

## CHAPTER 8

### *Exploring development and evolution on the tangled bank*

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When Michael Ruse was young, a linear model of knowledge generation prevailed. Scientists (and philosophers) make discoveries, and generate knowledge, on this view, then society uses (or doesn't use) that knowledge. According to this interpretation, using scientific knowledge usually makes society – and the world – better, though occasionally unfortunate applications make the world worse. In each case, the arrow of influence was thought to point from science to society.

Then after the 1970s, those emphasizing social contexts insisted on the importance of arrows pointing the other way as well, or even primarily. As an example, E. O. Wilson's presentation of sociobiology was seen as his having chosen a view about nature that could have been otherwise. Critics, starting with Wilson's colleagues and former students at Harvard, attacked Wilson, eventually dumping water on him at a meeting to demonstrate their objections. Society, on their view, could and should choose another biological view of human nature. This critique became part of a movement that insisted on understanding science as something that is socially constructed.

Of course, both these simplistic ideas of linear influence are limited and problematic. Instead, a great deal of lateral transfer of ideas also occurs, and what we have is much more nearly a tangled bank of influences at the intersection of science and society. Similarly with philosophical understanding of biology: when Michael Ruse began his career, the picture was much simpler with emphasis on reduction and levels of selection. David Hull's short 1974 textbook *Philosophy of the Biological Sciences* offered only two pages related to development, in particular causal laws of development largely based on genetics and focused on issues of reductionism.<sup>1</sup> In his own 1973 textbook *The Philosophy of Biology*, Michael Ruse acknowledged that he had emphasized evolutionary biology rather than covering

<sup>1</sup> Hull 1974.

every biological topic. He noted that “many areas of biology, for example, embryology, have been practically or entirely ignored. My silence about them should not be taken to indicate that I think them of no philosophical significance – I feel sure that, in fact, such areas harbour important problems awaiting discussion.”<sup>2</sup> In fact, with that work and subsequent books, Michael Ruse has gone far to help reveal that the bank of biological and of philosophical issues is indeed tangled and that it is worth marveling at the resulting “grandeur” that comes from the complexity and diversity.

The field called evo-devo gives us a nice example of just this sort of tangle of fields and issues, as well as a great deal of lateral transfer. In a blog entry on July 5, 2005, Michael Ruse asked “What are the big issues today?” He noted:

I pride myself on having a pretty good nose for a problem, and if I were going in the direction of straight philosophy of biology – as opposed to something that was going to bring in history, ever a fondness of mine – I would without hesitation go for evolutionary development, “EvoDevo.” I think some of the most incredible discoveries of recent years have come from this area – the amazing homologies between humans and fruitflies for starters.<sup>3</sup>

He went on to suggest that surely evo-devo will have something intriguing to say about human evolution, perhaps focusing on cognition, and therefore that evo-devo can impact our social understanding of ourselves.

In addition, the field that has come to be called evo-devo is also shaped by the society of biologists involved. In this chapter, we look briefly at the backgrounds and origins of the field, at what is at issue today, and at some trends for the future in biology and for philosophy of science amidst the entangled studies of development and evolution.

## Background

Darwin provided the first connections of embryology and evolution when he pointed to embryological facts and asserted that embryos provide the strongest support for his ideas of evolution, “second in importance to none in natural history.” In his *Autobiography*, he wrote that “Hardly any point gave me so much satisfaction when I was at work on the *Origin*, as the explanation of the wide difference in many classes between the embryo

<sup>2</sup> Ruse 1973, 218.    <sup>3</sup> Ruse 2005.

and the adult animal, and of the close resemblance of the embryos of the same class. No notice of this point was taken, as far as I remember, in the early reviews.”<sup>4</sup>

Darwin acknowledged that Ernst Haeckel had done far more with the connections than Darwin had and that it was therefore perhaps understandable that reviewers had not taken much notice of his own contributions. Enough has been written about Haeckel and ideas of recapitulation that we need not go over that ground again but can move on.

In 1896, Edmund Beecher Wilson wrote in what became his classic study of *The Cell in Development and Inheritance*, that “The cell-theory must therefore be placed beside the evolution-theory as one of the foundation stones of modern biology.” Yet he recognized that the two were very different fields of study, with different kinds of research and questions. One looked at individual cells from individual organisms, used the microscopic, and spent time inside in the lab, while the other started from natural historical study of behaviors and groups. Both have problems explaining how complex phenomena arise – but to Wilson, at the end of the nineteenth century, it seemed clear that inherited germ-plasm provides a basis for all biological phenomena. Wilson called for careful study of the cell, and also urged that finding intersections of the cell and evolutionary theories, with heredity and development at the core of both, as essential for real progress in the biological sciences.<sup>5</sup>

