Nonequivalent Loci and the Distribution of Mutant Effects

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ABSTRACT

It has been observed repeatedly that the distribution of new mutations of a quantitative trait has a kurtosis (a statistical measure of the distribution's shape) that is systematically larger than that of a normal distribution. Here we suggest that rather than being a property of individual loci that control the trait, the enhanced kurtosis is highly likely to be an emergent property that arises directly from the loci being mutationally nonequivalent. We present a method of incorporating nonequivalent loci into quantitative genetic modeling and give an approximate relation between the kurtosis of the mutant distribution and the degree of mutational nonequivalence of loci. We go on to ask whether incorporating the experimentally observed kurtosis through nonequivalent loci, rather than at locus level, affects any biologically important conclusions of quantitative genetic modeling. Concentrating on the maintenance of quantitative genetic variation by mutation-selection balance, we conclude that typically nonequivalent loci yield a genetic variance that is of order 10% smaller than that obtained from the previous approaches. For large populations, when the kurtosis is large, the genetic variance may be <50% of the result of equivalent loci, with Gaussian distributions of mutant effects.

EXPERIMENTAL measurements of mutant effects on a polygenic trait have consistently found that the distribution of mutant effects is leptokurtic, with a kurtosis (fourth central moment divided by the squared variance) that is in excess of the value 3 associated with a normal distribution. A prominent finding was the work on *P*-element insertions affecting Drosophila bristle number (Mackay *et al.* 1992; Lyman *et al.* 1996). This work yielded mutant distributions that were highly leptokurtic—with a kurtosis of order 40. In a recent review, Garcia-Dorado *et al.* (1999), while confirming this result, concluded that the *extreme* kurtosis of the sternopleural bristle mutations is not typical of other quantitative traits. However, all of the fitness and morphological traits they reviewed had distributions of mutant effects more leptokurtic than a normal distribution. A similar pattern appeared in the nine Drosophila characters assayed by Keightley and Ohnishi (1998). The range of experimental protocols and statistical techniques used in this work supports the notion that this pattern is not an experimental artifact and that a leptokurtic distribution of mutant effects is a real phenomenon.

A number of theoretical treatments have dealt with the implications of this kurtosis for biologically important quantities. The two most notable are the amount of genetic variance maintained by populations under mutation-selection balance (Fleming 1979; Keightley and Hill 1988; Bürger and Lande 1994; Bürger 1998) and the variance of the genetic variance among replicate lines and thus the predictability of dynamics under selection (Keightley and Hill 1989; Bürger and Lande 1994; Mackay *et al.* 1994). We note that an assumption, underlying all of these models, is that there are identical distributions of mutant effects at each locus. These distributions are necessarily leptokurtic, to yield the empirically observed kurtosis of the overall mutant distribution.

Here, by contrast, we propose an alternative model that suggests that the observed kurtosis of the distribution of mutant effects may be a property that emerges only at the trait level, regardless of the distribution of mutant effects at individual loci. The model relies crucially on the empirically motivated assumption that the loci contributing to a trait have different mutational effects and thus are nonequivalent.

There is abundant evidence suggesting that quantitative trait loci (QTL) are mutationally nonequivalent. Studies have shown that the proportion of phenotypic variance contributed by different QTL can vary widely (Falconer and Mackay 1996, ch. 21). More specifically, the evidence suggests that mutations at the overwhelming majority of QTL contribute small fractions of the phenotypic variance, while only a small number make more substantial contributions (Bost *et al.* 1999). Despite the evidence, such nonequivalence has been incorporated only rarely into population/quantitative genetic modeling. This is surely because parameterizing each locus separately makes models unwieldy, and overly cumbersome models often obscure the biological point being made.

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We present a new method of incorporating mutational nonequivalence of loci that avoids these problems. This is achieved by choosing the various mutational properties of each locus, at random, from a particular probability distribution. We then argue that certain observable quantities, such as the distribution of mutant trait effects, are "self averaging." As such, we can replace these observable quantities by their average over the randomly chosen mutational properties. This reduces the number of free parameters in the problem to the (assumed small) set required to specify the probability distribution of mutational properties of individual loci. In addition to an economy of description, the small set of free parameters can also be thought of as encapsulating the degree of nonequivalence of loci. Thus by exposing the influence of these parameters we can make explicit the influence of nonequivalent loci. In the first part of this article, we show explicitly the influence of these parameters on the distribution of new mutations. Having demonstrated that the kurtosis of the distribution of mutant effects may emerge through nonequivalent loci, we follow this up, in the second part of this article, by exploring other biological implications of our way of incorporating mutational kurtosis into the model. In particular we compare the implications for the level of genetic variance maintained at mutation-selection balance with the method of incorporating mutational kurtosis used in the theoretical articles cited above.

