



## Review

# Untangling the relationship between developmental and evolutionary integration

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## ARTICLE INFO

## Keywords:

Geometric Morphometrics

Ontogeny

Macroevolution

Modularity

## ABSTRACT

Patterns of integration and modularity among organismal traits are prevalent across the tree of life, and at multiple scales of biological organization. Over the past several decades, researchers have studied these patterns at the developmental, and evolutionary levels. While their work has identified the potential drivers of these patterns at different scales, there appears to be a lack of consensus on the relationship between developmental and evolutionary integration. Here, we review and summarize key studies and build a framework to describe the conceptual relationship between these patterns across organismal scales and illustrate how, and why some of these studies may have yielded seemingly conflicting outcomes. We find that among studies that analyze patterns of integration and modularity using morphological data, the lack of consensus may stem in part from the difficulty of fully disentangling the developmental and functional causes of integration. Nonetheless, in some empirical systems, patterns of evolutionary modularity have been found to coincide with expectations based on developmental processes, suggesting that in some circumstances, developmental modularity may translate to evolutionary modularity. We also advance an extension to Hallgrímsson et al.'s palimpsest model to describe how patterns of trait modularity may shift across different evolutionary scales. Finally, we also propose some directions for future research which will hopefully be useful for investigators interested in these issues.

## 1. Introduction

From bacteria to blue whales, biological complexity is a pervasive and captivating feature across the tree of life. Multicellular organisms are characterized by levels of biological organization consisting of organ systems, organs, tissues, cells, organelles, molecules, and atoms, each complete with functional specializations specific to a particular layer of organization. Interestingly, this amount of biological complexity was absent in life's earliest forms four billion years ago. Instead, studies have shown that biological complexity has generally increased over evolutionary time as organisms gradually evolved multicellularity and, eventually, specialized cell and organ types [49]. Biological complexity also increases over developmental timescales (to a point), as embryos develop into functionally and morphologically differentiated adults [24].

Evolutionary and developmental increases in complexity are thought to require significant degrees of modularity among traits. Such that there are few genetic pleiotropic effects (multiple traits under the influence of a single gene) among traits with differing functions, with most

pleiotropic effects confined to traits within a single functional or morphological complex [6,43,63,68,69]. From a morphological standpoint, this modularity of the genotype is also manifested in the phenotype: organismal traits are subdivided into complexes that exhibit higher degrees of integration within themselves and comparatively lower degrees of integration with other trait complexes [1,2,22,37,46,81]. Thus, modularity exists as a specific case of trait integration that is partitioned across developmental or functional blocks. Modularity is thought to be a prerequisite towards increasing complexity because it (1) allows for tissue and organ specification during development and (2) allows traits to evolve semi-autonomously. These two outcomes make it so that modular systems can respond to selective stimuli in ways that are quasi-independent of other nearby trait complexes. If trait modularity is maintained at macroevolutionary timescales within a lineage, it can result in mosaic evolution, where different functionally-associated traits within an organism may evolve at different rates [13,18].

Much has been said about the mechanisms driving patterns of developmental and evolutionary integration and modularity and the relationship between the two scales. Our review on this topic will

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<https://doi.org/10.1016/j.semcdb.2022.05.026>

Received 1 October 2021; Received in revised form 29 April 2022; Accepted 25 May 2022

Available online 2 June 2022

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attempt to cover a wide range of literature from different systems. However, in this review, we will mostly focus on vertebrate systems and morphological analyses in general, with particular emphasis on those that use a geometric morphometrics toolkit. More specifically, we will cover the drivers of integration and modularity at the developmental scale and at the evolutionary scale, respectively. We will also briefly discuss “functional integration” and how it relates to developmental and evolutionary integration and modularity. Later, we will summarize what is known about the relationship between patterns of evolutionary and developmental integration and modularity. We will conclude our review by discussing how developmental hypotheses of modularity can be evaluated at the evolutionary scale.

