Joint Effects of Pleiotropic Selection and Stabilizing Selection on the Maintenance of Quantitative Genetic Variation at Mutation-Selection Balance

Xu-Sheng Zhang1 and William G. Hill

Institute of Cell, Animal and Population Biology, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom

Manuscript received April 16, 2002
Accepted for publication June 10, 2002

ABSTRACT

In quantitative genetics, there are two basic “conflicting” observations: abundant polygenic variation and strong stabilizing selection that should rapidly deplete that variation. This conflict, although having attracted much theoretical attention, still stands open. Two classes of model have been proposed: real stabilizing selection directly on the metric trait under study and apparent stabilizing selection caused solely by the deleterious pleiotropic side effects of mutations on fitness. Here these models are combined and the total stabilizing selection observed is assumed to derive simultaneously through these two different mechanisms. Mutations have effects on a metric trait and on fitness, and both effects vary continuously. The genetic variance ($V_g$) and the observed strength of total stabilizing selection ($V_s$) are analyzed with a rare-alleles model. Both kinds of selection reduce $V_g$ but their roles in depleting it are not independent: the magnitude of pleiotropic selection depends on real stabilizing selection and such dependence is subject to the shape of the distributions of mutational effects. The genetic variation maintained thus depends on the kurtosis as well as the variance of mutational effects: All else being equal, $V_g$ increases with increasing leptokurtosis of mutational effects on fitness, while for a given distribution of mutational effects on fitness, $V_g$ decreases with increasing leptokurtosis of mutational effects on the trait. The $V_s$ and $V_g$ are determined primarily by real stabilizing selection while pleiotropic effects, which can be large, have only a limited impact. This finding provides some promise that a high heritability can be explained under strong total stabilizing selection for what are regarded as typical values of mutation and selection parameters.

1Corresponding author: Institute of Cell, Animal and Population Biology, University of Edinburgh, W. Mains Rd., Edinburgh EH9 3JT, United Kingdom. E-mail: xu-sheng.zhang@ed.ac.uk

Genetics 162: 459–471 (September 2002)
model can provide an explanation for observed levels of \( V_c \) but for only part of the strength of apparent stabilizing selection observed \( (V_s) \) and has the further defect that \( V_c \) increases without bound as the effective population size increases when the mutational effects are not completely correlated and the distribution of fitness effects is leptokurtic (Keightley and Hill 1990; Caralleiro and Keightley 1994). Such stabilizing selection induced solely by pleiotropic effects on fitness of mutations is referred to as “pleiotropic selection” in this article. There is a general relationship \( V_s \geq V_c^2/V_{m} \) (Barton 1990; Kondrashov and Turelli 1992; Gavrillets and de Jong 1993; Zhang et al. 2002); therefore the pure pleiotropic model cannot in principle explain both the observed levels of genetic variances and typical estimates of strengths of stabilizing selection, provided the mutational variance \( V_m \) is of the order \( 10^{-3} V_c \) as observed (Houle et al. 1996; Lynch and Walsh 1998; Lynch et al. 1999).

In addition to the above two hypotheses, many others such as overdominance (Wright 1935; Robertson 1956; Gillespie 1984; Barton 1990), frequency-dependent selection (Slatkin 1979; Barton 1990), genotype-by-environment interaction (Gillespie and Turelli 1989; Gimelfarb 1990; Zhivotovsky and Gavrillets 1992), and epistatic interaction (Zhivotovsky and Gavrillets 1992; Gavrillets and de Jong 1993) have been proposed to explain the maintenance of polygenic variation. All these models have their respective appeal and weaknesses in explaining the maintenance of polygenic variation.

Nevertheless, the real stabilizing selection and pleiotropic models are not mutually exclusive. Individual mutant alleles can have both deleterious pleiotropic effects on fitness and effects on the metric trait in question (Falconer and Mackay 1996). If the metric trait is not completely neutral, that is, the extreme phenotypes of the metric trait are less fit, natural selection takes place simultaneously through two different mechanisms: the deleterious pleiotropic effects on all other aspects of fitness and real stabilizing selection on the metric trait under study. Individuals that carry mutants are therefore selected against because of both deleterious pleiotropic effects of mutants \((i.e., \text{pleiotropic selection})\) and phenotypic deviations of the trait value from the optimum \((i.e., \text{real stabilizing selection})\). The strength of total stabilizing selection is therefore attributed to both kinds of natural selection. As Kondrashov and Turelli (1992, p. 615) noted, “A complete treatment should consider both direct and indirect selection on the quantitative trait.” Tanaka (1996) used a cohort-of-mutations model to combine both pleiotropic and real stabilizing selections and assumed that all mutations had an equal deleterious effect on fitness and a Gaussian distribution of effects on the target trait. However, this cannot readily account for both high heritabilities and strong stabilizing selection (Tanaka 1996, 1998). Although the assumption of an equal fitness effect for all mutations is a convenient way to obtain analytical approximations for \( V_c \) and \( V_s \) (Barton 1990; Kondrashov and Turelli 1992; Tanaka 1996), it lacks rigorous support, and experimental data illustrate the highly leptokurtic distribution of mutational effects on fitness (Mackay et al. 1992). As shown by Zhang et al. (2002), the shape of the distribution of mutational effects does affect the predictions of the pleiotropic model, so that it is necessary to take into account variation in effects of mutations both on the trait and on fitness.

In this study, a compound model of continuously varying effects of mutations on the trait and on fitness is constructed to investigate the maintenance of genetic variance and the observed strength of total stabilizing selection. The interaction between both kinds of selection and their overall impact on genetic variation and strength of total stabilizing selection are explored. We hope thereby to provide a possible explanation for the observations of both high genetic variance and the strong observed stabilizing selection.

**MODEL**

We assume additivity of gene action, linkage equilibrium, a random-mating diploid population, and rare mutant alleles. In accordance with the model of real stabilizing selection (Turelli 1984, 1985), the relative fitness of individuals that have a phenotypic value \( P \), the sum of the contributions from each locus plus a random independent environmental effect of mean zero, is assumed to be given by \( W(P) = \exp(-P^2/2\omega^2) \). The mean fitness of individuals with genotypic value \( G = \sum a_i \) is \( W(G) = \exp(-G^2/2V_{c}) \approx 1 - G^2/2V_{c} \) with \( V_{c} = \omega^2 + V_{c} \) measuring the intrinsic strength of real stabilizing selection. \( V_{c} \) is the environmental variance and is scaled as a unit of variance.

