Modularity and Integration

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Glossary

Developmental module Performs a specific role in developmental processes and corresponds to a set of cells, genes, or tissues that are relatively independent with respect to pattern formation and differentiation, or an autonomous developmental signaling pathway.

Evolutionary modules Sets of phenotypic elements evolving in coordinated fashion, because the elements are inherited together or because they are jointly selected.

Functional module Sets of traits or features that interact to perform some discrete function or task.

Genetic architecture Refers to the pattern of genetic effects that underlie the variation for a given set of phenotypic characters and its variational properties. A description of genetic architecture may include statements about gene and allele number, the distribution of allelic and mutational effects, and patterns of pleiotropy, dominance, and epistasis.

Genetic modules Sets of traits that are modular due to pleiotropy or linkage disequilibrium.

Genotype–phenotype map Depicts relationship between genetic variation and phenotypic variation; that is, it specifies which locus or loci affects each trait or traits.

Internal stabilizing selection Stabilizing selection due to the interaction of the phenotype with other internal characteristics of an organism, and is related to the need for coadaptation of traits to one another rather than to the external environment.

Linkage disequilibrium The nonrandom association of alleles at different loci.

Morphological integration Refers to the cohesion or association among morphological traits that are related functionally and/or developmentally. Traits that are integrated tend to covary together, and so this results in higher correlation between these traits when compared to traits that are not integrated.

Pleiotropy A single locus affecting two or more phenotypic traits.

Quasi-independence (quasi-autonomy) A lower than average grade of connectedness, for example, the elements of modules are highly interconnected, while being less connected to other modules. This 'quasi independence' may allow one character to change without affecting others.

Quantitative Trait Loci (QTL) Refers to DNA loci that affect quantitative traits.

Variational modules Set of covarying traits that vary relatively independently of other sets of traits. The reason for this relative independence of different sets of traits, or modules, is that pleiotropic loci with effects on traits belonging to different modules are less frequent than those within modules. These modules are recognized by higher correlations between traits in the same module and lower correlations between traits of different modules.

What Is Modularity and Integration?

Biology is rapidly embracing the challenge of dealing with multidimensional hierarchical systems as a way of moving forward and addressing questions that range from the genetic basis of diseases, behavior, or morphology, the ecological structure of communities, or the evolution of any of these features. To face this challenge we need both theoretical developments and methods capable of dealing with such complexity. At the core of all this lies the concept of modularity. In Biology, modularity refers to the pattern and magnitude of association among elements in a system. This pattern emerges whenever a high connectivity between some elements in the system exists, forming modules, and at the same time these same elements are more loosely associated to other elements that compose other modules. Modularity depends on the ability of a system to organize semi-autonomous parts, or even discrete elements, into a coherent whole. Modularity can be studied at nearly every scale of biological organization; and it has been described in a variety of contexts and observed in many model systems, in a wide range of disciplines and specialties. These include proteins (Han *et al.*, 2004), genes (Litvin *et al.*, 2009), cells (Hartwell *et al.*, 1999; Wagner, 1996), organs (Schlosser and Wagner, 2004), and ecosystems (Montoya *et al.*, 2006).

Here, we address modularity in the context of morphological quantitative traits and discuss the influence of genetic, functional, and developmental factors at this level. In this context, different parts of organisms can behave as modules because they exhibit some degree of independence, and are internally organized, reflecting their developmental origins and functions, as we will see later (Cheverud, 1996; Klingenberg, 2004).

Most of our current understanding of character correlations and on the evolution of complex continuous traits is influenced by the concept of morphological integration (Olson and Miller, 1951, 1958). Olson and Miller (1951, 1958) coined the term morphological integration to describe high levels of phenotypic correlation within subsets of morphological traits. Today, these sets of integrated traits related functionally and/or developmentally are termed modules. In a remarkable work addressing morphological variation and correlation in plants, Raissa Berg (1960) described a similar concept known as 'correlation pleiades.' As with morphological integration, correlation pleiades are based on the presence of high levels of

 doi:10.1016/B978-0-12-800049-6.00044-5

correlation between some parts of an organism, and low association between these and other parts of the same organism.

