Evolutionary developmental biology:
its concepts and history with a focus on
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REVIEW

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Abstract Evolutionary theory has been likened to a "universal acid" (Dennett 1995) that eats its way into more and more areas of science. Recently, developmental biology has been infused by evolutionary concepts and perspectives, and a new field of research—evolutionary developmental biology—has been created and is often called EvoDevo for short. However, this is not the first attempt to make a synthesis between these two areas of biology. In contrast, beginning right after the publication of Darwin's *Origin* in 1859, Ernst Haeckel formulated his biogenetic law in 1872, famously stating that ontogeny recapitulates phylogeny. Haeckel was in his turn influenced by pre-Darwinian thinkers such as Karl Ernst von Baer, who had noted that earlier developmental stages show similarities not seen in the adults. In this review, written for an audience of non-specialists, we first give an overview of the history of EvoDevo, especially the tradition emanating

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from Haeckel and other comparative embryologists and morphologists, which has often been neglected in discussions about the history of EvoDevo and evolutionary biology. Here we emphasize contributions from Russian and German scientists to compensate for the Anglo-American bias in the literature. In Germany, the direct influence of Ernst Haeckel was felt particularly in Jena, where he spent his entire career as a professor, and we give an overview of the "Jena school" of evolutionary morphology, with protagonists such as Oscar Hertwig, Ludwig Plate, and Victor Franz, who all developed ideas that we would nowadays think of as belonging to EvoDevo. Franz ideas about "biometabolic modi" are similar to those of a Russian comparative morphologist that visited Jena repeatedly, A. N. Sewertzoff, who made important contributions to what we now call heterochrony research—heterochrony meaning changes in the relative timing of developmental events. His student I. I. Schmalhausen became an important contributor to the synthetic theory of evolution in Russia and is only partly known outside of the Russian-reading world because only one of his many books was translated into English early on. He made many important contributions to evolutionary theory and we point out the important parallels between Schmalhausen's ideas (stabilizing selection, autonomization) and C. H. Waddington's (canalization, genetic assimilation). This is one of the many parallels that have contributed to an increased appreciation of the internationality of progress in evolutionary thinking in the first half of the twentieth century. A direct link between German and Russian evolutionary biology is provided by N. V. Timoféeff-Ressovsky, whose work on, e.g., fly genetics in Berlin is a crucial part of the history of evo-devo. To emphasize the international nature of heterochrony research as

predecessor to the modern era of EvoDevo, we include Sir G. R. de Beer's work in the UK. This historical part is followed by a short review of the discovery and importance of homeobox genes and of some of the major concepts that form the core of modern EvoDevo, such as modularity, constraints, and evolutionary novelties. Major trends in contemporary EvoDevo are then outlined, such as increased use of genomics and molecular genetics, computational and bioinformatics approaches, ecological developmental biology (eco-devo), and phylogenetically informed comparative embryology. Based on our survey, we end the review with an outlook on future trends and important issues in EvoDevo.

Introduction

> […] problems concerned with the orderly development of the individual are unrelated to those of the evolution of organisms through time (Wallace 1986, p. 149).

The importance of embryonic development for evolutionary biology has been discussed ever since Charles Darwin (1809–1882) and Ernst Haeckel (1834–1919); however, Modern Synthesis (Mayr and Provine 1980) approaches to evolution have often neglected development or treated it as a black box (Mayr and Provine 1980; Olsson and Hoßfeld 2007). Although Wallace's statement cited above is extreme, mid-twentieth-century mainstream evolutionary biology did not feel much need for an integration of developmental biology into its theoretical foundations. The fact that evolutionary questions have been of interest to some developmental biologists between the era of Darwin and Haeckel and modern times, i.e., that EvoDevo, as the field is often called by its practitioners, in fact has a history, is something that has received little attention. It has even been claimed that "Following a quiescent period of almost a century, present-day evo-devo erupted out of the discovery of the homeobox in the 1980s" (Arthur 2002, p. 757). It is the goal of this historical overview to show that the "between Ernst Haeckel and the homeobox" period was anything but quiescent (Olsson et al. 2009). We are helped by the recent upsurge in interest in the history of EvoDevo.

The history of EvoDevo in the Anglo-American world has received renewed attention recently as exemplified, e.g., by the work of Alan Love (e.g. Love 2006, 2009; Love and Raff 2003; Raff and Love 2004), whose scheme of the historical development of the relationship between evolution and development is reproduced here as Fig. 1. We have ourselves concentrated on the history of EvoDevo in the German- and Russian-speaking lands (Hoßfeld and Olsson

2003; Levit et al. 2004, 2006; Olsson 2007; Olsson et al. 2006, 2009; Levit 2007).

In Love's scheme (Fig. 1), he contrasts the "textbook version" (left) with an improved, updated version (right). In the left diagram, evolutionary biology is split from developmental biology, which was dominated by "Entwickelungsmechanik" (Developmental Mechanics) in the first third of the twentieth century. The developmental biologist Thomas H. Morgan (1866−1945) is seen as an example of the split between experimental embryology and genetics, which he helped to found and that later developed into molecular genetics. Another part of genetics, population genetics, became an important part of the Modern Synthesis of evolutionary biology (Junker 2004; Junker and Hoßfeld 2009; Mayr and Provine 1980). The progress in molecular biology led to the creation of a developmental genetics, which became a more and more dominant part of developmental biology. In the commonly held view presented to the left in Fig. 1, we today see a new EvoDevo synthesis of these two elements, developmental genetics and modern evolutionary biology. It has become clear, however, for example, through the work of Love and others [e.g., (Brigandt 2006) on Gavin R. de Beer (1899−1972)] in the English-language tradition, that this is too simple a view. The entire comparative embryology tradition, so strong in the German lands and in Russia in the wake of pioneers like Ernst Haeckel (Fig. 2) and Alexander Kowalevsky (1840–1901; see Raff and Love 2004), is completely left out of the picture. It is important to clarify the role of this tradition, mostly developed by invertebrate zoologists and at marine biology stations (Naples etc.) in addition to at universities, in the complicated genealogy of today's EvoDevo.

It is clear that Haeckel's Gastraea theory has been an inspiration for generations of comparative embryologists in several countries. The Gastraea is a hypothetical "Urform" from which all metazoans have evolved, according to Haeckel. It has left no paleontological traces and can therefore only be seen as the gastrula stage in the development of many extant animals:

> From these identical gastrulae of representatives of the most different animal phyla, from poriferans to vertebrates, I conclude, according to the biogenetic law, that the animal phyla have a common descent from one unique unknown ancestor, which in essence was identical to the gastrula: Gastraea (Haeckel 1872, 1: 467).

With his Gastraea theory, Haeckel thought he had proved the monophyletic origin of all multicellular animals. We have recently investigated how this idea was developed in the twentieth century by Scandinavian researchers. The Swedish zoologist Gösta Jägersten (1903–1993) explicitly
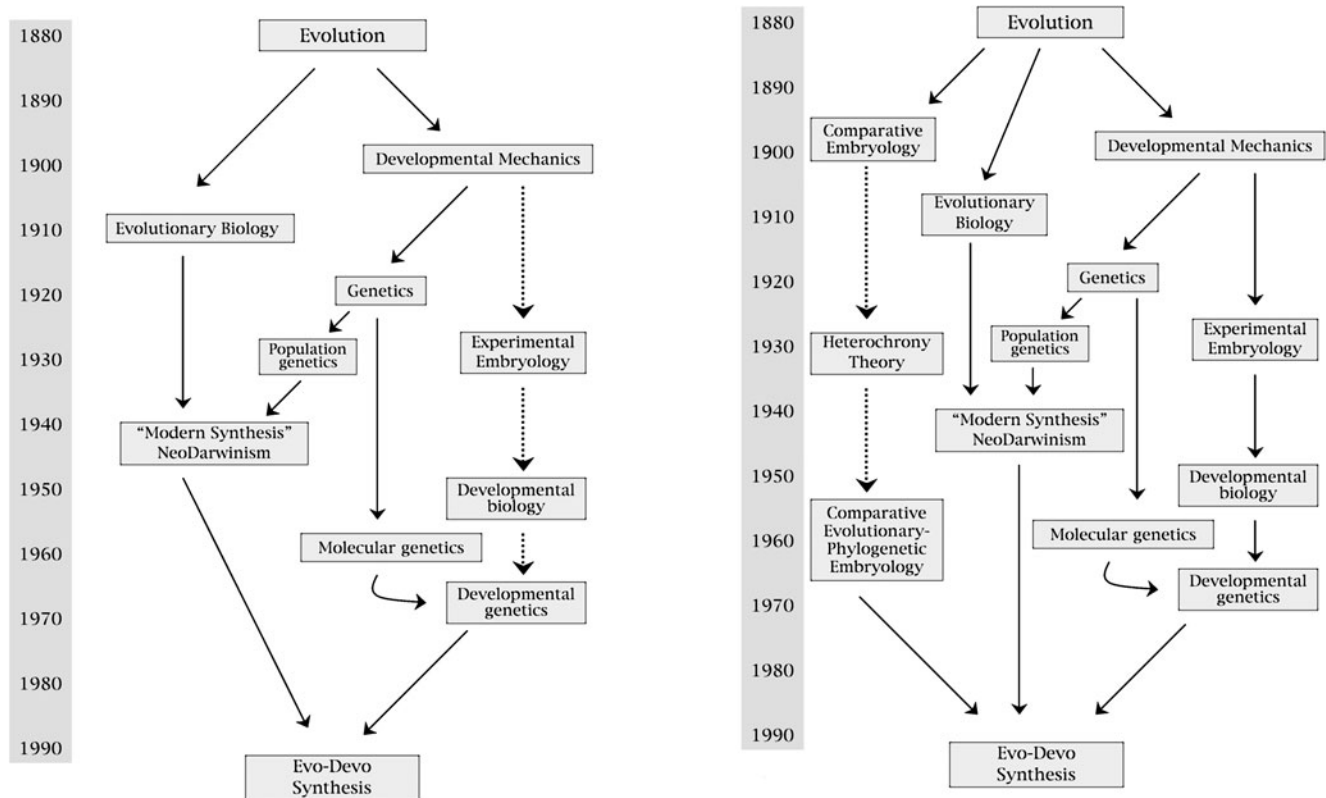
Fig. 1 Historical development of the relationship between evolutionary and developmental biology, as depicted in Love and Raff (2003). To the left the "textbook view" that evolutionary biology split up into "Entwickelungsmechanik" and evolutionary biology, followed by a divorce of genetics from experimental embryology—genetics became a research area in its own right. Later, the new molecular genetics fused with developmental biology, resulting in the powerful developmental genetics of the 1980s. Meanwhile, population genetics became the foundation for the Modern Synthesis in evolutionary biology. Currently, a new EvoDevo synthesis is underway. To the right is Love and Raff's revised version, where they point out that, in addition, there is a line going from the comparative embryology of Haeckel et al. over heterochrony research that also feeds into the present EvoDevo synthesis

