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Patterns of quantitative genetic variation in multiple dimensions

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Abstract A fundamental question for both evolutionary biologists and breeders is the extent to which genetic correlations limit the ability of populations to respond to selection. Here I view this topic from three perspectives. First, I propose several nondimensional statistics to quantify the genetic variation present in a suite of traits and to describe the extent to which correlations limit their selection response. A review of five data sets suggests that the total variation differs substantially between populations. In all cases analyzed, however, the "effective number of dimensions" is less than two: more than half of the total genetic variation is explained by a single combination of traits. Second, I consider how patterns of variation affect the average evolutionary response to selection in a random direction. When genetic variation lies in a small number of dimensions but there are a large number of traits under selection, then the average selection response will be reduced substantially from its potential maximum. Third, I discuss how a low genetic correlation between male fitness and female fitness limits the ability of populations to adapt. Data from two recent studies of natural populations suggest this correlation can diminish or even erase any genetic benefit to mate choice. Together these results suggest that adaptation (in natural populations) and genetic improvement (in domesticated populations) may often be as much constrained by patterns of genetic correlation as by the overall amount of genetic variation.

Keywords Constraint · Evolvability · Function-valued trait · Genetic correlation · Heritability · Selection response

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Introduction

What constrains how much natural and artificial selection can modify phenotypes? A naive reading of the quantitative genetics literature might leave one with the impression that there are virtually no limits. Long term artificial selection programs continue to show progress (e.g. with corn (Moose et al. 2004) and dairy cattle (Powell and Norman 2006)), the vast majority of traits that have been studied are heritable (Roff 1997), and mutation provides a constant source of new genetic variation (Houle et al. 1996). The conclusion seems to be that selection on almost any single trait will yield an evolutionary response. Indeed, Lewontin (1974, p. 92) proclaimed "there is good reason to suppose that any outbred population or cross between unrelated lines will contain enough variation with respect to almost any character to allow effective selection."

But the picture is quite different when suites of traits are considered together. The number of trait combinations that will respond to selection can be much smaller than the number of traits, even when each trait is heritable and all pairwise genetic correlations between them are less than 1 (Dickerson 1955; Lande 1979; Charlesworth 1990; Kirkpatrick and Lofsvold 1992; Blows 2007; Blows and Walsh 2008). Then the population is confined to evolve in a subspace with fewer dimensions than the number of traits under selection. Patterns of genetic correlations result in "genetic lines of least resistance" that can have major effects on long-term evolutionary trajectories (Schluter 1996).

Does genetic variation in natural and domesticated populations in fact impose this kind of constraint? Both evolutionary biologists and breeders have a lot riding on the answer. A central question in evolutionary biology is the degree to which the diversity of phenotypes we see in

nature reflects what selection favors vs. the constraints imposed by genetics and development (Maynard Smith et al. 1985; Phillips and Arnold 1999; Brakefield 2006; Roff and Fairbairn 2007). The ultimate benefit of artificial selection programs depends on whether economically favored traits can be decoupled from traits with deleterious effects (Brotherstone and Goddard 2005).

Artificial selection offers one approach to studying constraints. Weber (1990) selected on five bivariate relations relating to wing shape in *Drosophila melanogaster*, and found that all five pairs of relations can be altered. Beldade et al. (2002a, b) selected on two eyespots on the forewings of the butterfly *Bicyclus anynana*. They showed that the relative sizes of each eyespot can be altered independently of the other. The results from both experiments are surprising because we might expect that the developmental genetics of insect wings might impose constraints in these pairs of traits. What we do not know from these results, however, is whether there are constraints in higher dimensions (that is, combinations of more than two traits). These experiments only prove that the correlation between pairs of traits is less that one. These population may still be confined to evolve in a two-dimensional subspace. The ideal—but logistically inconceivable—experiment would be to select in all possible directions in a high-dimensional multivariate space.

A second approach to the study of constraints uses models to understand how patterns of genetic variation and correlation evolve. Under various assumptions concerning the underlying genetic and/or developmental principles, these constraints can in principle be predicted (e.g. Zhang et al. 2002; Jones et al. 2004; Schlosser and Wagner 2004; Hansen et al. 2006; Jones et al. 2007). These models are useful for understanding how constraints are affected by (for example) mutation rates and effective population size. Typically there is great uncertainty about the values for many of the parameters, however, and so it is not yet possible to extract from them robust quantitative conclusions.

This paper discusses a third way to study how quantitative genetic variation impacts adaptation. It is based on the analysis of standing genetic variation. First I present simple nondimensional statistics that describe the "effective number of dimensions", the maximum "evolvability", and the total genetic variation present in a suite of quantitative traits. The statistics are illustrated with an analysis of five data sets. Second, theoretical calculations show how a population's average response to selection in a random direction is affected by the effective number of dimensions and the actual number of traits under selection. Third, I review recent studies for variation in lifetime fitness in natural populations, highlighting an emerging conclusion that the genetic correlation between male and female fitness may be small or even negative. Together, these results suggest that genetic correlations between quantitative traits may be at least as important as the total amount of genetic variation in limiting a population's response to selection.

In addition to presenting some new empirical and theoretical results, I will also highlight several developments in evolutionary quantitative genetics that have appeared since the Second International Congress on Quantitative Genetics. These include multivariate data sets with both genetic variation and fitness measures, the use of the animal model in natural populations, advances in methods to analyze function-valued traits, new statistical methods and software for analyzing multivariate quantitative genetic data, and a general framework for multilocus modeling.

Quantifying genetic variation in many dimensions

The additive genetic covariance matrix **G** describes patterns of genetic variation for multiple traits in terms of their variances and covariances. But this is an opaque format for the information: simply inspecting the matrix doesn't reveal whether there are constraints. Looking at the correlation matrix rather than the covariance matrix will show pairs of traits that are completely coupled, but again does not immediately reveal constraints involving three or more traits.

The solution is to work with the eigenvectors, or principal components, of the additive genetic covariance matrix **G**. They define the combinations of traits that respond to selection independently of each other. The eigenvalues quantify the amount of genetic variation associated with each of these axes. A population's potential response to selection—and its constraints—are completely described by these quantities (reviewed by Blows 2007).

The genetic principal components for which there is no genetic variation define a *null space*, combinations of trait values that are inaccessible to evolution. Interest in identifying evolutionarily forbidden combinations has motivated studies aimed at determining how many eigenvalues of **G** are zero. Several empirical studies have suggested that one or more eigenvalues of **G** equal zero (Kirkpatrick and Lofsvold 1992; Hine and Blows 2006; Mcguigan and Blows 2007). In contrast, Mezey and Houle (2005) found genetic variation for all combinations of the 20 wing dimensions in flies that they measured.

