5

The Evolution of Developmental Interactions

Epistasis, Canalization, and Integration

SEAN H. RICE

"Epistasis," like "invertebrate," is a term that really means "everything else." Traditionally defined as a situation in which the consequences of an allele substitution at one locus are a function of what allele is present at another locus (Crow and Kimura 1970), epistasis includes all possible ways that gene products can conspire to shape phenotype, with the very unlikely exception of complete additivity. To name a phenomenon in this way has the curious effect of making it look like a special case, even if it is the most common situation. In fact, additivity is the special case, but since it involves no distinct mechanism, it is best thought of as simply one point on a continuum of possible kinds of gene interaction. A general theory of epistasis, therefore, should consider all of the ways that gene products can jointly contribute to phenotype; additivity is just one rare case that happens to have been quite well studied.

In this spirit, we seek a way to model the evolution of systems in which the underlying factors, genetic and environmental, that contribute to phenotype are allowed to interact in a range of different ways, including additively. A useful way to view this problem is to consider evolution on a phenotype landscape—a surface that defines phenotype as a function of any number of underlying genetic or environmental factors (S. H. Rice 1998a; see also Box 5.1). In the special case of additivity, the phenotype landscape is simply a sloping plane (see Fig. 5.1). Any nonadditive contribution of underlying factors to phenotype manifests itself as curvature of the surface (Fig. 5.1; see Box 5.1 for a more detailed discussion of the geometry and biology of phenotype landscapes).

It is important to keep in mind the distinction between "epistasis" and "epistatic variance." "Epistasis" is defined here as the influence of one genetic or

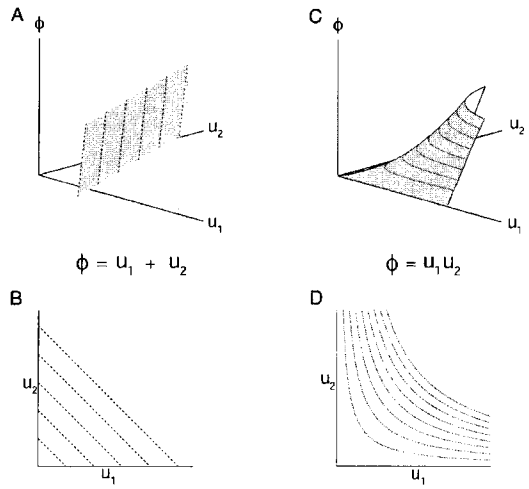

Figure 5.1 Examples of additive and nonadditive phenotype landscapes. The contour lines represent values of the underlying factors (u_1, u_2) that produce the same phenotypic value.

developmental factor on the phenotypic consequences of a change in another such factor. "Epistatic variance" is the component of population variance that is left over after we attribute as much variance as possible to additive and dominance effects. Even if two factors interact mechanistically in a completely nonadditive way, it is often possible to treat a substantial component of variance in the phenotype that results from this interaction as additive variance (see Cheverud, chap. 4, this volume; Goodnight, chap. 8, this volume; and Box 5.1 for further treatment of this issue).

Throughout this chapter, I will designate the value of some phenotypic character by ϕ and the values of underlying factors that contribute (through development) to that phenotype as u. Though these underlying factors could be thought of as continuous measures of the expression of different gene products, it is useful to extend the idea of epistasis to include interactions between quantitative characters in development. This extension does not add any new cases, since any nonadditive interaction between characters in development will almost certainly produce a nonadditive effect of some gene products, and it facilitates the study of some phenomena, such as canalization and integration, that are invisible to additive models.

One value of the analytical approach used here (see Box 5.1) is that it allows us to construct a wide range of hypothetical developmental systems and, when combined with a measure of fitness (see Fig. 5.2), can be used to study how evolution would proceed in each case. Most of this chapter will consider such hypothetical cases, for the purpose of deriving general results that relate to the evolution of canalization, phenotypic plasticity, and integration. It is worth noting, however, that we can sometimes construct a phenotype landscape for a real organism if we have a model for the development of some of the characters exhibited by that organism.

Box 5.1 Phenotype landscapes

A phenotype landscape is a plot of the value of a character (ϕ) as a function of some underlying factors ($u_1, u_2, \ldots$) that contribute to that character. An underlying factor may represent the degree of expression of some gene product, a quantitative character in development (such as the size of a particular tissue at a particular time), or an environmental factor that influences the phenotype (such as the temperature of an embryo at some particular stage in development). The interactions between these factors, which constitute the process of development, determine the shape of the phenotype landscape.

If the underlying factors contribute additively to phenotype, then the landscape is a plane with no curvature (Fig. 5.1A and 5.1B). If these factors contribute nonadditively (i.e., if there is epistasis), then the landscape is curved (Fig. 5.1C and 5.1D). How a population evolves on a phenotype landscape is determined by how selection acts on the character and by the local geometry of the landscape itself. Some geometric properties of such a landscape have straightforward biological interpretations. For example, the slope at any given point (indicated by the spacing between contours of equal phenotype in Fig. 5.1) measures the degree to which the value of ϕ is sensitive to variation in the underlying factors. Thus, if the slope at a point is low, then that value of the phenotype is locally buffered against genetic or environmental variation and is said to be canalized. Note that with complete additivity (Fig. 5.1A and 5.1B), selection cannot increase the degree of canalization since the contours are always equally spaced. With epistasis, the evolution of canalization becomes possible.

