

**THE CAMBRIDGE ENCYCLOPEDIA OF
DARWIN AND
EVOLUTIONARY THOUGHT**



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**CAMBRIDGE
UNIVERSITY PRESS**

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town,
Singapore, São Paulo, Delhi, Mexico City

Cambridge University Press
32 Avenue of the Americas, New York, NY 10013-2473, USA
www.cambridge.org
Information on this title: www.cambridge.org/9780521195317

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First published 2013

Printed in the United States of America

A catalog record for this publication is available from the British Library.

Library of Congress Cataloging in Publication Data
The Cambridge encyclopedia of Darwin and evolutionary thought /
[edited by] Michael Ruse.

p. cm.

Includes bibliographical references and index.

ISBN 978-0-521-19531-7 (hardback)

1. Darwin, Charles, 1809-1882 – Encyclopedias. 2. Evolution
(Biology) – Encyclopedias. I. Ruse, Michael.

QH360.2.c36 2012

576.8'203-dc23

2012010226

ISBN 978-0-521-19531-7 Hardback

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Developmental Evolution

Manfred D. Laubichler and Jane Maienschein

AS PART OF THE 2009 DARWIN celebrations, we have seen the emergence and widespread acceptance of a standard narrative of the history of evolutionary biology that construes a more or less direct line from Darwin to present-day evolutionary developmental biology, or evo-devo (Mayr 1982; Larson 2004; Carroll 2005; Zimmer 2006, 2009; Ruse and Travis 2009). It is a story of completions and syntheses that not only celebrates Darwin's genius but also implies an implicit progression of ideas, with inclusion of new empirical facts and methodological approaches within the general framework of Darwinism leading to an increasingly more complete understanding of the evolutionary process. This narrative involves both scientific and public discourses. It can be found in textbooks of evolutionary biology and in popular accounts of evolution; it is also the basis the many efforts to construct a more inclusive evolutionary worldview.

But the standard narrative "From Darwin to Evo Devo" is also woefully incomplete as it leaves out several important traditions within the history of evolutionary biology (Laubichler and Maienschein 2007). These neglected traditions are not fringe ideas with no relevance to current understanding of evolutionary processes that can therefore be relegated to the dustbin of history. Quite the contrary. The ideas and approaches that are part of a complementary tradition – namely, to explain the evolution of organisms in reference to the developmental mechanisms that first generate phenotypes and phenotypic variation – have informed some of the most important current evolutionary biology research programs, those in developmental evolution (devo-evo) and synthetic experimental evolution (SEE) (Wagner, Chiu, et al. 2000; Davidson 2006; Davidson and Erwin 2006; Laubichler 2007; Erwin and Davidson 2009).

In this essay we briefly discuss the standard narrative and contrast it with one of the complementary traditions focused on the role of developmental mechanisms in explaining phenotypic evolution. We then argue that a more inclusive understanding of the history of evolutionary biology can better inform present discussions and contribute to a broader synthesis of twenty-first-century evolutionary biology, one that also reflects more fully the richness of Darwin's original vision. We also argue that understanding these multiple trajectories within the history of evolutionary

biology sheds light on currently emerging transformations of evolutionary biology into a causal mechanistic science.

THE STANDARD NARRATIVE OF THE HISTORY OF EVOLUTIONARY BIOLOGY: FROM DARWIN TO EVO-DEVO

In its most basic form, the narrative begins with Charles Darwin, although some versions include pre-Darwinian conceptions of phenotypic transformations such as those of Lamarck, Goethe, or Geoffroy de Saint-Hilaire, all of whom emphasized the importance of internal, organismal, or developmental factors. Darwin himself is generally situated within the nineteenth-century British context. The intellectual environment includes such debates as the age of the earth, the new conception of Lyellian geology with its emphasis on actualism and uniformitarianism, expertise of animal and plant breeders, natural historians exploring the far reaches of the emerging empire, the whole package of continental science and *Naturphilosophie* (courtesy of Robert Grant, Darwin's mentor during his short-lived stint as a medical student in Edinburgh), Whewell's philosophy of science, Adam Smith's theories of economics, and Malthus's insights into the dynamics of populations.

Furthermore, as Darwin's biographers have shown in great detail, these intellectual concerns existed in a symbiotic relationship with the social and economic transformations of nineteenth-century Britain. There is now a widespread consensus that Darwin truly was a child of his time, and this is exactly why he could, in turn, affect it as much as he did (Desmond and Moore 1991; Browne 1995).

