

Theoretical Approaches to the Evolution of Development and Genetic Architecture

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Developmental evolutionary biology has, in the past decade, started to move beyond simply adapting traditional population and quantitative genetics models and has begun to develop mathematical approaches that are designed specifically to study the evolution of complex, nonadditive systems. This article first reviews some of these methods, discussing their strengths and shortcomings. The article then considers some of the principal questions to which these theoretical methods have been applied, including the evolution of canalization, modularity, and developmental associations between traits. I briefly discuss the kinds of data that could be used to test and apply the theories, as well as some consequences for other approaches to phenotypic evolution of discoveries from theoretical studies of developmental evolution.

Key words: evolutionary theory; evolution of development; genetic architecture; canalization; modularity

Introduction

Heritable variation is the raw material of evolution, and because most heritable phenotypic variation is translated through development from genetic variation, a complete theory of phenotypic evolution must be ready to incorporate all the complexities of development and genetic architecture. This was one of the motivations for the emergence of evolutionary developmental biology as a distinct field. However, much of the early interest in “evo-devo” came from developmental biologists who saw the relevance of comparative studies based on phylogenetic relationships. This is basically “devo” with a little bit of “evo” added for context. A truly synthetic theory needs to incorporate development and genetic architecture into the formal mathematical theory of evolution and then connect this theory back to developmental data. Here I review some recent steps toward such a synthesis.

I first discuss some of the theoretical methods that have recently been applied to studying the evolution of development and genetic architecture. My goal here is to outline how these methods work and what some of their strengths and weaknesses are. I then discuss some of the principal things that we have learned from application of these methods.

Methods for Modeling the Evolution of Development and Genetic Architecture

Quantitative Genetics

The most widely used approach to studying the evolution of continuous variables is quantitative genetics (Roff 1997; Lynch & Walsh 1998). Unfortunately, the very properties of quantitative genetic models that make them particularly useful for studying phenotypic evolution make them ill suited to the study of the evolution of genetic architecture.

Quantitative genetics theory makes several simplifying assumptions that make it mathematically tractable. The most important of these for our purposes is the assumption that

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only the additive contributions of genes to a phenotype play a significant role in evolution. The phenotypic consequences of nonadditive phenomena such as dominance and epistasis are averaged and grouped into components of phenotypic variance (Lynch & Walsh 1998). As I will discuss below, focusing only on additive contributions of genes to phenotype precludes most of the study of the evolution of genetic architecture.

Though many quantitative genetic models treat heritability and genetic covariance as fixed values, these change over a few generations (Bohren *et al.* 1966; Parker *et al.* 1970). Particular attention has been paid to genetic covariance since early studies suggested that this evolves faster than additive genetic variance (Bohren *et al.* 1966). Understanding exactly why genetic covariance changes has been difficult using only the machinery of quantitative genetics. Although results can be obtained under the assumption of weak selection and additivity of gene effects (Lande 1980), understanding the variation in genetic covariance seen in experimental studies will require explicit models of the specific gene interactions underlying quantitative traits (Riska 1989).

One approach is to study models of possible gene interactions. One such model that has received considerable attention is the resource partitioning model for two traits that are influenced by developmental processes that draw on the same resources (Sheridan & Barker 1974). Several authors have used variants of the resource partitioning model to study the evolution of genetic covariance (Riska 1986; Houle 1991; de Jong & van Noordwijk 1992). This work showed that when gene products interact nonadditively, genetic covariance changes in response to selection on phenotype and that this change is often not what we would expect from an additive model. The logical extension of these kinds of studies is to devise a set of methods that would allow us to investigate the evolutionary consequences of any kind of interaction between gene products. This is what phenotype landscape theory does.

Phenotype Landscape Models

Phenotype landscape models treat the value of some phenotypic trait (or set of traits) as a function of a set of underlying factors, which may be any measurable quantities, genetic or environmental, that contribute to phenotype (Rice 1998, 2002b; Wolf *et al.* 2001). Phenotypic traits that are subject to direct selection are generally represented by ϕ ; underlying factors that contribute to development of such traits are generally represented by u (although we will see cases where one trait plays both roles). Selection is captured by a separate function that maps phenotype to fitness. This structure is different from that taken in population genetics (such as the modifier models discussed later), where genotypes are generally mapped directly to fitness, skipping over phenotype. By explicitly inserting phenotype between the levels of genotype and fitness, phenotype landscape models allow us to distinguish between the ways that genes interact to influence phenotype (development and genetic architecture) and the ways that phenotypic traits interact to influence fitness (selection).

An individual organism is a point on the landscape, and a population is a distribution of such points. Figure 1A shows a phenotype landscape in which the underlying factors contribute additively to phenotype; thus, the landscape is uncurved. The contours are lines of equal phenotypic value. Fitness is not represented here, only phenotype as a function of the underlying factors. The landscape itself thus represents genetic architecture but says nothing about selection. Figure 1B shows a curved phenotype landscape, meaning that here the underlying factors interact nonadditively to influence phenotype (this is actually one of the phenotype functions used in the resource partitioning models mentioned earlier).

Curvature of the landscape allows genetic architecture to evolve. To see this, consider the points a and b on the contour plot in Figure 1D. At point a the landscape slopes steeply in the u_1 direction, meaning that a change in u_1 has

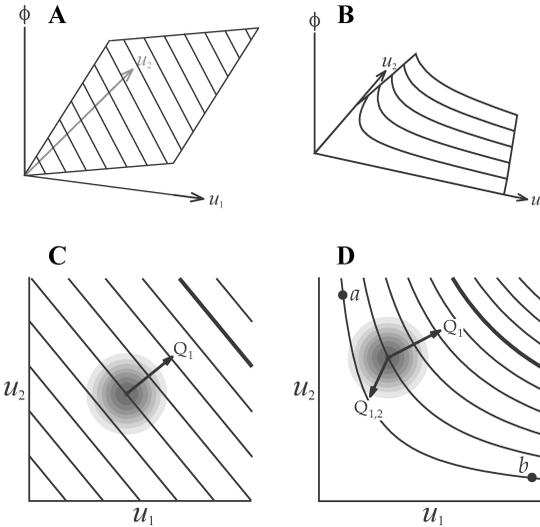


Figure 1. Examples of phenotype landscapes corresponding to **(A)** purely additive genetic effects and **(B)** nonadditive (epistatic) effects. In panels A and B, the vertical axis is phenotype, not fitness. **(C)** and **(D)** show contour plots of the landscapes in panels A and B, respectively. Shaded circles represent the distribution of individuals within a population, and the Q vectors are those described in the text.

a large effect on phenotype. A change in u_2 , though, produces little change in phenotype; moving along the u_2 axis at point a primarily just changes the slope in the u_1 direction. Thus, at point a , u_1 has a strong direct effect on phenotype and u_2 acts basically like a modifier of u_1 . This situation is exactly reversed at point b , where u_2 has a strong direct effect and u_1 acts like a modifier. This example illustrates why phenotype landscapes are useful for studying the evolution of genetic architecture; the relative roles of different underlying factors change as the population moves over a curved landscape.