From the above definitions, we can see that modularity and integration are interrelated concepts, as both of them deal with the interdependence between different structures based on developmental, genetic, and/or functional factors, and, moreover, are quantified by the degree of correlation or covariation among traits. In fact, they can be understood as two sides of the same coin. While the concept of morphological integration describes connections among parts of an organism, the concept of modularity stresses its relative independence or autonomy (Schlosser and Wagner, 2004; Wagner, 1996).

In biology, several types of modules have been recognized, including functional, developmental, genetic, evolutionary, and variational (Cheverud, 1996; Wagner *et al.*, 2007). A functional module is composed of characters or features that interact together on performing a task or function and are relatively independent in relation to other functional sets (Cheverud, 1996; Wagner *et al.*, 2007). Developmental modules correspond to set of cells, genes, or tissues that are relatively independent with respect to pattern formation and differentiation, or an autonomous regulatory control (Wagner *et al.*, 2007). Genetic integration occurs when sets of morphological elements are inherited together as a module, due to pleiotropy and/or linkage desequilibrium. These sets of morphological elements are more or less independently of other sets or modules (Cheverud, 1996). An evolutionary module is a set of morphological traits evolving in coordinated fashion, because the elements are inherited together or because they are jointly selected (Cheverud, 1996). Variational modularity is recognized by higher correlations between traits in the same module and lower correlations between traits of different modules, and can have different causes (Armbruster *et al.*, 2014; Grabowski *et al.*, 2011; Melo and Marroig, 2015; Young and Hallgrímsson, 2005).

The Causes of Modularity: Development and Function

A variational modularity is thought to be the outcome of functional and/or developmental relationships between traits (Berg, 1960; Cheverud, 1982; Olson and Miller, 1958; Porto *et al.*, 2009). These two forms of individual level integration are related because development can be viewed as a dynamic process, and functional integration in the adult is likely achieved through developmental integration (Cheverud, 1996). Moreover, the developmental process is the path by which genetic variation is translated into phenotypic variation (genotype–phenotype map *sensu*, Wagner and Altenberg, 1996). Consequently, the study of modularity is crucial to understand these developmental pathways.

Processes of shared function and development can act as an internal stabilizing selection force on the maintenance of the modular structure observed at the phenotypic level (Estes and Arnold, 2007; Porto *et al.*, 2013, 2009; Shirai and Marroig, 2010). This can be seen with a simple example: in almost all mammals the mandible and maxilla need to work together in order to function. Furthermore, these two bones share the same developmental origins. Thus, while a multitude of dietary habits exists, the shared internal development and function keep the two traits highly correlated in all mammals.

If we extend this example a bit further to four traits we can perhaps get a firmer grip on the origins of modularity in functional and developmental factors. Empirically, functional, and developmental integration can be measured by detecting the existence of groups of highly correlated traits. Under the hypothesis of modularity, one would expect that developmentally and functionally related traits would have a relatively higher correlation between them than the correlation among those without shared function or developmental origin/interaction (Cheverud, 1982). To illustrate this concept, we can look to **Figure 1** that presents four cranial traits measured in a bat skull and mandible. The first two traits, maxilla length and mandible length, are related to chewing function. Since both share the same function, it is expected that they present relatively higher correlation. In addition, these traits correspond to bones that share a common cellular origin in the neural crest, which reiterate the expectation of high correlation for both characters. Consider now the other two traits in **Figure 1**: frontal and parietal length. These two are not directly related with mastication but instead are primarily involved in brain protection. Moreover, these two bones share a common embryonic origin in the paraxial mesoderm cells. Accordingly, we would expect to find a high correlation between maxilla and mandible as well as a high correlation between parietal and frontal measurements. On the other hand, we would expect to find a considerably lower, or even absent, correlation between these two groups (**Figure 1**).

