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Varieties of Modules: Kinds, Levels, Origins, and Behaviors

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ABSTRACT This article began as a review of a conference, organized by Gerhard Schlosser, entitled "Modularity in Development and Evolution." The conference was held at, and sponsored by, the Hanse Wissenschaftskolleg in Delmenhorst, Germany in May, 2000. The article subsequently metamorphosed into a literature and concept review as well as an analysis of the differences in current perspectives on modularity. Consequently, I refer to general aspects of the conference but do not review particular presentations. I divide modules into three kinds: structural, developmental, and physiological. Every module fulfills none, one, or multiple functional roles. Two further orthogonal distinctions are important in this context: module-kinds versus module-variants-of-a-kind and reproducer versus nonreproducer modules. I review criteria for individuation of modules and mechanisms for the phylogenetic origin of modularity. I discuss conceptual and methodological differences between developmental and evolutionary biologists, in particular the difference between integration and competition perspectives on individualization and modular behavior. The variety in views regarding modularity presents challenges that require resolution in order to attain a comprehensive, rather than a piecemeal and fragmentary, evolutionary developmental biology. *J. Exp. Zool. (Mol. Dev. Evol.) 291:116–129, 2001.*

How is the development of individuals organized? How are individuals structured? What conditions are required for their evolvability? These questions have become increasingly important in studying the evolutionary developmental biology (Arthur, '88; Raff, '96, 2000; Wagner, '96, '99, 2001a,b). One set of answers to these questions revolves around the notion of modularity—the division of biological structure, development, and physiology into standardized and repeatable parts. Modules, that is, parts, exist at a variety of levels: molecular (including genetic), cellular, and morphological, among others. Although in some cases we may be unable to divide a biological individual into clear modules, in many, if not most, cases we can. Here I use the term "individual" in a broad sense to include, for example, single-celled protists, multicellular metazoans, and multiorganismic hymenopterans (ants, bees, and wasps), also called superorganisms. Modularity allows for evolvability (Kirschner and Gerhart, '98). Hierarchical modules can change and vary, thereby providing the material substrate for the evolutionary process.

Modularity is central to the current evolutionary developmental biology synthesis. Different concepts of modularity appear in fields such as comparative and functional morphology, developmental biology, systematics, and evolutionary biology. Articulating these differences increases understanding among fields and is necessary to bring phenomena pertinent to evolutionary developmental biology under one conceptual umbrella. My analysis of structural, developmental, and physiological modules aims at providing the foundation for the future project of indicating mapping principles among these kinds of modules. I review criteria for identification of modules. I discuss different views on the phylogenetic origin of modularity. I also discuss the tension between two perspectives on individualization and modular behavior—integration and competition. This particular tension, which has thus far not been clearly expressed in the literature, leads to misunderstandings among fields, in particular between developmental biology and evolutionary genetics. I analyze this tension in order to stimulate discussion among fields partial to each of the two perspectives; experiments and models in distinct fields might benefit from such discussion. This article is not about biological phenomena. My data are the

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different concepts biologists employ in understanding the modularity of biological phenomena.

I. STRUCTURAL, DEVELOPMENTAL, AND PHYSIOLOGICAL MODULES / FUNCTIONAL ROLES

There are different theoretical kinds of modules: structural, developmental, and physiological. These theoretical kinds are not necessarily mutually exclusive. For example, (adult) structural modules have a developmental history and are also engaged in multiple physiological processes. Fields tend to focus on one of the kinds—they may study the same organism but comparative morphology and systematics partition it into structural modules, developmental biology examines developmental modules, and physiology and functional morphology individuate parts according to activity, thereby analyzing physiological modules; evolutionary biology could be interested in any of these kinds. Choice of kind of module to study is a pragmatic matter and often there are overlaps among the different theoretical kinds of modules; for example, a particular part of an individual could be both a structural and a developmental module. In some cases, however, it may be best to think of a part as only one kind of module; for example, imaginal discs in insects could be properly considered developmental, and *not* structural or physiological, modules. In what follows I delineate these theoretical kinds of modules and briefly discuss the degree of exclusivity among them in concluding this section.

The discipline of comparative anatomy started with Aristotle (*Parts of Animals*, '93) and received an empirical and theoretical revival in the late eighteenth and early nineteenth centuries [Russell, '82('16); Appel, '87]. Comparative anatomists such as Georges Cuvier, Etienne Geoffroy Saint-Hilaire, and Richard Owen focused primarily on structural modules across taxa [Cuvier, '69(1805); Geoffroy Saint-Hilaire, '68(1818–1822); Owen, 1843, 1846; see introduction in Sloan, '92; Desmond, '82)]. *Structural modules* are parts that compose an organism at a time-slice of ontogeny, typically the adult stage. Individualized bones of vertebrates are paradigmatic structural modules. Perhaps the most detailed discussion of structural modules is found in Riedl ('78) who described biological organization in terms of standard, interdependent, repeated, and hierarchical structural parts. Structural modules at different levels tend to be *compositionally* related. That is, a structural module at a higher level will contain multiple structural modules at lower levels. Furthermore, distinct higher-level structural modules (e.g., liver versus kidney) will contain contrasting lower-level structural modules (cells and proteins specific to the liver versus those specific to the kidney). In short, hierarchical structural modules are often nested.