This example also illustrates why quantitative genetics is poorly suited to study the evolution of genetic architecture; by assuming that genes contribute additively to phenotype, quantitative genetics assumes a phenotype landscape like that in Figure 1A and C, on which genetic architecture cannot evolve because it is the same everywhere on the landscape.

The general mathematical theory for evolution on a phenotype landscape has been described by Rice (1998, 2002b). This theory describes evolution as the sum of a set of vectors (termed Q vectors) in the space of underlying factors, each vector corresponding to a different aspect of the local geometry of the landscape. The simplest Q vector, Q_1 , contains only first derivatives of phenotype with respect to the underlying factors and captures just the effects of directional selection to change the mean phenotype. If the distribution of underlying variation is normal and the landscape uncurved (as in Fig. 1C), then Q_1 is the only vector present. The vector $Q_{1,2}$ (containing both first and second derivatives of the landscape) appears on curved landscapes (Fig. 1D) and captures the effect of stabilizing selection to reduce phenotypic variance. The equations for these vectors are

$$Q_1 = \frac{1}{\bar{w}} \frac{\partial w}{\partial \phi} \langle P^2, D^1 \rangle \quad \text{and} \quad (1)$$

$$Q_{1,2} = \frac{1}{2\bar{w}} \frac{\partial^2 w}{\partial \phi^2} \langle P^4, D^1 \otimes D^2 \rangle.$$

Here, P^n is a tensor containing all the n th moments of the distribution of underlying variation, D^n is a tensor containing all the n th derivatives of phenotype with respect to the underlying factors, and w represents fitness. The general equation for all of the Q vectors present on an arbitrarily complex landscape is given by Rice (2002b).

The general theory of Q vectors applies to an arbitrarily complex developmental system with an arbitrary distribution of underlying variation. For many of the questions that we are interested in, though, a more restricted model is actually easier to work with. One way to simplify the general phenotype landscape model is to focus on a subset of possible landscape geometries. This approach is essentially what quantitative genetics does by considering only additive effects. A more complex, though still relatively tractable, set of models are the multilinear models (Hansen & Wagner 2001; Hermisson *et al.* 2003). In these models, many

underlying factors can interact, but each has a linear effect on the interactions between the others. Restricting our attention to a subset of surfaces increases our ability to study certain processes, such as the evolution of mutational variance (Hermisson *et al.* 2003). However, it also limits our ability to study other processes. For example, the third moment (measuring asymmetry) of the phenotype distribution cannot evolve on these multilinear landscapes.

Moments

The set of moments of a distribution characterize the shape of that distribution. The even moments measure symmetrical spread about the mean, and the odd moments measure asymmetry. The higher the order of a particular moment, the more sensitive it is to outliers. Throughout this discussion, we will sometimes come across “higher” (greater than second) moments of the distribution of underlying variation. Because nearly all evolutionary theory is couched in terms of the mean (first moment) and variance or covariance, it is worth briefly discussing why we need to consider higher moments in any discussion of the evolution of genetic architecture.

One rule of evolution is that if we want to calculate the change over time in the n th moment of the distribution of phenotypes, we need to know the current ($n + 1$)st and higher moments (Rice 2004b chap. 6; this fact follows from Price 1970). When we model directional phenotypic evolution, we are studying the change in the mean (first moment) of the phenotype distribution; we thus can model directional evolution, at least approximately, by considering only the variance of the current population distribution.

Most processes implicated in the evolution of development and genetic architecture involve selection to change more than just the mean phenotype in a population. Modeling the evolution of canalization requires that we consider the fourth moments of the distribution of underlying variation; the same goes for

the evolution of genetic covariance. Selection to change the overall degree of epistasis or to change the curvature of a reaction norm acts on the sixth moment (Rice 2004b). If we accept that selection for canalization, modularity, and phenotypic plasticity are among the important factors influencing the evolution of genetic architecture, then we clearly cannot ignore these higher moments. Some models have addressed the evolution of phenotypic variance without appearing to involve higher moments (e.g., Lande & Arnold 1983; Rice 1998). This approach is possible because these models assume a normal distribution of variation, and one property of the normal distribution is that all higher moments can be written in terms of the variances and covariances. Most distributions do not have this property, though, so these models can lead to substantial errors if the actual distributions that we are dealing with in nature are not exactly normal.

Consider the two distributions in Figure 2. These two distributions have the same variance and so would respond the same to directional selection on an uncurved landscape. However, because neither is a normal distribution, the higher moments are not constrained to be functions of the variance. In fact, the sixth moment of the distribution in Figure 2B is 10 times larger than the sixth moment of the distribution in Figure 2A. Thus, if we are interested in the evolution of phenotypic plasticity, selection to change the curvature of a reaction norm would be 10 times stronger for the population in Figure 2B than for the one in Figure 2A. This fact would be missed if we considered only the variance.

General Models and Dynamic Sufficiency

Our having to always look at higher moments to study the evolution of a particular moment brings up another issue relating to the use of phenotype landscape models. I refer to these models as being “general” because they can be applied to any evolving developmental

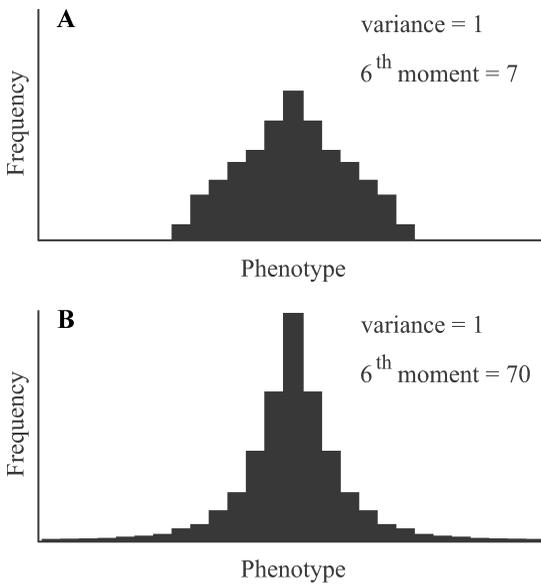


Figure 2. Two distributions with the same mean but different sixth moments.

system, regardless of the kinds of interactions involved between genes and the environment, the distribution of variation within a population, or the kind of selection acting on the system. This does not mean, though, that they answer all our questions. One reason for this is that we can use the most general phenotype landscape models only to calculate what will happen over one generation; they cannot be iterated indefinitely. Given the population distribution in generation t , we can calculate the mean in generation $t + 1$ only by using at least the variance in generation t . If we then want to calculate the mean in generation $t + 2$, we need the variance in generation $t + 1$, but this can be found only if we know at least the third moment in generation t . Therefore, we can iterate our model forward through time only if we specify all the moments in the current generation, which is not practical. These models are thus not dynamically sufficient.

If we assume that all distributions relevant to our system are multivariate normal, then our problem is solved because all the higher moments are functions of the second moments, so we can calculate them all. Applying this assumption makes phenotype landscape models

dynamically sufficient (Rice 1998). As I argued earlier, though, this approach rapidly yields incorrect answers (and misleading conclusions) when we are dealing with real populations, which are never exactly normally distributed. Although models that can be iterated indefinitely are clearly useful as descriptions of special cases, and allow us to investigate the types of dynamical behavior that evolution can exhibit, they are never truly general in the sense of applying to any evolving system.

