

Morphological Integration and Developmental Modularity

Christian Peter Klingenberg

Faculty of Life Sciences, The University of Manchester, Manchester M13 9PT, United Kingdom; email: cpk@manchester.ac.uk

Annu. Rev. Ecol. Syst. 2008. 39:115–32

First published online as a Review in Advance on August 26, 2008

The *Annual Review of Ecology, Evolution, and Systematics* is online at ecolsys.annualreviews.org

This article's doi:
10.1146/annurev.ecolsys.37.091305.110054

Copyright © 2008 by Annual Reviews.
All rights reserved

1543-592X/08/1201-0115\$20.00

Key Words

constraint, evolutionary quantitative genetics, evolvability, pleiotropy

Abstract

Biological systems, from molecular complexes to whole organisms and ecological interactions, tend to have a modular organization. Modules are sets of traits that are internally integrated by interactions among traits, but are relatively independent from other modules. The interactions within modules rely on different mechanisms, depending on the context of a study. For morphological traits, modularity occurs in developmental, genetic, functional, and evolutionary contexts. A range of methods for quantifying integration and modularity in morphological data is available, and a number of comparative and experimental designs can be used to compare the different contexts. How development produces covariation between traits can have substantial implications for understanding genetic variation and the potential for evolutionary change, but research in this area has only begun and many questions remain unanswered.

INTRODUCTION

Most organisms consist of recognizable parts that are coherent according to their developmental origins, structure, and function. The fact that body parts are easily identifiable as separate entities reflects their individuality and a degree of independence of each other. Nevertheless, it is also clear that this independence is far from complete because the parts of organisms are coordinated among one another and, ultimately, integrated throughout the whole organism. This tension between coordination and relative independence has been captured in the concepts of integration and modularity.

The concept of morphological integration has existed for more than half a century (Olson & Miller 1958) and has gained renewed attention in recent years (e.g., Pigliucci & Preston 2004). The fundamental ideas behind morphological integration, however, are much older and go back to the origin of biology as a science (e.g., contributions of Georges Cuvier; Mayr 1982, p. 460). Moreover, some of the specific factors that provide integration have themselves been the focus of long-standing interest, for instance allometry (Huxley 1932).

In recent years, modularity has become an active area of investigation in evolutionary developmental biology and related disciplines (e.g., Callebaut & Rasskin-Gutman 2005, Schlosser & Wagner 2004, Wagner et al. 2007). Modularity is a general property of many types of networks, not only in biology, but also in very different contexts such as social relationships, communication, and transportation (e.g., Girvan & Newman 2002, Sales-Pardo et al. 2007). Accordingly, the work on biological modularity has concerned itself with a wide range of levels of organization, including molecular interactions in networks of gene regulation (von Dassow & Meir 2004), metabolic networks (Ravasz et al. 2002), and networks of ecological interactions (Krause et al. 2003, Olesen et al. 2007). In this review, however, I focus primarily on the context of morphological studies, where modularity is a counterpart to morphological integration.

This review surveys some of the theoretical ideas concerning morphological integration and modularity, the methods to investigate them empirically, and some results from those studies. Both morphological integration and modularity are flexible concepts that can be used in different investigative contexts, from the analysis of standing variation of adult organisms through the study of developmental processes to the examination of phylogenetic diversification across entire clades. By linking these different contexts, integration and modularity can offer a better understanding of the developmental and genetic basis of morphological evolution.

MORPHOLOGICAL INTEGRATION AND MODULARITY

Integration and modularity are two closely related concepts. Integration is the cohesion among traits that results from interactions of the biological processes producing the phenotypic structures under study. Modularity refers to the relative degrees of connectivity in systems—a module is a unit that is tightly integrated internally but relatively independent from other such modules. In other words, modularity is about differences in the degree of integration of parts within and between sets of traits.

Integration

Morphological integration is mostly inferred from data on covariation of multiple traits. There can therefore be different degrees of emphasis on the strength of covariation, which is the extent to which different traits are linked to one another, and on the patterns of covariation, which are focused on the specific changes of traits that occur together.

The strength of integration is related to the distribution of variation over the dimensions of the phenotype space. Integration is strongest if all variation is concentrated in a single dimension, indicating perfect correlation of all measurements, and it is absent if variation is evenly distributed over all available dimensions. Following this logic, several indices of integration have been derived as functions of the eigenvalues of the correlation matrix of linear distance measurements (Cheverud et al. 1983; Wagner 1984, 1990). More recently, similar indices have been developed for geometric morphometrics (Willmore et al. 2006, Young 2006).

The patterns of integration have attracted increased attention in recent years, particularly with the increased use of geometric morphometrics. If traits are integrated with each other, morphological variation consists of coordinated movements of the parts of a structure relative to one another. A range of different analyses have been used to investigate and display the patterns of coordination in morphometric data (Bastir & Rosas 2005; Bookstein et al. 2003; Hallgrímsson et al. 2007; Klingenberg & Zaklan 2000; Klingenberg et al. 2001, 2003). Patterns of integration in an entire structure are usually investigated by principal component analysis and similar methods, whereas the covariation between different parts of a structure is often studied with methods such as partial least squares analysis (e.g., Bastir et al. 2005; Bookstein et al. 1990, 2003; Klingenberg & Zaklan 2000; Klingenberg et al. 2001; Rohlf & Corti 2000). All of these analyses consider landmarks to be integrated with each other if their variation is correlated, that is, if there is any stochastic association between shifts of the landmarks regardless of the direction of the movements of individual landmarks.

This definition of morphological integration is the most widespread, but by no means the only one that has been used in recent studies. For instance, Goswami (2006a,b, 2007) uses a mathematical formalism that implies a quite different definition of integration, which considers landmarks as integrated only if they move jointly and in the same or similar directions, but does not view them as integrated if their movements are correlated but in perpendicular or opposite directions. Yet another very different definition is that of Badyaev and colleagues in their studies of shrew mandibles, who consider landmarks integrated if they were located in the insertion area of the same muscle (Badyaev & Foresman 2000, Badyaev et al. 2005). Finally, in their study of evolutionary integration of the mandible in a group of rodents, Monteiro et al. (2005) defined evolutionary integration by the congruence of evolutionary distances derived from different portions of the mandible. Overall, therefore, it is clear that no general consensus on the meaning and measurement of morphological integration has been achieved. Readers are advised to exercise caution when comparing the results from different studies.

Modularity

Modules are units whose parts are tightly integrated by numerous and usually strong interactions. In contrast to this strong internal integration, only relatively few or weak interactions connect different modules. As a result, the integration between modules is weak relative to the strong integration within modules. These properties of modules are very general, and the uses of the principle of modularity are very diverse. For instance, it is applied as a design principle in engineering and management (Garud et al. 2002) and it has been found in a wide range of social and biological networks (Callebaut & Rasskin-Gutman 2005, Girvan & Newman 2002, Schlosser & Wagner 2004, Wagner et al. 2007).

In order to be applied usefully to biological problems, modularity requires a specific context that defines the nature of the interactions and often also imposes other conditions or limitations on the parts that belong to a module. It may be helpful to think of the nouns “module” and “modularity” as requiring an adjective, for instance “genetic” or “developmental,” which specifies the particular

context (likewise, the adjective “modular” requires an adverb that specifies the context). This context is essential for understanding how the modular system works, because it specifies the type of interactions that define the modules.

Depending on the context of a particular study, the interactions that establish the modules rely on different mechanisms. For instance, these interactions may concern the processes of gene regulation in genetic networks or the biochemical reactions in metabolic networks. In some contexts, information about the network of interactions is readily available, and analyses of modularity can directly use the connections between parts to identify modules (e.g., Girvan & Newman 2002, Guimerà & Nunes Amaral 2005, Rosvall & Bergstrom 2007). In other contexts, however, the interactions between parts are not easily observable, but must be inferred from the patterns of covariation between measured variables. For instance, gene regulatory modules may need to be deduced from shared patterns of gene expression in different experimental settings (Somogyi et al. 2004). Similarly, for morphological data, the developmental or evolutionary interactions must be inferred from covariation of morphological traits in experimental or comparative analyses.

Modules may relate directly to other concepts that traditionally have been used to describe the same units. For instance, morphological modules often correspond to organs recognized in comparative anatomy and they also may correspond to developmental fields (Davidson 1993, Gilbert et al. 1996). Similarly, gene regulatory modules may match known signaling pathways (e.g., chapters 3–6 in Schlosser & Wagner 2004). Because the data used to delimit modules usually are different from the criteria for recognizing the more traditional units, such congruence is evidence for the robustness of the modular structure. It is particularly informative to examine whether modules are congruent across different contexts, for example, if genetic or developmental modules match the subdivision of an organism or structure into functional modules, because the match or mismatch of modules can provide information about the origin of modularity (Breuker et al. 2006a, Cheverud 1996, Wagner & Altenberg 1996).