All these concerns shaped the intellectual challenge Darwin tried to answer: How can we explain the patterns of organismal diversity, their distribution in space and time, and the incredible adaptations of organisms to the challenges presented by their environment? His answer, first formulated shortly after returning from his *Beagle* voyage, was a genuine and novel synthesis of various ideas and observations. It culminated, after two decades of refinement, in two canonical insights: descent with modification and natural selection.

Conceptually, Darwin's theory represents a breakthrough by combining two types of observations into a common explanatory framework. Organisms vary, at least part of this variation is passed on through generations, and organisms compete for limited resources as a consequence of Malthusian dynamics. Many chapters in this volume deal with these issues in more detail, so here we can summarize this first stage in the standard narrative as follows: Darwin's explanation of evolution includes the origin of variation, inheritance of variation, and the fate of specific variants competing for resources within populations. In his writings, he made suggestions about the first problem, developed an idiosyncratic (and wrong) theory of inheritance, and brilliantly applied the logic of natural selection to analyze the consequences of this mechanism for a whole range of phenomena (from the evolution of reproductive division of labor

and the existence of ornaments and displays to the patterns of the fossil record).

The second part of the standard narrative focuses on the problem of inheritance, the issue that Darwin did not solve. Without a clear understanding of the material basis of heredity – in the form of distinct factors or genes – a variety of theoretical possibilities had been discussed, including several versions of neo-Lamarckism (to which Darwin himself was at least partially sympathetic, as he accepted the possibility of the inheritance of acquired characteristics).

The establishment of the rules of inheritance based on the Mendelian concept of discrete factors of inheritance that are passed on intact across generations, along with the subsequent discovery that these factors are localized on chromosomes, reinvigorated evolutionary thought. Building on mathematical and statistical methods that had been developed to describe and analyze variation and inheritance within populations, mathematical population genetics developed as a new foundation for evolutionary theory. It allowed exploration of the consequences of natural selection within populations, through the analysis of formal models, and it explicitly connected evolutionary and genetic analyses. It also solved the question of inheritance, insofar as it relates to patterns of transmission and the dynamics of genes/alleles within population (Provine 1971).

But population genetics introduced some substantial changes to the structure of evolutionary theory. The gene, as the unit of stable transmission between generations, now occupied a privileged position in accounts of the evolutionary process. And, while the combination of natural selection with gene-based views of inheritance provided a better understanding of the short-term consequences of evolutionary change, this early twentieth-century vision did not address the problem of the origin of variation. It simply assumed that variants of existing genes emerge as mutations and that the traces and consequences of these mutations can be studied and observed in populations. There were debates about the quality and size of mutational events (as in the debate between Mendelians and biometricians), but these were largely about the consequences and less about the causes of these different types of mutations.

This part of the standard narrative actually ignores several important lines of research. Here we discuss one such alternative that focused on the role of genes in developments, though there are others, such as those in cytology and cytological genetics (Laubichler 2003; Laubichler and Maienschein 2004, 2007; Laubichler, Aird, et al. 2007; Laubichler and Davidson 2008). In the progressive narrative of the history of evolutionary biology, this period mainly stands for two developments: the solution of the inheritance problem and the emergence of a mathematical approach that further emphasized what Ernst Mayr referred to as "populational thinking" (Mayr and Provine 1980; Mayr 1982).

For our purpose of contrasting the standard narrative with a complementary history of developmental evolution, we need to emphasize one important assumption that characterized