referred to Haeckel's work (Olsson 2007) and developed a theory of the "Evolution of the Metazoan Life Cycle" in the 1950s (Jägersten 1955, 1959) and 1960s (Jägersten 1968) and finally published it as a book in English in the early 1970s (Jägersten 1972). This "Bilaterogastraea" (Fig. 3), a bilaterally symmetrical stage after the Gastraea, builds directly upon Haeckel's ideas. This tradition has been taken up by, e.g., Claus Nielsen in his Trochaea theory from the mid-1980s (Nielsen 2001; Nielsen and Nørrevang 1985).

The Jena zoomorphologist Victor Franz (1883–1950) in Jena and his Russian colleague Aleksej N. Sewertzoff (1866–1936) were pioneers of heterochrony research and also belong to the tradition drawn in the right part of Fig. 1, together with heterochrony researchers in the US and Britian, such as Gavin de Beer. We have done a bit of research on them and other members of the "Jena tradition" of comparative embryology (Hoßfeld and Olsson 2003, 2007; Levit et al. 2004). Thus, in the last few years, a more differentiated view of the history of developmental biology and its relationship with evolutionary theory has started to emerge. This is, however, only a beginning and more work is urgently needed on almost all aspects of this fascinating subject.

The major questions of EvoDevo

An important aim of this paper is to show that the major questions of EvoDevo today have deep historical roots. Hall (2000) listed them as follows:

1. The origin and evolution of embryonic development
2. How modifications of development and developmental processes lead to the production of novel features
3. The adaptive plasticity of development in life history evolution
4. How ecology impacts on development to modulate evolutionary changes
5. The developmental basis of homology and homoplasy

This also shows that EvoDevo is not restricted to developmental genetics today but has a broader scope, and as we will see below, this can be explained by its historical roots.
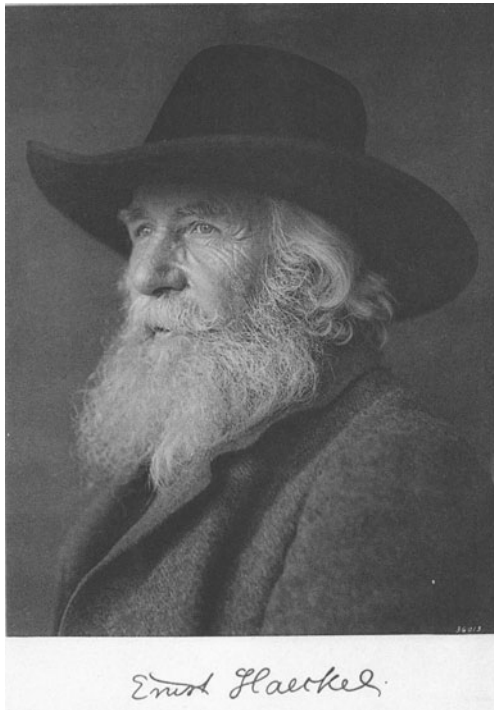
Fig. 2 Ernst Haeckel (Bildarchiv, Ernst-Haeckel-Haus, Jena)

The history of EvoDevo

> I bought the pig immediately, had it killed and the feet hacked off, and sent them to Darwin. Otto Zacharias in a letter to Ernst Haeckel, 21 May 1877.

Ernst Haeckel, atavisms, and the biogenetic law

Ernst Haeckel was inspired by his older colleague in Jena, the anatomist Carl Gegenbaur (1826–1903), who had been instrumental in bringing Haeckel to Jena as a professor. Gegenbaur wrote a number of research monographs and textbooks, which were seen as a model of critical investigation based on an extensive collection of facts, something Haeckel admired. Gegenbaur pioneered investigations into, e.g., vertebrate head development in an evolutionary context and incorporated an evolutionary view in his later work (Hoßfeld et al. 2003). In the pre-history of EvoDevo, Gegenbaur and Haeckel contributed importantly to creating an evolutionary morphology, specializing on vertebrates and invertebrates, respectively.

The quotation at the beginning of this part of the paper is from the journalist and plankton researcher Otto Zacharias (1846–1916), who was an important popularizer of Haeckel's "Darwinismus" and corresponded with Haeckel throughout the last quarter of the nineteenth century (Nöthlich et al. 2006). It illustrates the importance of Haeckel's so-called Biogenetic Law for discussions

about evolution in this era. In a letter from 1877, Zacharias describes how he came across, at the local marketplace, a pig with "thumbs," which are normally completely absent, developed on both forelimbs. Such atavistic mutations, which bring forth characters that have long been lost in the evolutionary line leading to an extant species, were seen as "throwbacks" to earlier eras and as important evidence for evolution as descent with modification. So excited was Zacharias by this discovery that he bought the pig and, after it had been slaughtered and the forelimbs "hacked off," sent at least one of the pig's feet to Charles Darwin and asked for his comments on the phenomenon and its importance for the theory of evolution. Darwin sent the foot to the anatomist and surgeon William Henry Flower (1831–1899) in London and wrote "The pigs-foot has been dispatched to day per Rail" on May 2, 1877. Flower made a thorough investigation and wrote back to Zacharias that he had seen similar examples before, but this was an unusually well-developed "pigs thumb" (Nöthlich et al. 2006).

Why did atavisms provoke such interest and enthusiasm in those days? An *atavism* is defined as the reappearance in a member of an extant species of a character that has been lost during phylogenesis, such as hind limbs in whales or teeth in birds. The direct cause might be that a developmental program that is normally not active in this species has been re-activated. In a classic paper, Brian Hall (1984) [see also Hall (1995)] has reviewed the developmental basis of atavisms. The biogenetic law could take atavisms into account without problems. They were just re-appearances of characters that had once been present during the phylogenesis of this line of descent. That such characters could appear in its present ontogenesis was in accordance with "ontogeny recapitulates phylogeny." Haeckel put great theoretical emphasis on the parallel between the stages of development of the embryo and the series from lower to higher forms of animals studied in comparative anatomy and systematics. Haeckel used the term "Entwickelung" (development) for both the development of the individual and "development" over evolutionary time. To these two parallels he added a third, based on paleontological data, the "development" of forms as seen in the fossil record. He put great emphasis on this threefold parallelism of the phyletic (paleontological), biontic (individual), and systematic developments (Haeckel 1866, II: 371ff). The explanation of this "threefold genealogical parallel" he called "The fundamental law of organic development, or in short form the 'biogenetic law'." Haeckel wrote about the reciprocal causal relationships in his *Generelle Morphologie der Organismen* (*General Morphology of Organisms*):

> "41. Ontogenesis is the short and fast recapitulation of phylogenesis, controlled through the physiological functions of inheritance (reproduction) and adaptation