Relationships Between Types of Modules

Even for morphological data, modularity can be studied in a variety of biological contexts and experimental or observational settings. Morphological data have been used to characterize developmental, genetic, functional, and evolutionary modules (Armbruster et al. 2004; Badyaev & Foresman 2004; Cheverud et al. 1997; Klingenberg et al. 2001, 2003, 2004; Monteiro et al. 2005). Examining the relationships between these different types of modules (**Figure 1**) can be informative about the underlying biological processes (Breuker et al. 2006a).

Because morphological structures are produced by developmental processes, it makes sense to start the discussion with developmental modules. These modules are defined by developmental interactions among the precursors that ultimately will form the parts of the finished structure. Developmental interactions, sometimes also called epigenetic interactions (Hall 1999, Hallgrímsson et al. 2007), encompass a wide range of processes such as developmental switches that lead to bifurcations of developmental pathways or signaling between tissues through various molecular mechanisms (e.g., Wilkins 2002). The common feature of developmental interactions is that they are the means by which developmental processes can mutually influence each other and therefore achieve a coordinated development of tissues, organs, and the whole organism. Developmental interactions can mediate the expression of genetic and environmental variation by transmitting their effects across different traits. Developmental modularity therefore contributes to the patterning of all components of phenotypic covariation among traits.

Genetic modularity refers to the patterns of joint effects of genes on the traits, which can be represented as a network of pleiotropic relations among traits (Nadeau et al. 2003). Genetic

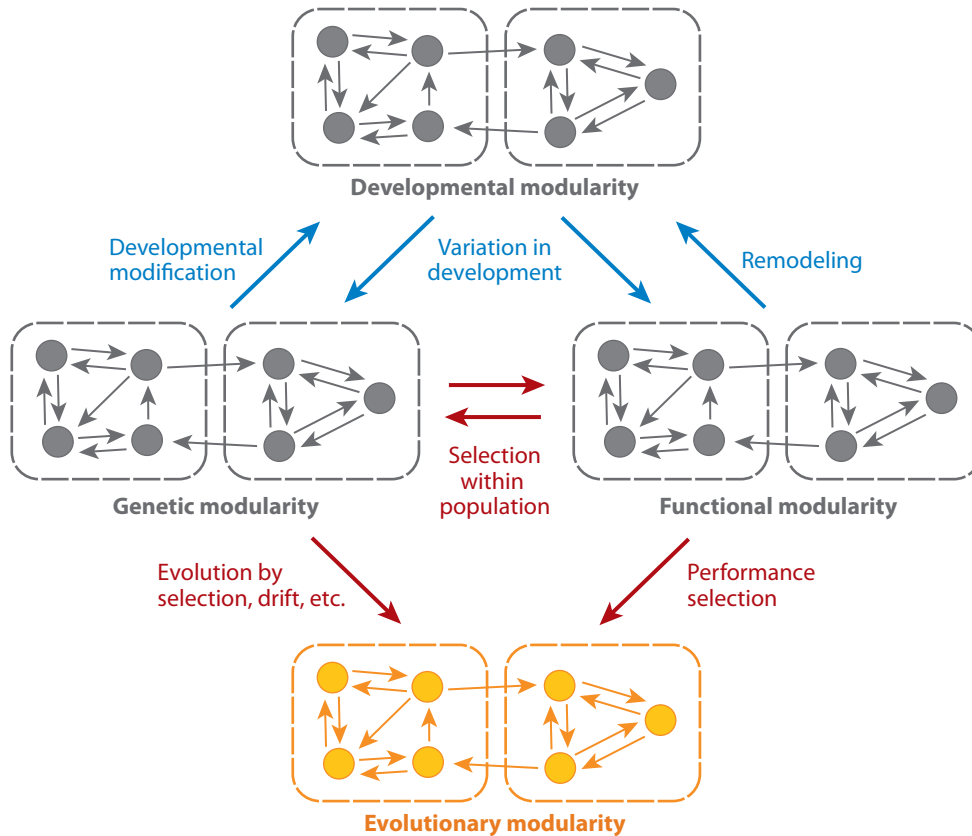


Figure 1

Types of modularity that concern morphological variation and the connections between them. Developmental, genetic, and functional modularity are based on processes taking place within extant individuals or populations (*gray diagrams*), whereas evolutionary modularity results from the history of divergence among evolutionary lineages in an entire clade (*orange diagram*). These types of modularity are mutually influencing each other through various processes within individuals (*blue arrows*) or within populations (*red arrows*). Developmental modularity has an effect on both genetic and functional modularity by modulating the available morphological variation. Genetic modularity feeds back to developmental modularity through the genetic control of development, whereas processes of tissue remodeling (e.g., bone remodeling under mechanical load) provide a feedback from function to developmental processes. At the population level, the process of natural selection establishes a two-way interaction between genetic and functional modularity. These effects of selection, jointly with the additional effect of genetic modularity on changes by drift, accumulate through time to constitute the evolutionary modularity of an evolving lineage or clade.

modularity has been discussed extensively in the context of the “genotype-phenotype map” (Mezey et al. 2000, Wagner 1996, Wagner & Altenberg 1996). Because developmental processes mediate the expression of genetic variation in phenotypic traits, developmental and genetic modularity are related. This relationship need not be a perfect congruence, however, because the expression of genetic variation is not exclusively controlled by developmental interactions. Moreover, genetic changes can influence developmental modularity by causing alterations in the interactions among the developmental pathways that affect the traits of interest (Klingenberg 2005).

Functional modularity refers to the interactions of traits in performing one or more functions. For instance, in the skull, these interactions include direct mechanical forces produced during

chewing and design trade-offs among functional contexts such as prey capture and processing, breathing, and vocalization. Because developmental processes form the structures that perform functions, developmental modularity is expected to influence functional morphology, even though it is by no means clear how strong this relationship is (Breuker et al. 2006a). Conversely, functional modularity can have an influence on developmental modularity by processes such as bone remodeling and other forms of plasticity in which mechanical load influences rates and direction of tissue growth (Enlow & Hans 1996, Herring 1993, West-Eberhard 2003). Some theoretical analyses hypothesized that selection causes functional and genetic modularity to converge (Cheverud 1996, Wagner 1996, Wagner & Altenberg 1996), and empirical studies have provided some support for this idea (Armbruster et al. 2004, Cheverud et al. 1997, Klingenberg et al. 2004, Mezey et al. 2000). In contrast, other studies indicate that different morphological structures can perform equivalent functions and, therefore, that considerable flexibility for neutral divergence may exist (Wainwright et al. 2005, Young et al. 2007).

Evolutionary modularity is due to the structured associations between the evolutionary divergence in different traits. A range of analyses have been used to characterize and compare patterns of modularity and integration in large-scale evolution (Goswami 2006a,b, 2007; Monteiro et al. 2005; Wroe & Milne 2007). As genetic variation is a critical determinant for evolutionary change by selection and drift (Lande 1979, Felsenstein 1988), genetic modularity contributes substantially to evolutionary modularity. Functional modularity is also an important determinant of evolutionary diversification because it provides a link between the modular structure of morphological traits and selection on performance in organismal functions. Systematic comparisons between evolutionary modularity and the other levels have not yet been published to date.

Research comparing modularity across the different levels has only begun relatively recently, and many aspects remain completely unexplored. This type of study has a precedent, however, because the distinction of types of modularity and integration closely parallels the distinction of different types of allometry (Cock 1966, Gould 1966) and the examination of relationships between them (Cheverud 1982, Klingenberg 1996, Klingenberg & Zimmermann 1992). As allometry is an important contributor to integration, linking the study of allometry to the more recent subjects of morphological integration and modularity seems both natural and promising.

Investigating Modularity with Morphological Data

To implement these concepts in empirical studies, investigators need methods for analyzing modularity in actual data. A wide range of such methods is available to identify modules from networks where the links between parts are specified explicitly at the outset of the analysis. Traditionally, hierarchical clustering has been used for this purpose, but these methods have a number of disadvantages (Girvan & Newman 2002). Other approaches identify modules from the pattern of connectivity among nodes in the network or from measures of the information content of the network (Girvan & Newman 2002, Guimerà & Nunes Amaral 2005, Radicchi et al. 2004, Rosvall & Bergstrom 2007, Sales-Pardo et al. 2007). Studies of morphological data, however, do not have this information on the network of interactions between the measured traits, but need to infer interactions from the patterns of covariation among traits.

