci in equilibrium populations are mutants with the smallest effect ($N_e s < 50$). However, most of the additive variance is contributed by mutants with intermediate to large effect ($N_e s > 100$). Mutants of different classes are nearly equally important in determining mean viability, because their effects and equilibrium frequencies are negatively correlated and cancel out in determining \bar{v} . Mutations of larger effect give rise to a smaller number of segregating loci and also a smaller equilibrium gene frequency. Most of the dominance variance comes from lethals and deleterious mutants of large effect, because they are highly recessive (Caballero and Keightley 1994).

Table 3 (bottom) shows the corresponding results after a bottleneck of two individuals. The relative contributions (in percentages) to between-line variance (V_B) and inbreeding depression (D) for each class of mutants are listed in addition to previous parameters for the equilibrium population. After the bottleneck, there is little difference between the frequencies of mutants (at segregating loci) of various classes. This occurs because, regardless of the magnitude of effect and the equilibrium frequency of a mutant in the equilibrium population, the mutant is likely to be represented by a single copy in the bottlenecked line if it is not lost. While the V_A from mutants of small effect ($N_e s < 100$) decreases slightly and that from mutants of larger effect ($N_e s > 100$) increases with bottlenecking, the overall V_A from all mutants increases substantially following the bottleneck event. Comparing the relative contributions to V_A and V_D before (top) and after (bottom) the bottleneck for each class of mutants, we see that the relative contribution from lethals is greatly increased and that from deleterious mutants decreased by the bottleneck event; and the smaller the effect of the mutants, the greater the decrease in relative contribution after the bottleneck.

TABLE 3

The frequencies and relative contributions to genetic variances and mean viability of mutants in different classes before (top) and after (bottom) a bottleneck of two individuals, using deleterious mutation parameters $\lambda = 0.4$, $\bar{s} = 0.03$, $\bar{h} = 0.36$, $\beta = 1$ from set I

	$N_e s$							Lethals
	0-50	50-100	100-200	200-300	300-400	400-500	>500	
$\bar{x} \times 10,000^a$	10.9	10.8	8.4	6.3	5.0	4.7	4.2	1.2
\bar{h}	0.48	0.46	0.41	0.35	0.31	0.27	0.17	0.03
M (%)	15.0	12.5	19.8	14.0	10.0	7.2	18.0	3.6
L (%)	60.1	7.9	9.3	6.3	4.3	3.1	7.7	1.3
V_A (%)	2.2	5.3	14.5	15.0	13.1	10.4	27.1	12.5
V_D (%)	1.0	1.8	5.1	6.7	5.7	5.9	41.3	32.5
\bar{v}	0.884	0.901	0.855	0.893	0.922	0.946	0.866	0.971
$\bar{x} \times 10$	2.71	2.54	2.53	2.52	2.51	2.51	2.51	2.50
L (%)	60.7	11.9	11.3	5.8	3.2	2.1	4.8	0.2
V_A (%)	0.2	0.5	1.8	2.4	2.4	2.4	16.3	74.0
V_D (%)	0.0	0.1	0.6	1.0	1.1	1.3	13.5	82.4
V_B (%)	0.3	0.8	2.5	3.0	3.0	2.9	17.1	70.5
\bar{v}	0.871	0.878	0.812	0.851	0.885	0.913	0.734	0.868
D	0.06	0.09	0.18	0.16	0.13	0.11	0.43	0.41

^a The effective size of the parental population is 10^4 , lethal mutation parameters are $\lambda = 0.015$, $\bar{h} = 0.03$. \bar{x} , mean mutant frequency at segregating loci; \bar{h} , average dominance coefficient; M (%), percentage of mutants generated in each generation; L (%), percentage of segregating loci; V_A (%), percentage contributed to additive variance; V_D (%), percentage contributed to dominance variance; V_B (%), percentage contributed to between-line genotypic variance; \bar{v} , mean viability caused by each class of mutants; D , inbreeding depression (as a percentage of the outbred mean).