MODEL AND RESULTS

Distribution of mutant effects: We use the continuum-of-alleles model introduced by Crow and Kimura (1964) and analyzed in the context of the maintenance of genetic variation by, among others, Kimura (1965), Lande (1976), and Turelli (1984). In Crow and Kimura's model of allelic mutation, the effect of a mutated offspring's allele, y', is given by the sum of the parental allelic effect, y, and a mutation effect x, thus $y' = y + x$. The effect of each new mutation at locus i is drawn from a continuous probability distribution, $f_i(x)$. It is assumed that the quantitative trait in question is controlled by n additively contributing diploid loci. Thus an individual's genotypic value, G, is given by $G = \Sigma_{i=1}^{n}(y_i + y_i^*)$, where y_i (y_i^*) is the effect of the allele of maternal (paternal) origin at locus i. Additivity means that at the level of the trait, there is no dominance or epistasis.

The distribution of single mutation effects for the trait, $F(x)$, is a weighted sum over the mutant distributions at each locus, with the weights proportional to the allelic mutation rate at each locus. In terms of the allelic mutation rate at the ith locus, μ_i, the mutation rate of the trait is $U = 2\Sigma_{i=1}^{n}\mu_i$ and the weighting of the ith locus is $c_i = 2\mu_i/U$. We then have

$$F(x) = \sum_{i=1}^{n} c_i f_i(x). \tag{1}$$

To experimentally measure this distribution requires either an asexual organism or a sexual line that is genetically homogeneous (homozygotic at each locus). Without such genetic homogeneity, the variation generated by recombination can mask the direct effects of $F(x)$.

For simplicity, we assume that the distribution of mutant effects at locus i, $f_i(x)$, is a parameterization of a "reference distribution," $g(z)$. This reference distribution has the properties that it (i) is normalized to unity, (ii) has unit variance, and (iii) has zero mean. The results given below apply for a range of distributions with these properties, but for concreteness, we introduce a specific form of the reference distribution, the Gaussian. This is the form of $f_i(x)$ adopted by Crow and Kimura (1964) and is given by

$$g(z) = \frac{1}{\sqrt{2\pi}}\exp\left(-\frac{z^2}{2}\right). \tag{2}$$

We derive the allelic mutation distribution at locus i, $f_i(x)$, from $g(z)$ by incorporating a parameter b_i (where $\infty > b_i > -\infty$) and a parameter v_i (where $v_i > 0$), as

$$f_i(x) = \frac{1}{\sqrt{v_i}}g\left(\frac{x - b_i}{\sqrt{v_i}}\right). \tag{3}$$

The distribution $f_i(x)$ of Equation 3 is normalized to unity, but incorporates a mutational bias, b_i, which is the mean deviation of a mutant allelic effect from the parental value. More importantly for this article, the distribution $f_i(x)$ possesses a variance of v_i—the variance of mutant allelic effects. It follows that in this model, each locus is characterized by the three quantities μ_i, b_i, and v_i, and we introduce nonequivalent loci by allowing variation in the values of these quantities across loci.

Initially, let us confine ourselves to the case of nonbiased (or uniformly biased) mutation. As such, we set all the b_i to zero and confine ourselves to variation only in the v_i (the more general case is discussed below).

To obtain the distribution of mutant effects, we substitute Equation 3 into Equation 1, yielding $F(x) = \Sigma_{i=1}^{n}(c_i/\sqrt{v_i})\,g(x/\sqrt{v_i})$. We assume mutational variances (v_i) at different loci have all been independently drawn at random from a particular probability distribution, $P(v)$, and that there is no correlation between allelic mutation rates (μ_i) and mutational variances. In such a case, the distribution of mutant trait effects, $F(x)$, when calculated for a typical set of mutational variances, will have moments that differ by terms of order $n^{-1/2}$ from moments calculated from an $F(x)$ that is averaged over all v_i; see appendix a for details. Thus an approximation of $F(x)$ is to replace it by its average over all v_i. Denoting quantities averaged over all v_i by an overbar, and using $\Sigma_{i=1}^{n}c_i = 1$, we find

$$\bar{F}(x) = \int_0^\infty dv_1 \int_0^\infty dv_2 \ldots \int_0^\infty dv_n F(x) \prod_{i=1}^n P(v_i) = \int_0^\infty P(v) \frac{1}{\sqrt{v}} g\left(\frac{x}{\sqrt{v}}\right) dv$$
$$= \int_0^\infty dv \int_{-\infty}^\infty dy \delta(x - \sqrt{v}y) P(v) g(y), \quad (4)$$

where the final form on the right-hand side of Equation 4 has been written in terms of a Dirac delta function, $\delta(\bullet)$. It follows directly from this final form that moments of $\bar{F}(x)$ factorize into a product of averages, one with respect to $P(v)$, the other with respect to $g(z)$:

$$\int_{-\infty}^\infty x^a \bar{F}(x)\, dx = \int_0^\infty v^{a/2} P(v)\, dv \int_{-\infty}^\infty y^a g(y)\, dy = \overline{v^{a/2}} \int_{-\infty}^\infty y^a g(y)\, dy. \quad (5)$$

