August 2024

Quantitative Genetics in Natural Populations

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MS accepted for publication:

***A.J. Wilson**, J. Poissant (2024). Quantitative genetics in natural populations. In 'Encyclopedia of Evolutionary Biology' 2nd Edition. Elsevier.*

Abstract
Phenotypes evolve under natural selection if, and only if, they are genetically variable. While evolutionary ecologists have long studied natural selection, it is only comparatively recently that quantitative genetic methods have been applied to wild populations. This fertile area of research is allowing us to scrutinize the genetic basis of (co)variation within- and among-traits, increasing our understanding of adaptive evolution in nature. Here we review some of the key principles, developments, challenges, and emerging directions in this field of research.

Keywords
Adaptation, Additive genetic variance, Animal model, Constraint, **G** matrix, Genetic architecture, Genetic correlation, Genotype-by-environment interaction, Genomic prediction, Heritability, Life history, Natural selection, Parent–offspring regression, Pedigree and Trade-off.

Glossary

Adaptation	Evolution of phenotypes conferring high fitness.
Additive genetic variance	A measure of the variation in a phenotypic trait that is attributable to additive genetic effects.
Animal model	A form of linear mixed effect model in which an individual's breeding value is fitted as a random effect. The most widely used statistical method for estimating quantitative genetic parameters in natural populations.
Associative effects	See Indirect Genetic Effects
$\boldsymbol{\beta}$	Vector of directional selection on a multivariate phenotype. Contains individual selection gradients (β) for a set of phenotypic traits.
Breeding value	The expected (additive) effect of an individual's genotype on phenotype, usually expressed relative to the population mean phenotype. As a latent rather than directly observable variable it may be estimated by measuring offspring phenotype, or may be predicted using, for example, an animal model. Variance in breeding values is the additive genetic variance.
Genomic breeding value:	A breeding value derived from an organism's DNA.
Directional selection	Selection that favours an increase or decrease in the population mean phenotype. For a single trait this means a non-zero selection differential (S) and gradient (β)
Evolutionary constraint	Broadly, any process that reduces the rate of adaptive evolution relative to naïve expectations. Constraint in **G** can be conceptualized as a relative lack of genetic variance in the direction of multivariate selection $\boldsymbol{\beta}$.
G matrix	Additive genetic variance–covariance matrix for a set of phenotypic traits.
Genetic correlation	A standardized measure of the (additive) genetic covariance between two traits.
Genetic merit	See breeding value.
Genomic prediction	The prediction of an organism's breeding value using genome-wide molecular markers and effects derived from a set of genotyped and phenotyped organisms.
Genome-wide association study (GWAS)	Test of association between alleles and phenotypes using a genome-wide set of markers. Used to try and identify genomic regions, and ultimately genes, contributing to additive genetic variance.
Genotype-by-environment interaction	A phenomenon that occurs when environmental effects on phenotype depend on genotype (and vice versa).
Genotype-environment correlation	Non-random assortment of genotypes across a heterogeneous environment.
Heritability	A standardized measure of additive genetic variance for a trait. Formally estimated (in the narrow sense) as the proportion of total phenotypic variance

	explained by additive genetic variance.
Identical by descent (IBD)	A DNA segment inherited by two or more individuals from a common ancestor.
Indirect genetic effect	Causal dependence of one individual's phenotype on the genotype of another.
Latent variable	In modeling, latent variables are those that are not directly observed but about which inferences can be made statistically. In quantitative genetic models, individual breeding values are often included as a latent variable.
Linkage disequilibrium (LD)	The nonrandom association of alleles at different loci.
Maternal effect	Causal influence of some characteristic(s) of mothers on the phenotype of their offspring (over and above the effect of genes inherited).
Molecular pedigree analysis	The use of molecular data (e.g., microsatellite genotypes, SNPs) to determine relationships and/or relatedness among individuals in a population.
Natural selection	A causal dependence of fitness on phenotype such that trait differences among individuals cause differences in survival and/or reproduction.
Parent–offspring regression	One statistical method for estimating heritabilities and other quantitative genetic parameters. For example, heritability can be estimated as the slope of a regression of offspring trait on midparent trait. Largely superseded by the animal model for studies of wild populations.
Phenotypic plasticity	Change in phenotype produced by a genotype in response to environmental factors.
Quantitative trait locus (QTL)	A locus influencing a quantitative trait.
Selection differential (S)	A measure of (directional) selection on a trait. Formally the covariance between trait and fitness.
Selection gradient (β)	A measure of (directional) selection on a trait closely related to the selection differential. Formally the partial regression of fitness on a trait.

Key points

- Quantititative genetics is the study of genetically complex (or polygenic) traits.
- To understand how traits evolve under natural selection, we need to determine the extent to which genetic factors contribute to phenotypic variation.
- Historically this was difficult to do in wild populations; quantitative genetic methods require knowledge of relationships or relatedness among individuals that was traditionally derived from controlled breeding experiments.
- Over recent decades development of molecular, genomic and statistical methods has made wild quantitative genetics feasible.
- We now use 'wild quantitative genetics' to address many fundamental questions in evolutionary ecology and, increasingly, to investigate the genetic architecture of complex phenotypes in non-model organisms.
- This chapter reviews what we have learned so far, highlights important challenges remaining, and aims to identify some of the exciting new directions for future research in the field.

Introduction

Quantitative genetics is a field of biological research that attempts to understand how genes affect the expression and evolution of complex phenotypic traits – that is, traits that are influenced by many different genes (as opposed to 'Mendelian traits' determined by a single gene). It is both a theoretical and empirical area of research. Theoretical models predict how traits will respond to selection as a function of parameters, such as heritabilities and genetic correlations, which describe their patterns of inheritance and (co)variation in a population (Figure 1). Empirical quantitative geneticists use statistical methods to estimate these parameters, and test hypotheses about how traits evolve. Although this field developed prior to the advent of modern sequencing technologies, genomic information is now increasingly used. This means the detailed genetic architecture underpinning heritable trait variation can now also be investigated. Because quantitative genetic theory is entirely general, at least for sexual diploid organisms, it can be applied to studies of any trait (e.g., disease resistance, growth rate, and social behaviors) in any population. However, because of the type and amount of data required to estimate quantitative genetic parameters, applying these methods *in situ* (i.e., in the field) in natural populations can be challenging. In this article, we provide a brief overview of this dynamic field of research, highlighting some ways in which quantitative genetic studies of natural populations are helping us to understand phenotypic evolution, and pointing to some challenges and opportunities facing the field. Before progressing, we first discuss the rationale for studying natural populations and provide a brief primer of some core concepts for readers with little or no prior exposure to quantitative genetics.

Why study wild populations?