The Origin of Modularity and Integration from a Genetic Perspective

From a genetic perspective, pleiotropy and linkage disequilibrium are the two mechanisms behind modularity and integration (Falconer and Mackay, 1996). Linkage disequilibrium is the nonrandom association of alleles at different loci. In other words, it is the presence of statistical associations between alleles compared to what would be expected if alleles were independently, randomly sampled from the population. This process leads to nonrandom co-occurrence of different combinations of trait values associated with different alleles. The relative contribution of linkage disequilibrium for modularity patterns is debatable, since recombination might break these associations. However, linkage disequilibrium can be actively maintained through natural selection (Barton and Turelli, 1989; Templeton, 2006). Pleiotropy, on the other hand, has a more established role on the emergence of modularity (Wright, 1980). Pleiotropy is a common property of many genes, and occurs when a gene affects the phenotypes of two or more traits (Cheverud, 2004; Hodgkin, 1998; Wagner and Zhang, 2011). Traditionally, it was believed that widespread pleiotropy could be prejudicial to the adaptation process. The rationale behind this is that, the more complex an organism is (in terms of a higher dimensional trait space), the less likely a pleiotropic mutation will be advantageous. This is because the larger the number of traits affected by a particular pleiotropic loci, the more unlikely it is for the changes caused by a mutation to be advantageous in all