If the spatial extent of the modules is clear, the measurement of morphological covariation is fairly straightforward. Traditional measurements of lengths as well as geometric methods for quantifying shape variation can be used to compute measures of covariation within and between modules. For instance, in *Arabidopsis*, floral and leaf traits tend to form separate genetic modules (Juenger et al. 2005). Analyses of mammalian limb bones show a more complex pattern of integration, because both the difference between fore- and hindlimbs and the serial homology

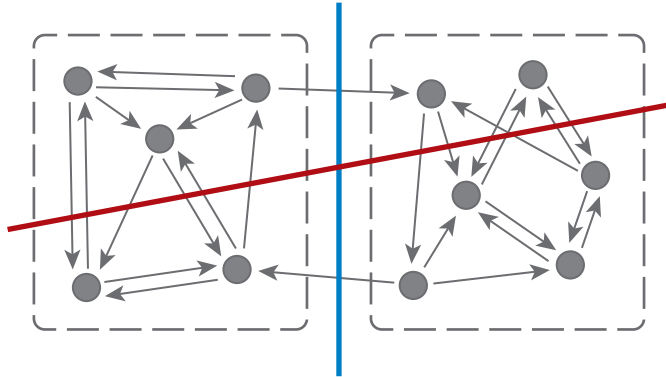


Figure 2

A strategy for delimiting morphological modules. A subdivision of the traits that correspond to the true boundary between modules (*blue line*) will produce subsets that are weakly correlated, because only a few interactions (*arrows*) link the traits in the two subsets. In contrast, a subdivision that does not correspond to the boundary between modules (*red line*) will result in subsets that are linked by many and strong within-module interactions, and therefore will yield a strong correlation between subsets.

of elements within limbs are reflected in the correlations between them (Young & Hallgrímsson 2005). Covariation of shape indicates that *Drosophila* wings consist of a single integrated developmental module, whereas the fore- and hindwings of bees are two separate developmental modules (Klingenberg & Zaklan 2000, Klingenberg et al. 2001).

A general strategy for delimiting modules is based on comparisons among different subdivisions of the total set of traits into subsets (**Figure 2**). This subdivision is analogous to the removal of links that connect different modules, as it is used in algorithms for network analysis (e.g., Girvan & Newman 2002). If the subdivision follows the true boundary between modules, the two subsets are linked only by relatively few or weak interactions (the *vertical blue line* in **Figure 2** only crosses two of the *arrows*). Accordingly, there will be a relatively low degree of covariation between the two subsets of traits. Conversely, if the subdivision into subsets does not follow the true boundary between modules, many of the strong interactions within modules will link traits in the different subsets (many *arrows* cross the *oblique red line* in **Figure 2**). As a consequence, the covariation between the two subsets will be strong in this situation. Therefore, it is possible to evaluate modularity in morphological data by subdividing the total set of traits into subsets and comparing the strengths of covariation between them.

This approach was used to evaluate the modularity of the mouse mandible. There is a long-established hypothesis that the mandible consists of two separate modules: an alveolar part that bears the teeth and the ascending ramus, to which muscles are attached and which articulates with the skull (Atchley & Hall 1991, Cheverud et al. 1997, Mezey et al. 2000). The covariation of geometric shape between these putative modules tends to be weaker than between alternative partitions of the mandible and thus supports the hypothesis of modularity, both for developmental and genetic modularity (Klingenberg et al. 2003, 2004). These results, although consistent overall with earlier results of the spatial distribution of statistically significant genetic effects on distance measurements (Cheverud et al. 1997, Mezey et al. 2000), differ in that they underscore that modularity is not necessarily an all-or-nothing occurrence, but can be a matter of degrees (Klingenberg et al. 2003).

A fundamentally different approach for studying modularity was used by Monteiro et al. (2005) in an analysis of evolutionary divergence of mandible shape in a group of rodents. These researchers

subdivided the mandible into developmental units according to the scheme of Atchley & Hall (1991) and computed a matrix of shape distances between all pairs of taxa for each of these units. Monteiro et al. (2005) assessed evolutionary integration by the matrix correlations among these distance matrices. In other words, they used the congruence of the evolutionary divergence of the different morphological units of the mandible as a measure of integration between pairs of units. Evolutionary modularity is indicated by a lack of congruence in the divergence of different morphological units, that is, if the units evolve independently of each other. The matrix correlations were then used for further analyses of the patterns of modularity and evolutionary integration, such as clustering and comparisons with hypothetical matrices (Monteiro et al. 2005).

Yet another approach was used in a series of papers by Goswami (2006a,b, 2007) on cranial integration and modularity in mammal skulls. These analyses, which were based on landmark data, used a somewhat unusual Procrustes fit without scaling to a standard size and a definition of integration among landmarks as their tendency to move in the same direction (most other studies consider landmarks as integrated if their positions are mutually correlated, even if they tend to move in opposite or perpendicular directions). Due to these two choices, variation in size almost inevitably produces integration among neighboring landmarks because their primary directions of movement, toward and away from the common center of gravity, are similar. This method may therefore partly account for the clustering of landmarks according to anatomical regions (Goswami 2006a). The analyses showed that the patterns of cranial modularity in the broad range of mammals studied were consistently associated with the phylogenetic distances between taxa, but diet had only a clear effect in a few of the taxa (Goswami 2006b, 2007). It is not entirely clear how these results would compare with more conventional analyses.

DEVELOPMENTAL ORIGINS OF COVARIATION AMONG TRAITS

Studies of morphological integration and modularity are based on data concerning covariation among morphological traits. This covariation is an outcome of the processes that formed the morphological structures under study, and it is therefore possible, within certain limits, to use morphological covariation to infer how the traits interact developmentally. Accordingly, it is useful to consider how developmental processes generate covariation among the resulting morphological traits (Klingenberg 2003a, 2004b, 2005; Riska 1986).

The metaphor of developmental pathways (e.g., Wilkins 2002) is helpful for understanding the developmental basis of the covariation of morphological traits. A developmental pathway denotes the ensemble of processes that generate a trait. It therefore is a summary term that incorporates a multitude of interacting molecular and cellular mechanisms that underpin the processes of organismal development, which can themselves be complex networks of interactions (Alonso 2008). An explanation of the covariation between traits needs to account for variation that is coordinated among multiple pathways. There are several developmental origins of morphological covariation, of which some rely on direct interactions between developmental pathways, whereas others do not involve interactions between pathways, but are due to simultaneous variation in separate pathways (**Figure 3**; Klingenberg 2003a, 2005). For characterizing developmental integration or modularity, which specifically focus on developmental interactions, it is important to distinguish these different origins of morphological covariation.

A range of different developmental mechanisms can produce interactions between developmental pathways and, as a consequence, generate covariation between morphological traits. Riska (1986) discussed several models in which a precursor tissue is divided into two parts that each give rise to a trait (**Figure 3**, *left*). In other words, this is a branching of the developmental pathway. Examples of this kind of process are the successive proliferation and partitioning of mesenchyme

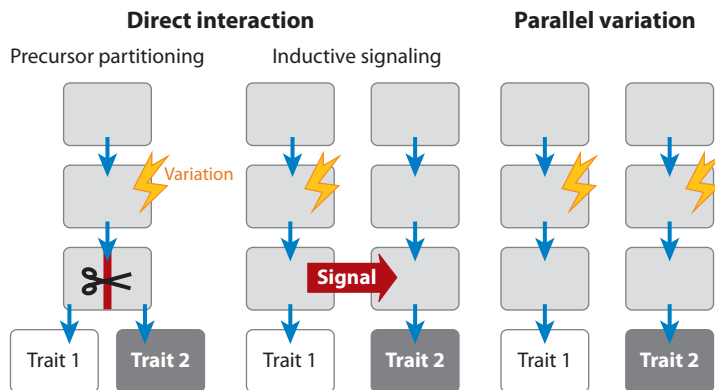


Figure 3

Different developmental origins of morphological covariation. Covariation of morphological traits can result from a direct interaction of the corresponding developmental pathways, for instance, by partitioning of a precursor tissue (*scissors symbol on left*) or by inductive signaling from one pathway to another (*red arrow in middle*). In both cases, variation from upstream in the pathway (*lightning bolts*) is transmitted to both resulting traits and causes covariation between them. Covariation between traits can also originate without direct developmental interactions (*right*). If two separate developmental pathways respond to the same outside stimulus, a correlation between traits can also arise. (Modified from Klingenberg 2005.)

cell populations that form the precursors of tetrapod limb bones (e.g., Mariani & Martin 2003) or the sequential subdivision of developmental fields (Davidson 1993, Arques et al. 2007). Depending on variation in the precursor or the process of partitioning, these models can produce different correlations between the traits: variation in the pathway “upstream” of the partitioning event can generate positive correlations, and variation in the process of fission itself can produce negative correlations (Riska 1986). Another mechanism responsible for interactions between pathways is inductive signaling (**Figure 3, middle**). For instance, signaling from the endoderm to the neural crest influences cell survival and patterning in the anterior neural crest (Brito et al. 2006, Couly et al. 2002). Variation in the pathway upstream of the source of the signaling can be transmitted through the signal to the other pathway, and it is afterward passed on in both pathways so that it affects both traits jointly. Direct interactions between developmental pathways can transmit variation from within the upstream portion of the pathway to both traits. This means that variation arising from the developmental processes themselves can produce covariation between the traits.