The rationale for taking evolutionary quantitative genetics from the lab to the field is simple. Theory tells us that natural selection leads to adaptation, but only if phenotypic variation arises, at least in part, from genetic effects. Field biologists have a long and successful tradition of studying natural selection, both through the optimality framework that characterizes much of behavioral ecology (Davies *et al.*, 2012) and through formal attempts to quantify putatively causal relationships between phenotype and fitness (Lande and Arnold, 1983; Endler, 1986; Kingsolver *et al.*, 2012). However, even the strongest directional selection can produce no evolutionary response in the absence of genetic variance. Ultimately, the adaptive potential of any population thus depends on the presence – and amount – of genetic variance for fitness itself (Fisher, 1930). Recent work suggests that wild populations can contain substantial genetic variance in fitness and so have high potential for rapid adaptive evolution (Bonnet *et al.*, 2022). But if we want to understand how specific traits contribute to overall adaptation, and why they sometimes respond to selection as expected but other times show stasis (Merilä and Sheldon, 2000), we need to know about trait inheritance as well as selection. How much genetic variation underpins phenotypic differences in wild populations? What is the genetic architecture of this variation? How is it distributed within- and among-traits that effect fitness to different degrees? Do genetic correlations among traits act as evolutionary constraints? Are there interactions between genetic and environmental effects on traits, and – more broadly – how do evolutionary and ecological processes influence each other under natural conditions? These are the sorts of questions that can be, and are being, addressed by researchers using quantitative genetic methods in natural populations.

Given the goal of understanding genetic variation in natural populations, researchers may use data collected from wild populations *in situ*, or from wild-derived populations housed under artificial (or semi-natural) conditions in the laboratory. The latter approach is common in plants (Heywood *et al.*, 2022), and while perhaps not feasible for all animals, has been applied to studies of insects (Niemelä *et al.*, 2013), rodents (Ginot *et al.*, 2022), primates (Zablocki-Thomas *et al.*, 2019), birds (Gerritsma *et al.*,

2023), and fish (Prentice *et al.*, 2023). Other captive environments, such as zoos, also afford opportunities for quantitative genetic research (Pelletier *et al.*, 2009). Studies of captive individuals are sometimes criticized on the grounds that resulting quantitative genetic parameter estimates are less ecologically relevant. A particular risk is that, as a consequence of genotype-by-environment interactions (discussed further below), estimated patterns of genetic (co)variance for traits in captivity will not represent those in the natural environment. Nonetheless, this drawback will often be more than offset by an increase in experimental tractability and ease of phenotypic data collection. Therefore, while we focus primarily on *in situ* studies of wild populations in this article, we take the view that *in situ* and *ex situ* studies are much better seen as complementary, rather than competing, approaches.

Genetic variation and covariation: a brief primer

Classical quantitative genetics uses known relationships, or pedigree structures, to investigate genetic variation in, and covariation between, phenotypic traits of interest (Figure 1). If the statistical methods used can sometimes seem complex, at least the underlying principle is straightforward. If variation in genes is an important determinant of phenotypic variation, then related pairs of individuals will tend to be phenotypically similar because they share alleles identically by descent (IBD). The more closely related individuals are, and so the more alleles they share, the more similar their phenotypes should be. Thus, by statistically quantifying the association between phenotypic and genetic similarity (i.e., relatedness) among individuals in a population we can estimate the genetic variance for a trait. In fact, genetic variance itself can be further partitioned into additive and non-additive components (the latter arising from dominance, epistasis, etc.; Falconer and Mackay, 1996). In most wild quantitative genetic studies, the additive genetic variance is of primary interest. This is primarily because it is the additive component that determines the predictable response to selection, though more pragmatically it is also because estimating other genetic components is difficult (but see e.g., Wolak, 2012). The more additive genetic variance there is, the more rapid a selection response can be. This idea is encapsulated in the univariate breeder's equation, $R=h^2S$. Here R is the per generation change in the mean phenotype (the 'response') which can be predicted as the product of S, a coefficient that measures the direction and strength of selection, and h^2, the narrow sense heritability. Heritability here is defined as the proportion of phenotypic variance (V_P) attributable to additive genetic variance (V_A). In reality, the breeder's equation is too simple to generally (if ever) be appropriate for predicting phenotypic change in the wild. This is because almost all the assumptions underpinning the model are likely to be violated in natural populations (Morrissey *et al.*, 2010). However, the point it illustrates nicely is that evolution (R) depends on both selection (S) and genetics (h^2).

In the same way that genetic effects can account for some of the observed trait variation, they may also explain covariation (or correlation) among traits. For instance, in many animals we find that larger individuals are (on average) more fecund. The positive covariance between body size and litter (or clutch) size may be due to environmental and/or genetic effects. If an individual, by chance, finds itself in a good habitat patch it may acquire more resource than average, allowing it to invest heavily in both growth and reproduction. Here trait covariance is driven by environmental effects. However, if size is heritable, it is also possible that the same genotypes that cause large size also predispose to producing more offspring. These two mechanisms are not mutually exclusive, illustrating the point that the overall phenotypic covariance between two traits may arise from a combination of both genetic and environmental effects. One can estimate the contribution of (additive) genetic effects to the covariance COV_A, which is often standardized to a genetic correlation r_G. For a pair of traits x and y, we can define $r_{G\mathrm{xy}} = \frac{COV_{A\mathrm{xy}}}{\sqrt{V_{A\mathrm{x}}V_{A\mathrm{y}}}}$. Nonzero genetic correlations arise from underlying pleiotropy and/or linkage disequilibrium and mean that traits are not genetically independent of one another. An important

consequence of this is that their selection responses will not be independent of one another either. We will return to this idea later.

Development of Quantitative Genetics in the Wild

Applying quantitative genetic approaches to studies of natural populations is not completely straightforward, firstly because relationships among individuals are typically unknown, and secondly because datasets from wild populations tend to be very different to those collected in carefully planned laboratory experiments. As such analyzing the data requires a somewhat different approach. Initial development of the field was tightly linked to two methodological advances that have allowed empiricists to overcome these challenges. The first involved inferring relatedness (and/or relationships) using molecular markers (Garant and Kruuk, 2005). The second involved the adoption of flexible statistical techniques originally developed by animal breeders (Wilson *et al.*, 2010). More recently, progress has been further facilitated by adoption of many additional molecular genetic, bioinformatic, and analytical tools. Novel phenotyping methods have also permitted an increased range of trait types to be studied, broadening the initial focus on morphology and life history which are relatively easy to measure in the field to include more behaviours (Gervais *et al.*, 2020), and traits measured using molecular techniques (e.g., immune function, (Sparks *et al.*, 2019; Marjamäki *et al.*, 2021); oxidative stress (Losdat *et al.*, 2014); telomere dynamics (Bauch *et al.*, 2022); microbiome variation (Grieneisen *et al.*, 2021)). Nonetheless, and regardless of trait type, inferring relatedness and using this data to inform statistical analyses remain at the core of this approach.

Inferring relatedness

Estimating genetic variance requires knowing the relatedness among individuals (i.e., the proportion of the genome shared identically by descent). In wild populations where relatedness is typically unknown, two strategies are possible. The first consists in predicting relatedness from an inferred pedigree, with values of, for example, 0.5 between parents and their offspring, 0.25 between half siblings, and 0.125 between first cousins. The second is to use estimates of pairwise relatedness inferred from molecular data rather than an explicit pedigree structure.