It is difficult to tell whether evolutionarily forbidden trait combinations are widespread for several reasons. Sampling results in substantial imprecision in estimates of the eigenvalues (Hill and Thompson 1978), and there are still unresolved statistical difficulties in determining

confidence limits on the estimates (Hine and Blows 2006). Second, under at least some statistical frameworks, estimates of the smallest eigenvalues are biased downwards (Hill and Thompson 1978; Hayes and Hill 1981). This can lead us to believe there is no variation for some dimensions where in fact there is. Third, the analyzes rest on the key assumption that the distribution of breeding values is Gaussian. If this assumption is violated, which it is certain to be, we do not know precisely what the eigenvalues tell us about constraints. Fourth, **G** itself can evolve as the result of changes in allele frequencies and disequilibria, and the appearance of new variation by mutation and migration. There is no guarantee that an eigenvalue that is 0 today will keep that value indefinitely. A final problem is a fundamental limitation of statistical inference: we can never prove that a quantity is exactly equal to 0.

Multivariate evolvability

One exit from this conundrum is to adopt a milder view of evolutionary constraints. We step back from the question of whether there are directions in multivariate space where selection absolutely cannot take the population. Instead, we focus on how strongly the pattern of genetic variation biases evolutionary trajectories. We might then ask how suites of traits or populations differ in how strongly they are constrained or biased. Questions of interest include: Is there typically more or less variation in domesticated vs. natural populations? Are function-valued traits more constrained than suites of scalar-valued traits? Unfortunately, this paper will not answer those questions because only five data sets are analyzed. But it will allow us to consider useful ways to quantify multivariate genetic variation, and to draw a tentative conclusion about the number of dimensions in which variation lies.

How are we to compare the evolutionary potential of milk production in cows, say, with that of a flower's scent? There are several issues to consider here. One is the scale of measurement: we need to compare traits that are measured in incommensurate units. A second issue is magnitude: we want to consider the evolutionary potential of traits that have very different means. A third consideration is that traits of interest can be scalar-valued (that is, consisting of a single datum for each individual's trait value) or function-valued (consisting of a curve, such as a growth trajectory or lactation curve).

The basic idea I will explore here extends Houle's (1992) notion of evolvability to multiple traits. The key is to work with proportions, dividing each measurement by its trait mean. This is not the only standardization possible, but for many situations it is the most natural (Hereford et al. 2004). Differences in means then represent proportions, and variances become squared coefficients of variation. Previous empirical and theoretical studies have explored this idea in the context of single traits (Houle 1992; Kirkpatrick 1996; Hansen et al. 2003).

When traits are standardized by their means, the multivariate version of Lande's (1979) equation for the response to selection is

$$\Delta\widetilde{\mathbf{z}} = \widetilde{\mathbf{G}}\widetilde{\beta} = (\mathbf{ERE})\widetilde{\beta} \quad (1)$$

where $\Delta\widetilde{\mathbf{z}}$ is the vector of selection responses, $\widetilde{\mathbf{G}}$ is the additive genetic covariance matrix, and $\widetilde{\beta}$ is the selection gradient vector. The tildes are to remind us that these are normalized quantities. Thus the elements of $\Delta\widetilde{\mathbf{z}}$ give the proportional change in the trait means caused by one generation of selection. The elements of $\widetilde{\beta}$ give the rate that relative fitness increases per proportional change in that trait's value, holding the values of the other traits constant.

As shown in Eq. 1, the normalized genetic covariance matrix can be decomposed into a product involving two quantities: $\widetilde{\mathbf{G}} = \mathbf{ERE}$, where **E** is a diagonal matrix with the additive genetic coefficients of variation or "evolvabilities" (Houle 1992) for each trait, and **R** is the matrix of genetic correlations. Thus the constraints implied by $\widetilde{\mathbf{G}}$ result from both the amount of genetic variation present for each trait (measured by **E**) and the correlations between them (which appear in **R**). The constraints are again quantified by the distribution of eigenvalues of $\widetilde{\mathbf{G}}$. I will denote these eigenvalues as λ_i, and order them from largest (λ_1) to smallest (λ_n).

Summarizing variation

Patterns of genetic variation can be summarized with the help of some simple summary statistics. The first of these is the *effective number of dimensions*, which I define as the sum of the eigenvalues divided by the largest eigenvalue:

$$n_{\mathrm{D}} = \sum_{i=1}^{n} \lambda_i/\lambda_1 \quad (2)$$

where n is the number of traits measured. If all genetic variation lies in a single dimension, then the effective number of dimensions is 1. At the other extreme, if all the (normalized) traits have equal amounts of variation and there are no genetic correlations between them, the effective number of dimensions is equal to the actual number of traits measured. Another way to think about n_{D} is that it is equal to the reciprocal of the fraction of total genetic variance contributed by the first principal component (eigenvector) of $\widetilde{\mathbf{G}}$. For example, if half the variation is explained by that principal component, then the effective number of dimensions is 2.

A second measure is the *maximum evolvability*, which is the square root of the largest eigenvalue:

$$e_{\max} = \sqrt{\lambda_1}. \quad (3)$$

The maximum evolvability is the genetic coefficient of variation for the combination of traits that has the greatest amount of genetic variation. It corresponds to Houle's (1992) definition of evolvability when there is only a single trait. Again, we are working with data that has been standardized by the trait means, and so $e_{\max}$ refers to a combination of traits in which there is the maximum genetic variation for proportional change.

The last summary statistic is the sum of the eigenvalues of $\widetilde{\mathbf{G}}$, which I refer to as the *total genetic variance*:

$$v_T = \sum_{i=1}^{n} \lambda_i = \lambda_1 n_D \quad (4)$$

The total genetic variance measures the population's overall potential to respond to selection on combinations of traits. Like the other summary statistics, v_T is based on the standardized data and so it has no dimensions.