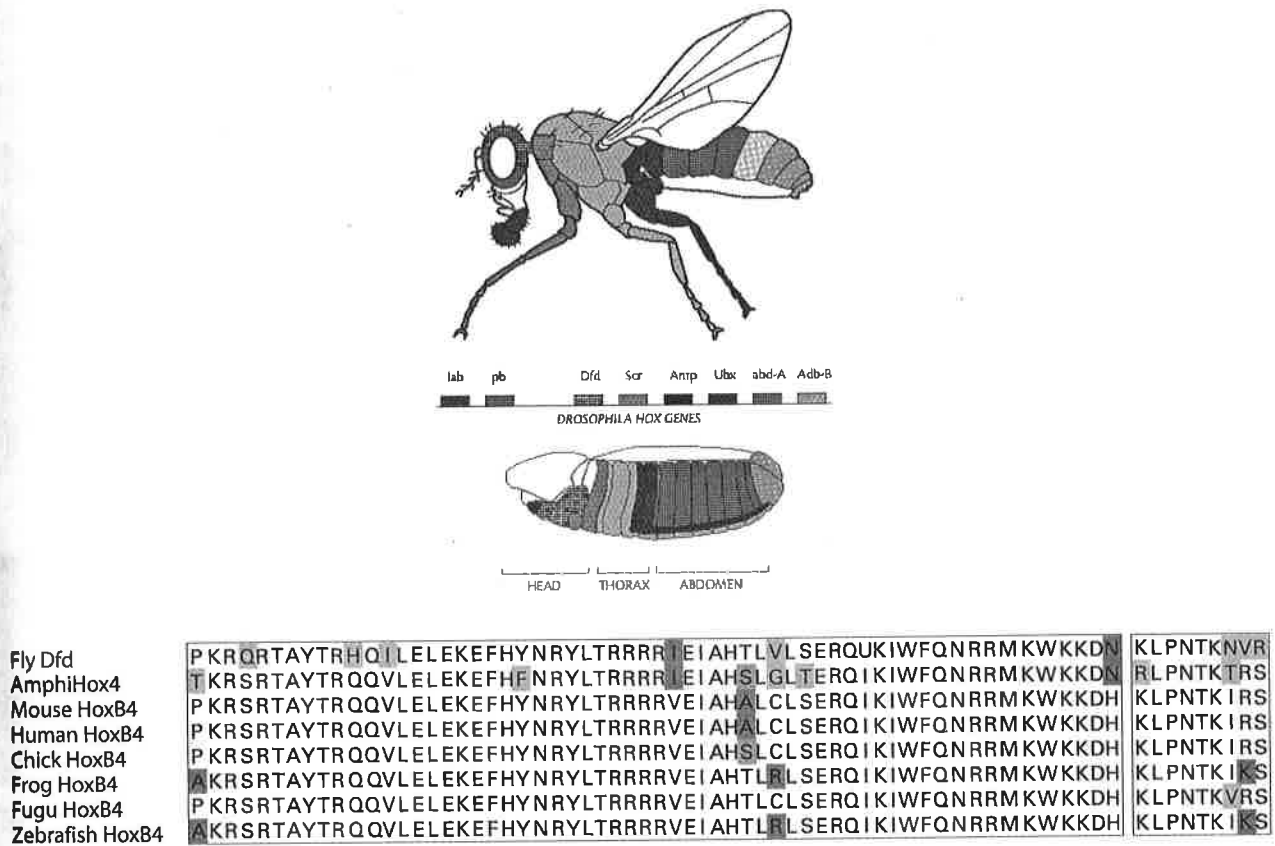


FIGURE 46.1. Hox genes. The genes controlling development in the fruit fly (*top*) and a comparison with homologous genes controlling development in other organisms including humans (*bottom*). This shows that the causes of development are not something newly created for each animal but part of a shared kit, where the genes function rather like Lego pieces – build one way and you get a fruit fly, build another way and you get a human. Permission: Sean B. Carroll et al., *From DNA to Diversity* (Oxford: Blackwell Scientific, 2001), 23, fig. 2.5, and 27, fig. 2.8

the population genetic (and also quantitative genetic) models developed within the modern synthesis framework. These models continued to emphasize the importance of the gene as the fundamental evolutionary unit. They also reinforced an additional formal assumption of population genetics, namely that the structure of the genotype-phenotype map (a technical term connecting genotype and phenotype or fitness values) is simple and that we can therefore describe the dynamics of evolutionary change solely on the level of genotypes.

Given the technical constraints of the time, such as the limited computational powers, this assumption of linearity was essential. And while it seemed to hold in some cases, the structural limitations of these models also contributed to an inherent discontent with the modern synthesis. Another central feature of mid-twentieth-century evolutionary biology connected with the formal structure of population genetic models has been its focus on adaptation and an implicit commitment to more or less gradual patterns of evolutionary change. Both of these assumptions were challenged in the 1970s and 1980s, mostly by paleontologists and developmental biologists, who contributed to the emerging field of evolutionary developmental biology representing the latest episode in the standard narrative of the history of evolutionary theory (Gould 1977; Laubichler and Maienschein 2007).

While early concerns of evo-devo focused on such issues as developmental constraints, punctuated equilibria in the fossil record, and heterochrony or life history evolution, today's version also includes results from comparative genomics and developmental genetics that have revealed the high degree of conservation of what has come to be known as the "genetic toolkit for development" (Carroll 2005; Carroll, Grenier, et al. 2005) (Fig. 46.1).

