Organisms and Organization

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Abstract

Organisms are organized both internally and externally. The centrality of the organism in examination of the hierarchy of biological organization and the kinds of "emergent properties" that develop from study of organization at one level relative to other levels are my themes. That centrality has not often been implicit in discussion of unifying concepts, even evolution. Few general or unifying principles integrate information derived from various levels of biological organization. However, as the genetic toolbox and other new techniques are now facilitating broader views of organisms and their internal and external interactions, and their evolution, some fundamental perspectives are emerging for many kinds of studies of biology. In particular, more hierarchical approaches are gaining favor in several areas of biology. Such approaches virtually demand the integration of data and theory from different levels of study. They require explicit delineations of methodology and clear definition of terms so that communication *per se* among scientists can become more integrative. In so doing, a hierarchy of theory will develop that demands ever further integration, potentially leading to unifying concepts and a general theory for biology.

Keywords

centrality, emergent properties, form and function, hierarchies, integration, module, organism

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Organisms *are* organized, internally and externally. Organization is "the connexion and coordination of parts for vital functions or processes" (Anonymous 1971), and, for purposes of this discussion, the definition applies to both the internal organization of an individual organism and the external organization of sets of organisms. For 200 years, and more, scientists have sought to learn more about the structural, functional, and developmental internal organization of organisms. Organisms have responded well to reductionistic approaches that identify mechanisms of life's processes, and to studies that illustrate external organization, or patterns of interactions of organisms with each other and the physical (biotic and abiotic) environment. At the same time, the organism has too rarely been central to discussions of the basic phenomena of biology, nor has it played much of a part in attempts to generate a theory of biology. The discussion that follows will emphasize the centrality of the organism in examination of the hierarchy of biological organization, consider the kinds of "emergent properties" that arise from study of organization at one level of the hierarchy relative to other levels, and discuss the need for integration across the hierarchy in order to understand the relationships of form, function, development, ecology, behavior, phylogeny, and evolution. Do general principles potentially arise from such integration so that a "theory of biology" is generated? This broad and perhaps eccentric overview will only sample the literature, rather than exhaustively surveying it, and attempt to be provocative, rather than conclusive.

There have been several attempts recently to "unify" biology, or even to "unify" *parts* of biology. Most have revolved around evolution as a unifying concept, with natural selection as a unifying mechanism (see Mayr and Provine 1980; Smocovitis 1996). Other recent attempts to find unifying principles for biological organization have looked at structures or functions of organisms, and sought unifying principles such as processes by which like structures or pathways are developed in a diversity of taxa. (The latter are a modern parallel to the efforts in the late 19th century to find unity in development so that development became a means to define and order organisms.) Genomic insights into development, structure, and function have changed the ways that we pursue questions of organization. Examples include Kung's (2005) work illustrating that lipids mediate mechanoreceptive structures in all animal phyla examined, Bock et al.'s (2001) research on membrane compartment organization, and Brown and colleagues' (e.g., Allen et al. 2005) work on metabolic scaling from molecules to large mammals and ecosystems. These latter attempts have resulted in either the correlation of patterns with processes or the revelation of conserved mechanisms (genes, pathways) that appear to encode the process or structure regardless of degree of relatedness of the taxa examined (homology and homoplasy). Other interesting attempts to unify parts of the hierarchy of biology include Hubbell's (2001) "unified neutral theory of biodiversity and biogeography" (which is now being tested *vis-à-vis* specific taxonomic groups and being found both useful and problematic; see Ostling 2005). But it remains that nearly all of these new efforts look at parts of the biological hierarchy, and are not centered on organisms and their organization *per se*.

Not many recent attempts have looked at the organization of whole organisms, but some researchers have sought it (see, e.g., D. B. Wake and Larson 1987; Stork 1992; Wagner and Laubichler 2001). This is not to say that there have not been some examinations of organismal organization—some recent explorations of whole organismal organization were exciting ventures in the last third of the 20th century that considered the evolution of complexity (e.g., Bonner 1988), the faces of evolution (e.g., Brooks and Wiley 1986), and a number of aspects of the organization of organisms, such as epigenetics, increase and differentiation of cells, cohesion, etc. (e.g., Riedl 1976; Mittenthal and Baskin 1992, and references therein). Many, in fact most, such studies sought physical (i.e., based on principles of physics, such as mechanics, and/or on information theory), not biological, principles that would allow a unified understanding of complexity and organization (e.g., Goodwin 1989; Mittenthal 1989; DeGuzman and Kelso 1992; Kauffman 1992, 1993; Mittenthal and Baskin 1992; Mittenthal et al. 1992; Nelson 1992; Newman 1992, 2003), often using chaos theory as their base (e.g., Lewin 1992). Upon examination, these efforts are strongly reminiscent of the attempts of the Vienna Circle and its offshoot, the Unity of Science Movement, to make biology a physics-based science, which was repudiated at the time by Ernst Mayr and Conrad Waddington (see Smocovitis 1996). Of course, more recent workers recognize the "maturity" of biology as a science, and are searching for means of expression of general biological principles, often through models and other quantitative expressions.