It is assumed that there are infinitely many loci on each individual and at each locus there is a continuum of possible mutational effects, but each locus has the same mutation distribution and loci are exchangeable. There are at most two alleles segregating at each locus: the wild type, which is assumed to be at optimum, and the mutant. Mutations have effects on a metric trait \((a)\) and pleiotropic deleterious effects on fitness \((s = 0)\), with a bivariate distribution \( h(a, s) \). If the metric trait undergoes real stabilizing selection due to mutations, the observed stabilizing selection would come from these two parts and the equivalent total selection coefficient within each individual is given by \( s^* = s + (1 - 2x)\alpha^2/(4V_{c}) \) (see Appendix A), where \( x \) is the frequency of the mutant allele. The equivalent total selection coefficient is in general not independent of the frequency of mutant alleles in this compound model. It is therefore less tractable (see Appendix A) than the pure pleiotropic model (Barton 1990; Keightley and Hill 1990), in which selection is assumed to act directly on the pleiotro-
pic effect on fitness of each mutant allele and the coefficient is always independent of the frequency of the mutant allele. With the assumption of real stabilizing selection (Turelli 1984; Keightley and Hill 1988), however, selection acts on the total effect of all mutants within individuals and hence depends on the frequency of mutant alleles (Robertson 1956). Such frequency dependence of selection leads to multiple equilibria (Bulmer 1985; Barton 1986) but, unless population size is very small, mutant alleles cannot increase to a high frequency without passing through an intermediate frequency, against which there is selection. The frequency of mutant alleles therefore remains very low (Bulmer 1989). With rare mutant alleles, the equivalent total selection coefficient within each individual organism can therefore be approximated by
\[
\tilde{s} = s + a^2/(4V_{st}).
\]  
(1)

In an infinite population the equilibrium genetic variance is
\[
V_s = 4\lambda V_{st}\int_{-\infty}^{\infty} \int_{0}^{\infty} h(a, s) \frac{a^2/(4V_{ss})}{\tilde{s}} \, da \, ds = 4\lambda V_{st} I_2,
\]  
(2)
in which \(I_2\) is determined by the distribution of mutational effects (see Appendix A), \(\lambda\) is the genome-wide mutation rate over all loci, and the strength of total stabilizing selection (i.e., that which would be observed regardless of its source) is
\[
V_{st} = \frac{V^2_{st}/V_{st} + \lambda_m - Cov_p V_{st}}{V^2_{st}/V_{st} + \lambda_m}.
\]  
(3)

Here \(Cov_p\) is the covariance of relative fitness and squared deviation due to pleiotropic effects on fitness of mutations (see Appendix A). When the pleiotropic selection is much stronger than real stabilizing selection, \(Cov_p \rightarrow V_m\) (cf. Bürger 2000; Zhang et al. 2002) and the strongest total selection applies with strength
\[
V_{st} = V^2_{st}/(V^2_{st}/V_{st} + \lambda_m) = V^2_{st},
\]  
when the pleiotropic effect is very weak in relation to real stabilizing selection, \(Cov_p \rightarrow 0\) and the strength of total stabilizing selection approaches \(V_{st}\). In general, the following inequality applies for the strength of total stabilizing selection:
\[
V^0_{st} < V_{st} < V_{st}.
\]  
(4)

Because the total covariance of relative fitness and squared deviation, \(Cov = V_{st} + V^2_{st}/V_{st}\), is larger than that both for the pure pleiotropic model, \(V_m\) (Bürger 2000; Zhang et al. 2002), and for real stabilizing selection, \(V_{st}/(2\lambda_m)\), the total stabilizing selection is certainly stronger than either individual component. The mutational variance on the trait \(V_m = \frac{1}{2}\lambda \epsilon^2_s\) where \(\epsilon^2_s\) is the variance of mutational effects on the trait, is observed to be of the order \(10^{-3}V_c\) (Houle et al. 1996; Lynch and Walsh 1998; Lynch et al. 1999; and this value is used in this study). Therefore \(V_{st}\) cannot be very large if a high \(V_c\) is to be maintained under strong total stabilizing selection (i.e., small \(V_{st}\)).

Although the properties of mutational effects on the metric trait and on fitness are crucial to evaluating \(V_c\) and \(V_{st}\), the distribution of mutational effects is hard to estimate accurately (Mackay and Langley 1990; Hill and Caballero 1992; Mackay et al. 1992; Davies et al. 1999; Elena and Moya 1999; Keightley et al. 2000; Shaw et al. 2000; Imhof and Schlötterer 2001; Wloch et al. 2001). Even for Drosophila, for which there are many studies, the data seem to suggest a highly skewed and leptokurtic distribution of mutational effects (Mackay and Langley 1990; Hill and Caballero 1992; Mackay et al. 1992), but fine-scale information is still lacking.

As in Keightley and Hill (1990), the distribution of mutational effects on the metric trait is assumed to be symmetrical about \(a = 0\), and only deleterious effects of mutations on fitness are assumed to occur, in accord with the classical view (Falconer and Mackay 1996). The variability of the distribution of \(a\) is defined in terms of \(\epsilon_a = 2\sqrt{E(a^2)}\) and for \(s\) is \(\epsilon_s = \sqrt{E(s^2)}\). For theoretical comparison, it is assumed in this study that mutational effects on the trait are, in increasing order of leptokurtosis, Gaussian, reflected gamma (\(\gamma/2\)), reflected gamma (\(\gamma/2\)), reflected squared gamma (\(\gamma/2\)), and reflected quartic gamma (\(\gamma/2\); mutational effects on fitness are equal, one-sided Gaussian, gamma (\(\gamma/2\)), gamma (\(\gamma/4\)), squared gamma (\(\gamma/2\)), and quartic gamma (\(\gamma/2\)), where gamma (\(B\)) denotes the gamma distribution with shape parameter \(B\). Those distributions, whose shapes are illustrated in Figure 1, cover a very wide range of all possible mutational effects.

RESULTS

Analytical approximations are obtained for some special cases for an infinite population and a rare-allele approximation, and numerical calculations were performed to provide support and to extend the results to more general situations. Simple results for some special situations are also presented within Keightley and Hill’s (1990) framework using Kimura’s (1969) diffusion approximation.