Within the standard narrative, evo-devo is mostly seen as a completion of the modern synthesis, the details of which are still unfolding (Carroll 2005; Zimmer 2009; Pigliucci and Müller 2010). This view allows commentators to contextualize some of the arguments within the evo-devo and evolutionary biology communities, such as those about the genetics underlying phenotypic change as necessary debates en route to a consensus. In this view, the main theoretical innovation of evo-devo lies in its treatment of the genotype-phenotype map, which is now seen as more complex and representative of the known facts of developmental genetics. This focus on the genotype-phenotype map also continues the well-established collaboration between theoretical and empirical work in evolutionary biology. While developmental geneticists uncover empirical details of how genes affect the development of phenotypes, theorists explore the formal

consequences of epistasis and complex genotype-phenotype maps within the framework of population genetic models. The emerging twenty-first-century evolutionary theory is thus very much like its twentieth-century predecessor, only better in the sense that it more adequately represents the known facts of development. But this also means that the primacy of evolutionary dynamics (in the form of population genetics) for all explanations of evolutionary transformations remains intact.

What can be seen, even from this very brief sketch, is that the standard narrative emphasizes a clear progression in the development of evolutionary theory, one grounded in Darwin's original conception and continuously incorporating new perspectives within a framework of population-based adaptive dynamics that has remained more or less unchanged for at least a century.

A BRIEF HISTORY OF DEVELOPMENTAL EVOLUTION: FROM DARWIN TO SYNTHETIC EXPERIMENTAL EVOLUTION

The standard history of evolutionary theory sketched in the preceding section is but one narrative organizing a whole range of complex historical developments connected with the idea of evolution. Alternative positions have been discussed, but for the most part these accounts have focused on critiques and challenges to the Darwinian mainstream that did not add up to a similarly substantive and successful research program (Bowler 1983, 1988). While it is, for instance, interesting to understand how neo-Lamarckian ideas persisted as a challenge to a Darwinian consensus, these ideas did not contribute much to our current understanding of evolutionary biology, which in turn might explain the widespread appeal of the standard narrative.

The alternative history we explore here is different in that it has, for the most part, not been considered in the context of evolutionary biology, even though, as we will argue, these developments have made substantial and central contributions to our understanding of the evolutionary process.

As with the standard narrative, we begin our story with Darwin. The same caveat, that many of the concerns discussed here have an important history before Darwin and that these antecedents influenced Darwin's thinking in important ways, is true here as well (Desmond and Moore 1991; R. J. Richards 1992; Browne 1995). We have already seen that Darwin recognized the origin of variation as an important problem. He collected numerous data on the specific patterns of variation found in populations, both natural and artificially selected, and offered several possible explanations for the existence of these variants. Among those, mechanisms of development were especially important. To quote just one of many passages throughout his oeuvre: "Our ignorance of the laws of variation is profound.... Changes of structure at an early age will generally affect parts subsequently developed; and there are very many other correlations of growth, the nature of which we are utterly unable to understand" (Darwin 1859, 167–68).

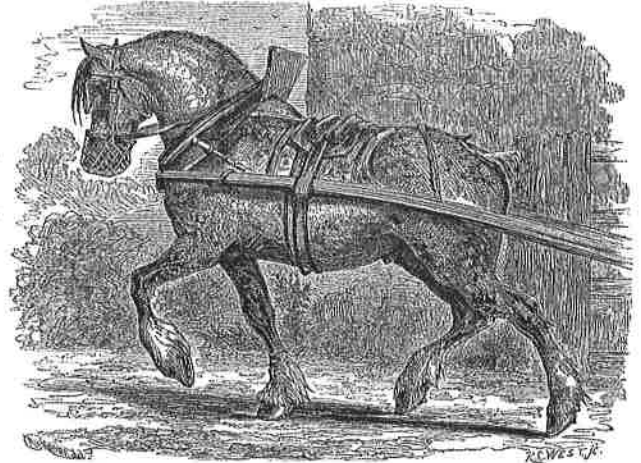


FIGURE 46.2. Race horses and draft horses. In the *Origin*, Darwin was particularly interested in the way in which natural selection tears apart the adults of organisms with very similar embryos. His hypothesis that natural selection works on variations that appear only later in individual development was given strong support by his studies of the practices of animal breeders. They are indifferent to juvenile features but select for desired adult features. A prime example is that of horse breeders, some of whom want strong workers (*top*) and others of whom want fast racers (*bottom*). Nineteenth-century etching from S. Sidney, J. Sinclair, and W. C. Arlington Blew, *The Book of the Horse* (London: Cassell, Peter and Galpin, 1893)

Darwin clearly recognized that developmental processes, such as the timing of embryological events or the correlations of growth, are essential components of any explanation of the origin of phenotypic variation. This close connection between embryology and evolutionary ideas was characteristic for much of the nineteenth century, both before and after the publication of the *Origin*, as has been pointed out repeatedly. We can therefore summarize that for Darwin as well as many of his contemporaries, development was an integral part of any explanation of phenotypic transformation and evolution and that the problem of the origin of variation was considered a major challenge for which developmental mechanisms offered possible solutions (Fig. 46.2).

