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Non-equivalent loci and mutation–selection balance

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Abstract

We consider the implications of mutationally non-equivalent loci for large populations of randomly mating diploid organisms under mutation–selection balance. Variation, across loci, of parameters such as the allelic mutational variance and the mutation rate, is shown to reduce the equilibrium genetic variance. This is proved to follow from the genetic variance contributed by a single locus having an underlying convexity. We give approximate results indicating the way small deviations of the mutational parameters, from their mean values, reduce the genetic variance. Numerical estimates of the size of the effect are given for more general variations of the parameters. Variation in the mutation rates has a significantly smaller effect than variation in the mutational variances. Under accepted parameter values, the reduction in genetic variance can be substantial.
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1. Introduction

A classic problem in population genetics is the maintenance of quantitative genetic variation under mutation–selection balance. This problem has received a great deal of attention in the literature, and a number of different models have been proposed. For reviews see e.g. Bulmer (1989), Bürger and Lande (1994) and Bürger (1998). An assumption shared by the majority of this work is that the loci controlling the trait are fully interchangeable—an assumption surely made for analytical convenience rather than biological accuracy. In previous work (Welch and Waxman, 2002), we investigated the consequences of relaxing this assumption. Using the continuum-of-alleles model of mutation introduced by Crow and Kimura (1964), we investigated the effects of allowing the distribution of mutant effects to vary between each locus controlling the trait. That paper included a numerical section on the maintenance of quantitative genetic variation. We showed that, for some parameter ranges, non-equivalent loci could substantially reduce the amount of genetic variation maintained at equilibrium.

Here, we extend this work by showing analytically that allowing the mutational properties of loci to vary is expected to reduce the equilibrium variance under most conditions. Furthermore, we extend the previous work by allowing not only the mutational variances but also the mutation rates to vary between loci. We note that variation in the mutation rates has a significantly smaller effect than variation in the mutational variances. As well as the continuum-of-alleles model used previously, we treat the discrete-allele stepwise mutation model introduced by Slatkin (1987). The comparison shows that our general conclusions are robust to this change of assumptions.

The model we consider describes an effectively infinite population of randomly mating dioecious sexual organisms, where the sexes do not exhibit any dimorphism. Individuals are characterised by a single phenotypic trait that is controlled by $2n$ alleles at n unlinked diploid loci. We assume additive genetics in which an individual's genotypic value, G, is given by $G = \sum_{j=1}^{n}(x_j + y_j)$, where x_j (y_j) is the effect of the maternally (paternally) originating allele at locus j. Thus at the level of the trait, there is no dominance or epistasis. Following Kimura (1965), we assume generations are overlapping, and hence time is continuous. We restrict our analysis to a description of equilibrium (see below). However, the conclusions we arrive at, also apply approximately to

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populations with discrete generations, when subject to weak selection. Fitness is determined entirely by stabilising selection on the trait. The fitness of individuals of genotypic value, G, is, following Kimura (1965), taken to have the form $-sG^2$ (which is defined up to an additive constant), where s is a positive parameter whose magnitude gives a measure of the intensity of selection and the optimal genotypic value has been taken to lie at $G=0$. This form of fitness function may, in discrete time models, be considered equivalent to nonoptimal selection (Haldane, 1954) when only small values of G^2 occur with any appreciable frequency.

Apart from the assumption of a quadratically declining fitness function, we also assume the population is in linkage and Hardy–Weinberg equilibrium. Many analyses of the full multilocus problem that incorporate linkage disequilibria have indicated that linkage equilibrium is a reasonable approximation (see e.g. Bulmer, 1989; Turelli and Barton, 1990). Under this assumption, the overall genetic variance can be determined by calculating the variance maintained at a single locus, and then summing over all loci. The equilibrium result is

$$\hat{V}_G = 2\sum_{j=1}^{n} \hat{\sigma}^2_{x,j}, \tag{1}$$

where $2\hat{\sigma}^2_{x,j}$ is the equilibrium genetic variance arising from locus j and the factor of 2 is due to diploidy.

It is, perhaps, necessary to emphasise that the conclusions we arrive at below, concerning the genetic variance, are based on unlinked loci in linkage equilibrium. We do not draw any conclusions about the genetic variance for linked loci, where linkage disequilibria may not be neglectable.

In what follows in the main text, we shall, for clarity, deal exclusively with Crow and Kimura's (1964) continuum-of-alleles model. Details of Slatkin's (1987) discrete-allele model are relegated to an appendix. It is shown there that the same general conclusions follow from both models.