The discipline of embryology also commenced with Aristotle (*Generation of Animals*, '90) and went through a series of transformations starting with the scientific revolution of the seventeenth century (Oppenheimer, '67; Churchill, '80, '91; Richards, '92). In 1817 the embryologist Christian Pander described the germ-layers of the chick embryo (Oppenheimer, '67; Churchill, '91). The entities of the germ-layer theory (i.e., endoderm, mesoderm, and ectoderm in most metazoan phyla) are paradigmatic examples of *developmental modules*—parts that are conceptualized as changing over ontogenetic time. Another meaning of developmental modules is a dynamic signaling module that induces *other* modules to change. Gilbert et al. ('96) review an example of this second meaning, morphogenetic fields, in the work of embryologists such as Charles M. Child, Hans Spemann, Joseph Needham, and Conrad H. Waddington. In either case, developmental modules participate in change over time. Although the distinction between structural and developmental modules is not always operationally straightforward, the two are conceptually separable. Theorization of the former arose out of the discipline of comparative (structural) anatomy investigating, predominantly, adult features often derived from the fossil record. Conceptualization regarding the latter originated from the field of embryology.

Structural and developmental modules are the traditional units for claims about homology. Biological investigators since the mid-eighteenth century have been interested in comparing parts—modules—across taxa to find patterns of similarity—homology. These patterns have been explained by different causes (e.g., the divine and transcendent order of nature or phylogenetic descent). Further exploration of the rich relationship between modularity and homology is beyond the scope of this article.

Processes and *functional* roles are closely associated. It is important to distinguish physiological or developmental processes from functions. These processes are activities whereas functions are selective or analytical *reasons* for these processes. A process may not have a function. Process and function have been tightly linked since Aristotle and were inextricably connected by the

natural theology interest in design and adaptation (Ospovat, '81) as well as by the work of 19th century physiology (Geison, '87). In this article I will deviate from this theoretical linkage and will differentiate physiological and developmental modules from functional roles. I consider functional roles as abstract categories that characterize the selective advantage of particular modules; material modules often fulfill functional roles.

Physiological modules are individuated by their activity. Similarly to structural modules, physiological modules tend to be studied in adults. The myriad relatively unique and nonoverlapping biochemical reactions occurring in the liver (or kidney, stomach, heart, etc.) singles out the liver (or kidney, stomach, heart, etc.) as a physiological module; in ant colonies we can also differentiate the "organs" of the colony according to relatively unique and nonoverlapping tasks (processes): foraging, maintenance, defense, and rearing. Note that physiological modules often have a function, but not necessarily so. Physiological modules may have consequences that are neutral with respect to either current or past selection; in that case the consequences are not functions (see Allen et al., '98 for contemporary discussions of function; Godfrey-Smith, '93 discusses two prominent views of functions).

Biologists such as Aristotle and Cuvier explained biological organization primarily in *functional* (and, since they did not make a distinction, *processual*) terms—function determined form [Russell, '82 ('16); Ghiselin, '69; Appel, '87; Richards, '92; Gerson, '98]. This perspective has often been resisted in fields such as comparative anatomy and embryology [Russell, '82 ('16), '24]. A module fulfills none, one, or multiple functional roles; furthermore, a particular module can serve various functional roles (e.g., a gene with pleiotropic effects) (see Wimsatt, '74, '97). Consider vision as a functional role. The structural modules of vision in arthropods and vertebrates are eyes, optic nerves, and ganglia or brain visual centers. Eyes serve the same function, but arthropod compound eyes and vertebrate camera eyes are not the same structural module. Furthermore, the physiological modules here are the activities occurring among these various structures. The processes of light-adjustment and focus are completely different in arthropods and vertebrates; arthropods have screening pigments and invariant focus whereas vertebrates vary pupil diameter and have variable focus due to lens muscles. There is, however, similarity in the genetic regulatory systems—the developmental modules—of these structural modules (Quiring et al., '94; Halder et al., '95; Raff, '96). In short, eyes in these two phyla fulfill the *same* functional role, are *similar* developmental modules, and are *different* structural and physiological modules.

Functional roles exist at *hierarchical* levels. For example, digestion can be analyzed into more particular functions such as mechanical and chemical breakdown of food, destruction of possible pathogens in the food, and differential absorption of macromolecules and water. Distinct structural modules of the digestive system (e.g., mouth, stomach, and intestines) fulfill these different functions. Wimsatt ('97) provides a foundation for an analysis of organization in terms of functional decomposition and "functional loops." Of particular interest are "overlapping" functional loops. Digestive functions, for example, are functionally complementary to circulatory and respiratory functions. Wimsatt's analysis of functional roles has received scarce attention but is worthwhile pursuing in an analysis of modularity.

At the conference on modularity in May, 2000 at Delmenhorst (see Raff and Raff, 2000), most presenters discussed either structural or developmental modules. Few characterized physiological modules or functional roles. However, Walter Fontana suggested that employing these different empirical and analytical decompositions ("theoretical perspectives" as described by Wimsatt, '74) would yield distinct spatio-temporally bounded modules. For example, although the heart and the eye are distinct structural modules in adult vertebrates, the mesoderm, which gives rise to the heart, is a developmental module involved in the induction of the vertebrate eye (Jacobson, '66), making the two interacting developmental modules and blurring the distinction between heart and eye as developmental modules. Thus, we return to an unresolved issue. A part may be considered a structural, developmental, and physiological module (e.g., a limb). This would be a case of complete nonexclusivity of these different kinds of modules. Alternatively, a sub-part, together with an aggregate of other sub-parts, may be a structural module, whereas the same sub-part together with a distinct, potentially partially overlapping, aggregate of sub-parts, may be a developmental or a physiological module. This would correspond to Fontana's suggestion and to Wimsatt's notion of "descriptive complexity" (Wimsatt, '74). Finally, a part could be properly considered only one theoretical kind of module (e.g., insect imaginal disks as developmental mod-

ules). These possibilities of overlap and nonoverlap among kinds of modules require further analysis.