Both the second and fourth moments of the distribution of mutant effects, approximated here by $\bar{F}(x)$, have been investigated by empirical workers and play important roles in quantitative genetic modeling. The second moment of $\bar{F}(x)$, when multiplied by the trait mutation rate, U, yields the input into the trait genetic variance from new mutations each generation and is usually denoted V_M (Lynch 1988; Houle *et al.* 1996). From Equation 5 we quickly find $V_M/U = \int x^2 \bar{F}(x)\, dx = \bar{v}$. Thus the variance of mutational effects is simply the averaged variance of a locus. With the kurtosis, κ, the situation is quite different. From Equation 5, our approximation of the kurtosis is

$$\kappa \simeq \frac{\int x^4 \bar{F}(x)\, dx}{\left(\int x^2 \bar{F}(x)\, dx\right)^2} = \frac{\overline{v^2}}{\bar{v}^2} \frac{\int y^4 g(y)\, dy}{\left(\int y^2 g(y)\, dy\right)^2}. \quad (6)$$

Using the fact that the squared coefficient of variation of the v, which we write as $CV^2(v)$, is defined as the variance of v divided by its squared mean, *i.e.*, $CV^2(v) = (\overline{v^2} - \bar{v}^2)/\bar{v}^2$, we can write Equation 6 as

$$\kappa \simeq \left[1 + CV^2(v)\right] \kappa_0, \quad (7)$$

where $\kappa_0 = (\int y^4 g(y)\, dy)/(\int y^2 g(y)\, dy)^2$ is the kurtosis associated with the distribution of mutant effects at a single locus or, equivalently, the kurtosis resulting from any number of loci with identical distributions of mutant allelic effects. Note that since $CV^2(v)$ is nonnegative, it follows from Equation 7 that $\kappa \geq \kappa_0$ and any variation in the v values yields $\kappa > \kappa_0$. As such the overall distribution of mutant effects will always have an enhanced kurtosis when compared to the distributions at locus level. Furthermore, this enhancement is directly proportional to the degree of nonequivalence of the loci, as expressed by the squared coefficient of variation of the distribution $P(v)$. Although this result follows from an approximate treatment, we show in appendix b that if the only mutational properties of loci that are different are the mutational variances (v_i), the result $\kappa \geq \kappa_0$ holds quite generally. The fact that combining two different-width Gaussians creates a leptokurtic compound distribution was noted by Wright (1968, pp. 211–215), in the context of Drosophila migration patterns.

Let us now allow variation in the mutational biases, b_i, to be taken into account. For independently chosen b's, with no correlation with other parameters, we find (details not given) a kurtosis of mutant trait effects of $\kappa \simeq (\kappa_0[1 + CV^2(v)] + 6\beta + \kappa_b\beta^2)/(1 + \beta)^2$, where $\beta = \mathrm{Var}(b)/\bar{v}$ and κ_b is the kurtosis of the distribution of the b's. When $\beta \ll 1$, the effect of differences in biases across loci is negligible and we recover the result for the kurtosis of mutational effects given in Equation 7. However, in the opposite limit, $\beta \gg 1$, the differences in bias dominate and the kurtosis is approximately equal to that of the b's. For intermediate values of β, the dependence of κ on β is nonmonotonic when $(\kappa_b + \kappa_0[1 + CV^2(v)] - 6)/(\kappa_b - 3) \geq 1$. In the following, we assume that $\beta \ll 1$ and that mutational biases have little effect on the results. This, although plausible, is mainly a convenience, as we have little empirical evidence to guide us as to an appropriate form for their distribution. Observations such as Clayton and Robertson's (1964) finding that Drosophila bristle-number mutations do not change the trait mean can tell us little about the bias at any particular locus.

In contrast to the biases, there *is* some empirical evidence available for the distribution of the mutational variances, $P(v)$. The aforementioned results from quantitative trait loci (QTL) analysis suggest that the vast majority of QTL contribute a very small proportion of phenotypic variance, while a much smaller number contribute a substantial proportion (Falconer and Mackay 1996; Bost *et al.* 1999, 2001). This suggests that the distribution of mutational variances may be L shaped; a candidate is the one-sided gamma distribution, $P_{\mathrm{gamma}}(v; q, \lambda)$, that vanishes for $v < 0$, and for $v > 0$ is given by

$$P_{\mathrm{gamma}}(v; q, \lambda) = \frac{v^{q-1} \exp(-v/\lambda)}{\lambda^q \Gamma(q)}, \quad (8)$$

where q and λ are parameters and $\Gamma(\bullet)$ denotes Euler's gamma function (Abramowitz and Stegun 1965). This distribution will be L shaped if the parameter q is smaller than unity. The enhancement of kurtosis in Equation 7 that results from the gamma form of $P(v)$ is given simply by $CV^2_{\mathrm{gamma}}(v) = \lambda^2 q/(\lambda q)^2 = 1/q$. If $q \ll 1$, the enhancement of kurtosis, resulting from nonequivalent loci (Equation 7), can be substantial. By way of illustration, note that q is related to another significant quantity, namely the expected proportion of loci that have a mutational variance smaller than the mean mutational variance, $\bar{v} = \lambda q$; this proportion is given by $\int_0^{\lambda q} P_{\mathrm{gamma}}(v; q, \lambda)\, dv = 1 - \Gamma(q, q)/\Gamma(q)$, where $\Gamma(a, z) = \int_z^\infty t^{a-1} e^{-t} dt$ is the incomplete gamma function. Thus, if ~82% of the loci affecting a trait have a mutational variance smaller than the mean mutational variance, as would occur if $q = 1/9$, then from Equation 7, an overall kurtosis of 40 would be entirely consistent with an allelic kurtosis, κ_0, of just 4.

