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The Innovation Triad: An EvoDevo Agenda

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ABSTRACT This article introduces a special issue on evolutionary innovation and morphological novelty, two interrelated themes that have received a remarkable increase of attention over the past few years. We begin with a discussion of the question of whether innovation and novelty represent distinct evolutionary problems that require a distinct conceptualization. We argue that the mechanisms of innovation and their phenotypic results—novelty—can only be properly addressed if they are distinguished from the standard evolutionary themes of variation and adaptation, and we present arguments for making such a distinction. We propose that origination, the first formation of biological structures, is another distinct problem of morphological evolution, and that together with innovation and novelty it constitutes a conceptual complex we call the innovation triad. We define a problem agenda of the triad, which separates the analysis of the initiating conditions from the mechanistic realization of innovation, and we discuss the theoretical problems that arise from treating innovation as distinct from variation. Further, we categorize the empirical approaches that address themes of the innovation triad in recognizing four major strands of research: the morphology and systematics program, the gene regulation program, the epigenetic program, and the theoretical biology program. We provide examples of each program, giving priority to contributions in the present issue. In conclusion, we observe that the innovation triad is one of the defining topics of EvoDevo research and may represent its most pertinent contribution to evolutionary theory. We point out that an inclusion of developmental systems properties into evolutionary theory represents a shift of explanatory emphasis from the external factors of natural selection to the internal dynamics of developmental systems, complementing adaptation with emergence, and contingency with inherency. *J. Exp. Zool. (Mol. Dev. Evol.) 304B:487–503, 2005.*

Evolutionary theory treats morphological evolution primarily from the point of view of variation and adaptation of characters. This approach provides satisfactory explanations of the targeted phenomena, but the adaptationist program has also been criticized for its limited scope (e.g., Williams, '66; Gould and Lewontin, '79; Emlen et al., '98). Such criticisms concern the exclusion of characters that are non-adaptive in their origin, as well as the exclusive selectionism and the gene centrism of the received theory, but rarely has an expanded or alternative research program that would overcome these shortcomings been suggested. Over the past several years, much as a consequence of a rising interest in understanding the role of embryonic development in evolution (EvoDevo), new programmatic goals have been addressed, such as constraints, modularity, or epigenetic factors in the origin of organismal body plans. This expanded approach to evolution has also brought to the fore a new set of related themes termed ''novelty'', ''innovation'', and ''origination'' (e.g., Carroll et al., 2001; Wagner, 2001; Gottlieb, 2002; Hall and Olson, 2003; Müller and Newman, 2003a; West-Eberhard, 2003) that together represent a conceptual complex that we term the ''innovation triad''. This special issue explores the plurality of views and positions in innovation research characteristic of a nascent area of scientific attention. The articles represent a selection of up-to-date accounts of empirical and theoretical approaches to innovation. In this introductory

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chapter, we will survey the conceptual foundations of the innovation triad, the problem agenda of a research program on innovation, the practical research initiatives taken so far, and the theoretical consequences of this approach for evolutionary theory.

The rapid spread of the terminology of innovation revived a long-standing discussion about whether or not the referenced phenomena and their underlying causal mechanisms are accommodated by the neo-Darwinian framework. Some authors argue that the appearance of new traits or characters that had no antecedent in the history of a taxon, and hence exhibit neither a phenotypic nor a genetic variation that is specific for the new trait, is not—or not fully—addressed by the received theory (Wagner et al., 2000; Love, 2003). Others see no necessity to invoke anything but the standard mechanisms of variation and selection to account for novelties (e.g., Hall, 2005, this issue). But there is a widespread consensus that the generative mechanisms of morphological evolution are underrepresented in the standard theory, which is one reason EvoDevo has expanded so explosively in the past decade. The EvoDevo program may in fact be able to answer perennial calls for an expansion of neo-Darwinian theory if it can demonstrate that it is able to solve biological problems that are not solved by the traditional discipline or by one of its subdomains, such as population genetics or developmental genetics (Müller, 2006). The innovation triad could become one of the key themes in this quest.

In exploring the potential of the innovation triad to represent a distinct domain of EvoDevo research, a number of questions arise. Among these the most important are: What is actually meant by ''origination'', ''innovation'', or ''novelty'', i.e., are there unambiguous definitions and examples of these phenomena? At what levels can these problems be addressed, and can this lead to distinct empirical research projects? Do such projects generate new insights, and are there good examples of experimental results? And what are the theoretical consequences: is anything explained that cannot be explained by the conventional theory, that is, is there at all a need for a distinct conceptualization of morphological novelty and the processes of origination and innovation? There is no agreement as yet on most of these questions, but clearly it only makes sense to concentrate on these issues if it can be shown that we deal with a sufficiently distinct problem, i.e., that the innovation triad is not part of the adaptation complex.

ADAPTATION vs. NOVELTY—VARIATION vs. INNOVATION

To make a distinction between adaptation and novelty implies that novelties represent a class of phenotypic change that differs from adaptive variation and hence constitutes a separate evolutionary problem in the same way that speciation is an evolutionary problem that is distinct from adaptation (see also Wagner and Lynch, this issue). Two possibilities can justify a distinction between adaptation and novelty: (1) the *mechanisms* involved in the generation of novelty may be different from those underlying variation and adaptation, and (2) the *consequences* of novelties could influence the dynamics of phenotypic evolution in a way that differs from variational change. In order to appreciate these distinctions, it is necessary to recapitulate briefly the essence of evolution through variation and adaptation.

Adaptations are generally understood as the evolutionary improvement (with regard to a particular performance) of an existing unit of phenotypic organization, based on the processes of heritable variation and natural selection (Futuyma, '86). It is widely agreed that adaptations augment the reproductive success of their bearers. Thus, favorable modifications will spread in a population and contribute to its overall ecological suitedness. The study and explanation of this aspect of phenotypic evolution constitutes what has been called the ''adaptationist program''. It treats phenotypic characters from the point of view of their adaptive significance. The key elements of this approach are: (1) the choice of a given character or trait for which an evolutionary adaptation is to be considered; (2) the demonstration of heritable variation for that trait; and (3) the demonstration that natural selection was able to act on this variation. The latter is generally regarded as the sufficient causal factor in the generation of adaptations. Hence natural selection represents the key element of all theoretical explanations of adaptations. Although heritable variation is sometimes difficult to demonstrate, and the determination of the precise role of natural selection can be problematic in a specific case, there is ample field and experimental evidence that these processes are active in adaptive evolution (Futuyma, '86; Rose and Lauder, '96). Further support comes from the

predictability of the expected changes of traits under selection.