Pure real stabilizing selection within a finite population, i.e., \(s = 0\), thus \(\tilde{s} = (1 - 2x)a^2/(4V_{st})\): The observed strength of real stabilizing selection is \(V_{st} = V_{st}/(2\lambda m)\). Because the total covariance of mutational effects on fitness, \(V_m\), increases and approaches the rare-allele approximation \(4\lambda V_{st}\) (Turelli 1984; see Figure 2). Theoretically, this is because the equilibrium frequencies of mutant genes, \(x\), become very small and the heterozygosity can thus be approximated by \(H(s) = 4x^2/\tilde{s}\) as the effective population size \(N_{e} \rightarrow \infty\) and thus
Figure 1.—The distribution of mutation effects, $s$, on fitness used in the study with $E(l(s)) = 1.0$ in each case. Here sq-gamma ($\frac{1}{2}$) and qt-gamma ($\frac{1}{2}$) represent squared gamma ($\frac{1}{2}$) and quartic gamma ($\frac{1}{2}$). The distribution of mutational effects, $a$, on the trait was symmetrical about $a = 0$, but with that of $|a|$ having the same range of distribution as $s$.

Figure 2.—Genetic variance maintained in the metric trait as a function of the effective population size under pure real stabilizing selection (i.e., $s = 0$). Two cases are investigated: $\lambda = 0.01$, $V_{s,r} = 10$ and $\lambda = 0.001$, $V_{s,r} = 100$. Results are shown for two distributions of mutational effects on the trait: gamma ($\frac{1}{2}$)-distributed effects (solid lines, essentially superimposed) and equal effects (dashed lines).

$N_{e}s \gg 1$. Figure 2 also shows that the genetic variance maintained in a finite population depends on the distribution of mutational effects (cf. Keightley and Hill 1988). Further, if mutational effects on the trait follow a reflected gamma ($\frac{1}{2}$), $V_{G}$ depends little on the mutation rates; whereas for equal mutational effects on the trait, $V_{G}$ in small populations depends heavily on the mutation rates for given $\lambda V_{s,r}$.

**Pure pleiotropic effects, where the target trait is completely neutral in itself** (i.e., $V_{s} \to \infty$) and $\hat{s} = s$: With all mutants having equal pleiotropic effects, the genetic variance is $V_{G} = 2V_{s}/s$ (Barton 1990), which is too small, given that the estimates of selection coefficients with detectable effects in the laboratory are in the range $s = 0.02$–$0.08$ (Crow and Simmons 1983; Keightley and Hill 1990; Caballero and Keightley 1994; Chavarras et al. 2001; Wloch et al. 2001). If, however, the pleiotropic effects vary among mutants, substantial variation can occur; indeed $V_{G}$ becomes unbounded for an infinite population if neutral mutants predominate (see Keightley and Hill 1990; Caballero and Keightley 1994; Zhang et al. 2002). Moreover, the pure pleiotropic model can only partially account for the “typical” rates for given $\lambda$. 

**Joint effects of both pleiotropic and real stabilizing selections within an infinite population, but assuming equal mutational effects on both the trait ($e_{a}$) and fitness ($s$):** From Equation 1, $\hat{s} = s + e_{a}/(4V_{s})$ and the approximation $H(\hat{s}) = 4\lambda/\hat{s}$ for an infinite population, the
genetic variance is given by

$$V_c = H(s)\epsilon_s^2/4 = 2V_m/(3 + \epsilon_s^2/(4V_m)).$$  \hspace{1cm} (5)$$

As the fourth moment and covariance are $m_i = V_i\epsilon_i^2/4$ and $\text{Cov}_p = V_3/2$, the strength of total stabilizing selection (real and apparent) is

$$V_a = (\epsilon_s^2/4 + 2V_c)/[3 + (\epsilon_s^2/4 + 2V_c)/V_a]$$

(see Appendix A). Equation 6 is a special case of Equation 3. With no pleiotropic effect of mutants (i.e., $s = 0$), selection comes solely from real stabilizing selection on the metric trait, $V_a = V_a$; with some pleiotropic effects on fitness, selection becomes stronger (i.e., $V_a$ decreases). The inclusion of a pleiotropic deleterious effect therefore decreases both the genetic variance and the strength of total stabilizing selection. Equation 5 is the same as that of Tanaka (1996) who assumed equal deleterious effects of mutations on fitness but Gaussian effects on the metric trait. In this case, the population average of the total selection coefficient is simply equal to the sum of the selection coefficients due to both kinds of selection (cf. Kondrashov and Turelli 1992; Tanaka 1996, 1998).

Joint effects, but assuming mutations have an equal pleiotropic effect on fitness (3) and a continuous distribution f(a) of mutational effects on the metric trait: In this situation Kimura’s (1969) diffusion theory leads to $H(s) = C(s) = 4s/\lambda s$ approximately, and $K(s) = 0$ approximately for an infinite population (Zhang et al. 2002). The genetic variance is $V_i = \int_{-\infty}^{\infty}[\lambda a^2/(3 + a^2/(4V_m))]f(a)da$, and the strength of total stabilizing selection is given by (A7), where the fourth moment is $m_i = \int_{-\infty}^{\infty}(\lambda a^4/4)/(3 + a^2/(4V_m)))f(a)da$, and the covariance between relative fitness and squared deviation due to pleiotropic effects is $\text{Cov}_p = V_3/2$. In the following we denote the population mean of the selection coefficients arising from real stabilizing selection by $\bar{\epsilon} = E(a^2/V_m) = \epsilon_s^2/V_m = 2V_m/(4\lambda V_m)$, i.e., twice the ratio of mutational variance to the genetic variance maintained in real stabilizing selection. For a neutral trait, $\bar{\epsilon} = 0$.