Using Equation 8, we can go further and evaluate Equation 4, the averaged distribution of mutant effects, yielding the exact result

$$\bar{F}_{\text{gamma}}(x) = \frac{1}{2^{q-1}\sqrt{\pi\lambda}\Gamma(q)}\left(\sqrt{\frac{2x^2}{\lambda}}\right)^{q-1/2} K_{q-1/2}\left(\sqrt{\frac{2x^2}{\lambda}}\right), \qquad (9)$$

where $K_a(z)$ is a Bessel function of the second type of order a and argument z (Abramowitz and Stegun 1965). In general, this distribution is highly leptokurtic; see Figure 1, where we plot the analytical form of Equation 9 against results of numerical simulation, to illustrate the validity of the averaging process.

Nonequivalent loci and the maintenance of genetic variance: It is now appropriate to ask whether generating the empirically observed kurtosis using nonequivalent loci, rather than incorporating it at locus level, via equivalent loci, has a significant effect on other quantities of biological interest. We concentrate on the maintenance of quantitative genetic variation in a single phenotypic trait, through the balance between mutation and stabilizing selection.

Keightley and Hill (1988) suggested that increasing the mutational kurtosis could have a dramatic effect on the amount of genetic variance maintained in small populations, but their claim was disputed by Bürger and Lande (1994) whose simulation results suggested that it had very little effect. We concentrate on very large, effectively infinite populations and compare the results of three classes of mutant distributions. The first case is mutationally equivalent loci each with a Gaussian distribution, henceforth abbreviated to EG; the second case is equivalent leptokurtic loci, henceforth EL; and the third is nonequivalent Gaussian loci, NG. Table 1 summarizes the differences between the three cases.

