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QUANTITATIVE GENETIC APPROACHES TO EVOLUTIONARY CONSTRAINT: HOW USEFUL?

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The study of evolutionary constraint is an active and important area, and genetic correlations and quantitative genetic techniques more generally have been the dominant approach to constraint. Here, I argue that genetic correlations are not very useful for studying constraint, review recent alternative approaches, and briefly discuss the state of our knowledge of the evolutionary importance of constraints caused by genetic variance and covariance.

KEY WORDS: **Adaptation, covariance, G-matrix, genetic correlation, selection gradient, variance.**

Gould and Lewontin's (1979) "Spandrels" paper warned biologists not to assume every trait was adaptive, arguing that many factors could constrain adaptive evolution. Since then, evolutionary constraints, here defined as a slowing or prevention of the evolution of an optimal combination of traits, have been the focus of a great deal of interest and debate (e.g., Maynard Smith et al. 1985; Antonovics and van Tienderen 1991; Pigliucci and Kaplan 2000). Quantitative genetic approaches, especially genetic correlations among traits, have been the dominant empirical methods for studying constraint on adaptation (e.g., Berenbaum et al. 1986; Clark 1987; McDaniel 2005; Vorburger 2005; Ashman and Majetic 2006). What I argue here is that most of the quantitative genetic literature has not been very informative about constraint for three reasons:

1. Genetic correlations by themselves provide no evidence for constraint on adaptation in the absence of information on the direction of selection on the traits, which is most often absent in studies reporting genetic correlations. Correlations can increase, constrain, or have no effect on the rate of adaptation.
2. The genetic correlation is a poor quantitative predictor of constraint because it is a ratio of the important quantitative predictors, that is, the additive genetic covariance and variances. Recently a number of other quantitative genetic metrics of constraint have been proposed; I will briefly review these with some thoughts on their strengths and weaknesses, and offer an additional metric that focuses on individual traits.
3. There is little or no direct evidence on how important constraints caused by genetic correlations (and the underlying additive genetic variances and covariances) are in nature; the only review of the literature to date and a number of artificial selection studies raise doubts about whether quantitative genetic parameters cause meaningful constraints.

I recognize that the first two points are not entirely novel, but I have not seen them explained fully in print nor do they seem to be widely appreciated in the empirical literature.

The Quantitative Genetic Approach in Brief

Before examining the problems with the use of genetic correlations to study constraints, it may be useful to review the quantitative genetic framework for quantifying phenotypic evolution. The rate of evolution of correlated quantitative traits under directional selection can be modeled using the familiar matrix equation

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(shown for two traits):

$$\begin{bmatrix} \Delta\overline{z_1} \\ \Delta\overline{z_2} \end{bmatrix} = \begin{bmatrix} G_{11}\ G_{12} \\ G_{21}\ G_{22} \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix}, \quad (1)$$

where $\Delta\bar{z}$ is the vector of changes in the means of the traits across one generation, in other words, the response to selection or the rate of phenotypic evolution, **G** is the matrix of additive genetic variances and covariances, and **β** is the vector of selection gradients measuring the strength and direction of directional selection. The **β** vector indicates the direction of adaptive evolution, that is, the multitrait trajectory that will produce the maximum increase in population mean fitness. The predicted change for trait 1 alone is

$$\Delta\overline{z_1} = G_{11}\beta_1 + G_{12}\beta_2 \quad (2)$$

The first term gives the response to direct selection on trait 1, which is the product of the additive genetic variance for trait 1 and the strength of that selection. The second term is the correlated response of trait 1 to selection on trait 2, which can either constrain or augment the total response to selection on trait 1. The response to direct selection will be augmented by the genetic covariance, that is, adaptive evolution will be accelerated, if the correlated response term has the same sign as the direct response term, but adaptive evolution will be constrained (slowed, but not necessarily prevented) if the two terms have opposite signs (see Conner and Hartl 2004 Table 6.7 for details). This leads directly to my first main point.

