Defending Evo-Devo: A Response to Hoekstra and Coyne*

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The study of evolutionary developmental biology ("evo-devo") has recently experienced a dramatic surge in popularity among researchers and theorists concerned with evolution. However, some biologists and philosophers remain skeptical of the claims of evo-devo. This paper discusses and responds to the recent high profile criticisms of evo-devo presented by biologists Hopi E. Hoekstra and Jerry A. Coyne. I argue that their objections are unconvincing. Indeed, empirical research supports the main tenets of evo-devo, including the claim that morphological evolution is the result of *cis*-regulatory change and the distinction that evo-devo draws between morphological and physiological traits.

1. Introduction. The study of evolution was transformed between the 1920s and 1950s. During this time, Mendelian genetics and Darwinian natural selection underwent a theoretical integration via the mathematical theory of population genetics, resulting in a new framework for the study of evolution that includes the fields of paleontology, botany, systematics, and zoology (Mayr and Provine 1980; Laubichler 2007). This so-called Modern Synthesis resulted in a fruitful population-based research framework that has dominated evolutionary biology since the mid-twentieth century. Many biologists (e.g., Gould 1982; Eldredge 1985), philosophers (e.g., Ghiselin 1980; Jablonka 2006) and historians (see discussions in Amundson 2005; Laubichler 2007), however, have argued that the theory developed during the Modern Synthesis is incomplete and, so, does not allow for a complete understanding of macroevolutionary phenomena.

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Indeed, many biologists, philosophers, and historians agree that we could better understand how species evolve, specifically the origin of morphological novelties and other macroevolutionary phenomena, by adding the studies of embryology and developmental biology to the research framework provided by the Modern Synthesis (e.g., Amundson 2005; Burian 2005; Carroll 2005; Carroll, Grenier, and Weatherbee 2005; Müller 2005). This general consensus can be traced back to controversy surrounding one of the major theoretical tenets of the Modern Synthesis, the tenet of extrapolation. According to this tenet, macroevolutionary phenomena are completely explained by microevolutionary processes, so, phenomena such as the origin of novel morphological varieties are thought to be explained by population genetics alone (Gilbert, Opitz, and Raff 1996, 358). Extrapolation from micro– to macroevolutionary phenomena has been criticized since the Modern Synthesis when geneticist Richard Goldschmidt (1940) and developmental biologist Conrad. H. Waddington (1940) questioned how the origin of new body structures could be explained by the accumulation of changes in gene frequency without embryological and developmental insights (Gilbert et al. 1996, 362).

In the 1970s and early 1980s, the tenet of extrapolation was further criticized by paleontologists Niles Eldredge and Stephen Jay Gould (Eldredge and Gould 1972; Gould and Eldredge 1977), along with other biologists (e.g., Stanley 1979; Ayala 1983), who argued that changes in gene frequencies in a population could not provide a complete explanation of the evolution of higher taxa and the origin of novel morphologies. Empirical studies in molecular evolution also support the claim that microevolutionary processes alone cannot explain macroevolutionary events (e.g., King and Wilson 1975). Today, many evolutionary theorists agree that because of the emphasis placed on microevolutionary processes and population genetics and the absence of developmental insights, the theoretical framework for the study of evolution provided by the Modern Synthesis precludes complete explanations of speciation and morphological variation across higher taxa (e.g., Gilbert et al. 1996; Amundson 2005; Burian 2005; Carroll 2005; Carroll et al. 2005; Müller 2005; Pigliucci 2007). These authors also agree that a closer look at the relationship between organismal development, genetics, and molecular evolution is needed for a complete explanation of macroevolutionary phenomena.

For molecular biologist Sean Carroll and like-minded developmental biologists, a revolution that integrates developmental biology with the framework provided by the Modern Synthesis is currently underway in the field of evolutionary developmental biology ("evo-devo"). Carroll claims that recent advances in evo-devo research have led to a new understanding of the role of developmental networks in the origin and evolution of organismal form (2005, x). It had long been assumed that the

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great variation in body structure observed across species was due to different developmental genes acting in different species. This, however, is not the case. Work carried out in the late twentieth century has revealed that despite incredible morphological differences, all complex animals, from *Drosophila* to dinosaurs, share a common set of genes that dictate the development of body patterning and form (e.g., Duboule and Dollé 1989; De Robertis 1997; Panganiban et al. 1997; Hersh and Carroll 2005). This research shows that the same developmental genes are responsible for incredibly different body forms and that differences in form are the result of differences in the regulation of these genes, not differences in the genes themselves (e.g., Britten and Davidson 1969, 1971; Davidson 2001; Valentine 2004; Carroll et al. 2005).