Figure 1 illustrates the patterns of variation described by these statistics when there are $n = 3$ traits. Within each set of axes an ellipsoid represents the distribution of additive genetic values. The ellipsoid has been rotated so that the axes of each panel are parallel to the genetic principal components (eigenvectors). The amount of variation is maximal along the horizontal axis, and is multiplied by a factor k in the axis coming towards the reader, and again by another factor k in the vertical axis. The three columns of panels show how the distribution of variation changes with k and n_D. On the right is the case with $k = 1$, where the effective number of dimensions is equal to the actual number of traits measured: $n_D = 3$. There is equal variation in all directions and so the cloud of variation is represented by a sphere. The column on the left shows the case for $k = 0.2$. Here the effective number of dimensions is $n_D = 1.25$, and the cloud is strongly eccentric. The rows of Fig. 1 show how the cloud of variation expands and contracts as a function of the total genetic variance, v_T. Moving from left to right across a row, the maximum evolvability $e_{\max}$ decreases and effective number of dimensions n_D increases so that the total variation remains constant.

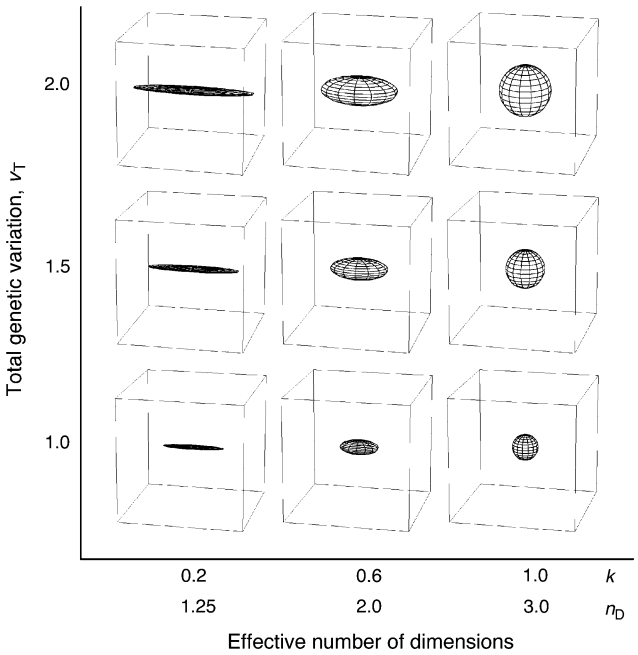

Fig. 1 Patterns of multivariate variation with $n = 3$ traits as a function of the effective number of dimensions (n_D) and the total genetic variation (v_T)

We will now use these summary statistics to explore genetic variation in two domesticated populations (dairy and beef cattle), one laboratory population (mice), and two natural populations (a fish and a fly). I will first consider data sets that are scalar-valued, that is, where each trait can be quantified by a single number. I then move to function-valued traits in which an individual's value for a trait changes with its age.

Before presenting the results from these analyses, I caution that this paper does not attempt to put confidence limits on the estimates of the summary statistics. Those would be necessary before any strong conclusions can be drawn. Determining the sampling properties of the statistics is a substantial project that should be pursued but that is beyond the scope of this paper.

Scalar-valued traits

The first data set comes from Meyer's (2005) study of Angus beef cattle. The combination of a very large sample size and sophisticated statistical analysis provides one of the most precise estimates of a genetic covariance matrix available for any population. Meyer estimated the genetic parameters from pedigrees that included 74,268 animals using genetic principal components based on restricted maximum likelihood. Four morphological traits were measured. Values in males and females are treated separately, and so the data consist of a total of 8 traits.

Two more data sets come from natural populations studied by McGuigan, Blows, and their colleagues. They studied variation in 21 distances between landmarks distributed across the bodies of rainbow fish, *Melanotaenia eachamensis* (McGuigan et al. 2005). Genetic parameters were estimated with data from 44 families of fish using analysis of variance. In a second study, McGuigan and Blows (2007) estimated variation for 10 distances between landmarks on the wings of *Drosophila bunnanda*. They analyzed the data collected from 488 families using restricted maximum likelihood (REML).

These studies provided estimates of the genetic correlation matrices, genetic variances, and the trait means. Those quantities allow us to calculate the nondimensional genetic covariance between traits i and j as $\widetilde{\mathbf{G}}_{ij} = r_{ij}\sqrt{G_{ii}G_{jj}}/\left(\bar{z}_i\bar{z}_j\right)$, where r_{ij} is the genetic correlation between i and j, G_{ii} is the genetic variance for trait i on the original measurement scale, and $\bar{z}_i$ is the trait's mean. The fish data were analyzed as the logs of the trait measurements, and so it was necessary to back-transform the data to the original scale of measurement before nondimensionalization. To do that I calculated the genetic variances for each trait i as $G_{ii}^2 = \left(\exp\left\{s_i^2\right\} - 1\right)\bar{z}_i^2$, where s_i^2 is the genetic variance of trait i for the log-transformed data. Finally, to calculate the genetic covariances, I assumed that the genetic correlations on the original measurement scale can be approximated by those on the log-transformed scale.

We can get a first impression about patterns of multivariate genetic variation by considering the Angus cattle data. The evolvabilities and genetic correlation matrix **R** are given in Table 1. The univariate evolvabilities suggest that there is substantial genetic variation available to selection. Six of the eight values are quite large, between 25 and 36%. Comparing the smallest to the largest evolvability, the values differ only by a factor of 4.

The picture of constraints, however, is quite different when we consider the multivariate perspective. Figure 2 shows that the eigenvalues of $\widetilde{\mathbf{G}}$ decline rapidly. This pattern holds when all 8 traits are taken together, and also when the traits in males and females are considered separately. Table 2 shows the summary statistics. A striking result is that the effective number of dimensions is only $n_D = 1.5$. This follows from the fact that well more than half (65%) of all genetic variation is accounted for by the first eigenvalue. The total genetic variance is $v_T = 0.2$ when all traits are taken together, and is smaller (as it must be) when females and males are considered separately. There appears to be somewhat more genetic variation in females than males. The maximum evolvability when both sexes are included is $e_{max} = 0.36$, which appears to be somewhat larger than the average value for evolvabilities of adult size measures reported by Houle (1992) in his survey of single traits.

