Abundant Genetic Variation + Strong Selection = Multivariate Genetic Constraints: A Geometric View of Adaptation

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Abstract

Evolutionary biology has struggled to explain the coexistence of two basic observations: genetic variation is found in almost all traits in the presence of strong natural and sexual selection in natural populations. These two observations are in direct conflict as such selection should deplete genetic variation. Furthermore, the presence of genetic variation in a trait, and selection acting on that trait, is often not sufficient for the trait to respond to selection. Here, we bring together geometric perspectives on mutation, selection, and genetic variation and show how the perceived incompatibility between these two observations is a consequence of taking a trait-by-trait approach to the multivariate problem of genetic variation and selection. We conclude that the simultaneous presence of widespead genetic variation in, and strong selection on, individual traits indicates that substantial mulitvariate genetic constraints are likely to be present in natural populations.

An unspeakable horror seized me. There was a darkness; then a dizzy, sickening sensation of sight that was not like seeing; I saw a Line that was no Line; Space that was not space: I was myself, and not myself. When I could find voice, I shrieked loud in agony, "Either this is madness or it is Hell". "It is neither," calmly replied the voice of the Sphere,

"*It is Knowledge.*"—*Flatland* (Edwin Abbott Abbott, 1884)

INTRODUCTION

At the core of evolutionary biology lie two observations from the natural world that together form one of the great scientific contradictions: substantial genetic variation is maintained in natural populations in the presence of strong selection. The first observation, the well-known ubiquity of genetic variation in individual traits (Lynch & Walsh 1998) has been demonstrated through numerous responses to artificial selection (Hill & Caballero 1992) and estimates of nonzero heritability (Mousseau & Roff 1987). There are few examples of traits that have been shown to have very low levels of genetic variance (Blows & Hoffmann 2005), and only the smallest of population sizes in nature appear to have an effect on the maintenance of genetic variation (Willi et al. 2007).

In addition to the presence of genetic variance in the vast majority of traits, the nature of this variation further exacerbates the contradiction. Life-history traits, which are more closely associated with fitness and, hence, assumed to be under stronger selection, tend to display more genetic variation (and even greater environmental variation and, hence, lower heritability) than other types of traits (Houle 1992). Mutational target size, rather than any association with the strength of selection, may therefore explain the variation among individual traits in standing genetic variance, as more complex life-history traits are affected by a greater proportion of the genome (Houle 1998).

Evidence for the second observation has been slower to accumulate, because it is based on measurements in natural populations: both linear and nonlinear selection in natural populations are common (Endler 1986, Kingsolver et al. 2001), and appear to be strong. Because strength is a relative term, the basis used to qualify such statements is critical. In the case of directional selection, Hereford et al. (2004) suggested a convenient approach that uses mean-standardized selection gradients that can then be compared to a selection gradient of one, which reflects the strength of selection on fitness itself. Comparisons on a mean-standardized scale are appropriate when the interest is in proportional changes in a trait (Houle 1992, Hansen & Houle 2008). Using a subset of the selection gradients collated by Kingsolver et al. (2001), Hereford et al. (2004) found that the median strength of directional selection is 31% of that on fitness itself. Johnson & Barton (2005) used the quadratic selection gradients collated by Kingsolver et al. (2001) to show that stabilizing selection is far stronger in natural populations than the typical values used in theoretical models to account for the observed levels of genetic variation.

As directional and stabilizing selection should deplete genetic variation, these two fundamental observations of widespread variation and strong selection are in direct conflict. Establishing plausible mechanisms that might account for the maintenance of so much genetic variation has been a priority in theoretical population genetics (Barton & Turelli 1987, Bulmer 1989, Bürger 1998, Turelli & Barton 2004, Zhang et al. 2002). To date however, there is currently no compelling explanation for the maintenance of the observed high levels of genetic variation in fitness traits given the established strength of selection (Johnson & Barton 2005).

The link between this fundamental contradiction at the heart of evolutionary biology on one hand, and genetic limitations to the response to selection on the other, may not be immediately apparent, but firmly establishing this link is the primary goal of this review. Placed in the context

of lots of genetic variation and lots of selection, it would be easy to dismiss the importance of genetic limitations to the response to selection, as these two conditions should equate to lots of evolution in natural populations. The problem is, they don't. Long-term studies of contemporary populations suggest stasis is more common than evolutionary change in the presence of both ample genetic variance and strong selection (Merilä et al. 2001, Kruuk et al. 2002). Similarly, selection experiments in which selection is applied in the direction of higher fitness by the organisms themselves tend to display no response (Hall et al. 2004, McGuigan et al. 2008). It therefore seems that the potential for evolutionary change measured in terms of individual trait heritabilities does not agree very well with the observed evolutionary changes under natural conditions or under laboratory conditions that attempt to closely mimic them.

Some Back-of-the-Envelope Calculations Point the Way

Although in isolation the generality of each of these two observations, widespread genetic variance and strong selection, is not in question given the enormous number of studies that underlie them, the apparent contradiction of their coexistence rests on a trait-by-trait assessment of quantitative variation and selection. Taking this approach ignores any pleiotropic genetic association among traits or the possibility of correlational selection among traits. Barton (1990; Johnson & Barton 2005) highlighted why a trait-by-trait approach might be misleading using two simple calculations:

1. **Pleiotropy: there cannot be a large number of genetically independent traits**. Determining the degree of pleiotropy is difficult, but the limited data on mutation rates suggest a lower limit to the number of genetically independent traits within an organism. With a per-trait mutation rate of around 0.1, and a whole-genome mutation rate of around 1, the number of pleiotropically independent traits is likely to be in the order of 10s rather than the 100s or 1000s.
2. **Correlational selection: there cannot be a large number of independent traits under true stabilizing selection**. If there are a large number of traits that exhibit substantial levels of genetic variation, and hence phenotypic variation, that are also under stabilizing selection, then many individuals must deviate significantly from the optimum phenotype, and average fitness must be low. Under a Gaussian model of stabilizing selection on n roughly equal (and phenotypically uncorrelated) traits, the reduction in fitness caused by a deviation from the optimum is approximately nV_G/V_s. Here, V_s measures the strenght of selection (smaller V_s, corresponding to a more sharply declining fitness function, equals stronger selection) and V_G is the additive variance for each trait. Given this amount of fitness reduction, only about 10 traits can have $V_s < 10\ V_G$.

These rough calculations suggest that trait-by-trait explanations of the natural world are doomed to fail. In this review, we outline the alternative to a trait-by-trait view of selection and genetic variation, building from Fisher's geometrical view of an organism. We show how the distribution of mutations, standing genetic variance among sets of traits, and the pattern of selection acting on them, do not conform to the two fundamental observations of the trait-by-trait approach. Ironically, we conclude that the apparent conflict between our two observations of widespread genetic variance and strong selection in natural populations may indicate that substantial multivariate genetic constraints on the response to selection are present in nature.