Fig. 3 a "Bilaterogastraea," b a later stage with the temporary intestine curved over a food particle, c longitudinal section, d ventral view, e cross-section, f a stage where the margins of the primitive mouth have fused in the middle part, the "Protocoeloma." From Jägersten (1955)
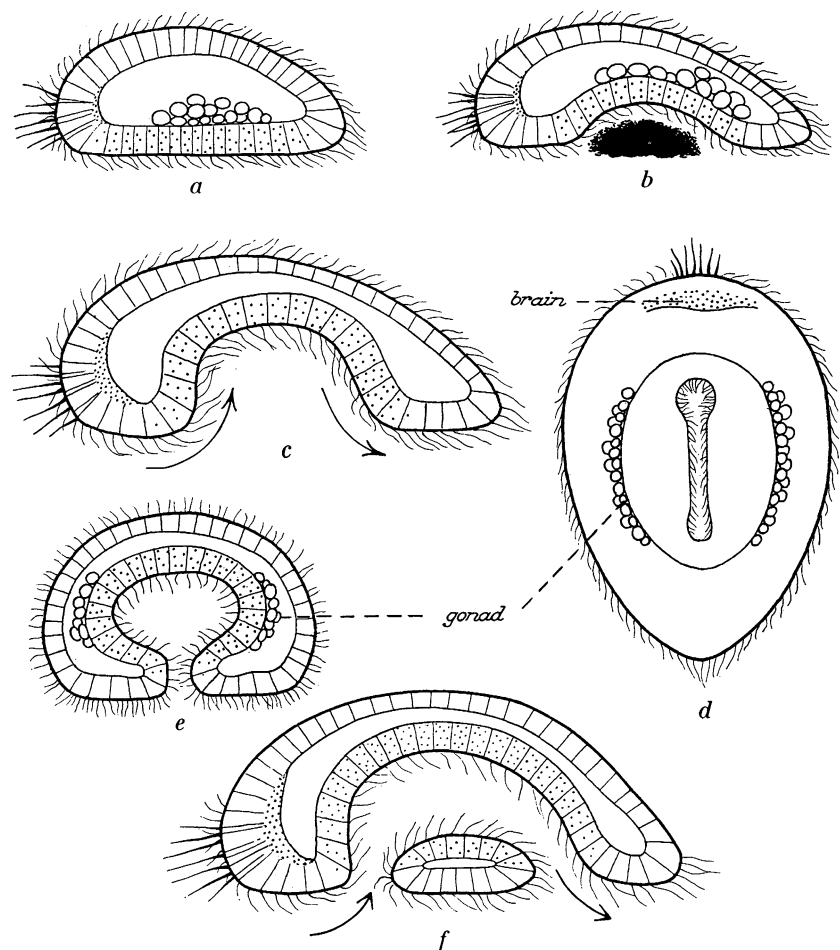
(nutrition). 42. The organic individual […] recapitulates through its fast and short individual development the most important of the changes in form, which the ancestors have gone through during the slow and long palaeontological development following the rules of inheritance and adaptation" (Haeckel 1866, II: 300).

Haeckel clearly realized the problems associated with this subject (Ulrich 1968; Uschmann 1966). The "complete and faithful recapitulation" becomes "effaced and shortened" because the "ontogenesis always chooses the straighter road." In addition, the recapitulation becomes "counterfeited and changed through secondary adaptations" and is therefore "better the more similar the conditions of existence were, under which the Bion and its ancestors have developed" (Haeckel 1866, II: 300). In order to describe these problems, Haeckel invented the concepts Cenogenie (secondary adaptation leading to non-recapitulation) and Palingenie ("real" recapitulation). He viewed inheritance and adaptation as the driving factors of the evolutionary process.

Also, Darwin himself pointed out the importance of embryology for revealing what he called "community of descent" (common origin in a phylogenetic sense). He put great value on this relationship for systematics (Darwin 1871, 1: 205). Maybe the most important contribution to discussing Haeckel's biogenetic law critically was Fritz "Desterro" Müller's book Für Darwin (Müller 1864). Müller studied crustaceans and came to the conclusion that evolutionary changes take place mostly through "Abirren" (literally, going astray; here divergence from the original developmental pathway) and "Hinausschreiten" (literally, transgress; here development beyond the endpoint of the original developmental pathway). Thus, Müller explained phylogenetic changes by reference to changes in ontogeny, while Haeckel did the opposite; he saw the explanation for ontogeny in phylogeny. The goals were also different. While Müller sought causal explanations, Haeckel erected a law based on his observations and also on the preconceived ideas encapsulated in the biogenetic law.

The discussions surrounding the biogenetic law exemplify the fertile interaction between embryology and comparative anatomy in the nineteenth century. They also show that ontogenetic results must be used with caution in evolutionary biology. When the concepts and terminology introduced by Haeckel did not suffice to answer the

questions at hand, several biologists tried to supplement or replace the biogenetic law (see below). These discussions became important milestones in the history of evolutionary developmental biology.

In sharp contrast to and in competition with evolutionary embryology, Wilhelm His (1831–1904) developed a reductionist embryology already in the 1870s. His was uninterested in using embryology to understand phylogeny and worked instead on the direct, mechanical influences on the development of organic forms. The formation of the embryo should ideally be explained by the deformations of an elastic sheet (His 1874). This was the beginning of the "Entwickelungsmechanik" tradition associated with Wilhelm Roux that led to the experimental embryology tradition in the twentieth century (Mocek 1974, 1998).

The "Jena school" and the prehistory of EvoDevo

Haeckel's student Oscar Hertwig (1849–1922) was one of the leading biologists in the late nineteenth and early twentieth centuries (Uschmann 1959). He studied medicine in Jena together with his brother Richard from 1868. Building upon Haeckel's "Gastraea theory" (Haeckel 1874), the Hertwig brothers then suggested, in their "Coelomtheorie" (Hertwig and Hertwig 1882) that the development of all germ layers can be explained by the simple principle of epithelium folding. The coelom theory led to investigations of mesoderm (the middle germ layer, between endoderm and ectoderm) development, and Oscar Hertwig became convinced that vertebrates are also enterocoelous, with the mesoderm forming as outpocketings from the primitive gut cells which slide in between endoderm and ectoderm.

Oscar Hertwig's relationship with his old teacher Ernst Haeckel deteriorated after 1900, when Hertwig had developed his criticism of "Darwinismus"—here meaning selectionist explanations—and in particular its application to ethical, political, and social questions (Hertwig 1916, 1918; Weindling 1991). Hertwig also criticized the biogenetic law, something Haeckel saw as a defection ("Abfall") from Darwinism (Uschmann 1959, p. 101). Especially in the book *Das Werden der Organismen* [The becoming of organisms] from 1916, Hertwig argued that the undirected variation which Darwin assumes and documents is not enough to explain the changes and progress seen in the evolutionary history of organisms. Drawing on the ideas of Lamarck and Naegeli, Hertwig tried to develop a theory to explain the (in his view) directional, regular, and progressive evolutionary changes as brought about partly by external and partly by internal causes. Oscar Hertwig argued that there are two main reasons why a reform of the Haeckelian biogenetic law is necessary: "Firstly it is

impossible to characterize scientifically the ontogenetic stages of an organism as a recapitulation of the forms which have followed each other in the long line of ancestors; secondly the external similarities of embryonic forms to lower species of animals do not allow any inference of a common descent, as is so often made" (Hertwig 1916, p. 441).

Oscar Hertwig wanted a more rigorous approach to comparative embryology than just assuming that ontogeny can tell us what the phylogeny must have been like. His careful discussions about the role of internal and external factors in evolution are important contributions to a debate that is still ongoing today.

Ernst Haeckel had falling-outs not only with Oscar Hertwig but with several of his students. In fact, he had a quite negative attitude towards the new histological techniques, and his comparative, phylogenetic approach to development was largely superseded by younger scientists (including his own former students) working in the "Entwickelungsmechanik" tradition founded by W. His and W. Roux. There is thus no "Jena School" in the sense of a line of pupils following in the wake of the master, but rather Haeckel attracted many bright students which were to develop their own scientific profiles (Geison and Holmes 1993). In 1908 Haeckel retired from his position as Director of the Institute of Zoology and Jena University offered the position to Ludwig Plate (1862–1937). Plate developed a synthetic approach that he called "Old-Darwinism," in which he kept the neo-Lamarckian factors that were important also for Darwin and Haeckel, along with orthogenesis (the idea that the direction of evolution is determined by internal processes and thus not by selection) and mutationism, where mutations decide the direction of evolution (Levit and Hoßfeld 2006). Another professor in Jena, the zoomorphologist Victor Franz (1883–1950), carried the strictly selectionist version of the Haeckelian tradition further. Franz saw his own contribution to the development of the theory of evolution foremost in his concept of "improvement" (Franz 1934, p 220), but he also worked on the biogenetic law. By creating his "biometabolic modi," which builds upon the work of von Baer, Fritz Müller, and Haeckel, Franz tried to give a genetic and developmental explanation of the biogenetic law (Rehkämpfer 1997). He divided the evolutionary changes of ontogeny into: (1) transgression, extension, or prolongation of the ontogeny beyond the former adult stage; (2) shortening or abbreviation of the ontogeny in comparison to the former adult stage; (3) divergence or deviation of the ontogeny in comparison to the corresponding former adult stage; and (4) a change in ontogeny that culminates at a certain stage. Franz intended to use such "modi" to accomplish a new and exact formulation of the

biogenetic law (Peters 1980; Trienes 1989; Uschmann 1953). His ideas on "biometabolic modi" are similar to those of a Russian scientist that visited Jena repeatedly, A.N. Sewertzoff, to which we now turn.