But does our new ability, derived through new tools that allow understanding of the genetic bases of aspects of organization, provide the kinds of generalizations that warrant the rubric "theoretical biology"? There are possibilities, but are they merely illustrations, rather than principles? For example, we now can investigate the commonality of the molecular and cellular bases of organization, the universality of some genes, the properties of the germ layers, epithelio-mesenchymal interactions, etc., and use them to assess the relationships of development, structure, and function. But what is "theoretical biology"?

I proceed from the thesis that *organisms* are the key to deriving a theory of organization; that *organisms* are the essential part of the biological hierarchy of organization; and that each of the levels of organization has intrinsic principles and extrinsic ones that affect other levels of the hierarchy for those organisms. I claim that the "emergent properties" of levels of organization are just beginning to be revealed and available for analysis; that the relationships between form, function, fitness, etc., can be re-examined in the light of new tools and new knowledge. I emphasize that the key to a theoretical biology has to do with understanding the permissiveness of biology—its capacity for change, as well as its currently more commonly studied conservation or constancy—and the many levels at which variation is generated and is important to the organization of organisms. Note that I do not specify the standard "molecules to cells to organisms to ecosystems" kind of hierarchy; unicellular organisms, syncytia, clones, some kinds of colonies, etc., differ in their hierarchical "placements." For example, a bacterium has a molecular and cellular organization that is not multicellular, but it is an organism that is part of a population and of a community and of an ecosystem—this is shared organization at the cellular level.

The reliance on physical principles, such as optimization, has not served theoretical biology particularly well, in my opinion. Organisms and their parts, and their interactions, more often *suffice* than achieve high performance criteria, in part because of the trade-offs of the interactions of structure, function, and performance at the multiple, integrated levels of the biological hierarchy. I will first examine current approaches to analysis of the hierarchy of biological organization (complexity), and then emergent properties of the structure–function relationships at various levels of the hierarchy that influence other levels of the hierarchy, above and below. I will look particularly at ways that such "emergent properties" might lend themselves to broader generalizations through integration. I use examples from a diversity of organisms, and their parts, and attempt to build a comparative base for understanding diversification (i.e., speciation, adaptation, radiation, morphological change), commonality, hierarchies, and integration among properties of hierarchies to see if new, common principles emerge that might contribute to a "theoretical biology." I assert that the centricity of the organism is essential to such considerations because we now have the tools to measure the parts of the organism developmentally and functionally, and to measure the ways that organisms interact at multiple levels of organization. For example, the population level may be most appropriate for assessing organismal interactions in a single generation or at a particular point in time, or even the nature of change across generations. However, without an organismal center to such studies, analysis is still of parts, not wholes. (I am not going to consider the issue of "parts and wholes," which has some relevance, but has been explored well by McShea (2000), McShea and Venit (2001), Zwick (2001), and Winther (2006)).

Hierarchies

Organisms are intrinsically hierarchically organized, and they contribute to and are parts of other levels of the hierarchy of biological organization. *No* level of the hierarchy exists in the absence of organisms. Research for hundreds of years has examined the parts of organisms, how they develop, how they function, and to some degree how they interact in the whole organism. The tendency during the last 100 years has been to take an ever-more-reductionistic approach to the organization of parts of organisms, largely because of the techniques that have become available and the natural interest in the bases of mechanisms of function (and structure). However, little attention has been paid (with some major exceptions, e.g., Ravasz et al. 2002) to looking at the contribution of the reductionistic discoveries to the organism as a whole, and to the way that it interacts with its environment. It is encouraging that more researchers are becoming interested in "rebuilding" the "atomized" organism in order to study the interactions across the levels of the hierarchy of organization, now that the analysis of complexity is a feasible challenge (e.g., see discussion of the nature of phenotypic plasticity and the way that reductionistic approaches parallel, rather than intersect with integrative research [papers in Hall et al. 2003]). Hierarchies and the integration of the features of hierarchies need more attention. The properties of organismal diversity may well be emergent attributes of the kinds of interactions across the hierarchy that are unique to a taxon, a structure, a pathway, or an ecological interaction. These ideas are not at all new. As Lauder (1982) pointed out in his introduction to the reprint of E. S. Russell's book, *Form and Function*, Russell approached organic patterns in terms of a hierarchy, and dealt with downward-organized processes and within-level analyses, but the focus of his hierarchy was the responses of the organism, but not to levels "above" that. He also had the view that integration of study across hierarchical levels would provide understanding of integrative behavioral patterns (function), whereas physiological and genetic analyses did not contribute to the study of such patterns (though they were otherwise informative).

