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ORIGINAL ARTICLE

The relationship between the pleiotropic phenotypic effects of a mutation fixed by selection

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A pleiotropic model of mutation is presented that allows for correlations between the effects of a new mutation and for the distribution of mutational effects to vary from being leptokurtic to normally distributed. Using this model I quantify how selection transforms the correlation between the effects of a new (random) mutation into the correlation between the effects of a mutation that is fixed by selection and contributes to an adaptation. Results suggest that under most conditions the correlation between the effects of a fixed mutation is less than the correlation between the effects of a new mutation. I also generalize previous results that quantified the expected size of a fixed mutation's effect on a character given an observed effect of that mutation on another character. In agreement with previous results, work here suggests that as the observed effect becomes large and beneficial the expected effect on another character approaches the expected effect of a new (random) mutation given the observed effect. Lastly, these theoretical results are related to recent empirical work that found beneficial mutations had a positive correlation in their pleiotropic effects.
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Introduction

In a comparative context, an adaptation is caused, in part, by mutations that are unique to a population relative to an ancestral or coextant population. These unique mutations may either be segregating or fixed in the population with the adaptation. Fixed mutations that are unique to a population may be a major source of alleles in quantitative trait locus (QTL) studies that are found to cause phenotypic differences between study populations. Furthermore, fixed mutations that are unique to a population may often form the basis of phenotypic differences between species and families (Stern, 2000).

Pleiotropy occurs when a mutation affects several phenotypic characters simultaneously. Pleiotropy is important in the evolution of an adaptation because it causes the characters that make up an adaptation to evolve dependently. Pleiotropy is generally considered to be a universal feature of the genetic architecture of an organism (Wright, 1968) and recent work using *Escherichia coli* supports the presence of pleiotropic mutational effects (Ostrowski *et al*., 2005), although empirical work in developmental biology may suggest that the extent of pleiotropy can be mediated (e.g., Stern, 2000). Recently, theoretical population geneticists have readdressed models that explore the consequences of pleiotropy on the genetics of adaptation, often building on the foundation laid by Fisher (1930) by using his geometrical model or models conceptually related to it. For instance, Orr (1998a, 1999) presented theoretical results that suggest the distribution of the selective effects of fixed mutations that contribute to an adaptation is approximately exponentially distributed, and appears to be independent of the underlying distribution of new mutational effects. Orr (2000) and Welch and Waxman (2003) sought to understand the consequence of pleiotropy on rates of adaptive evolution, by looking at the change in average fitness of a population as mutations sequentially fix. Their results suggest that pleiotropy often decreases the rate of increase in fitness, but there are some interesting conditions presented by Welch and Waxman (2003) when it does not. Barton (2001) investigated the consequence of pleiotropy on hybrid breakdown and heterosis in which hybridizing populations have adapted to the same or different environments and the environments may or may not fluctuate. Interesting and complicated dynamics arise due to the fact that, for instance, when mutations act pleiotropically, a mutation that is beneficial and is fixed in an environment and deleterious in a second environment can be beneficial or deleterious in an intermediate environment of a hybrid population, depending on the contingent make-up of mutations in the hybrid population. Otto (2004) recently presented a result that gives the expected decrease in fitness of a fixed mutation that is caused by it acting pleiotropically (the so-called 'Two steps forward, one step back' principle), whereby pleiotropy reduces the mean selective effect of a mutation that is fixed by selection by one-third. Griswold and Whitlock (2003) quantified the fraction of mutations fixed by selection that are expected to have a deleterious pleiotropic effect

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on a particular character. Their results showed that even low amounts of pleiotropy lead to a large fraction of fixed mutations having deleterious effects on a character, which may help explain why QTL studies often find alleles with apparently deleterious effects (e.g., Rieseberg *et al*., 2003). Furthermore, because mutations with deleterious pleiotropic effects frequently fix, this compromises the power of tests for natural selection, such as Orr's (1998b) sign-test (Griswold and Whitlock, 2003). Additionally, Griswold and Whitlock (2003) showed that there is a greater bias against detecting mutations with deleterious pleiotropic effects versus beneficial effects in a QTL study, in part, because deleterious effects are, on average, smaller than mutations with beneficial pleiotropic effects.

Previous theoretical studies of the consequences of pleiotropy on properties of fixed mutations have focused on the overall selective effect of a fixed mutation or the effect of the mutation on one of the several characters affected by it (with exception to an analysis by Otto (2004), see below). In this paper, I am interested in determining the relationship between the additive pleiotropic effects of a mutation that was fixed by selection. Theoretical models of the relationship between the pleiotropic effects of fixed mutations may help the interpretation of empirical work that found a positive relationship between the pleiotropic effects of beneficial mutations in *E. coli* (Ostrowski *et al*., 2005).

There are two types of relationships that I intend to study. The first is the correlations between the pleiotropic effects of a fixed mutation. I am particularly interested in determining whether there are general properties relating the correlations between the effects of a mutation that was fixed by selection to the correlations between the effects of a new (random) mutation.

The second relationship is the expected size of an effect of a fixed mutation on a character given an observed effect of that mutation on another character. I am particularly interested in determining the expected size of the effect of a fixed mutation on one character given that same mutation has a large beneficial effect on another character. Fisher (1930) inferred that new mutations of large effect are likely to have large deleterious pleiotropic effects. Recently, Otto (2004) showed that with respect to mutations that are fixed by selection this holds true, in part. In Otto's (2004) model, mutations have an effect on a focal character and an additional pleiotropic effect where it is assumed that this pleiotropic effect is unconditionally deleterious. Otto (2004) found that as the beneficial effect of a fixed mutation on a character becomes increasingly large, its expected pleiotropic effect becomes increasingly deleterious, but asymptotically toward a fixed limit: the expected pleiotropic effect of a fixed mutation approaches the average pleiotropic effect of a new mutation. Thus, on average, there is a limit to the extent that the pleiotropic effects of fixed mutations become increasingly deleterious as effects on a focal character become increasingly beneficial. In this paper, I extend Otto's (2004) analysis by allowing the average effect of a mutation per character to vary from being deleterious to beneficial, for correlated mutational effects between characters and for varying levels of pleiotropy.

Methods

Two types of mutational models will be explored. The first model is the familiar multivariate-normal model and the second is a new model that allows for correlated effects on different characters as well as positive levels of kurtosis on each character. The property of positive kurtosis has been observed in experiments (Mackay *et al*., 1992; Lyman *et al*., 1996) and has been predicted theoretically (Welch and Waxman, 2002).

The two selective models include one in which all characters are undergoing directional selection and the second in which some characters are undergoing purifying selection. This last approach is similar to that taken by Keightley and Hill (1990), Kondrashov and Turelli (1992) and Otto (2004) in that the pleiotropic effects of mutations are assumed to be unconditionally deleterious.

Next, the mutation models will be presented for both the pure directional and purifying selection models. Following this, equations describing the univariate and the bivariate distribution of the effects of fixed mutations are presented. Then, the **F** matrix, defined as the variance–covariance matrix of the effects of a fixed mutation, and the correlation in the effects of a fixed mutation are presented. Lastly, analyses will be performed to determine how the different mutation models give rise to different **F** matrices and different correlations of the effects of a fixed mutation.

