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S27-1 Integration and modularity in biological systems: a review

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Abstract Olson and Miller (1951, 1958) coined the term "morphological integration" to describe the observation that particular subsets of morphological traits tend to covary strongly over development and evolution, while other subsets are more weakly associated. Traits forming such subsets are said to be "integrated". Such patterns of association, they argued, are a reflection of underlying developmental and functional demands on organismal phenotypes. Olson and Miller reasoned that characterizing such patterns and exploring the causes and consequences of integration would lead to interesting insights about phenotypic evolution. In current usage, such sets of integrated traits are termed "modules". An expanded view of integration focuses not only on patterns of phenotypic covariation but considers the implications of modular patterns of organization over a wide range of biological problems. Theoretical, experimental, and methodological advances have increased our understanding of how and why modular systems are likely to evolve. I briefly review contributions from a variety of fields including quantitative genetics, studies of multivariate selection, developmental biology, and systems biology, and discuss why modularity is likely to be a key concept for advancing our understanding of complex biological systems.

Key words Morphological integration, Covariation, Modularity, Selection, Evolution

1 What is modularity?

Precise definitions of what constitutes modularity are surprisingly elusive (Chernoff and Magwene, 1999; Magwene, 2001). This, in part, may reflect the diversity of biological systems and the types of data for which the concept was introduced. While explicit criteria for defining or delimiting modularity are sometimes hard to come by, the key property of modular systems is that they exhibit strong interactions within themselves and weak interactions with others (Cheverud, 1982; Wagner and Altenberg, 1996; Magwene, 2001; Winther, 2001). A modular system is therefore one that can be broken down into a set of independent or semi-independent subsystems, each of which is integrated. In a biological context we often demand other criteria as well. For modularity to be of evolutionary relevance, for example, it must have a genetic basis (Cheverud, 1996; Wagner, 1996).

The idea that biological systems are fundamentally modular has been evoked to explain a variety of observations such as population level patterns of covariation among traits, mosaic patterns of evolution, and the compartmentalized effects of environmental, developmental and genetic perturbations (e.g., Olson and Miller, 1958; Kirschner and Gerhart, 1998; Bolker, 2000). How modular systems evolve and how modularity affects selection are currently the focus of a great deal of conceptual research, mathematical modeling, and experimental and observational inquiry.

2 Historical overview

The study of patterns of covariation among phenotypic traits as a tool for understanding the evolutionary and selective constraints on populations and species has a long history. Karl Pearson, one of the key founders of the biometric school, provided some of the earliest examples of using trait correlations to study populations and the effects of selection (Pearson, 1903).

Quantitative approaches focusing on the study of trait covariation also emerged from the work of population and quantitative geneticists. Chief among these was Sewall Wright (Wright, 1918, 1932). Wright's method of path analysis was applied to the study of phenotypic correlations among traits. Using exploratory path analyses, Wright made the case for the existence of general and special factors that explained patterns of correlation. General factors, such as size, contribute to patterns of correlation among most traits. Special factors correspond to explanations for correlations among particular subsets of traits. Often these special factors correspond to presumed functional or developmental modules (Wright, 1932, 1934; also Bookstein et al., 1985).

Developmental biologists have long been interested in patterns of integration and modularity among phenotypic traits. Early quantitative work includes Huxley's studies of allometry (Huxley, 1932). Needham's (1933) work on the dissociability of development, and subsequent studies of heterochrony, also support the concept that phenotypes, and the developmental processes that build them, are modular. Additional conceptual treatments relevant to modularity and integration can be found in Schmaulhausen (1947).

Olson and Miller drew from this background in developing their concept of Morphological Integration (Olson

and Miller, 1951, 1958). Olson and Miller never gave a formal definition of integration. Perhaps their most succinct statement is the following "...there exist groups of highly associated morphological dimensions within most organisms...such groups have important biological and evolutionary meaning" (Olson and Miller, 1960). Starting with their 1951 paper, Olson and Miller began to develop a conceptual and methodological basis for studying morphological integration. In particular, they laid out a statistical methodology for testing hypotheses of integration that they called the ρF model. The ρF model involved testing a set of empirically derived clusters of traits (ρ-groups) against trait sets derived by qualitative assessment of function or development (F-groups). In their book *Morphological Integration* (1958), Olson and Miller argued that there was sufficient evidence for the validity of ρ-groups such that a comparison with F-groups was no longer a necessary part of their model. They also described there a complex method for discovering sets of correlated traits.