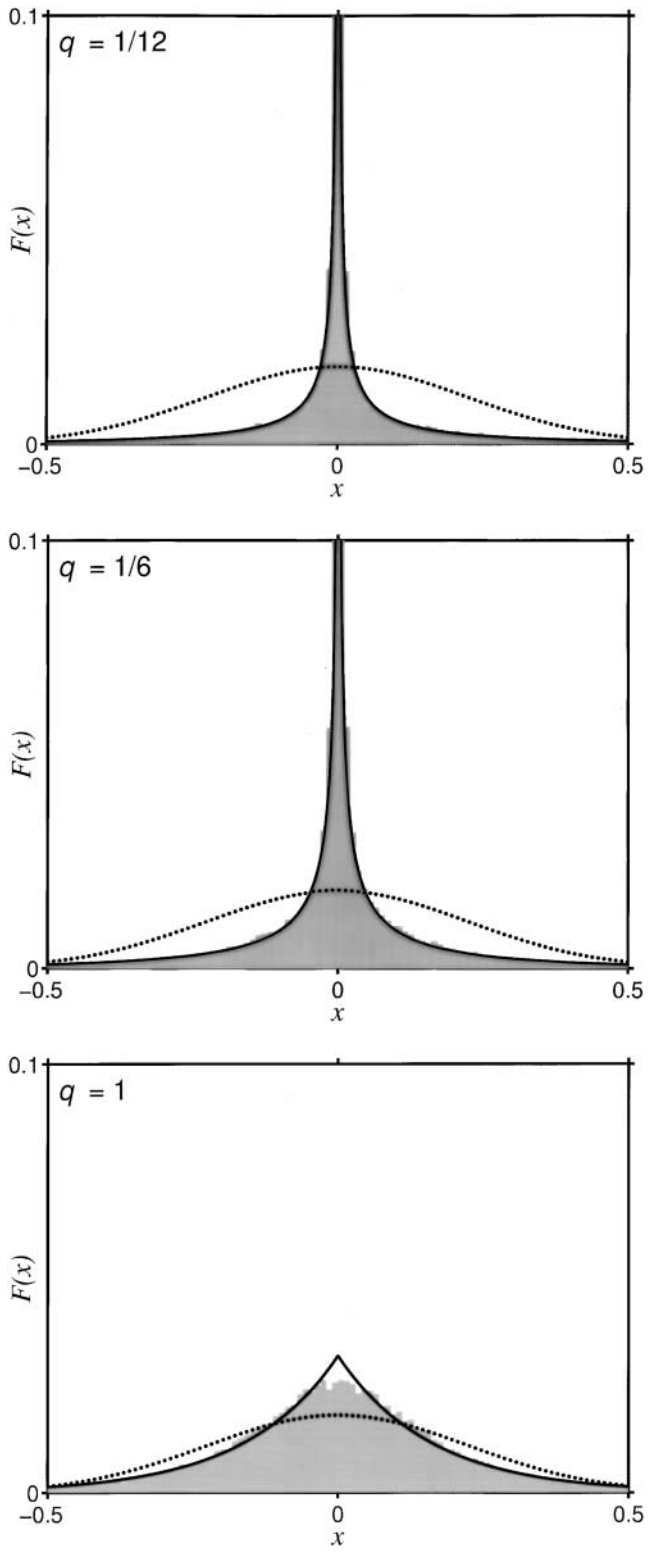

Figure 1.—Plots of the distribution of mutant effects, $F(x)$, are presented when mutant allelic effects at loci are all normally distributed around the parental value, but each locus has a randomly chosen mutational variance. The distribution of mutational variances was taken to be a one-sided gamma distribution of Equation 8, $P_{\text{gamma}}(v; q, \lambda)$. For all plots, the expected value of the gamma distribution, $\bar{v}$, was set to $\bar{v} = 0.05$ (see main text). This was achieved by choosing $\lambda = \bar{v}/q$. As a result, q is the only free parameter in the distribution. The solid line shows the averaged approximation of Equation 9 and the dotted line shows a Gaussian distribution with mean 0 and variance 0.05 for comparison. We show results for three values of q, namely $1/12$, $1/6$, and 1. These are chosen to give kurtoses close to 40, 20, and 6 (Equation 7), thereby encompassing both the extreme kurtosis measured for Drosophila sternopleural bristle (Mackay *et al.* 1992; Lyman *et al.* 1996) and a lower value typical of other observed traits (Garcia-Dorado *et al.* 1999). For the three values of q shown we calculate (see text) that the expected proportion of loci with a mutational variance smaller than the mean variance across all loci is ~84% for $q = 1/12$, 78% for $q = 1/6$, and 63% for $q = 1$. In addition, we carried out simulations, in which 20,000 mutations were generated from 200 equally mutable loci, whose v_i values were drawn at random from the appropriate $P(v)$ distribution. The histogram (gray area) shows a typical run. The fit of the data to the analytical approximation was generally good. For $q = 1$, the mean value of the kurtosis, over 1000 runs, with a new set of v_i drawn each time, was $\langle\kappa\rangle = 5.967$ with a standard error, σ, of 0.473, while the theoretical prediction was $E(\kappa) = [1 + \text{CV}^2(v)]\,\kappa_0 = 6$. For $q = 1/6$, the results were $\langle\kappa\rangle = 20.312$ compared with $E(\kappa) = 21$ and $\sigma = 4.867$. For $q = 1/12$, $\langle\kappa\rangle = 36.993$ while $E(\kappa) = 39$ and $\sigma = 12.000$.

TABLE 1

A summary of the three different cases of mutation that were considered in this work

Abbreviation	Mutation distribution of loci	Trait mutation distribution
EG	Equivalent, Gaussian	Nonleptokurtic
EL	Equivalent, leptokurtic	Leptokurtic
NG	Nonequivalent, Gaussian	Leptokurtic

The classic analyses of Crow and Kimura's model (Kimura 1965; Lande 1976; Turelli 1984) deal only with EG loci, while extended analyses by Fleming (1979) and Bürger (1998) treat EL loci to some extent, showing how mutational kurtosis enters, when small, as a correction to the approximations given in the earlier articles. Since substantial values of the kurtosis make analytical treatment difficult, we have solved the relevant equations numerically for all three cases.

We assume randomly mating populations, with discrete generations, and no sexual dimorphism. Furthermore, we follow all of the relevant articles cited above, by making the approximation of global linkage equilibrium (*cf.* Turelli and Barton 1990). Under these assumptions, the equilibrium genetic variance associated with the trait, V_G, can be determined by calculating the variance maintained at a single *haploid* locus, which, for locus i, we denote by $\hat{\sigma}^2_{y,i}$, and then summing over all loci:

$$V_G = 2\sum_{i=1}^{n}\hat{\sigma}^2_{y,i}. \tag{10}$$

The factor of 2 arises from diploidy.

If the average fitness of an individual with genotypic value G is given by $1 - sG^2$, we can find $\hat{\sigma}^2_{y,i}$ by solving the equation:

$$(sy_i^2 - s\sigma^2_{y,i} + \mu_i)\phi_i(y_i) = \mu_i\int f_i(y_i - x)\phi_i(x)\,dx \tag{11}$$

(Kimura 1965). This equation determines the equilibrium distribution of genetic values at locus i, $\phi_i(y_i)$, when y_i is defined so that $\hat{\sigma}^2_{y,i} = \int y^2\phi_i(y)\,dy$.

To allow a meaningful comparison of results for the three classes of mutant distribution, they were generated as follows. First we generated a sample of n mutational variances, $(v_1, v_2, \ldots, v_n)$ from the gamma distribution (Equation 8), where n is the number of loci. For all three classes of mutant distribution, we assumed, for simplicity, that the mutation rates at all loci were equal and the biases were all zero.

For the NG loci, the distribution of mutant *allelic* effects at locus i, namely $f_{NG,i}(x)$, was Gaussian, with a variance v_i (see Equation 3, with all b_i set to zero). As such, the overall (*i.e.*, trait) mutant distribution, $F_{NG}(x) = n^{-1}\Sigma_{i=1}^{n}(1/\sqrt{v_i})\,g(x/\sqrt{v_i})$, has a kurtosis that is given approximately by Equation 7, with $\kappa_0 = 3$.