II. CRITERIA OF MODULARITY

Here I explore different criteria for the recognition of structural, developmental, and physiological modules. *The more criteria a focal unit fulfills, the more justified we are in deeming it a module*. Other criteria for modularity may exist. Each criterion is not intended to be a necessary condition, nor is the sum of them meant to be sufficient. For example, a unit could still be considered a module even if it did not change over ontogenetic and phylogenetic time (thereby failing to fulfill criterion 4). These are pragmatic and operational criteria whose employment varies from case to case. Each criterion applies differently depending on whether structural, developmental or physiological modules are being examined.

(1) *Modules have differential genetic specifications* (Raff, '96; Wagner, '96; Wagner and Altenberg, '96; von Dassow and Munro, '99; Bolker, 2000; Mezey, Cheverud and Wagner, 2000; Cheverud, 2001). Modules at levels higher than the gene are constructed from genes relatively specific to that module. A gene can exhibit pleiotropic effects across two or more different modules, but, on average, each module has a *unique* and *nonoverlapping* genetic specification. Put differently, the same genes are sometimes expressed in different cell types, but sets of expressed genes and epistatic, as well as epigenetic, sets of interactions are cell-type specific. A good example of such specificity can be found in the differential activation of *Hox* genes for differential segment production in arthropods and vertebrates. Genetic specificity is applicable to structural modules. Consideration of developmental modules raises the further point that genetic specification also includes the regulatory network of genetic processes such as signaling cascades and *cis*-regulatory mechanisms. Whereas a description of the genetic specification of a structural module might just be a list of genes pertinent to that module, an equivalent description of a developmental module would add a *temporal* aspect to the list (i.e., the temporal and causal sequence of gene expression).

(2) *Modules are often repeated and conserved (a) within or across taxa, (b) at or across hierarchical levels, and (c) in different or similar contexts* (Raff, '96; Gerhart and Kirschner, '97). (a) Across taxa, we find structural modules such as cells or microtubules. As Gerhart and Kirschner ('97) describe in their chapter on regulatory linkage, as few as 16 different kinds of cell-signaling mechanisms, which are developmental modules, are conserved in metazoans. Repeated and conserved physiological modules such as sensory-information-processing centers are also ubiquitous (e.g., brains and ganglia). (b) Across hierarchical levels we find modular organization. Raff ('96, p. 330) provides the example of the hierarchical structure of cilia starting from tubulin protein molecules and ending with the ciliary bands (groups of ciliated cells) in embryos (see also Margulis, '93). The same lower-level modules can be part of different higher-level modules. For example, microtubules, hollow tubes consisting of two kinds of tubulin proteins, are part of both the cytoskeleton and cilia. Multiple limbs provide an example of repeated and conserved structural, developmental, and physiological modules at a particular hierarchical level. (c) Across different contexts, modules can develop differently, as in avian limb buds—one pair gives rise to legs, the other to wings. Conversely, across similar contexts modules develop similarly (e.g., tetrapod legs). Repetition and conservation occur because modules are more likely, over both ontogenetic and phylogenetic timescales, to arise from duplications of pre-existing modules followed by their co-option into new functional contexts rather than from the development of new modules (Simon, '62; Wimsatt, '74; Riedl, '78; Raff, '96; Wagner and Altenberg, '96; Gerhart and Kirschner, '97).

(3) *There is strong connectivity within—and weak connectivity among—modules* (Raff, '96; Wagner, '96; Gerhart and Kirschner, '97; Kirschner and Gerhart, '98; von Dassow and Munro, '99; Bolker, 2000). Needham ('33) used the term "dissociability" to refer to weak connectivity (Raff and Raff, 2000). Structural, developmental, and physiological modules are weakly linked with other modules. Wagner ('96) suggests that because of this we can explain the structure of organ systems independently of each other; modules change independently over evolution [i.e., they are "units of evolutionary transformation," Wagner ('96), p. 37]. Put differently, modules are semi-autonomous during both development and evolution. Wagner and Altenberg (Wagner, '96; Wagner and Altenberg, '96) propose a mechanistic reason for weak connectivity among modules: few inter-modular pleiotropic effects. Mechanistic reasons at other levels include cases of scant inductive interaction between developmental modules (e.g., modules

that are spatio-temporally distant) as well as instances of slight, if any, interaction between structural or physiological modules (e.g., vertebrae and salivary glands). Kirschner and Gerhart ('98) suggest a reason at the level of biochemical gene networks. In eukaryotic gene transcription, there is flexibility regarding input kinds (e.g., transcription factors), number, and location (e.g., *cis*-regulatory binding sites for a particular regulatory network are often far from each other). Thus, they argue, despite multiple complex genetic interactions, changes in the kinds, number, and locations of interactions among genes often do not affect the activity of the other genes in the gene network. These interactions are thus relatively dissociated from one another. Note that weak connectivity among modules is a cause of the conservation of their individuality across different taxa and contexts (criterion 2).