The morphological regularities of evolution—A.N., Sewertzoff

In 1911 Aleksej N. Sewertzoff was called to the chair in Zoology at Moscow University, where he founded a new laboratory of evolutionary morphology, of which Ivan I. Schmalhausen (see below) became a member. After Sewertzoff's death on December 19, 1936, Schmalhausen became the new director of the evolutionary morphology institute. Sewertzoff is seen as the doyen of an important school of evolutionary morphology in the Soviet Union and was a member of both the Soviet Union and the Ukraine academies of science.

Sewertzoff made important contributions to developing Haeckel's ideas on ontogeny and phylogeny into what we today call heterochrony research (Levit et al. 2004). In 1931, Sewertzoff published an important book in German, *Morphologische Gesetzmäßigkeiten der Evolution* [The morphological regularities of evolution]. Here he summarized the results, which he and his many students and collaborators had collected since 1891 on the comparative anatomy of vertebrates. Results from investigations into the morphology, embryology, and paleontology of vertebrates were brought together in Sewertzoff's discussions, something he called the "old method of threefold parallelism" and attributed to Haeckel (Sewertzoff 1931, p. 8), although the idea is much older and in fact pre-Darwinian. As the main goal of his book, Sewertzoff writes that he: "[…] gave [himself] the task […] to, based on the existing factual material from comparative morphology, come closer to a solution to the problem of the morphological regularities of evolution, and to bring a certain amount of order into the incredible diversity of approaches in phylogenetic research" (Sewertzoff 1931, VII, IX).

The book is 371-pages long and divided into two parts. The first part is called "The evolution of lower vertebrates" and consists in a solid exposition of their comparative anatomy and provides the basis for the more general evolutionary interpretations. In the second part, "The regularities of phylogenesis," Sewertzoff uses the "morphological regularities" as "the necessary condition for a causal investigation of phylogenesis," which could bring a certain order into "our ideas on the course of evolution" (Sewertzoff 1931, X). Here was a "wide field of activity which researchers have hardly set foot on, and where lots that is new and interesting can be found" (Sewertzoff 1931) by morphologists interested in phylogeny.

Sewertzoff distinguished between four different modes of morphophysiological evolution:

Aromorphosis This is characterized by rapid progressive morphophysiological changes of crucial macroevolutionary significance. It results in an increase of the organism's autonomy from its environment. As Schmalhausen, who later adopted this notion from his mentor, puts it: "Aromorphoses represent evolutionary processes releasing organisms from the excessively strong restrictions of the environment […]. The organism becomes more active and able to control vital resources" (Schmalhausen 1969, p. 410). The novelties that distinguish mammals from their reptilian ancestors, such as a four-chambered heart, the alveolar structure of the lungs, and diaphragmatic breathing, are an example of aromorphosis used by Sewertzoff.

Ideoadaptation These are restricted adaptations that fit the organism to certain environmental conditions. They have no influence on the general vitality of the organism (Sewertzoff 1949, p. 216). Sewertzoff saw the evolution of tortoises and turtles as a good example of ideoadaptive evolution. Land-living and aquatic forms are well adapted to their environments, but the adaptations have had little influence on the "degree of their organisation." *Aromorphosis* and *ideoadaptation* are two major transitions in evolution. A period of aromorphosis "is usually followed by a period of ideoadaptive phylogenetic development during which the descendants of an aromorphically transformed ancestral form increase their natural habitat and adapt to the new and various environments" (Sewertzoff 1949, p. 229).

Coenogenesis This refers to a phenomenon characterized by embryonic or larval characters which develop during ontogeny but later disappear. "We label as coenogeneses such embryonic and larval adaptations which develop in an organism during ontogenesis, but later disappear and which are immediately useful for the developing organism" (Sewertzoff 1949, p. 232).

Morphophysiological degeneration This is manifested by the reduction of the active organs combined with a strong development of the protective and reproductive organs (Sewertzoff 1931, pp. 147–163). *Morphophysiological regress* or *degeneration* should not be confused with *biological* regress. Degeneration is a simplification, decrease, or loss of certain functions and related structures, which may be caused by the transition to, e.g., a sessile or parasitic mode of existence. It is a kind of evolution directly opposite to aromorphosis, because in aromorphosis the organism becomes more complex, such as during the

transition from reptiles to mammals, when several organs (heart, lungs, etc.) increased in efficiency and complexity (Sewertzoff 1929, pp. 44–45; 1931, pp. 159–163; Schmalhausen 1969, pp. 418–419). In certain cases, Sewertzoff assumed, general morphophysiological degeneration can lead to biological (ecological) progress. For example, he saw tunicates with their simplified bodies and sessile adult stage as a product of biological progress by morphophysiological degeneration.

In summary, Sewertzoff distinguished four directions of morphophysiological evolution, discussed them in terms of progress and degradation, and contrasted them with the concept of biological progress (or regress). This was a decisive step in developing Haeckel's concept of dysteleology (Haeckel 1920, p. 219), i.e., an appeal to a strictly causal explanatory model of evolutionary progress. Sewertzoff's ideas on the different directions which morphophysiological evolution can take also laid the foundation for the Russian tradition in interpreting evolutionary progress. Schmalhausen's work is based on Sewertzoff's approach and the concepts and terms elaborated by Sewertzoff and Schmalhausen are still present in Russian textbooks on evolutionary biology but have remained almost unknown to the western EvoDevo community.

Another radical revision of Haeckel's view on the relationships between ontogeny and phylogeny was Sewertzoff's "Theory of Phylembryogenesis." It was an attempt to rescue the very idea of recapitulation. As the evolutionary morphologist Dietrich Starck (1908–2001) puts it: "[…] that the embryogenesis cannot be explained through phylogenesis alone, but that changes during embryonic development can become reasons for changes in the phylogenesis, and that an exactly coordinated test of phylogenesis and ontogenesis in highly specialized evolutionary lines" is necessary for understanding the "morphological regularities of evolution." Starting from the idea "that the changes in the structure of the adult animal (phylogenesis in the Haeckelian sense) are dependent upon changes in the process of ontogenesis of these structures themselves," Sewertzoff distinguished the following modes of change to the ontogeny that result in an evolution that is "progressive":

Anaboly (or terminal addition) This changes to ontogeny by extension. This should explain "von Baer's law" (K. E. von Baer, 1792–1876), which claims that features of the adult forms appear in a certain sequence during embryonic development and that this sequence corresponds to the hierarchy of systematic categories (e.g., family–genus–species) to which the individual belongs. Von Baer's law should not be confused with Haeckel's view "of the pressing back of adult ancestral stages into the young

stages of the descendants" (de Beer 1932). Anaboly corresponds to "Hinausschreiten" in Fritz Müller's scheme.

Deviation This is a departure from the usual course of ontogeny (corresponds to "Abirren" in Fritz Müller's scheme), which occurs in the middle stages: no extension of morphogenesis, only recapitulation of the stages up until the deviation. Sewertzoff adapted the term "middle stage deviation" from Victor Franz (Franz 1924).

Archallaxis This explains cases with no recapitulation at all. Briefly defined, archallaxis is an evolutionarily crucial modification occurring in the earliest stages of ontogeny (Sewertzoff 1931, pp. 266–299).

All three modes of phylembryogenesis exist in *positive* and *negative* forms. The negative form of anaboly is the deletion of the last stage of ontogeny (as opposed to its extension). Negative deviation and negative archallaxis means the regress of primordia in the middle or early stages of embryonic development, respectively (Sewertzoff 1949, p. 402). In summary, the theory of phylembryogenesis separated the problem of recapitulation from Haeckel's "biogenetic law." Sewertzoff could show that the recapitulation of features of the adult ancestors cannot even in principle take place by "middle stage deviation" and archallaxis because recapitulation can only take place if evolution works by terminal addition, i.e., if evolution is limited to adding stages to the end of the ontogeny. Therefore, recapitulation cannot be a reliable method for constructing phylogenies.