Whether Correlations Cause Evolutionary Constraint Depends upon the Direction of Selection

One reason this point is not widely appreciated is that the term genetic constraint has often been defined only in terms of the **G**-matrix, without considering selection (e.g., Arnold 1992; Hine and Blows 2006; Kirkpatrick 2009; see below). Defined this way, genetic constraints indicate potential evolutionary constraints, because the **G**-matrix can actually augment the rate of adaptive evolution depending on the relationship between **G** and the direction of selection. The easiest and most general way to think about whether a correlation or **G** can cause an evolutionary constraint is to consider the amount of additive genetic variance in the direction of selection in multivariate space. Therefore, in the simplest case of only two traits, the response to selection is maximized if the direction of selection is aligned with the major axis of the correlation (i.e., the direction of maximum genetic variance) and minimized if selection is perpendicular to the major axis (i.e., along the minor axis, the direction of minimum variance; Fig. 1).

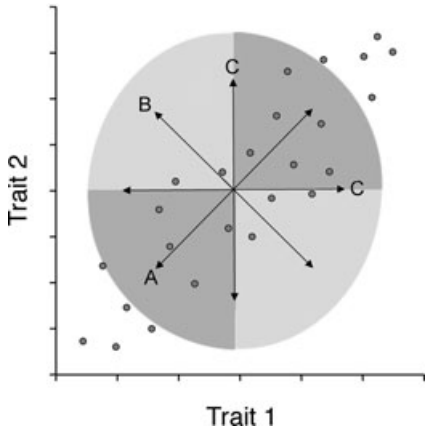

Figure 1. Graphical depiction of when genetic correlation (and covariance) constrain, augment, or have no effect on adaptive evolution. In this example, the genetic correlation between the two traits is positive, as depicted by the elliptical arrangement of points, which represent half-sibling family means. The four vectors represent four different directions of selection (β) on the two traits. If this vector falls anywhere in the dark gray regions, adaptive evolution of the two traits is augmented by the correlation (e.g., vector A) because this is the direction of maximum genetic variance in bivariate space. If β falls anywhere in the light gray regions (e.g., vector B) adaptive evolution is slowed, as this is the direction of minimum genetic variance. If β is exactly horizontal or vertical, the rate of evolution is unaffected, because β for one of the traits is 0.

More specifically, adaptive evolution is augmented if the vector of selection on the two traits (**β**, exemplified by the vector **A** in Fig. 1) lies in the dark gray regions of Fig. 1 because the two terms in equation (2) have the same sign. Adaptive evolution is constrained by the correlation if the direction of selection lies in the light gray regions (e.g., **β** = B) because the two terms are of opposite signs. While equation (2) focuses on trait 1, trait 2 is also constrained for the same reason. When selection is exactly in the vertical and horizontal directions (**β** = C), the rate of evolution is unaffected by the correlation because in each case **β** for one of the traits is 0, so the correlated response term for the selected trait is also 0. However, the correlation will cause the neutral trait to evolve in this case (see Conner and Hartl 2004 Fig. 6.11B for more details).

Thus, genetic correlations will cause constraint on adaptive evolution in some directions, but my second main point is the following.

Genetic Correlations are Misleading Quantitative Predictors of Evolutionary Change and Constraint

Genetic correlations are misleading because they are a ratio of the important parameters for modeling phenotypic evolution under

selection:

$$r_A = \frac{G_{12}}{\sqrt{G_{11} + G_{22}}} = \frac{\mathrm{cov_A}}{\sqrt{V_{A(1)} V_{A(2)}}} \quad (3)$$

That is, the additive genetic correlation between traits 1 and 2 is the additive genetic covariance between these traits divided by the square root of the additive genetic variances of each. Covariances are commonly standardized into correlations by dividing by the variances because covariances can take any value, and this value depends on the scale of measurement of the trait, so covariances are not comparable across traits. Correlations are directly comparable, but the fact that the three key components of the **G**-matrix that determine the rate of evolution are combined together make the correlation useless for predicting evolutionary change. For example, two populations can have the same genetic correlation but very different responses to selection if the variances and covariances scale together. The following pair of **G**-matrices results in a genetic correlation of 0.80, because in the second matrix the variances and covariance are simply doubled:

$$\begin{bmatrix} 0.25 & 0.20 \\ 0.20 & 0.25 \end{bmatrix} \quad \begin{bmatrix} 0.50 & 0.40 \\ 0.40 & 0.50 \end{bmatrix}$$

If selection perpendicular to the major axis is imposed such that the selection gradient on trait 1 is –2 and that on trait 2 is +2, then the predicted change in each trait with the second **G**-matrix would be double the response for the first matrix. Thus, a wide range of evolutionary rates or constraints on adaptive evolution can be obtained with the same genetic correlation just by scaling the **G**-matrix.