If the mean pleiotropic effect on fitness is much weaker than that from real stabilizing selection (i.e., $\bar{\epsilon} \ll \bar{\epsilon}$), the genetic variance approaches the rare-allele approximation $V_c = 4V_m$. In general $V_i = 4V_m\Sigma_{i=1}^\infty (-1)^{i-1}E(a^2)/(43V_m)^i$ (Moran 1968, p. 296). If $\bar{\epsilon} \gg \bar{\epsilon}$, the genetic variance can be approximated by

$$V_i \approx 2V_m/(\bar{\epsilon} + \kappa \bar{\epsilon})$$

(7)

Noting that the kurtosis $\kappa_4 = E(a^4)/E^2(a^2) = 1, 3,$ and $35/3$ for effects that are equally distributed, normally distributed, and distributed as a gamma ($\gamma$), respectively, Tanaka’s (1996) formula (i.e., Equation 5) is therefore accurate only for equal mutational effects on the trait. Although approximation (7) implies that highly leptokurtically distributed effects of mutations on the trait lead to a low genetic variance (see also Figure 2 for finite populations), Tanaka’s (1996) formula gives a good approximation for the situation in which $\bar{\epsilon} \gg \bar{\epsilon}$. The numerical results in Figure 3 show that expression (5) provides a close approximation to $V_i$ when $\lambda$ is either $>10^{-2}$ or $<10^{-6}$ for Gaussian effects of mutations on the trait or when $\lambda > 0.1$ for gamma ($\gamma$) effects of mutations. For other values of mutation rate, however, Tanaka’s (1996) results are much larger than numerical results for both Gaussian and reflected gamma ($\gamma$) mutational effects. When $\lambda = 10^{-4}$, for example, (5) gives $V_i = 0.028$, which is ~1.5 and 2.3 times as large as the numerical results for Gaussian and reflected gamma ($\gamma$) mutational effects, respectively.

Figure 3 clearly shows how both effects interfere and contribute to the overall outcome in $V_i$ and $V_a$. When the mutation rate is very low (e.g., $\lambda < 10^{-5}$) and each mutant has large effects on the trait relative to its effect on fitness, the results approach the house-of-cards approximation (Turelli 1984). If the mutation rate is high (e.g., $\lambda > 0.1$) and each mutant has a relatively small effect on the trait, the pleiotropic effect must be widespread and becomes the main force of selection, the genetic variance tends to that of Barton (1990) but the strength of total stabilizing selection approaches $V_i = (V_i/V_m)/[1 + 2V_m/(3V_m)]$, which is smaller than that of Barton (1990). If the mean pleiotropic effect is stronger than that of real stabilizing selection, i.e., $\bar{\epsilon} > \bar{\epsilon}$, expression (7) can give better approximations for $V_i$ than Tanaka’s (1996). One interesting phenomenon can be noted by comparing $V_i$ and $V_a$. In Figure 3: $V_i$ rises as the mutation rate increases while the total stabilizing selection becomes stronger (i.e., $V_a$ decreases). This is in sharp contrast to both real stabilizing selection, where as $\lambda$ increases $V_i$ increases but $V_a$ (= $V_a$) remains unchanged (Turelli 1984), and the pure pleiotropic model, where as $\lambda$ increases $V_a$ remains unchanged but $V_a$ decreases (Barton 1990; cf. Figure 5, c and d below).

General case: As shown above and by previous work (Barton 1990; Kondrashov and Turelli 1992; Tanaka 1996), the equal fitness effect assumption cannot provide a simultaneous explanation for the observed high heritability and strong stabilizing selection. If mutational effects on fitness vary across loci in the absence of real stabilizing selection a huge genetic variance can be generated (Keightley and Hill 1990; Zhang et al. 2002), so it is important to investigate the influence of variation in fitness effects on $V_i$ and $V_a$.

The first check is whether the unbounded $V_i$ with increasing population size is avoided with the inclusion of a real stabilizing selection on the trait. The example in Figure 4 shows that with even a weak real stabilizing selection (e.g., $V_i = 1000$), the genetic variance increases with effective population size $N$, when it is small,
but asymptotes when $N_e$ exceeds some large value. This asymptotic value of $V_C$ depends on the value of $V_{s,r}$, with a high $V_C$ for a weak real stabilizing selection (i.e., a large $V_{s,r}$). At the same time, the value of $V_C$ also increases and approaches a limit that is less than $V_{s,r}$. This implies that selection becomes weaker as the effective population size increases, but the total stabilizing selection is stronger than the real stabilizing selection.

Suppose that mutational effects on the trait are Gaussian and mutational effects on fitness follow a gamma ($\frac{1}{2}$) with mean $\bar{s}_p = E(s) = \epsilon_s/\sqrt{3}$. If these mutational effects are independent, the genetic variance for an infinite population can be expressed exactly as

$$V_C = 4\lambda V_{s,t}/(1 + \sqrt{\bar{s}_p / \bar{s}_s}) = 2V_m/(\bar{s}_s + \sqrt{\bar{s}_s \bar{s}_p})$$  \hspace{1cm} (8)

(see APPENDIX B), in which $\bar{s}_p$ is the population mean of selection coefficients due solely to pleiotropic effect on fitness and $\bar{s}_s$, as in (7), is due to real stabilizing selection. For an extreme situation where the pleiotropic effect is very weak (i.e., $\bar{s}_p \ll \bar{s}_s$), (8) tends to the house-of-cards approximation (Turelli 1984), $V_C = 4\lambda V_{s,t}$; while for $\bar{s}_p \gg \bar{s}_s$, the genetic variance reduces to

$$V_C = \sqrt{4\lambda V_{s,t}(2V_m/\bar{s}_p)}.$$  \hspace{1cm} (9)

This is the geometric mean of the genetic variance maintained by real stabilizing selection (Turelli 1984) and for the pleiotropic model with equal fitness effects (Barton 1990; Kondrashov and Turelli 1992). This genetic variance approaches infinity if the metric trait is neutral (i.e., $V_{s,t} \to \infty$) (cf. Keightley and Hill 1990), consistent with the results shown in Figure 4a. Equation 8 clearly shows that both kinds of selection reduce $V_C$ but the impact of pleiotropic selection depends on the magnitude of real stabilizing selection. This unequal influence of both kinds of selection on the genetic variation is due to the fact that large pleiotropic effects on fitness can induce only a high fitness deficit whereas large effects on the trait can lead to a high genetic variance as well as a high fitness deficit. If the total selection coefficient were defined as the ratio of mutational variance to the equilibrium genetic variance following Barton (1990), Kondrashov and Turelli