Some biologists have pointed to work around the end of the nineteenth century as the point of divergence of evolution and development. For example, Rudolf (Rudy) Raff and Thomas Kaufman noted in 1983 that though it seemed obvious that research in evolutionary biology should include a major study of developmental processes, this was not the case. As they put it, “Embryological development, which was so vital a part of evolutionary theory in the late nineteenth century, has been considered largely irrelevant in the twentieth.” Despite efforts by Hans Driesch and Thomas Hunt Morgan, which they cite as the two major efforts to join the two different fields, they felt that a truly modern synthesis had failed because of lack of enough understanding of developmental genetics. Yet in 1983, they felt that “the time has come to take the final step in the modern synthesis: To fuse embryology with genetics and evolution.”<sup>6</sup>

<sup>4</sup> Darwin 1859, 450; Barlow 1958, 125. Ernst Mayr especially liked to point to Darwin’s use of embryology, for example in Mayr 1982, 469–70.

<sup>5</sup> Wilson 1896. <sup>6</sup> Raff and Kaufman 1983, 1, 24.

Their perspective is valuable because Raff has become one of the leaders in the established field of evo-devo studies. That he saw the reconvergence of what had been divergent lines of research up to the 1980s or so is reinforced in another volume that he edited with Elizabeth Raff and that resulted from a symposium at the Marine Biological Laboratory – where much of the early work had been carried out. Here, in ~~the~~ 1987, the Ruffs pointed to two lines of research extending from Haeckel's emphasis on embryology as a way to get information about evolution and phylogenetic relationships on the one hand, and experimental embryology as a way to understand development of individual organisms on the other. For the first two-thirds of the twentieth century, it was very difficult to bring the two lines together, in large part because developmental biologists and evolutionary biologists use different methods, ask different questions, and "practitioners of one discipline are generally unaware of the paradigms and body of knowledge considered central to the second, and thus may have more than a little difficulty posing questions that can be considered nontrivial by members of the second discipline." Philosophical differences – by which they mean differences in epistemologies – ensured that little communication occurred at the intersections.<sup>7</sup>

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These founders provide one perspective on what kept the fields apart, but a quick look at some intervening contributors suggests that the story is more complicated and the fields more tangled than that. In a largely ignored paper presented at the bicentennial of the University of Pennsylvania and published in a volume on *Cytology, Genetics, and Evolution* that appeared in 1941, cytologist Clarence E. McClung pointed out that development involves a series of interactions of the organism with its changing environment, which allows multiple possible results that were not fixed by heredity. As McClung put it:

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Perhaps the problem might be stated specifically in this way: Since all organisms exhibit a common series of functions, and since functions are performed under the control of a recognizable series of agents within the chromosomes, there must exist a nuclear mechanism common to all organic types. Logically this would follow, and observation tells us that, at least in its major features, such a situation does exist, for cellular structure and behavior are essentially the same wherever found. Moreover, in the earlier and relatively simpler processes of development, strong likenesses prevail through all forms. But beyond this, what are we to expect? Does each advance in complexity, each new structural element mean additional

<sup>7</sup> Raff and Raff 1987.

gene controls or are they due to what might be called the better education of members of an existing system through new experiences?<sup>8</sup>

McClung called for more detailed study of the germ-plasm, and especially the interactions of genetics and cytology to get at the relations to development and evolution. Like Raff, Raff, and Kaufman, McClung recognized the need for more information. But his work reminds us not to assume that people were not trying to bring the fields together. The work also shows that some cytologists and embryologists were beginning by the 1940s to see that developmental processes are often conserved across different species, which suggests a strong hereditary and evolutionary impact on development.

Julian Huxley, in articulating "The Modern Synthesis," saw this as well. It has become popular for historians and biologists to assert that the synthesis ignored development, and many developmental biologists have called for correcting that slight. Yet Huxley did note in a section entitled "The Consequences of Differential Development" that different "rate-genes" control the rate and timing of developmental processes. Therefore, development is a key part of playing out of evolution.<sup>9</sup>

Stephen Jay Gould, in his 1977 *Ontogeny and Phylogeny*, said essentially the same thing, only at much greater length. He noted that his book was a personal favorite of his, on which he had expended a great deal of effort. There he pointed out to the intersection of ontogeny and phylogeny as focused on heterochrony – that is, the timing and rate of appearance of characteristics during development, which reflects evolutionary history.<sup>10</sup>

The 1970s and 1980s did begin to reveal a great deal more about the connections. As John Gerhart and Mark Kirschner noted in 1997, a "flood" of new experimental approaches and new results had "convinced everybody" that the underlying developmental mechanisms are conserved.<sup>11</sup> Instead of trying to find what is the same in development of different organisms, the question had shifted to how difference arises.