## 2. Development is a mostly integrated process

Organisms begin as aggregated cells which quickly gain specialized, emergent functions once differentiated into distinct germ layers. Whole organismal phenotype and function arise from this increasing complexity, brought about from the inclusion of more cell types, more interactions among different cell types, and alternative arrangements of these cell types in aggregate. The close interactions among these tissues, organs, and structures - enforced either by their proximity or a common orchestrating influence - defines developmental integration [8,37].

At the level of the organism, and during the process of development, patterns of integration and modularity manifest in unique and important ways. Generally, development has been described as an integrated process [8,78–80]. Development (changes in shape) and associated increases in size (growth) are considered to be global processes across an organism that have a strong integrating effect on patterns of trait covariation [38]. In mice and rats, for example, the development of the skull and limbs were found to be highly integrated, such that changes in size and function best explained patterns of covariation [78–80,82]. In neotropical electric fishes (*Gymnotiformes*), skull development is highly integrated between the face and braincase regions across a broad sampling of distantly related species [15]. In crickets and bees, high levels of developmental integration between wing modules have also been recovered [39,40]. Allometric scaling during development can also have a strong integrating effect on associated traits, by coordinating size and shape changes across the body. Likewise, integration studies that have corrected for allometric scaling have reported reduced levels of integration in their datasets [15,41]. Patterns of developmental integration have also been found to manifest at the “phylotypic” stage - the period during which the morphology of the embryo most closely resembles that of other members of its phylum [62], predicted that molecular signaling pathways would be acting synergistically among organ modules during this sensitive period. Therefore, as the theory goes, any perturbations to these interacting networks would disrupt burgeoning organ systems at their most vulnerable juncture (the ‘fragility’ hypothesis) and thus be strongly selected against [20,32]. Conversely, at both earlier (e.g., blastula, gastrula) and later (post organogenesis) stages, cellular- and tissue-level networks would be working independently as semi-autonomous entities (cells) or modules (tissues). Mutations that affect one system would then be less likely to cascade to other systems and thus less likely to produce a catastrophic outcome for the developing embryo. Evidence in support of the conserved-nature of mid-embryonic development is the high-level activity of conserved *cis*-regulatory regions and the flanking regions that orchestrate organogenesis during the phylotypic stage [65]. However, while evidence for the hourglass model of phylotypic stages appears well-borne out by molecular studies, there has been little support by detailed morphological studies [56], nor is the underlying mechanism for this pattern well-understood [32]. Whether the conserved nature of the phylotypic stage is due to stabilizing selection on critical molecular machinery, or whether the stage itself buffers or enforces changes is largely unknown, but either would suggest a strong signal of developmental integration [32].

High levels of integration during ontogeny are perhaps unsurprising.

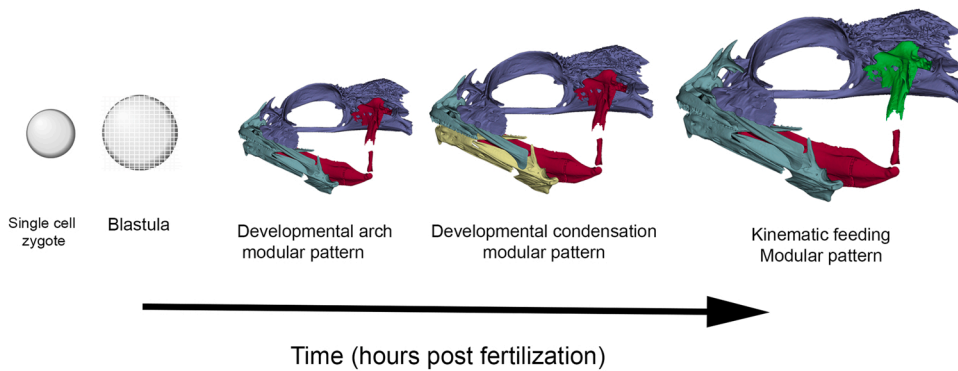
Still, in the face of this integration, there are conserved and well-defined pockets of modularity. In bilateral animals, *Hox* genes coordinate and modulate the expression of large networks of genes and, in doing so, play a fundamental role in specifying the positioning of various regions along the antero-posterior axis of the body [55,66]. These gene clusters are highly conserved across many animals and can even maintain their functions after being transplanted elsewhere [9,60,64,76]. Furthermore, the early stages of development often involve cell subdivision and differentiation without any actual growth, suggesting the presence of transient modular patterns [21].