Kimura (1965) (see also Bulmer, 1989) derived the equation describing the evolution of the distribution of effects of alleles of e.g. maternal origin, at locus j, assuming a continuum of alleles (Crow and Kimura, 1964). At equilibrium, we write this distribution as $\varphi_j(x_j)$ with an identical distribution for paternally originating alleles. Assuming x_j has been defined so it has a vanishing mean (as is completely adequate for considerations of genetic variance), it follows that $\hat{\sigma}^2_{x,j} = \int x_j^2 \varphi_j(x_j)\,\mathrm{d}x_j$. After averaging over the genetic background, made up of the remaining $2n-1$ alleles, it is found that $\varphi_j(x_j)$ obeys the one locus, haploid equation:

$$(sx_j^2+\mu_j)\varphi_j(x_j) - \mu_j \int f_j(x_j-y)\varphi_j(y)\,\mathrm{d}y = s\hat{\sigma}^2_{x,j}\varphi_j(x_j) \tag{2}$$

(Kimura, 1965). In this equation, $f_j(x_j-y)$ is the distribution of mutant allelic effects at locus j and the quantity μ_j is the allelic mutation rate at this locus. Note that we use the convention, both here, and in the following sections, that all integrations range from $-\infty$ to ∞ unless otherwise stated.

2. Introduction of non-equivalent loci

In general, mutationally non-equivalent loci have different rates of mutation, μ_j, and different distributions of mutant effects, $f_j(x)$. Empirically, little is known about the distributions of mutant effects, apart from the constraint that, as probability densities, they are non-negative and normalised to unity. They could, in principle, assume any number of plausible shapes. We follow the method introduced in Welch and Waxman, 2002, by assuming that the $f_j(x)$ at each locus can be derived by parameterising a "reference distribution" $g(x)$ which is a probability density with a variance of unity. Here we take $g(x)$ to be symmetric. The allelic mutation distribution at locus j follows from the reference distribution, $g(x)$, by the incorporation of a non-negative parameter v_j:

$$f_j(x) = \frac{1}{\sqrt{v_j}}\, g\left(\frac{x}{\sqrt{v_j}}\right). \tag{3}$$

The function $f_j(x)$ is normalised to unity, is symmetric (hence has a mean of zero), but has a variance of v_j. Non-equivalent loci are introduced into this model by allowing variation in the μ_j and v_j across loci. The results given below apply for a range of $g(x)$, including the Gaussian form adopted by Crow and Kimura (1964), i.e. $g(x) = (2\pi)^{-1/2}\exp(-x^2/2)$ which yields $f_j(x) = (2\pi v_j)^{-1/2}\exp(-x^2/(2v_j))$, although we shall not restrict ourselves to any one form of $g(x)$. It follows from Eq. (2) that the equilibrium genetic variance contributed by locus j depends on both the mutation rate, μ_j and the mutational variance, v_j, at that locus. To emphasise this dependence, we write $\hat{\sigma}^2_{x,j} = \hat{\sigma}^2_x(\mu_j, v_j)$.

Note that previously (Welch and Waxman, 2002), we also allowed the mean effect of mutations (mutational biases) to vary between loci. Since, if these biases are not large, this is expected to have little effect on the maintenance of genetic variance, we restrict ourselves here to mutations with a vanishing mean effect.

3. Genetic variance

To investigate the degree to which the non-equivalence of loci affects the level of genetic variance at mutation–selection balance, we examine the ratio $\hat{V}_G/\hat{V}_{G,0}$, where $\hat{V}_G$ is the equilibrium genetic variance

defined in Eq. (1) and $\hat{V}_{G,0}$ denotes the equilibrium genetic variance maintained when loci are equivalent—and every locus has a mutation rate equal to the mean mutation rate, μ_0, and a mutational variance equal to the mean mutational variance, v_0. These mean values are given by

$$\mu_0 = \frac{1}{n}\sum_{j=1}^{n}\mu_j, \quad v_0 = \frac{1}{n}\sum_{j=1}^{n} v_j. \tag{4}$$

The ratio of interest is, from Eq. (1),

$$\frac{\hat{V}_G}{\hat{V}_{G,0}} = \frac{\sum_{j=1}^{n} 2\hat{\sigma}_x^2(\mu_j, v_j)}{\sum_{j=1}^{n} 2\hat{\sigma}_x^2(\mu_0, v_0)} = \frac{1}{n}\sum_{j=1}^{n}\frac{\hat{\sigma}_x^2(\mu_j, v_j)}{\hat{\sigma}_x^2(\mu_0, v_0)}. \tag{5}$$