A GEOMETRIC VIEW OF MUTATIONS AND PHENOTYPES

A debate common across essentially all scales of biology (from metabolic networks to ecosystems) is the degree to which the various components of biological systems are at least somewhat

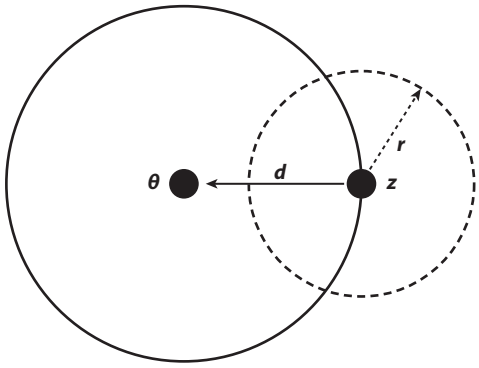

Figure 1

Fisher's (1930) model for the probability that a new mutation increases fitness. The optimal fitness value is given by θ; the phenotype of the individual about to experience a mutation is z, which is at (Euclidean) distance d from the optimum. The solid circle denotes the fitness contour passing through the current value z, so that all points inside this line have higher fitness than z. The effect of the new mutation is to move the expected phenotype by some (Euclidean) distance r in a random direction about z, with the space of possible new phenotypes denoted by the dotted circle. The probability of increased fitness is the fraction of the circumference of the dotted circle that resides inside (closer to θ) of the solid circle.

autonomous. On one hand, it is clear that every component is not completely independent, yet on the other hand there are certainly degrees of freedom even among sets of components under strong constraints. The issue is the effective number of independent components given some criteria. The traits that comprise an organism are certainly no different. A further issue is that the effective "degrees of freedom" may vary with the criteria. For example, it might prove to be the case that there are more developmental degrees of freedom than there are fitness degrees of freedom, so that (hypothetically) organisms have a greater flexibility to evolve than is observed, but this is constrained by evolution through natural selection being able to act (at any given time) independently on only a subset of the possible morphologies. Others might argue that the converse is true, with selection offering more degrees of freedom, but being constrained by variation at the developmental level.

Geometry offers a powerful approach for considering some of these issues, as first noted by Thompson (1917) in his attempt to place organismal morphology in a geometric framework. Thompson suggested we can view traits as forming a complex, high-dimensional geometric space. Such a viewpoint immediately suggests caution when attempting to infer the nature of this high-dimensional space by simply looking at the properties of the univariate projections for a few chosen traits. Edwin Abbot Abbott (1884), in his deep and quirky *Flatland*, noted the errors of such a Flatlandian view of complex structures, a central theme we return to.

Fisher (1930) offered a highly simplified, yet elegant and powerful, geometric argument relating the number of independent traits (as measured by fitness consequences) to the probability of adapation. **Figure 1** shows the basic structure of his model; the key parameters are the distance d the current phenotype is from a fitness optimum and the jump size r of a new mutation. For n traits, Fisher showed that the probability of adaptation (the mutation having higher fitness) is a function of a single parameter,

$$x = \frac{r\sqrt{n}}{2d}; \qquad 1.$$

the probability of adaptation is given by

$$p_{adp} = \frac{1}{\sqrt{2\pi}} \int_x^\infty \exp(-y^2/2)dy = 1 - erf(x), \qquad 2.$$

where *er f* denotes the error function. Fisher's critical observation was that this probability is a decreasing function of x, so that anything that increases x decreases the chance of adaptation, and conversely anything decreasing x increases the chance of adaptation. The key component of x is r/d, the ratio of the jump size of the mutation relative to the distance from the optimum. At large distances (large d), large mutations have a reasonable chance of increasing fitness. However, as the phenotype gets close to its optimal value, only small mutational jumps are likely to be adaptive. Further, x scales as the square root of the number of traits. Thus, the more traits, the smaller the chance of adaptation.

Kimura (1983) and Orr (1998, 2000) extended Fisher's model by considering the probability of fixation, not simply the probability that a mutation is adaptive. Mutations of very small effect have a probability of being adaptive approaching 0.5 [as $erf(0) = 0.5$], but a probability of fixation approaching that for a neutral allele. Orr (2000) found that the optimal jump size to maximize the probability of fixation is roughly $1.85d/\sqrt{n}$, again showing a "cost of complexity," with mutations affecting more traits having smaller optimal jump size. Orr found that the rate of adaptation is even more constrained by the number of traits, scaling faster than $1/n$. Hence, Fisher's model predicts the rate of fixation for highly pleiotropic mutations is a rapidly decreasing function of the number n of independent traits with direct effects on fitness.

It is critical to point out a key simplifying assumption made by Fisher: All traits have the same fitness curvature. A much more realistic view is that a fitness surface has a few dimensions under strong selection (and, hence, large curvature) and a very large number of dimensions of very low curvature (weak selection), a point also suggested by Barton (1990). Rice (1990) shows, in cases where the fitness surface varies across traits, that the probability of adaptation is a function of the "effective curvature," which is roughly their harmonic mean. Thus, the probability of adaptation is dominated by fitness surfaces of low curvature. On such a surface, the probability of an adaptive mutation is high, but its actual effect on fitness is very low and, hence, the fixation probability nearly neutral. Wagner et al. (2008a) recently suggested that a second assumption, namely that the total mutational effect d is assumed under the Fisher model to be independent of the number of traits, may be unwarranted. Their analysis of QTL data for 70 mouse skeletal traits showed that the vector of total mutational effects d scales with the number of traits (but also see Hermisson & McGregor 2008, Wagner et al. 2008b).

A GEOMETRIC VIEW OF GENETIC VARIATION

The importance of a geometrical view of genetic constraints is inherent in Fisher's concept of independent trait combinations comprising an organism's phenotype. The development of a multivariate view of genetic constraints was, however, very slow through the twentieth century (Arnold 1992), and it wasn't until Dickerson's (1955) illustration of how deceptive heritabilities and genetic correlations could be that a geometric approach to the level of genetic variance was taken. Dickerson considered four traits with a genetic covariance matrix $\mathbf{G}$ of the form

$$\mathbf{G} = c \cdot \begin{pmatrix} 1 & -1/3 & -1/3 & -1/3 \\ -1/3 & 1 & -1/3 & -1/3 \\ -1/3 & -1/3 & 1 & -1/3 \\ -1/3 & -1/3 & -1/3 & 1 \end{pmatrix}.$$

The diagonal elements in **G** correspond to the genetic variances of the traits, whereas the off-diagonal elements correspond to genetic covariances. Dickerson considered the response to selection on the index $I = z_1 + z_2 + z_3 + z_4$, which can be written as $I = \mathbf{b}^T\mathbf{z}$, where **b** is a vector of ones. Selection on I represents selecting on the combination of increasing all traits simultaneously. The genetic variance of I is given by $\mathbf{b}^T\mathbf{G}\mathbf{b}$ (Lin & Allaire 1977) and is zero for the above **G**, so that there is no response in the index despite each of its components having significant heritability. The reason for the lack of response follows from the geometry of **G**, which has a zero eigenvalue whose corresponding eigenvector points along the direction of I and, thus, has no genetic variance.