Figure 5.1 also illustrates why we may see a substantial "additive" component of variance even when the contributions of the underlying factors are completely nonadditive. At any given time, a population does not cover the entire landscape. In Fig. 5.1C and 5.1D, the equation that produces the landscape is completely nonadditive. However, if we look at a small region of the surface (similar to what a population covers at any given time), it will look very much like an uncurved plane. If the surface looks uncurved in a particular local region, then we can describe most of the variance in phenotype in that region in terms of "additive" effects of the underlying factors. Note, though, that if we move the local region covered by the population, the "additive" contributions of the different underlying factors will change, since the surface will still look relatively uncurved but will be tilted at a different angle.

Modeling evolution on a phenotype landscape requires that we assign some fitness function, $\mathbf{w}(\phi)$, to the character ϕ. Once we have this, we can construct a fitness landscape for the underlying factors (Fig. 5.2). The shape of this fitness landscape is thus determined by how the underlying factors contribute to phenotype and how phenotype contributes to fitness.

Figure 5.2 shows how to construct such a fitness landscape. Note that so long as there are more underlying factors than phenotypic characters that they contribute to, then the fitness landscape over the set of underlying factors will tend to consist of ridges that correspond to contours of equal phenotype. The idea that fitness landscapes are principally a network of ridges was suggested by Dobzhansky (1937) and has consequences for both morphological evolution and speciation (Wagner et al. 1994; Gavrilets and Hastings 1996). With the exception of Fig. 5.2, the contour lines in all figures in this chapter represent lines of equal phenotype, not equal fitness.

(continued)

Box 5.1 *(continued)*

In the following, I describe the critical mathematical terms that capture the local geometry of a phenotype landscape and discuss the developmental and evolutionary interpretations of these.

The Gradient

For a function, $\phi(u_1, u_2, \ldots, u_n)$, the gradient, $\nabla\phi$, is a vector defined as

$$\nabla\phi = \begin{bmatrix} \dfrac{\partial\phi}{\partial u_1} \\ \dfrac{\partial\phi}{\partial u_2} \\ \vdots \\ \dfrac{\partial\phi}{\partial u_n} \end{bmatrix}$$

This vector points in the direction of maximum increase in ϕ. It is thus the direction in which we would expect a population to move under directional selection to increase ϕ. The magnitude (length) of the gradient vector, denoted by $\|\nabla\phi\|$, is the actual slope in the steepest direction; it thus measures the sensitivity of the phenotype to variation in the underlying factors. A low value of $\|\nabla\phi\|$ represents a high degree of canalization, since a low slope means that phenotype is buffered against underlying variation.

The Epistasis Matrix and $\mathbf{E} \cdot \nabla\phi$

This is a matrix of second partial derivatives (sometimes called a Hessian matrix in mathematics books). The terms measure the curvature of the surface in different directions:

$$\mathbf{E} = \begin{bmatrix} \dfrac{\partial^2\phi}{\partial u_1^2} & \dfrac{\partial^2\phi}{\partial u_1 \partial u_2} & \cdots & \dfrac{\partial^2\phi}{\partial u_1 \partial u_n} \\ \dfrac{\partial^2\phi}{\partial u_2 \partial u_1} & \dfrac{\partial^2\phi}{\partial u_2^2} & & \vdots \\ \vdots & & \ddots & \\ \dfrac{\partial^2\phi}{\partial u_n \partial u_1} & \cdots & & \dfrac{\partial^2\phi}{\partial u_n^2} \end{bmatrix}$$

This matrix is symmetrical since $\partial^2\phi/\partial u_i \partial u_j = \partial^2\phi/\partial u_j \partial u_i$. These off-diagonal elements describe the degree to which a small change in one underlying factor influences the phenotypic consequences of a small change in the other. This is a continuous description of the classical definition of epistasis (Crow and Kimura 1970) as a situation in which a change in the allele at one locus alters the phenotypic consequences of a change in an allele at another locus.

(continued)

Box 5.1 (*continued*)

Multiplication of the gradient vector by the epistasis matrix yields a new vector, $\mathbf{E} \cdot \nabla\phi$, which points in the direction of maximum increase in slope. Movement in the opposite direction from this vector is thus the quickest way to achieve a canalized phenotype.

The Laplacian

The term $\nabla^2\phi$ is called the Laplacian and is defined as

$$\nabla^2\phi = \sum_i \frac{\partial^2\phi}{\partial u_i^2}$$

This is a number, rather than a vector, and measures the degree to which the surface is convex or concave. If the Laplacian is nonzero, then a nonskewed distribution of underlying characters will translate into a skewed phenotype distribution.

The Inner Product

This relates to the angle between vectors. Consider two vectors:

$$\boldsymbol{u} = \begin{bmatrix} u_1 \\ u_2 \\ \vdots \\ u_n \end{bmatrix}$$

and

$$\boldsymbol{v} = \begin{bmatrix} v_1 \\ v_2 \\ \vdots \\ v_n \end{bmatrix}$$

The inner product, written $\langle \boldsymbol{u}, \boldsymbol{v} \rangle$, is a number (not a vector) defined as

$$\langle \boldsymbol{u}, \boldsymbol{v} \rangle = \sum_{i=1}^{n} u_i v_i$$

Now define the magnitude (length) of each vector as $\|\boldsymbol{u}\|$ and $\|\boldsymbol{v}\|$, and the angle between them as θ. Then, the inner product is related to these as:

$$\langle u, v \rangle = \|u\| \, \|v\| \cos\theta$$

The inner product is thus zero if the vectors are at right angles, maximally positive if they point in the same direction, and maximally negative if they point in opposite directions. This is why the inner product of two phenotypic gradient vectors provides a measure of integration.