For the EL loci, the distributions of allelic effects at each locus were constructed to be exactly equal to the overall (*i.e.*, trait) mutant distribution in the NG case. Thus, the distribution of mutant allelic effects at locus i is given by $f_{EL,i}(x) = F_{NG}(x)$ for all i. As such, the overall (*i.e.*, trait) mutant distributions in EL and NG cases are identical, $F_{NG}(x) = F_{EL}(x)$, although resulting from very different distributions at locus level.

For the EG loci, each locus had the same mutational variance, which was set equal to $\langle v\rangle = n^{-1}\Sigma_{i=1}^{n}v_i$, which is the sample mean of the n values of v_i. Note that because n is finite, $\langle v\rangle$ does not exactly coincide with the expected value of v_i, namely $\bar{v}$.

As a result of the way the distributions of mutations were determined, the amount of variation contributed by new mutations, V_M, was identical in all *three* cases and was given by $V_M = 2n\mu\langle v\rangle$.

Rather than present a full numerical investigation, we make our point with a series of examples. Since V_M is one of the most well-characterized parameters in quantitative genetics, we chose the other parameters such that V_M was set to the "typical level" of $V_M = 10^{-3}$, with the environmental variance set to unity throughout (Lynch 1988; Houle *et al.* 1996). To aid comparison with previous work, we set the strength of selection, s, to equal 0.025 (Turelli 1984) and took the expected value of mutational variance, $\bar{v}$, to equal 0.05. This last value, often used in theoretical work, stems from Lande's (1976) extrapolation from the data of Russell *et al.* (1963). Since $V_M = 2n\mu\langle v\rangle = 10^{-3}$, the value $\langle v\rangle \approx 0.05$ approximately requires $2n\mu = 0.02$ and this left us the choice of generating the required V_M through either an implausibly large number of loci or an implausibly high mutation rate. With this in mind, we examined two regimes, first $n = 2000$ and $\mu = 10^{-5}$, and second, $n = 200$ and $\mu = 10^{-4}$. See Turelli (1984) and Lynch and Walsh (1998, Chap. 12) for a full discussion of these and other parameter values.

The results given in Figure 2 involved drawing the v_i values from the distribution $P_{gamma}(v; q, \bar{v}/q)$ for the three values of the shape parameter q used in Figure 1 that encompass the range of experimentally observed kurtoses (Garcia-Dorado *et al.* 1999).

These results and all other combinations we tried suggest strongly that $V_G(NG) < V_G(EL) < V_G$ (EG), where $V_G(EG)$ denotes the genetic variance maintained by EG loci and likewise for the other cases. In the most extreme case considered, however, the result for equivalent leptokurtic loci, $V_G(EL)$, is only ~12% smaller than the value of $V_G(NG)$ that followed from nonequivalent loci (via the method presented in this work). Thus while there are differences in the genetic variances of "equivalent leptokurtic" and "nonequivalent Gaussian" loci, these are not particularly large. There does thus not seem to be a significant sensitivity of the genetic variance on the precise way mutational leptokurtosis is incorporated into the model.

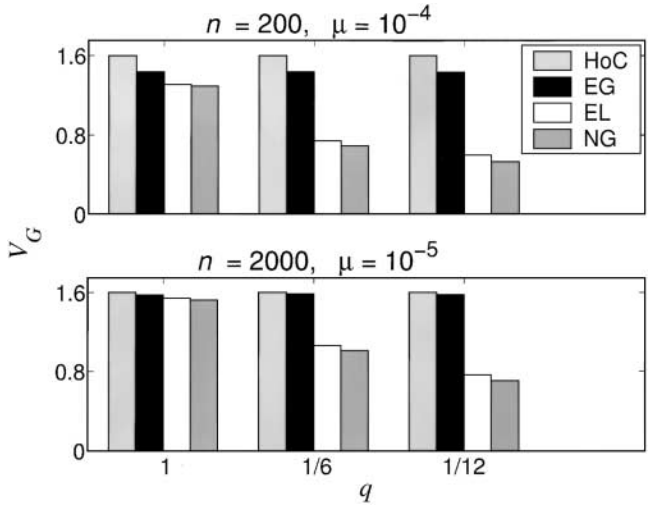

FIGURE 2.—The plot shows the level of genetic variance maintained by an infinite population (as explained in the text). For orientation, we have included (i) the level of genetic variance predicted by the house of cards approximation (light gray bar) and (ii–iv) plots for the genetic variance when (ii) loci are mutationally equivalent and have Gaussian distributions of mutant effects (solid bar), (iii) loci are mutationally equivalent and have leptokurtic distributions of mutant effects (open bar), and (iv) loci are mutationally nonequivalent and have Gaussian distributions of mutant effects (dark gray bar). As in Figure 1, we have drawn the mutational variances from a gamma distribution with three values of the shape parameter, q, namely $1/12$, $1/6$, and 1, thereby generating kurtoses of ~40, 20, and 6.