4. The consequence of non-equivalent loci

It may be observed that Eq. (5) has the form of an average of $\hat{\sigma}_x^2(\mu_j, v_j)/\hat{\sigma}_x^2(\mu_0, v_0)$ over all loci. The average is required only when there is variation in μ_j and v_j across loci. When any such variation is present, a very general property of $\hat{\sigma}_x^2(\mu, v)$ is exposed, namely an underlying convexity. In Appendix A, it is shown that we can write $\hat{\sigma}_x^2(\mu, v) = (\mu/s)h(sv/\mu)$, where the function $h(\zeta)$ is convex downwards, in the sense $d^2h(\zeta)/d\zeta^2 \leqslant 0$ and the net consequence of this, for the model under investigation, is that $\hat{V}_G/\hat{V}_{G,0}$ satisfies the inequality

$$\frac{\hat{V}_G}{\hat{V}_{G,0}} \leqslant 1. \tag{6}$$

Appendix A contains a proof of this. In Appendix B, we provide a similar analysis for the discrete-allele model with stepwise mutation. Thus, the variation of the mutational properties of loci results in a lowering of $\hat{V}_G/\hat{V}_{G,0}$ below its maximum value of unity. To understand more about this reduction, let us consider approximate results. An informative approach is the delta method (see e.g. Bulmer, 1967) which applies when the μ_j and v_j have only small deviations from their mean values. Since the delta method places no constraints on the value of the ratio sv_j/μ_j, the method covers the case $sv_j/\mu_j \gg 1$, where the House of Cards approximation holds (Turelli, 1984) and also the case $sv_j/\mu_j \ll 1$, where the Gaussian approximation holds (Kimura, 1965; Lande, 1976). A straightforward calculation, based on a Taylor expansion about the mean values of μ_j and v_j in Eq. (A.1), that appears in Appendix A, shows that to quadratic order in deviations,

$$\frac{\hat{V}_G}{\hat{V}_{G,0}} \simeq 1 - k\left[\frac{\mathrm{Var}(\mu)}{\mu_0^2} + \frac{\mathrm{Var}(v)}{v_0^2} - 2\frac{\mathrm{Cov}(\mu, v)}{\mu_0 v_0}\right]. \tag{7}$$

Here k is a positive constant that can be written in terms of the function $h(\zeta)$ that was introduced in Appendix A. It is given by $k = (sz_0)^2|h''(sz_0)|/[2h(sz_0)]$, where $z_0 = v_0/\mu_0$ and $h''(\zeta) = d^2h(\zeta)/d\zeta^2$.

The approximation in Eq. (7) explicitly shows that for μ_j and v_j that are uncorrelated and have only small deviations from their mean values, any variation in these parameters across loci generally reduces $\hat{V}_G/\hat{V}_{G,0}$. Negative correlations between μ_j and v_j further enhance the reduction in $\hat{V}_G/\hat{V}_{G,0}$, while positive correlations reduce the reduction. If such a correlation between the mutational variance contributed by a locus and its mutation rate does exist in nature, then we expect it to be negative. The rationale for this is that (i) negative correlations have often been invoked to reconcile estimates of the zygotic mutation rate of various quantitative characters with typical estimates of genic mutation rates at large-effect loci. Without negative correlations, the reconciliation would require extremely large numbers of loci affecting the trait (Turelli, 1984; Lynch and Walsh, 1998, Chapter 12); (ii) such a correlation has a very limited amount of empirical support (Mukai, 1964; Gregory, 1965). However, the evidence here is far from conclusive, and beyond the observation that a substantial positive correlation seems unlikely, little definite can be said (Lynch and Walsh, 1998, Chapter 12 contains a full discussion).

5. Origin of the reduction in genetic variance

The results above indicate that the genetic variance decreases when there is variation of μ_j and v_j across loci. The reasons for this are buried deep within the mathematics of Appendices A and B. We note, however, that the effect is *not* due to non-equivalent loci causing a reduction in the amount of variance *input* into the genetic variance by new mutations. To see this, note that the input of new mutations into the genetic variance, each generation, is

$$\begin{aligned} V_M &= \sum_{j=1}^{n} 2\mu_j v_j \\ &= 2n\mu_0 v_0 + 2n\frac{1}{n}\sum_{j=1}^{n}(\mu_j - \mu_0)(v_j - v_0) \\ &\equiv Uv_0 + 2n\,\mathrm{Cov}(\mu, v). \end{aligned} \tag{8}$$

Here $U = 2n\mu_0$ is the mutation rate for the trait across the genome. Thus, if there is no correlation between mutation rates and allelic mutational variances, non-equivalent loci yield $V_M = Uv_0$ which coincides with the result for equivalent loci, yet still there will generally be suppression of $\hat{V}_G$ relative to $\hat{V}_{G,0}$.