Conversely, the same response to selection can occur with different genetic correlations; consider these **G**-matrices:

$$\begin{bmatrix} 0.30 & 0.20 \\ 0.20 & 0.40 \end{bmatrix} \quad \begin{bmatrix} 0.40 & 0.30 \\ 0.30 & 0.50 \end{bmatrix}$$

These yield genetic correlations of 0.58 and 0.67, respectively, but if we apply the same perpendicular selection as before (selection gradients of –2 and +2) we get exactly the same evolutionary response in both cases (–0.2 for the first trait and +0.4 for the second). Note that this asymmetric response to selection by the two traits despite the equal magnitude of selection on them is due to differences in the genetic variances. This further illustrates that all the elements of the **G**-matrix are necessary to predict evolutionary change and thus constraint, and that by combining them into a single metric such as the genetic correlation we can be easily misled. To be clear, any genetic correlation will make evolution perpendicular to the major axis slower than in any other direction, but the magnitude of the correlation gives little information on the magnitude of this constraint.

The one situation in which the genetic correlation could be useful is when it is exactly 1, because this is the only time that evolution perpendicular to the correlation will be prevented rather than just slowed (Pease and Bull 1988). Mezey and Houle (2005) refer to this as an absolute constraint, as opposed to a quantitative constraint. A correlation of 1 occurs whenever the square root of the product of the two variances equals the covariance (see eq. 3 above); graphically, all the points in the bivariate plot are in a perfect straight line. Unfortunately, this still is not very useful empirically, because we can never show that a correlation is exactly 1 (Roff and Fairbairn 2007). Indeed, there is at least one case in the literature where evolution occurred in response to artificial selection perpendicular to a correlation that was estimated to be 1 (Frankino et al. 2007); clearly, the actual correlation was less than 1.

Other Constraint Metrics

If genetic correlations are not very useful, why have they been so widely used? The main reason is that, unlike the **G**-matrix, genetic correlations are a single standardized measure that can be compared across studies and traits. However, this is not an advantage if the answer is misleading. The solution is to measure constraint based on equation (1), that is, using selection gradients and the **G**-matrix, because this does give correct predictions of the rate of evolutionary change. However, we still need a metric that can be compared across traits and species, and more importantly we need a yardstick for comparison. In other words, if there is a constraint, how much is evolution slowed, and compared to what?

In the past five years or so, a number of mathematical approaches to quantifying constraints have been proposed based on all or part of equation (1) (reviewed by Simonsen and Stinchcombe 2010), although the basic ideas underlying many of them are older (e.g., Schluter 1996). While progress is clearly being made, these methods tend to require data that are difficult to acquire (but absolutely necessary for understanding evolutionary constraints) and the methods are advanced, difficult for many empiricists to implement, and the resulting measures not easy to interpret biologically. However, these difficulties are mirrored in the concept of constraint itself, which is surprisingly slippery and difficult to understand. Still, all these methods are better than the genetic correlation for assessing constraint. What follows is a conceptual review of many of these methods, which I place in four categories.

CALCULATE $\Delta\bar{z}$ OR FITNESS INCREASE WITH COVARIANCE SET = 0

One approach is to estimate the **G**-matrix, set the covariances to 0 so that only the variances are nonzero, and then compare either $\Delta\bar{z}$ (Smith and Rausher 2008) or the increase in fitness (Agrawal and Stinchcombe 2009) to those predicted with the natural variances and covariances. An advantage of this approach is that there is a clear standard for comparison, so that the degree of constraint can

be compared across traits and species with standardized values. This approach focuses entirely on the covariances, which may be an advantage for some questions, but constraints can also occur through the variances as well. The other approaches all examine the effects of the **G**-matrix in its entirety.