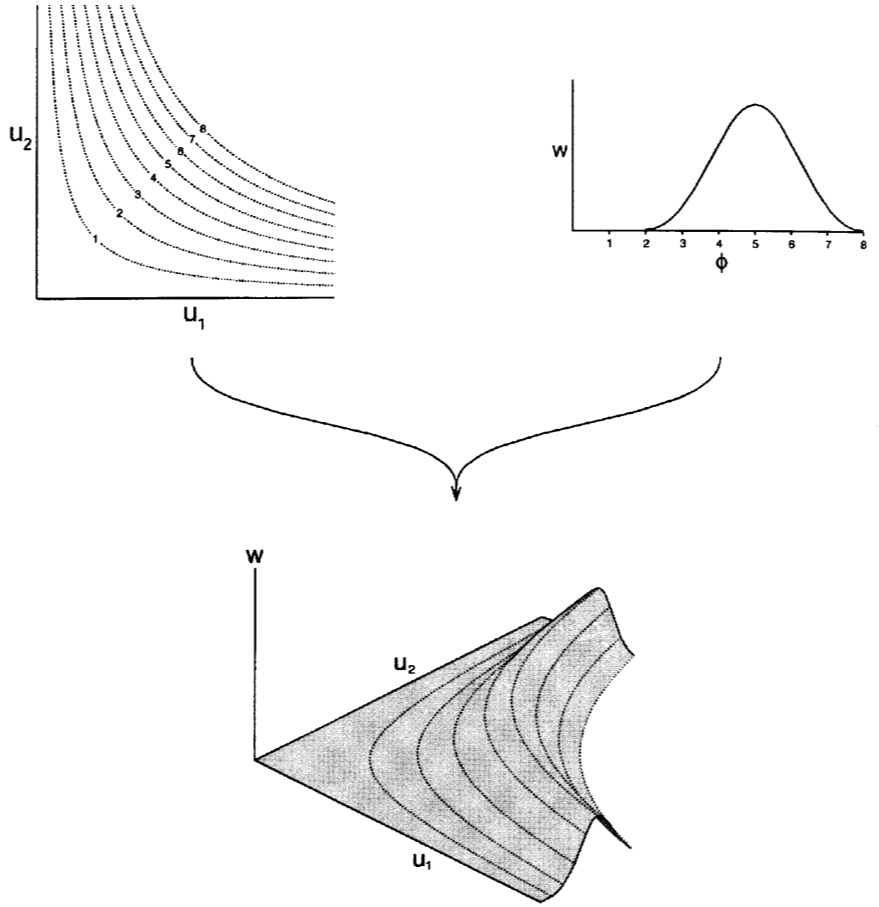

Figure 5.2 Construction of a fitness surface (bottom) over a space of underlying factors (u_1, u_2) from a phenotype landscape and a function that relates phenotype (ϕ) to fitness (w).

Figure 5.3 shows an example of an actual phenotype landscape for a character for which we can model development. The shells of gastropods and cephalopods grow through addition of new shell material around the lip of the shell's aperture. The shape of most gastropod and cephalopod shells is determined if we specify (1) the relative rates of shell production at different points around the aperture, (2) the growth rate of the aperture, (3) the total amount of shell produced relative to aperture size, and (4) the shape of the aperture. Figure 5.3 shows the phenotype landscape for the apex angle of a shell (measured as the degree to which the top of the shell is flattened) as a function of the last two of these factors (the others are held constant only for the purposes of drawing a two-dimensional surface). This particular character is ecologically significant, since crabs (a major predator in the intertidal zone) often break into shells by snapping off the spire. Such an attack is

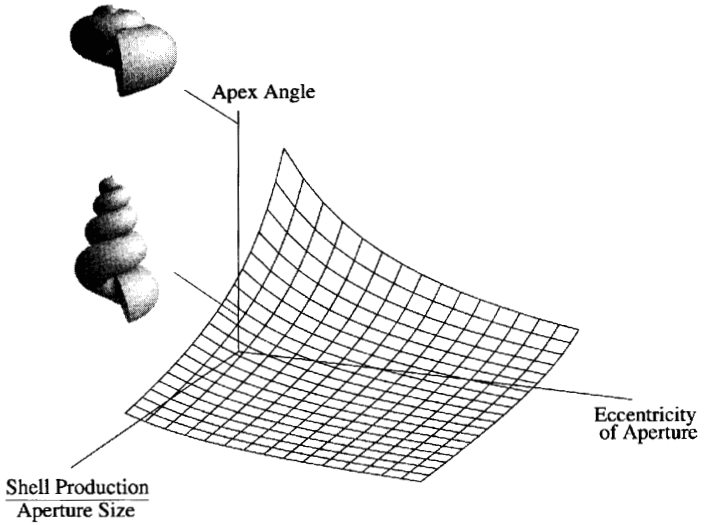

Figure 5.3 An actual phenotype landscape for gastropods. The character "apex angle" measures the degree to which the apex of the shell is flattened. The underlying factors considered are (1) the total rate of production of new shell material relative to aperture size and (2) the degree to which the aperture is elliptic (as opposed to circular) and elongated along the coiling axis.

made more difficult if the shell is not pointed (Vermeij 1987). See S. H. Rice (1998b) for a more extensive discussion of these and other developmental factors that influence shell form. The surface in Fig. 5.3 is definitely not flat, which echoes the fact that these underlying factors contribute nonadditively to the value of the apex angle. Modeling evolution on such a surface requires that we assign a fitness to each value of the phenotype, and then derive an equation for the joint change in the underlying factors as a result of selection on the phenotype to which they contribute.