To determine a pedigree structure it is sometimes possible to infer some relationships from observations of social interactions (e.g., nestlings or mother–offspring pairs identified from suckling in mammals). Pedigrees determined in this way are sometimes referred to as ‘social’ pedigrees. Unfortunately, this approach cannot be used in all taxa and may be inaccurate even when it can be applied. For instance, assuming nestlings are full-siblings is problematic in many passerine birds because extra-pair paternity is common. Thus social pedigrees can contain a lot of errors that in turn, can lead to biased quantitative genetic parameters and evolutionary inferences (Charmantier and Réale, 2005). The development of molecular markers, mainly microsatellite loci and single nucleotide polymorphisms (SNP) has, broadly speaking, provided a solution to this issue. Given a relatively small set of genetic markers (typically 10–40 microsatellites or 100-400 SNP), one can typically resolve close relationships within a population (e.g., parent–offspring and full-sibs) with satisfactory accuracy, allowing reconstruction of a ‘molecular’ pedigree even in the complete absence of behavioral information (Pemberton, 2008; Huisman, 2017). Although applicable to a large number of species, molecular pedigree reconstruction is nonetheless dependent on the presence of close relatives, meaning that the approach is most useful in (usually small) populations where a fair number of close relative are likely to be sampled. Molecular pedigrees are also generally imperfect due to genotyping errors and incomplete sampling (Morrissey *et al.*, 2007; Morrissey and Wilson, 2010; Huisman, 2017).

An alternative to using pedigrees to predict relatedness lies in estimating relatedness directly between all pairs of individuals using molecular markers (Wang, 2014). In principle this approach is potentially superior to pedigree-based methods because it estimates realized rather than expected relatedness (Visscher *et al.*, 2006; Speed and Balding, 2015). For example, under the pedigree approach all full-sibs pairs are assumed to share exactly 0.5 of their genome IBD, while in reality they vary around an expected population mean of 0.5 (Visscher *et al.*, 2006; Speed and Balding, 2015). Until the last decade or so, the pedigree approach was usually preferred in wild populations because estimating genome-wide relatedness accurately requires a very large number of markers. In particular, methods developed to take advantage of the small microsatellite datasets typical of molecular ecology in the 1990s and early 2000s were statistically very 'noisy' (Ritland, 1996; Wilson *et al.*, 2003; Frentiu *et al.*, 2008; Taylor, 2015). This issue can now be overcome by using very high densities of SNP markers to estimate so-called genomic relatedness matrices (GRM; Gienapp *et al.*, 2017). We are now seeing a large growth in 'pedigree-free' quantitative genetic studies as a consequence of the adoption of genomic technologies that can be used to estimate GRM (e.g., Bérénos *et al.*, 2014; Santure *et al.*, 2015; Perrier *et al.*, 2018a; Gervais *et al.*, 2020; Peters *et al.*, 2022; Guhlin *et al.*, 2023).

Linear mixed effect modeling and the 'animal model'

Heritabilities, genetic correlations, and other quantitative genetic parameters can be estimated from simple statistical techniques including linear regression and ANOVA. In particular, parent–offspring regression was used in a large number of early field studies (Grant and Grant, 1995). However, these methods are not very well suited to analyzing the patchy and unbalanced datasets (i.e., lots of missing data and variable family sizes) or complex pedigree structures (i.e., pedigrees containing many classes of relationship, often spanning multiple generations) typical of studies in the wild. Nor do these methods easily allow a researcher to account for uncontrolled environmental effects, for instance spatial or temporal variation in habitat quality. For evolutionary ecologists, testing environmental effects on phenotype is often an important aim in itself. In the context of quantitative genetic analyses, when relatives share environments (e.g., nest, maternal, or cohort effects) that are likely to influence phenotypes of interest, accounting for these 'common environment effects' is important to prevent environmentally driven resemblance among relatives from biasing estimates of genetic (co)variances (Kruuk and Hadfield, 2007).

The growth of quantitative genetics in the wild has been driven to a large degree by adoption of linear mixed effect models, and in particular the polygenic 'animal model,' in place of earlier statistical techniques. It is worth pointing out here that animal models are equally applicable to plants; the terminology simply reflects the method's development to allow analysis of complex pedigree structures as found in livestock systems. Early applications of animal models to natural systems immediately demonstrated its enormous potential (Réale *et al.*, 1999; Réale and Festa-Bianchet, 2000; Kruuk *et al.*, 2002), and this is now by far the most widely used analytical approach. A detailed explanation of the animal model is beyond the scope of this article but see, for example, Kruuk (2004), Postma and Charmantier (2007), and Wilson *et al.* (2010) for treatments intended to be accessible for readers with limited statistical or genetic expertise. For present purposes, it suffices to say that this approach allows estimation of additive genetic (co)variance structures underpinning patterns of trait variation and covariation. To do this, animal models include, for each trait, an individual's genetic merit or 'breeding value' as a random effect. Breeding values are latent variables that represent the effect of an individual's genotype relative to the population mean phenotype. They are usually defined as coming from a normal distribution with mean zero and variance equal to V_A – the additive genetic variance. The expectation that breeding values will covary among individuals as a function of relatedness, means that we can estimate V_A provided we have relatedness information and phenotypic data for individuals

in the population.

The animal model is very flexible and can be applied to any quantitative trait in any complex pedigree. It can be generalized to cope with non-Gaussian errors (e.g., if the trait of interest is binary or a count), and may be fitted using frequentist (e.g., restricted maximum likelihood) or Bayesian (e.g., Markov Chain Monte Carlo) inference methods in a range of statistical software applications (e.g., Meyer, 2007; Hadfield, 2010; Bürkner, 2017; Butler *et al.*, 2023). It is often applied to single traits in univariate form, but can also be used to model sets of traits in a multivariate analysis. The latter allows estimation of additive genetic covariances (COV_A) between traits (as well as V_A for each). It is also readily extended, for example, by including additional fixed and random effects to account for non-genetic intrinsic sources of variation within and among individuals (e.g., age, date of capture, and sex) and environmental sources of resemblance among individuals (e.g., nest, spatial, or cohort effects). This is particularly important because field studies are, by definition, not conducted under controlled conditions. Statistical separation of environmental and genetic influences on phenotype is therefore critical and can be challenging if, as is commonly the case, close relatives share environments as well as genes (Kruuk and Hadfield, 2007). In this scenario, explicitly modeling environmental effects helps to avoid upwardly biased heritability estimates (see Stopher *et al.*, 2012, for an excellent example), especially if combined with experimental approaches such as cross-fostering of eggs or offspring (Figure 2) which are possible in some taxa (Hadfield *et al.*, 2013).

Biological insights obtained from any statistical modelling approach are limited by data availability, and by the validity of model assumptions. While all quantitative genetic studies require a relatively large amount of data, the intrinsic difficulty of sampling wild, free-living organisms means that studies in natural populations often suffer from small sample sizes relative to those conducted in the lab or in other systems such as livestock species. This can mean reduced statistical power for hypothesis testing and/or high uncertainty associated with parameter estimates. Thus, while insightful findings emerge from individual case studies, researchers need to remain cognisant of study limitations and possible sources of bias that could not be controlled. There is thus a continuing need for replication, meta-analysis, and synthesis. Studies interrogating multiple datasets at once (e.g., Postma, 2014; Teplitsky *et al.*, 2014; Bonnet *et al.*, 2022) are increasing in popularity and this is a welcome development.