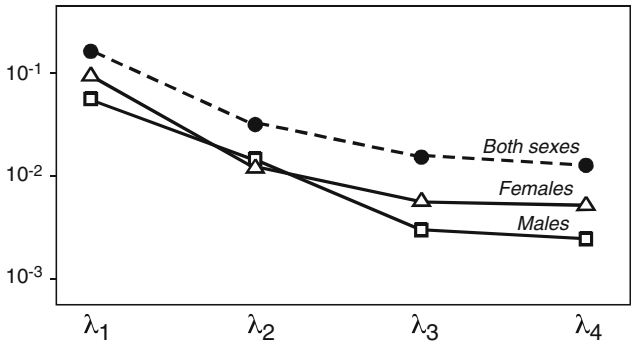

Fig. 2 The first four eigenvalues of the normalized genetic covariance matrix $\widetilde{\mathbf{G}}$ for the Angus cattle data set of Meyer (2005). Note that the y-axis is logarithmic

Results from analyses of the two other scalar-valued data sets are also shown in Table 2. The most striking pattern that emerges is that the effective number of dimensions varies over a narrow range of values and is always less than 2. The largest estimate is only 1.9, from the wing dimensions of female *Drosophila bunnanda*. This is perhaps surprising as one might expect developmental processes to generate more constraints on wing shape than, say, combinations of less functionally-related traits.

Values for the other summary statistics range widely. The total genetic variance, v_T, ranges from 0.002 (for fly wings) to 1.7 (for fish body dimensions). The maximum evolvability, e_{max}, ranges from 0.033 (for female fly wings) to 0.36 (for cattle morphological traits). These two statistics vary so much because the leading eigenvalues for the data sets vary over three orders of magnitude. To sum up, the effective number of dimensions seems remarkably

Table 1 The estimated nondimensionalized genetic correlation matrix **R** and the evolvabilities (along the diagonal, in bold) for Angus beef cattle, based on Meyer (2005a)

	P8.f	RIB.f	IMF.f	EMA.f	P8.m	RIB.m	IMF.m	EMA.m
P8.f	**0.36**	0.86	0.58	0.18	0.70	0.62	0.40	0.02
RIB.f		**0.33**	0.65	0.20	0.60	0.72	0.44	−0.01
IMF.f			**0.095**	0.18	0.28	0.35	0.72	−0.01
EMA.f				**0.25**	−0.01	0.02	0.03	0.82
P8.m					**0.28**	0.92	0.66	−0.08
RIB.m						**0.25**	0.71	−0.02
IMF.m							**0.087**	−0.01
EMA.m								**0.27**

The normalized genetic covariance function $\widetilde{\mathbf{G}}$ can be calculated from these values using Eq. 1. The traits are eye muscle area (EMA), fat depth at the 12th/13th rib (RIB), P8 fat depth (P8), and percentage intra-muscular fat (IMF). Traits in females are denoted by ".f" and traits in males by ".m"

Table 2 Analysis of normalized genetic variation in five populations

	N	n	n_D	e_{max}	v_T	$\overline{R}$	λ_1	λ_2	λ_3
Scalar-valued traits									
Angus cattle									
Both sexes	74,268	8	1.5	0.36	0.20	0.32	0.13	0.027	0.018
Males	35,345	4	1.3	0.25	0.083	0.45	0.063	0.015	0.0031
Females	34,649	4	1.3	0.30	0.12	0.44	0.093	0.013	0.0058
D. bunnanda									
Males	625	10	1.6	0.035	0.0020	0.29	0.0013	0.00038	0.00018
Females	759	10	1.9	0.033	0.0020	0.32	0.0011	0.00047	0.00021
M. eachamensis	375	21	1.2	1.2	1.7	0.18	1.4	0.18	0.057
Function-valued traits									
Holstein-Friesian cows	34,029	∞	1.1	0.27	0.078	0	0.074	0.0037	0.00042
ICR mice									
Males	1,346	∞	1.3	0.14	0.027	0	0.021	0.0048	0.00087
Females	1,347	∞	1.2	0.18	0.038	0	0.032	0.0052	0.00083

N is the number of individuals and n the number of traits measured. The next four columns give the summary statistics described in the text. The last three columns give the leading eigenvalues for $\widetilde{\mathbf{G}}$

consistent, but other measures of genetic variation differ substantially between populations and studies.

Function-valued traits

A situation where we might expect constraints to be particularly conspicuous is when traits are "function-valued". Here the phenotype of an individual is represented by a function rather than a set of distinct variables, such as traits that change with age or whose expression varies with an environmental variable. Function-valued traits appear in many contexts in evolutionary biology (Kirkpatrick and Heckman 1989; Kingsolver et al. 2001) and animal breeding (Schaeffer 2004; Meyer and Kirkpatrick 2005b).

Function-valued traits are an interesting place to look for constraints simply because it is certain that they are there. No animal can grow (or shrink) infinitely fast, so there must be some limits on the types of evolutionary changes that can be made to a growth trajectory.

We can study variation and constraint for function-valued traits by a direct extension of the tools used for standard scalar-valued traits. In place of the genetic covariance matrix we have a genetic covariance function that gives the additive genetic variation between all pairs of measurements (e.g. size at different ages, in the case of a growth study) (Kirkpatrick and Heckman 1989). The eigenvalues of the covariance function again tell us about the amount (or lack) of genetic variation for different genetic deformations in the shape of the function (Kirkpatrick and Lofsvold 1989, 1992).

The covariance function can be estimated conveniently and efficiently with "random regression" methods (Henderson 1982; Meyer and Hill 1997; Schaeffer 2004). These methods are now being applied to diverse phenotypes and organisms in both natural and domesticated populations. The eigenvalues of the estimated covariance function can be calculated (Kirkpatrick and Lofsvold 1992; Kirkpatrick and Meyer 2004), and from those we can compute the same summary statistics used above for scalar-valued data.

Here we will consider two data sets for function-valued traits. Riska et al. (1984) studied the growth trajectories of ICR randombred mice. They measured weight in males and females at 9 ages in 2,693 individuals in a cross-fostering design, and used analysis of variance to estimate genetic variances. (The variances are reported for log-transformed data, so the back-transformation described above was used to calculate the variances and covariances for nondimensional data.) Pander et al. (1993) studied genetic variation for lactation curves in Holstein-Friesian dairy cattle. Genetic parameters were estimated from a pedigree with 34029 individuals using REML. For this paper I used the genetic covariance function estimated by the method of asymmetric coefficients with $k = 9$ polynomials fitted (see Kirkpatrick et al. (1994)).

Results for the summary statistics are shown in Table 2. Lactation curves in Holstein-Friesian cows give the smallest estimate for the effective number of dimensions of any data set: $n_D = 1.1$. The values for mouse growth trajectories are a bit larger: $n_D = 1.2$ for males and 1.3 for females. The impression from these results is the effective number of dimensions for function-valued traits may tend to be smaller than for suites of scalar-valued traits, but the number of studies is too small to draw strong conclusions here. Again, the total genetic variation and maximum evolvability range widely in their values.