Modifier Models

Modifier models focus on a few loci (usually two or three) in which one locus acts as a modifier of the expression of the others. Modifier models have been used to study the evolution of dominance and of recombination (Feldman & Karlin 1971; Feldman & Krakauer 1976; Feldman *et al.* 1997). In modifier models, genotypes map directly to fitness, skipping over the intervening phenotype. The term *epistasis*, as used in these models, thus refers to nonadditive contributions of loci to fitness. Therefore, even genes that contribute additively to two different traits may be said to interact epistatically if the two traits contribute nonadditively to fitness. The modifier approach has been combined with the multilinear model approach by Kopp and Hermisson (2006). This method allows including more than three loci by assuming a specific kind of interaction among loci.

Because they borrow the well-established methods of two-locus population genetics, modifier models are good for studying the role that linkage and recombination may play in the evolution of genetic architecture. Recent applications of modifier models include Masel's (2005) study of the evolution of capacitance and Liberman and Feldman's (2005, 2006) studies of the evolution of epistatic interactions. Because modifier models deal with a relatively small number of discrete genotypes, they are good for dealing with discontinuities in the mapping from genotype to fitness.

Functional Mapping Models

The approaches discussed above tend to focus on one phenotypic trait, influenced by many loci. When multiple traits are considered, they are represented by a vector of values (Rice 2002b). Development, however, is a continuous process, and sometimes the “trait” that we are interested in is actually the growth process itself. The functional mapping approach (Ma *et al.* 2002; Wu *et al.* 2002; Wu & Hou 2006) deals with this problem by focusing on an ontogenetic trajectory. The ontogenetic trajectory, an idea borrowed from models of heterochrony (Alberch *et al.* 1979; Rice 1997, 2002a), is a plot of some phenotypic trait as a function of time or of another trait.

Earlier methods for analyzing ontogenetic trajectories simply compared the shapes of different trajectories, making no attempt to map the shape of these curves to underlying genetic processes. This approach can provide some limited insight into developmental evolution. Specifically, we can test whether or not a particular evolutionary transformation could have come about as a result of uniformly changing the rate, duration, or timing of developmental processes (Rice 2002a). Although changes of this sort (heterochrony) do sometimes appear to be important, they represent only a small subset of all of the ways in which development can change.

Functional mapping models greatly increase the utility of ontogenetic trajectories by parameterizing them in such a way that we can apply quantitative trait locus (QTL) methods to them. By using some general assumptions about underlying physiology, this approach allows us to draw much richer conclusions from ontogenetic trajectories that do not fit the restrictive conditions of heterochrony.

Artificial Gene Networks

The artificial gene network approach is primarily computational, rather than analytical. Such studies generally emphasize computer

simulations, the results of which are interpreted after the fact, rather than predictions based on the analysis of equations. Some analytical results can be obtained, though, especially for the earliest kinds of gene network studies.

A widely used approach to studying artificial gene networks was devised by A. Wagner (1996). Models of this type posit a population of genetic networks, each designed to resemble a set of transcription regulation genes. In each generation, recombination and mutation were simulated within each network, and then a selection process was imposed favoring those networks closest to a defined optimum. Wagner’s simulations showed that if there is epistasis in the networks, then the structure of the networks did evolve to become increasingly canalized. This type of simulated gene network has been used more recently by Siegal and Bergman (2002), to study the evolution of genetic architecture under different kinds of stabilizing selection, and by Azevedo *et al.* (2006), to study the consequences of sexual versus asexual reproduction.

General Results from Theoretical Studies

The methods outlined above have been used to investigate a wide range of questions. I now consider some of the major results.

Single-trait Distributions—Canalization and Capacitance

Canalization refers to buffering of phenotype against underlying genetic or environmental variation. This phenomenon (also referred to as “robustness”) has received extensive attention from researchers, and it was the desire to model the evolution of canalization that motivated much of the early development of modern theories for the evolution of development and genetic architecture (Wagner 1996; Wagner *et al.* 1997; Rice 1998, 2000; see reviews in de Visser *et al.* 2003 and Flatt 2005).

Canalization is generally thought to evolve in response to stabilizing selection, defined here as selection to reduce phenotypic variance (Rice 2004b). We can visualize the process as evolution of a population toward parts of the phenotype landscape that minimize phenotypic variance. If the underlying factors are uncorrelated and have equal variances, then points of maximum canalization for a particular phenotypic value are points of minimum slope along the contour corresponding to that value. However, changing the shape of the distribution of underlying variation will change the position of points of maximum canalization (compare populations A and B in Fig. 3). Points of maximum or minimum canalization along a contour occur wherever the vector $Q_{1,2}$ (from Equation 1) is normal to the contour line.

Nearly all analytical models that incorporate nonadditive interactions between loci (Wagner *et al.* 1997; Rice 1998; Proulx & Phillips 2005) or between genes and environmental variables (Gavrilets & Hastings 1994) exhibit some sort of canalization under stabilizing selection. The simplest genetic models focus on variation resulting from mutation, but in fact variation resulting directly from mutation is probably less relevant to developmental evolution than are other sources of variation, such as recombination, migration, and environmental fluctuation. Selection is efficient at reducing variation resulting directly from mutation, so the response of a population to selection to reduce variation is likely to be a rapid change in the mutation–selection equilibrium rather than a restructuring of genetic architecture (Wagner *et al.* 1997; Rice 2000).

Selection acts on the entire distribution of variation in a population, and this distribution may look different from the distribution of mutational effects alone. Hermisson *et al.* (2003) used a multilinear model to study the consequences of allowing the distribution of additive genetic variation to evolve as a population moves over a phenotype landscape. They found that if different underlying factors have different mutation rates, then at mutation–selection

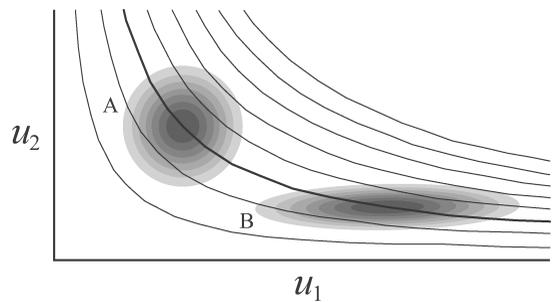


Figure 3. Two populations at points of maximum canalization along their contour, as determined by the shape of the landscape and the distribution of underlying variation.

equilibrium the population distribution tends to elongate along the axis corresponding to the underlying factor with the highest mutation rate. This effect shifts the point of maximum canalization away from the point of minimum slope and yields an equilibrium state resembling the population at point B in Figure 3 (the landscape in Fig. 3 is in fact a multilinear landscape). Significantly, the equilibrium was not at a point that minimized mutational variance.