(4) *Modules change and vary over ontogenetic and phylogenetic time* (Raff, '96; Wagner, '96; Wagner and Altenberg, '96; Gerhart and Kirschner, '97). An important distinction exists between change and variation (Oyama, 2000; Gordon, '91). Variation is measured at a fixed ontogenetic or phylogenetic time-slice and is measured *across* modules, characters, relations, or processes; change is a measure of alteration over time within a *particular* module, character, relation, or process. There can be change in the variation relations between modules (e.g., heterochronic shifts of two structures in two different taxa—see Gould, '77, and Arthur, 2000). Furthermore, phenotypic variation is often an outcome of modular change. Here, however, I want to keep the distinction simple: *variation is difference at a time-slice, change is transformation over time*. Modules *change* over *ontogenetic* time—this is the definition of one kind of developmental module. Structural modules are conceptualized as time-slices of the changing phenotype and hence do not have a temporal ontogenetic dimension per se. Typically they are adult structures. Some functional roles (e.g., respiration/gas exchange and digestion) do not change ontogenetically—they must be fulfilled at all times even if different structural, developmental, and physiological modules serve these functions. Other functional roles appear, and change, over ontogeny (e.g., sensory and reproductive functions). *Variation* among developmental modules in different taxa is ubiquitous; a module can even be lost in one of the taxa (Raff and Raff, 2000). *Change in*, and *variation among*, modules of all three kinds are rampant over *phylogenetic* time. One of the central efforts of the field of evolutionary developmental biology is to describe the changes within a taxon, and the variation among taxa, in developmental modules over evolutionary time. But sometimes evolutionary change in developmental modules does not lead to change in structural or physiological modules (e.g., Raff's two sea urchin species, *Heliocidaris erythrogramma* and *H. tuberculata*, attain almost identical adult structural and physiological modules despite drastic differences in developmental modules (Raff, '96)). Therefore, changes in developmental modules are not always indicative of evolutionary transformations in structural modules (see de Beer, '71). Depending on the level of analysis, functional roles also change over evolutionary time. Higher-level functions often do not change—organisms across all taxa maintain homeostasis, metabolize, and reproduce. Lower-level functions often do change—flying evolved from walking; both are instances of the higher-level function of locomotion.

A distinction between module-variants-of-a-kind and module-kinds can be made using these criteria. When modules are discussed it is sometimes ambiguous whether the modules are of the same or of different kinds. For example, arthropod limbs and ganglia are clearly distinct (structural and physiological, if not also developmental) module-kinds whereas different crustacean limbs are module-variants-of-a-kind. This distinction emphasizes the importance of modular variation (criterion 4), the status of modules as "units of evolutionary transformation," and the idea of parsimony of "transformation steps" as the criterion for classifying sets of modules into module-variants-of-a-kind (Wagner, '96, p. 37). Comparing crustacean limbs and mouthparts provides an interesting case where module-variants-of-a-kind probably became module-kinds. They became module-kinds when the genes involved in their specification became increasingly unique (criteria 1 and 3; e.g., pleiotropy is severed or new unique genes have few pleiotropic effects). Then a module-kind can vary independently from other module-kinds. Module-variants-of-a-kind have substantial overlap in their genetic specification and thus they partially co-vary–variational patterns are dependent (see Nagy and Williams, 2001 for an empirical discussion related to this distinction).

III. EVOLUTIONARY ORIGINS OF MODULARITY

Is modularity a derived or an ancestral character? This question pertains to the evolutionary

history of structural, developmental, and physiological modules. In this section I shall use the term "module" to include all three kinds. Perhaps individuals became modular as structural and functional specialization of entities evolved (modularity-as-derived). On the other hand, maybe individuals have always been modular (modularity-as-ancestral) and evolutionary transitions between levels of individuality—*individualization*—merely added to this modularity. The formation of higher-level individuals over evolutionary time, that is, individualization, includes multicellular individuals evolving from unicellular individuals (Buss, '87) and superorganisms evolving from organisms (Wheeler, '11, Wilson and Sober, '89, Ratnieks and Reeve, '92; for discussions of individualization see Maynard Smith and Száthmary, '95; Queller, '97; Griesemer, '99; Michod, '99a).

Some hold that modularity is a derived character. Wagner ('96) suggests a scenario with directional selection on character A and stabilizing selection on a suite of other characters. Dissociation of these characters into two independently varying modules—character A and all the other characters—will be selectively advantageous (Wagner, '96). Such dissociation is caused by the severing of genetic pleiotropic effects between character, or module, A and the suite of other characters, or modules. This is what Wagner calls *parcellation*.

Gerhart and Kirschner present a clade-selection view for the origin of modularity. They hold that lineages containing organisms with larger amounts of modularity left more offspring—more lineages—than those with smaller degrees of modularity (Gerhart and Kirschner, '97; Kirschner and Gerhart, '98; on clade selection see Eldredge, '85; Lloyd, '88; Gould and Lloyd, '99). The higher the degree of modularity, the larger the opportunity for, and range of, variation produced. More variation results, *ceteris paribus*, in more offspring lineages. In one sense they believe that modularity is ancestral—modularity existed in the successful clades from the beginning. In another sense they hold that modularity is derived—even in clades with modularity, modularity increased over time.

Another argument for the evolutionary origin of modularity stems from literature pertinent to complexity theory (Simon, '62; Wimsatt, '74). Herbert Simon employs a parable of two watchmakers, "Tempus" and "Hora," to argue that a modular hierarchical organization is more efficient than a nonhierarchical one (Simon, '62). While Tempus constructs his watches from start to finish, Hora organizes his watches into two hierarchical levels of subassemblies. Given constant interruptions from potential or actual customers, Hora has a higher probability than Tempus of finishing any given watch he starts. If Tempus gets interrupted he must start over; if Hora gets interrupted he only loses his work on a subassembly. Although modules do not remain unfinished or fall apart in the way that watches and their components do, this engineering parable can be analogized to the evolutionary process (Wimsatt, '74). Descent with modification will occur more efficiently in modular organisms, and lineages, where whole new subassemblies (i.e., modules) are not re-invented but are, instead, duplicated from existing ones and co-opted for new functions. It is unclear whether this is a modularity-as-derived view or a modularity-as-ancestral position.