Direct interactions between developmental pathways are not the only possible origin of covariation between morphological traits. If separate developmental pathways are sensitive to the same outside stimulus, the resulting variation can be transmitted simultaneously to multiple traits and will also manifest itself as covariation between traits (**Figure 3, right**). Variation in the pathways will therefore occur in parallel, even though the pathways are entirely separate and do not interact. This process relies on an external source of variation that affects multiple developmental processes simultaneously. Examples are variation in the environmental conditions experienced by different individuals, allelic differences in genes that take part in different developmental processes (“genuine pleiotropy” according to Pyeritz 1989), or even pharmacological treatment (Wang et al. 2007). Covariation between the resulting traits relies on the simultaneous input of variation into the different pathways. In contrast, variation from within any one of the pathways cannot be transmitted to another pathway; developmental variation arising in the pathways themselves therefore cannot generate covariation between the traits.

Inference from Morphometric Data

To distinguish covariation owing to direct interaction of developmental pathways from covariation due to parallel variation of separate pathways, investigators can try to eliminate genetic and environmental variation among organisms or to focus on variation that arises within the developmental pathways that form the adult traits under study. Because covariation owing to parallel variation of separate pathways requires extrinsic variation among individuals and because variation from within the separate pathways cannot produce covariation among traits, both these strategies remove the component of covariation owing to parallel variation of separate pathways. Accordingly, all the covariation in the resulting data will be due to direct interaction of developmental pathways.

An easy way to eliminate the effects of genetic and environmental variation among individuals and simultaneously to focus on variation from within the developmental pathways is to analyze data on fluctuating asymmetry (Klingenberg 2003a). Because the left and right sides of an individual share the same genome (except for somatic mutation) and experience nearly the same environment (except for sessile organisms), the study of fluctuating asymmetry is an effective way to eliminate genetic and environmental variation among individuals. Moreover, because fluctuating asymmetry originates from random perturbations of developmental processes (Klingenberg 2003b), the variation arises within the developmental pathways themselves. For both these reasons, covariation in the fluctuating asymmetry of different traits is exclusively due to covariation by direct developmental pathways (Klingenberg 2003a, 2004b, 2005).

By comparing patterns of covariation of fluctuating asymmetry with the patterns of covariation among individuals, it is possible to assess the role of direct developmental interactions in generating the covariation among individuals. Several studies have made such comparisons in a range of different organisms and with widely varying results. Analyses in the wings of *Drosophila* and other insects tended to produce good agreement between the patterns of covariation for fluctuating asymmetry and individual variation, and therefore suggest that direct developmental interaction is important for all levels of covariation (Breuker et al. 2006b, Debat et al. 2006, Klingenberg & McIntyre 1998, Klingenberg & Zaklan 2000, Klingenberg et al. 2001). In contrast, analyses in the skulls of mice and rhesus monkeys indicated poor agreement between levels of variation (Debat et al. 2000, Hallgrímsson et al. 2004, Willmore et al. 2005). Studies in the mouse mandible, on the other hand, showed good agreement (Leamy 1993, Klingenberg et al. 2003), suggesting that this is not simply a question of whether studies use mammals or insects. Clearly, studies in a wider range of taxa are necessary to provide a better understanding of the relative roles of covariation by direct interactions versus parallel variation of developmental pathways.

INTEGRATION OF GENE EFFECTS: PLEIOTROPY

Genetic variation has a key role in the evolutionary process. Therefore, understanding the factors that shape the available genetic variation is indispensable for understanding evolution. Integration of genetic effects manifests itself as simultaneous genetic effects on multiple traits, which have long been known in genetics as pleiotropy (Grüneberg 1938, Hadorn 1945, Hodgkin 1998, Pyeritz 1989). For understanding pleiotropy, a key question is how the simultaneous effects of a gene on multiple traits come about. In a pioneering paper, Grüneberg (1938) sketched a network of cause-and-effect relationships to account for the etiology of pleiotropic effects, and more recent discussions have expanded on this approach (Pyeritz 1989, He & Zhang 2006, Hodgkin 1998). Because the effects of allelic differences are expressed and transmitted through the developmental pathways that form the observable phenotype, the analysis of pleiotropy is closely related to the preceding general discussion about the developmental origin of covariation among traits.

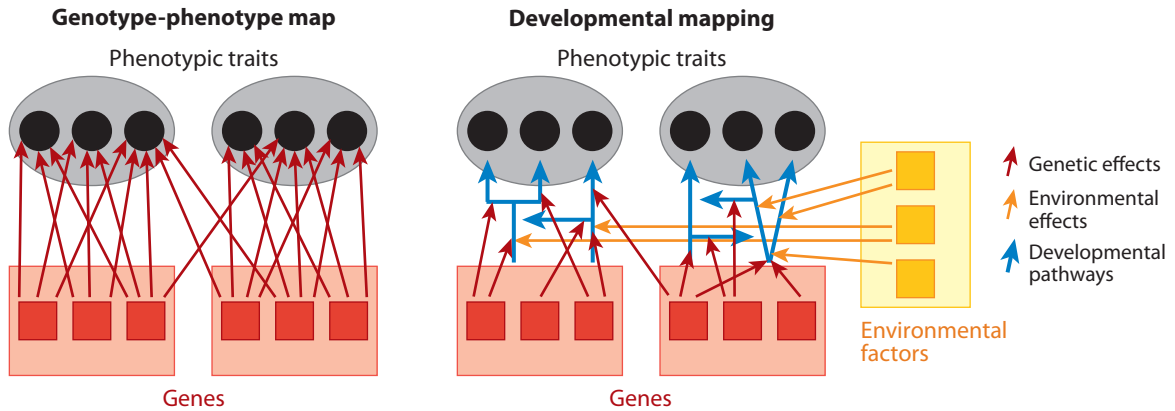


Figure 4

Two conceptual frameworks for the genetic architecture and evolution of morphological traits. The genotype-phenotype map (Wagner 1996, Wagner & Altenberg 1996) focuses on the relationship between genes (*red squares*) and phenotypic traits (*black circles*). Genetic effects (*red arrows*) directly link genes and phenotypic traits. Genetic modularity is defined by the distributions of these links over sets of genes and sets of traits. This review advances a broader perspective, developmental mapping (Klingenberg 2003b, 2004a), which emphasizes that genetic factors affect phenotypic traits by modulating the pathways of developmental system (*blue arrows*). Because it does not exclusively focus on genotypic factors, this perspective also can incorporate, for instance, environmental factors and their effects (*orange squares and arrows*). Modularity and integration result from the aggregate of these effects, as mediated by the developmental system.

By explicitly considering the system of developmental interactions that mediate between genes and the phenotypic traits, this perspective differs from the direct mapping between genotype and phenotype (Wagner 1996, Wagner & Altenberg 1996), as it has been widely used in evolutionary biology and related areas (Kell 2002, Mezey et al. 2000). Because development is central in this view, it can be called developmental mapping (Klingenberg 2003b, 2004a). As there is no exclusive focus on the genotype as a cause of phenotypic variation, this framework can easily incorporate additional factors such as environmental plasticity (Figure 4; West-Eberhard 2003).

Gene Action on Multiple Traits

Genes can simultaneously affect multiple traits through direct interactions of developmental pathways or through parallel effects on separate pathways. These two ways of how allelic differences cause joint differences in multiple traits are not easily distinguishable from empirical data, but have significant implications for the evolution of morphological integration (Klingenberg 2005). This distinction is somewhat different from other schemes to classify types of pleiotropy (Peyeritz 1989, He & Zhang 2006, Hodgkin 1998), which tend to focus on whether gene products such as proteins have one or more molecular functions, rather than the origin and transmission of effects on traits in the developmental system.