A formal framework for multivariate genetic constraints did not appear until Lande's (1979) development of the multivariate breeders equation $\Delta\mathbf{z} = \mathbf{G}\beta$, relating the vector of responses $\Delta\mathbf{z}$ (changes in trait means) with the genetic variance-covariance (**G**) matrix and the vector of linear selection gradients (β). Unfortunately, the implications of how genetic constraints are manifested within **G** remained largely underappreciated by evolutionary biologists, as the empirical focus has been primarily directed at the estimation and interpretation of the scaled individual components of **G** (trait heritabilities and bivariate genetic correlations) rather that the actual geometry of **G** (Blows 2007).

The Deceptive Nature of Simple Quantitative Genetic Parameters

With numerous experiments demonstrating genetic variance in almost any trait, the presence of genetic variance in a given metric character can be safely assumed (Lynch & Walsh 1998), and the lack of genetic variance has therefore been viewed as an unlikely mechanism for widespread genetic constraints (Brakefield 2003). Dickerson's (1955) example shows why this general observation has little value with regard to genetic constraints, when more than one trait is under selection and traits are genetically correlated to some extent. Even with (equal) genetic variance in all individual traits, in the presence of modest negative genetic correlations between them, there could exist trait combinations with no genetic variance (the eigenvectors associated with any zero eigenvalues) and, hence, no ability to respond to selection. Likewise, absence of negative correlations by no means guarantees that **G** is not singular, as one can easily construct singular matrices that contain only positive correlations.

In contrast to a lack of genetic variance in individual traits, genetic correlations have remained a central component of the discussion on life-history trade-offs and genetic constraints (Roff & Fairbairn 2007). There are two aspects to a genetic correlation that can be considered here. First, the magnitude of a genetic correlation has been taken as an indication of the strength of the genetic constraint. A number of two-trait artificial selection experiments have demonstrated that response along a direction orthogonal to strong genetic correlations is easily obtainable (Beldade et al. 2002, Conner 2003), suggesting that such genetic correlations do not represent effective constraints.

When viewed from a multivariate perspective, the success of such selection experiments emphasizes that bivariate genetic correlations should not be viewed as absolute constraints unless they are perfect (that is, equal to 1 or −1). Strong, but nonperfect, genetic correlations describe the distribution of genetic variance in the two-dimensional space and indicate that some (lower) level of genetic variance remains in the direction orthogonal to the major axis of the genetic correlation. Consequently, a response to selection under such conditions is not unexpected.

Second, the sign of genetic correlations has received considerable attention in determining genetic constraints among life-history traits. Lande (1982) and Rose (1982) first drew attention to the potential role that negative genetic correlations might have in underlying such trade-offs. A search for negative genetic correlations ensued, which established that most genetic correlations

are in fact positive, although with correlations among life-history traits tending to be more negative than either correlations among morphological or behavioral traits (Roff 1996).

In an early warning, Pease & Bull (1988) suggested that the focus on negative genetic correlations was misplaced, and under the assumption that more than two traits were involved, no consistent pattern of genetic covariance between any two traits should be expected. Returning to Dickerson's example, this **G** matrix was purposely constructed to result in an absolute genetic constraint for increasing all traits simultaneously by setting all genetic correlations to $-1/(n-1)$, but this should not be taken to indicate that all genetic correlations among important life-history traits are expected to be negative. For models where genetic correlations arise in part because of functional constraints among the traits, Charlesworth (1990, 1993) showed that at least one negative genetic correlation is required for a population to be at equilibrium under selection, but that in sufficiently complex situations (more than two traits), positive genetic correlations inevitably arise. Further, analysis of resource partitioning models (wherein some loci are involved in acquisition of the common resource for two traits and others are involved in partitioning this resource among the traits) show that positive genetic correlations can easily arise between traits, for example if there is significant genetic variation in resource allocation and little variance in partitioning (Houle 1991, van Noordwijk & de jong 1986). Because bivariate genetic correlations are therefore of little use in isolation in defining genetic constraints in all but the most simple of systems, alternative indicators of genetic constraint are required.

Understanding the Geometry of G is Critical to Understanding Constraints

The multivariate breeder's equation $\mathbf{\Delta z} = \mathbf{G}\boldsymbol{\beta}$ hides a great deal of biological complexity within its elegant framework. Matrix multiplication of a vector results in a rotation and scaling of the original vector to a new one. Thus, the response vector $\mathbf{\Delta z}$ represents a rotation and a scaling of the vector of selection gradients $\boldsymbol{\beta}$ by **G**. A classic result of Lande (1979) is that when the vector **z** of trait values is multivariate normal, $\boldsymbol{\beta}$ is the gradient of log mean fitness with respect to **z**. Thus, the direction given by $\boldsymbol{\beta}$ is the optimal direction to change the means of **z** to maximally increase mean fitness. The actual response $\mathbf{\Delta z}$ is rotated (and scaled) off of this optimal direction by **G**, and hence it is the geometry of this rotation (the geometry of **G** itself) that generates various levels of genetic constraints. In milder cases of constraint, the angle between the optimal and actual directions of response is modest. Such cases can include the sign of the change in a particular trait not equaling the sign of its selection gradient—the trait mean changes in a different direction than that favored by selection. Likewise, traits with large absolute values for their gradients may show small amounts of change. Scaling and rotation away from the optimal direction results in the rate of evolution being slowed down. Although this may not be a problem in many cases, in a rapidly changing environment a significant reduction in the rate of response may lead to population extinction. The extreme case of a constraint is when there is no response over the entire vector of traits.