It is apparent to evo-devo proponents that the study of individual organismal development and differential regulation of developmental genes does indeed have clear implications for our understanding of speciation and the origin and evolution of form (e.g., Davidson 2001; Valentine 2004; Carroll et al. 2005). The investigation of the developmental processes of individual organisms, starting with gene expression in the earliest embryological stages, has revealed that macroevolutionary phenomena such as speciation are intimately linked to the evolution of regulatory networks and developmental processes. Evo-devo researchers claim their work illustrates that there is much more to learn about evolution and promises to provide substantial insights into the intricacies of the origin and evolution of form, in particular, by investigating further the relationship between development and the evolution of regulatory networks in higher taxa (e.g., Carroll 2005).

Some biologists and philosophers interested in understanding evolution are skeptical of the conclusions of evo-devo research, and the call for the addition of embryological and developmental studies to the Modern Synthesis has been met with resistance (e.g., Mayr and Provine 1980; Hoekstra and Coyne 2007). Those skeptical of the importance of current evo-devo research to the study of evolution not only argue that evo-devo is theoretically problematic but that the so-called developmental revolution lacks empirical support as well. Recently, in a high profile examination of evo-devo, evolutionary biologists Hopi E. Hoekstra and Jerry A. Coyne (2007) present a skeptical analysis and critique of the main tenets of evo-devo. While they do not deny the relevance of embryology and developmental biology to the study of evolution, they do conclude that many of the claims of evo-devo lack empirical evidence and are at best premature. Because of this, Hoekstra and Coyne advocate a resistance to the developmental revolution championed by Carroll. In what follows, I discuss the relevant main tenets of evo-devo and Hoekstra and Coyne's arguments against them. I argue that Hoekstra and Coyne are mistaken. Indeed, my

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view is that empirical evidence from recent genetic and developmental studies shows that the criticisms offered by Hoekstra and Coyne are flawed and should fail to dissuade one from joining Carroll's developmental revolution.

To show that the criticisms of Hoekstra and Coyne can be successfully dismantled, I first discuss the evo-devo claim that *cis*-regulatory elements are the most likely sites of adaptive change leading to the evolution of form. I next discuss Hoekstra and Coyne's claim that evo-devoers have unfairly ignored available alternative explanations of the evolution of form and that other genetic changes, specifically gene duplication and subsequent functional divergence of paralogs, could be responsible for adaptive morphological divergence. I respond by using recent biological literature to show that researchers do acknowledge the role of gene duplication in the evolution of form but that such duplication does not play the causal role that Hoekstra and Coyne suggest. I next discuss the importance of the mode of post-duplication paralog divergence found in *Hox* genes for evo-devo's claim that form evolves differently than other physiological traits. Finally, I reconstruct Carroll's call for a developmental revolution in evolution studies. I conclude that a complete understanding of evolution must include an understanding of the evolution of form and that the time to embrace evo-devo is now.

2. Evo-Devo: Claims and Criticisms. One of the most revolutionary claims made by evo-devo researchers is that the evolution of animal form, from the spots on butterfly wings to the number of fingers on a human hand, is primarily the result of changes in *cis*-regulatory regions at the DNA level. These regulatory regions interact with transcription factors, proteins that bind to *cis*-regulatory elements and control when corresponding genes are turned on, present in the cell nuclei to assess the regulatory state of the cell. The expression of genes that code for transcription factors is dependent on the information gleaned from the interpretation of the cell's regulatory state. So, *cis*-regulatory regions, via interaction with the regulatory state of the cell, play an important causal role in the spatial and temporal expression of genes that code for transcription factors.

Evo-devo's claim that the evolution of form is the result of changes in *cis*-regulatory regions rests on the notion of modularity. One gene may be controlled by several regulatory elements, and regulatory elements may affect gene expression in one part of a developing organism without affecting expression in another region. Because of the multiplicity of *cis*-regulatory elements and the fact that different *cis*-regulatory elements can independently affect the expression of a gene at different times and locations, there is an enormous variety of regulatory outcomes. In other words, because of their modularity, *cis*-regulatory elements come in a

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myriad of combinations that lead to different patterns of gene expression. Different patterns of expression, caused by different combinations of modular regulatory elements, lead to differences in organismal patterning and form (Stern 2000; Davidson 2001; Carroll 2005).