To try to gain an intuitive understanding of why the reduction is occurring, we consider the simple case of just two loci. Let us write the mutation rates at the two loci as $\mu_1 = \mu_0 + \Delta_\mu$ and $\mu_2 = \mu_0 - \Delta_\mu$ and the mutational variances as $v_1 = v_0 + \Delta_v$ and $v_2 = v_0 - \Delta_v$, so the average mutation rate of the two loci is μ_0 and the

average mutational variance is v_0. Using Eq. (1) we have

$$\hat{V}_G \equiv \hat{V}_G(\Delta_\mu, \Delta_v) = 2\hat{\sigma}_x^2(\mu_0 + \Delta_\mu, v_0 + \Delta_v) + 2\hat{\sigma}_x^2(\mu_0 - \Delta_\mu, v_0 - \Delta_v). \quad (9)$$

In the House of Cards regime, selection at a locus is much stronger than mutation at the locus and $\mu/(sv) \ll 1$ (Turelli, 1984). This leads, with a Gaussian or similarly shaped smooth unimodal distribution of mutant allelic effects, to

$$\hat{\sigma}_x^2(\mu, v) \simeq \frac{\mu}{s} - \frac{c}{v}\left(\frac{\mu}{s}\right)^2, \quad (10)$$

where c is a positive constant of order unity. For a Gaussian mutation distribution, it has been estimated that when $\mu/(sv) \ll 1$, $\hat{\sigma}_x^2(\mu, v) \simeq \frac{\mu}{s} - \frac{\pi}{2}\frac{1}{v}(\frac{\mu}{s})^2$ (Bürger and Hofbauer, 1994; Bürger, 2000, Eq. (1.15)), thus, c in Eq. (10) is $\pi/2$. More refined estimates can be derived, but for the illustrative requirements of this section, all we need is an approximation of the form in Eq. (10). Another example that shows that for small μ, $\hat{\sigma}_x^2(\mu, v)$ is of the form given in Eq. (10) follows if we anticipate some of the results presented below. For a particular smooth unimodal, but non-Gaussian distribution of mutations, an exact result for the variance can be derived (Waxman, 2003) and is given in Eq. (12). Direct expansion of this exact result in powers of μ quickly shows that up to and including terms of $O(\mu^2)$, the variance, $\hat{\sigma}_x^2(\mu, v)$, is given by Eq. (10) with $c = 2$.

Having established the region of validity of Eq. (10), we employ it in Eq. (9) to obtain

$$\frac{\hat{V}_G(\Delta_\mu, \Delta_v)}{\hat{V}_G(0,0)} \simeq 1 - c\frac{(\mu_0\Delta_v - v_0\Delta_\mu)^2}{(v_0^2 - \Delta_v^2)\mu_0^2(v_0 s/\mu_0 - c)}. \quad (11)$$

The right-hand side is smaller than unity since $v_0 \pm \Delta_v$ are variances and hence non-negative, so $v_0^2 - \Delta_v^2 > 0$ and $v_0 s/\mu_0$, by assumption of the House of Cards regime, is $\gg 1$ and hence much larger than c which is $O(1)$.

We can thus see, from Eq. (11), that there is a reduction of the genetic variance for non-equivalent loci, $\hat{V}_G(\Delta_\mu, \Delta_v)$, below the variance associated with equivalent loci, $\hat{V}_G(0,0)$. The reduction occurs because of the presence of a term proportional to μ^2/v in Eq. (10). This reduction would not occur if $\hat{\sigma}_x^2(\mu, v)$ were simply taken as μ/s. Thus in the House of Cards regime, the reduction in the genetic variance is directly attributable to terms in $\hat{\sigma}_x^2(\mu, v)$ lying beyond the leading term. We note that the higher order correction to μ/s, that lead to the reduction of the genetic variance in the House of Cards regime, are very small terms.

In the Gaussian regime, selection at a locus is much weaker than mutation at the locus and $sv/\mu \ll 1$ (Kimura, 1965; Lande, 1976). This leads to $\hat{\sigma}_x^2(\mu, v) \simeq \sqrt{\mu v/(2s)}$ and we employ this result in Eq. (9). Using basic properties of the square root, it can be shown that for either Δ_μ or Δ_v (or both) non-vanishing, Eq. (9) yields a reduction in the genetic variance below the result of equivalent loci.

In both cases considered, it is evident that intrinsic non-linearities in $\hat{\sigma}_x^2(\mu, v)$ result in a net decrease in the genetic variance when loci are non-equivalent. Thus, the increase in variance gained at one locus, by e.g. increasing μ is more than offset by the decrease in variance at the other locus, because of the compensating decrease in μ. Similar behaviour is also exhibited when the v's are changed.

6. Numerical estimates

In order to see some effects of the non-equivalence of loci, we have carried out a numerical investigation. Our aim is to illustrate the magnitude of the reduction in genetic variance that could be expected. We consider two special cases: (i) the case of equally mutable loci with different mutational variances (variation in the v's with the μ's held constant), and (ii) loci with equal mutational variances but different rates of mutation (variation in the μ's with the v's held constant). Though unrealistic, they provide a crude estimate of the minimum magnitude of the effect, since the more plausible case, joint variation, perhaps with negatively correlated values, should always lead to a greater reduction. In addition, this separation allows us to see the influence of the two parameters in isolation and prevents us from increasing the number of unwarranted assumptions.