The geometry of **G** is given by its spectral decomposition, expressing **G** as a function of its eigenvalues and associated eigenvectors,

$$\mathbf{G} = \lambda_1 \mathbf{e}_1 \mathbf{e}_1^T + \lambda_2 \mathbf{e}_2 \mathbf{e}_2^T + \cdots + \lambda_n \mathbf{e}_n \mathbf{e}_n^T. \qquad 3.$$

Here, λ_i is an eigenvalue of **G** and $\mathbf{e}_i$ its associated eigenvector, satisfying $\mathbf{G}\mathbf{e}_i = \lambda_i \mathbf{e}_i$. Thus, the eigenvectors represent the coordinate system (axes) inherent in **G** (the rotational aspect of **G**), whereas λ_i represent the scaling on this new coordinate axis given by $\mathbf{e}_i$. The importance of this decomposition becomes apparent when we consider the projection of one vector onto another.

The projection of $\boldsymbol{\beta}$ on $\mathbf{e}_i$ is given by

$$\text{Proj}(\boldsymbol{\beta} \text{ on } \mathbf{e}_i) = \left(\mathbf{e}_i^T \boldsymbol{\beta}\right) \mathbf{e}_i. \quad 4.$$

Note that the inner product $\mathbf{e}_i^T \boldsymbol{\beta}$ is a scalar, whereas the actual direction of the projection is along the vector $\mathbf{e}_i$, so that the projection onto $\mathbf{e}_i$ is a scaled (by $\mathbf{e}_i^T \boldsymbol{\beta}$) vector pointing in the direction of $\mathbf{e}_i$. When we multiply $\mathbf{G}$ and $\boldsymbol{\beta}$, Equations 3 and 4 [noting that $\mathbf{e}_1 \mathbf{e}_1^T \boldsymbol{\beta} = (\mathbf{e}_1^T \boldsymbol{\beta}) \mathbf{e}_1$] imply

$$\begin{aligned} \boldsymbol{\Delta z} = \mathbf{G}\boldsymbol{\beta} &= \lambda_1 (\mathbf{e}_1^T \boldsymbol{\beta}) \mathbf{e}_1 + \lambda_2 (\mathbf{e}_2^T \boldsymbol{\beta}) \mathbf{e}_2 + \cdots + \lambda_n (\mathbf{e}_n^T \boldsymbol{\beta}) \mathbf{e}_n \\ &= \lambda_1 \text{Proj}(\boldsymbol{\beta} \text{ on } \mathbf{e}_1) + \lambda_2 \text{Proj}(\boldsymbol{\beta} \text{ on } \mathbf{e}_2) + \cdots + \lambda_n \text{Proj}(\boldsymbol{\beta} \text{ on } \mathbf{e}_n). \end{aligned} \quad 5.$$

Thus, we can break the response vector $\boldsymbol{\Delta \mathbf{z}}$ into the sum of scaled projections of $\boldsymbol{\beta}$ onto each of the eigenvectors of $\mathbf{G}$. If the majority of $\boldsymbol{\beta}$ lies along the direction of an eigenvector with a very small eigenvalue (that is, this direction accounts for very little of the total genetic variance in $\mathbf{G}$), then the response will also be small. A second way to view the constraints imposed by the geometry to $\mathbf{G}$ is to note that $\mathbf{e}_i^T \boldsymbol{\beta} = ||\boldsymbol{\beta}|| \cos[\theta(\boldsymbol{\beta}, \mathbf{e}_i)]$, where $\|\boldsymbol{\beta}\|$ is the length of the selection gradient and θ is the angle between the two vectors. Equation 5 then becomes

$$\boldsymbol{\Delta} z = ||\boldsymbol{\beta}|| \sum_{i=1}^{n} \lambda_i \cos[\theta(\boldsymbol{\beta}, \mathbf{e}_i)] \mathbf{e}_i. \quad 6.$$

The use of angles between $\boldsymbol{\beta}$ and geometric components of $\mathbf{G}$ in this fashion underlies a number of recent attempts to describe multivariate genetic constraints, which we detail below.

Multivariate Genetic Constraints

Armed now with an understanding of the geometry of $\mathbf{G}$, it can be readily shown why simple quantitative genetic measures of genetic variation and covariation have been unsuccessful in demonstrating genetic constraints. As both Equation 5 and Dickerson's example effectively show, it is the eigenvalues of the $\mathbf{G}$ matrix that are more informative than heritabilities or genetic correlations when considering genetic constraints. A zero eigenvalue suggests an absolute genetic constraint exists for some combination of the constituent traits (Lande 1979, Mezey & Houle 2005, Pease & Bull 1988). Consequently, the rank of $\mathbf{G}$ (the number of nonzero eigenvalues) provides a convenient and unambiguous way of determining the presence of absolute genetic constraints.

Unfortunately, defining an absolute multivariate genetic constraint is much easier than establishing the presence of one. To begin with, we operationally deal with an estimate $\hat{\mathbf{G}}$ of the true genetic covariance matrix, and this estimate is itself based on estimates of the breeding values. It is not possible to demonstrate in a hypothesis-testing sense that a particular trait or trait combination has zero genetic variance (Mezey & Houle 2005). Instead, there has been considerable recent interest in determining how much of the genetic variance estimated in a particular $\mathbf{G}$ matrix has statistical support, and how many dimensions (orthogonal trait combinations) are required to describe the subspace that this significant genetic variance is confined to.

The first issue to consider in determining whether $\mathbf{G}$ is of less than full rank, is the phenotypic dimensionality of the set of traits under study. Multivariate phenotypic measures can often exhibit very high phenotypic correlations among each other, particularly if they have been made on similar morphological traits (e.g., linear measures of body parts). If the resulting phenotypic covariance matrix ($\mathbf{P}$) is singular, redundant information is contained in the set of traits (the problem of multicollinearity), and $\mathbf{G}$ is also singular (Pease & Bull 1988). The rank of $\mathbf{P}$ therefore sets an

upper limit to the rank of **G** and can be estimated if repeated phenotypic measures are made on the same individuals (McGuigan & Blows 2007).

The statistical determination of the rank of a genetic covariance matrix is not straightforward and remains a subject of active inquiry (Meyer & Kirkpatrick 2008). In general, fitting reduced-rank covariance matrices at the appropriate level within a mixed-model framework is perhaps the most well-developed and readily available approach to this problem (Hine & Blows 2006, Kirkpatrick & Meyer 2004), but tends to produce biased estimates under a disconcertingly wide range of conditions (Meyer & Kirkpatrick 2008). A step-down approach, moving from full rank to lower ranks, helps identify when problems occur (Meyer & Kirkpatrick 2008).