Scott Gilbert modified his *Developmental Biology* textbook for the 6th edition in 2001, adding chapters on plants, medical implications, environmental regulation, and finally chapter 23 on "developmental mechanisms of evolutionary change."<sup>12</sup> Brian K. Hall and Wendy M. Olson's edited

<sup>8</sup> McClung 1941, 64.

<sup>9</sup> Huxley 1943 (dedicated to Morgan, "many-sided leader in biology's advance," 525–43 is a section on "Consequential Evolution: The Consequences of Differential Development").

<sup>10</sup> Gould 1977, 2.    <sup>11</sup> Gerhart and Kirschner 1997, ix.    <sup>12</sup> Gilbert 2006.

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collection of *Keywords and Concepts in Evolutionary Developmental Biology* in 2006 further demonstrated that studies at the intersection of evolution and development had come of age.<sup>13</sup> The next steps were to establish the research as a field, to celebrate convergence, and then to get down to the hard work of figuring out what the tangle of ideas and fields really involves and what progress is really being made.

### Establishment of evo-devo

The field gradually emerged as multiple different, and somewhat divergent, forces came together. Various different accounts – from participants as well as observers – offer different creation myths, but it is clear that a number of researchers coalesced around a number of related ideas at about the same time.<sup>14</sup>

Here we focus on just one (relatively recent) story that is well documented, and furthermore both of us were there to witness the event. This official stage in the emergence of evo-devo occurred at the annual meeting of the Society for Integrative and Comparative Biology (formerly the American Society of Zoologists) in 2000. SICB had just added a Division of Evolutionary Developmental Biology with Rudolf Raff as the inaugural chair. Richard Burian explained in his Introduction to the published symposium volume that the impetus grew out of the previous SICB meeting in Denver. At a breakfast, he recalled, Burian, Scott Gilbert, Paul Mabee, and Billie Swalla mapped out a symposium to explore the historical background of evo-devo. In fact, they ended up with three symposia, one historical to look at the past, present, and future of the new field, and the others to explore hox genes and “using phylogenies to test hypotheses about vertebrate evolution.” They clearly placed their emphasis on evolutionary aspects of developmental biology, and hence the name evo-devo.

Yet differences in underlying assumptions already appeared in the historical symposium entitled “Evolutionary Developmental Biology: Paradigms, Problems, and Prospects.” In his essay introducing the special symposium, Burian pointed to biological research at the end of the nineteenth century, when research flourished on cell division, embryology, evolution of species, fertilization, heredity, and phylogeny. “These problems,” he noted, “were generally held to be intimately interconnected, so much so that many biologists thought of them as inseparable, forming

<sup>13</sup> Hall and Olson 2006. <sup>14</sup> See Laubichler and Maienschein 2007, 2013.

a single nexus that covered what was eventually separated into cytology, embryology (later transformed into developmental biology), evolutionary biology, genetics, and reproductive biology." He went on: "From a current perspective it is very difficult to understand the ways in which all of these problems were tangled together at the end of the nineteenth century."<sup>15</sup>

Yet in the intervening century, all these areas of study had become specialized fields, each with its own underlying assumptions, different methodologies, and different ideas about the important questions. Studies of evolution of species (seen as relating to populations) and about embryonic development (relating to individual organisms and its parts) grew apart. Departmental organization reinforced the intellectual and methodological differences, so that in many institutions these two areas had little contact by the end of the twentieth century. Philosophy of biology followed the trend, so that those arguing about how to understand evolutionary levels of selection, for example, rarely thought of looking at developmental biology.

The 1990s started to change that trend, as Burian notes. New methods in biology, molecular and genetic techniques, and the discoveries associated with them widely began to transform studies of both development and evolution. Burian pointed to tools from phylogenetic systematics, the discovery of the conserved nature of transcription factors, the possibility of targeted gene knockouts, and the allure of hox genes as examples. Programs of philosophy of science meetings from the time show that a very few philosophers also began to look at development and ask epistemological questions about how we can best study individual and cellular development, and how that knowledge relates to study of evolution of populations. At the 2000 SICB symposium, papers on modularity and homology focused attention on the potential for intersections of fields.