To distinguish novelty from adaptation would mean that there is a difference in one or several of the key elements noted above. One of these differences already appears in step one: the choice of the character or character complex that is to be studied. In adaptation studies, the character is usually chosen for its capacity to demonstrate quantitative variation and adaptive modification. This requires that the character is already in existence in the chosen species; otherwise, it cannot exhibit any degree of variation. A novelty, by contrast would be a character that does not belong to the constitutive range of variation of a phenotypic precursor. Hence it is not usually chosen in such kinds of studies. Further differences lie in steps two and three, namely that heritable variation cannot be demonstrated at the incipient stage, and therefore selection could not act directly on the character since it is not yet in existence. Note that this does not automatically mean that selection has no role in the processes of innovation, since indirect effects are not excluded.

In the case of novelty, a number of definitions have been proposed. Early definitions have linked novelty to function. Mayr ('60) proposed that ''tentatively, one might restrict the designation 'evolutionary novelty' to any newly acquired structure or property which permits the assumption of a new function''. Such a broad definition, however useful at a taxonomic level, makes it difficult to distinguish between quantitative variational change (which may permit a new function), and qualitative structural novelty (which may also permit a new function) although Mayr favored the latter. Subsequent definitions have focused on the fact that novelties usually represent deviations from quantitative variation and constitute qualitative differences, as stated by Müller ('90) ''a qualitatively new structure with a discontinuous (developmental) origin'' or by West-Eberhard (2003) ''a novel trait (based on) a qualitatively distinct developmental variant''. Both definitions address the mechanistic mode of novelty generation by linking its origin to development, and they emphasize the qualitative change, although the former excludes a variational origin whereas the latter does not. Yet other definitions are associated with the term ''key innovation''. Here the definition of novelty is linked to its role in macroevolutionary processes (see below), when a new trait permits the exploitation of a new adaptive zone or facilitates species diversification (Liem, '74, '90; Galis and Drucker, '96).

The definitions of novelty provided above, although useful in their respective contexts, fail to provide an operational criterion that can distinguish novelty from variation at the phenotypic level. A suitable criterion can be based on a comparative character definition of morphological traits, such as provided by the homology concept. The homology criterion is part of a definition proposed by Müller and Wagner ('91), which says ''a novelty is a new constructional element in a bodyplan that neither has a homologous counterpart in the ancestral species nor in the same organism (serial homologue)''. This definition excludes characters that lie within the normal range of variation, or deviate only quantitatively from the ancestral morphological condition. But it includes those cases in which a new homologue has arisen through individualization of a preexisting serial element. The definition leaves the mechanistic mode of novelty origination open, i.e., it does not restrict it to developmental mechanisms alone. Although it can be argued that this definition is narrow, it at least permits one to identify unambiguous cases of novelty and is easy to apply (but see West-Eberhard, 2005, this issue).

The use of homology criteria in the novelty definition has sometimes led to the assumption that novelty is synonymous with various forms of apomorphy, as used in systematics, e.g., with synapomorphy (Stone and Hall, 2004) or autapomorphy (Hall, 2005, this issue). However, such a conflation is difficult to justify. Attributions of autapomorphy and synapomorphy are statements about the distribution of derived characters in taxonomical groups. But novelties represent the source or initial character from which these (syn- or aut-)apomorphies are derived. Feathers were a novelty when they first arose, but are not a novelty in extant birds, for which feathers are autapomorphic. The relevant EvoDevo problem of novelty is not the nature of the derived state (syn- or autapomorphic distribution among taxa) but it is one of mechanistic (developmental and evolutionary) origin. Although we may use the tables of apomorphies in a search for interesting novelties, the two categories are not equivalent, as emphasized earlier (Müller and Wagner, '91; see also Minelli and Fusco, 2005, this issue). Some apomorphies are rooted in a novelty, others are not. This is because the absence of a character, quantitative variations of size and shape, or a specific combination of traits can also qualify as an

apomorphy in the taxonomical sense. A second reason why apomorphies should not be regarded as equivalent with novelty is precisely because in doing so the differences in their causal origin are blurred. Apomorphies are easily explained by variation, novelties are not. Hence it does not help clarify the issue to equate novelty with apomorphy or one of its subcategories.

Just as a distinction can be made between adaptation and novelty as two classes of phenotypic outcome, it might prove necessary to make a distinction at the mechanistic level as well, regarding the processes that bring about such changes. As suggested above, the mechanisms underlying standard variation cannot be considered the source of phenotypic novelty if we accept that novelties represent characters for which no ancestral homologue has existed. The innovation mechanisms that introduce a new homologue into an existing, lineage-specific character assembly (bauplan) could be multifold. The possibilities include mutational and recombinatorial events, but other explanations favor a role for specific responses of developmental systems either to natural selection or to direct environmental induction, as discussed below.

Although the terms innovation and novelty are often used synonymously (e.g., Hall, 2005, this issue, but cf. Love, 2003; Müller and Wagner, 2003), the distinctions emphasized above suggest that *innovation* should be used preferentially to refer to the evolutionary modes and mechanisms underlying novelty generation, whereas *novelty* should designate a phenotypic outcome, such as ''morphological novelty'', ''physiological novelty'', or ''behavioral novelty''. But since *innovation* is frequently used in a non-specific sense so as to include the origins of major taxonomical groups as well, the use of qualifiers such as ''morphological innovation'' (= novelty) or ''functional innovation'' would also be sufficient to distinguish the products from the processes of innovation. In the usage adopted here, innovation pairs with variation at the level of evolutionary mechanism and novelty pairs with adaptation at the level of phenotypic result.