Although rank can be used as an indicator of the extent of absolute multivariate genetic constraint, milder genetic constraints can exist in the presence of full rank. A covariance matrix is considered "ill-conditioned" if the sizes of the eigenvalues have a very uneven distribution; for example, the dominant eigenvalue may be one or more orders of magnitude greater than those describing the remainder of the space. To quantify the extent of ill-condition of a genetic covariance matrix, Kirkpatrick (2009) proposed a measure of the effective number of dimensions based its eigenvalues,

$$n_D = \sum_{i=1}^{n} \frac{\lambda_i}{\lambda_1}, \qquad 7.$$

where a value of one indicates all the genetic variance in the set of traits is accounted for by the first (largest) eigenvalue λ_1, and a value of n indicates that the **G** matrix is spherical (that is, equal genetic variance exists in all directions). Wagner (1984) proposed a similar measure based on the variance of the eigenvalues λ_c of the correlation matrix associated with **G**

$$n_d = n - \sigma^2(\lambda_c). \qquad 8.$$

From the limited data sets available, Kirkrpatrick (2009) summarized the extent of multivariate constraints, finding that it is often the case that **G** matrices are ill-conditioned, with most of the genetic variance in a set of traits residing in the first one or two dimensions. These observations support Barton's first conjecture, that there is likely to be substantially fewer genetically independent traits than phenotypes measured.

A final important point is that highly ill-conditioned covariance matrices can arise even in the simplest setting—under the mutation-drift equilibrium where the eigenvalues of the mutational mutations are all uniform (that is, a spherical distribution of new mutational effects). Griswold et al. (2007) showed that the shared genealogies owing to drift results in the distribution of eigenvalues of **G**, that declines at an approximately exponential rate. Clearly, the importance of drift in shaping the geometry of **G** has been significantly underappreciated.

The Ultimate Genetic Constraint: Genetic Variance in Fitness

Of course, the ultimate genetic constraint is the genetic variance in fitness itself. There are several ways in which one can approach thinking about this variance. The first approach, and the one most used by empiricists, has been to attempt to measure the genetic variance in fitness using a univariate metric that represents fitness in some way. This is notoriously difficult in cross-sectional empiricial studies, as single fitness components are likely to be poor predictors of life-time reproductive success (Hunt et al. 2004). By their very nature, longitudinal studies under field conditions have a greater opportunity to measure the genetic variance in life-time reproductive success. Six recent applications of the animal model in pedigreed populations of free-living vertebrates (reviewed by Kirkpatrick 2009) currently suggest no clear pattern, with both zero and substantial

Table 1 Various historical measures of genetic constraints. z is a vector of *n* traits, which genotypic and genetic covariances matrices P and G, with $\lambda_1 \geq \lambda_2 \geq \cdots \lambda_n$ the *n* eigenvalues for G with $\mathbf{e}_i$ the (unit) eigenvector associated with λ_i

Dickerson (1955)	Low heritability along the trait index selection $I = \mathbf{b}^T\mathbf{z}$ $h_I^2 = \mathbf{b}^T\mathbf{G}\mathbf{b}/\mathbf{b}^T\mathbf{P}\mathbf{b} \simeq 0$, where selection is on the index *I*.
Lande (1979)	Singular **G**
Lande (1982), Rose (1982)	Negative genetic correlations
Wagner (1984)	Dispersion of eigenvalues of the correlation matrix for **G** $n_d = n - \sigma^2(\lambda_c)$
Schluter (1996)	Angle between leading eigenvector of **G** and response $\boldsymbol{\Delta}\mathbf{z}$ $\theta = \cos^{-1}(\mathbf{e}_1^T\boldsymbol{\beta}/\|\|\boldsymbol{\beta}\|\|)$
Hansen (2003)	Residual genetic variance remaining on **y** given **x**. $C(\mathbf{y}\|\mathbf{x}) = \mathbf{G}_\mathbf{y} - \mathbf{G}_\mathbf{yx}\mathbf{G}_\mathbf{x}^{-1}\mathbf{G}_\mathbf{xy}$
Blows et al. (2004)	Angle between $\boldsymbol{\beta}$ and the projection of $\boldsymbol{\beta}$ into the subspace of **G** given by its first $\boldsymbol{k}$ eigenvectors, namely the angle between **p** and $\boldsymbol{\beta}$, where $\mathbf{p} = \mathbf{P}_{roj}\boldsymbol{\beta} = \mathbf{A}(\mathbf{A}^T\mathbf{A})^{-1}\mathbf{A}^T\boldsymbol{\beta}$, with $\mathbf{P}_{roj} = \mathbf{A}(\mathbf{A}^T\mathbf{A})^{-1}\mathbf{A}^T$, where $\mathbf{A} = (\mathbf{e}_1, \mathbf{e}_2, \ldots, \mathbf{e}_k)$
Kirkpatrick (2009)	Dispersion of eigenvalues of **G** $n_D = \sum_{i=1}^{n} \lambda_i/\lambda_1$
Blows & Walsh (2008)	Angle θ between $\boldsymbol{\Delta}\mathbf{z}$ and β
Hansen & Houle (2008)	$\theta = \cos^{-1}(\boldsymbol{\Delta}\mathbf{z}^T\boldsymbol{\beta}/[\|\|\boldsymbol{\beta}\|\| \cdot \|\|\Delta\mathbf{z}\|\|])$

estimates reported. One complicating factor highlighted by Kirkpatrick (2009) is that the genetic correlation between male and female fitness may be negative as a consequence of the evolution of sexual dimorphism (Lande 1980). Therefore, some genetic variance for fitness in each sex may be maintained by this antagonistic pleiotropy. In other words, the maintenance of genetic variance in fitness needs to take into account the fact that genes occur in males and in females in successive generations in just the same fashion as when considering levels of genetic variance among multiple traits.

A second approach is more indirect: Determine which quantitative traits are associated with fitness using fitness-trait associations at the phenotypic level (Lande & Arnold 1983), and then determine how the multivariate distribution of genetic variance is oriented with respect to the direction of selection $\boldsymbol{\beta}$ (**Table 1**). This potentially allows us to infer from trait genetic variances the level of usable genetic variance in fitness. The first attempts along this line of reasoning were by Schluter (1996), who proposed that the angle between the first eigenvector of **G** with the major axis of population divergence is one indication of genetic constraint. Schluter found that, for recently diverged populations, the angle was small for a set of morphological traits that were likely to be under selection, suggesting that evolution trends to proceed along lines of genetic least resistance (that is, along axes of maximal genetic variation). Expanding upon this approach, Blows et al. (2004) considered a subspace of **G** composed of the first *k* eigenvectors accounting for the majority of the genetic variation. By projecting $\boldsymbol{\beta}$ onto this subspace (that is, taking the first *k* terms of either Equations 3 or 4), a measure of constraint is given by the angle between $\boldsymbol{\beta}$ and the projection of $\boldsymbol{\beta}$ into the subspace. If this angle is large, most usable genetic variation is orthogonal (or nearly so) to the direction of selection.