In subsequent decades the question of "generation" or *Entwicklung* became one of the prime research areas of the

emerging experimental biology. We use two nineteenth-century terms to highlight the fact that during this time the problem of the origin of organismal forms was seen as a more inclusive process that involves questions of inheritance, development, and evolution (Laubichler and Maienschein 2004). Historical scholarship has mostly focused on the highly influential theoretical ideas of August Weismann and debates triggered by his rejection of the inheritance of acquired characteristics, the concept of the separation of germline and soma, and his broadening of the action of selection, for which George Romanes coined the term “neo-Darwinism.” Weismann’s proposals paved the way for the subsequent separation of the different dimensions of “generation.” Once inheritance, through continuity of the germline, was conceptually separated from development (or the processes of differentiation and morphogenesis), it became possible to connect evolutionary transformations with patterns of hereditary transmission (Laubichler and Rheinberger 2006). This conceptual insight led to the establishment of population genetics.

But evolutionary concerns also influenced the work of numerous cell and developmental biologists during this period even though they often did not discuss their work explicitly in those terms. Here, as an example, we briefly discuss the work of Theodor Boveri, arguably one of the most influential experimental biologists of his time (Laubichler and Davidson 2008) (Fig. 46.3). Boveri’s major research questions were all related to “generation” in its inclusive sense. He studied among other things the behavior and functional role of chromosomes, fertilization, heredity – culminating in the chromosomal theory of inheritance, the structure of the egg, and the role of cytoplasm and nucleus in development and differentiation. His accomplishments in these areas are well documented. Less known are Boveri’s conceptual and institutional contributions to the tradition of developmental evolution.

Boveri summarized his views in his *Rektoratsrede* of 1906. In this inaugural speech, entitled “Organisms as Historical Beings,” Boveri (1906) argues that any explanation of the evolution of organisms must begin with an understanding of developmental processes because these represent the constructive mechanism that generates organisms; these processes are controlled by a highly structured system of hereditary materials located within the nucleus; and these phenomena have to be studied experimentally, with one experiment standing out: “to transform organisms in front of our eyes.” Boveri thus mapped out the research program of experimental developmental evolution: analyzing the ways the system of hereditary factors controls development and studying how changes to this system transform organisms before our eyes. This approach to evolution clearly focused on the primacy of understanding the origins of phenotypic variation experimentally before any attempt to study the consequences of natural selection. Boveri also realized that for such an ambitious research program to work, a new type of research institution would be needed. When he was asked to develop the plans for the Kaiser-Wilhelm-Institut für Biologie, he organized it to



FIGURE 46.3. Theodor Boveri (1862–1915), along with the American biologist Walter Sutton, was the discoverer of the fact that the units of inheritance are carried by the chromosomes. He made other significant discoveries, including the fact that cancer starts with the disruption of the chromosomes in a single cell, causing uncontrolled division. Permission: American Philosophical Society

support such a program of experimental developmental evolution (although he did not use this term).

Illness, however, prevented Boveri from finally accepting the post of founding director. Even though his successor Carl Correns made only a few changes, a good deal of Boveri’s vision was realized, partly as a result of the appointment of Richard Goldschmidt, arguably one of the most colorful characters in the history of biology. Here we are mostly concerned with his long-term study of physiological gene action in development and some of the conceptual conclusions he drew for understanding phenotypic evolution. Basically, Goldschmidt (1940) realized that mutations can have different phenotypic or morphological effects depending on which part of the developmental machinery they affect. And while some of his wilder speculations about large-scale rearrangements of the chromosomes and the dissolution of the gene as a unit did not work out, his recognition that regulatory mutations can have large-scale effects proved insightful. His approach also championed experimental analysis of how genes control development, a research program that his successor at the Kaiser Wilhelm Institute for biology, Alfred Kühn, also pursued. (Kühn succeeded Goldschmidt in 1936 after he was forced out of Germany.)