What distinguished Olson and Miller's work, however, was not their statistical methodology but rather the scope of their research program. They explicitly advocated a quantitative approach, based on multidimensional phenotypes; they analyzed and considered both neontological and paleontological data; and they provided perspectives on both the micro- and macro- evolutionary consequences of morphological integration.

Despite continued conceptual and theoretical interest in the concepts of modularity and integration (e.g. Riedl, 1978), relatively little empirical work addressing the issue directly appeared in the 1960s and 1970s. This situation began to change in the early 1980s when James Cheverud and coauthors suggested a quantitative genetics framework for studying the evolution of integration (Lande, 1979; Cheverud, 1982, 1984; Cheverud et al., 1983). This work put the concept of integration on a firmer theoretical basis, and also suggested more appropriate statistical tools for quantifying and assessing integrative patterns. Many of these developments are summarized in Chernoff and Magwene (1999).

3 Types of integration and modularity

Different categories of modularity have been defined to distinguish between explanatory hypotheses for modularity and integration. Common sets of categories are functional, developmental, genetic, and evolutionary modularity (Cheverud, 1996). Functional modules are sets of traits that are presumed to form a module because they interact to accomplish some function or task (Cheverud, 1996; Winther, 2001). Developmental modules are those that result from developmental processes which induce patterns of modularity such as common tissue origin or similar regulatory control (Atchley and Hall, 1991; Nemeschkal, 1999; Bolker, 2000). Genetic modules are sets of traits that are modular due to pleiotropy or linkage disequilibrium (Cheverud, 1996; Wagner, 1996). An evolutionary module is a set of traits that covary together over evolution, either because they are jointly inherited (due to genetic modularity) and/or jointly selected (Cheverud, 1996). A given set of traits may form a module of one or more of these types, and the extent to which these different explanations overlap can vary.

4 Measuring modularity

How is modularity in biological systems measured and quantified? This was one of the fundamental questions that Olson and Miller (1951, 1958) tried to address. Other workers have proposed a variety of statistical methods for quantifying modularity. These techniques include cluster analysis (Van Valen, 1965; Cheverud, 1982), matrix similarity tests (Cheverud et al., 1989), and path and confirmatory factor analyses (Zelditch, 1987, 1988). Concerted trait evolution over phylogenies may also be indicative of integration (Nemeschkal et al., 1992; Roth, 1996). A recent novel approach has been the use of fluctuating asymmetry to study developmental integration (Klingenberg and Zaklan, 2000; Klingenberg et al., 2001).

Recently, Magwene (2001) proposed the use of a statistical technique called Graphical Modeling as both an exploratory and confirmatory tool for studying modularity. Graphical modeling, and related methods such as Bayesian networks, are based on the statistical notion of conditional independence (Whittaker, 1990). A pair of traits is conditionally independent if their statistical interaction disappears upon conditioning (statistically) on some other trait or set of traits. Modules then correspond to sets of traits which all show strong conditional interactions with each other. This approach has a number of strengths, two of which are worth highlighting. Magwene (2001) shows that (1) conditional independence can be used to provide an unambiguous criterion for delimiting modules, and that (2) conditional independence among traits can be related to standard models of multivariate selection. This argument is similar to one made by Pearson nearly a century before (Pearson, 1903). Pearson argued that marginal correlations among traits were not the most informative type of interaction to study; rather, he saw that conditional interactions were fundamental to understanding the association of traits within populations and species.