The symposium ended with two keynote talks; one by Rudy Raff as Chair of the new division, the other by Yale biologist Günter Wagner. While Raff's talk was an affirmation of his previously published views and was ultimately not published in the symposium papers, Wagner and his co-authors (full disclosure – ML was one of them) pointed to underlying differences of view that challenge the claims of evo-devo as the best way to bring together the two fields.<sup>16</sup> In contrast to most papers, which focused on how evolutionary information and theories can be valuable for informing understanding of development, Wagner's team emphasized the

<sup>15</sup> Burian 2000. <sup>16</sup> Wagner *et al.* 2000.

use of developmental mechanisms for understanding evolution. The two perspectives, of evolutionary developmental biology (evo-devo) and of developmental evolution (devo-evo) respectively, ultimately go together, yes, but in more complex ways that recognize the tangle of issues and approaches.<sup>17</sup>

In the initial phase of institutional establishment of evo-devo and devo-evo the epistemological differences underlying these two perspectives also reflected different trajectories in training as well as different historical traditions. As a first approximation we can note that the majority of the proponents of evo-devo were initially trained in developmental biology and developmental genetics and were eager to adopt the insights derived from evolutionary and phylogenetic comparisons – such as the conservation of the *hox* genes, the focus on the second symposium – to the understanding of development and the evolution of developmental systems.

On the other hand many of the proponents of developmental evolution were trained either in evolutionary theory or evolutionary morphology, or they represented a unique combination of expertise such as developmental and molecular biology or developmental biology and paleontology. They had in common a focus on mechanistic explanations of phenotypic evolution and an interest in the origin of evolutionary innovations and of phenotypic variation more generally. A good number of those were also exposed to or had already contributed to a growing number of challenges to the orthodoxy of the Modern Synthesis of the 1940s.<sup>18</sup>

The boundaries between these two camps were, of course, fluid and not at all rigid, but they nevertheless represented two different epistemologies and sets of questions. These differences in orientation were also visible in the two major journals that came to represent the new field (and which were soon adopted as journals supported by the SICB Division.) Both of them were launched in 1999. *Evolution and Development* was established as a new journal under the editorship of Rudolf Raff, whereas *Molecular and Developmental Evolution* with Günter Wagner as editor-in-chief was first set up as a free-standing section of the *Journal of Experimental Zoology*, which had a long tradition in publishing articles at the intersection between development and evolution. It became an independent publication as the *Journal of Experimental Zoology, Part B: Molecular and Developmental Evolution* in 2003.

<sup>17</sup> Wagner *et al.* 2000.

<sup>18</sup> Laubichler 2009 and Laubichler and Maienschein 2013.

The two “camps” thus each have their own publication and even though there are areas of overlap, a comparison of the papers published in each journal does reveal different centers of gravity that map onto the underlying conceptual differences. The scientific questions investigated within both contexts have over the last decade become more popular and furthermore substantial progress has been made. Therefore an increasing number of publications devoted to both evo-devo and developmental evolution have more recently been published in leading generalist journals, such as *Science*, *Nature*, *Cell*, *PNAS*, etc., thus further blurring the boundaries between these viewpoints.

At the time of setting up the new SICB Division, Wagner was a candidate running for office. In his candidate’s statement, he noted the exciting prospects for the new research directions. Yet he also argued that:

The division is the first formal union of researchers in the field and will have to play a pivotal role in the process of defining the identity of the discipline. This process can only succeed if the division is able to attract the knowledge and talent of developmental biologists, evolutionary geneticists, morphologists, systematists and paleontologists. I strongly believe that each group makes an essential contribution to the developmental evolutionary synthesis. To make the integration of these contributions possible, the division should be perceived as a place where researchers from different backgrounds can communicate without facing disciplinary chauvinism. SICB has a strong tradition in this regard.

In running for office for the next year, he said that he planned to “draw on its accumulated organizational wisdom to reach this goal.”<sup>19</sup>

Wagner already recognized some of the social forces within biology that were likely to affect the efforts to form a new field. He envisioned the goal as a “synthesis” while others stressed the value of one field for the other. Much sociological literature has explored the conservative resistance to new ideas, especially in academia. When much hinges on one’s own field retaining a place of stature, participants resist letting go of their power. Thus, as we have explained, friendly sparring occurred around the question whether the field is really “evolutionary developmental biology” or should more properly be “developmental evolutionary biology.” The two are not the same, obviously, and this was not just a political attempt at priority. Rather, two different conceptions have coexisted from the beginning. Yet, again, it is not just a question of which of the two more

<sup>19</sup> See Günter Wagner’s statement on the SICB website: [www.sicb.org/newsletters/nlo4-2000/dedb.php3](http://www.sicb.org/newsletters/nlo4-2000/dedb.php3).

influenced the other; it is not a question of which of two directions the arrows point in. Rather, the arrows are sometimes bent, intertwined, and definitely entangled.