“Integration has an ontogeny...” [79] (Fig. 1). The complex process of multicellular development involves sequential changes in gene expression, and large shifts in signaling domains. These changes and shifts in cell signaling and gene expression can create transient patterns of modularity that persist for brief periods of time that are then incompletely overwritten with new signaling regimes. This was described by Hallgrímsson et al. [26] as a palimpsest; an ancient document where previous text was still partially visible due to incomplete erasure. Hallgrímsson’s palimpsest provides an explanation for the mismatch that can occur between patterns of developmental modularity and those of variational modularity (i.e., modularity studies at the scale of populations, usually quantified in a sample of adult individuals). In Fig. 1, we illustrate how organismal patterns of trait covariation can vary as developmental time increases, cell signaling regimes change, and the function of the individual trait shifts. These ontogenetic changes can partially overwrite previous patterns of trait covariation present at earlier developmental stages. Consequently, patterns and magnitudes of integration across different individuals can be difficult to predict even when the various developmental processes that are involved are well characterized. Evidence for the prevalence of the palimpsest can be found in a study by Conith et al. [11], where the authors find that developmental interactions among tissues that occur “above the genomic level” obfuscate the relationship between the genotype-phenotype map, and further recover little overlap in quantitative trait loci among traits that are developmentally integrated across the skull. These findings perhaps indicate that pleiotropy plays a limited role in structuring patterns of developmental covariance after a certain point in development, and that functional interactions or tissue-tissue interactions may overwrite earlier patterns of covariance which track QTL regions.

## 3. Evolution of integration

Evolutionary integration and modularity can be defined as inter-specific or between-generation patterns of trait covariation, or covariational patterns that are assessed over deep timescales; which in most cases require the incorporation of a phylogenetic hypothesis [13,37,81]. When these patterns are quantified instead at the population scale (i.e., within-generations), this is most often referred to in the literature as variational modularity [50]. While this review is focused on the relationships between developmental and evolutionary modularity, it is important to realize that evolutionary modularity arises as an outcome of processes that occur at the developmental and population levels.

Traits that are evolutionarily integrated are co-inherited or co-selected. Studies of evolutionary integration and modularity model trait covariation between different generations, and species at much larger timescales (e.g., millions of years) than developmental integration studies (e.g., several hours or days). And while changes in cell signaling regimes, growth, and tissue-tissue interactions can drive patterns of integration and modularity at the developmental level, at the evolutionary level, different processes have been found to drive variation in trait correlations between species and populations. Felsenstein [19] shows us that evolutionary integration can occur via genetic correlation among traits such that genetic variation in one trait is expected to be reflected in another trait. These genetic correlations can occur via pleiotropy where evolution across pleiotropically linked traits result in



**Fig. 1.** The ontogeny of integration. Patterns of integration and modularity can vary within an organism throughout their ontogeny. This conceptual schematic illustrates the shift in patterns of integration and modularity across a fish skull with increasing developmental time, modeling Hallgrímsson's developmental palimpsest. Different stages represent the timing of different tissue or functional interactions across skull components that may occur throughout an organism's ontogeny. Colors indicate module designation.

shared patterns of inheritance, or linkage disequilibrium, where there are non-random associations of alleles at different loci. However, linkage disequilibrium is generally thought to only be a transient source of integration that is eliminated after a few generations by recombination [8,58]. Co-selection or “selective covariance” (where genetically independent traits are linked by a shared selection gradient) can also drive patterns of evolutionary integration and modularity. In this latter scenario, traits may exhibit correlated changes if the covariation among them confers a selective advantage. In the case of selection-based patterns of integration, covariation among traits is expected to arise, at least at first, independently from genetic correlations [83]. Support for this hypothesis has been found recently in fishes, where patterns of evolutionary integration across the skull and fins were shaped by developmental tissue interactions between traits with little pleiotropic overlap between genomic regions (i.e., QTL regions; [54]; Conith et al. 2021). However, quantitative genetic models predict that traits that share similar functions will eventually be encompassed by shared pleiotropic interactions as the genotype-to-phenotype map evolves to reflect these associations [8,67].