Several simulated gene network studies have demonstrated that canalization can evolve *in silico*. A. Wagner (1996) found canalization around an optimum regulatory network. Siegal and Bergman (2002) used a similar simulation approach to study cases in which there was no optimum phenotype but rather just selection to minimize variance among one's descendants. This study found that genetic architecture evolves to minimize phenotypic variation even when there is no single “best” phenotype to be canalized. There has been some confusion about this work resulting from different uses of the term *stabilizing selection*. Siegal & Bergman define *stabilizing selection* as “selection for a particular optimum gene expression pattern.” Therefore, they interpret their results as showing that canalization can evolve without stabilizing selection. This definition of *stabilizing selection* is consistent with that given in many introductory texts, but it is not the same as the definition used in most of the evolutionary genetics literature, where *stabilizing selection* is defined as selection to reduce phenotypic variance and is

captured mathematically by the second partial derivative of fitness with phenotype [or the partial regression of fitness on $(\phi - \bar{\phi})^2$] (Lande & Arnold 1983; Rice 1998; Rice 2004b). A population may thus experience stabilizing selection, with a corresponding evolution of canalization, even when it is not near an optimal phenotype (Rice 1998). Under this definition, Siegal & Bergman's simulations imposed stabilizing selection within each lineage, so their result is exactly in line with prior predictions.

Azevedo *et al.* (2006) used simulated gene networks to compare the evolution of genetic architecture in asexual and sexual populations. They found that "mutational robustness" (canalization against mutational variation) evolved in both sexual and asexual populations when mutation rates were high but only in sexual populations when mutation rates were low or mutation was excluded. The key to this observation is that gene networks in sexual populations underwent recombination, whereas those in asexual populations did not. Canalization thus evolved primarily in response to underlying variation produced by recombination. This effect still registered as "mutational robustness," meaning that the genetic architecture that buffered against recombination variation also buffered against mutational variation.

The phenomenon of a system that is buffered against one source of underlying variation also being buffered against other sources of underlying variation has been called congruence (Ancel & Fontana 2000). Congruence is usually discussed in the context of comparing environmental canalization with mutational canalization and has been seen as important because of the limitations on mutational canalization discussed earlier. However, as the above example makes clear, mutation is not the only source of genetic variation. In addition to recombination, mutation, and environmental variation, the phenotypic (and genetic) variation within a local population is influenced by migration (Proulx & Phillips 2005). All these processes contribute variation that spurs selection for canalization.

Canalization clearly can evolve, and it does so in simulated genetic systems. Exactly how important selection for canalization is in structuring development in natural populations, though, is less clear. Other processes, such as selection for a particular covariance between traits (discussed later), also modify development and will tend to pull populations away from points of maximum canalization. Also, depending on the structure of the landscape, achieving maximum canalization for multiple traits at the same time may not be possible.

One observation that was long thought to provide evidence for canalization is that populations often express increased heritable variation after being perturbed either genetically (such as through the introduction of new alleles of large effect) or environmentally. In fact, though, several processes can cause variation to increase after perturbations even if the trait was not initially canalized (Goodnight 1988; Cheverud & Routman 1996; Hermisson & Wagner 2004).

A more direct way to assess whether genetic architecture is likely to have been structured by selection for canalization (or some other process) would be to reconstruct the phenotype landscape underlying a trait of interest. The most direct way would be to use a mechanistic model for development of the trait. Nijhout *et al.* (2006) recently used this approach for body size in *Manduca*. They drew on empirical studies to identify three underlying factors that jointly are sufficient to determine body size, and they calculated the function that maps these traits to size; this function is a phenotype landscape. This is an important approach that will surely become more common as we learn more about the mechanics of different developmental processes. Even with such a landscape, though, we cannot tell if a population is at a point of maximum canalization without further information about the distribution of variation of the underlying factors.

There is another approach to reconstructing phenotype landscapes that does not require mechanistic knowledge of development and, at

least approximately, scales the landscape according to the distribution of variation in each underlying factor. Regression-based QTL analysis (Visscher & Hopper 2001; Feingold 2002) basically involves constructing a multivariate regression of a phenotypic trait on a set of markers distributed throughout the genome. In most regression-based QTL studies, the coefficients of this regression are tested against a sampling distribution, and those markers corresponding to statistically significant coefficients are reported as putative QTLs. The entire analysis, though, effectively estimates the phenotype landscape, for which the individual QTLs play the roles of underlying factors. There are three points along each axis, presumably corresponding to different dosages of an allele at some locus closely linked to the marker.

Because such analyses generally start by imposing strong divergent selection on different strains and then produce inbred lines with extreme phenotypes, the original population distribution probably sat near the middle of the reconstructed landscape. The presence of a point of minimal slope in this region, although not a conclusive demonstration, is at least consistent with the hypothesis that the genetic architecture of that trait has been shaped by stabilizing selection. By contrast, if no point of minimum slope is found within the range of variation in the population, then selection for robustness alone is unlikely to explain the observed genetic architecture.

Figure 4 illustrates this approach by using data from Shimomura *et al.* (2001) on QTLs influencing circadian rhythms in mice. The landscape in Figure 4 has a saddle point near the center of the graph. Saddle points are points of zero slope at which the surface curves away positively in some directions and negatively in others. A population sitting near such a point is thus well canalized. These data are thus consistent with the hypothesis that the genetic architecture of this trait was substantially structured by stabilizing selection. The specific trait in this example, dissociation, measures the degree to which different parts of the circadian cycle are

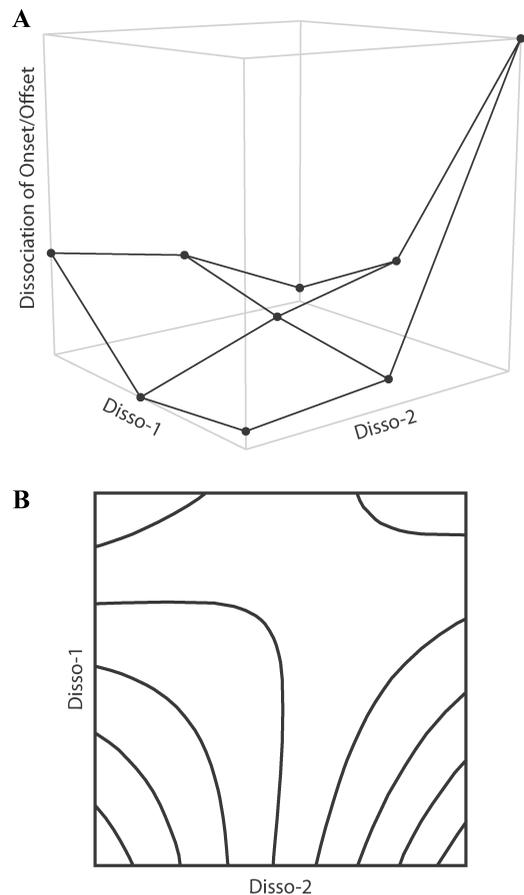


Figure 4. (A) Phenotype landscape for a trait relating to circadian rhythms in mice, reconstructed from data in Shimomura *et al.* (2001). (B) A quadratic surface fit to the data in panel A.

decoupled from one another. This value is near zero in the original population and is something that is probably always under strong stabilizing selection (it is generally maladaptive to have no connection between when an organism goes to sleep and when it wakes up). It is thus not surprising that this trait behaves as though it is well canalized.