Equation 5.1 describes evolution on a phenotype landscape for a single character that is a function of any number of underlying factors. Here, ϕ is some phenotypic character, $\nabla\phi$ is the gradient of the phenotype function (a vector that defines the direction in which ϕ changes most quickly; this points "uphill" on the surface), $\mathbf{E}$ is a matrix of second partial derivatives, and $\nabla^2\phi$ is the Laplacian function; $\mathbf{w}$ represents fitness (and is a function of ϕ), σ^2 represents phenotypic variance, and $\mathbf{H}$ is a matrix with heritability values of the different underlying factors along the diagonal, and zeros elsewhere. We want to study the change in the underlying factors, which we represent together as a vector, $\boldsymbol{u}$, defined as the transpose of $(u_1, u_2, \ldots, u_n)$. The change in the mean value of $\boldsymbol{u}$ over one generation is given by

$$\Delta\mathbf{u} = \frac{\mathbf{H}}{\bar{w}}\left[\sigma^2\frac{\partial\mathbf{w}}{\partial\phi}\nabla\phi + \sigma^4\frac{\partial^2\mathbf{w}}{\partial\phi^2}\mathbf{E}\nabla\phi + \frac{\sigma^4}{2}\frac{\partial^2\mathbf{w}}{\partial\phi^2}\nabla\phi\nabla^2\phi\right] \qquad (5.1)$$

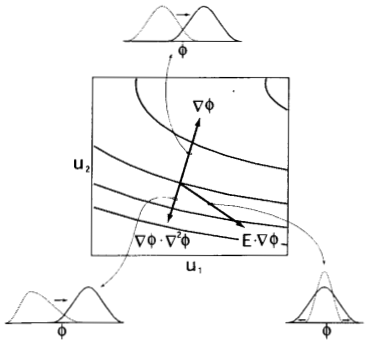

Figure 5.4 A geometric interpretation of the terms in eq. 5.1. Any movement in this space corresponds to some change in the values of the underlying factors u_1 and u_2. The three vectors point in the directions in which change in the u values most rapidly changes different aspects of the shape of the resulting phenotype distribution, shown in the surrounding diagrams.

[We assume here that the surface has continuous second derivatives and that the portion that a population covers at any particular time is well approximated by a quadratic function. We further assume that the axes have been transformed so as to eliminate covariances and equilibrate variances, such as by a principal components analysis. See S. H. Rice (1998a) for further discussion.]

Rather than focusing on the mathematical meanings of the various terms in eq. 5.1, I will describe what they mean geometrically and then discuss their biological interpretations. We can find the biology in this equation by noting that it describes movement in the space of underlying factors in terms of three vectors, $\nabla\phi$, $\mathbf{E}\nabla\phi$, and $\nabla\phi\cdot\nabla^2\phi$, which define the directions in the space of underlying factors that produce the most rapid change in, respectively, the mean, variance, and skewness of the phenotype distribution (Fig. 5.4). Each of these vectors is multiplied by a term that describes the strength of selection that acts to change the phenotype distribution in that particular way: $\sigma^2\cdot\partial\mathbf{w}/\partial\phi$ for change in the mean of the distribution, $\sigma^4\cdot\partial^2\mathbf{w}/\partial\phi^2$ for the variance, and $\sigma^4/2\cdot\partial^2\mathbf{w}/\partial\phi^2$ for skewness. Note that each of these terms has the familiar components of variance multiplied by the dependence of fitness on phenotype.

The three vectors in Fig. 5.4 correspond to the three terms on the right side of eq. 5.1. The peripheral diagrams show the kinds of changes in the shape of the phenotype distribution that are most quickly achieved by moving along each vector. Note that these are not necessarily orthogonal—moving along $\mathbf{E}\nabla\phi$ is likely to change the mean as well as the variance. [Keep in mind that the contour lines in this and other figures (not including Fig. 5.2, which contains an example of a fitness landscape) in this chapter are contours of equal phenotype, not fitness contours.]

By showing how to map changes in the shape of the phenotype distribution to changes in development, eq. 5.1 and Fig. 5.4 suggest a general way to think about phenotypic evolution. In classical population genetics, the thing that selection acts to change, and that models track, is allele frequency. This formalism does not translate well to morphology, where no single parameter presents itself as the obvious currency of evolution. It is also difficult to map phenotype frequency to allele frequency for most characters of interest. A tempting alternative to the view of evolution as change in allele frequency is to think of phenotypic evolution as change, over generations, in the overall shape of the phenotype distribution. (Note that this is really what the classical theory does. We are able to model evolution by

tracking allele frequencies only when allele frequency completely determines the distribution of genotypes, which are the things that are assigned fitness.) We see here that the different measures of the shape of the phenotype distribution emerge naturally, along with their associated selection coefficients, when we model evolution on a curved phenotype landscape.

Using the approach outlined above, we can begin to investigate how different kinds of selection act to reshape developmental systems. I will focus first on canalization and, then, by extending the model to include multiple characters, focus on the evolution of integration.

Canalization

Canalization refers to the buffering of phenotype against variation in underlying factors (Waddington 1949). In terms of evolution on a phenotype landscape, this means moving along a contour to a region of relatively low slope. It is apparent from Fig. 5.1 that this is impossible in a completely additive case, since slope is the same everywhere.

Wagner et al. (1997) and Stearns and Kawecki (1994) draw a distinction between genetic and environmental canalization based on the source of variation against which phenotype is buffered. The words "genetic" and "environmental" must be understood here in terms of their meanings in quantitative genetics, rather than by their ordinary meanings. The real distinction (understood by these authors) is between heritable and nonheritable. Some nonheritable sources of variation reside within the cell nucleus (Lynch and Walsh 1998), but are treated as "environmental" variables because they do not respond to selection. Similarly, an organism's external environment may be heritable if that organism modifies its surroundings (Laland et al. 1996) or simply chooses to lay her eggs in the same environment in which she hatched.