Conclusions about dimensionality

The effective number of dimensions is less than two, and often less than 1.5, in all of the five data sets considered here. Table 2 shows that the first genetic principal component (eigenvector) accounts for more than half of all genetic variation. In contrast, other nondimensional measures of variation (the maximum evolvability and the total genetic variation) vary over several orders of magnitude. The small and relatively constant estimates for the effective number of dimensions is an intriguing empirical observation which at present has no theoretical explanation, and indeed it is unclear how general that pattern may be. Hopefully these preliminary results will stimulate further analysis to determine if the pattern is robust and, if so, a search for its explanation. It would be interesting to see if similar conclusions hold for data sets that include more diverse mixtures of phenotypes, for example morphological, behavioral, and physiological traits.

These results might seem to convey a rather pessimistic message about the potential for evolutionary change: the data strongly suggest that there are many things that selection cannot do, at least in a short amount of time. But in fact this very observation has a practical advantage: it offers a way to simplify the problem of estimating genetic parameters substantially. One approach here is to assume a parametric form for the covariance function, then estimate its parameters (Jennrich and Schluchter 1986; Pletcher and Geyer 1999; Jaffrezic and Pletcher 2000; Jaffrezic et al. 2004). A second way to exploit the low dimensionality of genetic variance is to focus estimation directly on the principal components that contain the bulk of the variation (Kirkpatrick and Meyer 2004; Meyer and Kirkpatrick 2005a). Since most genetic variation falls along a relatively small number of axes, we can capture most the information about the genetic covariance matrix by estimating only those principal components. The strategy applies equally to function-valued traits, and to mixtures of scalar- and function-valued traits. Related approaches focus on estimating a reduced number of principal components of covariance matrices that emerge from certain experimental designs (Hine and Blows 2006).

Several advantages flow from estimation using principal components. One is that it reduces—dramatically, in many cases—the number of parameters to be estimated. The result is increased accuracy, enhanced stability of the estimates, and decreased computation. Yet another benefit is that this approach guarantees that estimates of the genetic covariance matrix (or function) will be positive semidefinite, without the negative variances and correlations outside the range $(-1, 1)$ that plague some other estimation schemes. There are, however, pitfalls. If an insufficient number of principal components are estimated, variation is inappropriately assigned to genetic and environmental sources, which results in biased estimates (Meyer and Kirkpatrick 2007).

The use of principal components as the basis for estimation is quite recent and to date has only been used in a handful of studies of domesticated (Meyer 2005, 2006a, 2007) and natural (Hine and Blows 2006; McGuigan and Blows 2007) populations. The release of the WOMBAT software package (Meyer 2006b), which includes the option of estimating genetic principal components, now makes the approach much more accessible. An interesting question is whether this and other advances in estimation will change our view of the importance of constraints.

Potential vs. realized constraints

Principal components that lack genetic variation represent potential constraints. They only pose a real problem for adaptation, however, if selection favors a change in one of the directions in which there is little or no variation. How often does that happen?

One way to quantify the answer is using what I will call the *average selection response*, denoted $\overline{R}$. The idea is based on a simple-minded model of how selection works, something like a quantitative-genetic analog of Fisher's (1952) famous model for the probability that a mutation with random pleiotropic effects on n traits will be adaptive. We imagine that selection acts by favoring arbitrary combinations of traits, pushing the population mean in a random direction in multivariate space. Our question is how much is the average evolutionary response diminished by genetic correlations and the uneven distribution of genetic variation among the traits. I will quantify the response as total evolutionary change, that is, the length of the vector $\Delta\bar{\mathbf{z}}$. (This is not the only measure of interest. T.F. Hansen and D. Houle (pers. comm.) suggest considering the average amount of change in the direction of the selection gradient β.) To find $\overline{R}$, we first calculate the focal population's average selection response to a random selection gradient of constant length. We then divide that result by the average response for a hypothetical population in which all genetic correlations are 0 and the evolvability of all traits is equal to the maximum evolvability of the focal population. (Alternatively, one might set the total genetic variance in the hypothetical population equal to that of the focal population.) Details of the calculations are given in the Appendix.

Results for the five data sets introduced earlier are shown in Table 2. The average selection response for scalar-valued traits is between 18 and 44% of what it would be in hypothetical unconstrained populations. The results give a different perspective than the other three summary

statistics because $\overline{R}$ is sensitive to the total number of traits. For example, the traits in male Angus cattle have the highest average selection response ($\overline{R} = 0.45$) while the fish has the lowest ($\overline{R} = 0.18$) despite the fact that the effective number of dimensions is very similar for the two. The low $\overline{R}$ in the fish results because there are a large number of traits ($n = 21$) and most combinations have little or no genetic variation. The effect of the number of traits is most extreme for function valued traits: here the average selection response must be 0 because there are an infinite number of trait combinations that have no variation.

To get more insight about how the number of traits and distribution of variation affect the average selection response, we can replace the real data in these calculations with an idealized population. Eigenvalues often decline in an approximately exponential (geometric) fashion (Kirkpatrick and Lofsvold 1992; Griswold et al. 2007). Accordingly, assume now that the ratio of the sizes of successive eigenvalues is k. The relation between k and the effective number of dimensions is

$$n_{\mathrm{D}} = \frac{1 - k^n}{1 - k}. \tag{5}$$

For example, if $k = ½$ then the second eigenvalue is half as large as the first. With $n = 2$ traits measured the effective number of traits is $n_{\mathrm{D}} = 1.5$, while with an infinite number of traits $n_{\mathrm{D}} = 2$. With $k = 0$ all the variation is contained in the single combination of traits described by the first principal component and $n_{\mathrm{D}} = 1$. The x-axis of Fig. 1 shows how n_{D} changes with other values of k when there are 3 traits measured.