Adaptation of Higher Moments

Selection could in principle act to change the third moment of a phenotype distribution (measuring the degree of asymmetry of the distribution) by moving the population to regions of the phenotype landscape with different

average curvature. Though we have no special name for this sort of selection, it will happen anytime that fitness drops off more steeply on one side of an optimum phenotype than on the other side. Such “skewing” selection should modify genetic architecture by pushing a population toward regions of the phenotype landscape at which the mean curvature is high.

Figure 5 shows a landscape that exhibits exactly the geometry that we would expect if there has been selection to skew the phenotype distribution (data from Shimomura *et al.* 2001). Unlike the saddle point in Figure 4, the surface in Figure 5 curves in the same way in all directions. As a consequence, the mean curvature is nonzero, meaning that a symmetrical distribution of underlying factors will produce an asymmetrical phenotype distribution. One hint that we have a reasonable picture of this phenotype landscape is that the distribution of this trait in the F2 generation of mice is in fact strongly negatively skewed (Fig. 5C). Though not an independent test of the data (these are the mice from which the data in the figure came), this finding at least confirms that our reconstruction of the landscape from nine points is not far off the shape of the actual surface.

That this trait has evolved to a place on its phenotype landscape that should produce a skewed phenotype distribution might be fortuitous—there is also a region of very low slope near the center of the figure. In fact, though, this is a trait for which we should expect selection to favor a skewed phenotype distribution. The phenotypic trait represented in Figure 5, “phase,” measures the time at which mice wake up relative to when it gets dark (which is when wild mice begin foraging). A phase value of zero means that the mouse awakes precisely when the lights go off, a negative value means that the mouse wakes up early, and a positive value means that it awakes after dark. Foraging studies suggest that, at least for nocturnal desert rodents, there is a substantial cost to foraging later at night because resources have been depleted by early foragers (Kotler *et al.* 1993; Brown *et al.* 1994). Waking up late

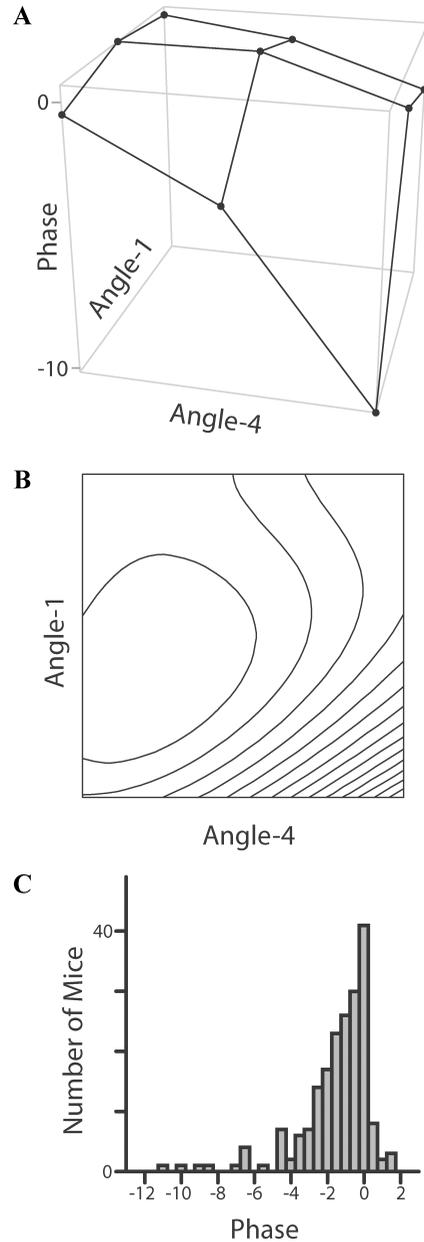


Figure 5. (A) Phenotype landscape for the trait “phase” (discussed in the text) reconstructed from the same source as Figure 4. (B) Best-fit cubic surface corresponding to data in panel A. (C) Distribution of the trait among the F2 progeny.

thus probably carries a substantial fitness cost. By contrast, waking up early does not impose such a cost; individuals simply wait until dark to begin foraging (Shimomura *et al.* 2001). Therefore, it is plausible that the genetic architecture

of this trait has been shaped by selection to both minimize phenotypic variation and to skew, in the direction that is least damaging, what variation remains.

This method of constructing phenotype landscapes has some serious limitations. We are constructing the landscape by using only three points along each axis, which is not particularly good resolution. Therefore, we must compare the observed F2 phenotype distribution with what we would predict from our reconstructed landscape (Fig. 5). Also, most methods of QTL analysis involve selecting different strains for different extreme phenotypes and then crossing these. We can thus view a slightly larger region of the phenotype landscape than was inhabited by the original population. Unfortunately, it also means that all information about the distribution of variation in the original population is lost.

That the extreme phenotypes crossed to generate the data were derived from variation in an initial population means that there is some correspondence, though not perfect, between the scaling of the axes on our reconstructed landscape and the amount of variation that was initially present in the population. Unfortunately, strong selection followed by inbreeding makes it impossible for us to know whether the underlying factors were initially correlated with one another (i.e., if the alleles at the loci in question were in gametic equilibrium or not). Some of these problems could perhaps be alleviated by noting the patterns of variation among extreme phenotypes in the population before selection and inbreeding.

The other side of canalization is capacitance, the expression—when a population experiences a new selection regime—of new heritable phenotypic variation. The term *capacitance* refers to the fact that the exposure of such variation could facilitate adaptive evolution and raises the possibility that development and genetic architecture could be structured to buffer phenotype under stabilizing selection and then abruptly express new heritable variation under conditions of directional or disruptive

selection. Capacitance could arise in two different ways. In one scenario, an environmental change (or other perturbation) causes genetic variation that is already present, but not expressed, to suddenly be expressed as phenotypic variation. In the second scenario, the perturbation causes the production of new genetic variation.

The phenomenon of capacitance actually arises easily from a wide range of models of developmental evolution and genetic architecture (Bergman & Siegal 2003; Hermisson & Wagner 2004; Masel 2005). Furthermore, the expression of novel variation when a population is stressed has been observed in several taxa (True & Lindquist 2000; Fares *et al.* 2002; Queitsch *et al.* 2002). Although this expression of variation may facilitate adaptive evolution, it does not follow that these systems have evolved, wholly or in part, from selection for evolvability. As noted above, the expression of variation is expected when a canalized system is disrupted and is a common occurrence even in noncanalized systems that involve substantial epistasis. Furthermore, error-prone DNA repair increases mutation rates when a population is stressed, but this is probably because error-prone repair is better than no repair at all, rather than selection to produce variation.

Though most instances of capacitance are probably by-products of genetic architecture and DNA repair systems, it is in principle possible for at least a limited kind of capacitance to evolve as a direct result of selection for variability. Masel (2005) used a modifier model to show that selection can lead to the fixation of modifier alleles that express variation at an optimal rate.