---

**Figure 3.** (a) Genetic variance maintained in the metric trait and (b) the strength of stabilizing selection on it as functions of the mutation rate. Mutational effects on the trait follow either a Gaussian or a reflected gamma ($\frac{1}{2}$) distribution or are equal ($|\epsilon| = \epsilon_s = \sqrt{2V_m/\lambda}$) and those on fitness are equal ($s = 0.02$). The effective population size is infinite and $V_{s,r} = 100$. The curves for equal are given by Equations 5 and 6.
Joint-Effect Model of Genetic Variation

Figure 4.—(a) Variation maintained in the metric trait and (b) the strength of real stabilizing selection as functions of the effective population size $N_e$. Both $V_G$ and $V_{st}$ are evaluated by Monte Carlo integration. Absolute values of mutational effects on the trait ($|a|$) and on fitness ($s$) are independent and both marginal distributions are gamma ($\frac{1}{2}$). Parameters of mutations $\lambda = 0.1$ and $\epsilon_s = 0.1$. Results are shown for three intrinsic strengths of real stabilizing selection, $V_{sr}$.

(1992), and Tanaka (1998). (8) implies that the expectation of the total selection coefficient is not simply the sum of both components, but a function, $s_T = s_s + \sqrt{s_s s_p}$. Further results are listed in Table 1.

Numerical results are shown in Figure 5 for a range of distributions of effects of mutations on the trait and on fitness such as equal, Gaussian, gamma ($\frac{1}{2}$), gamma ($\frac{1}{4}$), and gamma ($\frac{1}{8}$) (except symmetrical for $a$ and one-sided for $s$). With all other properties being the same, Tanaka’s (1996) formula (i.e., Equation 5 for equal effects $|a|$ and $s$) predicts the smallest $V_G$ and $V_{st}$ (i.e., the strongest selection). Further, the genetic variance maintained increases and total stabilizing selection becomes weaker as mutational effects on fitness become more leptokurtic (see also Table 1). This, albeit in agreement with the conclusion drawn by Zhang et al. (2002), differs from situations when the pleiotropic effect is assumed to be equal (see Figure 3). Comparison of the three curves in Figure 5a in which mutational effects on fitness follow the gamma ($\frac{1}{2}$) but effects on the trait are Gaussian, or gamma ($\frac{1}{4}$), or gamma ($\frac{1}{8}$), respectively, leads to the conclusion that a more leptokurtic distribution of mutational effects on the trait induces a smaller genetic variance given the same distribution of mutational effects on fitness and the same other properties (cf. Keightley and Hill 1988). Figure 5b shows that an increase in pleiotropic selection ($\epsilon_s$) leads to an increase in total stabilizing selection (i.e., decreasing $V_{sr}$). For equal mutation effects, Figure 5d shows that an increase in mutation rate can induce stronger total stabilizing selection, while for other distributed muta-

tion effects there is a value of mutation rate at which the total stabilizing selection is strongest. This behavior of $V_{sr}$ may differ from the pure pleiotropic model (Keightley and Hill 1990; Zhang et al. 2002).

In a realistic model, mutational effects on the trait and on fitness must be correlated (Keightley and Hill 1990). Although analytical treatment is never easy (if possible) when a correlation between mutational effects is included (e.g., Turelli 1985), it is important to con-
Exact results of \( I_1 = E[\xi/(\xi + s)] \), where \( \xi = a/\sqrt{4V_c} \) and the approximations for \( V_c \) when \( \xi \gg \xi \), for some distributions of mutational effects on the trait and independently on fitness.

<table>
<thead>
<tr>
<th>( g_a(s^*) )</th>
<th>( g_i(s^*) )</th>
<th>( I_1 ) (where ( \theta = \xi/\xi ))</th>
<th>( V_c ) when ( \xi \gg \xi )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaussian [3]</td>
<td>Exponential [6]</td>
<td>( \frac{1}{2 - 0} \left[ \frac{2 - \arctan \left( \frac{0}{\sqrt{2 - 0}} \right)}{\sqrt{2 - 0}} \right] ) if ( \theta &lt; 2; \frac{2V_c \ln \left( \frac{8\lambda V_c}{\xi} \right)}{\xi} )</td>
<td></td>
</tr>
<tr>
<td>Gaussian [3]</td>
<td>gamma (1/2) [11.7]</td>
<td>( \frac{1}{(1 + \sqrt{0})} )</td>
<td>( \sqrt{4\lambda V_c(2V_m/\xi)} )</td>
</tr>
<tr>
<td>Reflected exponential [6]</td>
<td>sq-exponential [70]</td>
<td>( \left{ 1 + \left[ \frac{\pi/2\sqrt{0} - (0 - 1 - 0) - \ln (0)}/(1 + 0) \right]/(1 + 0) \right} )</td>
<td>( 1.57\sqrt{4\lambda V_c(2V_m/\xi)} )</td>
</tr>
<tr>
<td>Reflected gamma (1/2) [11.7]</td>
<td>sq-gamma (1/2) [183.9]</td>
<td>( \left{ 1 + \left( \sqrt{0} - \sqrt{0}/(1 + 0) \right) \right} )</td>
<td>( 0.707\sqrt{4\lambda V_c(2V_m/\xi)} )</td>
</tr>
<tr>
<td>Reflected sq-gamma (1/2) [183.9]</td>
<td>qt-gamma (1/2) [46704]</td>
<td>( \left{ 1 + 0.654\sqrt{\sqrt{0} - \sqrt{0}} - 0.270\sqrt{\sqrt{0} - \sqrt{0}} \right} )</td>
<td>( 0.654\sqrt{4\lambda V_c(2V_m/\xi)} )</td>
</tr>
</tbody>
</table>

* sq-exponential, sq-gamma (1/2), and qt-gamma (1/2) represent squared exponential, squared gamma (1/2), and quartic gamma (1/2)-distributed mutational effects (one sided for fitness and symmetrical for the trait), respectively. The numbers in brackets [ ] are the ratios of the fourth moment to the squared variance, \( \kappa_4 = E(a^4)/E(a)^4 \), which describe the leptokurtoses of distributions.