We have suggested elsewhere that ''origination'' is yet another distinction that should be made in dealing with the generation of novelty (Müller and Newman, 2003b). Origination refers to the specific causality of the generative conditions that underlie both the first origins and the later innovations of phenotypes. But whereas innovation and novelty designate the processes and results of introducing new characters into already existing phenotypic themes of a certain architecture (bodyplans), origination emphasizes the very first beginnings of phenotypes, e.g., the origin of mutlicellular assemblies, of complex tissues, and of the generic forms that result from the self-organizational and physical principles of cell interaction (Newman, '92, '94). Because of presumably less integrated genetic underpinnings, greater phenotypic flexibility is suggested to have characterized the organismal forms of early stages of metazon evolution (Newman, '94; Newman and Müller, 2000). In this ''pre-Mendelian'' world, genetic inheritance and phenotypic realization would have been less strictly linked than in extant organisms (Newman and Müller, 2000; Newman, 2005). Hence it was argued that the predominant causalities for the origin of primary morphological forms would have depended less on programs of gene expression and more directly on the inherent physico-chemical properties of the involved cell and tissue assemblies. Our use of the term origination therefore refers to this principle (Müller and Newman, 2003b; Newman and Müller, 2005a, this issue) from which will have resulted an early repertoire of generic organismal structures, such as various kinds of tubes, rods, hollow, multilayered and segmented tissue masses that could later be elaborated upon by natural selection.

So far we have discussed the mechanistic arguments that support the adaptation vs. novelty and the variation vs. innovation distinction. As mentioned at the beginning of this section, a second justification for this distinction comes from the special role that novelties may have in the dynamics of phenotypic evolution. This argument is much more straightforward. Several well-studied examples indicate that morphological innovations can lead to the exploitation of new ecological niches and to rapid and multiple speciation events. This distinct effect of certain novelties is embodied in the concept of key innovation (Liem, '74, '90). The innovation of pharyngeal jaws in African cichlid fish provides a good example of such effects on the diversification and speciation of a taxon (Galis and Drucker, '96). The effect of key innovations is probably what Mayr meant by ''evolutionary avalanche'' in his 1960 paper. But although key innovations provide important material for the study of evolutionary dynamics (and for functional morphology), the particular macroevolutionary consequences of innovations do not inform us about the causation of novelty. The understanding, however, of the ecological

conditions that are associated with key innovations and major macroevolutionary events do assist in the explanation of novelty (Jablonski, 2005, this issue).

THE PROBLEM AGENDA OF THE INNOVATION TRIAD

If we assume that origination, innovation, and novelty represent a distinct complex of interrelated problems of phenotypic evolution, a number of theoretical issues arise in attempting to account for them. In particular, as with all biological phenomena, it will be necessary to distinguish what earlier had been called ultimate and proximate causation (Mayr, '61), and what may also be referred to as general initiating conditions vs. specific mechanistic realization. West-Eberhard (2003) addresses the same point by distinguishing ''initiation'' vs. ''sources'' of novel traits. Constraint, integration, and fixation represent further important issues that arise from regarding the innovation triad as distinct, and, finally, there is the problem of the transitional functionality of novelties.

Initiating conditions (ultimate causes)

A number of initiating causes for the origination of novelties have been proposed in the past, such as accumulative genetic variation, environmental influences, behavioral change, or change of function, depending on the point of view or preferred explanatory paradigm. Under strictly neo-Darwinian assumptions, for instance, accumulative gene mutation had been considered as the primary factor, as mentioned by Mayr ('60): ''The problem of the emergence of evolutionary novelties then consists in having to explain how a sufficient number of small gene mutations can be accumulated until the new structure has become sufficiently large to have selective value''. Although Mayr ('60) reaches the conclusion that ''mutation pressure plays a negligible role in the emergence of evolutionary novelties'', this had little impact on the general opinion that regarded molecular change as primary and selection as secondary. But since a phenotypic novelty often requires developmental modifications that are not within the mutational reach of the ancestral character state, alternative scenarios had to be considered. In more recent treatments, the notion of independent, incremental single locus mutations has been replaced by gene duplications, evolution of gene regulatory circuits by, e.g., promoter mutations, and gene recruitment, but the primacy of genetic change is maintained. The proposal that novelties could arise from pleiotropic by-products of genetic change, offered by Mayr ('60) is rarely voiced today.

Natural selection as the primary initiating cause has been invoked as frequently as genetic variation, despite Darwin's (1859) early warning that ''characters may have originated from quite secondary causes, independently from natural selection''. The ''selection paradox'', the fact that selection cannot act on characters that are not yet in existence, and hence cannot directly cause novelty, had been an early point of critique of Darwinism (Mivart, 1871), but any precaution resulting from it was largely abandoned in the neo-Darwinian era. A particular version of the selection problem arises with the concept of innovation through symbiosis (Margulis and Fester, '91). The central tenet of this view is the integration of smaller replicative units into higher level replicators, such as in the origin of the eukaryote cell from symbiosis with bacteria, or the association of cells that produce a multicellular organism, or the origin of colonies and eu-social communities in which only a few individuals reproduce (Buss, '87; Maynard-Smith and Szathmary, '95; Michod, '99). Such major transitions require cooperation among replicative units (cells or individuals) to form the higher level units by sacrificing the reproductive success of the lower level units. In these kinds of innovation, the problem is how the lower and the higher levels of selection are reconciled in the evolutionary process.

Concepts that assign the key locus of novelty initiation to the epigenetic properties of developmental systems involve selection in a more indirect way. Such proposals argue that incipient novelties arise as developmental side effects of selection that acts on other organismal parameters such as shape, size, or proportions, through the alteration of developmental processes, e.g., the modification of cell behaviors or of developmental timing (Hanken, '85; Müller, '90; Müller and Wagner, '91; Newman and Müller, 2000; see also Wagner and Lynch, 2005, this issue). In these and earlier views (Schmalhausen, '49), selection is regarded as a facilitating factor or as a general boundary condition rather than a direct cause of novelty. In these scenarios selection is non-specific with regard to the arising novelty; the specificity of the phenotypic outcome is provided by the developmental system under modification.