#### 4. Evolution of modularity

Modularity is thought to emerge in rapidly changing environments, where trait complexes with fewer pleiotropic connections are allowed to adapt more quickly than more integrated networks [3,34,35]. Some simulation studies suggest that there is selection against highly integrated systems and this may facilitate the emergence of modularity among traits [35]. Selection against high degrees of integration among traits can be seen in the case of “conditional evolvability” [27]. Conditional evolvability models the magnitude of a trait's response to a selection gradient while the trait is integrated with other traits that are under stabilizing selection. Model simulations have shown that traits evolving in this framework exhibit reduced rates of evolution over short time scales relative to unconstrained traits, and empirical studies have shown that models that incorporate conditional evolvability better explain the relationship between mutation rate and the rate of trait evolution in fly wings [28,30]. Population genetic models have demonstrated that while some degree of modularity does allow for more rapid adaptation, and can partially offset the cost of adding more traits into an integrated network [72]. A study by Wang et al. [70] examined pleiotropic effects among yeast, nematode, and mouse mutants and found that organisms with the highest adaptation rates exhibited intermediate levels of pleiotropic (or integrating) effects among genes and traits. Additional support for adaptability driving trait modularity can be found in simulation studies. In a particular simulation study by Kashtan and Alon [34], the authors found that by modularly varying evolutionary goals (i.e., environmental conditions) in their algorithm, they could induce the spontaneous evolution of modularity among different trait components. Furthermore, later studies have shown that in the absence of local extinction, computational networks exhibit high

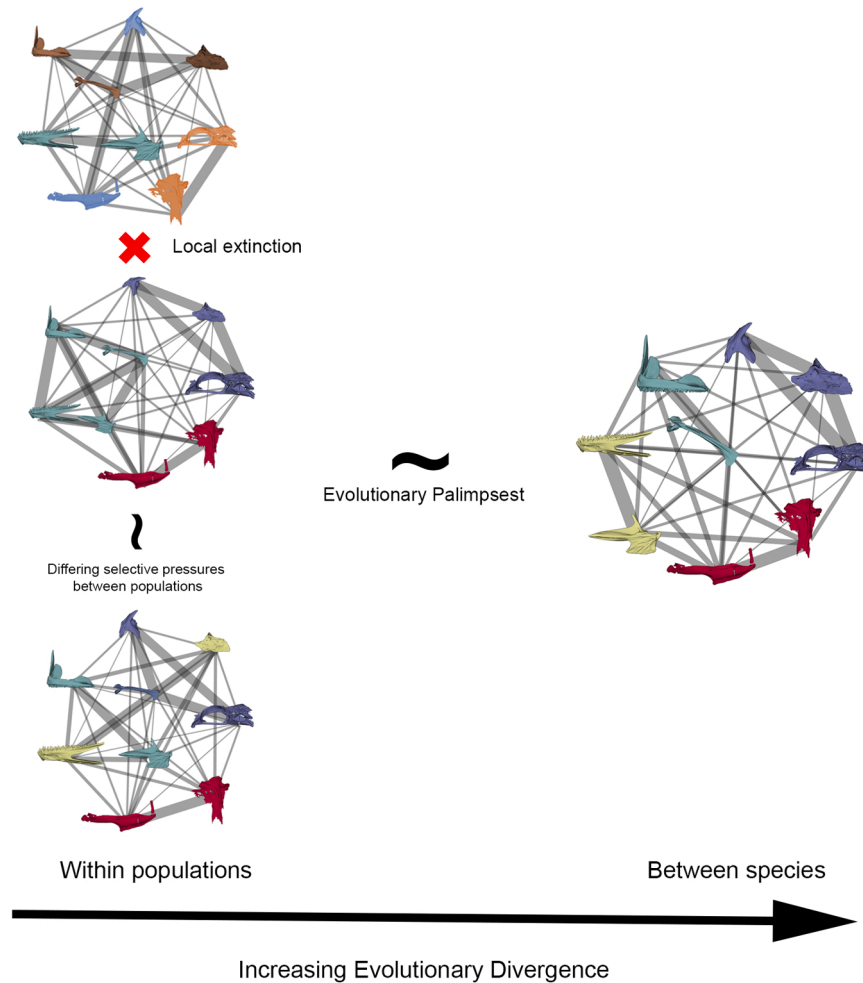
degrees of integration as they become locally optimized for their respective environments [36]. However, once local extinctions are introduced, computational networks become more modular to adapt to the newly available niches. These findings highlight two important things: (1) that patterns of modularity can shift between generations as environmental conditions shift, and (2) that extinction can play a major role in structuring the patterns of trait covariation observed today. Most of the species that ever lived on the planet have gone extinct. This necessarily leaves large gaps in our understanding of phylogenetic relationships and consequentially, patterns of evolutionary covariation [23]. This means that extinction may help to scramble the population-level signals of integration and promote adaptation, as well as obscure overall patterns of trait covariation at deeper timescales.