Before turning to arguments for modularity-as-ancestral, let us examine two models for individualization: *division-with-adhesion* and *merging* (Fig. 1). Queller ('97) calls the models "fraternal" and "egalitarian," respectively. Queller ('97) opines that kinship provides the alliance-forming mechanism for fraternal alliances. The related units of individuals such as a multicellular organism consisting of related cells or an ant-colony consisting of related ants cooperate—reproductive and somatic division of labor occurs—because of kin selection. With respect to egalitarian alliances, reciprocal efficiency-increasing division of labor furnishes the cooperation mechanism. The units of a prototypic cell—proto-mitochondria, proto-chloroplast and proto-cell—each benefited from adopting distinct tasks and reproducing individually in a coordinated and controlled fashion. Note that merging (Fig. 1C,D) could occur between fraternal (i.e., related) units—this is the only case where the two distinctions do not coincide exactly (David Queller, personal communication). The amount of kinship among modules of fraternal and egalitarian alliances is variable due to, for example, (1) somatic mutation in fraternal alliances, making the division-with-adhesion units more different than without such mutation, and (2) population sub-division of egalitarian units, making the merging units more similar than without such structure. The distinction will therefore here be made on topological and mechanistic, rather than on kinship, grounds.

Both division-with-adhesion and merging were required for the evolution of metazoans. These processes provided some "modularity for free"—early metazoans already contained structural, developmental, and physiological modules such as

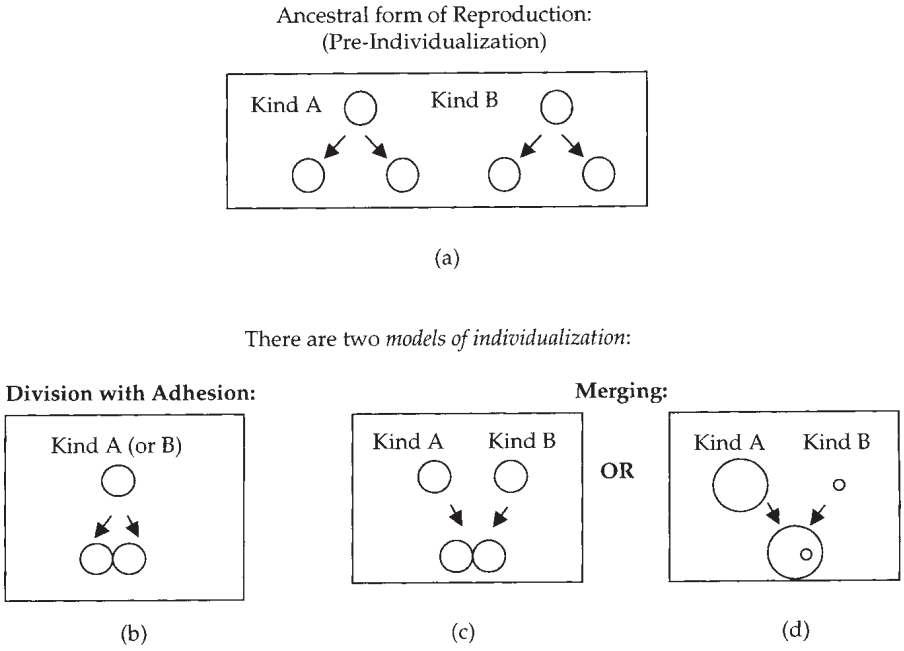

Fig. 1. Two models of individualization in their most general topological form. Circles represent discrete units such as chemical reaction cycles, cells, or organisms. Arrows indicate the production of offspring units. (**A**) The ancestral form reproduced by producing units at the same level. Higher-level individuals evolved either by the offspring units (**B**) adhering, as in the case of the evolution of multicellularity, or merging, as in the case of (**C**) slime molds or (**D**) endosymbiosis. Once a higher-level individual is produced, subsequent units at that level may be reproduced in a variety of ways. In (B) a subset of the adhering units might separate off (e.g., gametes) or the whole individual could divide (e.g., fission in plants). In (C) and (D) each kind of unit generally reproduces itself next to or inside the other unit [e.g., (C) slime mold variants or (D) mitochondria in eukaryotic cells]; one unit may, however, reproduce in a physically-detached manner (e.g., termites initially develop without their intestinal cellulose-digesting symbionts—they must acquire these from adults by anal feeding). Although there are many modes of reproduction once higher-level individuals arise, division with adhesion and merging are the two general topologies for their origin.

genes, organelles, and cells. Certainly some structures (e.g., organs) as well as labor division were derived characteristics, but a significant amount of modularity was ancestral—it arose "for free," simply as a consequence of the transition to a new level of individuality. For example, the merging process of endosymbiosis provided a significant amount of ancestral modularity for free (Margulis, '93; Maynard-Smith and Száthmary, '95).

A variety of views and mechanisms have been proposed for the evolutionary origins of modularity. Although they are not necessarily in competition, further work is required to characterize the appropriate mechanisms for particular contexts. The pertinent mechanism will depend on hierarchical level and kind of module under consideration.

IV. DISCIPLINARY DIFFERENCES BETWEEN DEVELOPMENTAL AND EVOLUTIONARY BIOLOGISTS

Two important sets of differences exist between developmental and evolutionary biologists. The former stress similarity and integration whereas the latter emphasize variation and competition. In this section I want to elucidate how these differences are pertinent to modularity and articulate the possible relations between them. Resolution of these differences is necessary for an evolutionary developmental biology synthesis.