Threshold effects that occur in developmental systems that undergo continuous variation are seen as one of the key factors in such epigenetic modes of novelty generation and could also account for seemingly ''saltatory'' appearances of novelty in phenotypic evolution although the conditions for its generation may have preexisted embryologically for a long time.

Another mode of novelty initiation based on embryonic development has received renewed attention, namely direct environmental influences on developmental processes (Gilbert, 2001; Hall et al., 2003; Müller, 2003a; West-Eberhard, 2003). Here neither selection nor novel genetic variation represent the initiating agent but rather the immediate influence of external physical and chemical factors. This view does not imply a Lamarckian mechanism but a response of the developmental system to an external (environmental) perturbation that goes beyond the species-specific range of variation (reaction norm), a mechanism termed phenotypic accommodation (West-Eberhard, 2005, this issue). The heritability of the environmentally induced change may then be consolidated by subsequent natural selection. The conditions that permit the system to overcome the limits of the reaction norm need further clarification, but based on an extensive survey of examples it was recently concluded that ''the most important initiator of evolutionary novelties is environmental induction'' (West-Eberhard, 2003). West-Eberhard points out that a major advantage of environmental induction over mutational change is that it can affect many (or all) members of a population at once.

An earlier statement of this evolutionary mechanism (Baldwin, '96) was termed the ''Baldwin effect'' by Simpson ('53) in a paper that argued for its marginality to the neo-Darwinian framework. Simpson's critique, however, assumed a straightforward genotype–phenotype relationship and did not consider either the extensive phenotypic plasticity of modern forms (West-Eberhard, 2003) or the possibility that ancient forms were even more plastic (Newman and Comper, '90; Newman and Müller, 2000). The fact, moreover, that organisms and their tissues at all stages of their evolution, in common with any material system, have inherent morphogenetic and other phenotypic properties that govern their response to external effects (Newman and Comper, '90; Newman and Müller, 2005b), indicates that accounts based on environmental considerations and those based on epigenetic considerations are inextricably connected.

The correspondences between macroevolutionary innovation rates and large-scale ecological patterns that seem to promote or sustain novelty origination (Jablonski, 2005, this issue) support the environmental connection, although this does not mean that the environmental effect is direct in all cases (see below). A special case of environment-induced novelty generation was described for the vertebrate skeletal system, where new skeletal elements can arise from altered embryonic motility that is easily influenced by external conditions (Müller, 2003a).

Behavioral change as an initiator of morphological novelty had been considered a primary factor in early discussions (Mayr, '58, '60). Behavioral change was proposed to act via the intensification or the change of a particular function, such as gait or flight. Sewertzoff ('31) had given special attention to the principle of intensification of function, although it appears that this would mostly result in the modification of existing structures, such as shifts of proportions, fusion, or loss of elements, but would rarely lead to the emergence of a new structural character. Mayr ('60) regarded not intensification but the change of function ''by far the most important principle'' in the origin of novelty and provides a thorough analysis of the conditions that are required for shifts of function to take place. However, he also reached the conclusion that the ''new'' structure resulting from shifts of function ''is merely a modification of a preceding structure''. This again circumvents the novelty problem. However, note the possibilities of a direct influence of the environment on embryonic behavior mentioned above (Müller, 2003a). Functional shift and functional decoupling have recently been evaluated (Galis, '96; Ganfornina and Sanchez, '99). The ''behavioral change comes first'' position has also been reemphasized and elaborated on in psychology. Behavioral flexibility based on developmental plasticity is thought to result in behavioral neophenotypes that in turn cause morphological innovation followed by genetic integration (Johnston and Gottlieb, '90; Gottlieb, '92).

Mechanistic realization (proximate causes)

If the initiating causes for innovation are unspecific and general, acting at the population level, the conditions for the physical realization of a specific novelty must be sought in development. This is the domain of EvoDevo and the critical

question is: What are the specific developmental mechanisms that underlie particular instances of novelty generation? Currently, the bulk of attention is focused on the evolution of new gene regulatory interactions and the recruitment of genes and gene circuits into new developmental functions, as seen in a growing number of examples (Shapiro et al., 2004; Colosimo et al., 2005). Understanding the kinetics (Bolouri and Davidson, 2003), dynamics (Cinquin and Demongeot, 2005), and topological aspects (von Dassow et al., 2000; Salazar-Ciudad et al., 2001a; 2003) of developmental gene regulation and their correlation with morphogenetic events will be central in this endeavor.

Applying such dynamical concepts to gene regulatory networks, including the possibilities of non-linear effects, raises the specter of gene changes acting as ''macromutations,'' i.e., the ''hopeful monster'' scenario (Goldschmidt, '40), long considered to have been retired from active consideration in evolutionary biology. Contrary to neo-Darwinian expectations, however, genes of large effect are, in fact, present in *Drosophila* populations (Tautz, '96) as well as in plants, where they are apparently involved in speciation (Gottlieb, '84; Bradshaw and Schemske, 2003). While such phenomena are rare (for the classical neo-Darwinian reasons) in populations of modern-day organisms, in the less developmentally canalized forms of earlier evolutionary periods they are likely to have been more prevalent (Newman and Müller, 2000; Newman, 2005).

The preceeding consideration is not intended to resurrect a macromutational scenario for the origins of innovation and novelty, but rather to highlight that any gene or gene regulatory changes involved in innovation only become morphogenetically relevant in the context of molecular, cellular, and tissue-level interactions that physically generate the new character. Since each level of biological organization includes its own emergent properties, it is a specific task of the EvoDevo research program to identify the relative importance of these mechanisms for the explanation of particular instances of innovation (Wagner et al., 2000). Candidate processes discussed in this volume include the establishment of new inductive interactions and cell specification mechanisms (Cebra-Thomas et al., 2005, this issue; Félix and Barrière, 2005, this issue; Hall, 2005, this issue; Minelli and Fusco, 2005, this issue), the redeployment of plesiomorphic molecular signaling pathways in hierarchically organized morphogenetic modules (Prum, 2005, this issue), the establishment of genetic individualization in existing organ primordia (Kramer and Jaramillo, 2005, this issue; Wagner and Lynch, 2005, this issue), and the genetic modulation of self-organizing cell and tissue properties followed by developmental autonomization (Newman and Müller, 2005a, this issue). These approaches will be discussed further in the section on research programs below.