**DISCUSSION**

The assumptions for the origin of both kinds of selection are distinct. In models of the origin of both kinds of selection, the selection on fitness is assumed to arise solely from the deviations of the trait's genetic variation from the optimal values (i.e., phenotypic selection). This is a consequence of the definition of selection (Turelli 1984). The pure pleiotype model (Kondrashov et al. 1994) explains that the total stabilizing selection observed on individuals (i.e., on overall fitness, ignoring any effect on the trait itself) is a consequence of direct effects of deleterious mutations (see Figure 6). Unless the correlation between \( \theta \) and \( \xi \) is large (see Figure 6), the impact of such a correlation on the results for \( V_c \) and \( I_1 \) is negligible. The impact of the effects of pleiotropy on the results is also negligible.
Joint-Effect Model of Genetic Variation

Figure 5.—Variation maintained in the metric trait in an infinite population and the strength of real stabilizing selection as functions of (a and b) the pleiotropic effect and (c and d) the mutation rate. The interaction of both effects of selection (pleiotropic effect and real stabilizing selection) has been investigated by either (a and b) fixing the effect of real stabilizing selection (i.e., $\lambda = 0.1$) or (c and d) fixing the pleiotropic effect (i.e., $\varepsilon_s = 0.1$). Results are shown for $V_s = 100$. For differently distributed mutational effects on the trait and on fitness, the same variabilities $\varepsilon_a$ and $\varepsilon_s$ are assumed, and mutational effects are independent. The symbols eq, $g_s$, gm1/2, gm1/4, and gm1/8 represent equally, Gaussian-, gamma (1⁄2)-, gamma (1⁄4)-, and gamma (1⁄8)-distributed mutational effects (one sided for fitness and symmetrical for the trait), respectively.

In contrast to Tanaka’s (1996, 1998) pleiotropic model, which includes both kinds of selection but assumes an equal deleterious effect on fitness for all mutants, the joint effect model presented here, which allows both mutational effects to vary, leads to quite different pictures of how both kinds of selection are responsible for $V_s$. As found by Tanaka (1996), and intuitively argued by Kondrashov and Turelli (1992), the total selection coefficient should be equal to a linear sum of that arising from real stabilizing selection and that solely attributable to pure pleiotropic effect: $s_T = 3\lambda + 3s_p$. As in general $3\lambda \gg 3s_p$ (Gillespie 1991; Kondrashov and Turelli 1992), the total selection coefficient is approximately equal to the pleiotropic effect $s_T \approx 3s_p$. Therefore pleiotropic effects on fitness can be large but their impact on $V_s$ is limited.

For a simple explanation of why a distribution of pleiotropic effects allows the model to generate high $V_s$, suppose that new mutations are divided into two equally possible classes: one with equal pleiotropic effect $s_1$, the other with $s_2$, but with both having the same effect on the trait (i.e., $\varepsilon_s$). The two classes contribute to $V_s$ as $2V_s/(s_1 + 3\lambda)$ and $2V_s/(s_2 + 3\lambda)$, respectively, from Tanaka (1996), and the total genetic variance main-
Figure 6.—The influence of the correlation ($\rho$) between absolute values of mutational effects on the metric trait ($|d|$) and on fitness ($s$) on (a) the genetic variance and (b) observed strength of apparent stabilizing selection. Mutational effects on the trait and fitness follow a bivariate gamma ($\gamma$). The mutation rate is $0.1$ and the intrinsic strength of real stabilizing selection is $V_{s,r} = 100$. Results are shown for three correlations.

tained is then larger than if all mutations have the same mean pleiotropic effect ($s_1 + s_2$)/2 because $[1/(s_1 + \bar{s}_1) + 1/(s_2 + \bar{s}_2)]/2 > 1/[(s_1 + s_2)/2 + \bar{s}]$. The numerical results show that if a very small minimum total selection coefficient, say $10^{-10}$, is assumed, the genetic variance maintained is nearly the same as that without such minimum fitness effect. As the mutant alleles of large effects on fitness would be quickly eliminated from the population, the genetic variance is attributable primarily to mildly deleterious mutations. The huge genetic variation generated in the joint effect model of continuously varying pleiotropic effects on fitness, therefore, comes mainly from “a class of alleles with significant effects on the character, but very little effect on fitness” (Barton 1990, p. 779).

It is also interesting to compare the prediction of the joint effect model with the house-of-cards approximation (see Equation 8, Table 1, and Figure 5); but if the pleiotropic effect is large, the genetic variance maintained is given by (9) for Gaussian effects on the trait and gamma ($\gamma$) effects on fitness of mutations. As the genome-wide mutation rate $\lambda$ exceeds $\lambda_n$, our prediction of $V_G$ may not be smaller than the house-of-cards approximation (cf. Tanaka 1996, 1998). For the typical estimate of strength of real stabilizing selection, $V_{s,r} = 20$ (Turelli 1984), $V_G = 0.4 \sqrt{\lambda/\bar{s}_r}$ from (9) under the condition $\bar{s}_r \gg \bar{s}_p$ (i.e., $\lambda \bar{s}_p \gg 2.5 \times 10^{-3}$). This implies that if both the mutation rate and the mean pleiotropic effect are of similar order, abundant genetic variation can be maintained, and less restrictive conditions are required if the mutational effects are more leptokurtic (see Table 1 and Figure 5).

The mutation rate $\lambda$ assumed in this study is the genome-wide mutation rate. Although all of the mutations may affect fitness to a varying degree, only a small fraction of them may be considered to appreciably affect the trait under study. It is, however, unrealistic to assume no effect and more appropriate to assume that the distribution of mutational effects on the trait is more lepto-
Joint-Effect Model of Genetic Variation

kurtic than on fitness (see Robertson 1967; Keightley and Hill 1988; Hill and Caballero 1992). The analyses of the joint effect model show that the genetic variance maintained at mutation-selection balance depends not only on the variance of mutational effects but also on their leptokurtosis. For a given distribution of mutational effects on fitness, a more leptokurtic mutational effect on the trait induces a smaller genetic variance, consistent with the results of Keightley and Hill (1988) who studied pure real stabilizing selection in finite populations. Even for this more realistic model, the joint effect model can still generate abundant genetic variation if mutational effects on fitness are sufficiently leptokurtic, say gamma ($\gamma_2$), and the genome-wide mutation rate is not $<0.01$ (see Figure 5).