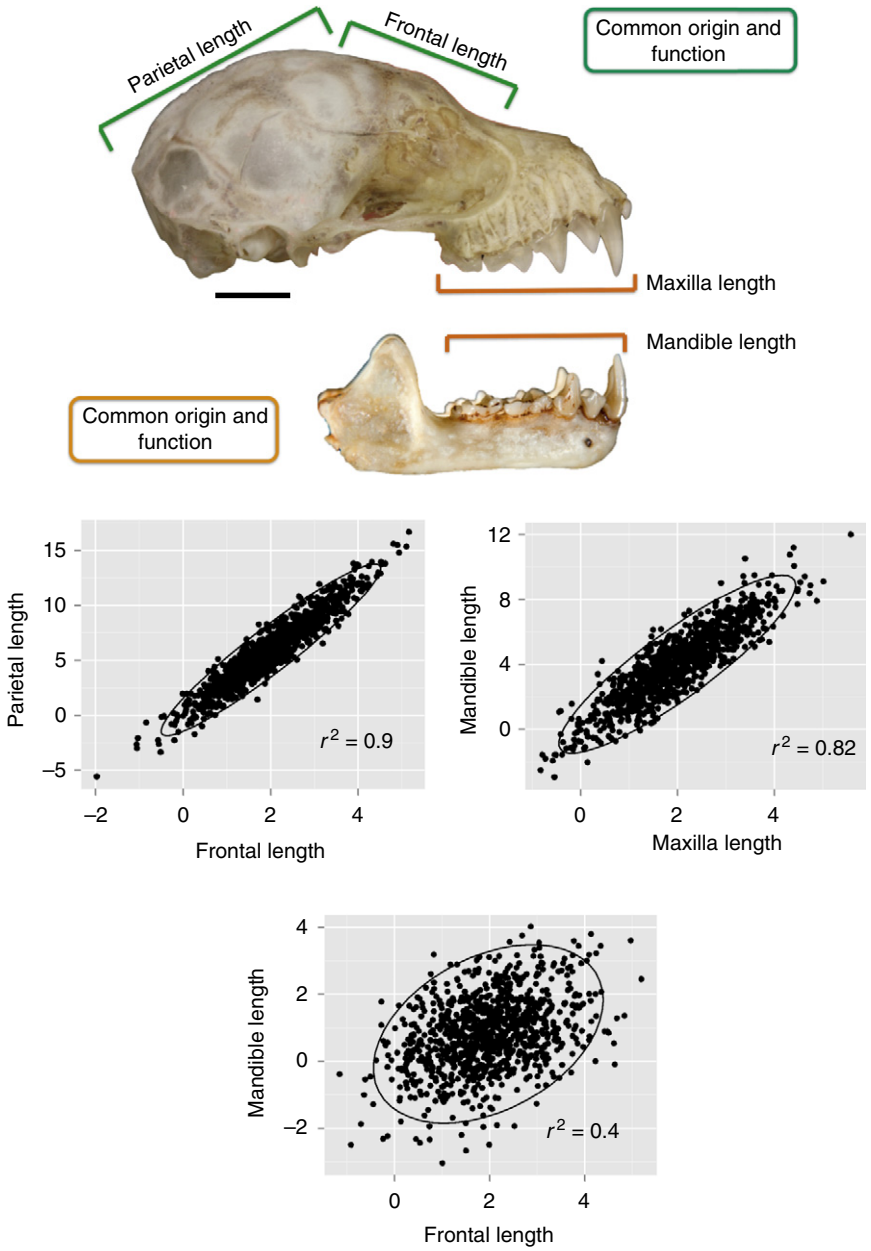

Figure 1 Hypothetical example of four cranial traits in a bat skull and mandible and their correlations. Note that developmentally and functionally related traits exhibited higher correlation. Green: parietal and frontal bones share a common embryonic origin in the paraxial mesoderm cells and are related in protect central nervous system. Orange: maxilla and mandible are related to chewing function and share a common cellular origin in the neural crest. Scale bar (black line) = 5 mm. Picture credits: *Daniela Rossoni.*

traits simultaneously; an issue known as 'the cost of complexity' (Fisher, 1930; Orr, 2000). From this point of view, the more complex an organism is, the more difficult it would be to respond to selection. Wagner (1996) was the first one to propose a model that could circumvent the complexity cost problem. He suggested that pleiotropic effects must be somewhat limited and related to function, creating modules of genetic effects that allow relative independence, in the same vein as the classical Olson and Miller modular organization. Indeed, there is considerable empirical evidence pointing to the emergence of modularity due to pleiotropic gene effects restricted to a set of functionally or developmentally related traits, a pattern known as modular pleiotropy (Cheverud, 2004, 1996; Cheverud *et al.*, 1997; Ehrich *et al.*, 2003; Leamy *et al.*, 1999; Mezey *et al.*, 2000; Pavlicev *et al.*, 2008; Vaughn *et al.*, 1999; Wagner *et al.*, 2007).

Pleiotropy can have both a constraining and a facilitating effect in the evolutionary process. It can be a constraint in the sense that the more traits a gene affects the more unlikely a mutation will be advantageous (Fisher, 1930; Orr, 2000). On the other hand, pleiotropy might be a facilitator of evolution, since populations whose individuals are organized in