Multivariate normal mutation

For a mutation that affects n characters, its vector of phenotypic effects, $\delta = (\delta_1, \delta_2, \ldots, \delta_n)$, is drawn from a multivariate normal distribution with probability density function (Kalbfleisch, 1985),

$$f_{\mathbf{M}}(\vec{\delta}) = \frac{\exp\left(-\frac{1}{2}(\vec{\delta} - \vec{\mu})^{\mathrm{T}}\mathbf{M}^{-1}(\vec{\delta} - \vec{\mu})\right)}{\sqrt{(2\pi)^n|\mathbf{M}|}} \quad (1)$$

In Equation (1), $\vec{\mu} = (\mu_1, \mu_2, \ldots, \mu_n)$ is a vector of average effects of mutations, T symbolizes the transpose of a vector and $|\mathbf{M}|$ is the determinant of the variance–covariance matrix of mutational effects (**M**).

Leptokurtic mutation

The vector of mutational effects on phenotypic characters is $\delta = \vec{\mu} + t\vec{z}$, where t is a gamma distributed random deviate with an average effect of $\alpha\beta$ and coefficient of variation $1/\sqrt{\alpha}$, $\vec{\mu} = (\mu_1, \mu_2, \ldots, \mu_n)$ is a vector of average effects, and $\vec{z}$ is a vector of normally distributed deviates in which the average effect of each element is zero such that they come from the multivariate distribution with probability density function,

$$\frac{\exp\left(-\frac{1}{2}\vec{z}^{\mathrm{T}}\mathbf{Q}^{-1}\vec{z}\right)}{\sqrt{(2\pi)^n|\mathbf{Q}|}} \quad (2)$$

In Equation (2), **Q** represents the variance–covariance matrix of effects of the $\vec{z}$ deviates. Because each element in the vector $\vec{z}$ has a mean effect of zero, multiplying each by a common t does not change the correlations that are generated by the **Q**-matrix (see Appendix A). Note that t and elements of $\vec{z}$ are uncorrelated. In this paper, for simplicity, $\alpha\beta = 1.0$ in all

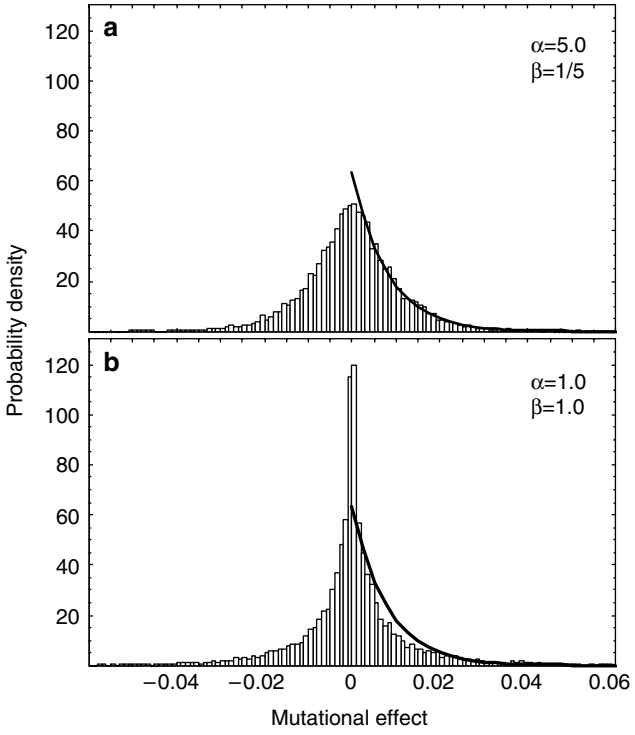

Figure 1 The distribution of effects of a new mutation on a character based on the leptokurtic model: (**a**) $\sigma^2 = 0.0001$, $\alpha = 5.0$ and $\beta = \frac{1}{5}$; and (**b**) $\sigma^2 = 0.0001$, $\alpha = 1.0$ and $\beta = 1.0$. In both cases, $\vec{\mu} = 0$. The solid line corresponds to one-half of a bilaterally symmetric exponential distribution. In both cases, the average magnitude of effects is 0.0079.

of the analyses. Let the function $f_{\mathbf{Q}}(\vec{\delta})$ be the distribution of leptokurtically distributed mutational effects.

In the leptokurtic mutation model, when $\alpha = 5.0$, such that the coefficient of variation of the distribution of gamma deviates is 0.447, the distribution of mutational effects is symmetric with nearly exponentially distributed magnitudes (Figure 1a). As the coefficient of variation of t grows larger, the distribution of mutational effects becomes more leptokurtic (Figure 1b), and as the coefficient of variation approaches zero, the distribution becomes normally distributed.

Unconditionally deleterious mutations

In the purifying selection model, the effects of mutations on some characters are unconditionally deleterious. In this paper, I subsume all of the unconditionally deleterious pleiotropic effects into one character and use the convention that this character be the last one out of n characters. Accordingly, the vector of mutational effects under the multivariate normal model of mutation is $\vec{\delta} = (\delta_1, \delta_2, \ldots, -|\delta_n|)$. In the multivariate normal case, the effects, δ_i, are drawn from Equation (1). In the leptokurtic case, $\delta_i = \mu_i + tz_i$ for $i = \{1, 2, \ldots, n\}$, and as in the pure directional selection case, t is a gamma distributed deviate, and z_i is a normally distributed deviate with a mean effect of zero coming from Equation (2). Let $f_{\mathbf{M}'}(\vec{\delta})$ represent the distribution of mutational effects based on the multivariate normal mutation model with unconditionally deleterious mutations, and let $f_{\mathbf{Q}'}(\vec{\delta})$ be the distribution of mutational effects based on the leptokurtic mutation model with unconditionally deleterious mutations.

Selection coefficients

From an evolutionary point-of-view, we assume that a population is experiencing directional selection on one or more phenotypic characters. Like the work of Orr (1998a, 1999), Griswold and Whitlock (2003) and Welch and Waxman (2003), we assume the rate of mutation is slow relative to the rate of fixation, such that mutations sequentially arise and fix. As such, there is no selective interference among mutations (Hill and Robertson, 1966). After each fixation, the fitness of a population is scaled to equal one and the heterozygous selection coefficient (s) of a new mutation is

$$s = \sum_{i=1}^{n} a_i \delta_i, \tag{3}$$

where a_i is a number that relates the phenotypic effect of a mutation on character i to fitness. This model of fitness assumes that there is linear directional selection on each character, for example, see Griswold and Whitlock (2003). By assuming linearity, nonlinear dominance effects are ignored in this model. Furthermore, by assuming that mutations sequentially fix, epistatic effects among segregating mutations are not considered in this model. Making the linearity assumption simplifies analysis, yet may miss important consequences of nonlinear effects such as dominance and epistasis.

Probability of fixation

The probability that a mutation with a selection coefficient of s fixes is $2s$ (Haldane, 1927; Crow and Kimura, 1970). This approximation assumes that only mutations that are beneficial overall fix, the effective size of the population is large and that selection is weak.