Multiple Trait Distributions—Modularity, Correlation, and Entanglement

Adaptation of an entire organism requires that different traits be able to evolve independently of one another. If any change in any underlying factor influenced every trait, then there would be no such independence and adaptive

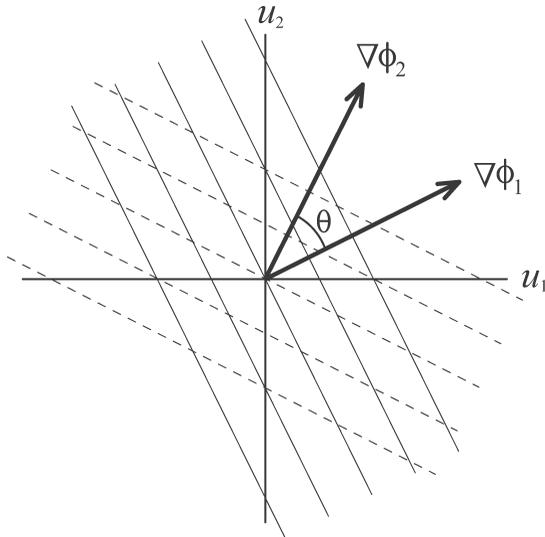


Figure 6. Two linear landscapes. Gradient vectors point uphill on their corresponding landscapes. The angle between these vectors determines the correlation between traits.

evolution would be effectively impossible. This problem is avoided if the genetic architecture allows suites of traits that function together to vary independently of one another. Along with canalization, modularity (especially as it relates to evolvability) is among the principal motivations for research into the evolution of genetic architecture (Hansen 2006).

Modularity is sometimes taken to imply that different sets of genes influence different modules (Wagner & Altenberg 1996). This inference is not necessarily true, though, because there can be evolutionarily independent modules that are influenced by many of the same genes. The genetic covariance between two traits is a function of the distribution of underlying variation and the genetic architecture that maps that variation to phenotypic variation. In an additive system (i.e., no epistasis) with underlying factors distributed independently, the genetic covariance between two traits is determined by the orientation of the two phenotype landscapes (Fig. 6). If the underlying factors have equal variances and no covariance, the correlation between two traits is simply $\text{cor}(\phi_1, \phi_2) = \cos(\theta)$, where θ is the

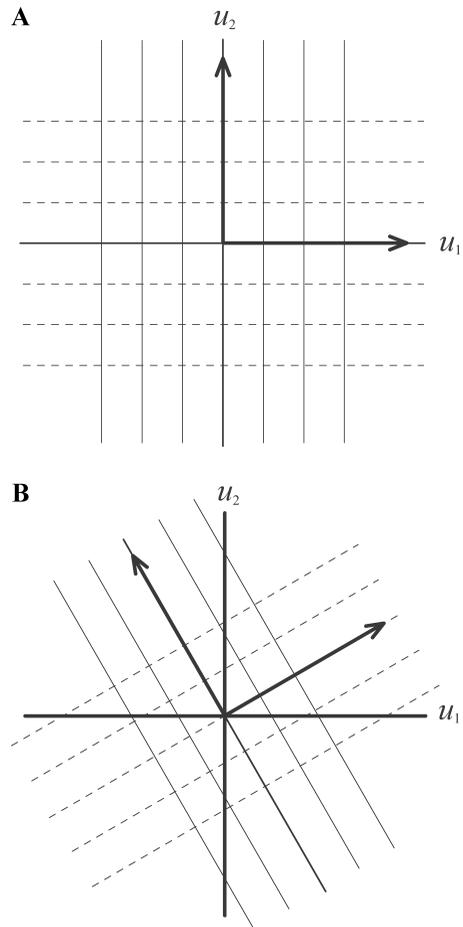


Figure 7. Two cases in which the correlation between the two traits is zero.

angle between the two gradient vectors (Rice 2004a).

Figure 7 shows two cases in which two different traits are genetically independent of one another. In Figure 7A each trait is influenced by a different underlying factor, whereas in Figure 7B both traits are influenced by the same two factors. Clearly, though, the traits in case B are just as independent as are those in case A; furthermore, there are an infinite number of possible scenarios in which both underlying factors contribute to both traits, but the traits remain independent. What matters is the relative orientation of the two phenotype landscapes. In fact, there is no reason to expect cases such as that in Figure 7A, where traits are independent because they are influenced by nonoverlapping

sets of genes, are the norm. Though the two cases in Figure 7 both exhibit zero covariance between the traits, they may not be identical with respect to evolvability. In the example in Figure 7B, each trait can change as a result of mutations in either underlying factor, meaning that each presents a larger target for mutations than do the traits in Figure 7A, each of which can be influenced by mutations in only one underlying factor. Though more mutations influence each trait in the second case, those mutations have a smaller effect than in the first case; the total mutational variance should thus be the same. Having a shorter waiting time until some mutation (albeit a small one) comes along, though, could influence evolvability. Supporting this claim, Hansen (2003) found that in simulations, evolvability was not maximized in systems with minimal pleiotropy.

Some studies based on simulated gene networks have suggested that selection for evolvability will in general favor increased modularity and decreased epistasis for fitness between different loci (Pepper 2003, Altenberg 2004). Using a modifier model, Liberman and Feldman (2006) showed that this result does not follow when loci are sufficiently closely linked. This outcome is not surprising when we note that recombination, which is an explicit part of Liberman and Feldman's model, is another process that reduces evolvability, here by actually destroying potentially adaptive variants.

The other side of modularity is developmental covariance between traits. Such covariance reduces the ability of traits to evolve independently but may increase the probability that they covary in adaptive ways. In quantitative genetics, patterns of covariation between traits are traditionally summarized using an additive genetic covariance matrix, otherwise known as a G matrix. The G matrix is an estimator of the expected parent-offspring covariance matrix, which is what determines how selection influences multivariate evolution in a system in which all phenotype landscapes are linear (Rice 2004b).

Classical quantitative genetics tended to treat G matrices as fixed, but it is now universally accepted that patterns of genetic covariance can and do evolve in natural populations. Jones *et al.* (2003) used simulations to study the evolution of G matrices under different conditions; they found that the pattern of genetic covariation is stabilized when mutations have substantial pleiotropic effects.

An important special case of evolution of covariance between traits is the evolution of phenotypic plasticity. Phenotypic plasticity has traditionally been studied using quantitative genetic models, treating either the value of a trait in different environments (Via & Lande 1985) or the reaction norm itself (Scheiner 1993) as traditional quantitative traits (see Via *et al.* 1995 for a review). More recently, though, several authors have begun to treat the evolution of phenotypic plasticity as a problem within developmental evolution, either as a variation on canalization (Debat & David 2001) or as a case of the evolution of developmental covariance (Rice 2004b, chap. 8).

The key to modeling the evolution of phenotypic plasticity as a kind of developmental covariance is recognizing that an environmental variable can be both an underlying factor for some phenotypic trait and, simultaneously, a trait in its own right (albeit generally not a heritable trait). That an environmental variable can be thought of as a phenotypic trait may seem less odd when we recognize that we are saying simply that the environment that an individual lives in is one of the factors that, jointly with the rest of its phenotype, determines its fitness.

Using this approach, Rice (2004b) showed that selection on the slope of a reaction norm involves two Q vectors, one of which is the same as the vector corresponding to canalization ($Q_{1,2}$ in Equation 1 above) and the other is a vector pointing in the direction of maximum sensitivity of the trait ϕ to the environmental factor. The sum of these two vectors moves the population precisely to the point on the landscape corresponding to the optimal reaction norm slope (assuming that such a point

exists and is reachable). The evolution of reaction norm slope thus does seem to contain the term for the evolution of canalization as a component. Rice also considered selection to change the curvature (rather than the slope) of a reaction norm and showed that this process is influenced by the sixth moment of the distribution of underlying variation, meaning that outliers strongly affect the evolution of reaction norm curvature.