If developmental pathways interact directly, effects from genes acting anywhere in the pathway upstream of the interaction (*lightning bolts* in Figure 3, *left* and *middle*) can have pleiotropic effects on both resulting traits. For directed interactions such as signaling, which have a source and a target, the transmission of effects to both pathways and traits is limited to the genes in the upstream portion of the source pathway, whereas the upstream genes in the receiving pathway cannot have such pleiotropic effects. A single signaling interaction can simultaneously transmit variation from a number of upstream loci to a set of traits, and therefore contribute to the pattern of

pleiotropic effects of all those loci. Therefore, there is a tendency for several genes to share similar patterns of pleiotropy through this mechanism. Note that, with this origin of pleiotropic effects, the gene providing the variation is distinct from the interaction of developmental pathways, and each potentially can evolve separately.

By contrast, if pleiotropy is by parallel variation in separate developmental pathways, the allelic differences that are the source of variation are also the factor that generates the association between traits (*lightning bolts* in **Figure 3**, *right*). Accordingly, each locus produces its pattern of pleiotropy independently of any other locus, depending on how the allelic differences affect each pathway. It is therefore difficult or impossible to predict the relationship between these patterns for different loci. If alleles of several loci mainly differ in the overall activity of a gene product, which increases or decreases consistently in several pathways, some correspondence of patterns of pleiotropy may be expected. This relationship will vanish, however, if the expression of the loci is differentially regulated in the different pathways.

Empirical studies of gene effects on multiple traits have mostly relied on mapping of quantitative trait loci (QTLs), that is, on establishing statistical relationships between phenotypic traits and genotypic markers. This methodology corresponds to a mapping of genotype and phenotype, and is forced to ignore the developmental processes that underpin these relationships (**Figure 4**). A series of studies in the mouse mandible used QTL mapping for morphometric measurements to demonstrate that the anterior and posterior parts of the mandible are separate modules (Cheverud et al. 1997, Klingenberg et al. 2004, Mezey et al. 2000). Because covariation of fluctuating asymmetry is similarly structured (Leamy 1993, Klingenberg et al. 2003), it is plausible that a substantial portion of the pleiotropic effects of the QTLs is due to direct interaction of developmental pathways (Klingenberg et al. 2004). Pleiotropic effects of QTLs were also found for the teeth and skull in the same intercross of mouse strains (Leamy et al. 1999, Workman et al. 2002). Somewhat similar results were obtained in sticklebacks, where it was found that marine and freshwater forms differ by QTL alleles that tend to affect landmarks in different body regions (Albert et al. 2008). For these examples, no inference on the developmental origin of pleiotropic QTL effects is possible.

Pleiotropy and Evolution

The combined effects of pleiotropy at all segregating loci in a population make up the genetic covariance structure, which has a substantial influence on the evolution of morphological traits (e.g., Cheverud 1984, Klingenberg 2005, Lande 1979, Schluter 1996). The genetic covariance structure can manifest itself as genetic constraints (Cheverud 1984) or developmental biases (Arthur 2004), which are properties of the genetic variation that limit the potential response to selection in certain directions of phenotypic space or deflect the response to selection in particular directions away from the direction of selection itself (Klingenberg & Leamy 2001, Schluter 1996).

Genetic constraints differ in strength. There can be absolute constraints, where there is no genetic variation at all in certain dimensions of the phenotypic space, and thus there can be no evolution in those directions (Klingenberg 2005, Lande 1979, Mezey & Houle 2005). Much more frequently, there are relative constraints where the amount of genetic variation differs according to the direction, but where some variation exists in every direction. Thus, there is some evolutionary response to selection in any direction, but it may differ in magnitude and may be more or less strongly deflected (Beldade et al. 2002, Klingenberg & Leamy 2001, Schluter 1996). Depending on the structure of the adaptive landscape, even relative constraints may have long-term consequences because it is possible that constraints deflect evolutionary trajectories so that populations may reach different adaptive peaks (Arthur 2004, Schluter 1996).

Pleiotropic gene effects contribute to genetic constraints regardless of the developmental mode by which they originate. Pleiotropic effects by direct interactions and by parallel variation of developmental pathways differ, however, in the probability and implications of evolutionary changes of pleiotropic effects themselves (Klingenberg 2005). Because interactions between developmental pathways are likely to have significant effects on the phenotypic outcome of the developmental process, such interactions are expected to be under stabilizing selection and therefore resist evolutionary change. As a by-product, this selective regime also stabilizes the pleiotropic effects of the genes upstream of the developmental interaction. If there is an evolutionary change of the developmental interaction, however, this change simultaneously affects the pleiotropic patterns of all the genes upstream of the interaction and may thus have a sudden and significant effect on the genetic covariance structure. As a result, the evolutionary dynamics of pleiotropic effects by direct interaction of developmental pathways may be of a somewhat stepwise nature (Klingenberg 2005).

By contrast, for pleiotropic effects by parallel variation of separate pathways, there is no relationship among the pleiotropic effects of different loci. Accordingly, parallel variation of developmental pathways potentially provides a considerable degree of evolutionary flexibility for pleiotropic effects and for the genetic covariance structure as a whole (Klingenberg 2005).

An entirely different kind of reasoning has been used in studies of the question whether pleiotropy and the genetic covariance structure are themselves adaptive. Various models have been advanced to show that genetic covariance structure can respond to selection and that standing variation might thus be the result of an adaptive process (Cheverud 1984, 1996; Jones et al. 2007; Wagner & Altenberg 1996; Wagner et al. 2007). To address this question for natural populations, however, is difficult. The match of functional and genetic modularity in the mouse mandible is consistent with this hypothesis (Cheverud et al. 1997, Klingenberg et al. 2004, Mezey et al. 2000), but the same pattern of modularity also applies to developmental variation (Klingenberg et al. 2003) and is thus open to a nonadaptive interpretation. A system where developmental and functional modules are incongruent would therefore be more informative (Breuker et al. 2006a), but no fully conclusive example is available. Floral traits in plants are promising in this respect and have yielded some suggestive results, but no unequivocal example of adaptive genetic modularity has been documented yet (Armbruster et al. 2004, Hansen et al. 2003).

INTEGRATION, MODULARITY AND EVOLVABILITY

Morphological integration and modularity have often been linked to the concept of evolvability in the recent literature (Cheverud 1996, Hansen & Houle 2004, Kirschner & Gerhart 1998, Klingenberg 2005, Wagner & Altenberg 1996). Different researchers have referred to a number of different concepts under this heading, which often refer to little more than the potential to respond to selection, that is, standing genetic variation in populations. A different and more interesting idea, however, is to think of evolvability as the propensity of developmental systems to produce new genetic variation, which is closer to the original meaning of the term and relates it to measurable quantities such as mutational variation (Jones et al. 2007, Wagner & Altenberg 1996).

To assess the potential for long-term evolutionary change, new sources of evidence in addition to standing variation in populations need to be accessed. Some studies have investigated the patterns of mutational variation using mutagenesis or mutation accumulation lines (Camara & Pigliucci 1999, Estes et al. 2005). These studies give an empirical snapshot of the mutational potential in the experimental population, which is a crucial factor in assessing evolvability. Because the mutational variation itself may evolve, however, caution is needed when extrapolating these results over long evolutionary timescales. Theoretical simulations suggest that the evolution of mutational covariance structure can be an important factor in determining evolvability (Jones et al. 2007).

There has been much debate on the role of single genes, particularly the heat-shock protein 90 (Hsp90), as determinants of evolvability (e.g., Rutherford 2003, Rutherford & Lindquist 1998, Wagner et al. 1999). More recent studies of Hsp90 have revealed that its effects on variability tend to be restricted to certain discrete traits that are normally invariant (Milton et al. 2006), but that the variability of quantitative traits is not consistently affected by Hsp90 (Debat et al. 2006, Milton et al. 2003). The expression of variation and asymmetry in quantitative traits appears to be controlled by many loci with small individual effects, rather than by a few key genes (Breuker et al. 2006b, Dworkin 2005).

Overall, there remain many challenges for the study of evolvability. In particular, to address the hypothesis of a match between genetic control and the functional role of morphological modules (Cheverud 1996, Wagner 1996, Wagner & Altenberg 1996), developmental aspects need to be incorporated explicitly in studies of evolvability. Moreover, the study of evolvability over a large evolutionary timescale requires explicit comparative approaches.