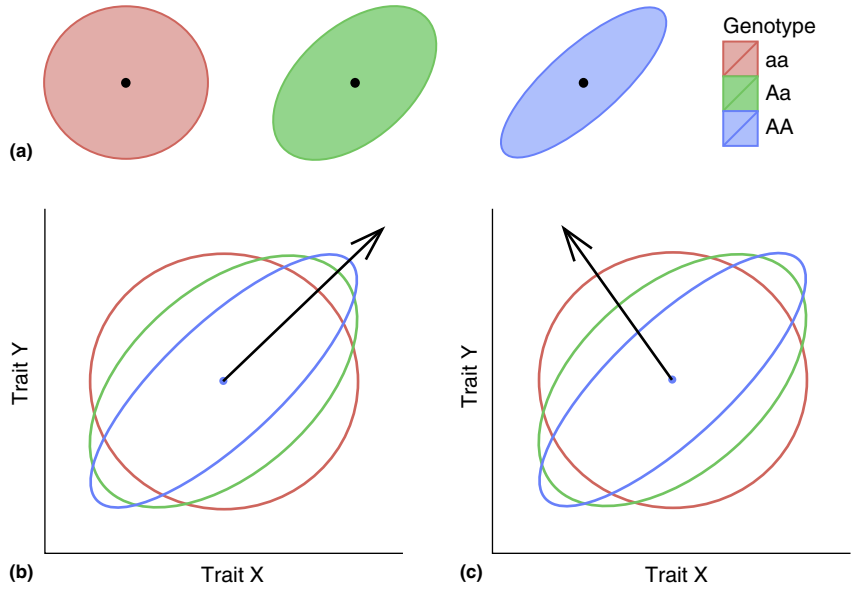

Figure 2 (a) Schematic representation of correlation between two traits for different genotypes. Genotype AA has a high correlation of 0.8 between trait X and Y; genotype *Aa* has a correlation of 0.5 and genotype *aa* has a correlation of zero between traits. The black dot in the center of each ellipse is the mean values for trait X and Y. (b and c) represent the three genotypes plotted together. In (b) we have selection (black arrow) favoring bigger individuals for both traits X and Y. In (c) we have selection favoring individuals smaller for trait X but bigger for trait Y. We might expect population b evolve in such a way to increase the positive covariation between traits and, therefore, we expect an increase of allele *A* frequency. We expect population c to evolve toward a decrease in the covariation between traits and, therefore, a decrease in frequency for allele *A* and increase for allele *a*. Adapted from Wagner, G.P., Pavlicev, M., Cheverud, J.M., 2007. The road to modularity. Nature Reviews Genetics 8 (12), 921–931.

developmentally and/or functionally restricted modules can respond to selection on a set of traits without perturbing the other sets (Griswold, 2006; Pavlicev *et al.*, 2011).

Also, pleiotropy itself can evolve, and for this there must be genetic variation in pleiotropic relations (Pavlicev *et al.*, 2011). This means that the relationship between traits can be genetically variable; and a possible source for this variation is a phenomenon called differential epistasis (Cheverud, 2004; Pavlicev *et al.*, 2011, 2008). Several studies have reported different loci presenting differential epistasis that are responsible for differences in the relationship between continuous traits. These loci are termed 'relationship Quantitative Trait Loci' or rQTL and refer to genomic regions that show variation in epistatic effects, altering pleiotropic relations and the correlation between phenotypic traits (Cheverud, 2004; Pavlicev *et al.*, 2011, 2008; Wolf *et al.*, 2005). To better understand this, let's imagine a rQTL loci with two alleles *A* and *a* (**Figure 2(a)**). Depending on the genotype, the covariation between traits X and Y is different, with a high positive correlation if the genotype is *AA*, a moderate positive correlation for genotype *Aa*, and no correlation between them for genotype *aa* (**Figure 2(a)**). As follows, we can say that the covariance between two traits depends on the genotype of this rQTL locus, although the genotype does not affect the traits means. If directional selection is favoring an increase for both traits (**Figure 2(b)**), we would expect allele A to increase its frequency in the population. This would happen because individuals with higher correlation between traits have higher values for both traits X and Y and would, therefore, be favored. On the other hand, if selection is acting for an increase of trait Y but a decrease of trait X (**Figure 2(c)**) we expect an increase of allele *a* frequency in the population. Again, the mechanistic reason for that would be that individuals *Aa* and *AA* have positive correlation between traits, which is been selected against in this case. It is easy to imagine how modular pleiotropy might appear in a population with this differential epistasis model: as long there are genetic variation in pleiotropy, natural selection can act leading to tighter or looser connections between traits (Pavlicev *et al.*, 2010).

Empirical Studies Investigating Modular Patterns

There is a vast literature on recognizing and characterizing modular patterns, especially concerning the mammalian skull. Thus, we will use the skull as a case study in order to exemplify the points raised earlier in this article. One of the forms of recognizing modules is by comparing correlation matrices from empirical data, and theoretical matrices based on hypotheses of functional/developmental relationships among characters. These theoretical hypotheses are strongly anchored on state-of-the-art literature about mammalian skull development (Cheverud, 1996, 1995; Moore, 1981; Smith, 1996, 1997, 2001). This methodology permits recognizing several different modules in different taxa, studied on a broad (orders and families), as well as on a more limited (as genus), phylogenetic framework (Ackermann and Cheverud, 2004; Cheverud, 1982; Marroig *et al.*, 2004; Marroig and Cheverud, 2001; Porto *et al.*, 2009, 2013; Shirai and Marroig, 2010).