Kühn, working with the flour moth *Ephestia*, attempted to fully characterize the causal chain of biochemical events that connects a gene (for eye color) with its phenotypic effect. He and co-workers discovered that gene action is based on two interacting pathways with multiple parts (one pathway of gene

products, the other of substances) that finally result in the phenotype. He later generalized this conception and argued that (1) each phenotype is the consequence of a complex network of interactions between genetic elements representing a "developmental physiological equilibrium"; (2) each phenotypic variant is the product of a different equilibrium state; and (3) evolution is the product of a series of transformations of developmental physiological equilibria. The details of Kühn's conception were highly speculative. He did not have much empirical evidence for his somewhat vague notion of "equilibrium," but it was also a clear expression of the logic of developmental evolution, and as such proved to be inspirational for some younger German and Swiss biologists (Kühn 1955; Laubichler and Rheinberger 2004).

The most immediate source of the present-day conception of developmental evolution dates back to the late 1960s and early 1970s. A seminal paper by Eric Davidson and Roy Britten, "Gene Regulation for Higher Cells: A Theory," published in *Science* in 1969, refocused many of the conceptual ideas related to differentiation and gene expression from earlier periods and connected them with the rapidly advancing field of molecular biology (Britten and Davidson 1969) (Plate XXXVI). The resulting theory provided a clear and logical formulation of how developmental processes are controlled by gene activity, how regulation of gene activity is the underlying mechanistic cause for differentiation, and how regulatory changes in gene expression are the direct cause for phenotypic variation.

From the very beginning, the evolutionary implications of the Britten-Davidson model, as it became known, were obvious. Britten and Davidson (1971) already discussed those in the original article as well as in a follow-up paper published two years later. And while traditional developmental biologists took some time to fully accept the regulatory- and genome-based reorientation of their field, some evolutionary theorists immediately recognized the implications of this proposal and its emphasis on regulatory networks. They developed a range of theoretical models that suggested that the structure of the genome and patterns of interactions between genes would show evidence of their evolutionary history. For example, these models proposed that those genes involved in fundamental developmental processes that arose early in evolution would be more conserved or have a higher "burden" (Riedl 1975; G. P. Wagner and Laubichler 2004).

As well as the theoretical implications of the Britten-Davidson model, empirical evidence for some of its conclusions began to emerge as well. One of the implications is that major phenotypic changes would more likely be the consequence of mutations in the regulatory sequences than those that code for structural proteins. This conclusion was supported by the observation that many functional proteins have highly pleiotropic effects, which would place their genes under strong stabilizing selection, whereas it was thought that the regulatory regions controlling their expression during development could be more variable. One of the first empirical studies supporting this idea was the classic paper by

Mary-Claire King and Alan Wilson (1975) comparing human and chimpanzee macromolecules. After surveying the available molecular evidence, they concluded that the observed phenotypic differences between these two species must be the result of regulatory mutations, in line with predictions of the Britten-Davidson model.

After these early theoretical and empirical discoveries, research into the molecular mechanisms of developmental evolution continued, despite some substantial technical difficulties. By the late 1970s and early 1980s, the question of the relationship between development and evolution had become a major concern within evolutionary biology.

The 1981 Dählem conference, organized by John Bonner (1982), represents a major landmark. It also highlights the substantial differences between the two approaches that would soon be known as evolutionary developmental biology and developmental evolution. The former takes the phenomenology of evolutionary and developmental patterns as its starting point and asks how developmental processes can add to the explanation of these observations. The best examples of this trend are the notions of developmental constraints, where developmental processes are thought to explain the fact that the observed phenotype space is spotty and mostly empty, and heterochrony, where changes in the timing of developmental processes are employed to explain large-scale and correlated changes in phenotypes. Both examples exemplify the structure of evolutionary developmental biology whereby developmental processes are incorporated into the standard framework of evolutionary theory, either as limits to variation (constraints) or as highly pleiotropic effects of genes affecting developmental timing.

Developmental evolution, on the other hand, emphasized the underlying genomic and regulatory mechanisms as the foundation of all evolutionary change. The main conceptual differences between these two approaches were that developmental evolution focused on (1) the genome as an integrated regulatory system rather than the single (or multiple) gene locus paradigm of standard evolutionary theory; (2) the mechanisms generating phenotypes and phenotypic variation as the primary step in all explanations of evolutionary change; and (3) a causal-mechanistic and experimental approach to the problem of evolution. Beginning in the 1990s, as the experimental repertoire of molecular biology expanded and available sequences brought about a more genome-based biology, empirical research in developmental evolution began to catch up with its conceptual and theoretical insights (E. H. Davidson 1990).