Lauder cites Gould's (1980) suggestion that

> a general theory of evolution would be rooted in a hierarchical view of nature, and will possess a common body of causes and constraints, but will recognize that they work in characteristically different ways upon the material of different levels—interdemic change, speciation, and patterns of macroevolution. As its second major departure from current orthodoxy, the new theory will restore to biology a concept of organism.

Hierarchical selection also has been considered, but received limited attention (see Gould 1998); Salthe (1985) also attempted to review hierarchical systems in evolution.

Some ecologists are taking a more direct approach to examining organisms in terms of their hierarchical relationships with each other and with their biotic and abiotic environments. Wisheu (1998) looked at patterns of habitat partitioning, and realized that patterns have been described, but that how they form is not yet understood. She examined 66 instances in the literature of experimental demonstrations of the formation of the patterns of habitat partitioning. She found that a variety of community organizations produce patterns of partitioning, and that shared preferences occur frequently. The kinds of study organisms and the kinds of resources that species use influence the patterns of partitioning that form. Wootton (1994) was concerned about "the degree to which the dynamics at one level of organization can be predicted by the behavior of its component parts at a lower level of organization." He notes that such an analysis can succeed only if the component parts do not change their behavior, regardless of other elements in the system, for example, behavior of multispecies communities being predictable only if the species pairs analyzed are not affected by other species in the community. His concern is whether such higher order interactions really occur. He emphasizes that the field has four problems with such analyses, including the definition of "higher order interactions," discrepancies between theoretical and empirical work, incongruities between statistical procedures and the theory being tested, and failure to really consider the theoretical framework being tested. He asks that investigators be specific about theory, and that more focus toward identifying mechanisms by which interactions can be modified be employed. It appears that a hierarchical approach may yield answers to questions of organismal–ecological interactions, but there are still problems in resolving appropriate questions and approaches to them.

Korn (2002) cogently commented that

> The study of hierarchies has passed through periods of enthusiasm followed by years of inactivity with little resolution achieved . . . About all that has been agreed upon is that hierarchies are composed of discrete levels (Weiss 1971) and a variety of types make it difficult to find common features (von Bertlanffy [*sic*], 1952).

Korn adopts Pattee's (1969) definition of a hierarchy as a "descending arrangement of constraints" that is associated with increasing "strengths." He notes that the term "constraint" has been used differently in evolutionary literature than in hierarchical theory, and attempts to resolve the issue. Subhierarchies have been recognized by many workers, and usually deal with the "lower" (descending) levels of the hierarchy; Korn's thesis is that the evolutionary and ecological subhierarchies must also be included in a complete hierarchical description of life. Korn (2002) defines birth as "when a cell is removed from the constraints of the organism and assumes its own organismal constraints"; death is the cessation of protein synthesis "because proteins and their products constitute components at high levels of the hierarchy." He considers these descriptions of selection at supraorganismal levels to be "new," but in fact they have been practiced, albeit rarely and without the label, by a few researchers (e.g., see comments on work by Pederson and Tuomi (1995), and others, below). Korn proposes that two types of selection operate at those levels, natural selection and hierarchical selection, so that selection occurs at dual levels. Strangely, he does not cite Gould's (1998) paper on "the necessity and difficulty of a hierarchical theory of selection," which argues that "we have failed to appreciate the range and power of selection at the levels above and below the organismic because we falsely extrapolate the defining properties of organisms to these other levels (which are characterized by quite different distinctive features)." Gould argued that there are two key principles: levels can interact positively, negatively, and orthogonally, not just negatively; and each hierarchical level differs from all others in both style and frequency of patterns in change and causal modes. Both Gould's and Korn's papers deserve considerable attention, and not just in the context of the nature of hierarchies.