According to Hoekstra and Coyne, modularity leads to "the most important" consequence for evo-devo: change in a modular *cis*-regulatory element avoids the negative pleiotropic effects often caused by change in a protein-coding region (2007, 999). This is because change in a *cis*-regulatory element may only affect when or where a single gene is expressed. Thus, changes in *cis*-regulatory regions, according to evo-devo, are more likely to be adaptive than changes in a structural gene. This conclusion leads to another, what Hoekstra and Coyne refer to as the "theoretical imperative for *cis*-regulation"—due to their modularity, *cis*-regulatory elements are the primary unit of evolutionary change responsible for variation in animal form (2007, 1000).

Hoekstra and Coyne are critical of these conclusions of evo-devo theory. They state that "there are several other ways to obviate the negative consequences of pleiotropy besides changing *cis*-regulatory elements. The most obvious is gene duplication followed by divergence of the duplicated copies" (2007, 1000). Their claim is that gene duplication is a more probable genetic mechanism for the evolution of form than *cis*-regulatory change. They site Susumu Ohno's (1970) book in order to argue that gene duplication is in fact quite pervasive and an important mechanism for the evolution of novel genes. In addition, Hoekstra and Coyne claim that Carroll, one of evo-devo's most prominent advocates, unfairly dismisses the available alternative genetic mechanism of gene duplication as a means for avoiding negative pleiotropic effects by claiming that such duplications are too rare to significantly contribute to evolutionary change. In general, Hoekstra and Coyne accuse Carroll of faulty logic, of excluding viable alternatives in the name of *cis*-regulatory change.

Hoekstra and Coyne's criticism of the *cis*-regulatory change hypothesis of evo-devo is unpersuasive, however. Recent biological studies make it clear that this criticism of evo-devo theory, that gene duplication and divergence is overlooked as an alternative to changes in *cis*-regulatory regions, is unconvincing. Indeed, researchers interested in the evolution of *Hox* genes, genes thought to play a significant role in the evolution of form and are shared by all complex animals, seem to agree that gene duplication has played an important role in the evolution of *Hox* genes. Evidence suggests that duplication events led to the four *Hox* clusters found in jawed vertebrates and that a separate duplication event took place approximately 400 million years ago after the divergence of ray-finned and lobe-finned fishes (McClintock et al. 2001). While biologists are still trying to pinpoint exactly when such duplication events took place,

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there is a consensus amongst *Hox* researchers that multiple duplication events played an important causal role in the evolution of *Hox* genes (e.g., Crow et al. 2006; Lemons and McGinnis 2006; Lynch, Roth, and Wagner 2006). The biological literature shows that gene duplication and subsequent functional divergence have not been overlooked by those studying the evolution of form. Instead, this research demonstrates that gene duplication has been embraced as part of the evolutionary history of genes that code for particular transcription factors.

In fact, it is the mode of post-duplication divergence that has important consequences for evo-devo, not the claim that gene duplication plays a role in the evolution of form. In further support of the claim that *cis*-regulatory changes are primarily responsible for morphological variation, the biological literature suggests that changes in regulatory elements post-duplication are selected for, leading to functional divergence in duplicated genes (e.g., Chiu et al. 2001; Fares et al. 2003; Hersh and Carroll 2005; Wagner et al. 2005). Interestingly, Hoekstra and Coyne do not consider the results of this research, which contradict their claim that "evo devo's enthusiasm for *cis*-regulatory changes is unfounded and premature" (2007, 996). The biological literature provides an abundance of support for the claim that novel expression patterns of *Hox* genes are present post-duplication as a result of regulatory change and that these regulatory changes are the result of natural selection (e.g., McClintock et al. 2001; Hersh and Carroll 2005; Crow et al. 2006). Thus, evo-devo's emphasis on *cis*-regulatory change is not unfounded or premature and is empirically supported, contra Hoekstra and Coyne. In other words, research results support evo-devo's claim that adaptive *cis*-regulatory change does play an important causal role in the evolution of form.

Hoekstra and Coyne further criticize the thesis that *cis*-regulatory change is responsible for adaptive changes in morphology. They argue many studies that claim *cis*-regulatory change is the predominant means for adaptive morphological change arrive at this conclusion without reference to the resulting phenotype. Without phenotypic information, there is no way of knowing whether a genetic change of any type is truly adaptive. However, Hersh and Carroll (2005) avoid this objection. A wing-specific regulatory element was identified for the *knot* gene, which is expressed during the development of *Drosophila* wings but not during the development of the haltere, small, club-shaped balancing organs located behind the wings. Their study reports that a minimal regulatory element in the haltere is not evolutionarily conserved but a second element is conserved. Surprisingly, this second regulatory element is located more than 500 bp from the minimal region. This finding, in addition to evidence of natural selection on *knot* regulatory elements, leads to Hersh and Carroll's conclusion that "selection is acting on a larger region than the

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minimally defined regulatory module" (2005, 1568). Here, we have empirical evidence of selection acting on *cis*-regulatory regions that are associated with a particular morphological phenotype, the *Drosophila* wing. Hence, Hersh and Carroll's work is evidence of *adaptive* regulatory change in reference to a particular phenotype, and Hoekstra and Coyne's objection does not apply to the results of Hersh and Carroll's study.