CONCLUSIONS AND PROSPECT

This review has touched on a variety of different ideas relating to morphological integration and modularity. An aspect of great importance in all of these ideas is that the developmental mechanisms generating the covariation among observable traits are of prime importance for understanding its evolutionary significance. Directly mapping the phenotype to the genotype (**Figure 4, left**), although it is an efficient approach for mapping genes and for population genetic studies over a short time horizon, is not sufficient for understanding the full evolutionary potential of the traits in the long run. Explicitly incorporating the developmental processes that mediate between genotype and phenotype is indispensable for that purpose (**Figure 4, right**). Moreover, this approach also allows the investigator to consider causative factors other than the genotype, such as environmental variation. Although such comprehensive developmental mapping is clearly a daunting task, new experimental resources and analytical methods are available that may make it feasible in the near future.

The study of morphological integration and modularity also offers a range of other challenges. A systematic study of the relationship between developmental, genetic, functional, and evolutionary variation remains to be carried out, even though there are several groups of organisms that should be feasible as “model clades” for this purpose. Also, the relative roles of morphological covariation by direct interaction and by parallel variation of developmental pathways have only been examined in a few study organisms, but no consistent overall picture has emerged from those studies yet. Finally, the question of the developmental basis of pleiotropic effects and its implications for evolvability of morphological traits is a vast and almost entirely unexplored field for new experimental and analytical approaches.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

- Albert AYK, Sawaya S, Vines TH, Knecht AK, Miller CT, et al. 2008. The genetics of adaptive shape shift in stickleback: pleiotropy and effect size. *Evolution* 62:76–85
- Alonso CR. 2008. The molecular biology underlying developmental evolution. In *Evolving Pathways: Key Themes in Evolutionary Developmental Biology*, ed. A Minelli, G Fusco, pp. 80–99. Cambridge, UK: Cambridge Univ. Press

- Armbruster WS, Pélabon C, Hansen TF, Mulder CPH. 2004. Floral integration, modularity, and accuracy: Distinguishing complex adaptations from genetic constraints. See Pigliucci & Preston 2004, pp. 23–49
- Arques CG, Doohan R, Sharpe J, Torres M. 2007. Cell tracing reveals a dorsoventral lineage restriction plane in the mouse limb bud mesenchyme. *Development* 134:3713–22
- Arthur W. 2004. *Biased Embryos and Evolution*. Cambridge, UK: Cambridge Univ. Press. 233 pp.
- Atchley WR, Hall BK. 1991. A model for development and evolution of complex morphological structures. *Biol. Rev.* 66:101–57
- Badyaev AV, Foresman KR. 2000. Extreme environmental change and evolution: stress-induced morphological variation is strongly concordant with patterns of evolutionary divergence in shrew mandibles. *Proc. R. Soc. Ser. B* 267:371–77
- Badyaev AV, Foresman KR. 2004. Evolution of morphological integration. I. Functional units channel stress-induced variation in shrew mandibles. *Am. Nat.* 163:868–79
- Badyaev AV, Foresman KR, Young RL. 2005. Evolution of morphological integration: Developmental accommodation of stress-induced variation. *Am. Nat.* 166:382–95
- Bastir M, Rosas A. 2005. Hierarchical nature of morphological integration and modularity in the human posterior face. *Am. J. Phys. Anthropol.* 128:26–34
- Bastir M, Rosas A, Sheets HD. 2005. The morphological integration of the hominoid skull: A partial least squares and PC analysis with implications for European middle pleistocene mandibular variation. In *Modern Morphometrics in Physical Anthropology*, ed. DE Slice, pp. 265–84. New York: Kluwer Acad.
- Beldade P, Koops K, Brakefield PM. 2002. Developmental constraints versus flexibility in morphological evolution. *Nature* 416:844–47
- Bookstein FL, Gunz P, Mitteroecker P, Prossinger H, Schaefer K, Seidler H. 2003. Cranial integration in *Homo*: singular warps analysis of the midsagittal plane in ontogeny and evolution. *J. Hum. Evol.* 44:167–87
- Bookstein FL, Sampson PD, Streissguth AP, Barr HM. 1990. Measuring “dose” and “response” with multivariate data using partial least squares techniques. *Commun. Stat.—Theory Methods* 19:765–804
- Breuker CJ, Debat V, Klingenberg CP. 2006a. Functional evo-devo. *Trends Ecol. Evol.* 21:488–92
- Breuker CJ, Patterson JS, Klingenberg CP. 2006b. A single basis for developmental buffering of *Drosophila* wing shape. *PLoS ONE* 1:e7
- Brito JM, Teillet M-A, Le Douarin NM. 2006. An early role for Sonic hedgehog from foregut endoderm in jaw development: Ensuring neural crest cell survival. *Proc. Natl. Acad. Sci. USA* 103:11607–12
- Callebaut W, Rasskin-Gutman D, eds. 2005. *Modularity: Understanding the Development and Evolution of Natural Complex Systems*. Cambridge, MA: MIT Press. 455 pp.
- Camara MD, Pigliucci M. 1999. Mutational contributions to genetic variance-covariance matrices: An experimental approach using induced mutations in *Arabidopsis thaliana*. *Evolution* 53:1692–703
- Cheverud JM. 1982. Relationships among ontogenetic, static, and evolutionary allometry. *Am. J. Phys. Anthropol.* 59:139–49
- Cheverud JM. 1984. Quantitative genetics and developmental constraints on evolution by selection. *J. Theor. Biol.* 110:155–71
- Cheverud JM. 1996. Developmental integration and the evolution of pleiotropy. *Am. Zool.* 36:44–50
- Cheverud JM, Routman EJ, Irschick DJ. 1997. Pleiotropic effects of individual gene loci on mandibular morphology. *Evolution* 51:2006–16
- Cheverud JM, Rutledge JJ, Atchley WR. 1983. Quantitative genetics of development: genetic correlations among age-specific trait values and the evolution of ontogeny. *Evolution* 37:895–905
- Cock AG. 1966. Genetical aspects of metrical growth and form in animals. *Q. Rev. Biol.* 41:131–90
- Couly G, Creuzet S, Bennaceur S, Vincent C, Le Douarin NM. 2002. Interactions between Hox-negative cephalic neural crest cells and the foregut endoderm in patterning the facial skeleton in the vertebrate head. *Development* 129:1061–73
- Davidson EH. 1993. Later embryogenesis: regulatory circuitry in morphogenetic fields. *Development* 118:665–90
- Debat V, Alibert P, David P, Paradis E, Auffray J-C. 2000. Independence between developmental stability and canalization in the skull of the house mouse. *Proc. R. Soc. London Ser. B* 267:423–30
- Debat V, Milton CC, Rutherford S, Klingenberg CP, Hoffmann AA. 2006. Hsp90 and the quantitative variation of wing shape in *Drosophila melanogaster*. *Evolution* 60:2529–38