Distributions of fixed effects

Given that a mutation has occurred, the probability that it has an effect δ_i on character i and eventually fixes is

$$g_k(\delta_i) = \iint \cdots \int 2 \sum_{\ell=1}^{n} a_\ell \delta_\ell f_k(\vec{\delta}) \mathrm{d}\delta_1 \, \mathrm{d}\delta_2 \cdots \mathrm{d}\delta_{i-1} \, \mathrm{d}\delta_{i+1} \cdots \mathrm{d}\delta_n \tag{4}$$

where $k \in \{\mathbf{M}, \mathbf{Q}, \mathbf{M}', \mathbf{Q}'\}$, such that Equation (4) is general for the four combinations of mutation and selection models. The integral in Equation (4) is evaluated over all values of δ such that the condition

$$\sum_{\ell=1}^{n} a_\ell \delta_\ell > 0 \tag{5}$$

is satisfied, which ensures that the overall fitness effect of a mutation is beneficial. The distribution of fixed mutational effects on character i is

$$c_k(\delta_i) = g_k(\delta_i) / \int_{-\infty}^{\infty} g_k(\delta_i) \, \mathrm{d}\delta_i \tag{6}$$

Similarly, the joint probability that a new mutation fixes that has an effect δ_i on character i and an effect δ_j on character j is

$$g_k(\delta_i, \delta_j) = \iint \cdots \int 2 \sum_{\ell=1}^{n} a_\ell \delta_\ell f_k(\vec{\delta}) \mathrm{d}\delta_1 \, \mathrm{d}\delta_2 \cdots \mathrm{d}\delta_{i-1} \mathrm{d}\delta_{i+1} \cdots \mathrm{d}\delta_{j-1} \mathrm{d}\delta_{j+1} \cdots \mathrm{d}\delta_n \tag{7}$$

where again the integral is evaluated such that condition (5) is met. The joint distribution of the effects of a fixed mutation on characters i and j is

$$c_k(\delta_i, \delta_j) = g_k(\delta_i, \delta_j) / \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} g_k(\delta_i, \delta_j)\mathrm{d}\delta_i\mathrm{d}\delta_j \tag{8}$$

Variance–covariance matrix of fixed mutational effects (F-matrix)

The variance–covariance matrix of the effects of a fixed mutation ($\mathbf{F}_k$) based on the kth model is

$$\mathbf{F}_k = \begin{pmatrix} V_k^{\mathrm{f}}(\delta_1) & \mathrm{Cov}_k^{\mathrm{f}}(\delta_1,\delta_2) & \cdots & \mathrm{Cov}_k^{\mathrm{f}}(\delta_1,\delta_n) \\ \mathrm{Cov}_k^{\mathrm{f}}(\delta_2,\delta_1) & V_k^{\mathrm{f}}(\delta_2) & \cdots & \mathrm{Cov}_k^{\mathrm{f}}(\delta_2,\delta_n) \\ \vdots & \vdots & \ddots & \vdots \\ \mathrm{Cov}_k^{\mathrm{f}}(\delta_n,\delta_1) & \mathrm{Cov}_k^{\mathrm{f}}(\delta_n,\delta_2) & \cdots & V_k^{\mathrm{f}}(\delta_n) \end{pmatrix} \tag{9}$$

where $V_k^{\mathrm{f}}(\delta_i)$ is the variance in the sizes of the effects of a fixed mutation on the ith character, and $\mathrm{Cov}_k^{\mathrm{f}}(\delta_i,\delta_j)$ is the covariance between the sizes of the effects of a fixed mutation on characters i and j. The superscript f designates that the statistic is for the effects of a fixed mutation. In contrast to the **G** matrix, or additive-genetic variance covariance matrix, of quantitative genetics, the **F** matrix as defined here is based on the effects of fixed mutations, whereas the **G** matrix is based on the effects of segregating mutations, the frequencies the mutations segregate and levels of linkage disequilibrium.

Relationship between the correlations from the multivariate normal and leptokurtic mutation models

In this section I seek to derive equations that relate the correlation in the effects a fixed mutation from the multivariate normal model to the correlation from the leptokurtic mutation model under pure directional and purifying selection. The following analysis assumes that the average effect of a random mutation is neutral, that is $\vec{\mu} = \vec{0}$. The analysis begins by first defining the function $\Gamma(t)$ to be the gamma probability density function with shape parameter α and scale parameter β. Next I rewrite the probability density functions $f_\kappa(\vec{\delta})$ for $\kappa \in \{\mathbf{Q},\mathbf{Q}'\}$, the leptokurtic mutation models, in terms of $\Gamma(t)$ and $f_\varepsilon(\vec{\delta})$ for $\varepsilon \in \{\mathbf{M},\mathbf{M}'\}$, that is, the gamma distribution and the multivariate normal mutation models, such that $f_\kappa(\vec{\delta}) = \Gamma(t) f_\varepsilon(\vec{z})$. This form of the function $f_\kappa(\vec{\delta})$ is informative because it highlights the fact that t and $\vec{z}$ are independent. Substituting $\Gamma(t) f_\varepsilon(\vec{z})$ in Equation (7) for $f_\kappa(\vec{\delta})$ yields the equation

$$g_\kappa(\delta_i,\delta_j) = \iint\cdots\int 2\sum_{\ell=1}^{n} a_\ell t z_\ell \Gamma(t) f_\varepsilon(\vec{z}) \times \mathrm{d}z_1\mathrm{d}z_2\cdots\mathrm{d}z_{i-1}\mathrm{d}z_{i+1}\cdots\mathrm{d}z_{j-1}\mathrm{d}z_{j+1}\cdots\mathrm{d}z_n \tag{10}$$

which can be rewritten as

$$g_\kappa(\delta_i,\delta_j) = t\Gamma(t) g_\varepsilon(z_i,z_j). \tag{11}$$

In Equation (11) the leptokurtic joint probability of fixation has been rewritten as the product of two independent probability densities namely, $\Gamma(t)$, the gamma distribution, and $g_\varepsilon(z_i,z_j)$ the joint probability of fixation density function for the multivariate normal model under the assumption that $\vec{\mu} = \vec{0}$. The joint distribution of the effects of a fixed mutation for the leptokurtic model is then

$$c_\kappa(\delta_i,\delta_j) = t\Gamma(t) c_\varepsilon(z_i,z_j)/E(t) \tag{12}$$

where $E(t)$ is the expected value of t. Based on a similar procedure, Equation (6) can be rewritten as

$$c_\kappa(\delta_i) = t\Gamma(t) c_\varepsilon(z_i)/E(t). \tag{13}$$

Using the standard formula for covariance, the covariance between the effects of a fixed mutation for the leptokurtic models is

$$\mathrm{Cov}_\kappa^{\mathrm{f}}(\delta_i,\delta_j) = E_\kappa^{\mathrm{f}}(\delta_i\delta_j) - E_\kappa^{\mathrm{f}}(\delta_i)E_\kappa^{\mathrm{f}}(\delta_j) \tag{14}$$

Given the relationships given in Equations (12) and (13), Equation (14) can be rewritten as

$$\mathrm{Cov}_\kappa^{\mathrm{f}}(\delta_i,\delta_j) = E_\kappa^{\mathrm{f}}(t^2 z_i z_j) - E_\kappa^{\mathrm{f}}(tz_i)E_\kappa^{\mathrm{f}}(tz_j) \tag{15a}$$

$$= E(t^3)E_\varepsilon^{\mathrm{f}}(z_i z_j) - E(t^2)E_\varepsilon^{\mathrm{f}}(z_i)E(t^2)E_\varepsilon^{\mathrm{f}}(z_j) \tag{15b}$$

$$= \beta^2(1+\alpha)(2+\alpha)E_\varepsilon^{\mathrm{f}}(z_i z_j) - \beta^2(1+\alpha)^2 E_\varepsilon^{\mathrm{f}}(z_i)E_\varepsilon^{\mathrm{f}}(z_j) \tag{15c}$$

and the variance in a fixed effect is given by

$$V_\kappa^{\mathrm{f}}(\delta_i) = \beta^2(1+\alpha)(2+\alpha)E_\varepsilon^{\mathrm{f}}(z_i^2) - \beta^2(1+\alpha)^2 E_\varepsilon^{\mathrm{f}}(z_i)^2. \tag{16}$$