The culmination of decades worth of detailed empirical and conceptual work in this area has been the transformation of the early ideas of regulatory networks proposed in the Britten-Davidson model into the fully characterized gene regulatory networks (GRNs) of today (E. H. Davidson 2001, 2006). The majority of the early and foundational work in this area has been done, by Eric Davidson and his collaborators, with the purple sea urchin as a model system. Today, molecular, genomics, and bioinformatics tools make it possible to

study developmental GRNs in an increasing number of organisms, thus allowing for a comparative analysis of GRNs. Such analysis is essential for a GRN-based explanation of evolutionary transformations. In this context several important findings have refined earlier conceptual ideas about the role of genomic regulatory systems in evolution. It is now clear that the modular and hierarchical structure of GRNs has important implications for understanding the origin and patterns of phenotypic variation. Different elements in the GRN have different variational properties; for example, those elements responsible for highly conserved body plan features (kernels) are generally more conserved than more downstream elements of the network (E. H. Davidson 2006; E. H. Davidson and Erwin 2006, 2009; Peter and Davidson 2009). This seems to confirm earlier ideas that the evolutionary history is also inscribed into the genomic developmental systems that control the development of organisms.

Eric Davidson (2006) has proposed a classification of genomic regulatory elements that includes the most conserved control elements or kernels; a set of multipurpose modules that are used in a variety of contexts (switches, plug-ins, and input-output devices); and the differentiation gene batteries, those sets of genes that characterize the specific cell state. Functional as well as comparative analysis of these different GRN elements reveals that changes in different parts of the network correspond to qualitatively different phenotypic and evolutionary transformations. These insights have reinvigorated a developmentally based approach to phylogenetic history. As kernel differences tend to map onto phylum- or superphylum-level morphological features, the evidence suggests that those which are part of the regulatory elements evolved before the separation into distinct lineages and body plans. Subsequent evolution of different parts of the network led to the elaboration of these body plans, while adaptive evolution and speciation tend to be caused by changes in downstream differentiation gene batteries or the ways these are deployed (E. H. Davidson, Peterson, et al. 1995; Erwin and Davidson 2002, 2009; E. H. Davidson and Erwin 2006, 2009). Many details of these evolutionary scenarios are still unknown, but the conceptual framework of developmental evolution has already transformed the way we research and interpret the origin and evolution of GRNs and of phenotypic evolution more generally. And as the evidence for conserved genes and a relatively low number of open reading frames continues to accumulate, the importance of regulatory evolution at multiple layers of control systems only increases.

The developmental evolution perspective also provides an interpretative framework for numerous molecular details that are being revealed in the context of genomic-based approaches. The majority of these findings, such as the discovery of multiple families of regulatory RNA molecules, points to an increasing importance of regulatory processes in both development and evolution.

The latest episode, currently unfolding, in the history of developmental evolution is, in many ways, the most radical transformation of evolutionary biology since the formulation

of population genetics early in the twentieth century. Previous experimental approaches to the study of evolution involved either long-term selection experiments, direct manipulation of phenotypic characters in order to measure their contributions to fitness, or the exposure to mutagens to increase the mutation rate. Today, on the basis of insights into the structure of GRNs a new kind of experimental approach to evolution is emerging, *synthetic experimental evolution* (Erwin and Davidson 2009). This approach studies the phenotypic consequences of targeted changes to GRNs, which will allow us to reengineer major phenotypic transformations in evolutionary history. The preconditions for these types of experiments are all within reach: (1) comparative analysis of GRNs of a species that has acquired a novel phenotypic character as well as of related species that represent the ancestral condition; (2) identification and experimental verification of those changes to the structure of the GRN that are causally sufficient to generate the novel phenotype; (3) targeted insertion of these GRN elements into the genome of the species representing the ancestral condition; and (4) testing the prediction that a rewired GRN will generate a phenotype similar to the one that has been acquired during the evolution of the derived lineage. Taken together, these experimental approaches enable us to study the developmental basis of evolutionary transformations and investigate how different kinds of phenotypic variation are generated.