This is especially true if one also takes the more recent developments into account. These include on the one hand a call for the explicit inclusion of ecological factors into the theoretical structure of evo-devo (“eco-evo-devo”) often paired with a (mostly) not very precise emphasis on “epigenetics,”<sup>20</sup> while on the other hand we have developments that take advantage of most up-to-date methods of synthetic and molecular biology in order to both experimentally and computationally reconstruct evolutionary transitions – the idea of synthetic experimental evolution (SEE).<sup>21</sup> The landscape of what used to be called evo-devo has thus become its own complex ecosystem and as such an object of considerable attraction for innovative work in the philosophy of biology. And indeed, philosophers and historians have been exploring this territory and have produced a considerable amount of scholarship, often encouraged by Michael Ruse as only he can.<sup>22</sup>

In the remaining part of this chapter we will not dwell on what has been accomplished, rather we will follow Michael Ruse’s advice and point towards some of the emerging questions at the intersection of developmental evolution, systems biology, synthetic biology, and computer science, as it is precisely at those “trading zones” between ideas, technologies, and epistemologies that we can best observe the tangled bank of mutual interactions between biology and society.

### **The future of developmental evolution and its HPS challenges**

Arguably, evo-devo and developmental evolution (the version of the problem we have been focusing on for more than a decade) have been among the most exciting areas of the life sciences, especially for a die-hard evolutionist like Michael Ruse. And indeed, there has been much talk about “completing the synthesis” and finally integrating development into evolutionary theory in evo-devo circles. For a historically inclined philosopher, such claims are the equivalent of a five-course meal, if not an “all-you-can-eat” buffet. And despite all the ink spilled by philosophers debunking the myth that evolution is necessarily progressive, the claims of “completing”

<sup>20</sup> Gilbert and Epel 2009. <sup>21</sup> Erwin and Davidson 2009.

<sup>22</sup> See for instance Laubichler and Maienschein 2007 and Laubichler and Maienschein 2009.

and “finally integrating” sound quite teleological. So there is much to question here about the development of scientific theories, what it means for a theory to be complete, or what integration actually stands for.

But these kinds of claims have mostly been associated with evo-devo. Here we will focus on developmental evolution, its future, and the challenges it raises for the historian and philosopher. So let's start at the beginning: more precisely, what are the major substantive differences between evo-devo and developmental evolution?<sup>23</sup>

We have seen that these were on display during the inaugural symposium of the SICB Division. Shortly thereafter Brian Hall wrote a guest editorial in *Evolution and Development* asking the question “Evo ~~devo~~ or ~~devo-evo~~ or ~~evo~~ – Does it matter?”<sup>24</sup> For Hall it clearly did. He pointed to some of the differences in emphasis between these two perspectives but also suggested that, if one takes all these claims to their logical conclusion then evo-devo presents a synthesis (completing the Modern Synthesis argument) while devo-evo, once fully developed, would represent a revolution. In 2000 much of what developmental evolution would eventually become was not clearly visible – and to be sure, there were, then as now, some differences in Brian Hall's view of devo-evo and in our (Wagner and Laubichler's) conception of developmental evolution. But in many ways Hall's argument that there is indeed a difference and that it matters foreshadowed much of what would happen in the next decade.

Let us now turn to what we see as the main differences between evo-devo and developmental evolution and focus primarily on historical and epistemological issues. On the level of experimental data we observe a convergence between the two approaches; therefore the remaining differences are largely interpretative and conceptual.

Evo-devo, as a synthesis that purportedly completes the efforts of the 1930s and 1940s by finally incorporating development into the theoretical structure of evolutionary theory, does accept the core theoretical assumptions of neo-Darwinian evolutionary biology, namely that all explanations of evolutionary change are ultimately provided by the (adaptive) dynamics within populations. Natural selection and random genetic drift are the processes that govern evolution. Phenotypic change, in this view, is predicated on the underlying dynamics of alleles. And while earlier models assumed that the map between genotypes and phenotypes is simple (linear or additive), new empirical evidence and theoretical considerations

(these were all lower case in the original title)

<sup>23</sup> Laubichler 2009. <sup>24</sup> Hall 2000.

soon challenged this convenient view. Understanding the more complex relationships between genotypes and phenotypes, such as observations on constraints on phenotypic variation and the apparent directionality of evolutionary transformations, then required considerations of development. Within evo-devo, the logical place of development within evolutionary theory was in explaining the details of the genotype–phenotype map without changing the explanatory structure of evolutionary biology, which, at its core, was still based on population dynamics.

Proponents of evo-devo also adopted a set of additional theoretical concepts in order to account for the patterns of phenotypic evolution and the rapidly emerging insights into the evolution of developmental systems. Within evo-devo these concepts – modularity, evolvability, constraints, homology (in all its modifications and expansions), plasticity, and, more recently, epigenetic and environmental factors – contribute to the theoretical description of the phenomenology of phenotypic evolution. Much of the ongoing work within evo-devo has focused on these aspects of the evolutionary process. But all of it has left the causal structure of evolutionary explanations untouched. At most it offered slight corrections to understandings of the role of natural selection – such as that developmental constraints provide limits to phenotypic variation – or offered additional “non-genetic” causal factors to the genotype–phenotype map – such as environmental factors or physical and chemical properties of cells. As Hall suggested in 2000, the focus here is on synthesis, incorporating additional causal factors and empirical details into the theoretical framework of evolutionary theory.