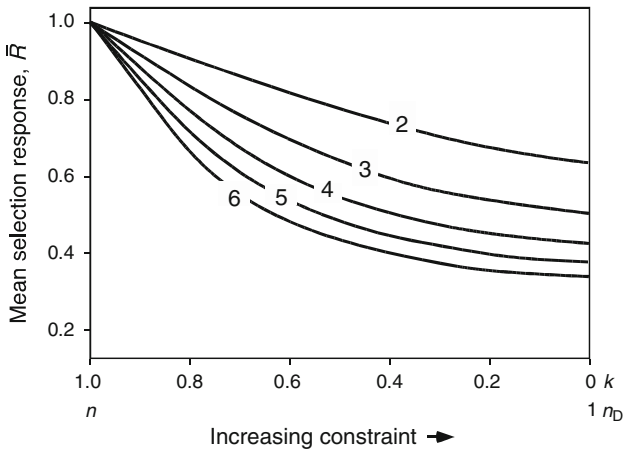

Fig. 3 The average selection response to a randomly oriented selection gradient as a function of the degree of constraint caused by genetic correlations between the traits. The numbers for each curve show n, the number of selected traits. On the x-axis, the effective number of dimensions n_{D} ranges from n (no constraint) to 1 (all variation lies in a single dimension)

Our question now is: How does the average selection response depend on k and on the number of traits under selection, n? Numerical calculations described in the Appendix give the results shown in Fig. 3. As expected, the average response declines as the effective number of dimensions decreases. This decline is faster when there are more traits under selection. That is because a randomly-oriented selection gradient has a greater chance of lying in a direction where there is little genetic variation.

When all genetic variation lies along just a single dimension ($k = 0$ and $n_{\mathrm{D}} = 1$), the relative selection response can be expressed analytically (see the Appendix). The relative selection response is then:

$$\overline{\mathrm{R}} = \frac{2\Gamma[n/2]}{(n-1)\Gamma(n-1)/2]\sqrt{\pi}}, \tag{6}$$

where $\Gamma[.]$ is the gamma function. This result is shown in Fig. 4. Genetic correlations reduce the selection response to 63% when two traits are under selection, and to 50% when there are three traits. As the number of traits grows, the average selection response continues to decline, but it does so quite slowly.

Depending on your intuition, one can come away with either an optimistic or a pessimistic message from these calculations. On the one hand, even if the effective number of traits is small, perhaps selection acts mainly on the space defined by those dimensions. Imagine that the force of selection is concentrated on just three phenotypic dimensions. Even if all genetic variation is concentrated along a single dimension within this space, the response to selection in an arbitrary direction will only decreased by about half relative to the response when selection is perfectly aligned with the dimension containing the most genetic variation. One can make a plausible argument that both natural and artificial selection, acting on traits like body size and growth rate, generate situations like this. Selection

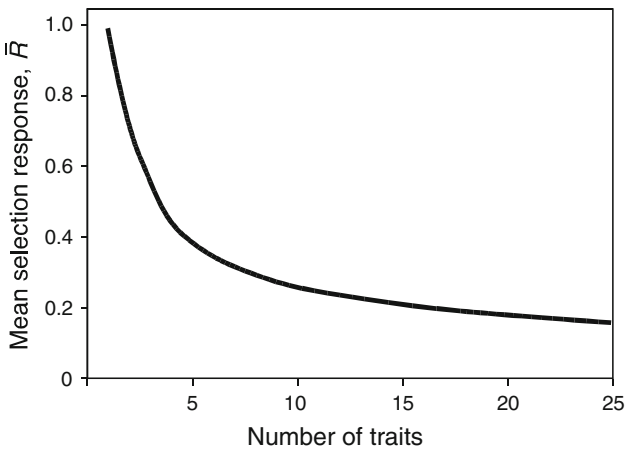

Fig. 4 The average selection response to a randomly oriented selection gradient when all genetic variation lies in a single dimension

then makes substantial progress even in the face of strong constraints. On the other hand, it is easy to envision a less benign universe: selection acts with equal probability on any of a large number of dimensions, yet genetic variation is present in very few of them. Then evolution creeps along compared to what it would do if the axes of selection and variation coincided.

Where along this spectrum nature actually lies can only be decided empirically. There has been a glaring lack of systems in which both genetic variation and patterns of selection have been estimated for at least a moderate number of traits. The recent appearance of data sets with both elements is thus an important and very welcome development (Blows 2007). Blows et al. (2004) and Hine et al. (2004) studied genetic variation and sexual selection for several cuticular hydrocarbons in *Drosophila serrata*. While there is substantial genetic variation for the individual traits, the selection gradient points in a direction that is nearly orthogonal to the dimensions where the variation lies. Hunt et al. (2007) considered the relation between stabilizing sexual selection and genetic variation for five components of male calls in crickets. They found that combinations of traits with stronger stabilizing selection tend to have reduced amounts of genetic variation. It will be exciting to see how general these results are with the accumulation of more studies that integrate both the pattern of selection and of genetic variation.

Genetic variation and correlations for fitness

Among all the traits under selection, fitness itself holds a place of unique importance. Unlike other quantitative traits, there is no doubt how fitness is selected! Several other issues are much less obvious, however, such as how fitness is determined and how to best measure it. Yet another key question is how much genetic variation for fitness exists in natural and domesticated populations. Fisher's (1952) Fundamental Theorem of Natural Selection is often misquoted as predicting there should be no additive genetic variation for fitness. In fact, Fisher made clear that mutation, changing environments, and other factors continually regenerate variation. The question is simply how much. Evolutionary biologists would very much like to know, since the answer sets important limits for the scope of fundamental processes such as the evolution of recombination and mate choice (Fowler et al. 1997; Kirkpatrick and Barton 1997).

Low estimates for the heritability for fitness components (Mousseau and Roff 1987) have left some workers with the impression that there is very little genetic variation. But heritabilities are determined in part by environmental sources of variation (Price and Schluter 1991). Thus for many purposes a more appropriate measure for genetic variance in fitness is again the evolvability, or genetic coefficient of variation. Indirect estimates (based for example on rates of adaptation) suggested that fitness in natural populations may often have evolvabilities in the range of 0.1 to 0.3 (Burt 1995). Until recently, however, direct information about genetic variation in fitness in natural populations was quite sparse.

The field has recently been energized by the application to natural populations of the so-called "animal model" developed by breeders (Kruuk 2004). This statistical framework uses information from an entire pedigree to estimate genetic parameters (Henderson 1950, 1984). Benefits over methods based on analysis of variance include more efficient use of the data and a likelihood estimation framework (Thompson 1973; Shaw 1987; Meyer 1989). A particular boon for estimating genetic components of fitness is that the animal model exploits information about individuals that leave no descendants. Kruuk (2004) reviews the development of the animal model for natural populations and highlights several intriguing new insights that have emerged.