Constraints

Phenotypic evolution is limited and biased by developmental constraints that have accumulated in the history of all taxa (Maynard Smith et al., '85; Schwenk and Wagner, 2003). Such constraints are another central EvoDevo principle. Innovations seem to arise in spite of such constraints and may sometimes require a relaxation or breaking up of constraints that prevailed in the ancestral state. Whether and how this occurs is an unresolved empirical question that needs to be addressed in future studies of innovation. Shifts of constraints have been described (Rienesl and Wagner, '92); other possibilities for constraint relaxation include mutational events or neutral phenotypic drift (Mayr, '60). Even in closely studied cases, the interpretation of whether or not developmental constraints had to be overcome for the origination of an innovation can differ substantially (Eberhard, 2001; Wagner and Müller, 2002). But constraints should not be understood only in a negative way, as mere limitations to phenotypic variation, since they can also provide taxon-specific opportunities for novelties to arise. A novelty can result from a constrained developmental system, not because genetic or developmental variation is relaxed, but precisely because the system is unable to respond by variation and is forced to transgress a developmental threshold. This can provide heightened potentialities for innovation in particular areas of phenotypic character space (Roth and Wake, '89; Arthur, 2001; Rasskin-Gutman, 2003).

Integration and fixation

If innovation is considered as an event that is not based on the continuous variation of a preexisting, integrated character but arises through any of the mechanisms discussed above, then the problem arises as to how the new character can be accommodated into the preexisting, constructional, developmental, and genetic systems of a taxon, in order to ensure functionality

and inheritance. The problem is not an immediate one, because if a novelty arises from a developmental response in one form or another, the same response will be elicited in every new generation and the novelty can remain epigenetically integrated for an extended period of time before genetic integration takes place. It is possibly a standard rule that epigenetic integration precedes the genetic integration of novelties (Newman and Müller, 2000). Similar concepts that emphasize epigenetic integration are generative entrenchment (Wimsatt, '86) and epigenetic traps (Wagner, '89).

As anticipated by Waddington ('56, '62), genetic integration follows from selection acting on the genetic variation that will arise with the spreading of a novel character. This will include orthologous and paralogous regulatory circuits that acquire new developmental roles over the course of evolution (Wray, '99; Wray and Lowe, 2000; Carroll et al., 2001). Evolving structure–function interrelationships (Galis, '96) integrate novel characters at the phenotypic level but will also contribute to genetic integration, with selection favoring the genetic linkage of functionally coupled characters (Wagner, '84; Bürger, '86). The evolving genome can thus gain control over the epigenetic conditions that prevail during the origination of novelties. Since epigenetic integration will usually come first, its patterns can provide the templates for both phenotypic and genetic integration (Newman and Müller, 2000; Müller, 2003b). Genetic integration will increasingly stabilize and overdetermine the generative processes, resulting in an ever-closer mapping between genotype and phenotype. Such transitions can be interpreted as a change from emergent to hierarchical gene networks (Salazar-Ciudad et al., 2001a,b). The sum of these processes locks in the novel characters that arose as a consequence of the mechanisms discussed above and thus will generate the stable, heritable building units of the phenotype that compose organismal body plans.

Transitional functionality

As mentioned above, morphological novelties are often associated with radically new functions that were not present in the primitive condition. It has therefore been assumed that a new function can be responsible for the origin of a novelty. The problem with this argument is that the derived function usually requires that the new organ is already fully developed, because it could not have executed the new function in its incipient state. The origin of insect wings is a good example. Small or rudimentary wings do not allow any form of flight and thus cannot be optimized for flight by natural selection. The solution to this problem was proposed to lie in a transfer of function, i.e., the new structure would initially have evolved serving a different function and would have become coopted into performing the derived function only subsequently (Mayr, '60). In the case of insect wings, for instance, it is assumed that they originally evolved as external gills of aquatic arthropods (Averof and Cohen, '97), which may then have served as ''sails'' for surface skimming (Marden and Kramer, '94), and became used and selected for flight only in a third transition of function.

The innovation triad, in its emphasis on epigenetic determinants, environmental influences and plasticity, provides new ways of conceptualizing abrupt morphological transitions. In particular, thresholds and other nonlinear effects in developmental systems, coupled with the potential of externally induced changes to affect populations and not only individuals, can render moot questions of phenotypic gradualism and thus transitional functionality (see below).

RESEARCH PROGRAMS ADDRESSING THE INNOVATION TRIAD

The innovation topic has been implicitly addressed in a number of research initiatives, but often without directly invoking themes of the innovation triad. Recently, more empirical studies explicitly address innovation issues, and a number of different strands of work can be discerned that we will here call ''programs'' for convenient distinction, although not many of the involved research groups would see their work as belonging to one program or another, since they all intersect. In accordance with an earlier categorization of EvoDevo projects (Müller, 2005), we distinguish four principal programs of innovation research (Table 1).

The morphology and systematics program

The factual basis of the occurrence of novelty in phenotypic evolution is provided by morphological and systematic investigations, many of which are paleontological. These data demonstrate the kinds, the frequency, and the pervasiveness of novelty generation in different phylogenetic lineages as well as the relation of these occur-

TABLE 1. Principal programs and issues of innovation research

Research programs	Issues addressed
Morphology and Systematics Program	Analysis of Morphological Novelty: • Identification and characterization • Phylogenetic patterns of occurrence • Frequencies of occurrence • Ecological distribution • Functional analysis
Gene Regulation Program	Analysis of Genetic Innovation: • Comparative gene expression • Gene regulatory evolution • Co-option and recruitment • Regulatory modules • Genetic individualization
Epigenetic Program	Analysis of Developmental Causation: • Physical and other generic properties of cells and tissues • Tissue self-organization • Dynamics of tissue interactions • Tissue geometry and architecture • Influences of external factors • Phenotypic plasticity • Experimental testing
Theoretical Biology Program	Conceptualization and Formalization: • Genotype–phenotype mapping • Measurement and quantification • Computational modeling • Simulation and prediction • Theory development

rences with anatomical, developmental, and environmental conditions. Another important function of the comparative program is the identification and characterization of novelties. Because of the intimate interlace of conserved and novel features in complex organismal bodyplans, it is necessary to define operational criteria by which complex characters can be disentangled and novelties can be recognized based on character theory (Müller and Wagner, '91; Wagner, 2001; Minelli and Fusco, 2005, this issue).