- Dworkin I. 2005. A study of canalization and developmental stability in the sternopleural bristle system of *Drosophila melanogaster*. *Evolution* 59:1500–9
- Enlow DH, Hans MG. 1996. *Essentials of Facial Growth*. Philadelphia: W. B. Saunders. 303 pp.
- Estes S, Ajie BC, Lynch M, Phillips PC. 2005. Spontaneous mutational correlations for life-history, morphological and behavioral characters in *Caenorhabditis elegans*. *Genetics* 170:645–53
- Felsenstein J. 1988. Phylogenies and quantitative characters. *Annu. Rev. Ecol. Syst.* 19:455–71
- Garud R, Kumaraswamy A, Langlois RN, eds. 2002. *Managing in the Modular Age: Architectures, Networks, and Organizations*. Oxford: Blackwell. 411 pp.
- Gilbert SF, Opitz JM, Raff RA. 1996. Resynthesizing evolutionary and developmental biology. *Dev. Biol.* 173:357–72
- Girvan M, Newman MEJ. 2002. Community structure in social and biological networks. *Proc. Natl. Acad. Sci. USA* 99:7821–26
- Goswami A. 2006a. Cranial modularity shifts during mammalian evolution. *Am. Nat.* 168:270–80
- Goswami A. 2006b. Morphological integration in the carnivoran skull. *Evolution* 60:169–83
- Goswami A. 2007. Phylogeny, diet and cranial integration in australodelphian marsupials. *PLoS ONE* 2:e995
- Gould SJ. 1966. Allometry and size in ontogeny and phylogeny. *Biol. Rev.* 41:587–640
- Grüneberg H. 1938. An analysis of the “pleiotropic” effects of a new lethal mutation in the rat (*Mus norvegicus*). *Proc. R. Soc. London Ser. B* 125:123–44
- Guimerà R, Nunes Amaral LA. 2005. Functional cartography of complex metabolic networks. *Nature* 433:895–900
- Hadorn E. 1945. Zur Pleiotropie der Genwirkung. *Arch. Julius Klaus-Stiftung Vererb.* 20(Suppl.):82–95
- Hall BK. 1999. *Evolutionary Developmental Biology*. Dordrecht, The Netherlands: Kluwer. 491 pp.
- Hallgrímsson B, Lieberman DE, Liu W, Ford-Hutchinson AF, Jirik FR. 2007. Epigenetic interactions and the structure of phenotypic variation in the cranium. *Evol. Dev.* 9:76–91
- Hallgrímsson B, Willmore K, Dorval C, Cooper DML. 2004. Craniofacial variability and modularity in macaques and mice. *J. Exp. Zool.* 302B:207–25
- Hansen TF, Armbruster WS, Carlson ML, Pélabon C. 2003. Evolvability and genetic constraint in *Dalechampia* blossoms: Genetic correlations and conditional evolvability. *J. Exp. Zool.* 296B:23–39
- Hansen TF, Houle D. 2004. Evolvability, stabilizing selection, and the problem of stasis. See Pigliucci & Preston 2004, pp. 130–50
- He X, Zhang J. 2006. Toward a molecular understanding of pleiotropy. *Genetics* 173:1885–91
- Herring SW. 1993. Formation of the vertebrate face: epigenetic and functional influences. *Am. Zool.* 33:472–83
- Hodgkin J. 1998. Seven types of pleiotropy. *Int. J. Dev. Biol.* 42:501–5
- Huxley JS. 1932. *Problems of Relative Growth*. Baltimore, MD: Johns Hopkins Univ. Press
- Jones AG, Arnold SJ, Bürger R. 2007. The mutation matrix and the evolution of evolvability. *Evolution* 61:727–45
- Juenger T, Pérez-Pérez JM, Bernal S, Micol JL. 2005. Quantitative trait loci mapping of floral and leaf morphology traits in *Arabidopsis thaliana*: evidence for modular genetic architecture. *Evol. Dev.* 7:259–71
- Kell DB. 2002. Genotype-phenotype mapping: genes as computer programs. *Trends Genet.* 18:555–59
- Kirschner M, Gerhart J. 1998. Evolvability. *Proc. Natl. Acad. Sci. USA* 95:8420–27
- Klingenberg CP. 1996. Multivariate allometry. In *Advances in Morphometrics*, ed. LF Marcus, M Corti, A Loy, GJP Naylor, DE Slice, pp. 23–49. New York: Plenum
- Klingenberg CP. 2003a. Developmental instability as a research tool: using patterns of fluctuating asymmetry to infer the developmental origins of morphological integration. In *Developmental Instability: Causes and Consequences*, ed. M Polak, pp. 427–42. New York: Oxford Univ. Press
- Klingenberg CP. 2003b. A developmental perspective on developmental instability: theory, models and mechanisms. In *Developmental Instability: Causes and Consequences*, ed. M Polak, pp. 14–34. New York: Oxford Univ. Press
- Klingenberg CP. 2004a. Dominance, nonlinear developmental mapping and developmental stability. In *The Biology of Genetic Dominance*, ed. RA Veitia, pp. 37–51. Austin, TX: Landes Bioscience
- Klingenberg CP. 2004b. Integration, modules and development: molecules to morphology to evolution. See Pigliucci & Preston 2004, pp. 213–30

- Klingenberg CP. 2005. Developmental constraints, modules and evolvability. In *Variation: A Central Concept in Biology*, ed. B Hallgrímsson, BK Hall, pp. 219–47. Burlington, MA: Elsevier
- Klingenberg CP, Badyaev AV, Sowry SM, Beckwith NJ. 2001. Inferring developmental modularity from morphological integration: analysis of individual variation and asymmetry in bumblebee wings. *Am. Nat.* 157:11–23
- Klingenberg CP, Leamy LJ. 2001. Quantitative genetics of geometric shape in the mouse mandible. *Evolution* 55:2342–52
- Klingenberg CP, Leamy LJ, Cheverud JM. 2004. Integration and modularity of quantitative trait locus effects on geometric shape in the mouse mandible. *Genetics* 166:1909–21
- Klingenberg CP, McIntyre GS. 1998. Geometric morphometrics of developmental instability: analyzing patterns of fluctuating asymmetry with Procrustes methods. *Evolution* 52:1363–75
- Klingenberg CP, Mebus K, Auffray J-C. 2003. Developmental integration in a complex morphological structure: how distinct are the modules in the mouse mandible? *Evol. Dev.* 5:522–31
- Klingenberg CP, Zaklan SD. 2000. Morphological integration between developmental compartments in the *Drosophila* wing. *Evolution* 54:1273–85
- Klingenberg CP, Zimmermann M. 1992. Static, ontogenetic, and evolutionary allometry: a multivariate comparison in nine species of water striders. *Am. Nat.* 140:601–20
- Krause AE, Frank KA, Mason DM, Ulanowicz RE, Taylor WW. 2003. Compartments revealed in food-web structure. *Nature* 426:282–85
- Lande R. 1979. Quantitative genetic analysis of multivariate evolution, applied to brain:body size allometry. *Evolution* 33:402–16
- Leamy L. 1993. Morphological integration of fluctuating asymmetry in the mouse mandible. *Genetica* 89:139–53
- Leamy LJ, Routman EJ, Cheverud JM. 1999. Quantitative trait loci for early- and late-developing skull characters in mice: a test of the genetic independence model of morphological integration. *Am. Nat.* 153:201–14
- Mariani FV, Martin GR. 2003. Deciphering skeletal patterning: clues from the limb. *Nature* 423:319–25
- Mayr E. 1982. *The Growth of Biological Thought: Diversity, Evolution, and Inheritance*. Cambridge, MA: Harvard Univ. Press. 974 pp.
- Mezey JG, Cheverud JM, Wagner GP. 2000. Is the genotype-phenotype map modular? A statistical approach using mouse quantitative trait loci data. *Genetics* 156:305–11
- Mezey JG, Houle D. 2005. The dimensionality of genetic variation for wing shape in *Drosophila melanogaster*. *Evolution* 59:1027–38
- Milton CC, Huynh B, Batterham P, Rutherford SL, Hoffmann AA. 2003. Quantitative trait symmetry independent of Hsp90 buffering: distinct modes of genetic canalization and developmental stability. *Proc. Natl. Acad. Sci. USA* 100:13396–401
- Milton CC, Ulane CM, Rutherford S. 2006. Control of canalization and evolvability by Hsp90. *PLoS ONE* 1:e75
- Monteiro LR, Bonato V, dos Reis SF. 2005. Evolutionary integration and morphological diversification in complex morphological structures: Mandible shape divergence in spiny rats (Rodentia, Echimyidae). *Evol. Dev.* 7:429–39
- Nadeau JH, Burrage LC, Restivo J, Pao Y-H, Churchill GA, Hoit BD. 2003. Pleiotropy, homeostasis, and functional networks based on assays of cardiovascular traits in genetically randomized populations. *Genome Res.* 13:2082–91
- Olesen JM, Bascompte J, Dupont YL, Jordano P. 2007. The modularity of pollination networks. *Proc. Natl. Acad. Sci. USA* 104:19891–96
- Olson EC, Miller RL. 1958. *Morphological Integration*. Chicago: Univ. Chicago Press
- Pigliucci M, Preston K, eds. 2004. *Phenotypic Integration: Studying the Ecology and Evolution of Complex Phenotypes*. New York: Oxford Univ. Press
- Pyeritz RE. 1989. Pleiotropy revisited: molecular explanations of a classic concept. *Am. J. Med. Genet.* 34:124–34
- Radicchi F, Castellano C, Cecconi F, Loreto V, Parisi D. 2004. Defining and identifying communities in networks. *Proc. Natl. Acad. Sci. USA* 101:2658–63