For inbreeding depression, most of the contributions are from lethals and deleterious mutants with the largest effect ($N_e s > 500$). Mutants of intermediate effect also result in a substantial part of the inbreeding depression. Deleterious mutations as a whole contribute about three-quarters of the depression, in contrast to the empirical observations (reviewed by Charlesworth and Charlesworth 1987) that roughly half the depression comes from deleterious mutants. Between-line variance comes mainly from mutants of intermediate to large effects, mostly from lethals. In summary, the changes in V_A , V_B , and D after bottlenecks are mainly caused by a small proportion of lethals and mutants with large effects and small dominance coefficients (recessive or partially recessive). This implies that the changes in V_A , V_B , and D are closely related; lines showing higher inbreeding depression or lower viability also have larger additive variances and potentially higher selection responses. This is supported by García *et al.* (1994), who found that, within a given inbreeding level, larger responses to selection for viability were obtained in lines with a lower mean viability (or higher depression), indicating a close relation between the decrease in mean viability (depression) and the increase in additive variance after inbreeding.

The magnitude of the changes in genetic variance and mean viability after a bottleneck depends on the size of the bottlenecked line and the number of bottlenecks experienced before flushing (inbreeding coefficient). The changes in absolute contribution of different

classes of mutants to V_A , V_B , and \bar{v} with inbreeding coefficient are shown in Figure 2, A-C. All classes of mutants act to increase V_B and decrease \bar{v} with inbreeding, while mutants of small effect ($N_e s < 100$) tend to decrease V_A slightly and mutants of large effect ($N_e s > 100$) tend to increase V_A with inbreeding. Most of the changes in V_A , V_B , and \bar{v} with inbreeding, however, come from lethals and mutants of large effect ($N_e s > 500$). Mutants of small effect ($N_e s < 100$) contribute little to the changes in V_A , V_B , and \bar{v} with inbreeding, though they constitute the major part of the mutants maintained in the equilibrium population (Table 3).

Results for deleterious mutation parameters $\lambda = 0.03$, $\bar{s} = 0.15$, $\bar{h} = 0.36$, $\beta = 3$ from set II and lethal mutation parameters $\lambda = 0.015$ and $\bar{h} = 0.03$ are shown in Table 4. In this case, lethal mutations play a more important role in determining both the equilibrium genetic properties in large populations at mutation-selection balance and the changes following bottlenecks. The equilibrium frequency of lethals is a little larger than that of deleterious mutants of large effect. This is because the equilibrium frequency of a mutant is determined by its heterozygotic effect (hs) (Crow and Kimura 1970). In this study, lethals are assumed highly recessive ($\bar{h} = 0.03$) but deleterious mutants are partially recessive ($\bar{h} = 0.36$). Deleterious mutants of large homozygous effect have the largest heterozygotic effect and therefore the lowest equilibrium frequency. The inbreeding depression is mainly from lethals, and only about a quarter of the depression is from deleterious mutants. This is in