There is a straightforward way to incorporate nonheritable effects into this model: for each environmental variable that influences phenotype, we simply add an axis to the space of underlying factors. Since we do not want to allow the population to evolve along the environmental axes as it does along the developmental ones, we simply put zeros in those entries in the matrix **H** that would correspond to the heritabilities of the environmental factors. Note that if we take a slice of the phenotype landscape along an axis that corresponds to an environmental variable, we have a norm of reaction for that phenotype relative to that environmental variable (see Wade, chap. 13, this volume; Brodie, chap. 1, this volume).

In this way, variation along the environmental axes can influence the direction of $\mathbf{E}\nabla\phi$, but the population cannot evolve along these axes. Though this differs from the conventional way that environmental effects are introduced into quantitative genetics models (as a component of variance that is simply added on to the equation), it has the conceptual advantage of treating aspects of the environment as full members of the developmental process, differing from internal biological factors only in that they are not heritable.

The issue of heritability is important for our understanding of the evolution of canalization. This is because there are two different ways to reduce phenotypic

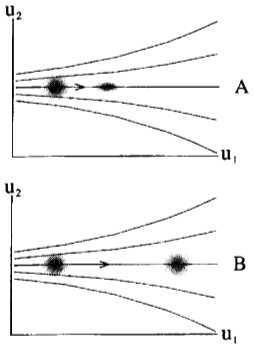

Figure 5.5 Evolution along an optimal contour under stabilizing selection. In both cases, variation in u_1 is heritable. In part (A), the variation in factor u_2 is partly heritable; reduction in phenotypic variance thus involves both reduction in the variance of u_2 and movement to a less steep (more canalized) part of the landscape (as indicated by the greater spacing between phenotype contours on the right side of each diagram). As the variance in u_2 gets smaller, selection to move along the contour becomes less strong. In part (B), u_2 is not heritable, so the only way to reduce phenotypic variation is to shift the system to a more canalized state.

variance: move to a point of lesser slope on the phenotype landscape (canalization) or modify the joint distribution of the underlying factors so that this distribution flattens along a contour. Both of these processes may be going on at the same time, but only the first involves a change in the process of development.

Figure 5.5 illustrates how heritability influences the outcome of canalizing selection. In each case, the underlying factor u_1 is heritable, so the population can evolve along the u_1 axis. How rapidly it does so, however, is influenced by the heritability of u_2. If the underlying factor u_2 is heritable, as in Fig. 5.5A, then a population that evolves along an optimal contour tends to become flattened along that contour, thereby reducing the strength of stabilizing selection and thus slowing further developmental evolution. If, on the other hand, u_2 is an "environmental" variable (Fig. 5.5B), then selection cannot reduce the variance in it and so phenotypic variance can be reduced only by movement to a region of higher canalization. Thus, environmental canalization will, in general, be more important than genetic canalization in driving the evolution of development. A similar result is seen in simulations carried out by Wagner et al. (1997). [This distinction, between change in development that minimizes the phenotypic consequences of underlying variation and reduction in the underlying variation itself, is similar to Waddington's (1953) distinction between canalization and "normalization."]

The converse of environmental canalization is the evolution of adaptive phenotypic plasticity. Here, fitness is directly influenced by some environmental underlying factor (rather than indirectly influenced through that factor's effect on phenotype), such that the optimum phenotype is a function of that environmental factor. Let us call this environmental underlying factor u_e, and denote the optimum phenotypic value by ϕ^*. (Note that the value of ϕ^* is determined by how selection acts on phenotype, not by development.) Selection will move a population towards a point (if it is accessible) at which $\partial\phi/\partial u_e = \partial\phi^*/\partial u_e$. That is, the population moves towards a point at which the dependence of phenotype on the environmental factor (this dependence being a function of the developmental process) matches the dependence of the optimum phenotype on that same factor (this being determined by the fitness function, irrespective of development). The evolution of adaptive phenotypic plasticity may thus entail movement away from a point of minimum slope, if the minimum attainable slope is less than $\partial\phi^*/\partial u_e$.

Integration

We have so far been able to envision evolution as movement of a population over a surface; this is because we have considered only the case of a single phenotypic character on which selection acts. Modeling the evolution of integration requires that we extend this model to include multiple phenotypic characters that are direct targets of selection.

In the multicharacter case, each character has its own phenotype landscape and many of these may be superimposed over the space of underlying factors. While this makes visualization of the process a bit more difficult, the model is actually a straightforward extension of the single character case.

The general model for selection that is acting on n phenotypic characters jointly influenced by any number of underlying factors is given in eq. 5.2:

$$\Delta\bar{\mathbf{u}} = \frac{\mathbf{H}}{\bar{W}}\left[\sigma^2 \sum_{i=1}^{n} \frac{\partial \mathbf{w}}{\partial \phi_i}\nabla\phi_i + \sigma^4 \sum_{i=1}^{n}\sum_{j=1}^{n} \frac{\partial^2 \mathbf{w}}{\partial\phi_i \partial\phi_j}\left(E_i\nabla\phi_j + \frac{1}{2}\nabla\phi_i\nabla^2\phi_j\right)\right] \qquad (5.2)$$

Written in this form, the structural similarity to eq. 5.1 is clear, but there are some new terms, such as $E_i\nabla\phi_j$ with $i \neq j$, for which the biological interpretation is not obvious. In order to see what new biology has emerged in this general case, it is helpful to rearrange eq. 5.2 in this way:

$$\Delta\bar{\mathbf{u}} = \frac{\mathbf{H}}{\bar{W}}\left[\sigma^2 \sum_{i=1}^{n} \frac{\partial \mathbf{w}}{\partial \phi_i}\nabla\phi_i + \sigma^4 \sum_{i=1}^{n} \frac{\partial^2 \mathbf{w}}{\partial\phi_i^2}\left(E_i\nabla\phi_i + \frac{1}{2}\nabla\phi_i\nabla^2\phi_i\right)\right.$$
$$\left. + \frac{\sigma^4}{2}\sum_{i\neq j}\sum_{j=1}^{n} \frac{\partial^2 \mathbf{w}}{\partial\phi_i\partial\phi_j}\left(\nabla\langle\nabla\phi_i, \nabla\phi_j\rangle + \nabla\phi_i\nabla^2\phi_j\right)\right] \qquad (5.3)$$