Environment's Role in Development and Inheritance

Classical evolutionary theory tended to treat the “environment” as something that influences selection but that is separate from the genetics or development of organisms. The example above shows that it can be fruitful to treat some environmental variables as part of the process of development—and even as one of the organism's phenotypic traits (Rice 2004b). Though in the simple model for the evolution of phenotypic plasticity I treated the environmental variable as nonheritable, often the environment really should be considered part of the genetic architecture. Environmental factors themselves may be heritable if parents influence the environment of their offspring (Laland & Sterelny 2006). Furthermore, given that the environment includes other organisms with which an individual interacts, the environment contains genes, some in close relatives. Wolf (2003) demonstrated that taking into account interactions with relatives can lead to substantial changes in quantitative genetic parameters.

In fact, the environment can influence heritability even if no environmental parameters are heritable. Consider a trait, ϕ , that is a linear function of a genetic factor, u_g , and an environmental factor, u_e . Now consider the trait in both parents and their offspring. For simplicity, assume that the genetic factor is passed on with perfect fidelity (such as in an asexual haploid organism), but the environment experienced by offspring is potentially different from the environment of their parents; call the parent's envi-

ronment u_{ep} and their offspring's environment u_{eo} . We can now write the values of the trait in parents (ϕ_p) and offspring (ϕ_o) as

$$\begin{aligned}\phi_p &= u_g + u_{ep} \quad \text{and} \\ \phi_o &= u_g + u_{eo}.\end{aligned}\tag{2}$$

Rice (2004a) shows that for this simple case, the regression of offspring phenotype on parent phenotype (i.e., the heritability of ϕ) is given by

$$\begin{aligned}\beta_{o,p} &= h^2 \\ &= \frac{\text{var}(u_g) + \text{cov}(u_g, u_{ep}) + \text{cov}(u_g, u_{eo}) + \text{cov}(u_{ep}, u_{eo})}{\text{var}(u_g) + \text{var}(u_{ep}) + 2\text{cov}(u_g, u_{ep})}.\end{aligned}\tag{3}$$

The environmental factor clearly influences heritability. Two of the terms in Equation 3 basically capture the heritability of the environment. The covariance between parental genotype and offspring environment [$\text{cov}(u_g, u_{eo})$] is expected to be important when parents partially construct their offspring's environment, which is common among organisms with parental care (Laland & Sterelny 2006). The covariance between parent's environment and their offspring's environment will be important in cases in which, for example, females prefer to lay eggs in the type of environment in which they were born.

The most surprising thing about Equation 3 is the presence of $\text{cov}(u_g, u_{ep})$, the covariance between parents' genotype and their environment, in both the numerator and denominator. This term thus influences heritability even if the offspring's environment is completely independent of their parents' environment. That is, if an environmental factor influences phenotype, and if there is any correlation between the parents' genotypes and the environments that they experience, then heritability of phenotype is altered even if the environmental factor itself is not heritable (Schlichting 1989; Rice 2004a). This example assumes only additive effects of the genotype and the environment. If we allow for any nonadditive interactions between any of the underlying factors, then heritability can evolve even in a constant environment with no change in mean phenotype (Rice 2004b).

Epistasis and Genetic Covariance

If there are epistatic interactions between the underlying factors, then the covariance between traits is no longer simply a function of the angle between the gradient vectors (Rice 2004a). There are two important consequences of this statement. First, correlation between traits that is due in part to epistatic interactions will change as the total amount of underlying variation in the population changes, even if the shape of the underlying distribution remains constant. Second, epistatic interactions influence other joint moments of the phenotype distribution, not just covariance. As a result, associations between traits resulting from epistasis are likely to influence evolutionary dynamics in ways that are undetectable to traditional quantitative genetic analyses.

One situation in which epistasis should have significant consequences for phenotypic evolution is the case of strongly developmentally correlated traits. If the patterns of epistasis for two strongly correlated traits are slightly different, the ability of the population to evolve against the correlation will tend to be asymmetrical. Figure 8 illustrates the consequences of modifying by a small amount the pattern of epistasis for one of two traits that are strongly developmentally correlated. A slight difference in curvature has little if any effect on the ability of the population to respond to selection that goes with the covariance (i.e., selecting to increase or decrease both traits, if the covariance is positive) but creates substantial asymmetry in the response to selection against the correlation (antagonistic selection). This effect is most pronounced when the two phenotype landscapes nearly coincide with one another.

Because even highly correlated traits will probably have at least slightly different genetic architectures, the phenomenon of asymmetrical responses to antagonistic selection should be the rule, rather than the exception, in multivariate evolution. In fact, asymmetrical responses to antagonistic selection have been noted for some time and recognized as de-

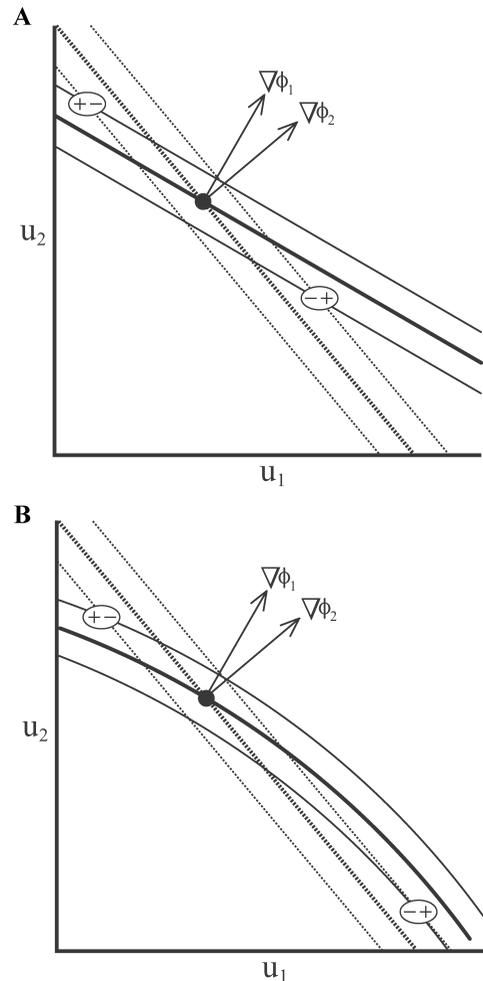


Figure 8. Consequence of introducing differential curvature into a system of two traits that are strongly correlated. The point marked (+ -) indicates where the population would have to move to increase trait 1 by one unit while decreasing trait 2 by one unit. The point marked (- +) is the converse, the point at which trait 1 is decreased, and trait 2 increased, each by one unit. **(A)** These two points are equidistant from the starting point, meaning that the population could as easily evolve in one direction as the other. **(B)** Differential curvature of the landscape for trait 1 has substantially moved the point (- +), meaning that it will require significantly more time to evolve to decrease trait 1 and increase trait 2 than to evolve the same phenotypic distance in the opposite direction.

viations from quantitative genetic predictions (Nordskog 1977; Scheiner & Istock 1991). Such asymmetries appear in many studies, though they are not always noted in the articles.