Emergent Properties and Integration: The Relationship Between Form and Function

A major feature of hierarchical organization is the way that the properties of any one level influence those of other levels, the latter not just those adjacent to the "key" level examined. One of the best studied is that of form and function, though it is only occasionally dealt with as a property of hierarchies. Often only one level of organization is studied, and results extrapolated to others. Such an approach is a long-standing one, used by Cuvier, for example, to suggest postures and behaviors of extinct vertebrates based on the characteristics of their bones as compared to those of extant species, presumably either related or having the same/similar behaviors, according to the "unity of plan" of organisms. It had been rare until recently for there to be rigorous and explicit analysis of hierarchical impacts and emergent properties introduced to such research—however, such studies are beginning to occur.

There is a large body of literature on form–function relationships, some with the old "which came first?" approach, but others seeking to integrate conceptually ideas about the nature of shape and form. Foci have varied, but two important efforts that focused on morphology *per se* are Olson and Miller's (1958) book called *Morphological Integration*, a search for quantitative expression of elements of structure, and Raup's examination of shape and form in morphospace, giving rise to what he called a "theoretical morphology" (e.g., Raup and Michelson 1965; Raup 1966, 1968) that includes growth, pattern formation, and constraints and flexibility that produce morphologies, given that morphospace is never filled.

Research on the properties of structure at diverse levels of the biological hierarchy is the now-standard theme, often with extensive consideration of the "functional properties" of the structure that is being analyzed. Much of the research does attempt to bridge levels, especially those between the organism's structure and its performance and/or behavior (function).

I will not fully explore this, citing only a few examples to give some background and to make the case for integration of research across levels of the hierarchy of organization in order to understand emergent properties and organismal evolution and function.

As Koehl (1996) noted, while making a strong case for quantitative mechanistic analyses of the way function depends on biological form, the actual "relationship between morphology and performance can be nonlinear, context-dependent, and sometimes surprising. In some cases, small changes in morphology or simple changes in size, can lead to novel functions, while in other cases changes in form can occur without performance consequences." She commented further that the effect of a specific change of morphology can depend on morphological or even habitat attributes of organisms—changes in size or habitat can allow new functions and novel consequences of changes in morphology. Organismal-level mechanistic research can be used in concert with other tools to gain insights about issues in ecology and evolution. The "selective advantage" of traits has been discussed using largely qualitative examples and rigorous mathematical models; quantitative correlations between structure and performance give more information about fitness and ecological role, and such research is burgeoning.

The searches for common features span the "lower" levels of the hierarchy from chemical properties to organismal function. Kung's (2005) work (mentioned above) on lipids mediating mechanoreceptor structure and function in all animals studied illustrates the subcellular level of commonality and constraint; Keaveny et al. (2004) is an integrative study of collagen chemistry as it influences trabecular bone structure and hence the mechanical properties of bone; while Jaasma et al. (2002) is similarly integrative in its examination of intraspecimen (within individual and across taxa) variation in tissue modulus of trabecular bone and its biomechanical effects. Such studies almost invariably conclude with a consideration of the effect of the structural and functional properties revealed at the subcellular through tissue (cell interaction) levels of the hierarchy of organization on the structure–function properties of the whole organism.

The literature now abounds with excellent studies of locomotion, feeding, and other functions/behaviors, including growth and reproduction, in animals and plants. Many of these are rigorously experimental, mostly in the laboratory but some in the field, the natural environment of the organisms studied. A difficulty exists in resolving laboratory and field results. In the laboratory, experimental conditions can be such that a few parameters judged relevant are analyzed, and other aspects are controlled, but performance can be pushed to its limits. In the field, selected parameters can be measured, but other conditions are difficult to control, and organisms rarely if ever perform at the limits of their structure–function possibilities in nature. Some scientists (mostly graduate students) are attempting to resolve this paradox. I will not explore that literature, except to say that its rigor and focus continue to increase and its expectation of "adaptationist" explanations is diminishing so that the analysis of the emerging properties of the structure, the physiology, and the behavior are pursued in an integrative manner (M. H. Wake 1990).

Research that deals with form–function relationships of organisms as properties of the way they deal with their environments ecologically and evolutionarily includes other levels of the hierarchy of biological organization that had long been difficult to analyze rigorously. Arnold's (1983) classic call for integration of "morphology, performance, and fitness" provided a quantitative approach to such studies to replace or revise the adaptationist considerations of many morphologists and ecologists. He and his collaborators have led the way in integrating quantitative genetics, morphology, physiology, behavior/performance, and selection in natural populations in the field. One of the aspects that had been considered difficult to approach is that of the evolution of organisms, because it was assumed that this historical property was not replicable or testable. On the one hand, an evolutionary/phylogenetic perspective can enhance the integration of properties of the suborganismal level to understand the organism and the taxon it represents (M. H. Wake 1990, among many). On the other hand, an analysis of the role of historical factors is essential to understanding the evolution (and development) of complex organismal functions, as elucidated by Lauder (1981), Lauder and Liem (1989), D. B. Wake and Roth (1989), and M. H. Wake (1992), to name but a few such commentaries. Lauder (1981) presented perhaps the clearest exposition of structural analysis in evolutionary biology, and it presages many of the points of the current article. Lauder envisioned a structural approach to testing historical hypotheses about the constraints imposed by phylogeny on organisms. He advocated examination of nested sets (hierarchies) of structural features in lineages, examination of general or emergent organizational properties of structural and functional systems, and comparative study of the consequences for structural and functional diversity of such features in related lineages.