Lessons and Limitations

Quantitative genetic analyses have now been used to test specific evolutionary hypotheses about a wide range of phenomena in wild populations. Examples include, but are not limited to studies of maternal effects (McAdam *et al.*, 2002; Quéméré *et al.*, 2018), parental care (MacColl and Hatchwell, 2003; Bell *et al.*, 2018), mating systems (Reid *et al.*, 2014; Dobson *et al.*, 2023), phenotypic plasticity (Nussey *et al.*, 2005), senescence (Brommer *et al.*, 2007b), sexual conflicts (Poissant *et al.*, 2016), social evolution (Charmantier *et al.*, 2007), adaptation to climate change (Bonnet *et al.*, 2017; Gienapp *et al.*, 2017), and predicting selection responses (Morrissey *et al.*, 2012a). This diversity of topics recapitulates the earlier point that quantitative genetic theory and methodology is very general. Space precludes detailed review of empirical findings here and the reader is referred elsewhere for more comprehensive reviews (see, e.g., Kruuk *et al.*, 2008; Wilson *et al.*, 2008; Charmantier *et al.*, 2014) and meta-analyses (e.g., Charmantier and Garant, 2005; Dochtermann *et al.*, 2019; Young and Postma, 2023). However, some general points emerging from studies to date are worth highlighting.

Genetic variance is widespread and abundant

A general conclusion emerging from the wealth of empirical studies is that natural populations harbor a

good deal of additive genetic variance (Postma, 2014). This is often true for traits thought to be under strong selection (Kruuk *et al.*, 2008), but also for measures of fitness itself (Bonnet *et al.*, 2022). Since, all else being equal, selection is expected to reduce genetic variance by fixing beneficial alleles and purging deleterious ones, this has led to interest in the question of what maintains genetic variation (Hunt *et al.*, 2007; Walsh and Blows, 2009). In fact, while it has long been argued that there should be an inverse relationship between genetic variation (measured as, e.g., trait heritability) and the strength of selection, this prediction relies on simplistic assumptions, and has only limited empirical support. Where heritability does decline with increasing selection, this pattern may be driven more by environmental contributions to V_P than by changes in V_A (e.g., Merilä and Sheldon, 2000; McCleery *et al.*, 2004; but see Teplitsky *et al.*, 2009 for a counter-example). One possibility is that traits more closely related to fitness (e.g., life history variables) may integrate more underlying genetic and physiological pathways, thus presenting a larger 'mutational target'. Simplistically, traits under strongest selection (which erodes standing genetic variance) might thus tend to have higher input of new genetic variance from mutations. While this hypothesis is difficult to test in the wild, there is at least some support from lab studies designed to estimate rates of per-generation increase in genetic variance from mutation accumulation (Conradsen *et al.*, 2022).

Evolutionary change is hard to predict and detect

The widespread finding of additive genetic variance, combined with the common presence of directional selection (i.e., favouring phenotypic change, Kingsolver *et al.*, 2012), leads to a general expectation of adaptive phenotypic change under simple evolutionary models such as the univariate breeder's equation. However, for those systems where estimates of both selection and heritability are available for the same traits, there if often less change than the breeder's equation predicts. This phenomenon is sometimes termed the 'paradox of stasis' (Merilä *et al.*, 2001). There are many possible reasons for mismatches between predicted and observed evolutionary change (see, e.g., Merilä *et al.*, 2001; Walsh and Blows, 2009; Morrissey *et al.*, 2010, for in-depth discussion). For instance, stasis could reflect evolutionary constraints arising from genetic correlations between a focal trait and other, correlated, traits under selection (Walsh and Blows, 2009) or 'indirect genetic effects' (Fokkema *et al.*, 2021); ideas we return to below. Alternatively, we may have fundamentally misidentified the 'targets' of selection, interpreting trait-fitness correlations as causal (i.e., selection) when they are not (Morrissey *et al.*, 2010). It has also been argued that adaptive evolution may be constrained by undetected stabilizing selection, or selection that fluctuates in direction over time or space. While stabilizing selection appears to be rare (Kingsolver *et al.*, 2012), this could simply be because it is difficult to detect (Haller and Hendry, 2014). There are also some very good specific examples of fluctuating selection in wild animals (Bonnet and Postma, 2018; Carrión *et al.*, 2022), although the empirical case for its importance more generally is limited (Morrissey and Hadfield, 2012; Siepielski *et al.*, 2013).

If the paradox of stasis is well-documented in the wild-quantitative genetic literature, it is also true that examples of rapid phenotypic change in wild populations can be found (Hairston Jr *et al.*, 2005). However, the extent to which rapid changes are explained by genetic responses to directional selection (i.e., evolutionary change) as opposed to, for instance, phenotypic plasticity and/or changing population demography (Ozgul *et al.*, 2010), is often less clear. This highlights the important consideration that quantitative genetic models are intended to predict selection responses only. A selection response can only reasonably be equated to total phenotypic change if environments are constant and genetic drift is negligible, conditions that will rarely (if ever) hold true. Separating genetic from non-genetic components of phenotypic change is possible using animal model-based approaches (Postma, 2006; Hadfield *et al.*, 2010). In simple terms, temporal trends in (predicted) breeding values over time (e.g., year of birth) should be indicative of genetic change in the population. Such trends

have now been quite widely reported in the literature, although the earliest empirical examples used statistical methods no longer considered valid (e.g., Coltman *et al.*, 2003; Garant *et al.*, 2004; Wilson *et al.*, 2007). Hadfield *et al.* (2010) explained the problem with those earlier studies and presented a robust method for detecting trends in breeding values that has become standard in the field (e.g., Pigeon *et al.*, 2016; Bonnet *et al.*, 2019; Hunter *et al.*, 2022). These later studies have confirmed that genetic responses to selection are indeed occurring in some quantitative traits, but quantifying them without bias from other drivers of phenotypic change (e.g., climate change) remains quite challenging. Moreover, mismatches between predicted and estimated rates of evolution are still common (O'Sullivan *et al.*, 2019).

Trade-offs may not constrain adaptation in quite the way we think

Accepting that there is commonly less evolutionary change than might be predicted from our estimates of directional selection and heritability, we must consider what constrains trait evolution. In life history theory and evolutionary ecology, the most widely hypothesized form of evolutionary constraint is that of the trade-off between two traits (or fitness components) that 'compete' for resource allocation. An individual with limited resource can only allocate more to one trait (e.g., egg size) at a cost to the other (e.g., egg number). It has long been proposed that genetic correlations between traits involved in such resource allocation trade-offs should constrain evolution (Roff, 1997). With traits defined so as to be under positive selection (e.g., fecundity and survival), then a constraint arises from a negative genetic correlation. In this scenario, genotypes associated with high fecundity are not necessarily selectively advantageous because they come with the cost of reduced survival. In other words, selection is unable to optimize each trait independently, and the predicted outcome will be a compromise.

Interestingly, while trade-offs are central to many models of evolutionary outcomes in behavioral ecology and life history studies, quantitative genetic analyses of wild populations have often failed to document the negative genetic correlations predicted (e.g., Coltman *et al.*, 2005; Kruuk *et al.*, 2008, for broader scale patterns). In fact, genetic correlations that are positive (with respect to fitness consequences) are rather more prevalent than negative ones (Chang *et al.*, 2024). This doesn't necessarily mean individuals are not subject to allocation trade-offs, although perhaps their life histories are more strongly shaped by other factors (e.g., variation in resource acquired). However, taken at face value, it poses an interesting challenge to the long-standing view that allocation trade-offs inevitably lead to genetic correlations that constrain adaptive evolution. One interpretation is that negative genetic correlations between traits in trade-offs are rarely detected because of relationships with additional (and potentially unmeasured) aspects of phenotype. If so, bivariate (i.e., two trait) models will rarely be sufficient to identify evolutionary constraint (Walsh and Blows, 2009) such that fully multivariate studies are required (Morrissey *et al.*, 2012b; also discussed further below). Another possibility, is that positive genetic correlations among resource-dependent traits reflect underlying genetic variance in individual 'quality' (*sensu* Wilson and Nussey, 2010); high-quality genotypes tend to have greater resource acquisition and so can allocate more to all competing demands (de Jong and van Noordwijk, 1992; Wilson, 2014). If so, the obvious next question is what maintains genetic variance in resource acquisition? Could input of new mutations into a population be sufficient to prevent directional selection from eroding genetic variance in quality, or might social processes like competition for resource acquisition be important sources of evolutionary constraint (Wilson, 2014)?