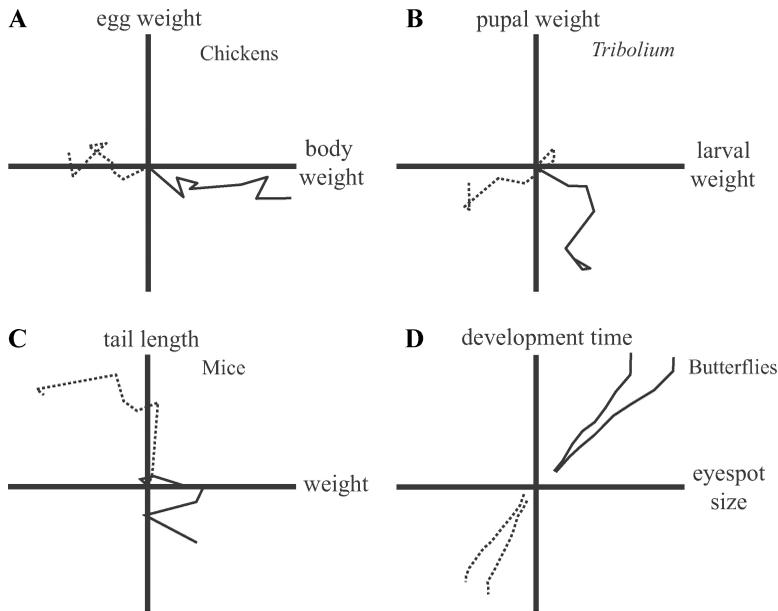


Figure 9. Examples of asymmetrical responses to antagonistic selection. **(A–C)** Traits are positively correlated, and the two trajectories represent the results of selecting against the correlation. **(D)** Traits are negatively correlated, and two replicates are shown for each direction. Data are from Nordskog 1977 (panel A), Bell & Burris 1973 (panel B), Rutledge *et al.* 1973 (panel C), and Zijlstra *et al.* 2003 (panel D). Panels A–C are after Roff (1997).

Figure 9 shows four examples from diverse organisms.

Developmental Entanglement

The examples of an asymmetrical response to selection suggest that traits can be associated in ways that are not accurately captured by covariance. Rice (2004a) used the term *entanglement* to describe the general case in which selection to change some moment of a phenotype distribution also leads to change in some other moment. Genetic covariance, which causes selection on the mean (first moment) of one trait to influence the evolution of the mean of another trait, is one kind of entanglement, but there are many other ways in which the evolution of different traits can be linked.

Figure 10 shows a simple case in which two traits are uncorrelated, so selection to change the mean of one has no effect on the mean of the other, but are nonetheless entangled such that stabilizing selection on one changes the mean

of the other. Rice (2004a) provides an example of three phenotypic traits that are entangled such that directional selection on any one trait changes the covariance between the other two traits. Given the complexity of developmental systems, forms of entanglement other than covariance between traits are probably common.

Drift

Nearly all theoretical research into the evolution of development has focused on selection as the process driving evolution. Drift undoubtedly plays a role, though, and may well be more important in developmental evolution than it is in the evolution of mean phenotypes. Rice (1998) calculated the strength of canalizing selection moving a population along a phenotype contour and found that this force becomes weak as a population approaches a point of maximum canalization. Furthermore, the point of maximum canalization along a contour is a function of the distribution of variation within

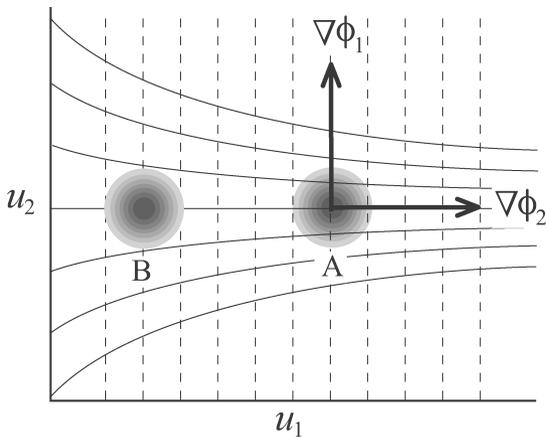


Figure 10. Example of entanglement in which traits 1 and 2 are uncorrelated, but selection to reduce the variance of trait 1 would cause directional change in the mean of trait 2. The vectors $\nabla\phi_1$ and $\nabla\phi_2$ point in the directions of maximum increase in traits ϕ_1 and ϕ_2 , respectively. Stabilizing selection on ϕ_1 will push the population from point A toward point B, where the landscape is less steep and therefore phenotype is more buffered against underlying variation.

the population, which is likely to change because of random sampling if population size is reduced. We thus expect that moderate-sized populations, even if they are large enough for selection to keep them near an optimal phenotype contour, may well drift along the contour away from points of maximum canalization.

Such developmental drift on a curved landscape could facilitate speciation. Gavrilets (2003) and Gavrilets and Gravner (1997) have emphasized the significance for speciation of “hole” adaptive landscapes. These are landscapes on which the regions of highest fitness are not isolated peaks but rather form a network of interconnecting ridges. This is exactly what we expect for fitness landscapes over the space of underlying factors (Rice 1998, 2000). Here, the ridges of high fitness correspond to optimal phenotype contours. Temporarily isolated populations that drift away from one another on an optimal contour can rapidly wind up on opposite sides of a fitness “hole.” If such populations come back into contact (geographically, not on the phenotype landscape), hybrids will

not lie on the optimal contour and will be selected against.

Conclusion

We now have a fairly large catalogue of processes that in principle can lead to the evolution of development and genetic architecture. These processes include all kinds of selection that act to change the shape of the phenotype distribution (e.g., selection for canalization, integration, phenotypic plasticity, and evolvability) as well as drift in development that may yield no change in mean phenotype. Most, if not all, of these processes probably do influence developmental evolution in natural populations. These phenomena—and others that are sure to arise—suggest that we will need to make some changes both in the ways that we gather data and the ways that we build theories.

Most of the data used in traditional evo-devo research comes directly from developmental biology. It is thus largely concerned with specific genes that have large effects when mutated in the lab and has little to say about the distribution of genetic variation that actually contributes to phenotypic variation in natural populations. The details of the distribution of underlying genetic and environmental variation are even more important to understanding how the development of a trait evolves than they are to understanding the evolution of trait itself. Empirical research in evo-devo may thus have to expand out of the lab and into the field more than it has.

On the theory side: Phenotypic evolutionary theory has been dominated by quantitative genetics, which was made tractable and useful by minimizing the relevance of most of the phenomena that this review has discussed. Several innovative researchers have devised ways to apply the concepts of quantitative genetics to developmental evolution. However, the presence of fourth moments in models for the evolution of even simple phenomena such as canalization, and the asymmetrical effects of complex developmental entanglement, make it

clear that a body of theory based on partitioning phenotypic variance is inadequate for capturing the complexity of developmental evolution. We thus face the task of building a coherent and widely applicable mathematical evolutionary theory that does not discount the complexity that we now know to underlie essentially all phenotypic traits.

Conflicts of Interest

The author declares no conflicts of interest.

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