A useful benchmark result is the house of cards approximation (TURELLI 1984), which is closely related to a scheme of mutation introduced by KINGMAN (1978). This approximation applies to loci with $vs/\mu \gg 1$ and when applicable, yields a genetic variance of $2n\mu/s$. It works tolerably well for the EG loci in the regime where $n = 2000$ and $\mu = 10^{-4}$ and extremely well for the EG loci in the regime where $n = 2000$, $\mu = 10^{-5}$ (see Figure 2).

For both EL and NG loci, the genetic variance can, in some cases, be <50% of the genetic variance of EG loci and thus of the house of cards approximation. The reason for this is different in the two cases.

For EL loci BÜRGER (1998) proved that the house of cards approximation will always be an *over*estimate when the locus distributions are leptokurtic. We have demonstrated here that the correction can be substantial when the distributions are highly leptokurtic (but still within the empirically observed range of kurtoses).

For NG loci, Bürger's results do not apply, since at each locus, the distribution of mutant effects is itself Gaussian. There are, however, a range of mutational variances present in the loci controlling the trait, and the genetic variance is a sum over the genetic variances arising from loci with different mutational variances. Turelli's result applies well only to loci for which $v \geq 10\mu/s$. In this work, the expected proportion of loci lying *outside* the house of cards regime is $\int_0^{10\mu/s} P_{\text{gamma}}(v;\ q,\ \bar{v}/q)\,dv = 1 - \Gamma(q, 10\mu q/(s\bar{v}))/\Gamma(q)$, where $\Gamma(a, z) = \int_z^\infty t^{a-1}e^{-t}dt$ is the incomplete gamma function. When $10\mu q/(s\bar{v}) \ll 1$ this proportion is well approximated by $(1/(q\Gamma(q)))/(10\mu q/(s\bar{v}))^q$. As an example of the numbers that can be expected, we note that for $\mu = 10^{-5}$, $s = 0.025$, and $\bar{v} = 0.05$, the proportion of loci lying outside the house of cards regime is ~69% for $q = 1/12$, 52% for $q = 1/6$, and 8% for $q = 1$.

DISCUSSION

There is a tradition within quantitative genetic modeling of assuming that all loci can be treated as fully equivalent "average" loci. Although this may be adequate for many practical purposes, in some cases, it can have a significant effect on the results of the analyses (GIMELFARB 1986; HASTINGS and HOM 1990). A second approach, which avoids the assumption of equivalence, is to categorize loci as either "major" or "minor," *i.e.*, of having alleles with large or small phenotypic effect, and to treat each in a qualitatively different fashion (LANDE 1983). Here, we have presented a third strategy that treats major and minor loci in a unified fashion, as extremes of a continuum. We could call those loci with the highest c_i values major loci in our model, although due to continuity of $f_i(x)$, they are still capable of generating mutations with close to zero phenotypic effect. The existence of "isoalleles" at major loci offers empirical support for this (LYNCH and WALSH 1998, pp. 322–323). We have shown that the reduced set of free parameters needed for this model can be viewed as encapsulating the degree of nonequivalence of loci. Thus, by exposing the influence of these parameters we can make explicit the implications of nonequivalent loci.

With this model, we have shown that the observed kurtosis in the distribution of mutant effects can plausibly be attributed to variation in the mutational properties of the loci, rather than to leptokurtic distributions at each locus. Conversely, we suggest that the distributions at each locus [denoted here by $f_i(x)$], are likely to have lower kurtoses than that of the overall distribution, $F(x)$. Thus, to the extent that any biological prediction depends on high levels of kurtosis at locus level, that prediction would have to be revised in the direction of smaller effects from kurtosis. This conclusion does require that the assumptions leading to Equation 7 hold, at least roughly, and perhaps the most cautious conclusion is that knowledge of the distribution of mutations on the trait allows very little to be inferred about the distribution of mutant effects at individual loci.

We went on to examine the maintenance of genetic variance by mutation-selection balance, since the role of mutational kurtosis here has been controversial. Our findings show that, in large populations, substantial differences are possible. In particular, for values of muta-

tional kurtosis measured empirically, the reduction can be >50%. Furthermore, incorporating this kurtosis through nonequivalent loci, rather than at locus level, leads to a further reduction. However, our findings indicate that the differences between the results for "nonequivalent Gaussian" loci and "equivalent leptokurtic" loci are not large, typically ~10%.

In conclusion, although a substantial proportion of standing genetic variation may result from mutation-selection balance (Bürger and Lande 1994), our findings make it even more difficult to reconcile the results of simple models with the high heritabilities and strong selection observed in nature (see Turelli 1984). As such, our results make alternative explanations likely. Prominent candidates include the assertion that much of the observed stabilizing selection is merely "apparent," the result of deleterious pleiotropic effects of mutations affecting quantitative traits (see Barton 1990; Gavrilets and DeJong 1993; Nuzhdin *et al.* 1995), and the suggestion that population subdivision (*e.g.*, Goldstein and Holsinger 1992; Lythgoe 1997) or environmental change (Bürger 1999; Waxman and Peck 1999) may play an important role.