A multivariate view of adaptation and constraint is useful

Natural selection does not act on phenotypic traits in isolation from each other. Rather it is the process whereby differences in fitness arise (causally) from among individual variation in the multivariate phenotype (i.e., the set of all traits describing an individual's morphology, behavior, life history, and

physiology). Many traits will be under selection, and genetic correlations among them mean that they are not free to evolve independently. Explicit recognition of this leads somewhat inescapably to the view that multivariate studies will be necessary to fully understand adaptation and evolutionary constraint (Blows, 2007; Blows and Walsh, 2009; Walsh and Blows, 2009). If empiricists have been a bit slow to embrace this, opting more commonly to focus on single traits or at best pairs of traits (e.g., homologous male and female traits; Poissant *et al.*, 2010, or those putatively linked by trade-offs as outlined above), then there are at least sensible and pragmatic reasons for this. Firstly, it is difficult to obtain phenotypic data on all traits that might be important determinants of fitness, particularly in the field where sampling individuals at all can be challenging! Secondly, as the number of traits to be considered rises, the number of quantitative genetic parameters to be estimated from the data increases rapidly, exacerbating the statistical challenges outlined earlier.

Nonetheless, failure to accurately predict change or explain stasis from univariate and bivariate studies of wild populations is leading researchers to model larger sets of traits (e.g., Coltman *et al.*, 2005; Morrissey *et al.*, 2012b; Walling *et al.*, 2014; Poissant *et al.*, 2016; Chantepie *et al.*, 2024). The starting point is usually to estimate the additive genetic variance–covariance matrix **G** among traits and a vector describing directional selection on each trait $\boldsymbol{\beta}$, to predict the multivariate response (**R**) using the multivariate breeders equation, $\mathbf{R}=\mathbf{G}\boldsymbol{\beta}$ (Lande, 1982). Figure 3 illustrates this for the simplest (two traits) case, in which negative genetic covariance between positively selected traits constrains adaptation (i.e., the trade-off scenario discussed earlier). Importantly however, this multivariate approach to quantifying adaptive potential and constraint extends to any number of traits in a multivariate phenotype.

Uncovering the genetic architecture of quantitative traits remains a work in progress

Classical quantitative genetics approaches describe trait inheritance (Lynch and Walsh, 1998) and provide us with predictive models for adaptive phenotypic evolution (Walsh and Lynch, 2018). However, they do not characterize the loci underpinning trait variation, which considerably limits our understanding of the mechanisms and evolutionary processes involved (Hansen, 2006; Barrett and Schluter, 2008; Slate *et al.*, 2010). Substantial progress has been made toward describing the genetic architecture of quantitative traits in humans (Lappalainen *et al.*, 2024), agricultural species (Liu *et al.*, 2022), and laboratory models such as *Drosophila melanogaster*, *Mus musculus,* and *Caenorhabditis elegans* (Flint and Mackay, 2009; Evans *et al.*, 2021). Though still limited in comparison to these areas, research on the genetic architecture of quantitative traits in natural populations is now blossoming (see Schielzeth and Husby, 2014; Santure and Garant, 2018; Johnston *et al.*, 2022 for recent reviews of the field).

Traditionally, most studies on genetic architectures have sought to map loci responsible for phenotypic variation (Mackay, 2001). The general principle behind *quantitative trait locus* (QTL) mapping is fairly simple. In brief, *linkage disequilibrium* (LD) between genetic markers and causal polymorphisms generates statistical associations between markers and phenotypes. This signal, coupled to knowing where in the genome the markers are located allows mapping of QTL (Mackay, 2001). Experimental crosses are often used to facilitate QTL mapping efforts in non-model species, but it is also possible to map QTL directly in unmanipulated wild populations (Schielzeth and Husby, 2014). The first attempts at QTL mapping in natural populations used genome-wide pedigree linkage analysis (e.g., Slate et al. 2002, Beraldi et al. 2007, Poissant et al. 2012). This relies on LD generated by recombination events within pedigrees (George *et al.*, 2000; Slate, 2005) and has the advantage of only requiring a few hundred markers. However, it also suffers from low statistical power and resolution (Santure *et al.*,

2013; Slate, 2013) and, as a consequence, has been replaced by genome-wide association studies (GWAS, McCarthy *et al.*, 2008). Since GWAS require more markers (from tens to hundreds of thousands) their application in the wild only became feasible following the development of high throughput genotyping methods (Slate *et al.*, 2010; Schielzeth and Husby, 2014) including SNP arrays (Kim *et al.*, 2018; Lundregan *et al.*, 2018; Malenfant *et al.*, 2018) and diverse genotyping-by-sequencing techniques (e.g., Peterson *et al.*, 2012; Gavriliuc *et al.*, 2022; Guhlin *et al.*, 2023). GWAS relies on LD generated by historical recombination and, relative to traditional QTL mapping, offers finer resolution (Devlin and Risch, 1995), increased power (Risch and Merikangas, 1996), and the ability to estimate allele-specific effects on phenotype. Other advantages include not being dependent on having a genetic linkage map or pedigree (Slate *et al.*, 2010; Schielzeth and Husby, 2014).

Aside from finding genomic regions contributing to heritable variation, another main goal of studies on genetic architectures has been to determine whether complex traits do generally follow the assumptions of the infinitesimal (polygenic) model. Early studies of natural populations may have given the impression that, contrary to the infinitesimal model, variation in many traits was explained by a relatively small number of loci with moderate to large effects. However, in hindsight most of these studies either focused on traits expected to have simple architectures *a priori* (e.g., Colosimo *et al.*, 2004; Beraldi *et al.*, 2006; van't Hof *et al.*, 2011) or suffered from well-known upward bias in estimated QTL effect sizes due to modest sample sizes (Beavis, 1998; Slate, 2013). While GWAS in wild populations typically includes a few thousand individuals (or a few tens of thousands at most), those in humans and livestock now sometimes include millions! (Yengo *et al.*, 2022; Liang *et al.*, 2023). Sample size is now well recognised as the main limitation of genomic architecture studies conducted in the wild and requires careful consideration of power issues when interpreting results (Santure and Garant, 2018). Nonetheless, provided this is kept in mind research on genetic architectures in the wild can certainly provide valuable insights.