Developmental evolution, on the other hand, is more radical and aims to transform the explanatory structure of theories of phenotypic evolution. At the SICB symposium we tried to capture this in the title of our paper, “Developmental Evolution as a Mechanistic Science: The Inference from Developmental Mechanisms to Evolutionary Processes” (Wagner *et al.* 2000). Our emphasis here was on developmental mechanism as a primary explanation for processes of phenotypic evolution. But to contextualize this claim, we need to provide some historical background.

Darwinian evolutionary theory started with the recognition of the importance of variation and the realization that heritable variation paired with competition will lead to selection (either natural or artificial). As a consequence the distribution of variants within populations will shift. Since variation has been recognized as an obvious characteristic of natural populations, Darwin and his successors devoted more time to uncovering

the causes of inheritance – a necessary condition for natural selection to work – than on trying to understand the causes of variation as such. But this does not mean that they were unaware of the problem. For Darwin the origin of variation was an important part of his theory and he considered developmental mechanisms to be a central part of the explanation of phenotypic variation even though he did not have as many empirical data for this problem as he did for many of the other questions he was investigating.

After Darwin the problem of variation was attracting considerable interest. Many studies dealt with quantitative descriptions of variation, its geographical distribution, and its patterns of inheritance.<sup>25</sup> Developmental considerations about the origin of variation also played a role, albeit smaller, as discussed below. But of all the concepts associated with variation, the one that had the most profound impact on evolutionary theory was the notion of distinct “factors” – soon to be called genes – as the hereditary causes of variation. Genes, and their proposed variants or alleles, could not only account for specific (Mendelian) patterns of inheritance, they also gave a precise meaning to one conception of the origin of variation, namely the idea of mutation. If characters are caused by genes, then any variation in such a character could be attributed to a mutation in the underlying gene(s). Soon evidence (1) that mutations can appear spontaneously and (2) that these mutations are inherited in predictable patterns began to accumulate.

As a consequence, evolutionary changes were then described by mutations and the subsequent dynamics of these mutations within population. The level of genes (or genotypes) and population and quantitative genetics (in both mathematical and experimental versions) became the primary focus of evolutionary theory. Early on geneticists and evolutionary biologists realized that not all characters follow simple patterns of inheritance. A number of theoretical ideas were introduced to account for these increasing complexities including pleiotropy, epistasis, penetrance, expressivity, and any number of models of multi-genic patterns of inheritance.<sup>26</sup> Common to all of these concepts has been the theoretical assumption that in the context of phenotypic evolution mutations, in whatever shape or form, are a sufficient explanation and that ultimately phenotypic evolution can be described at the level of the genotype.

Once this focus on the genotype had been established – and it is the core assumption of all models of population and quantitative genetics,

<sup>25</sup> See for example Bateson 1992. <sup>26</sup> See Laubichler and Sarkar 2002.

which are, in turn, the explanatory basis of evolutionary theory from the Modern Synthesis onward – the remaining problem was to fill in the gaps in the genotype–phenotype map. And this is, as we have seen, the *raison d'être* of evo-devo, to provide this missing piece of the evolutionary synthesis. This, at least, is the semi-teleological and triumphalist narrative that has become the party line of much of evolutionary biology and its various popularizers.

Even though we were only able to provide a sketchy description here and not a complete or adequate historical account, any historian or philosopher of biology should now be quite skeptical and ask: really, is this all that has been going on in twentieth-century evolutionary biology? Is evolutionary theory indeed approaching the kind of completion that the proponents of evo-devo seem to advocate? And what would that mean? Might it be the triumph of the Darwinian Method that Michael Ruse and his peers were discussing several decades ago?

Well, the tensions that were on display during the 2000 SICB meeting clearly suggest otherwise. So we need to ask, what are the conceptual antecedents for ~~the~~ developmental evolution and what is meant by mechanistic science? Where does the inspiration for the possible revolution that Hall and others associate with developmental evolution come from? This brings us to proportionally much less understood or studied trajectories within the history of post-Darwinian biology. All we can do here is to sketch one alternative that has focused on the role of developmental mechanisms in explanations of phenotypic evolution.