Letting $\delta'_i = z_i$ and $\delta'_i = z_j$ to denote effects from the multivariate normal model, the correlation in the effects of a fixed mutation for the leptokurtic model is

$$\rho_\kappa^{\mathrm{f}}(\delta_i,\delta_j) = \frac{(2+\alpha)E_\varepsilon^{\mathrm{f}}(\delta'_i\delta'_j) - (1+\alpha)E_\varepsilon^{\mathrm{f}}(\delta'_i)E_\varepsilon^{\mathrm{f}}(\delta'_j)}{\sqrt{(2+\alpha)E_\varepsilon^{\mathrm{f}}(\delta'^2_i) - (1+\alpha)E_\varepsilon^{\mathrm{f}}(\delta'_i)^2}\sqrt{(2+\alpha)E_\varepsilon^{\mathrm{f}}(\delta'^2_j) - (1+\alpha)E_\varepsilon^{\mathrm{f}}(\delta'_j)^2}} \tag{17}$$

As argued in Appendix B and as numerical analyses suggests, for a wide range of parameters values, $\rho_{\mathbf{Q}}^{\mathrm{f}}(\delta_i,\delta_j) \geqslant \rho_{\mathbf{M}}^{\mathrm{f}}(\delta'_i\delta'_j)$ and $\rho_{\mathbf{Q}'}^{\mathrm{f}}(\delta_i,\delta_j) \geqslant \rho_{\mathbf{M}'}^{\mathrm{f}}(\delta'_i\delta'_j)$. That is, the correlation between the effects of a fixed mutation when new mutations are more leptokurtically distributed is greater than or equal to the correlation between the effects of a fixed mutation when new mutations are normally distributed, assuming that the correlation between the effects of a new mutation are the same. (Appendix B gives the mathematical conditions for which this claim is true.) Furthermore, it can be shown that $\lim_{\alpha\to\infty}\rho_{\mathbf{Q}}^{\mathrm{f}}(\delta_i,\delta_j) = \rho_{\mathbf{M}}^{\mathrm{f}}(\delta'_i,\delta'_j)$ and $\lim_{\alpha\to\infty}\rho_{\mathbf{Q}'}^{\mathrm{f}}(\delta_i,\delta_j) = \rho_{\mathbf{M}'}^{\mathrm{f}}(\delta'_i,\delta'_j)$, as is expected since the leptokurtic mutational distributions become approximately normally distributed as $\alpha\to\infty$.

For $\vec{\mu} \neq \vec{0}$, I was not able to prove that the correlations between effects of fixed mutations from the leptokurtic model are always greater than or equal to correlations from the multivariate-normal model. Thus far (see results), numerical analyses suggest leptokurtic correlations are greater than multivariate-normal correlations.

Analysis and results

In the following analysis positive effects of mutations are beneficial and negative effects are deleterious. For $n = 2$,

equations were evaluated numerically in Mathematica v.4.1, in which the default numerical integration function was used. For $n>2$, Monte Carlo integration was used and the program was written in C following the approach of Press *et al*. (1992, p 305).

Correlations between the effects of a new beneficial mutation

In Figure 2a, the effects of mutations that pleiotropically affect two characters that may arise randomly over the history of a population are plotted according to the multivariate normal model. In this example, the effects of a new mutation are uncorrelated and have equal variances. In the pure directional selection model, for a mutation to be beneficial and fix, the condition given by Equation (5) must be met. For $n=2$, this condition is represented by a line in which mutations above and to the right of the line are beneficial with respect to fitness (the gray line in Figure 2a). If mutations that are deleterious overall are separated from mutations that are beneficial overall, and the axis of the principal components of the effects of mutations that are beneficial overall are drawn, the major axis of variation of the effects of beneficial mutations (solid-dark line in Figure 2a) is parallel to the line satisfying the condition