In line with findings in humans and other intensively studied species, multiple lines of evidence now suggest that most complex traits of particular interest to evolutionary ecologists (e.g., behaviours, growth, life history traits) are indeed influenced by a very large number of genes (Santure and Garant, 2018). This evidence includes regular lack of significant associations in reasonably powered GWAS (e.g., Kim *et al.*, 2018; Malenfant *et al.*, 2018; Peters *et al.*, 2022; Gauzere *et al.*, 2023), frequent positive correlations between chromosome length and the amount of genetic variance they explain (Yang *et al.*, 2011; Kemppainen and Husby, 2018), and multi-locus approaches suggesting independent contributions from very large numbers of loci (e.g., Santure *et al.*, 2015; Ashraf *et al.*, 2022). Nonetheless, genetic architectures do vary considerably among studied traits including robust evidence for occasional large effects loci (e.g., Zan and Carlborg, 2018; Sparks *et al.*, 2019; Ashraf *et al.*, 2022). Additional genomic research in the wild will thus play an important role in understanding the factors that shape variation in genetic architectures across traits, populations, and species (Rajon and Plotkin, 2013; Timpson *et al.*, 2018; Simons *et al.*, 2022), and how this variation influences both adaptive evolution (Sella and Barton, 2019) and eco-evolutionary dynamics (Yamamichi, 2022).

Emerging Directions

Increasing the range of study organisms and focal traits

Early quantitative genetic studies in wild populations focused disproportionately on a relatively small number of long-term ecological data sets in which individuals are marked and tracked across their lifetimes (Clutton-Brock and Sheldon, 2010); for specific examples see Réale *et al.* (1999); Kruuk *et al.* (2002); McAdam *et al.* (2002); McCleery *et al.* (2004); Brommer *et al.* (2007a). This reflected the need

for deep, well-connected pedigrees, and a strong interest in systems where fitness metrics such as lifetime reproductive success were available to facilitate parallel studies of selection. These datasets were, and of course remain, immensely valuable for all sorts of studies in ecology and evolutionary biology. However, they are also taxonomically biased toward avian (especially passerine) and mammalian (notably ungulate) species frequently living under particular conditions (e.g., super-abundance of nesting sites in the form of nest boxes, predator free islands). Furthermore, the need for high volume data limited, at least to a degree, the set of traits investigated. Specifically, early studies tended to focus much more on readily measured morphological and life history traits for which historical data were also available than on, for example, behavioral or physiological traits.

If we hope to learn general lessons from quantitative genetic analyses of natural populations then obtaining suitable data on more diverse taxa and traits should be prioritized. Trait diversity is now increasing, with growing interest in, for example, the genetic basis of variation in animal personality (Dingemanse *et al.*, 2009; Poissant *et al.*, 2013), dispersal (Charmantier *et al.*, 2011), space use (Gervais *et al.*, 2020; Gervais *et al.*, 2022), disease resistance (Lundregan *et al.*, 2020), and immune function (Graham *et al.*, 2010; Sparks *et al.*, 2019). Technological developments mean we can now consider gene expression (Tung *et al.*, 2015), protein expression (Diz *et al.*, 2012) and host microbiomes (Grieneisen *et al.*, 2021) as phenotypes of interest as well. Taxonomic diversity was initially increased through wider user of molecular pedigree analysis in fish (Wilson and Ferguson, 2002; Koch *et al.*, 2008), invertebrates (Bretman *et al.*, 2011) and other systems where social pedigrees could not be inferred by observation. Over the last decade the development of pedigree-free methods (Bérénos *et al.*, 2014; Aase *et al.*, 2022) provided opportunities for even more taxonomic generality. Additionally, efforts to better integrate the largely animal-focussed field of wild quantitative genetics, with the field of plant evolutionary ecology should be productive (Stinchcombe, 2014), particularly since plant systems often provide greater scope for experimentation (e.g., Walter *et al.*, 2023).

Non-independence of genetic and environmental effects: from GxE to IGE and GEC

Although quantitative genetics seeks to disentangle genetic from environmental influences on phenotype there are several interesting phenomena that blur this distinction. First, *genotype-by-environment interactions* (GxE) occur when the effect of environmental conditions on phenotype depends on genotype. This means that, for a single trait, V_A will be sensitive to environmental conditions. It also means that phenotypic plasticity is genetically variable and so could itself be conceptualized as a trait that will evolve under selection. Second, if a trait is plastic to the 'social environment' provided by interacting conspecifics the possibility of *indirect genetic effects* (IGE; Moore *et al.*, 1997) also arises. IGE are also known as *associative effects* (Griffing, 1967; Griffing, 1976) and occur when the genotype of one individual causally influences the phenotype of another. For example, postnatal growth rates in mammals depend on the quantity of milk provided by mothers. In this case, offspring phenotype (growth) depends on the 'environment' provided by its mother's milk, which in turn depends on the maternal genotype. In the presence of IGE, genetic control of observed phenotypes is 'shared' between interacting individuals, which could be parents and offspring (McAdam *et al.*, 2002; Wilson *et al.*, 2005), mating partners (Brommer and Rattiste, 2008; Teplitsky *et al.*, 2010), competitors (Wilson *et al.*, 2011), or cooperators (Charmantier *et al.*, 2007). Because individuals – and so their genotypes – determine the social environment, social environments can evolve with major consequences for evolutionary dynamics. For example, if individuals differ (genetically) in competitive ability then IGE will constrain adaptation of resource dependent life history traits (Hadfield *et al.*, 2011; Wilson, 2014). A third phenomenon is that of *genotype-environment correlation* (GEC). This is when genotypes are not distributed randomly with respect to environment effects. GEC poses a challenge for wild quantitative genetics as, for example, heritability estimates can be upwardly biased if

close relatives share environmental influences on their phenotypes. However, GEC can also arise through heritable variation in phenotypes of interest such as habitat preference, social dominance, niche construction, or social assortment (Edelaar and Bolnick, 2019; Fokkema *et al.*, 2021).

GxE, IGE and CEC are distinct phenomena but will often overlap and co-occur in ways we are just beginning to recognize. Identifying and disentangling these phenomena is therefore a major challenge for wild quantitative genetics, but also represents an important opportunity for future research. If the argument for studying quantitative genetics in the field is to understand genetic variation under ecologically relevant conditions, then the field needs to embrace this real world complexity. Fortunately development of theory and statistically tractable modelling tools is progressing rapidly in these areas (Bijma *et al.*, 2007; Baud *et al.*, 2021; Martin and Jaeggi, 2022; Munar-Delgado *et al.*, 2023) setting the stage for more empirical work.

Comparative quantitative genetics

To date, single population studies have dominated the wild quantitative genetic literature. This is unsurprising given the empirical work involved in robustly estimating quantitative genetic parameters in just one population. However, in a few cases it has been possible to obtain replicate estimates of **G** for a defined set of traits across multiple populations (or species) with recent shared ancestry. Such comparative studies have been limited so far but will hopefully become more common as (i) open science practices increase data sharing among groups (see e.g., Chantepie *et al.*, 2024 for a comparative study involving ten populations of great tits *Parus major*) and (ii) uptake of pedigree-free methods (i.e., GRM based analyses) reduces reliance on data from populations with existing multi-generation pedigrees. Comparative studies are particularly valuable for assessing the generality of conclusions, but will also provide opportunities to investigate the evolutionary and ecological stability of **G** (in terms of size, orientation and 'shape'; see Phillips and Arnold, 1999). This is a long-standing area of uncertainty with major implications. Since quantitative genetic variation depends on allele frequencies we know it must be altered by selection, drift, mutation and gene flow. Thus the question is not whether **G** evolves, but rather how quickly it evolves. If **G** is relatively stable, then evolutionary constraints will be conserved across populations and we expect macro-evolutionary divergence of phenotypes to occur most rapidly along directions of phenotypic change in which **G** contains high variance (Schluter, 1996). Conversely, if **G** is very labile and evolves rapidly, then micro-evolutionary constraints will be more transient and perhaps population specific. Comparative studies will allow us to better understand what timeframes it is reasonable – and not just convenient – to assume stability.