From a developmental perspective, metatherian mammals (marsupials) present a similar modular pattern. Porto *et al.* (2009), analyzing five different orders of metatherians, reported a strong integration among facial traits, especially oral and nasal subregions. In contrast, the other 10 orders of eutherians mammals also evaluated by these authors exhibited a more variable modular pattern, with the vast majority of orders displaying a significant oral integration, but also with a broad contrast between neural and facial integration. These contrasting results between two mammals' infraclasses may reflect their developmental history, as metatherians present an early development of the facial traits because newborn survival depends directly on its ability to suckle (Smith, 1996). Differently, eutherians have more variation in neonatal states (having both highly altricial and precocial neonates) and a longer intrauterine growth (Smith, 2001, 1997). All these results indicate that shared development and function structures the current diversity of mammalian patterns of modularity/integration as expected by Olson and Miller (1958) hypothesis.

Another approach to the study of modularity is mapping QTLs in genomes. Along this line, one of the first direct evidences of modular genetic architecture organization came from the study of QTLs affecting different regions in the mouse mandible. Cheverud *et al.* (1997) used crossings between two inbreed lines of mice with very different sizes and a set of known markers to map genomic regions that affected linear distances measured on the mouse mandible. Using these experiments, they were able to show that most pleiotropic effects were restricted to one of the two regions in the mandible, the alveolar region and the ascending ramus, each related to different functions. The teeth are inserted at the alveolar region, while the ascending ramus is home to most muscle insertions. While both regions are related to mastication, the genetic effects are somewhat independent, with only 23% of the observed QTLs affecting both regions at the same time.

More recently, working with the same mouse strains as Cheverud, Kenney-Hunt *et al.* (2008) measured the number of shared QTLs between a series of skeletal traits. They expand the scope to include 70 traits, both in the skull and post-skull, painting a remarkable picture of the pleiotropic structure controlling skeletal development in mice. A total of 798 QTLs were identified, with many of the QTLs affecting more than one trait, indicating frequent pleiotropy. The authors used the information on pleiotropy to create a genetic effects adjacency matrix between traits, where traits that shared more pleiotropic QTLs were more related. This adjacency matrix was then compared to the correlation matrix between traits, and this showed a relatively high and significant correlation. These results suggested that phenotypic correlations are in part determined by shared pleiotropic effects.

On a larger scale, Wang *et al.* (2010) used a large dataset of yeast, nematode, and mouse mutants to show that the gene-trait relationship is highly modular, with most genes having small localized effects, and only a few genes having widespread pleiotropic effects and large effect sizes. This leads to an offset of Orr's cost of complexity, and allows for intermediate levels of complexity to exist via modularity.

Evolutionary Implications and Some Caveats

Studying the modularity, or the morphological integration of organisms, is fundamental to understand the evolution of complex features, as the modular structure influences multivariate evolution. The relationship between the inherited patterns of modular covariation and directional selection may, for example, restrict or facilitate certain evolutionary paths for a population. One way to appreciate the effects of genetic covariance upon the magnitude and direction of evolution is portrayed in **Figure 3** (adapted from Arnold *et al.*, 2001; Marroig and Cheverud, 2010). In this hypothetical adaptive landscape, three populations (a, b, and c) differ in their current position in relation to the adaptive peak. All three populations share the same basic genetic covariance pattern. Selection will push all three populations to the nearest adaptive peak, but the orientation of the selection gradient will differ due to their differences in current position on the landscape. While selection in all three populations specifies the shortest linear path to the peak, the realized evolutionary trajectory (Δz) from generation to generation may be quite different. In fact, if the two axes of major genetic variance are not aligned (population c) with the direction of selection, the evolutionary response to selection will be curvilinear (**Figure 3**, right panel). Furthermore, this curvilinear trajectory would be biased by the line of least resistance (defined as the linear combination having maximum genetic variance within a population, see (Schluter, 1996) embodied in the G-matrix. Because in this simple example (with only two dimensions) the first line of least resistance holds almost twice as much variation as the second one, the initial response in population c would be strongly biased in the direction of the largest genetic variance. It is also important to note how the line of least resistance influences not only the direction but also the magnitude of the evolutionary response along the path of selection. This point is made clear when comparing populations a and b. The magnitude of the response in population a is much larger than in population b. This reflects the fact that in population a, the first line of least resistance is aligned with the selected dimension; while in population b, the second line of least resistance is the one aligned with the direction of selection (β). The difference in response magnitude between a and b due to the variance differences even overcomes differences in strength of selection due to the fact that the path between a and the peak has a shallower slope than the path between b and the peak that is steeper and therefore reflects stronger selection. This example clearly shows that correlation among traits would bias the direction, influence the magnitude and pace of evolution on a microevolutionary (few generations) scale. Whether or not these modularity/integration patterns affect at macroevolutionary scales (species groups, generas, families, and so on) is an open question, but most biologists agree that such influence should decrease with time.