The fact that developmental biologists stress *similarity* among, and *stereotypical* patterns of change for, particular modules, characters, processes, and relations whereas evolutionary biologists emphasize *variation* among, and *differences* in patterns of change for, these phenomena has been discussed but requires more attention (Raff, '96, p. 20–22; Griesemer, '94). Developmental biologists seek to compose the narrative of the typical developmental pathway for a developmental module. For example, presentations at the Delmenhorst conference regarding *cis*-regulatory networks generally assumed that typological kinds of networks exist (i.e., a particular gene network in a particular species was identical in all organ-

isms of that species). Identity of elements leads to stereotyped patterns of change in the module. Interestingly, developmental biologists utilize the power of variation in techniques such as mutational analysis. But examining mutants, that is, variation, is merely a means to the description of the stereotypical developmental pathway. The goal, the descriptive narrative, usually lacks the sub-narratives of ontogenetic differences among mutants. Similarly, in developmental genetics typical gene sequences are produced for a particular species. Input sequence variants are compared to produce the consensus species sequence, thereby eliminating variation in favor of similarity. Abolishing variation seems to be a desirable and useful strategy in a field that seeks to understand the robust developmental mechanisms of modules.

Evolutionary biologists study the origins of intra- and inter-specific diversity. They investigate modular variation at multiple levels. Regardless of which mechanism(s) the particular evolutionary biologist considers most important (e.g., natural selection, genetic drift, developmental constraints, migration), she is invariably interested in variation as material for evolutionary change. Evolutionary biologists understand developmental biology as the field that provides the rules of transformation, or constraints, for variation (Maynard Smith et al., '85; James Cheverud, personal communication; for interesting discussion of the implications of using the term "constraint" rather than "cause" see Gould, '89 and Oyama, '93). More discussion is required on similarity and variation among modules as well as fixity and change of modules.

A significant tension between developmental and evolutionary biologists lies in the role assigned to selection both when (1) a transition between levels of individuality, that is, the process of individualization, occurs and (2) when a transition has occurred and integrated developmental wholes, that is, individuals, have been established. I characterize two perspectives: *integration* and *competition* (See Winther, 2002 for more detailed analysis). Developmental biologists, as well as morphologists, tend to hold the integration view. They are interested in the particular interactive mechanisms within and among modules. Evolutionary biologists, in particular evolutionary geneticists, generally adopt the competition view. They are interested in the multi-level selective forces that exist within and among individuals and that change the frequencies both of hierarchically organized modules and of the genes involved in their determination. I will briefly analyze these two perspectives in the context of two fields of investigation: the process of individualization and the process of modular behavior within well-integrated individuals. I will then provide three different interpretations of these debates.

As a consequence of individualization previous lower-level individuals become modules of higher-level individuals (Fig. 1). As a focal example, let us consider the transition from unicellularity to multicellularity. According to the integration perspective, a mechanistic story involving cell-adhesion and cell-signaling processes accounts for the origin of the higher-level individual (Bonner, '98). A separate hypothesis regarding the division of labor between different cells (modules) could also be generated. This co-option of modules to new specialized functional contexts leads to multicellular individuals with higher fitness than either their unicellular or multicellular competitors which have, respectively, none or less division of labor. Some proponents of the integration perspective deny selection among modules as they originate and change over evolutionary time; *selection occurs only among the highest-level integrated individuals*. Integration, according to these proponents occurs rapidly during transitions (Rudolf Raff and Lewis Wolpert, personal communication). Other adherents of the integration perspective hold that multi-level selection occurs *only* during these transitions and not once well-integrated individuals are established (Ellen Larsen, Daniel McShea and Günter Wagner, personal communication).

According to the competition perspective, multilevel selection fueled the transition from unicellularity to multicellularity. At the cell-lineage level there was, and continues to be, strong selection favoring variant lineages (developmental modules) that proliferate at rates higher than others or that become reproductive (i.e., germ-line) lineages, or both. At the organism level there was, and still is, strong selection for mechanisms that *control* such variants (Buss, '83, '87; Maynard Smith and Szathmáry, '95; Michod, '99a,b; Blackstone and Ellison, 2000). Selection thus works in opposite directions at the two levels. Control of early cell division by maternal cytoplasmic mRNA and proteins, early germ-line sequestration, and secondary somatic differentiation either originated or were maintained, or both, by strong selection at the organism level (Buss, '87). Raff suggests that developmental interactions, rather than multilevel selective processes, explain these three phenomena; if a selective explanation were desired then some hypothesis in terms of increased eco-

logical efficiency or developmental integration, or both, leading to higher reproductive success at *only* the organism level would be the correct one (Rudolf Raff, personal communication). Not only do the explanatory mechanisms differ between these perspectives, but which phenomena require explanation also differ.

Group and kin selection arguments can be discerned in the competition view (on the relationship between group and kin selection see Hamilton, '64a,b, but especially, '75; Price, '70, '95; Uyenoyama and Feldman, '80; Wade, '80, '85, '96; Lloyd, '88; Queller, '92a,b; Sober and Wilson, '98). Group selection exists whenever there is differential reproductive success of groups—this is usually accompanied with lower-level individual selection, thereby allowing for a multi-level selective process. When groups have a kin structure, kin selection also exists. Buss ('87) focuses on a defector-cooperator fitness structure in which defectors have higher fitness than cooperators within groups, but lower fitness at the group level; groups with higher defector frequency have lower group fitness. In this case the group is the organism and the individual is the cell. There is group (organism) selection for control methods, such as germline sequestration, to increase cell cooperation and diminish cell defection.