5 Evolution of modularity

What is the "unintegrated state"? Do phenotypes typically evolve from a state of overall strong correlation among traits, or is the ancestral state one in which most traits are independent. The idea that modularity evolves by breaking down interactions among traits has been labeled the "Fission" model; modularity built up from initially independent traits has been termed the "Fusion" model (Riska, 1986; parcellation and integration *sensu* Wagner, 1996). Riska (1986) argues: "high genetic correlation is simpler than and antecedent to zero genetic correlation." There is, however, little empirical evidence to support either view. While that evidence may be sparse, a variety of mathematical treat-

ments provide some insights into the types of genetic architectures and selective regimes which may favor the evolution of modularity or lead to changes in modularity (Cheverud, 1984; Wagner, 1984, 1988; Bürger, 1986; Rice, 1998, 2000).

6 Systems biology

In the past, methodological difficulties usually limited studies of modularity and integration to the consideration of a limited number of traits; even in the most ambitious studies usually less than 50 variables of interest were considered. Technological advances over the last decade have begun to change this as high-throughput technologies allow researchers to assay the state of hundreds, even thousands, of variables simultaneously (Brown and Botstein, 1999). The richness of such data has begun to be exploited by researchers interested in the organizational properties of biological systems. The concepts of modularity and integration have begun to be exploited in this context, in analyses of systems such as metabolic pathways (Ravasz et al., 2002) and genetic regulatory networks (Magwene, unpublished).

From a practical point of view, modularity is a useful concept for breaking down a complex system into sets of smaller subsystems, each of which can be studied in isolation. If the break down is consistent with the actual patterns of (semi) independence, then little or no information about the behavior of the system as a whole is lost. Modularity therefore provides an important conceptual and experimental handle for dealing with the complications faced when we study complex biological processes.

7 Relation to other concepts

Modularity and integration have been related to other phenomena of evolutionary interest such as buffering and canalization and the evolvability of biological systems (Altenberg, 1995; Wagner and Altenberg, 1996; Kirschner and Gerhart, 1998). For example, it has been argued that modular patterns of organization help to buffer against developmental noise and mutation. Modularity may therefore be an important mechanism which helps to produce normal phenotypes in the face of imprecise regulatory control (Kirschner and Gerhart, 1998; von Dassow et al., 2000).

8 Outlook

Modularity and integration have emerged as key concepts for studying organismal phenotypes and the molecular, developmental, and evolutionary processes which affect them. The research cited above represents only a small portion of the growing body of work that bears on our understanding of modularity and integration. Future research, in particular the development of experimental tools to test hypotheses of modularity and techniques for quantifying modularity with diverse types of data, will contribute to a greater understanding of the organizational properties of complex biological systems.

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References

Altenberg L, 1995. Genome growth and the evolution of the genotype-phenotype map. In: Banzhaf W, Eeckman FH ed. Evolution and Biocomputation: Computational Models of Evolution. Springer-Verlag Lecture Notes in Computer Sciences 899: 205 – 259.

Bolker JA, 2000. Modularity in development and why it matters to Evo-Devo. Amer. Zool. 40: 770–776.

Bookstein FL, Chernoff B, Elder R, Humphries J, Smith G, Strauss R, 1985. Morphometrics in Evolutionary Biology. Philadelphia, PA: Academy of Natural Sciences.

Brown PO, Botstein D, 1999. Exploring the new world of the genome with DNA microarrays. Nature Genetics 1(suppl.): 33–37.

Bürger R, 1996. Constraints for the evolution of functionally coupled characters: a nonlinear analysis of a phenotypic model. Evolution 40: 182–193.

Chernoff B, Magwene PM, 1999. Morphological integration: forty years later. In: Olson EC, Miller RL ed. Morphological Integration. Chicago: University of Chicago Press, 319–353.

Cheverud JM, 1982. Phenotypic, genetic, and environmental morphological integration in the cranium. Evolution 36: 499–516.

Cheverud JM, 1984. Quantitative genetics and developmental constraints on evolution by selection. J. Theor. Biol. 110: 155–172.

Cheverud JM, 1996. Developmental integration and the evolution of pleiotropy. Amer. Zool. 36: 44–50.

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.

Cheverud JM, Wagner GP, Dow MM, 1989. Methods for the comparative analysis of variation patterns. Syst. Zool. 38: 201–213.