DIMENSIONS OF G THAT LACK VARIANCE

One of these is to test for dimensions of the **G**-matrix that lack variance (Hine and Blows 2006; Kirkpatrick 2009). This is referred to as the effective dimensionality of the **G**-matrix, because if one or more dimensions have lack variance then evolution will be constrained to be in those "effective" dimensions for which variance exists. There is some controversy over how to properly test for dimensions lacking variance, with different methods giving different results (Hine and Blows 2006), but to my mind a bigger problem is that no test can prove that the variance is exactly 0 using a crossing design such as parent–offspring regression or half-sibling analysis (Barton and Partridge 2000; Kirkpatrick 2009). There will always be some variance around the estimates, and in practice that variance is often large—recall the example above where the genetic correlation was estimated to be 1, but artificial selection perpendicular to that correlation produced a rapid response (Frankino et al. 2007). Another disadvantage of this approach is that it does not incorporate selection, which all the other methods discussed below do. As with the genetic correlation, whether lack of variance in some dimension of **G** causes evolutionary constraint depends on the direction of selection.

ANGLE BETWEEN β AND THE MAJOR AXES OF G

A related approach that avoids these disadvantages is to quantify the angles between the vector of selection gradients ($\boldsymbol{\beta}$) and the major axes of **G** (Blows et al. 2004). The closer the angles are to 90° (perpendicular), the greater the constraint. However, these angles are very difficult to interpret—it is clear that 90° means maximum constraint, but how much constraint does a 75° angle cause, for example? Furthermore, Simonsen and Stinchcombe (2010) found very different levels of inferred constraint using this method depending on whether or how the traits are standardized. This lack of consistency is problematic because without some kind of standardization it is difficult or impossible to compare the degree of constraint across different traits, studies, and organisms.

COMPARE β TO $\Delta\bar{z}$

Another related approach is to compare the vector of selection gradients ($\boldsymbol{\beta}$) to the vector of predicted responses to selection ($\Delta\bar{z}$); the difference between the two is entirely due to **G**, as the latter is the product $\mathbf{G}\boldsymbol{\beta}$ (eq. 1). This is an appealing approach, because it compares what is adaptive, as measured by the selection gradients (see Conner and Hartl 2004), to the phenotypic evolution that will occur in the next generation, directly addressing constraints on adaptation caused by **G**, including both the genetic variances and covariances. Conner and Via (1992) compared selection gradients for individual traits to the corresponding predicted responses without applying any additional statistics. Smith and Rausher (2008) used bootstrapping to test for differences between the directions of the selection gradient and response vectors.

Perhaps the most comprehensive quantitative genetic measure of constraints is Hansen and Houle's (2008) unconditional evolvability, which is a projection of the response vector on to the selection gradient vector (see their Fig. 1). This measure includes both the angle between the vectors, and the reduction in length of the response vector relative to the selection vector, both caused by the **G**-matrix. The shorter the projection, the slower the rate of adaptation and thus the greater the constraint. This method quantifies the predicted evolution over one generation in the direction of the $\boldsymbol{\beta}$ vector, that is, the most adaptive direction that maximizes the increase in fitness. Standardization based on the mean is built into this method, facilitating comparisons across traits, studies, and organisms, but this method lacks a clear standard for determining the relative amount of constraint among traits, which is a very difficult problem in general (see below). Note that this method is multivariate; that is, the projection is in multivariate space, so it is hard to understand the degree of constraint on each individual trait. Elsewhere I have argued for the importance of studying individual traits identified based on the biology of the organism rather than multivariate statistical constructs (Conner 2007).