Both temporal and ecological patterns of innovation emerge from paleontological surveys (Jablonski and Bottjer, '90; Nitecki, '90; Erwin, '93; Eble, '99; Jablonski, 2005, this issue). In these contexts innovation is predominantly defined in a macroevolutionary sense, emphasizing speciation and the origin of higher taxa, but in many cases these events are concurrent with the appearance of morphological novelty. Such studies indicate that novelties do not originate at random but are often related to instances of environmental change and to heterogeneous ecological domains. Patterns of origination of major marine invertebrate taxa, for instance, are clearly different in the onshore vs. offshore venues (Jablonski, 2005, this issue). This points towards different large-scale driving mechanisms, such as sea-level changes, salinity or oxygen changes, and other oceanographic influences. The onshore bias might be attributed to a higher frequency of such habitat disturbances that can in turn affect nutrient supply, population genetic dynamics, phenotypic plasticity, and other life history parameters. Other paleontological surveys show differences in the ratio of major to minor morphological innovations (Eble, '99). Jablonski (2005, this issue) suggests that an observed origination bias allows two interpretations: either direct environmental influence on the genetic–developmental systems of the affected taxa, or a preferential preservation of innovations in the onshore environment.

Functional morphology has played an important role in the first conceptualizations of EvoDevo, in particular with regard to the origin of innovations. The vertebrate feeding apparatus is one of the best analyzed functional systems including studies in fish (Liem, '74, '90; Galis and Drucker, '96), amphibians (Roth and Wake, '85, '89), reptiles (Frazzetta, '75; Jayne et al., 2002), and many other taxa. Recent non-vertebrate examples include the pulsatile organs in insects (Pass, 2000) and the moveable abdominal lobes in male sepsid flies (Eberhard, 2001). Although the functional morphology approach to innovation is less prominent today, many of the functional explanations of novelty include the mobilization of developmental processes (Roth and Wake, '85; Galis, '96).

The gene regulation program

The bulk of present innovation studies concentrates on the evolution of developmental control genes and gene regulation networks (Carroll et al., 2001; Davidson, 2001; Wilkins, 2002). This aims at demonstrating the specific genetic changes that are associated with novelty generation, with a major focus on the *Hox* genes. Well-documented cases include the innovation of eye spot patterns in butterfly wings (Keys et al., '99; Nijhout, 2001). *Hox* gene-associated changes in axial differentiation

(Burke et al., '95; Gaunt, 2000; Nowicki and Burke, 2000), the vertebrate limb (Sordino et al., '95; Shubin et al., '97; Crawford, 2003; Wagner and Chiu, 2003), and innovation in the cephalopod neural system and brachial crown (Lee et al., 2003). In plants, good evidence for the genetic basis of innovation is obtained from the evolution floral organs (Kramer and Jaramillo, 2005, this issue).

Besides the ubiquitous documentation of changing gene expression patterns associated with novelty and of evolving gene regulation, a number of themes emerge as key topics in the field. One is the cooption or recruitment of regulatory circuits and signaling pathways that were already established in the primitive condition before a morphological novelty arose. Cooption can include transcription factors, paracrine signaling proteins, cell adhesion molecules, and other proteins involved in the regulation of cell behavior. Cooption has been documented in many instances of innovation, such as the Shh–Bmp2 interaction in the development of avian feather germs, which is necessary for a suite of morphological innovations in feather structure (Harris et al., 2002; Prum, 2005, this issue). In cephalopod evolution, it has been shown that Hox orthologues have been recruited multiple times and in divergence from the ''colinearity rule,'' which describes the usual correspondence between chromosomal order and spatiotemporal expression of these genes, during the formation of novel structures (Lee et al., 2003).

Modularity is another frequent theme in the novelty-related evolution of gene regulation, emphasizing the fact that gene recruitment often concerns not individual genes but entire sets of regulatory pathways, such as the Notch–Delta signaling pathway. But modularity also has wider implications since it encompasses not only genetic but also epigenetic components and higher levels of organismal organization (Schlosser and Wagner, 2004; Callebaut et al., 2005). Modularity is a way to increase evolvability, i.e., a clade's capacity to generate variation (and innovation), and regulatory modules seem to be able also to evolve in a (nearly) neutral way, without a direct effect on the related morphology (Félix and Barrière, 2005, this issue). The general modular nature of genetic and epigenetic developmental regulation therefore seems not only a means to generate morphological novelty but also contributes to phenotypic stability in the face of changing developmental regulation (von Dassow and Munro, '99). Hence one of the central issues in EvoDevo, the relationship between gene regulation and the evolving phenotype, requires an analysis of modularity in the genotype–phenotype map (Altenberg, 2005).

Genetic individualization is an emerging topic in the gene regulation approach to novelty. The recruitment of molecular signaling modules and their interaction with organ identity gene networks seem to be characteristic modes for establishing the individuality of morphological novelties. The establishment of organ identity networks that are dedicated to the individuation of structures is required in the evolutionary consolidation of novelties, because it confers the quasi-independence (Lewontin, '78; Wagner, this volume) necessary for selection to act on them. Two examples discussed in the present issue (Kramer and Jaramillo, 2005; Wagner and Lynch, 2005) suggest that complex patterns of conservation and divergence characterize the evolution of identity programs. An unavoidable general shortcoming of the evolutionary genetics program is that (with few exceptions) we can only study the genetics of extant organisms. There is no guarantee that the genes associated with present developmental processes are also the ones that were causally responsible for the innovations which they regulate today.