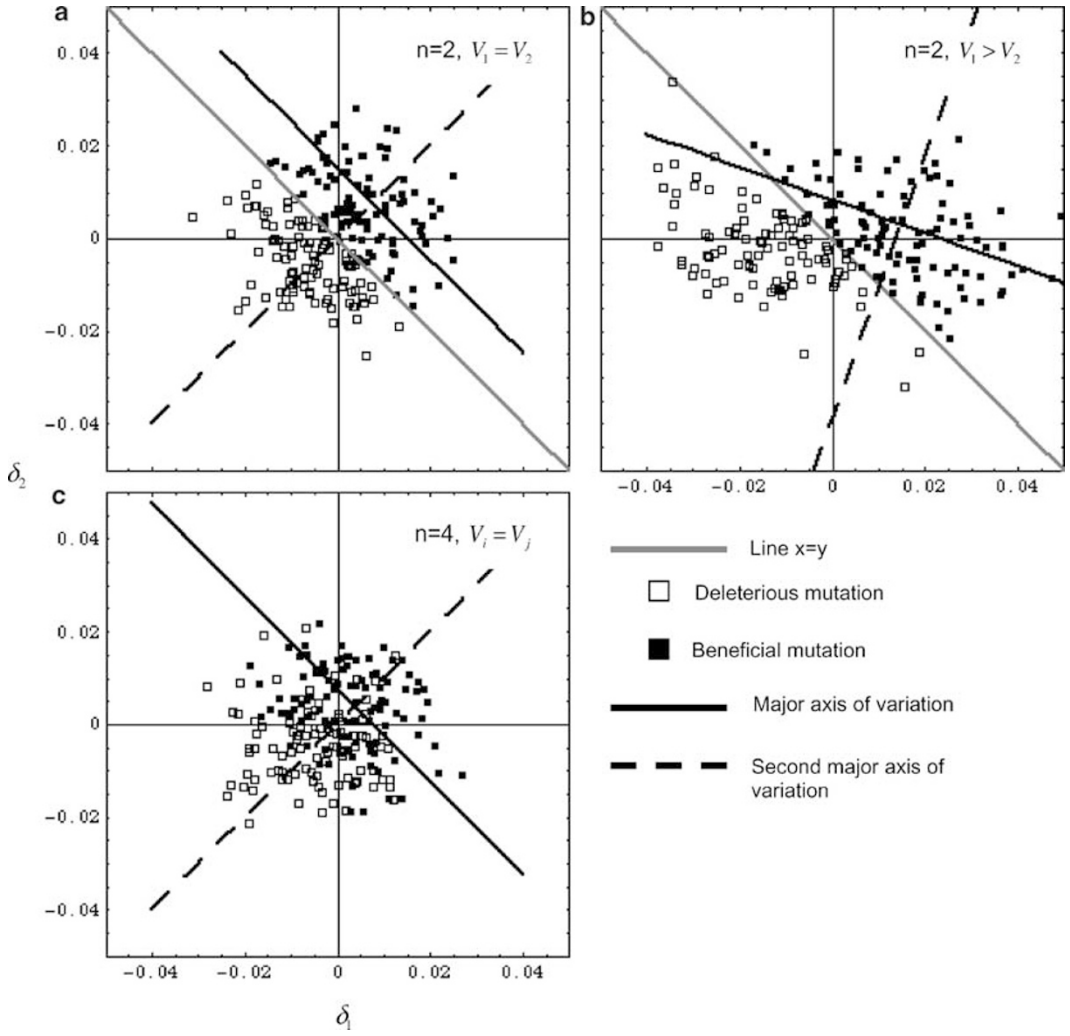

Figure 2 (**a**) The effects of mutations on two characters under the multivariate normal mutation model in which $\sigma^2=0.0001$ for both characters and the effects of new mutations are uncorrelated (open and closed boxes). The gray line separates mutations that are beneficial overall (closed boxes) from deleterious mutations (open boxes) when $\vec{a}=(1,1)$. The axis along which the major principal component of variation of beneficial mutations lies is parallel to the line $\delta_2=-\delta_1$ (solid line). The second major principal component lies along an axis that is perpendicular to the first principal component (dashed line). The average correlation between the effects of a beneficial mutation is about -0.46. (**b**) The effects of mutations on two characters under the multivariate normal mutation model in which $\sigma_1^2=0.0004$ and $\sigma_2^2=0.0001$ and the effects of new mutations are uncorrelated (open and closed boxes). As in (**a**), the gray line separates beneficial mutations (closed boxes) from deleterious mutations (open boxes) when $\vec{a}=(1,1)$. The solid line gives the axis of the major principal component of variation of beneficial mutations and the dashed line gives the axis of the second major principal component. The average correlation between the effects of a beneficial mutation is about -0.38. (**c**) The effects of mutations on two characters is plotted when mutation pleiotropically affects four characters. The effects of new mutations are multivariate-normal, uncorrelated and all mutational variances are 0.0001. Effects from mutations that are beneficial overall are given by closed boxes, and effects from mutations that are deleterious overall are given by open boxes. The solid line gives the axis of the major principal component of variation of the effects of beneficial mutations and the dashed line gives the axis of the second major principal component. The average correlation between the effects of a beneficial mutation is about -0.19.

$\sum_{i=1}^{2}\alpha_i\delta_i = 0$. Accordingly, the correlation in the effects of a beneficial mutation is negative, even though the correlation between the effects of new mutations is zero.

When the variances in the effects of new mutations are unequal and there are no covariances, the major axis of variation of the effects of beneficial mutations is rotated away from the line satisfying the condition $\sum_{i=1}^{2}\alpha_i\delta_i = 0$ toward the axis with the larger mutational variance (Figure 2b). Accordingly, the expected magnitude of the correlation between the effects of a beneficial mutation is less than when variances in the effects of new mutations are equal, but it is still negative. When mutations pleiotropically affect four characters, mutations that are beneficial overall satisfy the condition, $\sum_{i=1}^{4}\alpha_i\delta_i > 0$. Here, the effects of beneficial mutations on two of the four characters are negatively correlated (Figure 2c), but the correlation is weaker because there is less dependence of fitness on these two characters.

The correlation between the effects of a fixed mutation: pure directional selection

For characters that are undergoing directional selection, numerical results indicate that the correlation between the effects of a fixed mutation is less than or equal to the correlation between the effects of a new mutation (Tables 1 and 2). Consequently, even when the correlation between the effects of a new mutation is zero, the

Table 1 The correlation between the effects of a mutation fixed by selection (fixed mutation correlation) versus the correlation between the effects of a random mutation (mutation correlation)[a]

Mutation correlation	*Fixed mutation correlation*					
	n = 2			n = 3[b]		
	Normal	*Lepto*[c]*: α = 5*	*Lepto: α = 1*	*Normal*	*Lepto: α = 5*	*Lepto: α = 1*
−0.96	−0.98	−0.97	−0.96	−0.96	−0.96	−0.96
−0.80	−0.91	−0.86	−0.81	−0.83	−0.82	−0.81
−0.66	−0.84	−0.76	−0.67	−0.73	−0.71	−0.67
−0.47	−0.73	−0.62	−0.49	−0.60	−0.55	−0.48
−0.25	−0.59	−0.43	−0.27	−0.44	−0.36	−0.27
0.0	−0.40	−0.21	−0.02	−0.24	−0.13	−0.02
0.25	−0.17	0.04	0.23	−0.01	0.11	0.24
0.47	0.09	0.29	0.45	0.23	0.35	0.46
0.66	0.35	0.52	0.64	0.47	0.57	0.65
0.80	0.59	0.71	0.79	0.67	0.74	0.80
0.96	0.91	0.94	0.96	0.93	0.95	0.96

In the table, fixed mutation and random mutation correlations are between characters one and two.
[a]All variances in the **M** and **Q** matrices are equal to 0.0001, $\vec{\mu} = \vec{0}$, and all selection strength parameters are equal to 1.0. All characters are experiencing directional selection.
[b]Random mutational effects between characters one and three and two and three are uncorrelated, on average.
[c]In the leptokurtic model $\alpha\beta = 1.0$.

Table 2 The correlation between the effects of a mutation fixed by selection (fixed mutation correlation) versus the correlation between the effects of a random mutation (mutation correlation)[a]

Mutation correlation	*Fixed mutation correlation*					
	$\rho_{13} = \rho_{23} = 0.2$			$\rho_{13} = \rho_{23} = -0.4$		
	Normal	*Lepto*[b]*: α = 5*	*Lepto: α = 1*	*Normal*	*Lepto: α = 5*	*Lepto: α = 1*
−0.50	−0.67	−0.60	−0.52	−0.52	−0.52	−0.50
−0.25	−0.49	−0.39	−0.27	−0.36	−0.32	−0.26
0.0	−0.28	−0.15	−0.02	−0.17	−0.10	−0.01
0.25	−0.04	0.10	0.23	0.04	0.13	0.24
0.50	0.24	0.37	0.49	0.30	0.39	0.49
	$\rho_{13} = 0.2$, $\rho_{23} = -0.4$			$\rho_{13} = 0.4$, $\rho_{23} = -0.2$		
−0.50	−0.58	−0.55	−0.51	−0.64	−0.58	−0.51
−0.25	−0.41	−0.34	−0.26	−0.46	−0.37	−0.27
0.0	−0.20	−0.11	−0.01	−0.25	−0.13	−0.02
0.25	0.03	0.13	0.24	−0.01	0.12	0.24
0.50	0.31	0.40	0.49	0.28	0.39	0.49

Here $n = 3$ and fixed mutation and random mutation correlations are between characters one and two. Subsection headings give the random mutation correlations between characters one and three and two and three.
[a]All variances in the **M** and **Q** matrices are equal to 0.0001, $\vec{\mu} = \vec{0}$, and all selection strength parameters are equal to 1.0. All characters are experiencing directional selection.
[b]In the leptokurtic model $\alpha\beta = 1.0$.

correlation between the effects of a fixed mutation can be substantially negative. When the distribution of the effects of new mutations is extremely leptokurtic ($\alpha = 1$), the correlation between the effects of a fixed mutation is nearly equal to the correlation between the effects of a new mutation. For $n = 2$, the correlation between the effects of a fixed mutation does not become positive until the correlation between the effects of new mutations is about 0.25 in the leptokurtic case with parameters $\alpha = 5.0$ and $\beta = 1/5$ and about 0.45 in the multivariate normal case (Table 1).