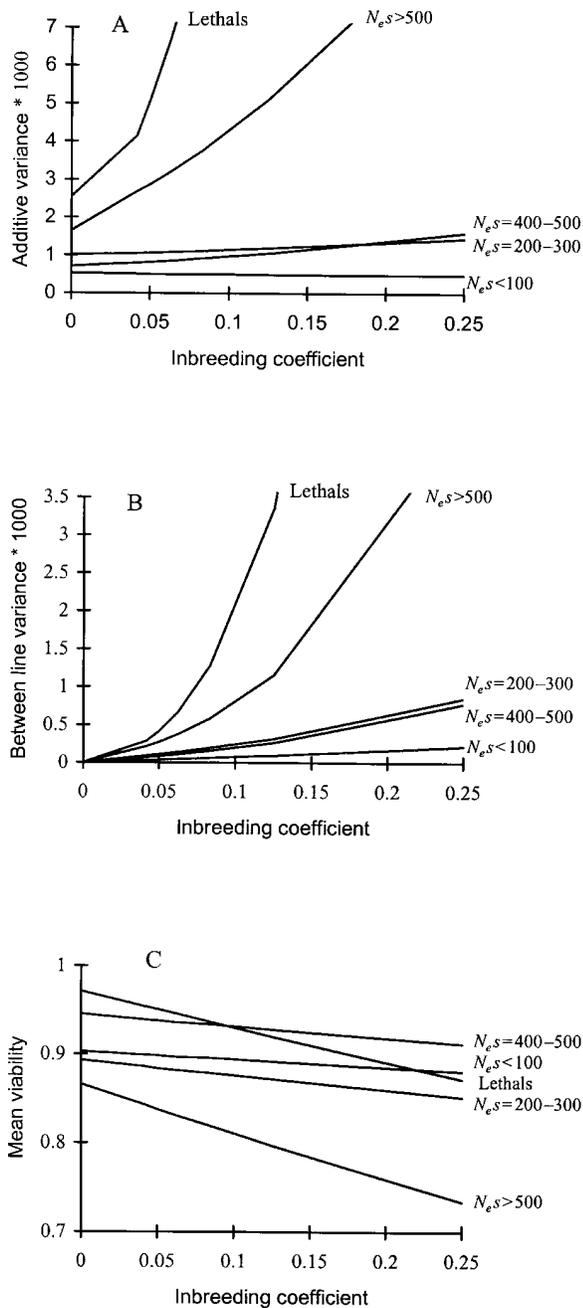


Figure 2.—Changes in absolute contributions to additive variance (A), between-line variance (B), and mean viability (C) with inbreeding for different classes of mutants. The deleterious mutation parameters are $\lambda = 0.4$, $\bar{s} = 0.03$, $\bar{h} = 0.36$, $\beta = 1$, lethal mutation parameters $\lambda = 0.015$, $\bar{h} = 0.03$, and the effective size of the equilibrium population $N_e = 10^4$.

contrast to the results for mutation parameter set I (Table 3) and is also different from empirical observations (Charlesworth and Charlesworth 1987).

DISCUSSION

Using mutation parameters derived from various mutation accumulation experiments, we have inferred the

equilibrium distribution of frequencies of mutants of various effects and dominance coefficients for viability in populations at mutation-selection balance. We have evaluated the equilibrium mean viability, genetic variances, and their redistribution following bottlenecks or inbreeding and compared these with empirical observations in *D. melanogaster* and *T. castaneum*.

From the mutation parameters of set I (using $\lambda = 0.4$, $\bar{s} = 0.03$, $\bar{h} = 0.36$, $\beta = 1$), the predicted additive and dominance variances in a large outbred population at mutation-selection balance are in agreement with observations, but the predicted mean viability is much lower than empirical estimates. Synergistic epistasis can reduce the mutation load and increase the mean viability. For example, quadratic and similar models can reduce the load by as much as 50% (Crow 1993). However, synergistic epistasis also reduces genetic variances, which are already close to the lower bound of empirical estimates (Table 2) under the multiplicative model. From the mutation parameters of set II (using $\lambda = 0.03$, $\bar{s} = 0.15$, $\bar{h} = 0.36$, $\beta = 3$), the predicted equilibrium mean viability is reasonable but the predicted genetic variances are smaller than empirical observations. The relatively high genetic variances estimated in natural populations (Mukai 1985) may be partly because of balancing selection. In southern Japanese populations of *Drosophila*, balancing selection has been inferred to be contributing to the high variation (Mukai and Nagano 1983). As will be shown, large equilibrium genetic variances can also be because of small effective population size.

Both sets of mutation parameters give reasonable predictions for the redistribution in genetic variance following bottlenecks. The empirical observations of changes in additive variance, between-line variance, and heritability following bottlenecks (López-Fanjul and Villaverde 1989; García *et al.* 1994; Fernández *et al.* 1995) are explained well by our model employing both sets of mutation parameters, at least for low inbreeding levels ($F \leq 0.25$). With much higher inbreeding ($F > 0.25$), purging selection would become important. It is difficult to predict changes of heritability following bottlenecks, because V_E may change with inbreeding (Falconer and Mackay 1996). From García *et al.* (1994), the maximum h^2 was at $F = 0.25$ while the maximum V_A was at $F = 0.5$, implying an alteration in V_E due to inbreeding. Because it is not possible to obtain separate estimates of V_E from García *et al.* (1994), we assume a constant V_E in predicting h^2 . Nevertheless, the predicted changes in heritability are compatible with various empirical results.