Sewertzoff's work was carried on by his student Ivan I. Schmalhausen (Levit et al. 2006), who intellectually was an important "architect" of the Modern Synthesis, especially in the Russian-reading world, but has been largely neglected in the traditional historiography of the modern synthesis, e.g., in Mayr and Provine (1980). However, this traditional view is now being challenged, and we hope that a more comprehensive view that takes the parallel developments in different countries into account will prevail (Junker and Hoßfeld 2009). Very similar ideas were developed on the other side of the Iron Curtain, most prominently by the leading British biologist Conrad Hal Waddington.

The organism as a whole and the factors of evolution—Ivan I. Schmalhausen

Ivan Ivanovich Schmalhausen (1884–1963; Fig. 4), after a long and distinguished career as an empirical scientist (Levit et al. 2006), started to write down his theoretical ideas relatively late. He was 53 years old when he published his first book on evolution named (in literal translation) *The Organism as a Whole in its Individual and Historical Development* (1938). Here he develops a

Fig. 4 Ivan I. Schmalhausen. Courtesy of Nauka Press, Moscow

synthetic and holistic view of the organism that has come back in recent years within the EvoDevo field. Schmalhausen objects to the neo-Darwinian understanding of the organism as a "mosaic of characters" and criticizes the simplified concept of evolution as "differentiation" as opposed to "integration" to use his vocabulary. He writes that he wants to "concentrate on […] that relative integrity, which is characteristic for the developing organism, i.e., the integrative factors of ontogeny and phylogeny and their role in the very process of individual and historical development […]. These problems have been completely neglected." (Schmalhausen 1938, p. 4).

In later works, he defined integration as a mutual adaptedness of all parts and functions of the organism, providing general stability to the system (Schmalhausen 1969, p. 337). True to Sewertzoff's school, Schmalhausen combined both morphological and physiological approaches to the problem of differentiation and integrity and talked about "morphophysiological progress."

There is sufficient evidence, Schmalhausen argued, supporting the idea of correlations at all stages of ontogeny. These correlations determine the course of ontogeny. It is evident already at the blastomere stage because, when isolated, a separate blastomere develops differently from when in an intact embryo. However, one can observe correlations also in late developmental stages. Schmalhausen mentions endocrine control in vertebrate development as an example. The organism develops as a whole at all

developmental stages due to the complex system of regulative correlations (Schmalhausen 1938, pp. 14–15).

Outside the Russian-speaking countries, Schmalhausen is mostly known for his theory of stabilizing selection. The book in which he presented his ideas, *Factors of evolution*, written in isolation in the Soviet Union in the 1940s, was first translated into English due to the support of Dobzhansky in 1949 (Schmalhausen 1949) and recently published also in German (Hoßfeld and Olsson 2002; Hoßfeld et al. 2010). The theory of stabilizing selection is the theory of "autonomization" (genetic assimilation, see below) and "normalization" (re-establishment of the normal phenotype) of populations and is at the center of Schmalhausen's theoretical heritage. Schmalhausen credits the American naturalist John T. Gulick (1832–1923), who coined the concepts "balanced" and "unbalanced" selection, as his forerunner (Gulick 1905). He follows Gulick in that he distinguishes two kinds of selection, i.e., dynamic and stabilizing selection. Dynamic, or directional, selection is caused by changes in "ecological conditions and biocenotic relationships" (Schmalhausen 1969, p. 237), when existing developmental mechanisms are confronted with new circumstances. This leads to a shift in the mean value or "norm" or, in disruptive selection, to the creation of two or more new norms. This is, Schmalhausen argued, a very Darwinian form of natural selection, adaptation to novel environments. Instead of "environment," Schmalhausen used the more precise term "biogeocenosis." He wrote: "Thus, the foundation of the dynamic form of natural selection is the changing position of a population in the biogeocenosis, which confers advantages to certain variants, while others appear to be in an unfavourable position" (Schmalhausen 1969, p. 237). The concept of biogeocenosis was coined by Schmalhausen's friend Vladimir N. Sukachev (1880–1967) and refers to the elementary structural unit of the biosphere, which includes both biotic and abiotic environments functioning as an interconnected system. Schmalhausen was aware of the analogous term "ecosystem" coined in 1935 by Arthur Tansley (1871–1955) but preferred "biogeocenosis" as a more precise term which attaches biocoenoses to certain geographical landscapes.

In contrast to the dynamic form of selection, stabilizing selection operates in stable biogeocenoses, i.e., in a situation of dynamic equilibrium between populations and biogeocenosis undergoing certain (e.g., cyclic) changes. Under these circumstances, when an environmental factor fluctuates around a mean value, the so-called norm has adaptive advantages leading to stabilization of phenotypes and populations. The effect of stabilizing selection "increases in the presence of the rapid and at the same time irregular fluctuations of environmental factors (continental or montane climate, passive transfer or migration of organisms etc.)" (Schmalhausen 1990, p. 144). With

"stabilization" Schmalhausen meant the acquisition of more independence from external factors and from factors which influence the process of individual development. Stabilizing selection can be a "dynamic" and essentially creative force continually establishing new patterns of ontogenetic development. In an unpublished manuscript, Schmalhausen clearly states that stabilizing selection means "radical transformation [perestrojka] of individual development" (Schmalgausen 1988, p. 138). Mutations are the driving force for this: "During the process of selecting normal individuals, the elimination of harmful variations takes place as well, and, at the same time, a continuous summation of all these mutations takes place, which can be integrated into the normal phenotype" (Schmalhausen 1969, p. 238).

Stabilizing selection, as described by Schmalhausen, operates dichotomously, on the one hand stabilizing the genetic structure of the population and on the other hand optimizing development in such a way that the so-called norm of reaction becomes restricted, which makes the organism more autonomous in relation to its environment. A norm of reaction is a specific reaction of the organism to certain environmental conditions (*modifications*) and is determined by the organism's prehistory (Schmalhausen 1946, p. 19) or, in other words, it consists of the range of phenotypic expression of a given genotype (Wake 1996). For example, leaves of *Anemone pulsatilla* that have developed in the shade are much more cleft compared to light-exposed leaves of the same plant. A simple example of a modification is the transformation of muscles

as a result of regular training. Such modifications are non-heritable and not necessarily adaptive. Non-adaptive reactions, which Schmalhausen calls "morphoses," take place either if an organism finds itself in a new environment or as a result of a mutation. Under predictable environmental conditions, stabilizing selection protects adaptive reactions "against possible disturbances by fortuitous external influences" (Schmalhausen 1949, p. 81). Yet these two forms of selection (dynamic and stabilizing) are abstractions. In biological reality, both types of selection operate simultaneously. Environmental conditions change continually and dynamic selection occurs continuously. However, Schmalhausen thought that environmental changes are often slow enough to allow stabilizing selection to take effect. In his book on the origin of terrestrial vertebrates, which was translated into English, Schmalhausen (1968) tries to summarize his view of the evolutionary process in the form of a general scheme (Fig. 5).

Schmalhausen and Waddington

It has been pointed out repeatedly that Schmalhausen's stabilizing selection looks similar to Conrad Hal Waddington's (1905–1975) concept of "canalization" and that Schmalhausen's "autonomization" is the same as Waddington's "genetic assimilation" often associated also with the so-called "Baldwin effect" (after James M. Baldwin, 1861–1934; see, e.g., Gilbert 1994, 2003; Hall 1998; Matsuda 1987). As Gilbert puts it: "Genetic assimilation is the process by which a phenotypic response
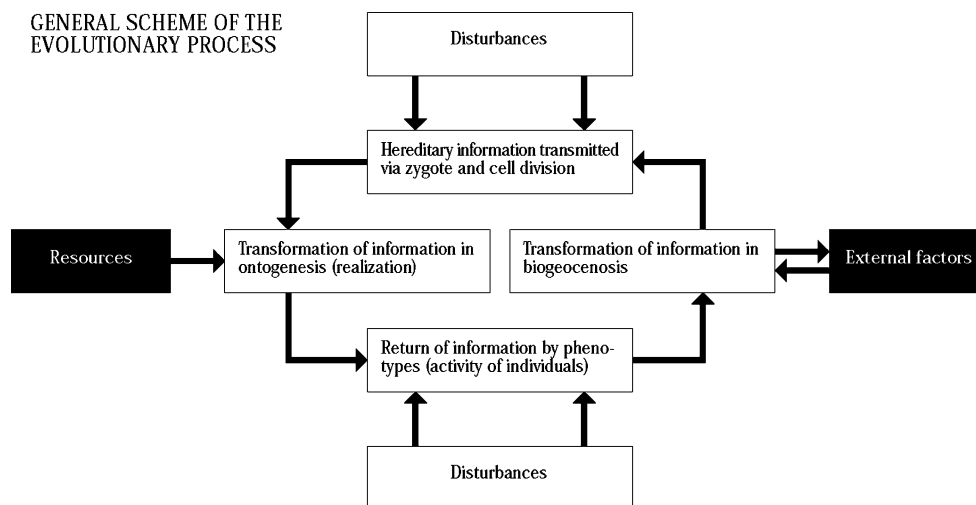