Next, I evaluate the consequences of having two characters pleiotropically linked to an additional character (Table 1, $n = 3$). When two characters are pleiotropically linked to a third character (which may be considered to be a combined effect of several other characters), but the correlations between the effects of a new mutation on the two characters with the third are zero, the correlation between the effects of a fixed mutation on the first two characters is closer to, but still less than, the correlation between the effects of a new mutation for the first two characters.

Furthermore, if two characters are pleiotropically linked to a third, and new mutations have correlated effects between the first two characters and the third, numerical results suggest that the correlation between the effects of a fixed mutation on the first two characters will be less than the correlation between the effects of a new mutation on these two characters (Table 2). In the upper left section of Table 2, new mutations have equal and positively correlated effects between the two characters and the third character, and numerical results suggest that under these conditions, the fixed mutation correlation is still less than the new mutation correlation. In the upper right section of Table 2, the correlations between the effects of new mutations on the two characters and the third character are negative and of the same magnitude, and again numerical results suggest that under these conditions, the fixed mutation correlation is still less than the new mutation correlation. The last two sections of Table 2 provide cases when new mutations are such that one of the first two characters is positively correlated with the third and the other character is negatively correlated. Numerical results suggest that whether magnitude of the negative correlation is greater or less than the positive correlation, the correlation between the effects of a fixed mutation on the first two characters is less than the correlation between the effects of a new mutation on these two characters. Only small to moderate correlations between the effects of new mutations on the first two characters were numerically analyzed because of the restriction on the variance–covariance matrix to have a positive determinant. Individual cases were numerically analyzed when the magnitude of correlations between the effects of new mutations on the first two characters were greater than 0.50 and these two characters also had correlated effects with the third. All of these results suggest that the correlation between the effects of a fixed mutation was less than the correlation between the effects of a new mutation.

The correlation between the effects of a fixed mutation: with purifying selection

In the presence of purifying selection and unless the mutational distribution is extremely leptokurtic, numerical results suggest that the correlation between the effects of a fixed mutation is less than the correlation between the effects of a new mutation (Table 3). This appears to be true even if the strength of purifying selection on the deleterious pleiotropic effects is stronger than the characters under directional selection. For instance, if $\alpha_3 = 10.0$ for the character under purifying selection, the correlation between the effects of a fixed mutation in the multivariate normal model increases slightly to -0.39 from -0.43 in the absence of purifying selection. When the distribution of new mutational effects is leptokurtic such that $\alpha = 5.0$ and $\beta = 1/5$, the increase is to -0.10 from -0.17. When the distribution is

Table 3 The correlation between the effects of a mutation fixed by selection (fixed mutation correlation) versus the correlation between the effects of a random mutation (mutation correlation)[a]

Mutation correlation	*Fixed mutation correlation*				
	$\mu_i = 0$: $i \in \{1,2\}$			$\mu_i = -0.001$: $i \in \{1,2\}$	$\mu_i = -0.01$: $i \in \{1,2\}$
	Normal	*Lepto*[b]: $\alpha = 5$	*Lepto:* $\alpha = 1$	*Normal*	*Normal*
−0.96	−0.98	−0.97	−0.95	−0.99	−0.99
−0.80	−0.91	−0.85	−0.76	−0.93	−0.97
−0.66	−0.85	−0.74	−0.61	−0.86	−0.93
−0.47	−0.75	−0.59	−0.41	−0.76	−0.87
−0.25	−0.61	−0.40	−0.19	−0.63	−0.77
0.0	−0.43	−0.17	0.06	−0.47	−0.62
0.25	−0.19	0.09	0.31	−0.22	−0.41
0.47	0.06	0.33	0.51	0.05	−0.15
0.66	0.33	0.55	0.69	0.34	0.14
0.80	0.57	0.73	0.82	0.56	0.41
0.96	0.90	0.94	0.96	0.90	0.89

Here $n = 3$ and the third character is experiencing purifying selection such that all mutations are deleterious for this character. Subsection headings give the average mutational effect on characters one and two, such that in the last two columns, mutations are on average deleterious for these characters. Fixed mutation and random mutation correlations are for characters one and two.

[a]All variances in the **M** and **Q** matrices are equal to 0.0001 and all selection strength parameters are equal to 1.0. Characters one and two are experiencing directional selection.

[b]In the leptokurtic model $\alpha\beta = 1.0$.

extremely leptokurtic such that $\alpha = 1.0$ and $\beta = 1.0$, the increase is to 0.13 from 0.06; here the correlation between the effects of a fixed mutation is greater than the correlation between the effects of a new mutation, which is zero.

Furthermore, when the effects of mutations on the characters undergoing directional selection are deleterious, on average, and other character(s) are experiencing purifying selection, the correlation between the effects of a fixed mutation on the characters undergoing directional selection is still less than the correlation for new mutations (Table 3, two right-side columns). In fact, the correlations are less than the new mutation correlations to an even greater extent than if mutations were neutral, on average, for the characters under directional selection. As was noted before, if the strength of selection on the character(s) undergoing purifying selection is increased, then the correlation between the effects of a fixed mutation on characters undergoing directional selection increases; for instance, when $a_3 = 10.0$ and $\mu_i = -0.01$ for i equal to one and two, the correlation between the effects of a fixed mutation is -0.57 for the multivariate normal model (assuming a mutational correlation of zero).

Conditional expectations of joint mutational effects

When the correlations between the effects of a new mutation are less than or equal to zero, numerical analysis suggests that selection induces a negative relationship between the expected size of the effect of a fixed mutation on one character given an observed effect on another character (Figure 3a–b, solid, dashed and dash-dotted curves). If the correlations between the effects of a new mutation are positive, numerical analysis suggests that the relationship between the sizes of the effects of a fixed mutation can still be negative, although it becomes positive for large and positive mutational effects on the observed character (Figure 3a–b, dotted curves). When there is a mixture of positive and negative correlations between characters affected by new mutation, for characters that are positively correlated, numerical results suggests that the relationship between the size of a fixed effect on one of the characters given an effect on the other is at first negative and then becomes positive (Figure 3c, solid line). When there is a mixture of positive and negative mutational correlations, characters that are negatively correlated are expected to have a negative relationship between the effects of fixed mutations (Figure 3c, dashed line).

Although not explicitly shown in Figure 3, numerical results also suggest that in all cases as the magnitude of a fixed mutational effect on a particular character becomes increasing large and beneficial, the expected size of an effect on a second character approaches the expected size of a random mutation given the effect on the first character. This analysis involved conditioning on beneficial effects greater than the maximum in Figure 3 of 0.05 and measuring the expected effect on a second character. In each case, the expected effect approached the expected effect of a random mutation given the size of the beneficial effect.

Discussion

The results of this paper suggest that selection causes the correlation in the effects of a fixed mutation to be less than the correlation in the effects of a new mutation, unless the distribution of new mutational effects is extremely leptokurtic. The consequence of this is that even when the effects of new mutations are uncorrelated between two characters, the correlation in the effects of a fixed mutation is expected to be negative. Furthermore, the correlation between the effects of a fixed mutation often remains negative even when the correlation between the effects of a new mutation is strongly positive. The reason the correlation between the effects of a fixed mutation is sometimes negative even when the correlation between the effects of a new mutation is positive is that selection cuts the major axis of variation of new mutations in half, which under some conditions cause the major axis of variation of beneficial mutations to switch from having a positive slope to having a negative slope. After this initial separation of mutations into those that are beneficial and deleterious, there is no sufficient variation in the mutations with beneficial effects, following the subsequent differential fixation of mutations, to generate a positive slope, on average, between the effects of a fixed mutation. There is insufficient variation because even with a moderate positive correlation, new mutations with simultaneous and relatively large beneficial effects on two characters are still relatively rare.