As a consequence of these developments, developmental evolution is now becoming a causal mechanistic and experimental science that is closely aligned with two transformative paradigms of twenty-first-century biology: systems biology and synthetic biology. An emphasis on genomic regulatory systems (such as GRNs) is only a first step in the direction of a more inclusive systems focus within developmental evolution. The consequences of a number of additional regulatory systems – from microRNAs to epigenetic systems – for developmental evolution are also being investigated. However, all these additional layers of regulatory control are being anchored by the regulatory genome, which therefore occupies a privileged position within both developmental and evolutionary processes. Additional connections to systems and synthetic biology are methodological and include a close connection between targeted experimental interventions designed to reengineer functional control circuits and mathematical and bioinformatical approaches.

With regard to our original question how these developments change the narrative of the history of evolutionary biology, we can conclude that developmental evolution represents a theoretical and conceptual departure from standard evolutionary explanations and their focus on the adaptive dynamics of populations. Developmental evolution is a return to the more inclusive focus of Darwinism, with its emphasis on both the origin of variation as well as the fate of variants within populations. While the latter has been well studied during the past century, the former involves significant conceptual and methodological changes that represent a departure from mainstream twentieth-century evolutionary biology.

CONCLUSION

Our brief exploration of multiple pathways in the history of evolutionary biology offers a much richer and more diverse picture than the standard narrative "From Darwin to Evo-Devo" suggests. Furthermore, many of these previously neglected episodes shed new light on current developments in evolutionary theory. The possibilities enabled by the emerging causal-mechanistic understanding of phenotypic evolution arguably represent the most dramatic transformation of evolutionary theory in decades. Yet the roots of this conceptual reorientation of evolutionary biology can only partially be found within the mainstream history of the field as it has been portrayed so far. Rather the antecedents of much of this work fall within the alternative tradition sketched here. As a result, the history of evolutionary biology increasingly resembles our current understanding of evolutionary history; we no longer see a linear or simple branching pattern, with one "progressive" trunk and major and minor branches diverging from it. Quite the opposite, we see the same reticulate pattern and horizontal as well as vertical transmission of ideas (genes/memes) that characterizes the majority of evolutionary events (especially in the microbial domain).

Having a more complete understanding of the history of evolutionary theory since Darwin has important practical implications. Early twenty-first-century evolutionary biology emphasizes the need for synthesis, either as a "completion of the modern synthesis" or in the form of a new synthesis. Both of these calls require the integration of radically different conceptual frameworks, experimental traditions, fundamental assumptions, and epistemologies in order to achieve a more inclusive understanding of the evolutionary process. Without successful integration of the different domains of developmental and evolutionary biology, the developmental evolution or evo-devo project will fail. After an initial period of enthusiasm, the field has now entered a phase of routine data generation. What is still largely left undone is the hard work of conceptual integration that is required for a true theoretical synthesis.

In this context critical historical perspectives are essential. They will enable us to evaluate the often-hidden assumptions of certain models and concepts. The examples discussed here

can serve as an illustration. Do we build our new synthesis of twenty-first-century evolutionary biology within the conceptual framework of population-based adaptive dynamics – which implies that developmental mechanisms feature as an explanation of the genotype-phenotype map – or do we represent the evolutionary process within a causal-mechanistic framework that can be captured by the following logical structure: (1) all phenotypes are the product of developmental mechanisms; (2) all phenotypic variation is therefore a consequence of a corresponding variation in the developmental process; (3) understanding these developmental processes provides a causal-mechanistic explanation for the origin of phenotypic variation (Darwin's first question); (4) the subsequent fate of phenotypic variation can be analyzed within the population-based framework of adaptive dynamics.

To fully appreciate the differences between these two proposed versions of a twenty-first-century synthesis of evolutionary theory we need to understand how each of those viewpoints emerged historically and what epistemological assumptions guide the integration of developmental and evolutionary perspectives. As we have seen, the possibilities of synthetic experimental evolution represent a significant addition to the standard experimental repertoire of evolutionary biology, which is no longer confined to comparative and functional analysis or selection experiments. The ability to reconstruct major phenotypic transitions in evolutionary history through the manipulation of the underlying developmental mechanisms turns evolutionary biology into a mechanistic science. One consequence of this emerging transformation of evolutionary biology is that the standard distinction between proximate and ultimate causes no longer serves as the most obvious way to separate explanatory paradigms within (evolutionary) biology.

Evolutionary biology thus continues to evolve. And insofar as embryological considerations were already central to the earliest formulations of evolutionary theory, the current resurgence of developmental approaches reveals some of the deep conceptual structures at the core of evolutionary thought. Darwin, for once, would not be surprised and, we suspect, would be intrigued by the new experimental approaches and the possibility of causal-mechanistic explanations of phenotypic evolution.