Parameter set I gives a predicted inbreeding depression much higher than the empirical observations. The total inbreeding depression predicted from set II agrees more closely with the observations, but the depression comes mostly from lethals. The discrepancy may be partly caused by the dominance model, because inbreeding depression is very sensitive to the distribution

TABLE 4

The frequencies and relative contributions to genetic variances and mean viability of mutants in different classes before (top) and after (bottom) a bottleneck of two individuals, using deleterious mutation parameters $\lambda = 0.03$, $\bar{s} = 0.15$, $\bar{h} = 0.36$, $\beta = 3$ from set II

	$N_e s$						Lethals
	0-666	666-1333	1333-2000	2000-2666	2666-3333	>3333	
$\bar{x} \times 10,000^a$	4.0	2.2	1.7	1.4	1.1	1.1	1.2
\bar{h}	0.46	0.42	0.37	0.33	0.30	0.24	0.03
M (%)	5.2	16.2	17.2	12.4	7.3	8.3	33.3
L (%)	6.0	16.9	17.0	11.9	6.8	7.6	33.8
V_A (%)	1.8	11.5	18.0	17.6	12.7	17.2	21.7
V_D (%)	0.4	3.3	4.7	4.7	2.3	6.2	78.4
\bar{v}	0.995	0.986	0.985	0.988	0.992	0.991	0.971
$\bar{x} \times 10$	2.51	2.50	2.50	2.50	2.50	2.50	2.50
L (%)	14.6	23.8	17.9	10.6	4.8	5.5	22.6
V_A (%)	0.1	1.1	2.0	2.2	1.7	3.4	89.4
V_D (%)	0.0	0.4	0.9	1.1	0.7	2.0	94.8
V_B (%)	0.2	1.5	2.6	2.8	2.1	4.0	86.8
\bar{v}	0.994	0.980	0.977	0.982	0.988	0.984	0.872
D	0.01	0.02	0.02	0.02	0.01	0.02	0.41

^a See footnote of Table 3.

of dominance coefficients. Our present dominance model comes from an analysis of the experimental data of mutants of relatively large effect (Caballero and Keightley 1994). Therefore, mutants of small effect, which are the majority of all mutants with set I, may not be well described by our model. A better understanding of the distribution of dominance coefficients of mutants is required.

Results for other combinations of mutation parameters were also obtained. Mutation parameters intermediate between the two sets give predictions that seem to fit well with all the empirical observations. For example, with deleterious mutation parameters $\lambda = 0.1$, $\bar{s} = 0.1$, $\bar{h} = 0.36$, $\beta = 2$ and lethal parameters $\lambda = 0.015$ and $\bar{h} = 0.03$, the predicted mean viability (0.80), additive (0.0060) and dominance (0.0003) variances (from deleterious mutants alone) and heritability (0.09) in populations under mutation-selection balance, and the inbreeding depression (0.79, 48% from detrimental), increases in additive variance ($V_{AF}/V_{A0} = 8.6$), heritability ($h_F^2/h_0^2 = 3.5$), and between-line variance ($(V_{BF} - V_{B0})/V_{A0} = 3.7$) after a bottleneck of two individuals, are in close agreement with observations from various experiments listed in Table 2. Unfortunately, however, there is little experimental evidence available to support these intermediate mutation parameters. Several possible causes for the wide discrepancy between the two sets of mutation parameters have been proposed (Keightley 1996; García-Dorado 1997). The difficulty in estimating the mutation parameters accurately comes mainly from mutants of extremely small effect. The mutation rate and effect may be confounded in mutation accumulation experiments. More refined experimental work is required.

Throughout this study the effective size (N_e) of the ancestral population is assumed to be 10^4 . In fact, the genetic properties of the equilibrium population and their redistribution after bottlenecks are little affected by N_e , if it is larger than 10^4 . The changes with N_e in mean viability, additive variance, and dominance variance in the equilibrium population are shown in Figure 3, and the changes with N_e in the increases in additive variance (V_{AF}/V_{A0}), heritability (h_F^2/h_0^2), between-line variance ($(V_{BF} - V_{B0})/V_{A0}$), and inbreeding depression (D) following a bottleneck of two individuals are shown in Figure 4. The equilibrium genetic variances increase with decreasing N_e (Figure 3). This is especially evident for dominance variance. One possible cause of the high observed genetic variances in certain populations (Mukai 1985) may be that these populations have a small effective size, presumably due to a bottleneck. The equilibrium mean viability increases only slightly with decreasing N_e (Figure 3). The magnitude of the changes in viability, genetic variance, and heritability after bottlenecks increases with increasing N_e . However, all these changes become approximately asymptotic when $N_e > 10^4$.