Buss does not consider relatedness among cells and thereby overlooks the relevance of a special form of multi-level selection—kin selection. The basic idea of kin selection is that an allele that is correlated with, or causes, a behavior lowering the immediate fitness of a benefactor may actually increase in frequency (i.e., be selected) when the recipients of the behavior are close kin who have a high probability of carrying the same allele. Although kin selection is sometimes believed to occur at only one level—usually at the genetic—Feldman, Queller, Uyenoyama, Wade, and Wilson, among others, have shown that it has an individual as well as a group component (see previous references). Gene frequencies change as a consequence of multi-level selective dynamics of kin groups. Maynard Smith and Szathmáry ('95), as well as Michod ('99a,b), emphasize the high genetic relatedness among cells of a single organism. This high relatedness, which is a consequence of the fact that all cells arise from a single cell, allows for kin selection. Michod describes this kin selection using the hierarchical Price covariance equation—there is scant within-organism (among-cell-module) selection, whereas there is significant among-organism selection. This is precisely Wilson and Sober's definition of an individual (Wilson and Sober, '89, p 343). Kin selection is a strong force for the origin and maintenance of cell cooperation. At least two forms of multi-level selection are therefore involved in the evolution of multicellularity: (1) group (organism) selection for higher-level control methods and (2) kin selection, which has group (organism) and individual (cell) components. Individualization at other levels also involves these two forms of multi-level selection.

Note that the criteria utilized to *define* an individual at a focal level differ between the two perspectives: the integration view employs developmental and physiological mechanisms whereas the competition position assesses the relative strength of selection at different levels.

These two perspectives also differ in their description of modular behavior *within* well-integrated individuals. The integration view focuses on *mechanistic nonselective* interactions among modules. Such interactions often lead to complex emergent behaviors. Larsen, a cell biologist, and McLaughlin (Larsen and McLaughlin, '87; Larsen, '92) describe emergent tissue and organ behaviors from "simple-minded" genes and cells. They propose that although cells (physiological modules in this case) can only exhibit a few fundamental behaviors (e.g., division, growth, matrix secretion), interactions among such modules can give rise to complex behaviors. Gordon, a behavioral ecologist, and co-workers show that interactions among individual ants—which are structural modules of the colony, developmental modules that change over time, and physiological modules that divide labor—cause complex emergent behaviors (Gordon et al., '92; Gordon, '99; Winther, 2001). The integration view also pervades complexity theory, which investigates stable attractor states reached by complex networks of often-simple components (Kauffman, '93; see also Goodwin, '94). In this literature, selection is often, but not always, modeled as acting on a *whole* network. Much work in developmental biology and physiology that is not concerned with emergent behavior, also adopts the integration approach (Delmenhorst conference presentations; see also Mackie, '86).

In contrast, the competition approach conceptualizes modular behavior as a fundamentally *selective* process in which the frequencies of modules, and the genes involved in determining them, change. Otto and Orive ('95), who are both population geneticists, show that intra-organismal cell-lineage selection can drastically reduce the harmful mutation rate found in the offspring of

such an organism; furthermore, such selection can also diminish the mutation load found within a population (see also Klekowski and Kazarinova-Fukshansky, '84). Organisms with the appropriate amount of intra-organismal selection would increase in frequency as a consequence of organismic and, possibly, demic selection. Nunney ('99) also investigates the role of multi-level selection in organisms using the example of cancer (see also Buss, '87). A cancer is "reap[ing] a short-term reproductive benefit at the expense of the long-term success of the lineage (the individual) from which [it] ar[ose]" (Nunney, '99, p 248). Otto and Orive, as well as Nunney, investigate competition among modules of well-integrated organisms (see also Hurst, Atlan and Bengtsson, '96; Michod, '99a).

The difference between these two perspectives is emphasized by an important distinction between developmental modules that reproduce individually as a unit and those that do not (Günter Wagner, personal communication). We need to acknowledge that reproductive capacity can be lost or acquired over time (James Griesemer, personal communication). *Reproducer* modules are entities that reproduce, at some specified time, within higher-level individuals; as in the case of somatic cells, most of these modules reproduce in a limited "dead-end" fashion (I use "reproducer" in the sense used by Griesemer, 2000). *Nonreproducer* modules are emergent entities such as internal organs, limbs and possibly cell vacuoles that do not reproduce individually as a unit at a particular time; they are often composed of reproducer modules. In most cases, reproducer modules are part of the biological genealogical hierarchy. That is, these modules reproduced as independent wholes in the phylogenetic past. But some reproducer modules may originate from previously nonreproducer modules; such cases would be rare (James Griesemer, personal communication). Furthermore, nonreproducer modules are generally not units of the biological genealogical hierarchy. However, cases such as complete worker sterility in some ant genera are exceptions. These are examples of nonreproducer modules that are part of the biological genealogical hierarchy and not emergent entities within individuals. The competition approach can only be interested in reproducer modules since those are the only ones that can be part of a multi-level selective process at some specified time. The integration approach is interested in both kinds.

A distinction between replicators and interactors is often made (Dawkins, '85 ('76); Hull, '80; Brandon, '82; for a review, see Lloyd, 2000). Replicators are units of which copies are made. Interactors are units that interact, as a whole, with their environment and consequently survive differentially; this differential survival leads to the differential replication of the units—replicators—that produce the interactors. Typically, genes, or groups of genes in linkage disequilibrium due to, for example, epistasis for fitness, are considered replicators. Hierarchies of replicators have also been suggested (Brandon, '90; Roth, '94). Higher-level hierarchical modules and individuals are considered interactors. Griesemer's process-based reproducer concept is likely to lead to a reformulation of the function-based replicator/interactor distinction (Griesemer, 2000). Although a complete characterization of the competition view would require an analysis of modules as replicators, interactors, and/or reproducers, the general contrast between the integration and competition view that I have developed here can be articulated without such an analysis (see also Winther, 2002).