Relative to the multivariate-normal model, the correlation between the effects of a fixed mutation in the leptokurtic model appears to be closer to the correlation between the effects of a new mutation. The reason for this may be that in the leptokurtic model, random mutations typically have either very small effects on all characters and are not likely to fix, or have a moderate to large sized effect on a single character and very small ones on the others. The very small effects do not affect that mutations probability of fixing very much and so when you look at fixed mutations, correlations are closer to being random. When mutations are normally distributed, you are more likely to get mutations of small to moderate size on two or more characters and these effects factor into its probability of fixation.

In agreement with Otto (2004), the results suggest that given a mutation that was fixed by selection has a large beneficial effect on a character, the effect on a second character under directional selection is expected to equal the average size of a new mutation given the effect on the first character. This paper has suggested that this is true when the effects of mutations are, on average, deleterious, neutral and beneficial, when new mutations have correlated effects and for varying levels of pleiotropy. If the effects of a new mutation are expected to be uncorrelated between characters and the average effect is zero, then given a mutation that was fixed with a large beneficial effect on one character, the expectation is that it will have little to no effect on another character. If mutations have deleterious effects, on average, given a fixed mutation with an increasingly large beneficial effect on one character, it is expected to have an effect on another character that asymptotically approaches the average random effect of a mutation, which is deleterious. Correlations between the effects of a new mutation cause the expected size of the effect on the second character (given the effect on the first character) to be greater or less than zero, depending on the direction of the correlation.

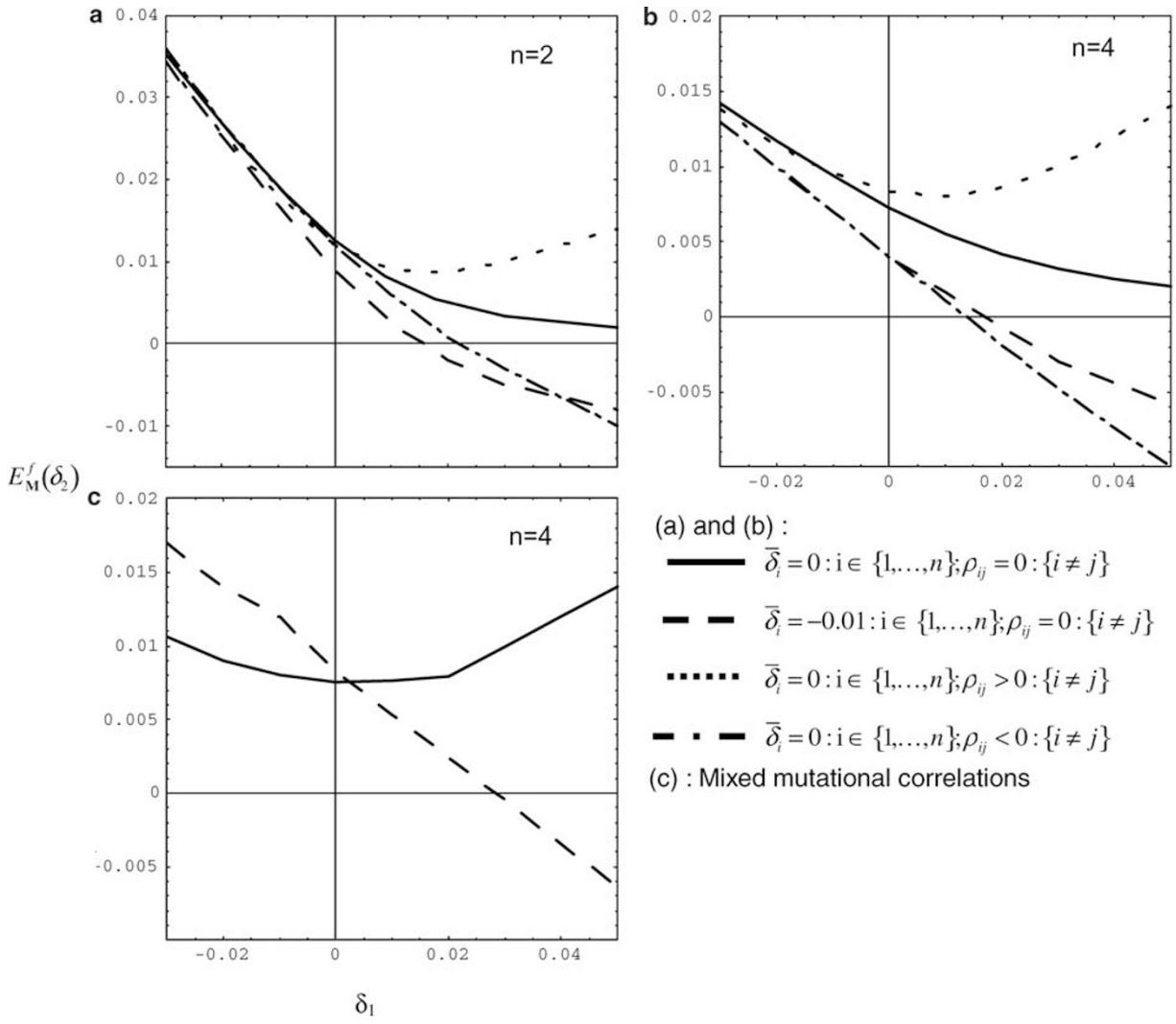

Figure 3 (**a**) For mutations that pleiotropically affect two characters, the expected size of a fixed mutational effect on a character is plotted on the y axis given an effect on the other character (x axis). (**b**) The expected size of a fixed mutational effect on one of the other characters (y axis), given that a fixed mutation has a particular effect (x axis) on a character when mutations pleiotropically affect four characters. Solid lines correspond to the case when the average effect of a mutation on a character was zero and the effects of new mutations were uncorrelated, the dashed lines correspond to the case when the average effect on a character was deleterious, such that $\delta_i = -0.01$ and the effects of new mutations were uncorrelated, the dotted-line corresponds to the case when the correlations between the effects of new mutations for all characters is 0.25 and the average effect of a mutation was zero for all characters, and dashed-dotted lines correspond to the case when the correlations between the effects of new mutations for all characters -0.25 and the average effect of a mutation was zero for all characters. (**c**) As in part (**b**), mutations pleiotropically affect four characters, but now new mutations have a mixture of positive and negative correlations, such that the correlation matrix is {{1.0,−0.25,−0.25,−0.25}, {−0.25,1.0,0.25,0.25}, {−0.25,0.25,1.0,0.25}, {−0.25,0.25,0.25,1.0}}. The solid line corresponds to the expected effect of a mutation on character three given an effect on character two, such that they are both positively correlated and positively correlated with another character, but these three characters are negatively correlated to the first. The dashed curve corresponds to the case of the expected effect of a mutation on character two, three or four, given an effect on character one, such that in this case the conditional expectation is between characters that are negatively correlated. In all cases, numerical analysis suggests that as the effect of a mutation on one character becomes increasingly large and beneficial, the expected size of an effect on another character approaches the expected size of a random mutation given the effect on the first character. For instance, in parts (**a**) and (**b**), the solid lines asymptotically approach zero and the dashed lines asymptotically approach -0.01. In all figures, mutations were drawn from the multivariate-normal mutation model and the mutational variances per character were each 0.0001.