Finally, it is important to keep in mind that when looking at modularity/integration patterns at a given age (adults are by far the most commonly studied) we should interpret patterns as a product of a continuous development. Thus, the covariance observed in a population might not be a simple result of separate or discrete developmental factors. In fact, the development process influencing the covariance between characters

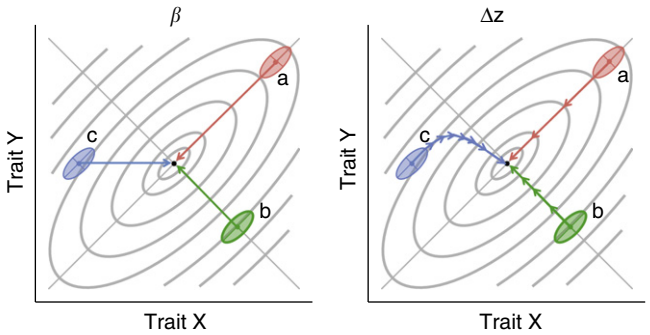

Figure 3 A hypothetical adaptive landscape for two traits (X and Y) with the black dot marking the adaptive optima (peak), and gray ellipses indicating isoclines of subsequent smaller fitness. Three populations (a, b, and c) are shown with their corresponding patterns of variance and covariance for both traits. The points inside each ellipse represent the mean value for the traits in that population. Left panel shows the direction of selection (β), and right panel the evolutionary trajectory (Δz). As we can see at the left panel, selection (β) is acting linearly in the three populations attracting them to the adaptive peak. Because each population is at a specific place in the adaptive landscape, the response to selection will be different in each population (right panel). Population a, which has its major axis of variance (represented by the longest axis of the ellipse) aligned with the adaptive landscape, will have a linear and fast response to selection. In few generations (represented by the number of arrows in the graph) it will reach the adaptive peak. Population b has its second axis of variance aligned with the adaptive landscape. Therefore, the response to selection will also be fast and linear, although not as fast as in population a. On the other hand, population c, which axis of variation is not aligned with the adaptive landscape, will take more generations to reach the adaptive peak and the trajectory will be deflected by the pattern of covariance. Adapted from Arnold, S.J., Pfrender, M.E., Jones, A.G., 2001. The adaptive landscape as a conceptual bridge between micro- and macroevolution. Genetica 112–113, 9–32; Marroig, G., Cheverud, J.M., 2010. Size as a line of least resistance II: Direct selection on size or correlated response due to constraints? Evolution 64 (5), 1470–1488.

observed at the population level is variable over time and space during ontogeny and, hence, later factors can overlap and obscure the signal of earlier factors affecting the covariance structure. The combined effect of these developmental processes suggests viewing the covariance as a palimpsest (Hallgrímsson *et al.*, 2009) where the underlying determinants of integration and modularity cannot be easily decipherable from the covariance or correlation data. Furthermore, distinct developmental factors per se are most likely not independent but instead might present various degrees of correlation among them in a hierarchical way, and thus one should not expect that modularity patterns in a population of adult organisms would be a simple amalgamate or sum of individual components parts. Thus, modules still need to be integrated in larger hierarchical functional complex structures (like the mammalian skull) and the process of growth during development is one, if not the most important, agent of such integration (Porto *et al.*, 2013). Yet, the study of variational modularity patterns can give us clues of these underlying developmental factors, since it is informative for many aspects of its underlying genetics and is critical for our comprehension of organismal evolution.

See also: Modularity and Integration in Evo-Devo. Multivariate Quantitative Genetics. Quantitative Trait Variation, Molecular Basis of. Systems in Evolutionary Systems Biology

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