Now that I have sketched these two different approaches I will analyze three interpretations regarding their relation: the *irreconcilable*, *different questions* and *nonoverlapping* interpretations. Note that here the analysis is raised one conceptual level. Up to this point in the article, I have discussed commitments employed in the study of nature. Now I will discuss interpretations regarding the relationship between two particular perspectives—integration and competition. Put differently, now the interpretations regarding the perspectives, rather than the perspectives themselves, are under study.

One interpretation is that the two perspectives are irreconcilable. Consider the following question, Why do cells cooperate? The integration perspective would answer this question in terms of *mechanistic integration* at the cellular level; this provided a fitness advantage at the organismic level. The competition perspective would employ multi-level kin selection processes to account for what it interprets as *selective cooperation* by the cells. The integration view holds that only one level of individuality in any particular case is also the level of selection. Competition occurs only among functionally-integrated and ecologically-efficient modular systems. Lower-level competition does not occur, "Competition [between cell lineages] really means only a breakdown in a developmental regulatory system" (Raff, '88, p 445). Wolpert formulates similar critiques of Buss ('87) (Wolpert, '90). In contrast, the competition view

argues that all levels of individuality are actual or potential levels of selection. Integration mechanisms are byproducts of multi-level selection and exist precisely to suppress within-individual selection. If the irreconcilable interpretation is correct, then experimental tests to decide between the two perspectives should be possible.

Although some proponents of the integration approach deny multi-level selection (Raff and Wolpert), others do not (Larsen, McShea, and Wagner). Similarly, many proponents of the competition view take integrative mechanisms seriously even if they focus on the *subset* of mechanisms that suppress modular defection. They do not deny that other mechanisms are present. Thus, a different questions interpretation exists at the sociological level of analysis. That is, proponents of each of these views are focusing on different aspects of the processes of individualization and modular behavior. One side is interested in developmental and physiological processes, or proximate causes, whereas the other side is interested in selective dynamics, or ultimate causes. Each perspective also considers different kinds of answers as legitimate explanations. This interpretation has its source in the "semantic view of theories" in philosophy of science (van Fraassen, '80; for an application of the different questions approach see Lloyd, 2000). The semantic view emphasizes that the relation between theory, data, and the questions used to frame investigations *depend* on the interests and preferences of the investigator. There is no unitary relation between theory and data—such relations depend on the commitments of the researcher.

Although it may be true that, sociologically, most researchers do focus on one or the other perspective, some embrace both perspectives and argue that integration is appropriate for describing modular behavior within well-integrated individuals whereas competition is suitable for describing the multi-level selection dynamics during individualization (Günter Wagner, personal communication). This nonoverlapping interpretation accepts that different questions can be asked but claims that some questions are more appropriate than others for particular processes. For example, questions regarding multi-level selection are considered inappropriate once well-integrated individuals are established. In that case, questions regarding integration and the formation of nonreproducer modules (e.g., internal organs and limbs) would be pertinent. Multi-level selection questions become appropriate when individuality is "lost" through, for example, somatic-cell mutation or intra-colony genetic variation. In short, this interpretation is a claim about processes in nature: the competition approach is important during individualization whereas the integration perspective is pertinent when well-integrated modular individuals exist.

The logical structure of this division of interpretations is that questions of interest can either be understood as *different* or the same. If they are the same, then the answers provided by each perspective can be seen either as *irreconcilable* or as *nonoverlapping*, that is, applying at different times or in distinct contexts. A philosopher of science, whose work is to investigate different research programs and therefore need not commit to any particular one, might be inclined to choose the different questions interpretation. A scientist, who must commit to a particular research program, methodologically if not intellectually, at least for a period of their career, would probably choose either the irreconcilable or nonoverlapping interpretation. Here I will not further adjudicate among interpretations.

V. VARIETIES OF MODULES: CONSENSUS AND DISAGREEMENT

As revealed by the variety of concepts of modularity, biologists approach the nascent field of evolutionary developmental biology from the perspective of their own field whether it be comparative or functional morphology, systematics, developmental or evolutionary biology. An analysis of modularity is therefore a useful locus for an analysis of biological concepts and "theoretical perspectives" (Wimsatt, '74). Here I have articulated three different theoretical kinds of modules: structural, developmental, and physiological. Every module fulfills none, one or more functional roles; the same functional role can be performed by one or more modules (section I). More work is required to express the empirical and theoretical mapping principles among these kinds of modules. There are two further orthogonal distinctions regarding modules: module-kinds versus module-variants-of-a-kind and reproducer versus nonreproducer modules. There are modules at various levels and biologists agree on individuation criteria for modules (section II). Biologists disagree about the phylogenetic origin of modularity (section III).

A particularly important difference exists between two perspectives on individualization and modular behavior—integration and competition (section IV). Morphology and developmental biology tend to employ an integrative perspective whereas evolutionary genetics generally uses a

competition perspective. Further work is required to determine which of these perspectives, if either, tend to be adopted in systematics, ecology, and paleontology, among others. Some researchers have implicitly or explicitly begun to synthesize these perspectives (Gould and Lloyd, '99; Griesemer, 2000; Schlosser, personal communication). However, the kind of, and even desirability of, synthesis between integration and competition perspectives requires further investigation. In summary, although no consensus over the concept of modularity exists, further empirical and conceptual work on the topic is necessary and welcome.

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