Fig. 5 General scheme of the evolutionary process. Redrawn and slightly modified from Schmalhausen (1968), p. 42. Schmalhausen saw evolution as a cybernetic process with many interacting parts and adaptive evolution as based on both forms of natural selection (stabilizing and directional) and as representing a complex body of self-regulating systems ranging from the "organism as a whole" to the biogeocenosis. In this scheme, if we start by following the central ring

of arrows, is shown how hereditary information is transformed into organisms through ontogeny, using up resources. The individual produced by ontogeny, through its activity (affected by disturbances), transforms information in its ecosystem (biogeocenosis), which is under the influence of external factors. The biogeocenosis in its turn affects the transformation of hereditary information, which can suffer disturbances

to the environment becomes, through the process of selection, taken over by the genotype so that it becomes independent of the original environmental inducer. This idea had several predecessors, including those hypotheses of J. M. Baldwin, and is essentially the same as Schmalhausen's hypothesis of genetic stabilization" (Gilbert 2003). Brian Hall expressed the same idea: "In Russia, Ivan Schmalhausen independently arrived at mechanisms extraordinarily similar to Waddington's genetic assimilation and canalization. He called his processes autonomization and stabilizing selection and invoked norm of reaction" […] "Schmalhausen's autonomization was Waddington's genetic assimilation and *vice versa*" (Hall 1998, p. 311). Moreover, both Schmalhausen and Waddington thought about development in terms of a "cybernetic process" (Waddington 1975, p. 209–230; Gilbert 2003). With so much parallelism, the question arises whether there was any difference in principle between their theories. How do the "Baldwin effect" and "genetic assimilation" relate to "stabilizing selection"?

The simplest case is the "Baldwin effect" because Schmalhausen and Waddington both commented on it. The Baldwin effect was seen by Waddington as an alternative to his genetic assimilation. Most of Waddington's and Schmalhausen's contemporaries understood the concept "to be that organisms may be able, by nongenetic mechanisms, to adapt themselves to a strange environment, in which they can persist until such time as random mutation throws up a new allele which will produce the required developmental modification" (Waddington 1975, p. 89). Waddington himself viewed the Baldwin effect as a "theoretical possibility," however, "at most no more than the limiting case toward which genetic assimilation tends when the operation of selection of the genetically controlled capacity to respond is minimally effective" (Waddington 1975, pp. 90, 92).

Schmalhausen was against equating stabilizing selection with the Baldwin effect. Thus, the well-known Russian geneticist Mikhail M. Kamshilov (1910–1979), who worked in close cooperation with Schmalhausen for many years, reported that Schmalhausen had told him in early 1946 that he only used the Baldwin effect as a "pedagogical device" to make the concept more illustrative (Kamshilov 1974). In the posthumously published comments to the second edition of the *Problems of Darwinism*, Schmalhausen (1969) made an assertive statement: "The critics have suggested that what I understand under stabilizing selection is in fact a variety of phenomena. This is wrong. I call that form of selection stabilizing selection, which G. Simpson later called centripetal selection. The results of this kind of selection are diverse, but not the stabilizing selection itself (this I have pointed out earlier). *The suggestions about the similarity [of stabilizing selection] and the Baldwin effect*

are wrong (our italics). The Baldwin effect is a by-product of stabilizing selection under certain conditions. The theory of stabilizing selection is not a Lamarckian one. It is completely compatible with our modern conception of Darwinism. However, it also contributes something new—the idea of a stable hereditary apparatus as a basis for the mechanism of individual development for its progressive autonomization. In addition to much indirect evidence, there are also experimental data in favor of this theory (Kamshilov, Waddington)" (Schmalgausen 1983, p. 351). In another part of this paper, Schmalhausen also clearly supported Waddington's notion of canalization: "Every adaptive modification is an expression of a norm of reaction, which went the long way of historical development under changing conditions. It is connected with the establishment of 'canals' through which a certain modification develops (Waddington talks about the 'canalisation' of development). An external factor operates only to switch the development into one of the existing canals" (Schmalgausen 1983, p. 350).

These ideas are related to current research on phenotypic plasticity, one of the major questions in modern EvoDevo, and its role and importance for evolution, a controversial topic in today's evolutionary biology. West-Eberhard (2003) provides a comprehensive overview of this field of research.

Nikolai V. Timoféeff-Ressovsky: between genetics and EvoDevo

Nikolai Vladimirovich Timoféeff-Ressovsky (1900–1981) was a Russian-German biologist who did much of his most important work in Berlin. He covered a wide field of research, including molecular and population genetics, radiation biology, evolutionary biology, and developmental genetics (Levit and Hoßfeld 2009). He was also controversial politically. Here we focus on parts of his research program relevant to EvoDevo. Timoféeff-Ressovsky is well known for having introduced the concepts of *penetrance* and *expressivity,* which reflect that "the rate expression (penetrance) and the degree and the form of manifestation (expressivity) of a gene depend on the genotype it belongs to" (Blumenfeld et al. 2000). During the late 1930s and 1940s, Timoféeff-Ressovsky established a population genetics in Germany based on a broad range of empirical data gained from both field and laboratory research. He worked on the role of evolutionary factors, analyzed the role of recessive mutations, and discussed data and findings with colleagues from different areas of biology. He was adamant about the randomness and lack of direction of mutations and supported this thesis with mutation experiments in fruit flies (Fig. 6). He was doubtlessly one of the co-architects of the Modern Synthesis (Reif et al. 2000). His mutation studies were only a fraction of his research
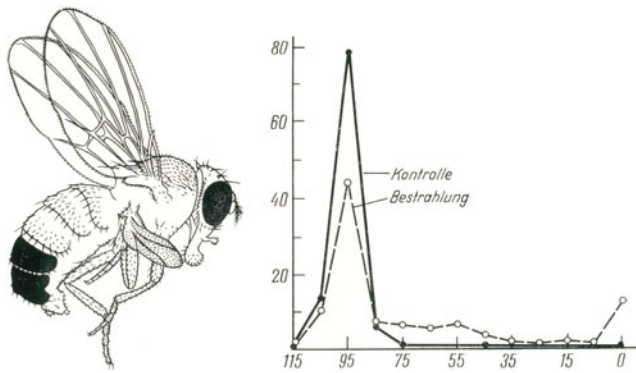
Fig. 6 "The mutation process is random and directionless" (Timoféeff-Ressovsky et al. 1975, p. 85). Timoféeff-Ressovsky illustrates this Darwinian thesis by two examples: *Left*, the mutation *tetraptera* of *Drosophila melanogaster* (*sensu* B. L. Astaurov, 1927) is an example of a *Großmutation* [major mutation], which leads "to the occurrence of a character of another order" (Timoféeff-Ressovsky et al. 1975, p. 83). The halteres have undergone a homeotic transformation and taken on wing identity. *Right*, the curve reflecting the minor mutations [*Kleinmutationen*] of relative vitality in *D. melanogaster*. *Bestrahlung*—radiation; *Kontrolle*—control group. *Abscissa*, the number of males in the crossbreeding expressed as a percentage of the number of normal females. *Ordinate*, the percentage of corresponding crossings (control group = 837 individuals; the irradiated group = 868 individuals) (from Timoféeff-Ressovsky et al. 1975, p. 83)

program, and he had wide-ranging theoretical interests. In one of his most important review articles, "Genetics and Evolution" (Timoféeff-Ressovsky 1939), he discussed the importance of genetic constraints on variation and investigated the relative importance of various factors of evolution (Reif et al. 2000). His research program was explicitly directed towards an all-embracing theory of evolution at all levels of organization of living matter, from the molecular level to the biogeocenoses (ecosystems) and the biosphere. A harmonized model of micro- and macro-evolutionary processes including ecological, biogeochemical, and global approaches would then form an interdisciplinary basis for an expanded theory, in which development was an integrated part. A textbook on evolutionary theory that he wrote with two colleagues appeared in German translation (Timoféeff-Ressovsky et al. 1975).

Embryos, ancestors, and heterochrony—Sir Gavin R. De Beer

Research into the relationship between evolution and development, after the original boost by Ernst Haeckel's influential propaganda for the Biogenetic Law, continued in the comparative morphology tradition in both Europe and North America. The classical treatment of this history is "Ontogeny and Phylogeny" by Stephen Jay Gould (Gould 1977). One important researcher who bridged the time period between Haeckel and Gould was Sir Gavin Rylands de Beer (Brigandt 2006). Just like our other examples, we are using him to characterize a school of thought, in this case heterochrony research in the first half of the twentieth century, in the English-speaking world. de Beer was born into a family whose extraordinary wealth was based on diamonds. Richard Fortey recently described him as "born with so many silver spoons in his mouth that he must have had problems eating" (Fortey 2008). From this secure position, de Beer embarked upon a remarkable career, finally becoming the Director of what is nowadays called The Natural History Museum in London. His training was in comparative morphology and experimental embryology, about which he wrote a textbook in 1934 with Sir Julian Huxley as co-author (Huxley and de Beer 1934).