- Ravasz E, Somera AL, Mongru DA, Oltvai ZN, Barabási A-L. 2002. Hierarchical organization of modularity in metabolic networks. *Science* 297:1551–55
- Riska B. 1986. Some models for development, growth, and morphometric correlation. *Evolution* 40:1303–11
- Rohlf FJ, Corti M. 2000. The use of two-block partial least-squares to study covariation in shape. *Syst. Biol.* 49:740–53
- Rosvall M, Bergstrom CT. 2007. An information-theoretic framework for resolving community structure in complex networks. *Proc. Natl. Acad. Sci. USA* 104:7327–31
- Rutherford SL. 2003. Between genotype and phenotype: protein chaperones and evolvability. *Nat. Rev. Genet.* 4:263–74
- Rutherford SL, Lindquist S. 1998. Hsp90 as a capacitor for morphological evolution. *Nature* 396:336–42
- Sales-Pardo M, Guimerà R, Moreira AA, Nunes Amaral LA. 2007. Extracting the hierarchical organization of complex systems. *Proc. Natl. Acad. Sci. USA* 104:15224–29
- Schlosser G, Wagner GP, eds. 2004. *Modularity in Development and Evolution*. Chicago: Univ. Chicago Press. 600 pp.
- Schluter D. 1996. Adaptive radiation along genetic lines of least resistance. *Evolution* 50:1766–74
- Somogyi R, Fuhrman S, Anderson G, Madill C, Greller LD, Chang B. 2004. Systematic exploration and mining of gene expression data provides evidence for higher-order, modular regulation. See Schlosser & Wagner 2004, pp. 203–21
- von Dassow G, Meir E. 2004. Exploring modularity with dynamical models of gene networks. See Schlosser & Wagner 2004, pp. 244–87
- Wagner GP. 1984. On the eigenvalue distribution of genetic and phenotypic dispersion matrices: evidence for a nonrandom organization of quantitative character variation. *J. Math. Biol.* 21:77–95
- Wagner GP. 1990. A comparative study of morphological integration in *Apis mellifera* (Insecta, Hymenoptera). *Z. Zool. Syst. Evol. Forsch.* 28:48–61
- Wagner GP. 1996. Homologues, natural kinds and the evolution of modularity. *Am. Zool.* 36:36–43
- Wagner GP, Altenberg L. 1996. Complex adaptations and the evolution of evolvability. *Evolution* 50:967–76
- Wagner GP, Chiu C-H, Hansen TF. 1999. Is Hsp90 a regulator of evolvability? *J. Exp. Zool.* 285:116–68
- Wagner GP, Pavlicev M, Cheverud JM. 2007. The road to modularity. *Nat. Rev. Genet.* 8:921–31
- Wainwright PC, Alfaro ME, Bolnick DI, Hulseley CD. 2005. Many-to-one mapping of form to function: A general principle in organismal design? *Integr. Comp. Biol.* 45:256–62
- Wang C-Y, Liu P-Y, Liao JK. 2007. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol. Med.* 14:37–44
- West-Eberhard MJ. 2003. *Developmental Plasticity and Evolution*. New York: Oxford Univ. Press. 794 pp.
- Wilkins AS. 2002. *The Evolution of Developmental Pathways*. Sunderland, MA: Sinauer Assoc. 603 pp.
- Willmore KE, Klingenberg CP, Hallgrímsson B. 2005. The relationship between fluctuating asymmetry and environmental variance in rhesus macaque skulls. *Evolution* 59:898–909
- Willmore KE, Leamy L, Hallgrímsson B. 2006. Effects of developmental and functional interactions on mouse cranial variability through late ontogeny. *Evol. Dev.* 8:550–67
- Workman MS, Leamy LJ, Routman EJ, Cheverud JM. 2002. Analysis of quantitative trait locus effects on the size and shape of mandibular molars in mice. *Genetics* 160:1573–86
- Wroe S, Milne N. 2007. Convergence and remarkably consistent constraint in the evolution of carnivore skull shape. *Evolution* 61:1251–60
- Young NM. 2006. Function, ontogeny and canalization of shape variance in the primate scapula. *J. Anat.* 209:623–36
- Young NM, Hallgrímsson B. 2005. Serial homology and the evolution of mammalian limb covariation structure. *Evolution* 59:2691–704
- Young RL, Haselkorn TS, Badyaev AV. 2007. Functional equivalence of morphologies enables morphological and ecological diversity. *Evolution* 61:2480–92



Contents

Top Predators as Conservation Tools: Ecological Rationale,
Assumptions, and Efficacy
*Fabrizio Sergio, Tim Caro, Danielle Brown, Barbara Clucas, Jennifer Hunter,
James Ketchum, Katherine McHugh, and Fernando Hiraldo* 1

Revisiting the Impact of Inversions in Evolution: From Population
Genetic Markers to Drivers of Adaptive Shifts and Speciation?
Ary A. Hoffmann and Loren H. Rieseberg 21

Radial Symmetry, the Anterior/Posterior Axis, and Echinoderm
Hox Genes
Rich Mooi and Bruno David 43

The Great American Schism: Divergence of Marine Organisms After
the Rise of the Central American Isthmus
H.A. Lessios 63

The Ecological Performance of Protected Areas
*Kevin J. Gaston, Sarah F. Jackson, Lisette Cantú-Salazar,
and Gabriela Cruz-Piñón* 93

Morphological Integration and Developmental Modularity
Christian Peter Klingenberg 115

Herbivory from Individuals to Ecosystems
Oswald J. Schmitz 133

Stoichiometry and Nutrition of Plant Growth in Natural Communities
Göran I. Ågren 153

Plague Minnow or Mosquito Fish? A Review of the Biology
and Impacts of Introduced *Gambusia* Species
Graham H. Pyke 171

The Impact of Natural Selection on the Genome: Emerging Patterns
in *Drosophila* and *Arabidopsis*
Stephen I. Wright and Peter Andolfatto 193

Sanctions, Cooperation, and the Stability of Plant-Rhizosphere Mutualisms <i>E. Toby Kiers and R. Ford Denison</i>	215
Shade Tolerance, a Key Plant Feature of Complex Nature and Consequences <i>Fernando Valladares and Ülo Niinemets</i>	237
The Impacts of Fisheries on Marine Ecosystems and the Transition to Ecosystem-Based Management <i>Larry B. Crowder, Elliott L. Hazen, Naomi Avissar, Rhema Bjorkland, Catherine Latanich, and Matthew B. Ogburn</i>	259
The Performance of the Endangered Species Act <i>Mark W. Schwartz</i>	279
Phylogenetic Approaches to the Study of Extinction <i>Andy Purvis</i>	301
Adaptation to Marginal Habitats <i>Tadeusz J. Karwecki</i>	321
Conspecific Brood Parasitism in Birds: A Life-History Perspective <i>Bruce E. Lyon and John McA. Eadie</i>	343
Stratocladistics: Integrating Temporal Data and Character Data in Phylogenetic Inference <i>Daniel C. Fisher</i>	365
The Evolution of Animal Weapons <i>Douglas J. Emlen</i>	387
Unpacking β : Within-Host Dynamics and the Evolutionary Ecology of Pathogen Transmission <i>Michael F. Antolin</i>	415
Evolutionary Ecology of Figs and Their Associates: Recent Progress and Outstanding Puzzles <i>Edward Allen Herre, K. Charlotte Jandér, and Carlos Alberto Machado</i>	439
The Earliest Land Plants <i>Patricia G. Gensel</i>	459
Spatial Dynamics of Foodwebs <i>Priyanga Amarasekare</i>	479
Species Selection: Theory and Data <i>David Jablonski</i>	501

New Answers for Old Questions: The Evolutionary Quantitative Genetics of Wild Animal Populations <i>Loeske E.B. Kruuk, Jon Slate, and Alastair J. Wilson</i>	525
Wake Up and Smell the Roses: The Ecology and Evolution of Floral Scent <i>Robert A. Raguso</i>	549
Ever Since Owen: Changing Perspectives on the Early Evolution of Tetrapods <i>Michael I. Coates, Marcello Ruta, and Matt Friedman</i>	571
Pandora's Box Contained Bait: The Global Problem of Introduced Earthworms <i>Paul F. Hendrix, Mac A. Callabam, Jr., John M. Drake, Ching-Yu Huang, Sam W. James, Bruce A. Snyder, and Weixin Zhang</i>	593
Trait-Based Community Ecology of Phytoplankton <i>Elena Litchman and Christopher A. Klausmeier</i>	615
What Limits Trees in C ₄ Grasslands and Savannas? <i>William J. Bond</i>	641

Indexes

Cumulative Index of Contributing Authors, Volumes 35–39	661
Cumulative Index of Chapter Titles, Volumes 35–39	665

Errata

An online log of corrections to *Annual Review of Ecology, Evolution, and Systematics* articles may be found at <http://ecolsys.annualreviews.org/errata.shtml>