The epigenetic program

The epigenetic approach investigates the generic properties of developmental systems in the origination of novelty, explicitly addressing the nonprogrammed aspects of development (Newman and Müller, 2000). This includes the physical properties of biological materials, the self-organizational capacities of cell and tissue assemblies, the dynamics of developmental interactions, the role of geometry and tissue architecture, the influence of external and environmental parameters, and all other factors that affect the development of organismal form—regardless of whether their role in generating novelty is associated with concurrent changes in the genetic hardwiring or not. (Epigenetic is here used in its original meaning, as derived from ''epigenesis'' and not from ''epigenetics'' in the sense of non-DNA-based modulation of gene activity; see Müller and Newman, 2003b.)

Epigenetic novelty origination can be tested by experimental procedures in vivo or in vitro through the alteration of the epigenetic context in which a developmental process takes place. Local and global perturbations of development

yield information about the generative capacity of developmental systems. Cell dissociation and aggregation or tissue recombination fall into this category, as do many classical excision and transplantation experiments, or alterations of environmental conditions, which all produce alternative morphologies while keeping the genetic background constant. In vitro recombinations of different tissue types, for instance, demonstrate the role of cell surface tension in tissue arrangements (Steinberg, '63, 2003), and the influence of extracellular and structural cues (Bissell et al., 2003). Under natural conditions, recombination of tissues seems to be a frequent mode of innovation, as in the origin of external cheek pouches of geomyoid rodents, where a minor shift of epithelial invagination results in a new tissue interaction that produces a fur-lined external pouch from an internal one (Brylski and Hall, '88a,b).

An exemplary case of novelty generation through heterotopic tissue recombination is the turtle carapace (Burke, '89; Gilbert et al., 2001; Loredo et al., 2001; Cebra-Thomas et al., 2005, this issue). Whereas in the primitive condition the reptilian ribs do not interact with the dermis, in carapace-forming turtles the ribs and dermal tissues interact. The initiating condition could have been selection favoring proportional body changes that brought the embryonic ribs closer to the dermis. Once in contact with the dermis the ribs act as initiating centers for dermal ossification. Rib and carapace growth may have subsequently become coordinated and stabilized through an epidermal–mesenchymal signaling center, the carapacial ridge, recruited from a preexisting signaling complex. This model proposed by Cebra-Thomas and coworkers contains all the previously postulated elements for stepwise novelty generation: epigenetic generation, developmental integration, and genetic fixation (Müller and Newman, '99). Whether this suite of events actually took place phylogenetically requires further corroboration.

Origination and innovation of the vertebrate limb skeleton is another case in support of epigenetic initiation discussed in this issue. Most current models of limb development based on the genetic regulation of extant limbs sidestep the mechanistic question of how the skeletal patterns arose initially and how new elements were added. Newman and Müller, 2005a (this issue) describe a model in which the self-organizational properties of precartilage mesenchymal tissue provide a basic template for the limb skeletal pattern that could later be elaborated upon by evolution. A network of cell and molecular interactions in limb bud precartilage cells has been shown both in vitro and in vivo to provide a core mechanism for the generation of patterns of discrete aggregates, leading to nodules and bars of cartilage. In silico embodiments of this mechanism, employing ''reaction'' (i.e., gene regulation and biosynthesis of key products) and ''diffusion'' (i.e., local spread of secreted morphogens), demonstrate that this network is capable of producing ''bare-bones'' skeletal patterns in a spatiotemporally regulated fashion without the need for programmed control over the emerging pattern (Hentschel et al., 2004). By the recruitment of additional cellular and molecular processes for developmental regulation, the basic patterns could have become refined, stabilized, and integrated at both epigenetic and genetic levels. The subsequent innovation and addition (or loss) of skeletal elements is proposed to have occurred also as a consequence of the biosynthetically reactive chondrogenic mesenchyme, in particular when thresholds defined by the dynamics of the limb skeletogenic system were exceeded. Other strands of the epigenetic program that focus on environmental induction, phenotypic plasticity, phenotypic accommodation, hormonal influences, and other effects of external and ecological factors have been, in part, discussed above. Excellent overviews and detailed examples can be found in several books and reviews (Schlichting and Pigliucci, '98; Gilbert, 2001; Pigliucci, 2001; Hall et al., 2003; West-Eberhard, 2003).

The theoretical biology program

Theoretical biology serves two functions: The conceptual characterization of biological problems (including the history of its ideas, theory relations, definitions, etc.) and their formalization (using mathematics, modeling, and simulation). In both areas the treatment of innovation has made significant progress over the past decades. Since Mayr's ('60) paper, in which innovation was perceived from an exclusively gradualistic and variational perspective, the conceptualization of the innovation problem has greatly diversified. Individual treatments sharpened the appreciation of its theoretical importance to a number of subfields (Frazetta, '70; Futuyma, '86; John and Miklos, '88; McKinney, '88). The 1988 symposium and ensuing volume (Nitecki, '90) were a first attempt to integrate the different approaches,

dealing with innovation and novelty in a variety of different disciplines including development (Müller, '90; Raff et al., '90). As a consequence, the novelty problem was reconceptualized and placed in an EvoDevo framework (Müller and Wagner, '91). With the spread of EvoDevo, innovation and novelty became increasingly regular parts of the theoretical characterization of several different areas (Gottlieb, '92; Raff, '96; Gerhart and Kirschner, '97; Carroll et al., 2001; Wagner, 2001; Hall and Olson, 2003a; Minelli, 2003; Müller and Newman, 2003a; West-Eberhard, 2003; Callebaut et al., 2005). A growing number of metatheoretical treatments reflect this intensified interest (Love, 2003; Robert, 2004; Laubichler and Maienschein, 2006).

Formalization has also progressed. In particular, the innovation problem has been addressed in the fields of biometrics, multivariate statistics, computational modeling, and other areas of bioinformatics. One approach aims at quantifying the novelty-associated dynamics of gene, cell, and tissue interactions by developing computational tools for the three-dimensional representation of gene expression and other markers of cellular activity (Streicher et al., 2000; Sharpe et al., 2002; Weninger and Mohun, 2002), and new algorithms are being designed for the analysis of such data (Fontoura Costa et al., 2004).