The scanty data for multicellular eukaryotes are consistent with any value of $\lambda$ between 0.1 and 100 (Charlesworth et al. 1990; Kondrashov and Turelli 1992; Lynch et al. 1999; Kumar and Subramanian 2002). Recent studies on Caenorhabditis elegans, however, show that the mutation rate for life history traits is $<1.0$ and is of the order $10^{-3}$ (Keightley and Caballero 1997; Garcia-Dorado et al. 1999; Vassilieva and Lynch 1999). The best estimate of the average selection coefficient against heterozygous mutations is $E[s/2] = 0.02$ (Crow and Simmons 1983). Data for Drosophila bristle traits show that $\lambda$ is in the range $0.09-1.0$ and $\epsilon$, in the range $0.01-0.2$ (Keightley and Hill 1990; Caballero and Keightley 1994). Data for competitive viability in Drosophila suggest that $\lambda \approx 0.01$ and $E[s] \leq 0.08$ (Chavarrias et al. 2001). Data for yeast Saccharomyces cerevisiae show that $\lambda$ is of the order $10^{-3}$ and $E[s/2]$ is in the range $0.01-0.05$ (Wloch et al. 2001). Even with such large pleiotropic effects, our joint effect model, which assumes leptokurtic effects both on the trait and on fitness of mutations, predicts high heritabilities under strong total stabilizing selection unless $\lambda$ is very small, say $<0.01$ (see Equation 8, Figure 5, and Table 1). But the estimates of mutation and selection parameters are not very reliable (Kondrashov 1998; Lynch et al. 1999; Kingsolver et al. 2001). Mutation rates are usually underestimated and mean fitness effects are usually overestimated as the effects of most mutants may be too small to be detected (Kondrashov and Turelli 1992; Davies et al. 1999; Lynch et al. 1999). The observation of high heritabilities and strong total stabilizing selection may then be interpreted in terms of the joint effect model of continuously varying mutational effects.

In summary, the joint effect model presented here shows that $V_g$ and $V_c$ are determined primarily by real stabilizing selection while pleiotropic effects, which can be large, have only a limited impact. With an abundant supply of mutations and leptokurtic mutational effects on fitness, the joint effect model can induce a significant amount of stabilizing selection as well as a substantial genetic variance, even with a mutational variance on the trait as low as $V_m = 10^{-3}V_c$ (cf. Barton 1990). Combining both kinds of selection and allowing mutational effects on the metric trait and on fitness both to vary change the picture of the mutation-selection model and therefore enable the mutation-selection balance to be a plausible cause of quantitative variation.

We are grateful to Nick Barton, Brian Charlesworth, Peter Keightley, Jinliang Wang, and a referee for helpful comments and Ian White for help in proving Equation 8. This work was supported by a grant from the Biotechnology and Biological Sciences Research Council (R35986).

**LITERATURE CITED**


The effect of selection against extreme genetic variance can be evaluated by the equation 

\[ \text{equation} \]

and Kondrashov, A. S., Kingsolver, J. G., H. E. Hoekstra, J. M. Hoekstra, D. Berrigan,

pleiotropic effects on all other traits, with

Kimura, M.,

1969 The number of heterozygous nucleotide sites

Gillespie, J. H.,

and Robertson, A., 1956 The effect of selection against extreme devi-

Gillespie, J. H.,

470 X.-S. Zhang and W. G. Hill

Lynch, M., J. Blanchard, D. Houle, T. Kibota, S. Schultz

1998 Measuring spontaneous deleterious muta-

a bivariate distribution,

Hill, W. G., and A. Caballero, 1992 Artificial selection experimen-

1992 Deleterious mutations, A. Caballero,

1990 How much genetic variation can be maintained

and inferences about equilibrium. A random-mating diploid population is as-

Properties of ethylmethane sulfonate-induced mutations affect-

properties of traits in E. coli. Genetics 143: 1467–1483.

Imhof, M., and C. Schröter, 2001 Fitness effects of advanta-


Kumar, M., 1969 The number of heterozygous nucleotide sites maintained in a finite population due to steady flow of mutations. Genetics 61: 893–903.


Kumar, S. N. Vignieri, and A. Caballero.


Robertson, A., 1956 The effect of selection against extreme devi-

ants based on deviation or on homozygosis. J. Genet. 54: 236–248.

Robertson, A., 1967 The nature of quantitative genetic variation, pp. 26–280 in Heritage from Mendel, edited by A. Brink. The University of Wisconsin Press, Madison, WI.

Shaw, R. G., D. L. Byers and E. Darro, 2000 Spontaneous muta-

tional effects on reproductive traits of Arabidopsis thaliana. Genet-

ics 155: 369–378.


Wright, S., 1935 The analysis of variance and the correlations between relatives with respect to deviations from an optimum. J. Genet. 30: 243–256.


Communicating editor: J. B. Walsh

APPENDIX A

Let us assume that the gene action within and across loci is additive and loci are unlinked and in linkage equilibrium. A random-mating diploid population is assumed. Mutations in a diploid individual have an effect on a metric trait with the difference in value between homozygotes and a net effect on fitness that includes pleiotropic effects on all other traits, with the difference in fitness between homozygotes. There is therefore a bivariate distribution, \( h(a, s) \), of \( a \) and \( s \) for alleles affecting the trait. If there is real stabilizing selection, the total observed stabilizing selection would come from these two parts. Following the method of Falconer and Mackay (1996, p. 27), the mutant allele frequency within a single-locus model is given by \( x = \{x - x(1 - x)[s/2 + a^2/(8V_a)]/[2w] \} \) with the mean fitness given by \( w = 1 - x(1 - x)^2/(4V_a) \) if the previous frequency is \( x \). With weak selection (i.e., \( w \approx 1 \)), the change in the mutant allele frequency is \( \Delta x = x_1 - x = -x(1 - x) [s^2/2(1 - 2a^2/(8V_a))]. \) Thus the equivalent total selection coefficients are

\[
\sigma = s + (1 - 2a^2)/(4V_a)
\]

(c.f. Robertson 1956; Bulmer 1985; Keightley and Hill 1988). With Kumar’s (1969) diffusion approximations under the infinite independent loci model, the genetic variance can be evaluated by the equation

\[
\sigma_i = \int_0^1 \int_{-1}^{1} h(a, s)\Phi(x; s) 2s(1 - x)a^2 dx da
\]