The first part of eq. 5.3 is just the single-character equation applied separately to each of n characters; the second part (lower line) describes change in the joint distribution of phenotypic characters. Just as the terms in eq. 5.1, for the one-character case, correspond to vectors along which different aspects of the shape of the phenotype distribution change, the new term in eq. 5.3 corresponds to the direction along which the joint phenotype distribution changes. The most interesting term here is $\nabla\langle\nabla\phi_i, \nabla\phi_j\rangle$, the gradient of the inner product of the two phenotypic gradient vectors. This is a vector that shows the direction to move in order to most quickly produce a correlation between characters i and j (Fig. 5.6).

[The inner product of two vectors ($\langle , \rangle$) relates to the angle between them; this is zero when they are at right angles, large and positive when they point in the same direction, and negative when they point in opposite directions (see Box 5.1 for details). Thus, $\nabla\langle\nabla\phi_1, \nabla\phi_2\rangle$, the direction of maximum increase in $\langle\nabla\phi_1, \nabla\phi_2\rangle$, is a new vector that points in the direction along which $\nabla\phi_1$ and $\nabla\phi_2$ most quickly line up with one another. Movement along this vector leads to increased developmental correlation between the characters.]

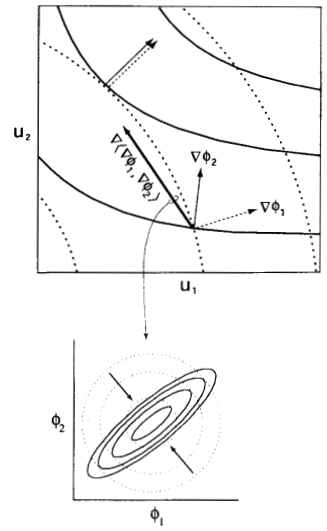

Figure 5.6 Two different phenotype functions. The solid lines in the top figure represent the contours of one phenotypic landscape, the dashed lines the contours of the other. At every point, each landscape has its own gradient vector. Where these vectors line up, the two characters are "integrated" in that they respond in the same way to changes in underlying developmental factors. The vector $\nabla\langle\nabla\phi_1, \nabla\phi_2\rangle$ points in the direction in which integration occurs most rapidly. The lower figure shows the consequences of movement along this vector for the joint distribution of phenotypic characters.

If the gradient vectors for two characters point in the same direction, then any change in development that alters one character also alters the other in the same way. If these vectors point in opposite directions, then the characters will be negatively correlated. Correlations that arise in this way are due to the structure of the developmental system, not just the distribution of alleles. This therefore represents true integration—change in the structure of the developmental system such that characters are influenced (locally) in the same ways by the same set of underlying factors.

Equation 5.3 shows that two characters tend to become positively or negatively correlated, depending on the sign of $\partial^2 w/\partial\phi_1\partial\phi_2$, which measures the degree to which a change in ϕ_1 alters the fitness consequences of a change in ϕ_2—in other words, the degree to which the two phenotypic characters interact in their contribution to fitness. If this term is zero, then there is no selection for integration. Thus, in the two-character case, we can see selection for either a positive or negative correlation, or no selection on the correlation at all. What does not appear to be possible is selection that would move the system to a point at which the characters maintain independent variation; there is no such thing as selection for *deintegration*.

This changes when we consider three or more characters. Consider selection to be acting jointly on three characters such that the fitness function ($\mathbf{w}$) has the following property:

$$\frac{\partial^2 \mathbf{w}}{\partial\phi_1\partial\phi_2} < 0 \qquad \frac{\partial^2 \mathbf{w}}{\partial\phi_1\partial\phi_3} < 0 \qquad \frac{\partial^2 \mathbf{w}}{\partial\phi_2\partial\phi_3} < 0 \qquad (5.4)$$

In such a case, selection would tend to move the population to a point in the space of underlying factors where each pair of gradient vectors point in opposite

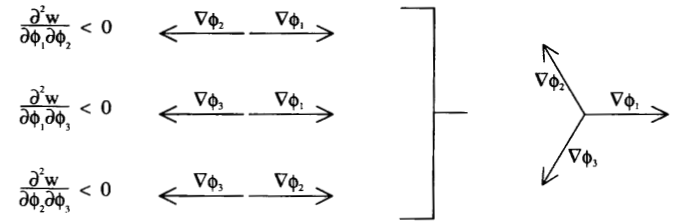

Figure 5.7 A condition under which selection favors deintegration. The three gradient vectors essentially repel one another (i.e., are in opposition), which leads to the maintenance of independent variation in the different characters.

directions (all characters are negatively correlated with one another). But this is impossible for three or more dimensions—if $\nabla\phi_2$ and $\nabla\phi_3$ both point in the opposite direction to $\nabla\phi_1$, then they cannot point opposite to one another. Thus, in such a case the gradient vectors essentially repel one another, which leads to the maintenance of independent variation in the different characters (Fig. 5.7).

The simplest fitness function that meets these criteria is one for which selection acts on the sum of different phenotypic characters. We might imagine a case in which selection acts on surface area of a structure that is composed of many flat elements, such as the roof of the cranium in vertebrates—the set of skull roof bones together must cover the brain, but the relative contributions of different bones is (in most cases) not important. Note that to say that selection acts on the sum of a set of elements is not the same as to say that those elements contribute additively to fitness (that would be the case only if fitness were a linear function of the sum).