The central work for our purposes in this review, however, is de Beer's *Embryology and Evolution* (de Beer 1930), which in later editions was renamed *Embryos and Ancestors*. Here de Beer builds upon the work of Walter Garstang (1868–1949) who famously quipped that "Ontogeny does not recapitulate Phylogeny: it creates it" (Garstang 1922, p. 32). Like Garstang, de Beer criticized the Biogenetic Law and tried to dig deeper into the relationship between evolution and development. He saw phylogeny as a succession of ontogenies and rejected Haeckel's notion of phylogeny as the "mechanical cause" of ontogeny. It must be the other way around. He developed a classification of different types of heterochrony and gave heterochronic processes a central role in morphological evolution. He also proposed a genetic mechanism that could explain heterochronic phenomena using Goldschmidt's new concept of "rate genes" that were supposed to control the speed of development. de Beer suggested a classification into eight different types of heterochrony, in part corresponding to schemes developed by others, such as Sewertzoff in Russia. de Beer's categories were divided into four that concern the introduction of novelties in evolution (caenogenesis [a term introduced by Haeckel for larval specializations], adult variation, deviation, reduction) and four that were directly related to changes in the timing of developmental processes. Among these four, hypermorphosis and acceleration lead to recapitulation, whereas the other two (neoteny and retardation) do not. de Beer saw neoteny as an important way of making new (higher) taxa in evolution and introduced the concept *clandestine evolution* as a way of reconciling gradualism with the gaps in the fossil record. Imagine that most novel characters are introduced in early stages of ontogeny. They will then not be present in the adults, whose skeletons are fossilized. However, if neoteny brings these characters to expression in the adult, then their evolution will appear sudden. de Beer had many interesting ideas, and this is certainly one of the more novel ones.

The history of EvoDevo and the major questions

If we go back to the five major questions of EvoDevo listed earlier in the paper (1—origin and evolution of embryonic development, 2—origin of novelties, 3—phenotypic plasticity, 4—role of ecology, 5—homology/homoplasy), we can see that Haeckel's Gastraea theory addresses most of these questions (1, 2, 4, and 5). As we have seen, the Gastraea theory did not stay in the state Haeckel left it but was developed further, most importantly into the Bilaterogastraea and Trochaea theories (by Jägersten and Nielsen, respectively) within comparative invertebrate embryology. Nielsen, in particular, has developed elaborate scenarios for the origin of major groups of animals, which start with Haeckel's Blastaea und Gastraea stages.

Oscar Hertwig's discussion about internal and external causes for evolution has its counterpart in the modern debate about a role for development in deciding the tempo and direction of evolution. Oscar Hertwig would not agree with today's ultraselectionist standpoint (taken by, e.g., Richard Dawkins) that function decides form completely. Hertwig did not see an important role in evolution for selection (this has been shown only in the last 50 years or so). He also criticized the idea that similarities between embryos from different animal groups were useful for phylogenetic analysis, which formed such an important part of Haeckel's research program. It was clear to Oscar Hertwig that embryonic similarities could be caused by convergent evolution. His work thus covered questions 2, 3, und 4 (novelties, plasticity, and the role of ecology).

Victor Franz, A. N. Sewertzoff, and G. R. de Beer were important for developing heterochrony research and how this relates to question 2, the origin on evolutionary novelties. de Beer also contributed to question 5 (homology and development). Understanding the genetic basis of heterochrony remains a challenge, and today several "heterochrony genes" have been identified, in particular in the nematode *Caenorhabditis elegans*. Franz also thought that evolution is progressive, an idea which has remained controversial. He believed that selection automatically leads to improved adaptation. Only much later was it realized that the environment might well change relatively fast, so that adaptation might not improve, as formulated in the "Red Queen" hypothesis. The strength of Sewertzoff's model of evolution was the synthesis of results from comparative anatomy and embryology with the new insights from the developing "Modern synthesis" (Starck 1965, p. 60; Levit et al. 2004). This was followed up by his student I.I. Schmalhausen, who also put great emphasis on integrating ecology into his synthesis. Thereby, he was important in addressing question 4, in addition to his work on question 3 (reaction norms and phenotypic plasticity). Lastly, Timoféeff-Ressovsky was part of the very important effort to apply genetics to understand, e.g., the origin of evolutionary novelties (question 2) and forms a bridge to modern developmental genetics and the analysis of homeotic mutations to which we now turn.

The basic structure of animal development—the homeobox

Developmental biology and EvoDevo got an important push when the methods of molecular genetics became more commonly used in the 1980s. So-called homeotic mutations in the fruit fly were at the center of attention. In these mutations, it seemed that a segment of the body got the wrong identity, e.g., wings instead of halteres or legs instead of antennae. In 1984, it was shown that the mutated genes shared 180-bp conserved sequences, the homeobox. This recent history has been described, for example, by one of the main researchers contributing to it, Walter Gehring (1998; Lodish et al. 2003).

The main surprise came when researchers started to search for homeobox genes in other animal phyla. It soon became clear that multicellular animals share a conserved system for establishing segment identity along the anterior–posterior axis and that the similarities on the molecular level were astoundingly large, including details like the arrangement of genes along a chromosome. Unlike the heterochrony research tradition, which had concentrated on how the differences in adult morphology can be explained by changes in the timing of development, the focus now shifted towards describing the genes and developmental mechanisms that even very distantly related animals, such as flies and vertebrates, have in common. This was an important shift of emphasis. As more and more species get their genomes sequenced, it has become clear that many other genes (often transcription factors like the homeobox genes) are also highly conserved in both structure and function, such as the *Pax-6* gene important for eye development regardless of the type of eye (i.e., camera or compound) produced in different animals. The concept of a "molecular toolkit" made up mostly of networks of transcription factors and a handful of signaling cascades has become popular, and the evolutionary question becomes to understand how this limited toolkit has given rise to the enormous diversity of body plans seen among multicellular animals (see, e.g., Carroll et al. 2005).

Important concepts in contemporary EvoDevo

An important task for today's EvoDevo is to really develop a synthesis of different research traditions and integrate different approaches. It is important to create a common

language that researchers from different schools of thought can easily learn. Some basic concepts provide a necessary backbone for today's EvoDevo and can facilitate communication between researchers taking part in this synthetic endeavor (Hall 1998; Hall and Olson 2003; Raff 1996; Raff et al. 1999). Here we review three important unifying concepts in EvoDevo: modularity, developmental constraints, and evolutionary novelties.

Modularity

In a seminal essay on the narrative structure of Ian Fleming's James Bond stories, Umberto Eco (1966) shows that they always consist of certain elements, such as flirting with Miss Moneypenny, meeting M to get the assignment, visiting Q, meeting the villain, meeting the Bond girl, getting caught, fed and tortured by the villain, killing the villain and destroying his secret headquarters, etc. These modules are re-arranged between the different movies, and by tagging them (A, B, C…) it is possible to represent each Bond movie by a string of letters. Many other phenomena show this type of modularity, made up of parts that have a certain amount of individuality and independence, and living organisms and their development are no exception. Plants are obviously modular, but also animals must show a certain modularity if they are to be flexible enough to evolve at all.

If animals were not divided into modules or body parts with some degree of independence, it would be impossible to change one part of the animal (through a mutation in the germ line) without this having correlated effects on the rest of the organism. This would preclude the diversification into the large number of body plans or Baupläne that we observe in both extant and extinct animals, i.e., there would be no evolvability (Kirschner and Gerhard 1998, 2005). The idea that any change to an animal's well-functioning morphology would be deleterious was an important reason for Cuvier to deny the possibility of morphological change over time, or evolution (Coleman 1962). So how does modularity work in development and evolution?

One important starting point for modern EvoDevo was the discovery that different types of animals, belonging to different phyla and showing different body plans, could still have important processes in their development regulated by homologous genes (such as the *Hox* genes described above) or gene regulatory networks (GRNs). It was also found that these GRNs could be used to control the development of different body parts at different times of development in the same organism, for example, the role of *distalless* and its allies in regulating both early and late patterning processes, such as leg and antenna outgrowth on the one hand and eye spots on butterfly wings on the other (Carroll et al. 2005).

This can potentially lead to constraints (see below) if a GRN is controlling several modules or to modularity if the GRN has a more restricted function. Importantly, when a novel structure, such as the eye spots on lepidopteran wings, evolves, a GRN can be co-opted to have a new function in this newly evolved module. Such modules might be units of evolution (Schlosser 2002), and there is a growing discussion about how to define and interpret modularity in EvoDevo (see, e.g., Schlosser and Wagner 2004; von Dassow and Munro 1999, for reviews).