We have already indicated that Darwin argued that developmental processes can provide an explanation of the origin of phenotypic variation, even though, as he put it, “our ignorance” on these matters is “profound.” In subsequent decades experimental cell biologists and embryologists learned a lot about these developmental processes and how they bring about organismal form. Some, such as Theodor Boveri or Thomas Hunt Morgan, were clearly also thinking about what role these insights can play in understanding evolution. But their take on the evolutionary process was different. They did not focus primarily on the actions of natural selection; rather they were concerned with the mechanistic, i.e. developmental basis for phenotypic transformations. ~~How~~ **How** can understanding development help us understand the diversity of organismal forms? In other words, their evolutionary focus was on the origin or the generation of variation and not on the relative success of existing variants.<sup>27</sup>

<sup>27</sup> See Laubichler and Maienschein 2013.

This focus was in part conceptual, in part also a consequence of their methods of experimentation, which focused on specific controllable interventions to reveal the causal chains that built organismal phenotypes. In light of this methodological separation we can then understand Boveri's claim that the holy grail of an experimental understanding of evolution would be "to transform one organism in front of our eyes into another."<sup>28</sup> Not by generations of selective breeding, but by experimental manipulation of the developmental processes that ultimately generate phenotypes in the first place. Much of this was beyond the technical reach of early twentieth-century biology. Boveri, for example, was keenly aware of the substantial challenges that such an experimental and mechanistic approach to problems of phenotypic evolution entailed, and when he was invited to design the Kaiser Wilhelm Institute for Biology he used that opportunity to put together an institute that would be capable of contribution to this agenda. Even though illness prevented him from actually taking up that post himself, with some modifications his plan was implemented and the institute did become for decades a major hub for work in that tradition.

The major conceptual idea behind Boveri's idea that it should be possible to "transform an organism into another" was the notion that development is controlled by a complex regulatory system of anlagen, located in the nucleus, but interacting also with the cytoplasm. The idea here is relatively simple. As cells differentiate in the course of development and become increasingly specialized in a coordinated fashion, the expression of the hereditary material, which causes differentiation, must be highly regulated. Many difficult and elegant observations, from his famous disperm experiments to the studies of chromosomal diminution in *Ascaris*, contributed to these insights (as well as the chromosomal theory of inheritance). But conceptually the situation is relatively clear. Between the totipotency of the fertilized egg and the differentiated cell types, the expression of the hereditary substances must be regulated. The question was, how.

Morgan, for instance, argued that this could be accomplished through interactions with the cytoplasm and the environment. Boveri and others emphasized that the structure and composition of the cytoplasm at one time is the product of previous actions of the hereditary, i.e. nuclear, substance and focused more on the regulatory properties of the hereditary system as such. In any case, clear experimental evidence was difficult to come by.<sup>29</sup> Individual observations and experimental systems, such as those by

interacting

↑ add comment

<sup>28</sup> Boveri 1906.

<sup>29</sup> Boveri 1906 and Laubichler and Davidson 2008.

Goldschmidt and Kühn, Goldschmidt's successor at the Kaiser Wilhelm Institute, solved some small pieces of the puzzle by revealing some small details of the structure of the hereditary system, such as the notion of macro- or regulatory mutations as the cause of homeotic transformations or the dissection of single genetic pathways and reaction-chains.<sup>30</sup>

The situation changed with the advent of molecular biology. The discovery of the structure of DNA and subsequently the role of different types of RNA in transcription and translation of the hereditary material provided a concrete molecular foundation for both development and heredity. The original and vague conception of a regulatory system of hereditary Anlagen gave way to concrete models of gene regulation, foremost among them the Britten–Davidson model of Gene Regulatory Networks (GRN) from 1969.<sup>31</sup> This model focused specifically on both the developmental and evolutionary implications of what we would now call a regulatory genomic system. It proposed, among other things, that changes/mutations in different elements of the genome will have different phenotypic consequences and that regulatory mutations will be involved in producing major phenotypic transformation (those that have been associated with body-plan features). Conceptually, this idea opens up an avenue that could eventually allow us to realize Boveri's challenge: "to transform an organism into another."

But much needed to happen first. The Britten–Davidson model was a logical argument based on fundamental insights into the notion of developmental evolution and whatever little concrete molecular information was available at the time. Decades and many molecular and genomics revolutions later the logical structure of the model stood the test of time. But now we also have the ability to actually fill in all the concrete details. The results are increasingly complete gene regulatory networks, such as those that controls the first 36 hours of the life of a sea urchin embryo.<sup>32</sup> It is now also widely accepted that a mutation is not a mutation is not a mutation.<sup>33</sup> The conserved nature and role of transcription factors, such as the *hox* genes, strongly suggests that there is a difference between different types of genetic and phenotypic variation. Small-scale variation in often quantitative traits, such as body size or coloration, is often controlled by single-locus polymorphisms (or a small number of loci) and fits the paradigm of population and quantitative genetics. Larger-scale or body-plan

<sup>30</sup> Laubichler and Rheinberger 2004.