We can visualize this sort of fitness function for three characters (ϕ_1, ϕ_2, ϕ_3) by considering a space of these characters in which fitness drops off as we move away from the two-dimensional plane defined by $\phi_1 + \phi_2 + \phi_3 = C$, where C is some constant. An important point that is not visually apparent in the three-dimensional case is that as the dimension of the system (the number of characters) gets larger, more and more of the phenotypic variation lies close to the plane. Figure 5.8 illustrates this by showing a plot of the proportion of the surface area of an n-dimensional sphere that lies close to an $(n-1)$-dimensional plane that bisects it. For our purposes, think of the plane in Fig. 5.8 as the $(n-1)$-dimensional set of points at which the n phenotypic characters sum to the optimal value. Points close to the plane are effectively neutral (since they all have nearly the same sum). The fact that for large n most of the surface of a sphere lies close to the plane thus means that most variation is neutral in that case. Drift will therefore be most pronounced when there are many elements whose sum determines fitness, and will become less significant as elements are lost.

In such a case, eq. 5.3 predicts that selection will, where possible, break up correlations between characters. Closely related species should be expected to show substantial nonadaptive variation in such characters, and, over time, individual elements will tend to be lost by drift, just as neutral alleles are. This prediction squares well with observed trends in vertebrate skull evolution.

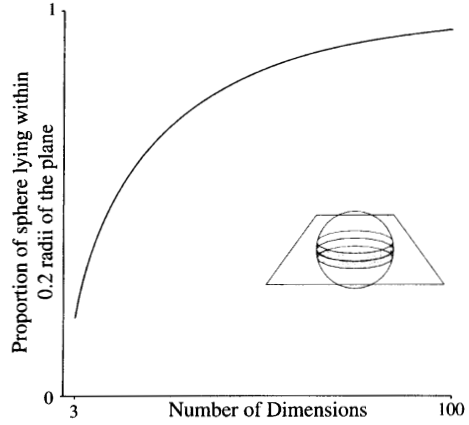

Figure 5.8 Demonstration that the amount of variation that is effectively neutral increases with the dimension (number of elements) in a case in which selection acts on the sum of many elements. The curve shows the proportion of the surface of an n-sphere that lies close to an $(n-1)$-dimensional flat surface on which the sphere is centered.

Closely related vertebrates often exhibit substantial differences in the relative sizes, and even the positions, of skull bones (Fig. 5.9). Of course, this variation could be the result of selection for different orientations in the different species. Testing the predictions of the model discussed above requires us to consider the pattern of variation between bones within a species; the model predicts that correlations between skull bones should be low, thereby providing the raw material for drift to rearrange them. By contrast, if differences between-species result from selection, then we should expect high within-species correlations among different skull elements. In the case of the muskrat zygomatic arch shown in Fig. 5.9B, the expectation of the drift hypothesis seems to be upheld.

The jugal and maxilla bones, which differ substantially between-species in their contribution to the arch, show little correlation within muskrats (Fig. 5.10). This suggests that the relative contributions of these bones to the zygomatic arch is not under much stabilizing selection, and keeps open the possibility that the between-species variation results from drift. I do not, at present, know the heritabilities of these bones within a species, and thus cannot say for sure whether drift could rearrange them. It is interesting to note, however, that there is a strong correlation between the left and right maxilla. Although this does not speak directly of heritability, it does suggest that the variation in bone size is not simply a result of developmental noise.

Drift in skull elements may manifest itself in a much larger scale pattern than can be seen within the rodents. A pronounced long-term trend in vertebrate evolution, which proceeds in parallel in lineages as different as crossopterygian fish, amphibians, and mammal-like reptiles, has been the successive loss of skeletal elements in the skull roof (Fig. 5.11; Romer and Parsons 1977; Hildebrand 1995). This trend is difficult to explain by selection alone, both because it has proceeded independently in very different environments and because it has taken place over very long periods of time, but it is exactly what we should expect if the sizes of skull elements have been drifting.