Of great importance for evo-devo theory is the sharp distinction between morphological and all other traits, which are classified together as "physiological" traits. Evo-devoers claim that morphological traits are different from physiological traits because they evolve differently—morphological traits evolve via regulatory changes while physiological traits evolve via structural or coding-region changes. Hoekstra and Coyne argue that this distinction is not adequately justified by advocates of evo-devo because there is no good reason to believe that the genetic changes responsible for the evolution of form are different from genetic changes responsible for physiological traits. In fact, they claim, "the omission of 'physiological' traits from [evo-devo] theory fails to acknowledge the tremendous amount of already-existing data showing that the adaptive evolution of such traits usually involves changes in structural regions" (2007, 997).

But there is a likely biological justification for the distinction between morphological and physiological traits. Researchers agree that gene duplication has led to multiple *Hox* clusters in complex animals, and evidence suggests that the mode of post-duplication functional divergence of paralogous *Hox* genes is unlike other mechanisms of divergence (e.g., Chiu et al. 2001; Wagner et al. 2005; Lynch et al. 2006). For example, Crow et al. (2006) claim that evidence for strong directional selection on both paralogs post-duplication is inconsistent with traditional models of functional divergence, such as the neofunctionalization and subfunctionalization models. Such results suggest that the mode of post-duplication divergence of *Hox* genes is novel and distinct from known divergence mechanisms. Similarly, Lynch et al. (2006) state that the mechanism for duplicated *Hox* gene divergence does not follow known mechanisms and remains unknown.

The biological literature suggests that after a duplication event, *Hox* genes may diverge in function via a unique mechanism that distinguishes *Hox* genes from other duplicated genes. This unique mechanism may involve a window of increased "evolvability" immediately following a duplication event, which is not seen in other genes (Wagner et al. 2005; Crow et al. 2006). This is evidence that suggests that the genes involved in the evolution of form do indeed diverge, and thus, evolve, differently than genes responsible for physiological traits. This means that the distinction between morphological traits and physiological traits is biolog-

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ically justified. The possibility that the distinction may be justified by further exploration of the mechanism of *Hox* gene divergence warrants continued research.

3. Conclusion. Our understanding of how species change over time has dramatically progressed since the 1859 publication of Darwin's *On the Origin of Species*. In the past 150 years, biologists have made advances in the study of evolution from a multitude of different research perspectives. From genetics to animal behavior, from proteomics to psychology, evolutionary questions and explanations abound. However, we still know relatively little about how the developmental processes and morphologies characteristic of different species diverged over time. The recent developmental research discussed above clearly contributes to our understanding of the evolution of developmental genes and consequently the evolution of morphological traits in complex organisms. There is considerable evidence for evo-devo's claim that regulatory changes play an important role in the evolution of form. There is also good evidence that *Hox* genes evolve differently than other genes since they do not follow any of the traditional models of post-duplication divergence. This novelty, along with the role of regulatory change in the evolution of form, represents biological justification of the claim that morphological traits truly evolve differently than physiological traits. Nonetheless, further evo-devo research is needed for a more detailed understanding of how *Hox* genes and other developmental genes evolve.

As evo-devo research continues, it promises to answer many more of our questions about the evolution of form. In particular, embryological and developmental research promises to further explain how *Hox* genes causally contribute to the development of an impressive array of different organismal forms. This paradox of morphology, the question of how a family of similar genes can contribute to the development of drastically different forms, represents one of many gaps in our understanding of evolution. As Carroll correctly argues, the results coming out of evo-devo research programs provide hope that such developmental puzzles can and will be solved by paying more attention to developmental processes. Studying these processes and how they have changed over time will further our understanding of evolution in general.

The debate surrounding the importance of evo-devo and the integration of developmental studies with the theoretical framework provided by the Modern Synthesis threatens to stagnate progress in evolution studies. The threat of stagnation is real and exists because the synthetic theory of evolution developed during the Modern Synthesis is indeed unable to provide an adequate framework for the study of macroevolution. That this is true is made obvious by what we do not know about evolution.

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Our understanding of the evolution of form is drastically limited, which suggests that evo-devo should be integrated with the framework of the Modern Synthesis in order to increase our understanding of how organisms evolved to have such remarkably different shapes and structures.

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