A Single-Trait Measure OF Relative Constraint

A simple way to compare the degree of constraint among individual traits derived from the methods in the previous section is to calculate the ratio of $\Delta\bar{z}$ over $\boldsymbol{\beta}$ for each trait individually. The estimate of $\Delta\bar{z}$ is obtained from equation (1), so this method incorporates all constraints that are reflected in the **G**-matrix, including variances and covariances among all measured traits (Fig. 2). It can be loosely described as the proportion of adaptive evolution (estimated by $\boldsymbol{\beta}$) that is predicted to actually occur across one generation ($\Delta\bar{z}$). I say loosely because $\boldsymbol{\beta}$ is a slope (change in relative fitness per unit change in the trait) and $\Delta\bar{z}$ is a change across one generation in trait mean. Therefore, the ratio does not have very clear meaning by itself, but if $\boldsymbol{\beta}$ and $\Delta\bar{z}$ are mean standardized (Hansen and Houle 2008), the ratio is useful for comparing the degree of constraint across traits, studies, and organisms.

This approach combines some of the advantages of several of the approaches discussed above. First, there is a clear standard for judging the magnitude of the constraint, because it is the

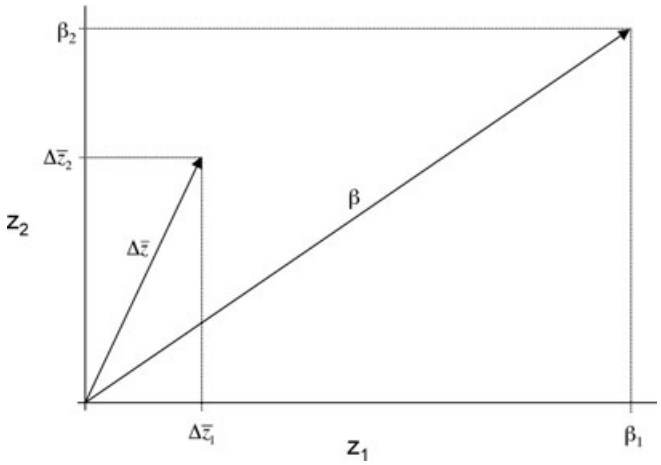

Figure 2. Graphical comparison of $\Delta\bar{z}$ to β for two traits. The axes represent the two traits. β is the vector of direct selection on the two traits indicating the direction of maximum increase in relative fitness; β_1 and β_2 are the selection gradients for each trait. Similarly, $\Delta\bar{z}$ is the vector of responses to selection for the two traits, and $\Delta\bar{z}_1$ and $\Delta\bar{z}_2$ are the responses for each trait. Constraints on adaptive evolution occur when the $\Delta\bar{z}$ vector is shorter than the β vector and/or when there is an angle between them; all differences between these vectors are caused by the G-matrix (see eq. 1), and both the shortening and the angle can be caused by the genetic variances for each trait, the covariance between them, or both. The difference between the projections of these two vectors on each axis (i.e., β_1 vs $\Delta\bar{z}_1$ and β_2 vs $\Delta\bar{z}_2$) gives the degree to which each trait is constrained by the G-matrix. In this example, trait 1 is far more constrained by the G-matrix than trait 2.

predicted evolution divided by the strength of selection. Second, this method provides a measure of constraint for each individual trait, so that it is much easier to relate to the biology of the organism. Finally, this metric is also much easier to calculate and interpret than the multivariate measures. The main drawback of this method applies to all the methods that compare $\Delta\bar{z}$ to $\boldsymbol{\beta}$, that is, they require estimates of both the **G**-matrix and selection gradients, preferably in the same populations and estimated in the field, and rarely have investigators succeeded in collecting these data. However, there is no substitute for this information if the goal is to understand quantitative genetic constraints on adaptive evolution.

As an example, I measured selection and the **G-**matrix in the field for three floral traits in wild radish (Table 1; Conner et al. 2003). The mean-standardized values for $\boldsymbol{\beta}$ show strong directional selection to increase ovule number, weaker selection to increase petal length, and still weaker selection to decrease stigma exsertion (the amount that the stigma protrudes from the corolla tube). The predicted changes across one generation ($\Delta\bar{z}$) are all positive and much smaller than the selection gradients. The ratio of $\Delta\bar{z}$ to $\boldsymbol{\beta}$ shows that petal length was more strongly constrained than ovule number, but that both are predicted to evolve in the adaptive direction (i.e., to increase). The constraint on petal length is mainly due to it having the smallest mean-standardized additive variance (0.012) leading to a very small direct response to selection. The negative value for the stigma exsertion ratio means that the predicted evolution is in the opposite direction as selection, so rather than adaptive evolution being just slowed, the trait is predicted to evolve in the maladaptive direction, that is, increase rather than decrease.