What have we learned with the animal model about genetic variation for lifetime fitness in natural populations? There does indeed seem to be substantial genetic variation for total fitness. Evolvability has been estimated for various measures of fitness in red deer (Kruuk et al. 2000; Foerster et al. 2007), great tits (Mccleery et al. 2004), humans (Pettay et al. 2005), and collared flycatchers (Qvarnstrom et al. 2006; Brommer et al. 2007). Evolvability estimates of 0 have been reported for female red deer (Kruuk et al. 2000) and male humans (Pettay et al. 2005). On the other hand, dramatically large values have also been reported: 0.55 for the evolvability of lifetime reproductive success in female humans (Pettay et al. 2005), 0.61 for in male red deer and 0.99 in female red deer (Foerster et al. 2007).

Another emerging pattern is that genetic variation for fitness in males and females appears to be largely uncoupled. There are two factors at play here. The first is that there are often large differences between the evolvabilities of fitnesses in males and females. It is not unusual for their estimates to differ by a factor of 2 or more. The second is that the genetic correlation between female and male fitness, denoted r_W^{fm}, is not large and positive. In fact, the genetic correlation between male fitness and female fitness may often be near zero or even negative. This conclusion seems contrary to the conventional view that intersex genetic correlations are often near 1 (Lande 1980). In fact, strong positive intersex correlations for morphological and physiological traits can result in a negative intersex correlation for fitness when the optima for males and females differ.

The first estimates from natural populations for the intersex correlation in fitness have appeared very recently. Two estimates of r_W^{fm} have been made for collared flycatchers, giving values of 0.23 (Qvarnstrom et al. 2006) and −0.85 (Brommer et al. 2007). The value estimated for red deer is −0.48. (These values are based on lifetime reproductive success as the fitness measure; other measures are also reported by these authors.) It is important to note, however, that these estimates have large standard errors, and that there are important unresolved issues regarding how best to estimate fitness.

These are not the only reports of negative intersex genetic correlations for fitness. The first findings came from an important series of studies of laboratory populations of *Drosophila* (Chippindale et al. 2001; Pischedda and Chippindale 2006; Prasad et al. 2007). Negative intersex correlations have also been reported for fitness components in dioecious plants (Meagher 1992; Delph et al. 2004), snakes (Forsman 1995), lizards (Calsbeek and Sinervo 2004), and crickets (Fedorka and Mousseau 2004). Thus the genetic component of fitness may often be weakly or even negatively correlated in males and females.

What is the evolutionary significance if male and female fitness are in fact evolutionarily uncoupled? A flurry of consequences might follow concerning rates of adaptation, the maintenance of adaptive and neutral genetic variation, and the evolution of recombination. Here I will focus on yet another consequence, which regards the evolution of mate choice. Some (but not all) theories of sexual selection are built on the idea that female mating preferences evolve for males that have high breeding values for fitness; this is the so-called "good genes" theory of sexual selection (Kirkpatrick and Ryan 1991). To quantify this argument, we need to rely on theory to calculate how rapidly a mating preference will evolve as the result of the genetic benefit it receives by being associated with these good genes. The challenge is how to do that calculation without information about how mates are chosen or about the genetics of mate choice, male display traits, and fitness genes.

New results from quantitative genetics theory make this possible. Barton and Turelli (1991) developed a remarkably general framework for multilocus modeling that makes two major advances over previous approaches. First, it allows for exact descriptions of complex genetic systems, allowing for any numbers of genes and distribution of their effects. Second, under many situations the dynamics can be approximated to high accuracy with simple expressions using the "quasi-linkage equilibrium", or QLE, approximation. More recently, the Barton-Turelli framework has been both generalized and simplified (Kirkpatrick et al. 2002).

These tools now allow us to calculate how mating preferences evolve in terms of the genetic parameters estimated from natural populations. The change in the mean preference caused by good genes is

$$\Delta\overline{P} = \frac{1}{2}\rho_{PT} h_P^2 h_T r_{TW} \left(\frac{\sqrt{G_W^m} + r_W^{fm}\sqrt{G_W^f}}{2} \right) \quad (7)$$

where the change in the mean preference $\Delta\overline{P}$ is measured in units of phenotypic standard deviations (Kirkpatrick and Hall 2004). On the right, ρ_{PT} is the phenotypic correlation among mated pairs between the female's preference and the male's display trait, h_P^2 and h_T are the heritability of the preference and the square root of the heritability of the display trait, and r_{TW} is the genetic correlation between a male's display trait and his lifetime fitness. A key point is that this first set of terms cannot be larger than 1. Thus the upper limit to the force of indirect selection is determined by what follows.

The quantity inside the parentheses of Eq. 7 shows the impact of genetic variation in fitness. The quantities $\sqrt{G_W^f}$ and $\sqrt{G_W^m}$ are the evolvabilities of female and male fitness, and r_W^{fm} is again the genetic correlation between male and female fitness. Thus strong indirect selection on the preference results when fitness has large evolvabilities in both sexes and the correlation between them is high. Conversely, a negative intersex correlation can nullify the genetic benefit of mating with a high-fitness male. (The relative weightings of male and female evolvabilities is affected by sex linkage. Equation 6 assumes autosomal inheritance, but analogous results are available for other cases (Kirkpatrick and Hall 2004).)

Table 3 shows the implications. Taking the point estimates of the genetic parameters at face value, it appears that the intersex genetic correlation could largely eliminate the genetic benefits to female mate choice. The next to last column in Table 3 shows the estimate for the quantity in parenthesis in Eq. 7. The last column shows the decrease in the good genes effect caused by the imperfect intersex correlation (that is, relative to a hypothetical population in which $r_W^{fm} = 1$). We see that the genetic benefit of mating a high fitness male is decreased by 42–114%. Thus the

Table 3 Evolvabilities in males and females and the intersex correlation of lifetime reproductive success in two natural populations

Species	$\sqrt{G_W^m}$	$\sqrt{G_W^f}$	r_W^{mf}	$\left(\frac{\sqrt{G_W^m}+r_W^{mf}\sqrt{G_W^f}}{2}\right)$	% loss
Collared flycatcher[a]	0.18	0.22	0.23	0.12	42
Collared flycatcher[b]	0.22	0.35	−0.85	−0.040	114
Red deer[c]	0.80	0.44	−0.48	0.29	53

See text for explanation of the last two columns

[a] (Qvarnstrom et al. 2006)

[b] (Brommer et al. 2007)

[c] (Foerster et al. 2007)

negative intersex correlation might completely erase any potential good genes effect.

The results on genetic variation for fitness add a new perspective on the role of constraints. It was long assumed that genetic variation for fitness was a limiting quantity in evolution. The recent wave of data from natural populations suggests that in fact a potentially even more important factor is that genes may typically have very different fitness effects in males and females.