Lauder (1981) emphasized three examples of emergent organizational properties: structural complexity, repetition of parts (see below re modules), and the decoupling of primitively constrained systems. He indicated that both transformational and relational hypotheses should be examined, and "to the degree that such hypotheses about form are corroborated, they provide evidence for an underlying regularity in the transformation of organic design that may be a consequence of the hierarchical organization of structural and functional patterns in organisms" (p. 430). He points out that such an approach allows alternative views of such structure–function properties as "key innovations." The latter had been considered untestable in terms of causation and adaptation, because most are presumed to have evolved only once. However, if a "key innovation" is merely a component of a structural network that has been focused on in terms of a role in the biology of a lineage, it can be incorporated into an emergent structural framework based on resolution of transformational and relational hypotheses, and does not involve relationship to speciation rate—a concept that deserves more attention. There are other approaches to the concept of novelties, some based primarily on definitions, some on processes of analysis (e.g., Müller 2003).

Emergent Properties and Integration: The Conserved and Constant Versus the Derived and Permissive

The properties of organisms that are conserved and common among parts of organisms, and even populations of organisms (see above), are receiving a great deal of attention by researchers at present; some of these considerations are alluded to above. The genetic toolbox is allowing us to unravel patterns of development, and to understand aspects of the basis for the evolution of new structures, functions, and even forms (e.g., expansion of Hox gene expression domains in body axis formation and loss of limbs in snakes; Cohn and Tickle 1999). We know now that many organisms (the majority of animals and some plants and fungi) throughout the hierarchy of life share certain common genes and common regulatory pathways. We also know that certain taxa (e.g., some plethodontid salamanders) have long periods of evolutionary stasis so that they do not change morphologically over vast periods of evolutionary time, in which they apparently exist in very stable environmental conditions, but we also know that they may be deeply divided genetically, so under selection at some time (see D. B. Wake et al. 1983). At the same time, there are numerous examples of constantly ongoing selection, usually in environmentally variable situations, in which phenotypes alter very frequently. A beautifully developed example of that mode is Darwin's finches (Grant and Grant 1989). The latter example is phenotypically flexible and evolutionarily permissive, the former is constrained and constant in morphology, and probably genetically.

There is a huge literature on "constraints"; I will not attempt to review it all, but simply deal with the kind of constraint that structure imposes on form and function. It is important to recognize that structure exists at all levels of the hierarchy of biological organization, as already implied. I will oversimplify—a major "constraint" is that of history or phylogeny as it reflects the structure of organisms. I have already alluded to the attempts to "unify" structure–function relationships across taxa at subcellular, cellular, organismal, and evolutionary levels of the hierarchy. The point is obvious: if mostly the same components "build" a structure or an organism, there is a high probability of limitation to potential diversification and occupancy of morphospace. If cartilage is fundamental to the body plan, rather than chiton, structure/function/ecology/evolution will be "permitted" certain parameters of development, function, and diversification, but not others. This point recurs in the literature, mostly implicitly but also explicitly.

How, then, do body plans come into being and evolve? This question has been approached for a long time and from many perspectives. Recently Arthur (1997) and Minelli (2003) have provided useful analyses and reviewed the long-unanswered questions; many of us have looked at them from the perspective of our own research emphases (e.g., M. H. Wake 1990, 2001, 2003). Despite all this attention, Amundson (2005) asserts that developmental biologists, including EvoDevo practitioners, have accepted, rather than investigated, body plans, and then worked with their development and modification. Müller and Newman's (2003) edited volume on the origination of organismal form, and the contributions therein, should start to dispel Amundson's contention. Rasskin-Gutman (2003) looks carefully at "boundary constraints for the emergence of form." He describes morphological organization in terms of organizational levels, and characterizes them. He states "Each organizational level acts on the others in a *non-hierarchical* [emphasis mine] way. Constraints arise as a result of these interactions." He calls into play connectivity early in development, and invokes a "cascade of differentiations and secondary inductions" that shape tissues and organs. Rasskin-Guttman uses the boundaries that are established as landmarks for comparative analysis, and considers that boundaries delimit modules, invoking limb development as a general example. (Hall (2003) questions whether this is really a new approach.) Finally, Rasskin-Gutman provides empirical data and methods of analysis. He asks the appropriate questions: whether law-like principles can be derived at the boundary level, how boundary patterns are related to each other, and whether they constrain the appearance of other boundary patterns. The key question is the first one, for which there is as yet no answer.