Modularity ties in nicely with the concept of heterochrony that has traditionally been so important for linking evolution and development (Goswami et al. 2009). If organisms and their developmental regulation can be divided up into modules, it is easy to explain heterochronic changes as a partial decoupling of modules, which can then evolve different growth rates or onset and offset points for growth, leading to morphological differentiation.

Developmental constraints

In the absence of modularity, we would indeed run into the problem formulated by Cuvier that any change in one part of an organism would lead to deleterious side effects in other parts of the organism. Although modularity tends to prevent this from happening, we often see what Darwin called "correlation of parts," for example, that changes in the size of one character over time, such as body size, lead to a correlated, often allometric change in another character, such as antler size. In a famous paper, Stephen Jay Gould used this to argue that the giant antlers of the Irish elk could be explained as an allometric side effect of an increase in general body size (Gould 1974). Different disciplines within biology have dealt with the "correlation of parts," and different labels have been used to describe phenomena related to it, e.g., genetic correlations, pleiotropic effects, allometries, functional integration, or developmental constraints. Another type of phenomena often invoked in the context of constraints is missing morphologies in morphospace or missing combinations of traits, such as why grass-eating snakes have never evolved. This might be simply caused by historical contingency or "phylogenetic inertia," as emphasized by Gould (1989), or by constraints. Constraints, although potentially important, have proven elusive conceptually, but there is consensus on the general idea. Kurt Schwenk and Günter Wagner have written that "Constraints are mechanisms or processes that limit the ability of the phenotype to evolve or bias it along certain paths" (Schwenk and Wagner 2003). It is important to make it clear that phenomena that are often invoked as support for the importance of constraints might have other explanations. Morphological stasis, as seen, for example, in so-called living fossils such as the coelacanth can either

be explained by reference to some (mostly unknown) constraint that hinders morphological diversification or by stabilizing selection. It is often impossible to know which explanation is the most important in such cases.

Important attempts to explain why there are constraints on morphological evolution include the work in Vienna in the 1970s by Rupert Riedl (1925–2005), laid out in his book "Order in living organisms" from 1978 (published in German in 1975 as "Ordnung des Lebendigen"). Here Riedl introduces the term "burden" to account for the evolutionary conservation of body plans. Riedl thought that different characters evolve at very different rates, and those with the highest "burden" evolve at the slowest rates. A paper describing Riedl's ideas has recently been published by Wagner and Laubichler (2004), and we refer the interested reader to it for more information about Riedl and his ideas. In it Wagner and Laubichler write that "Burden is the idea that the likelihood that a character changes during evolution depends on the number and the importance of functions and characters depending on it." Similar ideas have been developed by others, for example, Wimsatt's "generative entrenchment" (Wimsatt 1986).

One person that contributed greatly to the renewed interest among morphologists in the connection between evolution and development in the late 1970s and early 1980s, but sadly died very young, was Pere Alberch (1954–1998; see the recent book edited by Rasskin-Gutman and De Renzi (2009) for a collection of his papers and an appreciation of his work). Alberch wrote important papers on heterochrony, constraints, and evolutionary novelties (e.g., Alberch et al. 1979; Alberch 1980, 1989) and inspired many of today's practitioners of EvoDevo.

Evolutionary novelties

An important aspect of evolution is the generation of novelties. Intuitively, it is easy to think of novel structures or functions that must have had major consequences for the evolutionary radiation of a certain group of organisms. The angiosperm flower, paired fins, flight in birds, pterosaurs, and bats, and hair and mammae in mammals are just a few examples and the list can easily be made much longer. Just like constraints, novelties have been used to mean different things by different authors (see Pigliucci 2008 for an overview). It is possible to hold the view that "Novelties and apomorphies are essentially the same" (Arthur 2000), but this goes against the notion that novelties should refer to something of importance for the evolution of major groups or for adaptive radiations rather than something that is useful for distinguishing between closely related species. We would, for example, consider the shield (carapax and plastron) of turtles to be a novelty but hardly the subtle differences in form and coloration of the shield between the

different species of Galapagos turtles present on the different islands in the archipelago.

Another possibility is to focus on the function rather than the structure of the novelty. Ernst Mayr wrote that "Any newly acquired structure or property that permits the performance of a new function, which, in turn, will open a new adaptive zone" is a novelty (Mayr 1963). This allows for relatively subtle changes to be called novelties and can be contrasted with the much more rigorous view taken by some structurally oriented researchers. In an influential paper, Gerd Müller and Günter Wagner have suggested that a novelty (or evolutionary innovation as they call it) must be "neither homologous to any structure in the ancestral species nor homonomous [serially homologous] to any other structure of the same organism" (Müller and Wagner 1991). This very strict definition of evolutionary novelty would, if adopted, lead to the disqualification of structures often considered to be important novelties, such as the wings of birds, pterosaurs, and bats, because it is trivial to see that they are homologous to the forelimbs of other tetrapods and the pectoral fins of all gnathostomes. Wagner and Lynch (2009) make this distinction and point out that they consider feathers a novelty but not wings.

Recent trends in EvoDevo

EvoDevo is often seen as part of contemporary attempts to extend or expand the Modern Synthesis (Pigliucci and Müller 2010). The major trend within EvoDevo remains the increased use of molecular genetics, including genomics, transcriptomics, and proteomics, to further our mechanistic understanding of development. In addition, as Gerd Müller has pointed out repeatedly (e.g., Müller 2007), several other parallel trends or research programs can be discerned. One is a trend towards using computational and bioinformatics approaches to understand development and how developmental processes evolve; another is the integration of ecological and environmental aspects of developmental biology into what is often called EcoDevo (Gilbert 2001). As we have seen above, this environmental aspect was always important in the Russian tradition. It is sometimes forgotten that another important trend is continued work, especially in marine invertebrates (Love 2009), on developing a phylogenetically informed comparative embryology. Also, work on the developmental basis of homology (and homoplasy) remains an important part of EvoDevo.

The promise and perils of EvoDevo

Despite some controversy about the exact meaning of each of the concepts of modularity, constraints, and evolutionary

novelty, they are at the center of the integration of different research traditions so important in modern EvoDevo research (Moczek 2008). We expect the coming years to shed more light on many of the details of the developmental mechanisms underlying evolutionary changes and also to solve some important current controversies in the field. One such controversy is whether regulatory mutations are more important than mutations in structural genes, as has often been assumed. The developmental biologist Eric Davidson, for example, wrote that "…there is in fact no other way to conceive of the basis of evolutionary change in bilaterian form than by change in the underlying developmental gene regulatory networks. This of course means change in the *cis*-regulatory DNA linkages that determine the functional architecture of all such networks" (Davidson 2001).

This view that *cis*-regulatory evolution has been more important than mutations in structural genes (such as transcription factors) has recently been criticized (Hoekstra and Coyne 2007; Wagner and Lynch 2009, but see, e.g., Wray 2007) on both empirical and theoretical grounds. Hoekstra and Coyne (2007) argue that "…changes in *both* the structure and regulation of genes have been important in adaptation, that their relative importance will not be known for a considerable time, and that the role of structural mutations in morphological evolution—and other adaptive changes—is unlikely to be trivial." On the other hand, recent work has shown that, above the species level, *cis*-regulatory changes are more common than coding changes (Stern and Orgogozo 2008) and that *cis*-regulatory changes are also more common in genes affecting morphology than in genes affecting physiology (Liao et al. 2010). We will need much more empirical work to solve this question.

Work at the molecular level now dominates EvoDevo and will do so even more in the future. It remains important to not lose the connection to more classical fields, such as paleontology, morphology, and comparative embryology, without which the integrative nature of EvoDevo will largely disappear. Wagner and Larsson (2003) have called for "…a synthesis in which the guiding hand of comparative anatomy and paleontology determines the agenda of a collaboration between molecular evolution and mechanistic molecular biology." We fully agree to this and hope for a truly synthetic future for EvoDevo.

Despite the fact that many of us see the future of EvoDevo in an expansion of the array of organisms investigated, towards a more complete sampling of organisms, some argue against this trend. The developmental geneticist Ralf Sommer recently wrote (Sommer 2009) that, "to understand phenotypic change and novelty, researchers who investigate evo-devo in animals should choose a limited number of model organisms in which to develop a sophisticated methodological tool kit for functional investigations." While it is very important to gain a deeper

understanding of the developmental genetics of a few model organisms, we think this can be achieved without sacrificing the broader comparative perspective.

Clearly, a true synthesis of the different disciplines that feed in to modern (and future) EvoDevo is hampered by the different agendas that researchers trained in different disciplines bring with them when they enter the EvoDevo field and which we have exemplified above. Only the future will tell if there is enough willingness to listen and learn from each other to produce a truly novel evolutionary synthesis that integrates developmental biology at its core, without becoming a developmental genetics that is comparative and evolutionary only in a very narrow and limited sense, with the comparisons limited to a few, phylogenetically widely scattered model species.

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