These conclusions are tentative. To date we have results from a few populations, and those have large standard errors and uncertainties regarding the measures of fitness. There is another important caveat to these results. The animal model assumes that the phenotypic contribution made by a given genotype is constant in time. For fitness, that implies among other things that the population is growing exponentially. Density regulation makes the fitness produced by a given genotype frequency-dependent. As a result, genotypes are producing different fitness phenotypes in different generations, which violates the assumptions of the statistical model. How this affects the estimates of standing genetic variation for fitness is an important problem yet to be resolved. Selection experiments (Chippindale et al. 2001; Pischedda and Chippindale 2006; Prasad et al. 2007) and controlled breeding (Luo et al. 2005) will be critical as complimentary approaches to the analysis of variation in natural populations.

Conclusions

The role of genetic correlations in limiting selection response has been long recognized, but to date there has been little effort to look for general patterns. Opportunities to do so are expanding with the appearance of more multivariate and function-valued data sets, and the development of new statistical methods for analyzing them. Nondimensional statistics such as the ones suggested here allow us to compare diverse organisms and phenotypes, and provide a new way to quantify evolutionary constraints. The few data sets analyzed in this paper suggest that while overall levels of genetic variation differ widely, genetic correlations may typically reduce a population's effective number of evolutionary dimensions to something less than two. The fundamental reasons for this pattern (if it is indeed general) are unknown and warrant investigation. If natural and artificial selection typically act in directions (that is, on trait combinations) that are random with respect to the axes of genetic variation, then the selection response will much smaller than its potential maximum. The rate of adaptation can also be greatly compromised by the absence of a strong positive genetic correlation between the sexes for fitness, as suggested from recent studies of natural populations. An important research program for evolutionary quantitative genetics is to explore the relation between patterns of genetic variation and selection on multivariate and function-valued phenotypes.

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Appendix

Our goal is to calculate $\overline{R}$, the average relative selection response to a selection gradient pointing in a random direction and with a fixed magnitude. Selection response is defined here as the length (norm) of $\Delta\tilde{\mathbf{z}}$, the vector of proportional changes in the trait means. We will calculate that response relative to a hypothetical unconstrained population whose eigenvalues are all equal to the maximum eigenvalue of the focal population.

The average selection response is

$$\bar{R} = \frac{\int_0^{\pi}\int_0^{\pi}\cdots\int_0^{2\pi} R(\Theta)\left(\frac{dS}{d\Theta}\right)d\theta_1 d\theta_2 \ldots d\theta_{n-1}}{\lambda_1 \int_0^{\pi}\int_0^{\pi}\cdots\int_0^{2\pi}\left(\frac{dS}{d\Theta}\right)d\theta_1 d\theta_2 \ldots d\theta_{n-1}} \tag{A1}$$

The numerator is the expected selection response in the focal population, and the denominator is the response in the hypothetical unconstrained population. $R(\Theta)$ is the selection response to a selection gradient oriented in the direction given by the angles in the vector Θ whose elements are $\theta_1,\theta_2,\ldots,\theta_{n-1}$. The ratio $(dS/d\Theta)$ is the change in surface area of a unit sphere per change in the angles Θ, and is given by

$$\frac{dS}{d\Theta} = 2\prod_{i=1}^{n-2}\sin^i\theta_i \tag{A2}$$

(see http://en.wikipedia.org/wiki/Hypersphere).

Without loss of generality, we can choose coordinates that diagonalize the genetic covariance matrix. Then the eigenvalues are equal to the genetic variances (ordered from largest to smallest). The magnitude of the selection response to a given selection gradient β is

$$R = \left[\sum_{i=1}^{n}(\lambda_i\beta_i)^2\right]^{1/2} \tag{A3}$$

where λ_i is again the ith eigenvalue and β_i is the element of the selection gradient corresponding to that trait. For a selection gradient of unit length, R can be converted to the polar coordinates of Eq. A1 using

$$\beta_i = \cos^*_{i,n}(\theta_i) \prod_{j=1}^{i-1} \sin(\theta_j) \tag{A4}$$

where

$$\cos^*_{i,n}(\theta_i) = \begin{cases} \cos(\theta_i) & \text{if } i \neq n \\ 1 & \text{if } i = n \end{cases} \tag{A5}$$

Substituting Eqs. A2–A5 into (A1) gives the average selection response $\overline{R}$ in terms of integrals that can be evaluated numerically once the eigenvalues are specified.

I calculated $\overline{R}$ this way using *Mathematica* (Wolfram 2003) for the three scalar-valued data sets. The results are shown in Table 2. For the function-valued traits, the average selection response is 0 because only a finite number of eigenvalues are positive, but there are an infinite number of trait combinations on which selection could theoretically act.

To better understand how the distribution of eigenvalues affects $\overline{R}$, I then considered hypothetical populations in which the eigenvalues decline geometrically (exponentially). The ratio of successive eigenvalues of the standardized genetic covariance matrix, which is constant, is denoted k. Thus $k = 1$ is the case where all traits have equal genetic variance and no correlation, while if $k = 0$ all genetic variation lies along a single dimension. It is convenient to set the leading eigenvector to $\lambda_1 = 1$. The value of the ith eigenvalue is then

$$\lambda_i = k^{i-1}\lambda_1. \tag{A6}$$

Substituting that expression into (A3) and then numerically integrating (A1) using *Mathematica* (Wolfram 2003) gives the results shown in Fig. 3.

It is possible to get simple analytic expressions for two special cases. With $k = 1$, the population has no constraints, and one can show Eq. A1 is equal to unity (as it must). At the other extreme, consider the case of $k = 0$, so that all genetic variation lies in a single dimension. Then we get

$$\begin{aligned} \bar{R} &= \frac{\int_0^{\pi}\int_0^{\pi}\cdots\int_0^{2\pi} |\cos\theta_1| (\prod_{k=1}^{n-2} \sin^k\theta_k) d\theta_1 d\theta_2 \ldots d\theta_{n-1}}{\int_0^{\pi}\int_0^{\pi}\cdots\int_0^{2\pi} (\prod_{k=1}^{n-2} \sin^k\theta_k) d\theta_1 d\theta_2 \ldots d\theta_{n-1}} \\ &= \frac{2\Gamma(n/2)}{(n-1)\sqrt{\pi}\Gamma((n-1)/2)} \end{aligned} \tag{A7}$$

where $\Gamma()$ is the gamma function. This appears in the text as Eq. 5.

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