Although using subspaces of **G** in this way allows a dissection of how the majority of genetic variance is orientated with respect to either the observed direction of evolutionary change (Schluter 1996) or in the direction of $\boldsymbol{\beta}$ (Blows et al. 2004), the entire space of **G** is not considered using such

approaches. A first step in incorporating the entire space of **G** in a measure of genetic constraint is the genetic variation associated with selection on the index $w = \boldsymbol{\beta}^T\mathbf{z}$, which is given by $\boldsymbol{\beta}^T\mathbf{G}\boldsymbol{\beta}$ (Lin & Allaire 1977). We can also think of this as the projection of $\boldsymbol{\beta}$ through **G** (**Table 1**), returning the genetic variance in the direction of selection. Although this measure is useful if interpreted in the context of the level of genetic variance in univariate traits (e.g., Van Homrigh et al. 2007), it does not provide a metric of constraint that can be easily compared across studies in the absense of this study-specific context. A widely applicable metric to measure multivariate constraint that can be compared across studies is the angle between $\boldsymbol{\beta}$ and the predicted response to selection from the multivariate breeders equation, $\boldsymbol{\Delta}\mathbf{z}$ (Blows & Walsh 2008, Hansen & Houle 2008) (**Table 1**). Here, an angle of zero would be indicative of no constraint, whereas an angle of 90° Would represent an absolute constraint. It is important to note that this multivariate definition of genetic constraint removes the need (suggested by Roff & Fairbairn 2007) for maintaining a distinction between absolute and milder genetic constraints.

Finally, Kirkpatrick (2009), Wagner et al. (2008a), and Hansen & Houle (2008) provide related metrics for determining the general tendency for a particular **G** matrix to act as a constraint given a randomly chosen selection gradient (**Table 1**). Of particular interest here is the demonstration by Kirkpatrick (2009) that as the number of traits under selection increases, the average selection response in a random direction decreases for a given effective number of dimensions, suggesting an additional cost of complexity to those already identified (Fisher 1930, Orr 1998). This arises because most of the genetic variation in **G** is concentrated in a lower-order space.

Conditional Genetic Variance in Fitness and Missing Traits

A third approach to thinking about the genetic variance in fitness is Robertson's secondary theorem of natural selection, which considers the genetic covariance between a set of traits and fitness (Crow & Nagylaki 1976; Robertson 1966, 1968). Robertson's theorem states that the response in a trait equals the additive genetic covariance of the trait with fitness,

$$\Delta z = \sigma_A(z, w). \qquad 9.$$

This formulation immediately suggests that even though a set of traits may be under selection, not all of the genetic variance in these traits may contribute to the response to selection as some of this genetic variance may not genetically covary with fitness. Surprisingly, the concept of traits genetically covarying with fitness has had a limited impact on empirical studies. Rausher (1992; Stinchcombe et al. 2002) pointed out that determining the fitness-traits associations commonly conducted at the phenotypic level using multiple regression (Lande & Arnold 1983) might be better applied on genotypic values (sire means or predicted breeding values). In this fashion, any environmental covariance would be removed from the fitness-trait associations. Unfortunately, using predicted breeding values in this way is likely to result in biased estimates (Hadfield 2008, Postma 2006).

An alternative approach to the analysis of the genetic covariance between fitness and candidate traits is to model the genetic basis of fitness and the traits together in a single framework. For example, a first step would be to model the genetic covariance between fitness and a single trait in a bivariate genetic analysis (Hadfield 2008). When more traits are involved, the choice of statistical framework is not so straightforward (Thompson 2008) as the underlying biological model involves an element of causation; the trait values result in fitness and not vice versa. The notion that a part of the genetic variance in a focal trait covarys with genetic variance in a set of other traits, and that another part of the genetic variance in the focal trait does not, has been an important concept in applications of index selection (Kempthorne & Nordskog 1959). More recently, this approach

has been developed in an evolutionary context by Hansen and colleagues (Hansen 2003, Hansen et al. 2003, Hansen & Houle 2008). Hansen (2003; Hansen et al. 2003) defined the conditional genetic variance for a vector of traits **y** as that part of the genetic variance in **y** that is independent of the genetic variance in a set of traits **x**,

$$C(\mathbf{y}|\mathbf{x}) = \mathbf{G}_{\mathbf{y}} - \mathbf{G}_{\mathbf{yx}}\mathbf{G}_{\mathbf{x}}^{-1}\mathbf{G}_{\mathbf{xy}}. \quad 10.$$

If one now considers **y** in Equation 10 to be the univariate trait of fitness, it is possible to ask the very useful question: How much of the genetic variance in fitness is explained by the genetic variance in the traits in **x**? This is important because it offers the possibility to address perhaps the major problem in multivariate analyses of selection and genetic constraint—determining whether important traits that confer fitness have been left out of the analysis. Taking $\mathbf{y} = w$, Equation 10 becomes

$$\sigma^2(w|\mathbf{z}) = \sigma^2(w) - \sigma(\mathbf{z}^T, w)\mathbf{G}_{\mathbf{z}}^{-1}\sigma(w, \mathbf{z}). \quad 11.$$

Recalling Equation 9 gives $\sigma(w, \mathbf{z}) = \boldsymbol{\Delta}\mathbf{z} = \mathbf{G}\boldsymbol{\beta}$, and Equation 11 becomes

$$\sigma^2(w) - \sigma^2(w|\mathbf{z}) = (\boldsymbol{\Delta}\mathbf{z})^T\,\mathbf{G}^{-1}\boldsymbol{\Delta}\mathbf{z} = \boldsymbol{\beta}^T\mathbf{G}\boldsymbol{\beta}. \quad 12.$$

Thus, the genetic variance in fitness not accounted for by **z** is just $\sigma^2(w) - \boldsymbol{\beta}^T\mathbf{G}\boldsymbol{\beta}$. If this difference is small, we have likely included most important traits in our analysis. It is important to remember that Equations 11 and 12 refer to the additive genetic variance of fitness, as opposed to the absolute variance in fitness itself.

The concept of conditional genetic variance is closely aligned with the concept of morphological integration of the phenotype (Hansen et al. 2003), where sets of traits (modules) display higher phenotypic correlations among each than between modules (Cheverud 1996, Olson & Miller 1958, Wagner & Altenberg 1996). Mitteroecker & Bookstein (2007) suggested the use of factor analysis as one way of identifying integrated sets of phenotypic traits:

$$\hat{\boldsymbol{\Sigma}} = \boldsymbol{\Lambda}\boldsymbol{\Lambda}^T + \boldsymbol{\Psi}, \quad 13.$$

where $\boldsymbol{\Lambda}$ is a lower triangular matrix of constants that represent the factor loadings of the underlying latent variables, and $\boldsymbol{\Psi}$ is a diagonal matrix containing the specific variances for each trait. Specific variances in such a model represent that part of the variation in a trait that is independent from the other traits included in the model. The part of the variation in a trait that is shared with the other traits in the model is captured by the factors modeled in $\boldsymbol{\Lambda}$. Often it is desirable to model $\hat{\boldsymbol{\Sigma}}$ as less than full rank.