Thus, positive values of the ratio are a good measure of the amount that adaptive evolution is slowed relative to what would produce the maximum increase in fitness, but indicate that the trait is evolving in the adaptive direction. Negative values of the ratio indicate an even more severe constraint, that is, the trait is evolving in the opposite direction to that which would increase adaptation. However, when the ratio is negative, that is, $\Delta\bar{z}$ and $\boldsymbol{\beta}$ have opposite signs, relative values are not useful for comparative purposes.

Does the *G*-Matrix Cause Evolutionarily Meaningful Constraint?

Despite the clear utility of the methods mentioned above, especially those based on comparison of $\Delta\bar{z}$ to $\boldsymbol{\beta}$, it is not clear that any of them can answer the fundamental question of whether the **G**-matrix causes evolutionarily significant constraint. The limited empirical evidence to date suggests that it usually does not. The first line of evidence is that selection is most often not close to perpendicular to the major axes of correlations in natural populations. Agrawal and Stinchcombe (2009) conducted a meta-analysis of species for which estimates of both the **G-** or **P-**matrix and selection gradients were available. They compared the rate of adaptation (fitness increase) predicted using the estimated **G**- or **P-**matrix to that predicted when the off-diagonal elements of the matrix (i.e., the covariances) were set to 0. They found that, averaged over the 45 studies, the rate of adaptation was not affected by setting the covariances to 0, and the few studies where there was evidence for substantial constraint (slowing of adaptation) were balanced by a similar number of studies showing a substantial augmentation of the rate of evolution by the covariances. In other words, selection parallel to the major axis (augmentation) was just as common as selection perpendicular (constraint), but in most cases covariances had little effect on the rate of adaptation. Note that this approach focuses only on the covariances, and does not address the degree to which adaptation is constrained by the variances.

There is also a growing body of work using artificial selection perpendicular to the major axis of genetic correlations; in most cases, a significant response to selection occurs over just a few generations (Bell and Burris 1973; Weber 1990;

Table 1. Mean standardized G-matrix, selection gradients (β), and evolutionary predictions estimated in the field for three wild radish floral traits. Selection gradients are based on lifetime female fitness, that is, seed production in these annual plants; see Conner et al. 2003 for G-matrix methods. The direct response is the product of the additive variance and selection gradient for each trait, and the correlated response is the sum of the products of the selection gradients for each of the other traits and the additive genetic covariance between those traits and the focal trait (see eqs. 1 and 2). $\Delta\bar{z}$ is the total predicted evolutionary change in the mean over one generation and is the sum of the direct and correlated responses. The ratio of $\Delta\bar{z}$ over β is a comparative measure of constraint on adaptive evolution of each trait caused by the G-matrix. See Conner and Hartl 2004 pp. 219–223 for further general explanation.

	G-matrix			β	Direct Response	Correlated Response	$\Delta\bar{z}$	$\Delta\bar{z}/\beta$
Petal length	0.012	0.025	0.002	0.433	0.005	−0.001	0.005	0.011
Stigma exsertion	0.025	0.092	0.014	−0.205	−0.019	0.052	0.033	−0.162
Ovule no./flower	0.002	0.014	0.034	2.918	0.098	−0.002	0.096	0.033

Wilkinson 1993; Stanton and Young 1994; Emlen 1996; Beldade et al. 2002; Frankino et al. 2005, 2007; Conner et al. 2011). There are a two exceptions in which there is no response to selection perpendicular to a correlation (Dorn and Mitchell-Olds 1991; Allen et al. 2008); these more convincingly show a constraint caused by the **G**-matrix than studies that show a genetic correlation of 1 or a **G**-matrix of reduced dimensionality. One of these (Dorn and Mitchell-Olds 1991) is the only one of these studies that selected perpendicular to a negative correlation that represents a clear trade-off (size and flowering time). The other studies that found responses to perpendicular artificial selection were on positively correlated traits, mostly between sizes of morphological traits, where trade-offs are not likely. These studies are also confined to two traits only; it would be very interesting (and challenging) to artificially select along the axis of minimum variance in multivariate space (Kirkpatrick 2009). There have been some studies that report no response to natural selection either in the lab (Hall et al. 2004; McGuigan et al. 2008) or the field (Kruuk et al. 2002; Ozgul et al. 2009). One explanation for this result is a lack of variance in the direction of selection, but another likely explanation is unmeasured selection opposing the known selection (e.g., mortality before the trait is expressed; Grafen 1988).