These results aid in the interpretation of recent work that studied the pleiotropic effects of beneficial mutations in *E. coli* (Ostrowski *et al*., 2005). They found that beneficial mutations commonly had pleiotropic effects in two or more environments. Furthermore, they found that the effects of beneficial mutations were positively correlated in different environments. Based on the theory presented in this paper, to attain a positive correlation in the effects of beneficial mutations requires the effects of random mutations to be positively correlated and that this positive correlation be stronger than what was observed among beneficial mutations.

Model assumptions

In populations of small size, where random genetic drift is important, mutations with an overall deleterious fitness effect may fix. This would weaken the boundary

condition given by Equation (5), which may cause fixed mutations to have correlations that are nearer the new mutational correlation.

In the unconditionally deleterious mutation model, I did not perform a complete analysis of the relationship between levels of kurtosis and correlations between the characters under directional selection and the characters under purifying selection on the **F** matrix. Work by Zhang and co-workers has shown that genetic variance and strengths of stabilizing selection can be affected by these properties of the mutational distribution (Zhang *et al*., 2002, 2004; Zhang and Hill, 2002). It is left for further study to determine the consequences of varying levels of kurtosis and correlations between characters under directional and characters under purifying selection.

The phenotypic and fitness landscapes were linear in this paper. Work by Peters *et al*. (2003) has shown that deleterious mutations are often recessive. If this is also true for the deleterious pleiotropic effects of mutations, be they mutations that have fitness effects that are beneficial or deleterious overall, then the quantitative results in this paper are likely to change. In particular, the correlation between the effects of a fixed mutation is likely to be nearer that of new mutations because the deleterious pleiotropic effects are masked. Whether there will be a flip such that the correlation between the effects of a fixed mutation is greater than new mutation is an open question.

Epistasis is another important factor that was not modeled here. Depending on the genetic background, the pleiotropic effects of mutations may change. It is possible that mutations may be selected for nullifying the deleterious pleiotropic effects of other mutations that have previously fixed. This may cause the correlation between the effects of a fixed mutation to collapse towards zero. Other consequences of epistasis are also possible and left for further study.

Conclusions

This paper has shown how selection transforms the underlying genetic architecture of new mutations into the genetic architecture of an adaptation. Different underlying mutational genetic architectures give rise to different genetic architectures of adaptations. Generally, results suggest that the correlation among the effects of a fixed mutation is less than the correlation among the effects of a new mutation. Additionally, the results extend and support Otto's (2004) results that indicated that given a fixed mutation with a large and beneficial effect on one character, it is expected that the mutation's effect on a second character approaches the expected effect of a random mutation conditioned on the effect of the first.

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Appendix A

Proof that mutational correlations in the leptokurtic model are equal to the correlations in the Q-matrix

The covariance between the effects of a new mutation $\delta_i = \mu_i + tz_i$ and $\delta_j = \mu_j + tz_j$ from the leptokurtic model is given by the equation,

$$E[(\mu_i + tz_i - E(\mu_i + tz_i))(\mu_j + tz_j - E(\mu_j + tz_j))], \qquad \text{(A1)}$$

where E denotes an expectation. Expanding (A1) and taking expectations yields the equation,

$$E[t^2]E[z_i z_j] - E[t]^2 E[z_i]E[z_j] \qquad \text{(A2)}$$

Noting that $E[z_1] = 0$ and $E[z_2] = 0$ simplifies (A2) into the equation,

$$E[t^2]E[z_i z_j] \qquad \text{(A3)}$$

The correlation between effects $\delta_i = \mu_i + tz_i$ and $\delta_j = \mu_j + tz_j$ from the leptokurtic model is then

$$\frac{E[z_i z_j]}{\sqrt{V[z_i]}\sqrt{V[z_j]}} \qquad \text{(A4)}$$

which is the same as the correlation between deviates z_i and z_j.

Appendix B

Derivation of conditions when $\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j) \geqslant \rho^{\mathrm{f}}_{\mathbf{M}}(\delta'_i,\delta'_j)$

As was noted in the main section, $\lim_{\alpha\to\infty} \rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j) = \rho^{\mathrm{f}}_{\mathbf{M}}(\delta'_i,\delta'_j)$. Thus, if $\partial\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j)/\partial\alpha < 0$ for all $\alpha > 0$, then $\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j) \geqslant \rho^{\mathrm{f}}_{\mathbf{M}}(\delta_i,\delta_j)$, provided that $\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j)$ is smooth over the interval $0 < \alpha < \infty$. That is, if $\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j)$ is a decreasing function of α as $\alpha \to \infty$ and $\lim_{\alpha\to\infty} \rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j) = \rho^{\mathrm{f}}_{\mathbf{M}}(\delta'_i,\delta'_j)$, then it follows that $\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j) \geqslant \rho^{\mathrm{f}}_{\mathbf{M}}(\delta_i,\delta_j)$ for $\alpha > 0$. The derivative of $\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j)$ with respect to α is

$$\frac{\partial\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j)}{\partial\alpha} = \frac{-2((1+\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i\delta'_j) - \alpha E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_j))}{2((2+\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta_i{}'^2) - (1+\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i)^2)^{3/2}((2+\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta_j{}'^2) - (1+\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_j)^2)^{3/2}} \qquad \text{(B1)}$$

The denominator is always positive, so the numerator defines when $\partial\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j)/\partial\alpha < 0$. Right away it is clear that when $\mathrm{Cov}^{\mathrm{f}}_{\mathbf{M}}(\delta'_i,\delta'_j) \geqslant 0$, $\partial\rho^{\mathrm{f}}_{\mathbf{Q}}(\delta_i,\delta_j)/\partial\alpha < 0$ for $\alpha > 0$ because when $\mathrm{Cov}^{\mathrm{f}}_{\mathbf{M}}(\delta'_i,\delta'_j) \geqslant 0$, $E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i\delta'_j) - E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_j) \geqslant 0$ and it follows that $(1+\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i\delta'_j) - \alpha E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_j) > 0$.

When $\mathrm{Cov}^{\mathrm{f}}_{\mathbf{M}}(\delta'_i,\delta'_j) < 0$, the condition $(1+\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i\delta'_j) - \alpha E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_j) > 0$ still must be satisfied for the correlation in the leptokurtic model to be greater than in the multivariate normal model. Rewriting the condition as $E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_j) < ((1+\alpha)/\alpha)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i\delta'_j)$ and taking the limit as $\alpha \to 0$, the condition is easily met. When $\alpha \to \infty$, the condition becomes more restrictive because $E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i)E^{\mathrm{f}}_{\mathbf{M}}(\delta'_j) > E^{\mathrm{f}}_{\mathbf{M}}(\delta'_i\delta'_j)$ if $\mathrm{Cov}^{\mathrm{f}}_{\mathbf{M}}(\delta'_i,\delta'_j) < 0$. But it is also true that as $\alpha \to \infty$, the leptokurtic model of mutation approaches the multivariate normal case, and it is therefore expected that the correlation from the leptokurtic model converge on the multivariate normal correlation. For the range of parameter values that were studied in the main text, the correlation between the effects of a fixed mutation from the leptokurtic model was always greater than or equal to that from the multivariate normal model.