In the model investigated in this article, we assume that mutation-selection balance is the only source of genetic variation. If part of the genetic variance observed in natural populations is because of some form of balancing selection, we can recalculate the increments in variance after bottlenecks by taking this into account (A. García-Dorado, personal communication). For example, from Table 2 the average empirical additive variance is 0.028. From set I the predicted V_{A0} is 0.0059 because of deleterious mutants and 0.0009 because of lethals, so we can assume that balancing

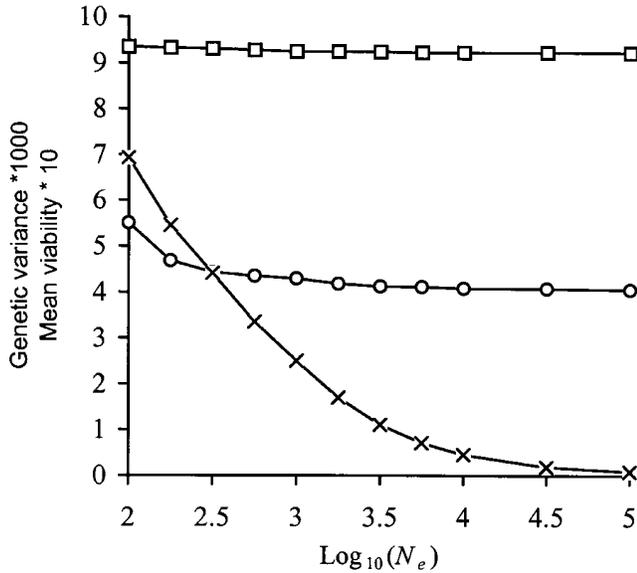


Figure 3.—Changes with effective population size (plotted on \log_{10} scale) in equilibrium mean viability (\square), additive variance (\circ) and dominance variance (\times). Predictions are made using deleterious mutation parameters $\lambda = 0.03$, $\bar{s} = 0.2$, $\bar{h} = 0.36$, $\beta = 3$ and lethal mutation parameters $\lambda = 0.015$, $\bar{h} = 0.03$.

selection accounts for an amount of $0.028 - 0.0059 - 0.0009 = 0.0212$. The predicted proportional increase in V_A after a bottleneck of two individuals is 9.4 in Table 2, so the real proportional increase in variance considering also the variance maintained by balancing selection would be $[(0.0059 + 0.0009) \times 9.4 + 0.0212] / 0.028 = 3.0$, which is in accordance with the observed increases for viability in *Drosophila* (1.6 from García *et al.* 1994; 5.0 from López-Fanjul and Villaverde 1989). A similar argument using set II gives a predicted increase of 2.7.

In our model, we did not consider purging selection, deviation from Hardy-Weinberg proportions, linkage disequilibrium, or epistasis. The effect of purging selection is expected to increase with inbreeding. At initial inbreeding, purging selection is weak and our model provides reasonable predictions. Deviation from Hardy-Weinberg proportions occurs in small populations (Wang 1996) and may result in a small decrease in V_A for additive genes and a large increase in V_A for rare recessives (Wang *et al.* 1998). Here we are interested in populations after bottlenecks (in the flush phase), as were Willis and Orr (1993). Linkage disequilibrium is involved during bottlenecks and may persist for some generations after flushing. It contributes to V_G but has little effect on V_A and V_B (Avery and Hill 1979). Epistasis plays an important role in various theories of evolution and speciation (Cheverud and Routman 1996), and theoretical work has shown that genetic drift during bottlenecks can “convert” epistatic variance (*e.g.*, Goodnight 1988) into V_A , resulting in an increase in V_A following bottlenecks. However, evidence for epistasis