#### 5. The evolutionary palimpsest

Studies of evolutionary integration and modularity have shown widely divergent findings across different clades of organisms ranging from strong patterns of modularity corresponding to differential functions among trait complexes, to tightly conserved patterns of integration that have persisted for millions of years [14,16,33,51,53,59,71]. Some studies have also found that patterns of evolutionary integration are scale-dependent and that patterns of integration between closely related species may differ substantially from larger, more inclusive clades ([51]; Fig. 2). In Fig. 2, we introduce the “evolutionary palimpsest” which illustrates how patterns of covariation can vary with evolutionary time and divergence. Evolution occurs at the population level; therefore, organismal traits respond to selective pressures at the population level. As populations diverge and become species, they are likely to experience different selective gradients. By analyzing multiple species to quantify patterns of evolutionary integration and modularity, we merge populations that likely evolved under differing selective pressures and may have evolved distinct patterns of trait covariation. As a result, the patterns of covariation that are recovered between species are potentially a composite of several different covariation patterns that have been smeared together, partially overwritten each other, and now result in a palimpsest. If patterns of trait covariation rapidly evolve among populations, this palimpsest can confound analyses of evolutionary integration. However, some studies have shown that patterns of integration and modularity are highly conserved across large clades [48,71], which suggests that the interspecific approach can yet offer some valuable insights. Hallgrímsson et al. [26] first proposed the palimpsest as a means of understanding how the “determinants of covariance can be myriad, can overlap and can erase or obscure each other's effects.” We believe this concept is generalizable to characterizing the complicated tapestry of integration at evolutionary timescales.

#### 6. Functional integration

“Functional integration” has come to refer to several different scales



**Fig. 2.** The evolutionary palimpsest. Patterns of integration and modularity are subject to change between generations, populations and between species. This conceptual schematic illustrates the macroevolutionary processes that may influence a shift in patterns of integration between populations and between species in the fish skull. Width of network connections corresponds to the strength of covariance between different bones. Color indicates module designation.

of integration and has a fairly diverse application in the literature [17, 37]. “Functional integration” has been used to describe traits that are functionally linked across developmental or evolutionary timescales [7, 10, 12, 80, 82] or in the case of biomechanical studies, mobile traits that are linked kinematically while accomplishing a particular function (e.g., the various bones involved in buccal expansion in fishes) [57, 73, 74]. Empirically, it can be challenging to disentangle patterns of developmental integration from patterns of functional integration. One way to do this is to test developmental or functional hypotheses of covariation and compare the fit of these hypotheses to the data [77]. However, function can induce morphological changes during an organism’s development [31], which can further obfuscate the distinction between development and function. Attempts have been made to disentangle developmental and functional integration by measuring the covariation in fluctuating asymmetry (FA) between components, with the expectation that trait variation in FA is random unless the components are linked developmentally [25, 42, 77]. Despite the difficulty in identifying functional integration, this process potentially plays an important role in bridging the gap between late-stage patterns of developmental integration and evolutionary patterns of integration as studies have shown that evolutionary patterns of integration and modularity frequently reflect functional relationships among traits [45, 77].