(Zhang et al. 2002), the variance of squared deviations is

\[
\sigma_{xx} = \int_0^1 \int_{-1}^{1} h(a, s)\Phi(x; s) x(2s(1 - x) - 3[2s(1 - x)])^2 a^2 dx da + 2V_a = m_s + 2V_a
\]

(A3)
and the covariance of relative fitness (taking positive values because \(s\) is defined to be positive) and the squared deviation is

\[
\text{Cov}(w, (z - z_m)^2) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} h(a, s) \Phi(x; s) 
\times 2x^2(1 - x)(1 - 2x) a^2 z_m^2 \text{d}x \text{d}a + \frac{V_G}{2V_v}.
\]

(A4)

Thus the covariance is partitioned into two parts: one due to pleiotropic selection and the other due to stabilizing selection. In the above equations \(\Phi(x; s)\) is the equilibrium frequency distribution of mutations, given by

\[
\Phi(x; s) = \frac{4N_s \lambda}{x(1 - x) G(x)} \int_{-\infty}^{\infty} G(\xi) d\xi = \exp\left\{-2N_s x (s + (1 - x)a^2) \right\}.
\]

If a population has a large effective size \(N_s\), such that \(2N_s a^2 / (4V_v) \gg 1\), numerical calculations show that the distribution function \(\Phi(x; s)\) is finite only for very small values of \(x\); that is, the equilibrium frequency of mutant alleles is very small, \(x \approx 0\). With the assumption that the mutant alleles are very rare, the equivalent total selection coefficient can be approximated by

\[
\hat{s} = s + a^2 / (4V_v).
\]

(A5)

Thus the equilibrium genetic variance is

\[
V_G = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} h(a, s) H(\xi - 3K(s)) (a^2 / 4) \text{d}a \text{d}w = -V_G / [2 \text{Cov}(w, (z - z_m)^2)]
\]

\[
= (m_1 + 2V_v^2) /[2 \text{Cov}(w, (z - z_m)^2)].
\]

(A7)

The fourth moment is \(m_4 = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} h(a, s) [H(\xi - 3K(s)) (a^4 / 16)] \text{d}a \text{d}w\) and the covariance of relative fitness and squared deviation is \(\text{Cov}(w, (z - z_m)^2) = \text{Cov}_p + \text{Cov}_r\), in which \(\text{Cov}_p = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} h(a, s) C(s) (s^2 / 2) (a^2 / 4) \text{d}a \text{d}w\) is the contribution due to pleiotropic effects of mutations and \(\text{Cov}_r = V_G / (2V_v)\) due to real stabilizing selection. The expressions for the heterozygosity, \(H(\hat{s})\), and for \(K(s)\) and \(C(s)\) are given by Zhang et al. (2002) by replacing \(s\) by \(\hat{s}\). In contrast with Keightley and Hill (1990), who assumed that the strength of stabilizing selection is measured in phenotypic standard deviation units and thus is a dimensionless quantity, \(V_G\) in this article is used in the same way as that in Turelli (1984) and thus has a dimension of genetic variance.

For an infinite population, by using the approximations \(H(\hat{s}) = C(\hat{s}) = 4x / \pi V_v\) and \(K(s) = 0\), the expressions for the genetic variance and strength of the total stabilizing selection reduce to those given in (2) and (3). Equation 3 is obtained by noting that

\[
V_G = 4 \lambda \int_{-\infty}^{\infty} h(a, s) [s^2 / 4] \text{d}a + 2V_v^2
\]

\[
= 4 \lambda V_G \int_{-\infty}^{\infty} [h(a, s) [s^2 / 4] \text{d}a + 2V_v^2,
\]

where \(\text{Cov}_p = 4 \lambda \int_{-\infty}^{\infty} h(a, s) [s^2 / 4] \text{d}a\), and the covariance of relative fitness and squared deviation \(\text{Cov}(w, (z - z_m)^2) = \text{Cov}_p + V_G^2 / 2V_v\).

APPENDIX B

We consider the evaluation of genetic variance assuming that the population is under stabilizing selection because of the joint effect of pleiotropic and real stabilizing selections and that both mutational effects are independent. If mutational effects on the trait and on fitness follow distributions \(g_i(a),\) where \(-\infty < a < \infty,\) and \(g_2(s),\) where \(0 < s < \infty,\) respectively, then evaluation of \(V_G = 4 \lambda V_{\xi_2}\), according to (2) is equivalent to the expectation,

\[
L_i = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} g_i(a) g_2(s) [\xi^2 / (\xi^2 + s)] \text{d}a \text{d}s = E[\xi^2 / (\xi^2 + s)],
\]

in which scaled effects on the trait \(\xi = a / \sqrt{4 \lambda V_G}\) are symmetrical about 0 and distributed with mean 0 and variance \(\hat{\xi} = \xi^2 / 4 \lambda V_G\). This integral can be obtained exactly for some types of mutational effects and the results are listed in Table 1, showing that \(L_i\) depends on only the ratio \(\hat{\xi} / \xi\), confirmed by numerical calculations on other types of mutational effects. The population mean of the total selection coefficient is thus given by \(s_t = \hat{\xi} / L_i\). One example is where mutations have Gaussian effects on the trait and gamma (\(\xi\)) effects on fitness (i.e., a squared Gaussian random variable). Making the transformation \((\xi, s)\) to \((\xi, v)\), whereby the ratio \(v = (s / \xi) / (\xi^2 / \xi)\) is \(F\)-distributed with 1 d.f. in both the numerator and denominator, integrating \(v\) leads to the density function of \(v, \phi(v) = 1 / [\pi (1 + v^2)]^2\) (Moran 1968, p. 332). Noting that \(s^2 / (\xi^2 + s) = 1 / [1 + (\hat{\xi} / \xi)] v\), we have \(E[\xi^2 / (\xi^2 + s)] = (1 + (\hat{\xi} / \xi)] v\), hence \(E[\xi^2 / (\xi^2 + s)] = \int_0^1 \phi(v) [1 + (\hat{\xi} / \xi)] v^{-1} \text{d}v = \int_0^1 [2 / (\pi (1 + t^2)(1 + (\hat{\xi} / \xi)^2))] \text{d}t = 1 / (1 + \sqrt{\hat{\xi}}).

Thus the expectation is determined only by the ratio of \(\hat{\xi}\) to \(\xi\).