In fact **G** may also be labile over ecological timescales since genotype-by-environment interactions (GxE) causes within generation change in genetic variances and covariances (Wood and Brodie, 2015). Since GxE is genetic variance in phenotypic plasticity, the long-standing question of whether plasticity facilitates or constrains phenotypic adaptation (Fox *et al.*, 2019) can be restated in terms of **G**'s ecological lability. Is **G** stable across environments? If not, does GxE tend to increase or decrease the amount of variance in **G** aligned with selection (Berdal and Dochtermann, 2019)? Such questions can be addressed by modelling GxE across environmental temporal heterogeneity in a single population (Hayward *et al.*, 2018), but a complementary strategy might be to estimate **G** in multiple populations across an environmental gradient. Again this highlights the value of more comparative quantitative genetic studies.

Emerging applications of omics data

As already noted the use of genomic data in wild quantitative genetics is rapidly expanding. Genomic data allow mapping QTL but also increase the number of traits that can be measured (e.g., gene

expression, Tung *et al.*, 2015; recombination rates, Johnston *et al.*, 2016; methylation patterns, Hu *et al.*, 2021; aging, Rutledge *et al.*, 2022), the number of systems in which quantitative genetics analyses can be performed (Bérénos *et al.*, 2014; Aase *et al.*, 2022), and the type of questions that can be addressed (Johnston *et al.*, 2022). For example, genetic architecture analyses can be extended to consider genetic covariances and constraints (Hughes and Leips, 2017), inbreeding depression (Stoffel *et al.*, 2021; Hewett *et al.*, 2024), epigenetics (Husby, 2022), and structural variation (Delmore *et al.*, 2023).

One of the most recent, and most promising, applications of genomic data in wild quantitative genetics is genomic prediction. This consists of predicting the breeding value (and hence phenotype) of individuals in the absence of phenotypic information using molecular marker data (Meuwissen *et al.*, 2001; McGaugh *et al.*, 2021). Though conceptually similar to predicting breeding values of unmeasured individuals using pedigree information (e.g., Réale *et al.*, 2009), the use of genomic data greatly extends the range of possible applications (McGaugh *et al.*, 2021). For example, genomic prediction can be used to predict breeding values in different populations to study adaptive differentiation (e.g., Bosse *et al.*, 2017) or the phenotypic expression of genotypes in different (including future) environments (Crossa *et al.*, 2022). Genomic prediction models can also complement GWAS and related analyses to make inferences about genetic architectures (e.g., Ashraf *et al.*, 2022), test for micro-evolutionary change (Hunter *et al.*, 2022), and study mate choice (McGaugh *et al.*, 2021). As with other quantitative genetic analyses the accuracy of genomic prediction is limited by sample size, but also by the composition of the initial 'training population' (comprising individuals with measured phenotypes as well as genomic data, Hayes *et al.*, 2009; Cuyabano *et al.*, 2024). Although these factors may limit usefulness in some circumstances, genomic prediction is a versatile approach with many applications and we anticipate broad uptake in the coming years.

Applied quantitative genetics in the wild

While much quantitative genetic research in humans and agricultural species has an applied focus, research in the wild has primarily sought to advance our fundamental understanding of evolutionary ecology. An increasing number of studies are using quantitative genetics to investigate the adaptive potential of populations impacted by anthropogenic effects including urbanization (Perrier *et al.*, 2018b), selective harvesting (Pigeon *et al.*, 2016), and climate change. In the latter context, adaptation could occur through evolution of heritable phenological traits (Richards *et al.*, 2020) or thermal tolerance (Elder *et al.*, 2022). The extent to which this may aid persistence of threatened populations is unknown and convincing examples of 'evolutionary rescue' are scarce (Carlson *et al.*, 2014). Nonetheless, the recent finding that genetic variance for fitness itself is widespread provides at least some cause for optimism (Bonnet *et al.*, 2022). Conservation genetics has, for most of its history, been dominated by population genetic rather than quantitative genetic views of variation and how to maintain it, despite genetic concerns arising primarily from quantitative genetic considerations (Frankham, 1999). However, as genomic methods increasingly sweep away old boundaries between disciplines (Capblancq *et al.*, 2020), it is becoming clear that quantitative genetic perspectives could, and probably should, play a greater role in informing practical and conservation management strategies (Kosch *et al.*, 2022; Sauve *et al.*, 2022).

Conclusion

Since the late 1990s we have witnessed a rapid increase in the number of quantitative genetic studies of wild populations *in situ* (Charmantier *et al.*, 2014). As developments in genotyping technologies and analytical techniques have now democratized this type of analysis to virtually any species, the field will likely see an even more dramatic increase in popularity in the years to come. Although there are

important limitations and challenges, if the goal is to understand phenotypic evolution in the wild as a dynamic and ongoing process, then quantitative genetic analyses provide clear benefits. This is because, in contrast to other approaches in evolutionary ecology (e.g., behavioral ecology and life history theory), it rejects the implicit assumption that adaptation can be studied while ignoring all genetic considerations. By recognizing that adaptive evolution depends on both natural selection and genetic (co)variation, quantitative genetic studies of wild populations provide understanding of both how natural selection has shaped phenotypes in the past, and how it will do so in the future.

See also

Adaptive Landscapes. Genotype-by-Environment Interaction. Maternal Effects. Multivariate Quantitative Genetics. Natural Selection, Measuring. Quantitative Genetic Variation. Social Effects. Quantitative Genetic Variation, Comparing Patterns of. Genomic Prediction.

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Figure 1 Quantitative genetic theory predicts phenotypic evolution as a function of natural selection and genetic variation (dark gray box). To use this predictive theory, empiricists must therefore estimate the genetic variation underpinning a trait (or traits) of interest. In wild populations this is most commonly done by modeling the individual phenotypes *Yi* of animals of known relatedness to each other (see main text for detail). In the simplest case, *Yi* is specified as the population mean, plus deviations attributable to genotype (the 'breeding value'), and (unknown) environmental effects experienced.