## 7. The link between developmental and evolutionary integration

If patterns of developmental and evolutionary integration model interactions among trait complexes at vastly different timescales, can there truly be any link between the two? Such a link can be found under specific circumstances. During development, patterns of integration and modularity can change dramatically within an individual, and the morphologies of traits change as tissues appear and disappear during development. However, like Hallgrímsson’s palimpsest (Fig. 1), the signal of modularity-past may not altogether be lost, and some remnants may persist at the termination of ontogeny. It is therefore possible to target these later stages of ontogeny to evaluate different hypotheses of modularity across species. In many organisms, the allometric component of ontogeny is temporary; which means that after reaching a certain size, organismal shape change with growth becomes more or less asymptotic [4, 47, 75]. Even in the case of indeterminate growth, many species experience a reduction in shape change after reaching a certain size [29]. By isolating this terminal phase of ontogeny (e.g., sexually mature individuals) it is possible to evaluate various developmental hypotheses of modularity across species. In some cases, developmental hypotheses of modularity are best explained by patterns of modularity across species, even when compared to functionally-oriented hypotheses [40, 44]. These results suggest that some developmental patterns of trait covariation can be conserved and maintained across deep evolutionary time [14, 16, 18]. However, results like these are likely clade-specific, as



other studies have instead favored functional hypotheses of modularity over developmental ones [52,77]. To evaluate this relationship more comprehensively, it will be necessary to evaluate hypotheses of developmental modularity across several closely related species (a process which can be labor intensive) to determine whether patterns are mutable between even closely related species. With enough species sampled using this approach, it would even be possible to evaluate the evolution of developmental modularity. Studies suggest that in most cases, developmental patterns of modularity will be conserved between species [5,48]; however, some cases may arise where there are shifts or changes in patterns of covariation that may reflect a change in function or cell signaling within a particular lineage due to selection.

## 8. Conclusion

Integration and modularity are believed to play a central role in the accumulation of biological complexity over both evolutionary and developmental timescales. However, the link between developmental integration and evolutionary integration has been described as tenuous at best. At the developmental level, patterns of integration and modularity are constantly shifting and changing within an organism, all while occurring in the face of an overall increase in size, which frequently acts as an integrating force (Fig. 1). Meanwhile at the evolutionary level, patterns of trait covariation can shift among generations and may more strongly reflect patterns of shared function within trait complexes than developmental tissue origins or dynamics – though not necessarily (Fig. 2).

So, what is the relationship between developmental and evolutionary integration? It depends. Some studies have shown that patterns of developmental integration and modularity can be conserved through deep-time and that differences are detectable between species. However, other studies have shown that these patterns are often unstable across different scales (e.g., between species vs. between genera). In this review, we advance an evolutionary palimpsest model that describes the how population-level patterns of covariation can obscure and overwrite each other when compared across larger evolutionary timescales. We also illustrate a path forward for potentially reconciling developmental and evolutionary integration that involves testing hypotheses over later stages of ontogeny and comparing homologous structures across many species in a phylogenetic context. However, these approaches currently limit investigations to a specific range of phenotypes. In the future, it would be valuable to develop, or more completely incorporate, landmark-free methods (e.g., [61]) for quantifying patterns of trait covariation and to develop analytical methods that can account for missing structures to more accurately model the ontogenetic and evolutionary process. It would also be worthwhile to incorporate more complex models of integration and modularity at the evolutionary level, perhaps using an “integration through time” approach that attempts to capture changes in evolutionary modularity at different time intervals throughout a clade’s history.

To conclude, studies of patterns of trait covariation at developmental and evolutionary scales have yielded valuable insights into how organismal traits develop and evolve over time. While the relationship between these two processes is considered to be highly variable, we believe that the intersection between these two areas represents an exciting and active area of research, with the potential to inform our understanding of evolutionary processes as a whole and the generation of phenotypic variation in particular.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

## Acknowledgments

We would like to thank the countless researchers who paved the way

for our review.

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