The kind of empirical study that might begin to shed some light on such questions is, for example, one that treats individuals as modules (see below). Sanchez and Lasker (2003) investigated colony architecture and patterns of morphological integration by considering the polyps of octocorals as modules. Replication of those modules generates complex colonial forms. They reasoned that if polyp and colony (supramodule) traits are highly integrated, then changes at the module level might change colony architecture. However, if groups of traits evolve semi-independently, then colony structure might not be affected. Their quantitative analysis showed that branching (colony forming) characters of the octocorals are independent of characters of the polyps. They concluded that branching during colony development might represent an emergent level of integration and modularity. This sort of study is hierarchical, integrative, and deals with body plans—the polyp and the colony, and their relationships.

Change happens; evolution occurs; developmental patterns modify. I have alluded to several factors that are becoming understood to promote diversification. They include modification of development by gene duplications, changes in timing of gene activity, changes in interactions among genes, later modifications of interactions among regulatory proteins, etc., all at suborganismal levels of the biological hierarchy of organization. Organismally and supraorganismally, such modifications as change in size or shape, change in use of resources provided by the habitat, the effects of climatic and other environmental modification, etc., can drive directional change in populations, and even speciation and extinction. Despite many well-studied empirical examples of such change, and the fact that organisms are effective in their environments so long as they can outstrip, accommodate, or influence the rate of environmental change, we see the flexibility and permissivity of biological organization so that some taxa respond to environmental change whenever it occurs (Darwin's finches, above) and some remain quite stable morphologically and otherwise (some plethodontid salamanders, above). We do not yet have good ideas as to why members of some lineages exhibit stasis and some phenotypic plasticity, except for correlation with environmental components that we construe as selection factors, and, in some cases, limitations set by aspects of intrinsic architecture—the structuralist perspective. We know much more about what *constrains* development, structure, function, and evolution than we do about what *promotes* flexibility of response and change. Some experimental work is beginning to provide some answers (e.g., Lenski's work on bacteria), and some models generate some tests, but there does not yet seem to be any general or unifying theory. In part, this may be *because* of our emphasis on constraints, rather than the less approachable permissivity. However, this paradigm is changing: Lewontin (2000) emphasized the capacity of organisms to change their environments as they evolve, and that this changes the conditions of evolution. Laland and his colleagues (Odling-Smee et al. 2003) label these processes "niche construction" and they are investigating them as elements of co-evolution and "ecological inheritance." They assert that ecological inheritance enables the persistence of organisms from generation to generation, with their legacy of genes and modified selection pressures. This promises to identify ways that natural selection does, and does not, work, and that "niche construction" may be a major principle in the evolution of organisms.

General Properties: Concepts of the Module and Modularity

The term "module" has been used several times in this article, and requires some attention in this context. The module is a now-standard conceptual tool for analysis in developmental biology, and to some degree in ecology and evolutionary biology. A diversity of definitions of a "module" continue to abound, as Bolker (2000) commented. She wisely sought a definition that would be "applicable at different levels of the biological hierarchy," but also stated that modules must be "defined with respect to a specified level of the hierarchy, so that the general definition could deal with both analyses of emerging causal relationships between levels and studies of the interconnections of modules of the same type." She suggested that designation of a developmental structure, process, or function as a "module" is a testable hypothesis, and that ensuing discussions could provide a common ground for developmental and evolutionary biologists. A year later, Gilbert and Bolker (2001a, b) determined that "signal transduction pathways that integrate embryonic development, . . . both within species and between species," constitute homologous modules, and they then discuss "process homology." Gass and Bolker (2003) return to the theme that organisms are "the integration of partially independent, interacting units and several hierarchical levels" (= modules). Like others, they try to reconcile the "dissociability of elements of the phenotype" that they say evolutionists see with the "process of construction" that they view as the currency for developmental biologists (much of the recent literature on modules is focused on trying to unify development and evolution—EvoDevo; see below).