Even with this simplification, there is a significant amount of flexibility associated with the estimates, since there are choices to be made for the distributions of the μ_j and v_j, the choice of the reference distribution, $g(x)$, as well as the specification of parameter values.

For the reference distribution, we have chosen the form shown in Fig. 1; this does not differ greatly from a Gaussian distribution in appearance, and corresponds to $g(x) = x/\sinh(\pi x/\sqrt{2})$; it has a mean of zero, a variance of 1 and a kurtosis of 4.

The virtue of this $g(x)$ is that, using Eq. (3), Eq. (2) can be solved exactly. The genetic variance following from this $g(x)$ differs little from that calculated with a Gaussian distribution (as used in most of the previous work on this subject) and leads to (Waxman, 2003)

$$\hat{\sigma}_x^2(\mu, v) = 2\mu s^{-1}[\sqrt{1 + 8\mu/(sv)} + 1]^{-1}. \quad (12)$$

For completeness, we state that the exact result, following from the choice $g(x) = x/\sinh(\pi x/\sqrt{2})$, that was derived in Waxman (2003). With $\beta = \frac{1}{2}(\sqrt{1 + \frac{8u}{sv}} - 1)$ and $\Gamma(\bullet)$ denoting Euler's Gamma function, the distribution of allelic effects of, e.g. maternal origin at a locus with mutation rate u and mutational variance

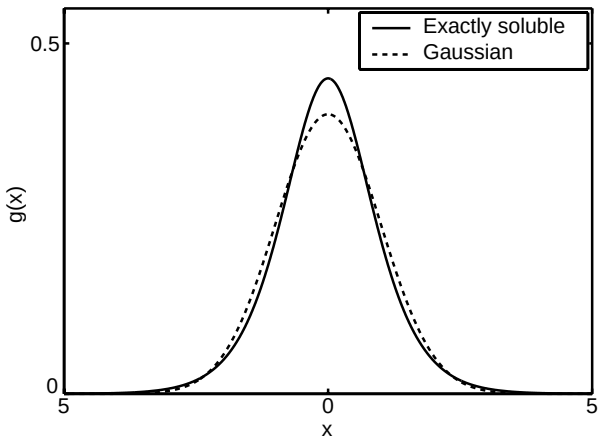

Fig. 1. A plot of the profile of the distribution of mutant effects, $g(x) = x/\sinh(\pi x/\sqrt{2})$, that was adopted for the numerical calculations of this work. This choice of $g(x)$ allows Eq. (2) to be solved exactly. As far as appearance and reasonableness are concerned, there is very little to distinguish between the form of the chosen $g(x)$ and the Gaussian distribution, $(2\pi)^{-1/2}\exp(-x^2/2)$. In the plot, the Gaussian distribution is plotted for comparison (dashed curve).

v is given by

$$\varphi(x) = (2^{\beta-3/2}/(\pi\sqrt{v}))|\Gamma(\beta/2 + ix/\sqrt{2v})|^2/\Gamma(\beta).$$

Note that the result of Eq. (12) fully interpolates between the Gaussian and House of Cards limits when sv/μ ranges from being very small to being very large.

Rather than choose a particular set of μ's and v's for our numerical estimates, we approximate the sum in Eq. (5) by an integral involving the probability density of μ and v: $P(\mu, v)$. This approximation differs from a typical value of the sum by a correction of order $1/\sqrt{n}$, where n is the number of loci. Using Eq. (12) in Eq. (5) and replacing the sum by an integral yields

$$\frac{\hat{V}_G}{\hat{V}_{G,0}} \simeq \int_0^\infty d\mu \int_0^\infty dv\, P(\mu, v)\frac{\mu}{\mu_0}\frac{\sqrt{1 + 8\mu_0/(sv_0)} + 1}{\sqrt{1 + 8\mu/(sv)} + 1}. \tag{13}$$