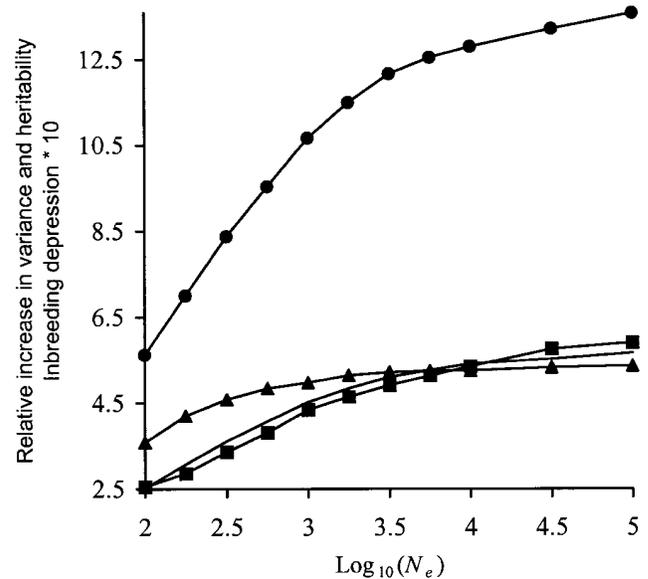


Figure 4.—Changes with effective population size (plotted on \log_{10} scale) in the relative increase in additive variance V_{AF}/V_{A0} (\bullet), between-line variance $(V_{BF} - V_{B0})/V_{A0}$ (\blacksquare), heritability h_F^2/h_0^2 (\blacktriangle), and inbreeding depression $D \times 10$ (\times) after a single bottleneck of two individuals. Predictions are made using deleterious mutation parameters $\lambda = 0.03$, $\bar{s} = 0.2$, $\bar{h} = 0.36$, $\beta = 3$ and lethal mutation parameters $\lambda = 0.015$, $\bar{h} = 0.03$.

affecting quantitative traits is scarce (Barton and Turelli 1989). When epistatic variances are found, they are often small relative to V_A (*e.g.*, Paterson *et al.* 1990). In this study, we did not include epistasis; we have found that dominance alone could explain most of the changes in mean viability (depression), additive variance, heritability, and between-line variance observed in empirical studies with bottlenecks. We may make the tentative conclusion that, for fitness components and other traits related to fitness showing large inbreeding depression, the bottleneck effect is mainly due to dominance.

In the dominance model, the increased additive variance is always accompanied by a severe inbreeding depression. In García *et al.*'s (1994) experiment, the final mean viability of upward selected lines with and without subdivision (inbreeding) was not significantly different, though heritability and selection response were increased in subdivided (inbred) populations. In Fernández *et al.*'s (1995) experiment, higher responses to selection for increasing viability in *T. castaneum* were obtained in inbred lines, but they were accompanied by only $\sim 50\%$ recovery of the inbreeding depression incurred. Thus, the evolutionary significance of the increased additive variance caused by a bottleneck event is uncertain (Fernández *et al.* 1995). However, at least for the following cases bottlenecks are beneficial to selection. First, if the bottleneck event is accompanied by a change in the environment so that harmful genes become less harmful or even beneficial, then the bottle-

neck effect may be of relevance to evolution or speciation. Second, under the dominance model as described above, rare recessive mutants tend to become homozygous with inbreeding, leading to both an increased additive variance and a decreased mean. Without line crossing the increased selection response in inbred lines is usually confounded with depression, resulting in no eventual change or even a decrease in the final mean compared with outbred selection lines (Fernández *et al.* 1995). If bottlenecked lines are crossed after selection, however, inbreeding depression disappears and there may be an apparent increase in the mean of selected trait compared with outbred selection lines. This has been demonstrated by Barrett and Charlesworth (1991). Third, in some cases, conflicts between natural and artificial selection are found in domestic animals and plants; some genes harmful to animals or plants may be useful to humans. Because of the harmful effects and (partial) recessivity of these genes, they are held at very low frequencies in mutation-selection balance. Thus, a deliberate bottleneck or inbreeding will disrupt the equilibrium and increase additive variance and artificial selection response.

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