''Systems biology'' strategies are also leading to insights into necessary and sufficient conditions for phenotypic innovations. For example, dynamical systems-based modeling of cell clusters, such as would have existed at the beginnings of multicellularity, has disclosed a new physical principle, ''isologous diversification,'' that may bear on the origination of cell differentiation (Furusawa and Kaneko, 2000). In addition, experimentally motivated modeling of specific developmental systems, such as tooth development (Jernvall, 2000; Jernvall et al., 2000; Salazar-Ciudad and Jernvall, 2002) and limb development (Hentschel et al., 2004), has permitted the devising of simulations that can illustrate and predict how the differential activation of genes and gene products influences morphogenesis and innovation. The question of innovation has also motivated a recategorization of mechanisms of developmental pattern formation in terms of their likehood, under mutational change, to produce morphological novelties (Salazar-Ciudad et al., 2001a,b).

Consideration of the dynamical and topological properties of the gene networks associated with developmental mechanisms provides additional insight into sources of innovation and its complement, developmental, and evolutionary robustness. In silico (Salazar-Ciudad et al., 2001a) or artificial biochemical–genetic (Isalan et al., 2005) models for such networks have disclosed generic properties that promote the formation of novel patterns. Computational models for developmental genetic networks can be caused to undergo simulated evolution and can help identify network constructional principles that render the system susceptible to significant deviations from an initial pattern (i.e., novelty) or resistant to such deviations (i.e., robustness) (von Dassow et al., 2000; Salazar-Ciudad et al., 2001a; Ingolia, 2004).

Modeling analyses have also led to questioning the widely assumed gradualism of phenotypic innovation, the neo-Darwinian default which, until recently, had little challenge from experimentally based theoretical models. Salazar-Ciudad and Jernvall, 2005 (this issue), considering tooth development as an evolving ''morphodynamic'' process, show that gradual variation is only expected to occur in relatively simple phenotypes whereas complex phenotypes exhibit less gradual variation and have a tendency towards early accelerations vs. late decelerations of innovation rates during phylogenetic diversification. These predictions seem to correlate with the evidence from the fossil record (Erwin, '93).

The morphospace concept provides another fertile theoretical approach to innovation. ''Generative morphospaces'' in particular provide a tool by which the range of possible patterns that are produced from a set of developmental rules can be compared with forms that did or did not appear in natural systems (Thomas and Reif, '93; Eble, 2001; Rasskin-Gutman, 2003). These models can be used to detect general rules that underlie the patterns of phenotypic variation and innovation and to derive predictions about the generative capacities of a given developmental system. Morphospace modeling indicates that only a limited number of phenotypic solutions can be obtained from a given developmental system, even in the presence of ample genetic variation. But these effects are not only limitational. Certain morphological solutions are more likely to arise than others, independent of the molecular and genetic circuitry associated with their generation, pointing to inherent properties of the developmental system involved (McGhee, '99; Stadler et al., 2001). Similar results arise from the modeling of RNA genotype–phenotype maps (Fontana, 2001, 2002).

IMPLICATIONS OF A RESEARCH FOCUS ON INNOVATION

The multitude of concepts and programs reviewed above indicates a growing awareness in evolutionary biology of the problems of the innovation triad. This change reflects a shift of attention from the phenomenon of variation and the modes of its preservation toward the phenomenon of innovation and the modes of its generation. At the same time there is a general hesitation to accept the consequences of such a change of conceptual focus. There is concern that treating innovation as a distinct problem might undermine the basic neo-Darwinian framework (e.g., Hall, 2005, this issue). This need not be the case, though. Selection has a causal role both in adaptation and in innovation. But since morphological novelty denotes a qualitative deviation from the purely quantitative phenomena of variation (the focus of the neo-Darwinian framework), a shift of explanatory weight is required. In adaptation, the motive force resides in natural selection acting on an underlying substrate—heritable variation—the necessary boundary condition. In innovation, natural selection represents the boundary condition, whereas the properties of developmental systems provide the motive force for the ensuing change.

As we become more familiar with the themes of the innovation triad, and more information is generated on its various subtopics, the advantages of making the variation–innovation distinction will become clearer. On the one hand, it establishes a new epistemological position in the study of the phenotypic level of organismal evolution, a position that is not limited by the necessity to conform to the variation–adaptation paradigm. The limitations implicit in the requirement to perceive all morphological change as a gradual transition series, e.g., feathers from scales, or limbs from lateral folds, has impeded the understanding of phenotypic evolution. On the other hand, it assigns a central role to internal causation, as advocated earlier (Bateson, 1894; Baldwin, 1896; Roth and Wake, '85), and thus liberates evolutionary theorists from the requirement to search for purely external causes of phenotypic evolution, as implied by the adaptationist paradigm. As a consequence, a suite of new empirical research programs concentrating on the mechanistic causes of innovation become possible and complement other guiding themes of EvoDevo such as constraint, modularity, and homology. Therefore, the variation–innovation distinction does not oppose neo-Darwinism but, on the contrary, has a distinctly synthesizing effect on evolutionary theory, because innovation requires the inclusion of development (Love, 2003).

The new general tenets that will be added to evolutionary theory by a focus on innovation may be called ''emergence'' and ''inherency''. Emergence has for a long time been seen as an essential property of evolving complex systems, such as development, without formal representation in the theory of evolution. Emergence denotes the non-foreseeable element in the processes of origination and innovation, for example, when the recombination of two (or more) preexisting components leads to unpredicted results. In his discussion of innovation, and criticism of the received terminology, Lorenz ('73) had suggested calling the evolutionary recombination phenomenon ''fulguration'', emphasizing the suddenness and historical singularity of such events. While his suggestion is unlikely to be followed, it emphasizes the long-felt need to account for emergence in evolutionary theory. A mechanistic concept of innovation could fill this void by moving beyond the neo-Darwinian focus on variation–selection dynamics which implies a pervasively gradualistic model of evolution.

Inherency is a second general property of evolving systems. It complements the contingency emphasized by the neo-Darwinian side of evolutionary theory. Whereas historical contingency denotes the lawful dependency of evolutionary change on earlier conditions that involved a large component of chance, inherency represents the tendency to organize and change along preferred routes, leading, unless inhibited, to predictable outcomes (Newman and Müller, 2005b). Emergence and inherency represent those generative principles that are missing from the standard evolutionary framework and which are now in the process of being incorporated into a more complete theory by EvoDevo.

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