This statistical framework can be extended to incorporate the modeling of conditional genetic variance where the factor-analytic covariance structure in Equation 13 is fit at the appropriate genetic level of a quantitative genetic experimental design in a mixed model. Although Equation 10 allows the genetic variance in a trait to be partitioned, and the resulting conditional genetic variance is a REML estimate if the constituent genetic variances and covariances have been estimated using REML (Hansen et al. 2003), such a mixed model employing a factor-analytic covariance structure would allow the conditional genetic variance to be estimated within an hypothesis-testing framework. Hansen's conditional genetic variance would then equate to the specific variances in $\boldsymbol{\Psi}$. The specific genetic variances from such a model could then be tested for significance using standard log likelihood ratio tests. If it was determined that fitness had a nonzero specific genetic variance, it could then be concluded that important traits that contribute to fitness have been excluded from the analysis.

A GEOMETRIC VIEW OF NONLINEAR SELECTION

Quantitative genetics has developed over the past 100 years with a great deal of interaction between animal and plant breeders on the one hand, and evolutionary biologists on the other. One area in which perhaps not enough emphasis has been placed on where the interests of these two groups diverge is in the response to selection. Artificial selection has been very successful in achieving a response to selection in virtually any trait, which is likely to have been a consequence of selection for very simple (unidimensional in most cases) metric traits (Riska 1989). Hansen & Houle (2004) suggested that such responses might be based on the genetic variance generated by numerous deleterious pleiotropic mutations ("junk" genetic variance) and that most such variation would be unlikely to form the basis of a response to selection in natural populations. Irrespective of whether the genetic details of the response to selection may differ between artificial selection and selection in natural populations (an open question, Hansen & Houle 2008), the geometry of multivariate genetic variance and the direction of linear selection can have important consequences for the response to selection as outlined in detail above.

Although directional (linear) selection is the primary concern of animal and plant breeders, it is not the only, or perhaps even the most frequent, form of selection expected in natural populations. Nonlinear selection, and particularly stabilizing (Travis 1989) and correlational (Lande & Arnold 1983, Schluter & Nychka 1994) selection are predicted to be very common if natural populations closely track selective optima in the field. It was therefore surprising when a review of empirical estimates of nonlinear selection found little evidence for strong stabilizing (or disruptive) selection in natural populations, and there seemed little interest in correlational selection gradients from empiricists at all (Kingsolver et al. 2001).

Just as ignoring the geometry of multivariate genetic variance is likely to have given a misleading impression of the level of genetic variance, ignoring the geometry of selection appears to have hidden a number of important observations on the strength of nonlinear selection and it's occurrence across multiple traits. As originally formulated by Lande & Arnold (1983), the quadratic approximation of the individual fitness surface (after standardizing traits to have mean zero) is given by

$$w(\mathbf{z}) = a + \sum_{i=1}^{n} b_1 z_i + \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} \gamma_{ij} z_i z_j = a + \mathbf{b}^T\mathbf{z} + \frac{1}{2}\mathbf{z}^T\boldsymbol{\gamma}\mathbf{z}. \qquad 14.$$

When $\mathbf{z}$ is multivariate normal, then $\mathbf{b} = \boldsymbol{\beta}$. Because the γ_{ij} are partial regression coefficients, they predict the change in expected fitness w caused by changing the associated quadratic deviation, while holding all other variables constant. Increasing $z_j z_k$ by one unit in such a way as to hold all other variables and all other pairwise combinations of characters constant, relative fitness is expected to change by γ_{jk} for $j \neq k$ and by $\gamma_{jj}/2$ if $j = k$ (the difference arises because $\gamma_{jk} = \gamma_{kj}$, so that γ_{jk} appears twice in the regression unless $j = k$). The coefficients of $\boldsymbol{\gamma}$ thus describe the nature of selection on quadratic deviations from the mean for both single characters and pairwise combinations of characters. $\gamma_{ii} < 0$ implies fitness is expected to decrease as z_i moves away (in either direction) from its mean (convex selection). Similarly, $\gamma_{ii} > 0$ implies fitness is expected to increase as i moves away from its mean (concave selection). Turning to combinations of characters, nonzero values of γ_{jk} ($j \neq k$) suggest the presence of correlation selection—$\gamma_{jk} > 0$ suggests selection for a positive phenotypic correlation between characters j and k, whereas $y_{jk} < 0$ suggests selection for a negative phenotypic correlation. Although it seems straightforward to infer the overall nature of selection by simply looking at the various γ_{ii} combinations individually, this can give a very misleading picture about the geometry of the fitness surface. Such a pairwise comparison is akin to attempting to infer constraints on selection from individual elements of $\mathbf{G}$. As was the case for

G, we need to examine the geometry (the eigenvalues and eigenvectors) of $\boldsymbol{\gamma}$ in order to obtain a true picture of the nature of any quadratic selection.

The difficulties in interpreting the nature of selection represented by $\boldsymbol{\gamma}$ arise because of the cross-product terms γ_{ij}. A simple matrix transformation can remove these (Phillips & Arnold 1989). Define the matrix $\mathbf{U} = (\mathbf{e}_1, \mathbf{e}_2, \ldots, \mathbf{e}_n)$, where $\mathbf{e}_i$ is the ith eigenvalue of $\boldsymbol{\gamma}$. The transformation $\mathbf{y} = \mathbf{U}^T\mathbf{z}$ removes all cross-product terms in the quadratic form, giving

$$w(\mathbf{z}) = a + \sum_{i=1}^{n} \theta_i y_i + \frac{1}{2} \sum_{i=1}^{n} \lambda_i y_i^2, \qquad 15.$$

where $\theta_i = \mathbf{e}_i^T\mathbf{b}$ and $y_i = \mathbf{e}_i^T\mathbf{z}$; λ_i and $\mathbf{e}_i$ are the eigenvalues and associated unit eigenvectors of $\boldsymbol{\gamma}$. The eigenvalues define independent combinations of traits (canonical axes) $\mathbf{y}_i = \mathbf{e}_i^T\mathbf{z}$, and λ_i indicates the nature and amount of curvature of the surface along each canonical axis. Along the axis defined by $y_i = \mathbf{e}_i^T\mathbf{z}$, the individual fitness function has positive curvature (is concave) if $\lambda_i > 0$, has negative curvature (convex) if $\lambda_i < 0$, or has no curvature (a plane) if $\lambda_i = 0$. The amount of curvature is indicated by the magnitude of λ_i, the larger the value of $|\lambda_i|$, the more extreme is the curvature.