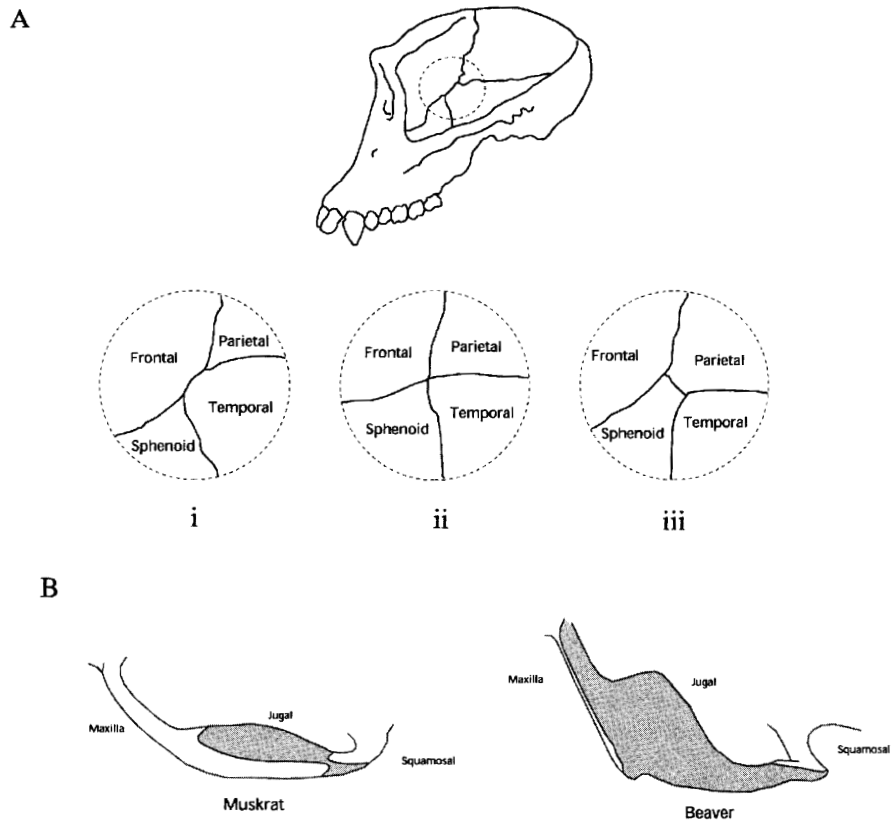

Figure 5.9 Variation in skull bone shape between closely related species. (A) The pterion region of the primate skull: (i) arrangement that characterizes the common chimpanzee, (ii) arrangement that characterizes the pygmy chimpanzee, (iii) arrangement that is most common in humans; however, all three arrangements are seen in humans. (B) The zygomatic arch of a muskrat and a beaver, showing the change in the relative contribution of the jugal bone.

Thus, drift, made possible by selection for deintegration, may have played an important role in at least one large-scale evolutionary trend. Most elements of the axial skeleton will not behave in this way since selection tends to act on the ratio, rather than the sum, of bones involved in articulating joints. In such cases, the fitness function will not meet the conditions in eq. 5.4 and selection will shape development so as to induce positive correlations between different elements.

Given that skull bones are generally identified by their positions relative to other bones (i.e., the interparietal is the bone between the parietals and the supraoccipital), the results presented above suggest that caution is needed in the assessment of homology between skull bones in different vertebrates, especially those—like the early crossopterygians—that have many small skull elements. We should also note

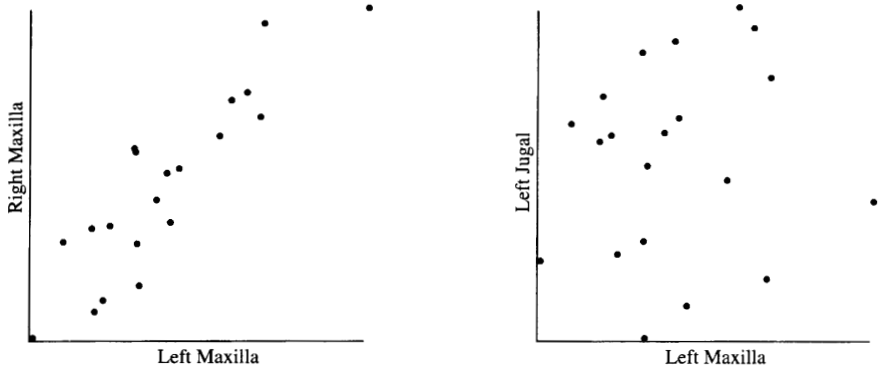

Figure 5.10 Scatter plots of linear measurements of two bones in the zygomatic arch of muskrats (specimens from the Yale Peabody Museum of Natural History). The left figure plots the maxilla on the right versus the left side, and shows a high degree of symmetry. The second plot shows values of the maxilla on the left side versus the jugal on the same side. These two bones are uncorrelated with one another, even within a species.

that there are adaptive reasons to maintain a minimum number of skull elements in some organisms, such as the need for flexibility of the skull during its passage through the birth canal in humans, and the articulating joints found in the skulls of some lizards and birds.

Though deintegration occurs when selection acts on the sum of many characters, it is possible only when those characters are the result of developmental factors that

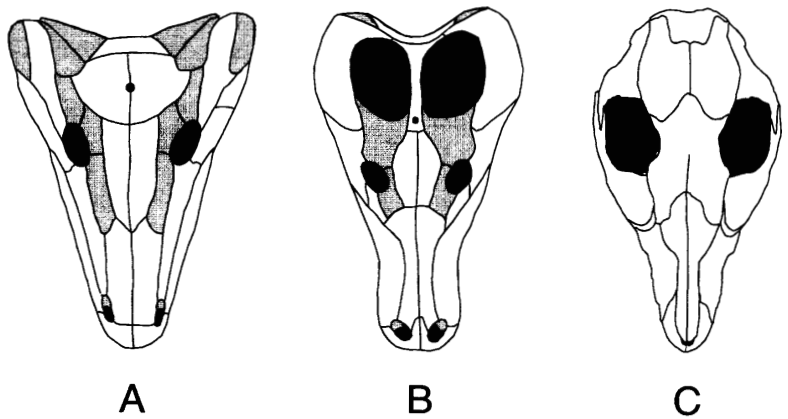

Figure 5.11 Representative skulls of (A) an early reptile (cotylosaur), (B) a therapsid, and (C) a mammal (opossum), showing the loss of skull elements. Shaded bones are ultimately lost. [Parts (A) and (B) are modified from Romer and Parsons (1977), Part (C) from Yale Peabody Museum.]

interact epistatically, thereby allowing selection to shape patterns of developmental variation and covariation. The same holds for the evolution of integration, canalization, and adaptive phenotypic plasticity. None of these phenomena could occur on a surface like that shown in Fig. 5.1A. Only with epistasis, captured here as curvature of a phenotype landscape, can selection to change the shape of a phenotype distribution achieve this by restructuring development.

Acknowledgments Melissa Garcia gathered the muskrat skull data. Conversations with Günter Wagner greatly improved and clarified the ideas and reviews from the editors, and two anonymous reviewers greatly improved the presentation.