For the fixed parameters, we use accepted estimates that facilitate comparison with other work, and so take $s = 0.025$, $\mu_0 = 10^{-5}$ and $v_0 = 0.05$ (see e.g. Lande, 1976; Turelli, 1984). When varying the v's alone, we have $P(\mu, v) = \delta(\mu - \mu_0)P^*(v)$, where $\delta(\bullet)$ denotes a Dirac delta function and $P^*(v)$, is a univariate distribution. Equivalently, when varying the μ's, we take $P(\mu, v) = \delta(v - v_0)P^{**}(\mu)$ with $P^{**}(\mu)$ another univariate distribution. Although we are largely ignorant of the distribution of mutation rates in nature, empirical evidence suggests that the distribution of v's is L-shaped, with the majority of loci contributing a small amount to the mutational variance and a few loci contributing larger amounts (Falconer and Mackay, 1996; Bost et al., 1999). We have argued (Welch and Waxman, 2002) that a single-sided gamma distribution may be an appropriate choice. We thus take $P^*(v) = P_\Gamma(v; v_0, q)$, where

$$P_\Gamma(v; v_0, q) = \begin{cases} 0, & v < 0, \\ \dfrac{v^{q-1}\exp(-qv/v_0)}{\Gamma(q)(v_0/q)^q}, & v > 0 \end{cases} \tag{14}$$

is a single-sided gamma distribution with mean v_0 and shape parameter q such that the distribution is L-shaped for $q < 1$ and is roughly bell-shaped for $q > 1$.

Here, we use a single-sided gamma distribution to also characterise the μ's, thus we take $P^{**}(\mu) = P_\Gamma(\mu; \mu_0, q)$.

Fig. 2 shows curves for the proportional reduction in equilibrium genetic variance, i.e. $\hat{V}_G/\hat{V}_{G,0}$, for various values of the shape parameter q.

It is clear that varying the mutation rates has a significantly smaller effect than varying the mutational variances. For variable μ's, an extremely small q is needed to cause a significant reduction. By contrast, with variable v's, a sharp fall off in $\hat{V}_G/\hat{V}_{G,0}$ is seen to occur when $q < 0.2$. Given the empirical evidence for an L-shaped distribution of the mutational variances, this is likely to be the range of biological relevance. Given the magnitude of effects seen for variable μ's and v's alone, it is clear that joint variation could lead to a significant reduction.

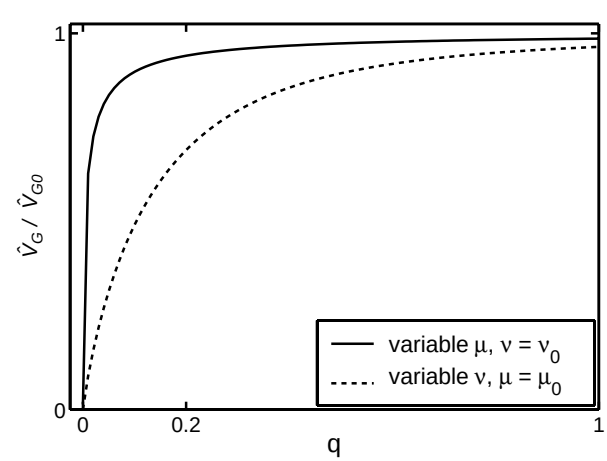

Fig. 2. Plots of the ratio $\hat{V}_G/\hat{V}_{G,0}$ are given as a function of the parameter q characterising the gamma distribution of non-equivalent loci, where $\hat{V}_G$ is the equilibrium genetic variance for non-equivalent loci and $\hat{V}_{G,0}$ the equilibrium genetic variance for equivalent loci. The upper plot corresponds to variation in the allelic mutation rates but no variation in the allelic mutational variances. The lower plot corresponds to variation in the allelic mutational variances but no variation in the allelic mutation rates. The figure shows the proportional reduction in the genetic variance maintained at mutation–selection balance. Both μ's and v's were drawn from a gamma distribution with the parameter q as in Eq. (14). Other parameters are given in the text. The plots utilise simplified forms of Eq. (13) given in Appendix C.

7. Summary and discussion

The majority of models that examine the maintenance of quantitative genetic variation through mutation–selection balance have assumed, either implicitly or as an analytical convenience, that all loci are mutationally equivalent. Here, we have shown that this assumption, while it may not affect the amount of variance contributed by new mutations, can have a significant effect on the amount of variance maintained at equilibrium. The variance is not increased and generally is decreased. We have based our calculations on the continuum-of-alleles model of mutation (Crow and Kimura, 1964) and the discrete-allele, stepwise mutation model of Slatkin (1987).

Our conclusions agree with, and strengthen, the findings of Turelli (1984), that the strong stabilising selection and high heritabilities observed in nature may be difficult to reconcile with simple mutation–selection balance models. We note that for a single locus, the House of Cards approximation always overestimates the true equilibrium variance in Kimura's model (Bürger, 1986; Bürger and Hofbauer, 1994). The present analysis shows that with multiple loci in linkage equilibrium, this overestimate may be much more severe than inferred from the single-locus result—if the mutational variances (and mutation rates) of the loci are sufficiently different.

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Appendix A

In this appendix, we prove that $\hat{V}_G/\hat{V}_{G,0} \leqslant 1$, where $\hat{V}_G$ ($\hat{V}_{G,0}$) is the equilibrium genetic variance for non-equivalent (equivalent) loci.