Some kinds of modules are quantifiable and have reliability for developmental and evolutionary studies, as explored by Clarke and Mittenthal (1992). But Hanken et al. (2001) cautioned that often the definitions of modules currently in vogue (e.g., those for limb development in arthropods and vertebrates) are often narrowly described, despite the caveats expressed, and in order to consider all possibilities, must be expanded. Hanken's example—of limb development in a direct-developing frog, *Eleutherodactylus coqui*, in which many of the "standard" elements of vertebrate limb development (e.g., apical epidermal ridge) are not present—apparently correlated with the reproductive mode and consequent developmental pattern of the frog. But if a "limb is a limb is a limb," the definition of that module must be more inclusive, as a hierarchical approach demands. Nagy and Williams (2001) go much further in their challenge to the "modularity paradigm." They examine the common view that arthropod limbs are series of serially repeated structures, and that limbs therefore are built of identical subunits (= modules). They looked then for functionally semiautonomous mechanisms of limb development that are conserved between species, and the implication that "a modular body plan is a complete and continuous identity of structural modules." Nagy and Williams determined that arthropods are not simply composed of identical repeated units, but that different lineages have different expressions of modularity, so it is an evolutionarily variable character. Furthermore, limbs, though conserved in "some patterning processes that position the limb primordia, much of limb development is not conserved." Nagy and Williams advocate reanalyzing arthropod limb development in terms of axial diversification and mechanisms of segmentation.

Shubin and Davis (2004), while accepting the notion of the limb as a module, also make the point that modules exist at several levels within limbs, from combinations of skeletal and developmental parts to the whole organ, and consider the limb to be "in an environment that is physically separated from the main axis of the body" so that it both has its own hierarchy of organization and is part of the organism's hierarchy. In fact, in my opinion, these examples, taken from an apparently similar developmental and evolutionary process, the establishment of limbs, provide evidence for the emergent properties of interactions of multiple levels of the hierarchy of biological organization of organisms and taxa in which *modification* of *elements* of a common pattern yields a unit, or module, the limb, that is homologous to that of other limbs—and accordingly we could debate the nature of homology.

At the same time as the quest for unification of evolution and development, the "module" has become the currency for searching for and examining patterns in common among like structures at several levels of the hierarchy of biological organization. Ravasz et al. (2002) examined metabolic networks of 43 kinds of organisms and found "small, highly connected topologic modules that combine in a hierarchical manner into larger, less cohesive units . . . ." The modules are spatially and/or chemically isolated functional units that are composed of a diversity of cellular components and have specific functions, but are fundamental to cellular organization. They suggest that the hierarchical network "may be generic to system-level cellular organization."

An example of a similar approach to modules at a very different level of the hierarchy of biological organization is Pederson and Tuomi's (1995) examination of hierarchical selection and fitness in modular and clonal organisms. They consider modules to be the "basic units of construction" and "distinguishable, iterated, multicellular units of construction which jointly make up larger physically coherent units." They considered growth in organisms, colonies, and clones made up of modules, and determined that modular growth generates at least three kinds of hierarchies: (1) morphological (phenotypic characters of both the modules that are repeated by developmental processes and the units themselves [organisms, colonies, clones]). The functional hierarchy (2) deals with the levels of interaction and the relationships between fitness and the phenotypic characters at different levels of modular organization, and the demographic hierarchy (3) is a nested one of units that are replicated by asexual propagation. In the demographic hierarchy, each level has specific birth and death rates so that fitness and selection can be evaluated. Another example is one that treats individuals as modules. Davidson et al. (2003) examine the transitions from isolated individuals to colonies in the development and evolution of metazoans, a study that integrates several levels of the biological hierarchy. These diverse examples illustrate the power of the use of the "module" (with very different definitions of the term among the authors) as a unit of study that can facilitate integration across many levels of the hierarchy of biological organization.

Winther (2001) tried to organize modules into three kinds: structural, developmental, and physiological. He stated that a module can fulfill no, one, or multiple functional roles. He is particularly interested in individuation of modules, and the phylogenetic origin of modularity, particularly the mechanistic bases for that origin. He considered the conceptual and methodological differences between developmental and evolutionary biologists, and pled that the diversity of views regarding modularity be resolved so that a "comprehensive, rather than a piecemeal and fragmentary, evolutionary developmental biology" could be attained. Given that the "module" has become the currency for investigation at all levels of the hierarchy or biological organization, some reconciliation of definition and use is warranted.