Kirschner M, Gerhart J, 1998. Evolvability. Proc. Natl. Acad. Sci. USA 95: 8 420–8 427.

Klingenberg CP, Zaklan SD, 2000. Morphological integration between developmental compartments in the *Drosophila* wing. Evolution 54: 1 273–1 285.

Klingenberg CP, Badyaev AV, Sowry SM, Beckwith NJ, 2001. Inferring developmental modularity from morphological integration: analysis of individual variation and asymmetry in bumblebee wings. Amer. Nat. 157: 11–23.

Lande R, 1979. Quantitative genetic analysis of multivariate evolution, applied to brain-body size allometry. Evolution 33: 402–416.

Magwene PM, 2001. New tools for studying integration and modularity. Evolution 55: 1 734–1 745.

Nemeschkal HL, 1999. Morphometric correlation patterns of adult birds (Fringillidae: Passeriformes and Columbiformes) mirror the expression of developmental control genes. Evolution 53: 899–918.

Nemeschkal HL, Elzen R van den, Brieschke H, 1992. The morphometric extraction of character complex accomplishing common biological roles: Avian skeletons as a case study. Z. Zool. Syst. Evolut-forsch 30: 201–219.

Olson EC, Miller RL, 1951. A mathematical model applied to a study of the evolution of species. Evolution 5: 325–338.

Olson EC, Miller RL, 1958. Morphological Integration. Chicago: University of Chicago Press. (Reprinted 1999).

Pearson K, 1903. Mathematical contributions to the theory of evolution. XI. On the influence of natural selection on the variability and correlation of organs. Phil. Trans. R. Soc. Lond. A 200: 1–66.

Ravasz E, Somera AL, Mongru DA, Oltvai ZN, Barabasi A-L, 2002. Hierarchical organization of modularity in metabolic networks. Science 297: 1 551–1 555.

Rice SH, 1998. The evolution of canalization and the breaking of von Baer's laws: Modeling the evolution of development with epistasis. Evolution 52: 647–656.

Rice SH, 2000. The evolution of developmental interactions: epistasis, canalization, and integration. In: Wolf JB, Brodie ED, Wade MJ, eds. Epistasis and the Evolutionary Process. New York: Oxford University Press, 82–98.

Riedl R, 1978. Order in Living Organisms. New York: John Wiley and Sons.

Riska B, 1986. Some models for development, growth, and morphometric correlation. Evolution 40: 1 303–1 311.

Roth VL, 1996. Cranial integration in the Sciuridae. Amer. Zool. 36: 14–23.

Van Valen L, 1965. The study of morphological integration. Evolution 19: 347–349.

von Dassow G, Meir E, Munro EM, Odell GM, 2000. The segment polarity network is a robust developmental module. Nature 406: 188–192.

Wagner GP, 1984. Coevolution of functionally constrained characters: prerequisites of adapative versatility. BioSystems 17: 51–55.

Wagner GP, 1988. The influence of variation and of developmental constraints on the rate of multivariate phenotypic evolution. J. Evol. Biol. 1: 45–66.

Wagner GP, 1996. Homologoues, natural kinds and the evolution of modularity. Amer. Zool. 39: 36–43.

Wagner GP, Altenberg L, 1996. Complex adaptations and the evolution of evolvability. Evolution 50: 967–976.

Whittaker J, 1990. Graphical Models in Applied Mathematical Multivariate Statistics. New York: John Wiley and Sons.

Winther RG, 2001. Varieties of modules: kinds, levels, origins, and behaviors. J. Exper. Zool. 291: 116–129.

Wright S, 1918. On the nature of size factors. Genetics 15: 603–619.

Wright S, 1932. General, group and special size factors. Genetics 15: 603–619.

Wright S, 1934. The method of path coefficients. Ann. Math. Stat. 5: 161–215.

Zelditch ML, 1987. Evaluating models of developmental integration in the laboratory rat using confirmatory factor analysis. Syst. Zool. 36: 368–380.

Zelditch ML, 1988. Ontogenetic variation in patterns of phenotypic integration in the laboratory rat. Evolution 42: 28–41.