To proceed, let $\hat{\sigma}_x^2(\mu, v)$ be the equilibrium variance of allelic effects, of single parental origin, at a locus with mutation rate μ and mutational variance v. Note that $\hat{\sigma}_x^2(\mu, v)$ only depends on the parameters s, μ and v in the form $\hat{\sigma}_x^2(\mu, v) = (\mu/s)h(vs/\mu)$, where the function $h(\zeta)$ is convex downwards: $d^2h(\zeta)/d\zeta^2 \leqslant 0$. To prove this, substitute Eq. (3) into Eq. (2) and make the change of variables $x = \sqrt{v}X$, $y = \sqrt{v}Y$ and set $\varphi_j(x) = \psi(X)$. This yields the eigenvalue equation $\int L(X, Y)\psi(Y)\, dY = [s\hat{\sigma}_x^2(\mu, v)/\mu]\psi(X)$ where, with $\delta(\bullet)$ a Dirac delta function, $L(X, Y) = [(sv/\mu)X^2 + 1]\delta(X - Y) - g(X - Y)$ is a linear operator, $\psi(X)$ is an eigenfunction and $s\hat{\sigma}_x^2(\mu, v)/\mu$ the eigenvalue. On inspection, $L(X, Y)$ depends only on the combination of parameters sv/μ. Consequently, the eigenvalue $s\hat{\sigma}_x^2(\mu, v)/\mu$, can itself only depend on sv/μ. We thus write $s\hat{\sigma}_x^2(\mu, v)/\mu = h(sv/\mu)$ for an unknown function $h(\zeta)$ whose form depends on $g(X)$. A homogeneity relation equivalent to $s\hat{\sigma}_x^2(\mu, v)/\mu = h(sv/\mu)$ was conjectured by Bürger (1986).

Consideration of dynamics (results not shown) indicate that $h(sv/\mu)$ is the smallest eigenvalue of $L(X, Y)$ and furthermore $h(sv/\mu)$ must be <1, so $\psi(X)$ is normalisable. We make the assumption that $\psi(X)$ is square integrable over $(-\infty, \infty)$, and an example where this applies is when $g(X) \leqslant g_{max}$ for some $g_{max} < \infty$. We then observe (i) the operator $L(X, Y)$ is, up to an irrelevant Fourier transform, identical to the Hamiltonian operator of one dimensional non-relativistic quantum mechanics with a non-negative potential. Hence, (ii) its smallest eigenvalue $s\hat{\sigma}_x^2(\mu, v)/\mu = h(sv/\mu)$ is non-negative, it has a unique square integrable eigenfunction and the eigenvalue is guaranteed to lie in the discrete spectrum. (iii) The fact that $h(sv/\mu)$ is the smallest eigenvalue means that if we calculate its series expansion $h(\zeta + \varepsilon) = h(\zeta) + \varepsilon\, dh(\zeta)/d\zeta + (\varepsilon^2/2)\, d^2h(\zeta)/d\zeta^2 + \cdots$ via standard non-degenerate perturbation theory, with ε the strength of the perturbation, then we are guaranteed that the second-order term $(\varepsilon^2/2)\, d^2h(\zeta)/d\zeta^2$ is $\leqslant 0$, thus $h(\zeta)$ is convex. Proofs of (i)–(iii) can be found in textbooks on quantum theory (e.g. Merzbacher, 1970).

We can thus write Eq. (5) in terms of the convex function $h(\zeta)$ as

$$\frac{\hat{V}_G}{\hat{V}_{G,0}} = \frac{1}{n}\sum_{j=1}^{n} \frac{\mu_j h(sv_j/\mu_j)}{\mu_0 h(sv_0/\mu_0)}. \tag{A.1}$$

This takes the form of an average, where locus j occurs with weight $\omega_j = \mu_j/(n\mu_0)$. Since, $\mu_0 = \sum_{j=1}^{n} \mu_j/n$, it follows that $\sum_{j=1}^{n} \omega_j = 1$. Convexity of $h(\zeta)$ allows application of Jensen's inequality (Gradsteyn and Ryzhik, 1980) in the form $\sum_{j=1}^{n} \omega_j h(sv_j/\mu_j) \leqslant h(\sum_{j=1}^{n} \omega_j sv_j/\mu_j)$. Since $\sum_{j=1}^{n} \omega_j sv_j/\mu_j = sv_0/\mu_0$, we have $\sum_{j=1}^{n} \omega_j h(sv_j/\mu_j) \leqslant h(sv_0/\mu_0)$ and using this in Eq. (A.1) yields the inequality, $\hat{V}_G/\hat{V}_{G,0} \leqslant 1$.