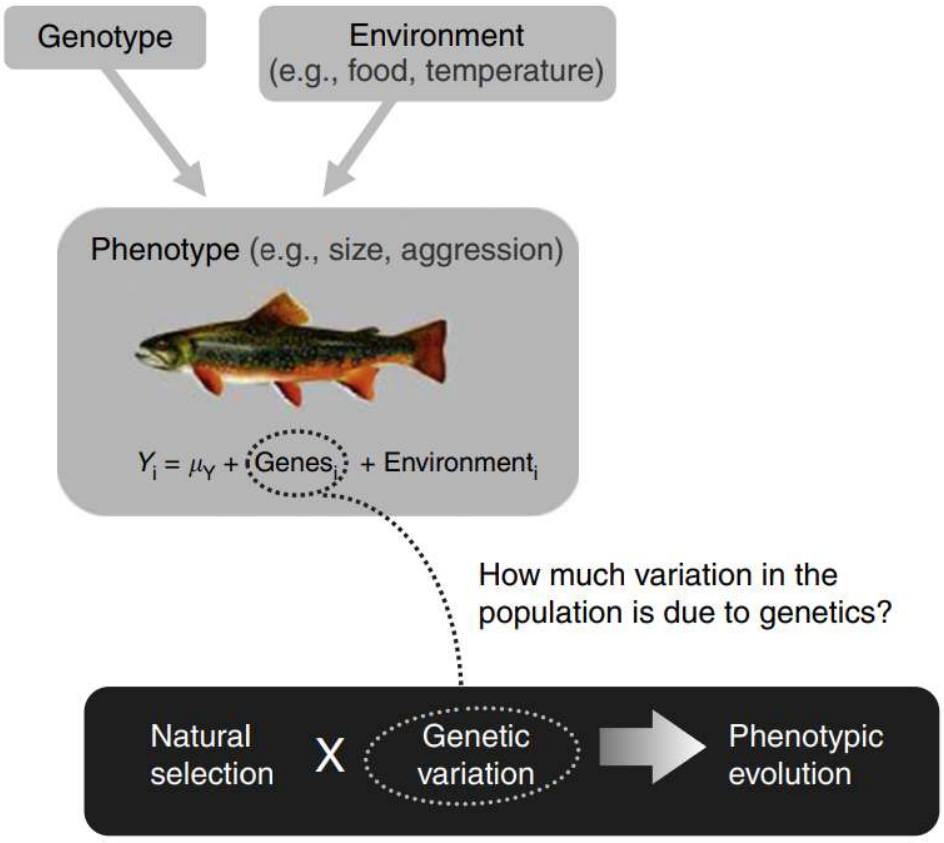

Figure 2 Cross-fostering is an experimental technique useful for disentangling genetic from environmental sources of variation in offspring phenotype. Parental birds influence offspring phenotype both via genetic inheritance (solid arrows) and through provision of the early life environment (dotted arrows, e.g., amount of food being provisioned to the nest). In the absence of experimental manipulation (a) these effects are completely confounded within each family (color) and so difficult to tease apart statistically. This problem is alleviated by cross-fostering designs in which hatchlings (or eggs) are exchanged between nests. Individuals now have genetic siblings elsewhere (i.e., sharing genes but not environment) and foster-siblings in their own nests (i.e., sharing environment but not genes). Cross-fostering is most widely used in wild bird studies but has also been successfully applied to mammals and insects in the lab.

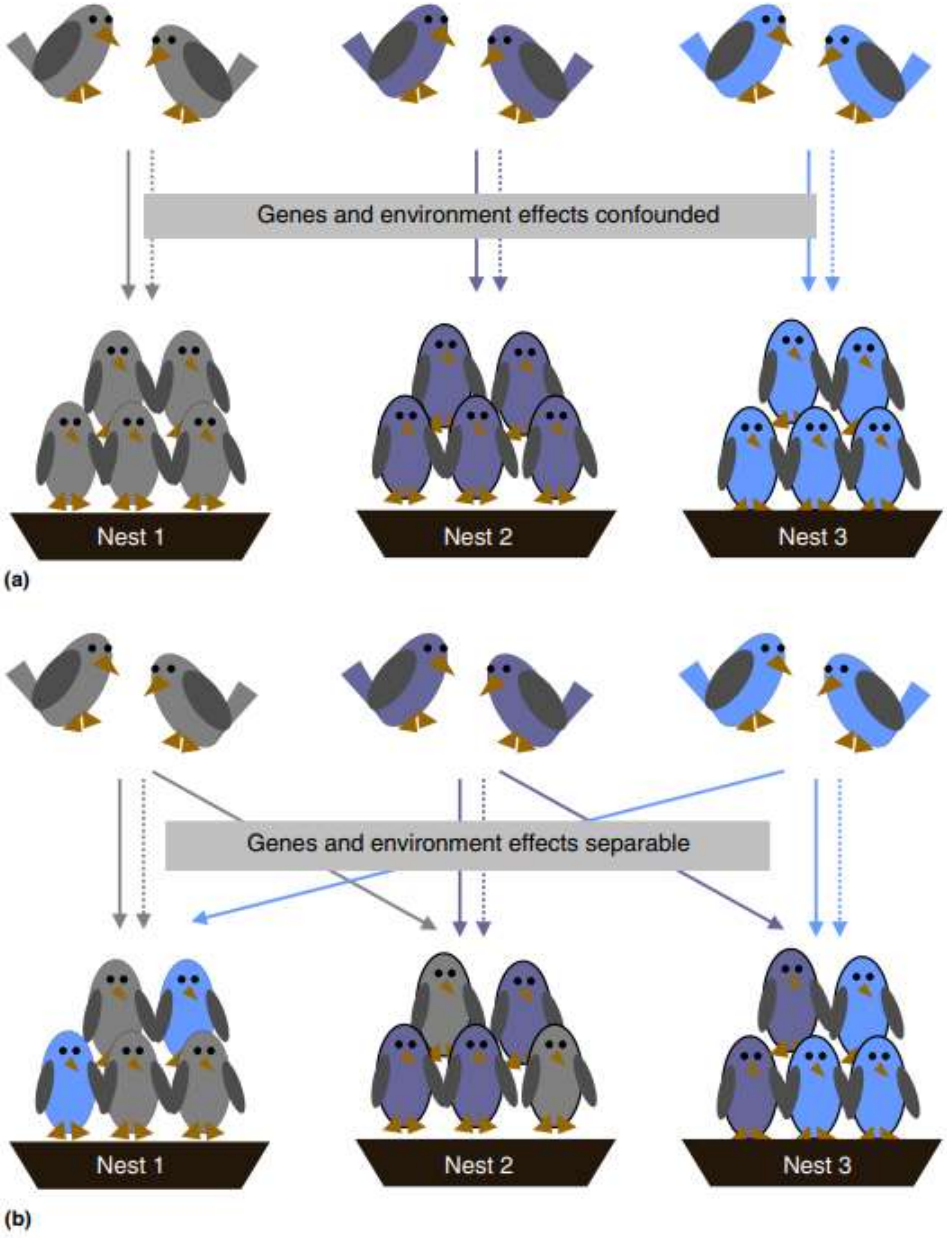

Figure 3 Trade-offs as a source of evolutionary constraint. Imagine a population in which clutch size (CS) and egg size (ES) are both under positive direction selection (with standardized selection gradients β equal to 0.25 on both traits) and genetically variable (with VA(ES)=0.5 and VA(CS)=0.15). While the univariate breeder's equation predicts a moderate increase in mean phenotype for each trait, the predictions responses under a bivariate model are much if there is a negative genetic correlation between them (here $COVA$=−0.25 so rG=−0.91). In fact, the bivariate model actually predicts a decrease in mean clutch size despite the positive selection on it. This scenario is depicted graphically in (b) where breeding values (black circles) for each trait are normally distributed but also covary negatively. This means that the major axis of genetic variation for the bivariate phenotype (red line) does not align with the direction of selection (blue arrow). Some adaption (i.e., evolution toward darker blue phenotypic space) is still possible so the constraint is not absolute. However, the rate of adaption is limited by the relative lack of genetic variation in the direction of selection.