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APPENDIX

Here, we specialize to the case of nonbiased mutation, where all b_i are set to zero. We estimate the typical error incurred by using the v averaged distribution of mutations, $\bar{F}(x)$, in place of $F(x)$. We approach this by focusing on averaged deviations of moments. Let M_a denote the ath moment of x: $M_a = \int_{-\infty}^{\infty} x^a F(x)\,dx$ [with a

restricted to $a = 2, 3, 4, \ldots$ since the mean of $g(x)$ vanishing results in M_1 always being zero]. A straightforward calculation, using $F(x) = \Sigma_{i=1}^{n}(c_i/\sqrt{v_i})\,g(x/\sqrt{v_i})$, yields

$$\frac{\overline{(M_a - \overline{M}_a)^2}}{(\overline{M}_a)^2} = \frac{\overline{v^a} - (\overline{v^{a/2}})^2}{(\overline{v^{a/2}})^2} \sum_{i=1}^{n} c_i^2.$$

We have $c_i = 2\mu_i/U$ and $U = 2\Sigma_{i=1}^{n}\mu_i$ so $\Sigma_{i=1}^{n}c_i = 1$ and assuming mutation rates at the n loci do not have a large amount of variation, this indicates that a typical c_i is roughly $1/n$. Thus we have the estimate $\Sigma_{i=1}^{n}\, c_i^2 \sim n \times (1/n)^2 = 1/n$ so

$$\frac{\overline{(M_a - \overline{M}_a)^2}}{(\overline{M}_a)^2} \sim \frac{1}{n}\,\frac{\overline{v^a} - (\overline{v^{a/2}})^2}{(\overline{v^{a/2}})^2}$$

and this leads to the estimate

$$\int_{-\infty}^{\infty} x^a F(x)\,dx = M_a \sim \overline{M}_a \times \left(1 \pm \frac{1}{\sqrt{n}}\sqrt{\frac{\overline{v^a} - (\overline{v^{a/2}})^2}{(\overline{v^{a/2}})^2}}\right).$$

Thus the *fractional* error on M_a is controlled by the factor $1/\sqrt{n}$ and $F(x)$ can be thought of as self-averaging; its typical behavior is similar to that of its average over v and in Figure 1 we illustrate this. As an example, consider the variance of x. We have

$$M_2 \sim \overline{M}_2 \times \left(1 \pm \frac{1}{\sqrt{n}}\sqrt{\frac{\overline{v^2} - \overline{v}^2}{\overline{v}^2}}\right)$$

and the fractional error on the variance is of order $\mathrm{CV}(v)/\sqrt{n}$ with $\mathrm{CV}^2(v) = [\overline{v^2} - \overline{v}^2]/\overline{v}^2$. Higher moments are also controlled by the factor $1/\sqrt{n}$ but, as might be expected, these become noisier: The fractional error on M_a is of order $\mathrm{CV}(v^{a/2})/\sqrt{n}$ and $\mathrm{CV}(v^{a/2})$ generally grows with a.

APPENDIX B

Here, we show the general validity of the inequality $\kappa \geq \kappa_0$ that relates the kurtosis of the distribution of mutant trait effects, κ, and the kurtosis associated with the distribution of mutant effects at a single locus, $\kappa_0 = (\int y^4 g(y)\,dy)/(\int y^2 g(y)\,dy)^2$, when there is variation only in the mutational variances and no other parameters.

To prove the inequality for the distribution $F(x) = \Sigma_{i=1}^{n}(c_i/\sqrt{v_i})\,g(x/\sqrt{v_i})$, we note that it has a mean of zero [because $g(y)$ is even] and its second and fourth moments are $\int_{-\infty}^{\infty}x^2F(x)\,dx = \Sigma_{i=1}^{n}c_iv_i\int_{-\infty}^{\infty}y^2g(y)\,dy$, $\int_{-\infty}^{\infty}x^4F(x)\,dx = \Sigma_{i=1}^{n}c_iv_i^2\int_{-\infty}^{\infty}y^4g(y)\,dy$. Thus its kurtosis is

$$\kappa = \frac{\int_{-\infty}^{\infty}x^4F(x)\,dx}{\left(\int_{-\infty}^{\infty}x^2F(x)\,dx\right)^2} = \frac{\sum_{i=1}^{n}c_iv_i^2\int_{-\infty}^{\infty}y^4g(y)\,dy}{\left(\sum_{i=1}^{n}c_iv_i\int_{-\infty}^{\infty}y^2g(y)\,dy\right)^2} = \frac{\sum_{i=1}^{n}c_iv_i^2}{(\sum_{i=1}^{n}c_iv_i)^2}\kappa_0.$$

It follows that

$$\frac{\kappa}{\kappa_0} - 1 = \frac{\sum_{i=1}^{n}c_iv_i^2 - (\sum_{i=1}^{n}c_iv_i)^2}{(\sum_{i=1}^{n}c_iv_i)^2}$$

and the right-hand side of this equation is always nonnegative, hence generally, *i.e.*, with no approximation, $\kappa \geq \kappa_0$.