<sup>31</sup> Britten and Davidson 1969.

<sup>32</sup> Davidson 2011 and Erwin and Davidson 2009.

<sup>33</sup> Carroll 2008 and Davidson 2006.

features, on the other hand, are the product of regulatory evolution, i.e. changes in the genomic regulatory systems that control development. The theoretical challenge for evolutionary theory is how to integrate and accommodate these two types of genomic changes. Different perspectives on this problem are also at the heart of the evo-devo vs. developmental evolution divide, also a very rich area of research for historians and philosophers of biology.

But this is not all. Rather than suggesting some ways for this problem to be conceptualized from theoretical, epistemological, or historical perspectives, we want to end this brief historical sketch with a quick look at what the future of developmental evolution will likely bring, which, incidentally will bring us back full circle to the turn of the twentieth century and Boveri. Conceptually, the idea of gene regulatory networks as the mechanistic cause controlling development and evolution offers some tantalizing possibilities to actually “transform organisms into each other,” or, at the very least, reconstruct evolutionary transformations.<sup>34</sup> The basic logic is again rather straightforward. If we know the GRN of a lineage that acquired a major evolutionary novelty and if we compare it with the GRN of a related lineage that lacks this new feature, we can investigate what kind of regulatory changes contributed to the emergence of a novelty. This is not easy, but doable. The comparison will thus suggest a hypothesis about the causes of phenotypic evolutionary change. Taking advantage of molecular techniques, it will be, in some cases, possible to engineer the GRN of embryos in the lineage representing the ancestral condition and see if they will express, even in rudiments, the novel feature characteristic of the derived condition. This method of synthetic experimental evolution will (and does) then provide an experimental test for hypotheses about the causes of major phenotypic transformation or novelties, exactly as Boveri envisioned it more than a century ago.

Synthetic experimental evolution is more than just a highly specialized experimental procedure. Conceptually, it does represent the kind of revolution that Brian Hall and others, including us, have been arguing that developmental evolution actually is. We now see, in concrete terms, what it means to have a developmental understanding of phenotypic evolution and how understanding the origin of variation is the starting point of all (future) theories of phenotypic evolution. Furthermore, GRNs can now also be turned into computational models, as they are basically Boolean networks (albeit quite complex ones). This opens up the possibility of not

<sup>34</sup> Erwin and Davidson 2009.

just in vivo, but also in silico synthetic experimental evolution and provides us with the computational foundation for a formal theory of phenotypic evolution.<sup>35</sup> Again, we were only able to scratch the surface here, but it should be clear that these developments provide huge employment opportunities for historians and philosophers of biology.

### Conclusions

Clearly, developmental evolution represents exciting science, with many discoveries shedding new light on old questions. But single insights, such as recent findings about the developmental hourglass or any number of other results, are only part of the story.<sup>36</sup> The transformative potential of developmental evolution is realized in its conceptual structure and the ability to provide an explanation for the origin of variation in terms of developmental mechanisms anchored by the four-dimensional regulatory genome.

As a consequence, developmental evolution does indeed have the kind of revolutionary conceptual and explanatory structure that we, as well as Hall, suggested more than a decade ago. We have argued here that in the context of developmental evolution the causal structure of evolutionary explanation has shifted from a primacy of population-level dynamics to the primacy of developmental mechanisms and that explaining the origin of variation rather than the fate of variants within populations is the first and most important problem for all theories of phenotypic evolution.

Not that evolutionary dynamics are unimportant, rather they act as a (relatively well-understood) filter for variation and as such account for changes over time. But, as many critics of Darwin have pointed out over the last 150 years, selection by itself does not generate variation, and the assumption that mutations, at whatever constant rate, are all that is needed for natural selection to work is no longer a valid argument in light of what we have learned about the complex links between genotype and phenotype. Rather, an understanding of phenotypic evolution that is grounded in the mechanistic interactions of complex regulatory networks, from genomes to the environment, and that will allow us to devise synthetic experimental approaches, both in vivo and in silico, is now feasible. Evolutionary biology will thus become a mechanistic science and, among many other implications, this will also mean that we will finally transcend

<sup>35</sup> Peter *et al.* 2012.

<sup>36</sup> Prud'Homme and Gompel 2010 and Kalinka *et al.* 2010.

the canonical distinction between “proximate” and “ultimate” causes, over which philosophers of biology have spilled so much ink.

Much of what we have sketched here is still in its infancy, but it should be clear that Michael Ruse has been right to wish for a long life. There are many interesting challenges for a historian and/or philosopher of biology in that domain, and yes, today’s and tomorrow’s evolutionary theory is not your grandfather’s evolutionary theory. It is your great-grandfather’s again!

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