Appendix B

In this appendix, we work within the discrete-allele, stepwise model of mutation (Slatkin, 1987) and prove that $\hat{V}_G/\hat{V}_{G,0} \leqslant 1$, where $\hat{V}_G$ ($\hat{V}_{G,0}$) is the equilibrium genetic variance for non-equivalent (equivalent) loci.

To proceed, note that the analogue of Eq. (2) for a locus with mutation rate μ is

$$s(k\Delta)^2 p(k) + \mu\{p(k) - \tfrac{1}{2}[p(k+1) + p(k-1)]\} = s\hat{\sigma}_x^2 p(k), \tag{B.1}$$

where alleles have effects $k \times \Delta$ with $k = 0, \pm 1, \pm 2, \ldots$, the quantity Δ is a parameter of the theory and $p(k)$ is the frequency of alleles at the locus of single parental origin, with effect $k \times \Delta$. The quantity $\hat{\sigma}_x^2 = \sum_{k=-\infty}^{\infty} (k\Delta)^2 p(k)$ is the equilibrium variance arising from alleles of single parental origin.

Note that $\hat{\sigma}_x^2$ depends only on parameters in the form $\hat{\sigma}_x^2 = (\mu/s)h(\Delta^2 s/\mu)$, where the function $h(\zeta)$ is convex downwards: $d^2h(\zeta)/d\zeta^2 \leqslant 0$. To prove the above we divide Eq. (B.1) by μ yielding

$$\sum_j L(k,j)p(j) = \frac{s\hat{\sigma}_x^2}{\mu} p(k), \tag{B.2}$$

where $L(k,j) = \frac{s(k\Delta)^2}{\mu}\delta_{k,j} + \{\delta_{k,j} - \frac{1}{2}[\delta_{k+1,j} + \delta_{k-1,j}]\}$ and $\delta_{j,k}$ is a Kronecker delta that is 1 for $j = k$ and zero otherwise. Eq. (B.2) takes the form of an eigenvalue equation where $L(k,j)$ is a linear operator, $p(k)$ the eigenvector and $s\hat{\sigma}_x^2/\mu$ the eigenvalue. On inspection, $L(k,j)$ depends only on parameters in the problem in the combination $s\Delta^2/\mu$, hence the eigenvalue, $s\hat{\sigma}_x^2/\mu$, can itself only depend on $s\hat{\sigma}_x^2/\mu$ and we write $s\hat{\sigma}_x^2/\mu = h(s\Delta^2/\mu)$ for an unknown function $h(\zeta)$.

Considerations of dynamics indicate that $h(s\Delta^2/\mu)$ is the smallest eigenvalue of $L(k,j)$.

Note that an alternative representation of $L(k,j)$ is as its discrete Fourier transform. With $i = \sqrt{-1}$,

$$\sum_{k,j} \exp[i(\alpha k - \beta j)]L(k,j) = \left\{-\frac{s\Delta^2}{\mu}\frac{\partial^2}{\partial\alpha^2} + [1 - \cos(\alpha)]\right\}\delta(\alpha - \beta)$$

and this coincides with the Hamiltonian operator of one-dimensional non-relativistic quantum mechanics with a non-negative potential and coordinate α restricted to the interval $[-\pi, \pi]$. Once this is appreciated, the arguments used in Appendix A yield convexity of $h(\zeta)$, i.e. $d^2h(\zeta)/d\zeta^2 \leqslant 0$. Eq. (5) takes the form $\hat{V}_G/\hat{V}_{G,0} = n^{-1}\sum_{j=1}^{n}(\mu_j h(s\Delta^2/\mu_j)/\mu_0 h(s\Delta^2/\mu_0))$ and arguments presented in Appendix A yield $\hat{V}_G/\hat{V}_{G,0} \leqslant 1$ for stepwise mutations.

Appendix C

The fact that either the mutation rates (μ's), or the mutational variances (v's) are held constant in Fig. 1 allows us to use simplified forms of Eq. (13). These both make use of the compound parameter, $r = 8\mu_0/(sv_0)$ and using the values adopted in the main text, $s = 0.025$, $\mu_0 = 10^{-5}$ and $v_0 = 0.05$ yields $r = 0.064$. When the v's are held constant, we have $\hat{V}_G/\hat{V}_{G,0} \simeq (\sqrt{1+r} + 1)[\Gamma(q+1)]^{-1}\int_0^\infty(\sqrt{1 + yr/q} + 1)^{-1}y^q e^{-y}\,dy$, and when the μ's are held constant, we have

$$\hat{V}_G/\hat{V}_{G,0} \simeq (\sqrt{1+r} + 1)[\Gamma(q)]^{-1} \times \int_0^\infty (\sqrt{y + qr} + \sqrt{y})^{-1} y^{q-1/2} e^{-y}\,dy.$$

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