The studies in nature reviewed by Agrawal and Stinchcombe (2009) and the artificial selection studies only address short-term constraints, that is, roughly from one to 10 generations. The body of work on evolution along "genetic lines of least resistance" (Schluter 1996) addresses the role of genetic covariances in causing longer term constraints. Several studies have now shown that related species tend to diverge along the major axis of a genetic covariance measured in one of the species, but some species diverge significantly from this direction (Schluter 1996; Baker and Wilkinson 2003; Begin and Roff 2004; Marroig and Cheverud 2005; McGuigan et al. 2005; Conner 2006; Renaud et al. 2006). Thus, if most species are constrained to the genetic lines of least resistance, some seem to be able to break free of this constraint. Still, if most species are constrained to a small area of phenotypic space, this is clearly evolutionarily significant. Unfortunately, the fact that most species lie near the major axis may not imply constraint at all, but rather that this is a ridge in the fitness surface, and thus the pattern is adaptive. It is difficult to distinguish the constraint from adaptive hypotheses with comparative data alone; estimates of selection are also necessary, but impossible when studying species that diverged long ago. Studying the divergence of populations within species using this framework may be more fruitful, as estimates of selection in the present will more closely reflect the recent past selection leading to divergence (e.g., Chenoweth et al. 2010).

This leads back to the short-term studies, and the key question of how to assess whether a constraint is evolutionarily significant. A few yardsticks have been used or proposed, but most studies of constraints to date have not really addressed evolutionary significance. Conner et al. (2011) selected on a trait for which natural selection had already been measured, and so were able to estimate that the phenotypic change caused by artificial selection would lead to a very large change in mean fitness in the field. We also estimated that the most extreme phenotypes in the family Brassicaceae would be reached in less than 100 generations at the rate of change under artificial selection.

The best measure of the evolutionary significance of a constraint may be whether it is likely to cause extinction. In other words, does the constraint slow the rate of adaptation relative to the rate of change in the environment enough so that extinction results? Perhaps the study that comes closest to this difficult standard is that of Etterson and Shaw (2001), in which the evolution of traits involved in adaptation to global warming was predicted to be slowed by genetic covariances enough that population mean fitness would suffer.

Conclusions

For a variety of reasons we know constraints on adaptation are important (reviewed in Futuyma 2010); to me, the most compelling

of these is that most species that have existed on earth are now extinct. However, I would argue that the quantitative genetic approach has thus far failed to provide evidence for the evolutionary importance of constraints due to genetic variances and covariances. This might just suggest that quantitative genetics is the wrong approach, but it seems likely that most constraints on short-term phenotypic evolution would be reflected in **G**-matrix, and it is hard to argue for strong constraints when artificial selection almost always produces rapid responses. Certainly, more studies that select perpendicular to strong negative correlations between traits that are involved in a trade-off are needed; perhaps stronger constraints would be found here. Although challenging, artificially selecting in the direction of least variance in multivariate space would address whether constraints mainly occur in more than two dimensions; McGuigan et al. (2008) reported a lack of response to sexual selection in the direction lacking variance in nine *Drosophila* cuticular hydrocarbons. Another unresolved issue is whether the perpendicular artificial selection causes deleterious correlated responses in other unmeasured traits; this issue has been poorly addressed in previous studies. Finally, it could be that individual traits are not strongly constrained (i.e., the "character constraints" in Futuyma 2010 are not important) but that there are quite different processes that create "whole organism stasis" (Futuyma 2010). Clearly, the causes and consequences of constraint are open questions that should provide fertile ground for future evolutionary studies.

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