Consider the following three $\boldsymbol{\gamma}$ matrices, which differ only in their off-diagonal term:

$$\gamma_1 = \begin{pmatrix} -2 & 0.25 \\ 0.25 & -1 \end{pmatrix}, \quad \gamma_2 = \begin{pmatrix} -2 & 1.41 \\ 1.41 & -1 \end{pmatrix}, \quad \gamma_3 = \begin{pmatrix} -2 & 4 \\ 4 & -1 \end{pmatrix}.$$

Simple inspection of the diagonal elements γ_{ii} suggests convex selection on both traits. However, the eigenvalues for these three matrices are as follows. For matrix 1, $\lambda = -2.06, -0.94$, indeed suggesting convex selection on both canonical axes (independent combinations of traits). For matrix two, they are -3.0, 0, so that there is strong convex selection along one axis, but no quadratic selection along the other. Finally, for matrix three, $\lambda = 2.53, -5.53$, suggesting strong convex selection on one axis, but significant concave selection on the other. Thus, much like h^2, the γ_{ii} in isolation can be very misleading. These geometrical properties inherent in such quadratic response surfaces, although set out in detail by Phillips & Arnold (1989), made little impact on the empirical investigation of the frequency and strength of nonlinear selection, manifesting in an underappreciation of the role of correlational selection gradients (Kingsolver et al. 2001).

There are two main conclusions to be drawn from taking a geometrical view of nonlinear selection. First, Blows & Brooks (2003) showed that nonlinear selection is likely to be much stronger on some trait combinations (the major canonical axes of the individual fitness surface) than previously observed for individual traits by Kingsolver et al. (2001). Stinchcombe et al. (2008) demonstrated that the true strength of selection on these traits combinations is likely to be even stronger than indicated by the analysis of Blows & Brooks (2003), because there has been confusion in the literature over the relationship between quadratic selection gradients and the regression coefficients obtained from standard statistical software, often resulting in the value of γ_{ii} being under-reported by a factor of two.

Second, though some trait combinations have strong nonlinear selection acting on them, other trait combinations do not. In a situation exactly analogous to that seen with **G** matrices, where the distribution of the eigenvalues of **G** may tell a very different story than the levels of genetic variance in individual traits, trait combinations may vary substantially in the strength of nonlinear selection acting on them in comparison to individual traits. The concentration of nonlinear selection along a reduced number of the major axes of the individual fitness surface supports Barton's (1990, p. 779) second conjecture that only a few traits can be under strong stabilizing selection.

A GEOMETRIC VIEW OF THE EVOLUTION OF GENETIC VARIANCE

We began this review with two conflicting observations; substantial levels of genetic variance are maintained in the presence of strong selection in natural populations. Taking the geometric view of genetic variation and selection outlined above suggests that these two observations based on single traits are too simplistic. But how might geometry help reconcile these two observations? One possibility is that directional and stabilizing selection do indeed deplete genetic variance as expected, but this effect has been hidden in the geometrical complexity of multiple traits.

Although artificial directional selection is almost always successful in changing the population mean, directional selection under field conditions often is not (Kruuk et al. 2002, Merilä et al. 2001). This key difference between artificial selection and selection under field conditions could be explained if persistent directional selection depletes genetic variance in the combination of traits under selection. The study of sexually selected traits is particularly useful here as male sexually selected traits are often relatively easy to identify and selection generated by mate choice can be readily quantified. The association between the direction of sexual selection and very low levels of genetic variance in multiple populations and species of *Drosophila* (Blows et al. 2004; Hine et al. 2004, 2009; Van Homrigh et al. 2007) suggests that genetic variance is depleted in the trait combinations under sexual selection, whereas substantial levels of genetic variance are maintained in the individual traits.

Finally, the presence of strong stabilizing selection on some trait combinations, selection that is far too strong to allow the maintenance of much genetic variance (Johnson & Barton 2005), suggests that such stabilizing selection may also be effective at depleting genetic variance and, hence, shaping the patterns of genetic constraint represented by the **G** matrix. Under the assumptions of weak net pleiotropy and a Gaussian distribution of allelic effects at each locus, under constant selection the matrix should evolve to have approximately the same orientation as the individual fitness surface (Arnold et al. 2001, Cheverud 1984, Lande 1980). That is, trait combinations experiencing strong stabilizing selection should display little genetic variance, whereas those trait combinations under weak selection should be able to maintain greater levels of genetic variance. Hunt et al. (2007) provided empirical support for such an association for male call traits under multivariate stabilizing sexual selection in a cricket.

CONCLUSIONS

It is possible to come away from a discussion of multivariate genetic constraints feeling pessimistic about our ability to ever capture all the traits necessary in an analysis to be able to make useful inferences about the response to natural (or sexual) selection in natural populations (Pigliucci 2006). We can point to at least two avenues of inquiry that provide considerable hope in our struggle to escape from Flatland. First, modeling fitness in quantitative genetic analyses with target traits will provide a way of at least determining whether a researcher has correctly identified the important traits, and whether there are missing traits that display substantial genetic covariance with fitness. Of course, this is easier said than done. Obtaining suitable, all-encompassing measures of fitness, such as life-time reproductive success, is difficult, and often these fitness measures won't have the same distribution as standard metric traits (Shaw et al. 2008, Thompson 2008).

Second, the true dimensionality of the problem we face may be much less than the number of phenotypes we can measure. Barton's two insights, with which we began this review, have been lent support by recent experimental evidence. There are just a few trait combinations in most available data sets that account for the vast majority of the estimated genetic variance in those traits. In addition, strong stabilizing selection appears to be confined to just a few of the available trait combinations.

So, what can we now say about the two fundamental observations, ubiquitous genetic variance and strong selection, that form such a contradiction at the core of evolutionary biology? In the end, though coexistence is incompatible on a trait-by-trait basis, there may in fact be no incompatibility from a multivariate perspective. The presence of so much genetic variance in the presence of selection suggests that axes of strong selection may be associated with axes of low genetic variance, and vice versa. For single fitness components, mutational target size may be sufficiently large, and the genetic correlation with fitness sufficiently weak, for substantial amounts of genetic variance to be maintained. As combinations of fitness components become more tightly genetically correlated with fitness, the strength of selection may become sufficient to deplete levels of genetic variance in such combinations, while maintaining substantial levels of genetic variance in the individual traits. Hence, the presence of this incompatibility on a trait-by-trait basis may be a signature of strong multivariate genetic constraints in natural populations.

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