Conclusions

I have decried, in various passages in this article, the absence of general or unifying principles that are biologically based and that integrate information about various levels of biological organization. However, most of the empirical examples I select to make my case about the centrality of the organism, the importance of viewing organismal organization from multiple levels of the hierarchy of biological organization, and emergent properties of levels of organization that have effects, often profound ones, on levels both below and above the level studied, *are* ones whose authors are already employing, in various ways, aspects of the approaches I believe will yield a better understanding of biology. Some new general principles are emerging to join those already developed; the genetic toolbox is facilitating understanding of properties that are conserved or constrained, and those that are "new," at many levels of organization. A hierarchical approach is beginning to gain favor among those who wish to understand organisms and their internal and external interactions. Integration of data from different levels of study is almost implicit in hierarchical studies, but should be made explicit, and a clear methodology described. One of the difficulties in determining the degree to which principles are general has to do with the definitions of terms used in common, but with different significance, by subcultures of biology. For example, as I have described, a module can be almost anything, depending on the context of study—a biochemical pathway, a part of an individual such as a limb, an individual, or probably even a species. (Similarly, such concepts as homology can have multiple meanings unless the concept is bounded at different levels.) If not agreement on a definition, at least a clear delineation of the intended use of common terms must be presented to facilitate understanding; without it, the argument developed is seriously weakened. Experimental design must be explicit, and theory or principle being tested clearly characterized. At the same time, it seems clear that a general approach to many questions in biology, if not a unifying theory, is emerging. There are similarities in approach to questions among members of the subdisciplines of biology without much communication or discussion, a convergence on pattern and process analysis. Quantitative tools are much more accessible to biologists of all disciplines.

Winther (2006) attempts to resolve the dilemma of different approaches and definitions by the different subcultures of biology and to provide for a more coherent assessment of biological theories, and, importantly, biological theorizing. He describes two styles of "biological theorizing": *compositional* biology, which concerns parts and wholes and their functions and capacities, and *formal* biology, which deals with mathematical laws and models that represent quantitative terms. Winther believes that comparative and functional morphologists and developmental, cellular, and molecular biologists use the compositional framework, and theoretical population geneticists and ecologists the formal framework. He notes that the fundamental differences in the two styles lie in their methodologies of theorizing. He then comments that each style examines similar sets of phenomena in the same biological system in distinct ways (he uses development in organisms as his example) so that it is possible to reach conflicting conclusions about the processes and entities of the system. Winther states that the theoretical conflicts arise because each style "yearns for completeness," that is, it takes its own methods to develop a general theory as necessary and sufficient to explain all the data in question. He distinguishes between a style of theorizing and a theoretical perspective. The former is a general style (in compositional biology) "that commits to general explanatory, modeling and part-identification strategies." The theoretical perspectives in compositional biology develop "very specific forms of explanation, modeling, and part-identification." Much of Winther's discussion is framed in his concern about the importance of parts in biological theory. He notes in his conclusions that compositional and formal styles of doing biology are radically different, and endorse distinctly different explanatory modes. He states, "It is often supposed that formal biology is *the* theoretical biology." He asserts that, though compositional biology has been called stamp collecting or obsession with mechanistic detail, it too is highly theoretical, especially in the way it deals with part-identification and part-based explanation. Winther finds it ironic that compositional style, fundamental to research in so much of biology, has received little philosophical attention. He believes that a detailed philosophical analysis of compositional biology is necessary for both theoretical and practical reasons. He concludes by saying that the differences have less to do with the part of biology being studied, and more with the deep methodological differences between the two and the consequent differences in theory construction. Given that both styles operate in contemporary biology, Winther recommends that members of each of the two traditions should explore ways of relating to the other culture rather than trying to force theory and experiment into their own worldview, and he closes by suggesting that a "translation manual" between the two biological styles would be useful.

Given that it appears that some fundamentals of perspective are beginning to emerge for certain kinds of studies in biology, even though methodologies and even definitions differ and consequently restrict communication and a different kind of "integration," Winther's attempt to reconcile the differences in styles of theorizing has great merit. More attention should be paid to the tradition out of which one approaches investigation in biology, including theory formation, experimental design, and the nature of analysis and conclusion. A large part of "integrative" biology is communication among scientists, not just bridging within the study framework. Because "integrative biology" is now attempting to equip scientists to be knowledgeable of the approaches and data across subfields of biology in order to examine the properties of the different levels of the biological hierarchy of organization and the influences of those levels on each other, scientists should acquaint themselves with similarities and differences among methodologies and approaches to science. There is room for two styles of theorizing; biologists need to know more about them. I expect that new theoretical perspectives will emerge from integrative studies of organisms throughout the hierarchy of biological organization (levels determined by the complexity of the question); I expect that a first step, one we have been in for a while, is the development of a hierarchy of theory that itself deserves and demands integration.

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