REVIEW

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Theories, laws, and models in evo-devo

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Abstract

Evolutionary developmental biology (evo-devo) is the study of the evolution of developmental mechanisms. Here, I review some of the theories, models, and laws in evo-devo, past and present. Nineteenth-century evo-devo was dominated by recapitulation theory and archetypes. It also gave us germ layer theory, the vertebral theory of the skull, floral organs as modified leaves, and the "inverted invertebrate" theory, among others. Newer theories and models include the frameshift theory, the genetic toolkit for development, the ABC model of flower development, the developmental hourglass, the zootype, Urbilateria, and the hox code. Some of these new theories show the influence of archetypes and recapitulation. Interestingly, recent studies support the old "primordial leaf," "inverted invertebrate," and "segmented head" theories. Furthermore, von Baer's first three laws may now need to be rehabilitated, and the hourglass model modified, in view of what Abzhanov has pointed out about the maternal-zygotic transition. There are many supposed "laws" of evo-devo but I argue that these are merely generalizations about trends in particular lineages. I argue that the "body plan" is an archetype, and is often used in such a way that it lacks any scientific meaning. Looking to the future, one challenge for evo-devo will be to develop new theories and models to accommodate the wealth of new data from high-throughput sequencing, including single-cell sequencing. One step in this direction is the use of sophisticated in silico analyses, as in the "transcriptomic hourglass" models.

KEYWORDS
evo-devo, hourglass, phylotypic period, phylotypic stage, recapitulation, regulatory evolution, zootype

1 | INTRODUCTION

1.1 | Evolutionary developmental biology (evo-devo)

Evolutionary developmental biology (evo-devo) is a new name for an old discipline. Gould traces its roots to pre-Socratics (Gould, 1977).

However, evo-devo did not become evolutionary, in the Darwinian sense, until 1859 when *Origin of Species* was published (C. Darwin, 1859). Evo-devo flourished in the 19th and early 20th centuries (Gould, 1977; Hertwig, 1906b; Rádl, 1909; Rieppel, 1988; Russell, 1916). In Germany, one can recognize it in the discipline of systematic morphology, a "synthesis of comparative anatomy, palaeomorphology, embryology and systematics" (Naef, 1917, p. 69).

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Interest in evolutionary developmental biology waned with the rise of experimental embryology or *Entwicklungsmechanik*, and genetics (Gilbert et al., 1996). Interestingly, Roux predicted that a new discipline of "comparative developmental mechanisms" might lie in the future (Roux, 1895a, p. 441). In 1977, Gould examined the history of recapitulation theory and heterochrony in his book *Ontogeny and Phylogeny*. The book, which set a high standard of scholarship, stimulated interest in evolutionary developmental biology. Soon afterward, a Dahlem Workshop on evolution and development, and a symposium in Sussex, were held (Bonner et al., 1982; Goodwin et al., 1983).

Homeobox genes were cloned in 1984, first in *Drosophila*, then in mammals (discussed by Duboule, 2009). The confluence of these and other events led to the establishment of a new discipline "in the interstices between molecular biology, geology, and evolution" (Davidson, quoted in Roush & Pennisi, 1997). This new discipline acquired the nickname "evo-devo" (C. S. Goodman & Coughlin, 2000).

Before I consider some of the theories, laws, and models in evo-devo, I begin with a brief explanation of what these scientific statements are.

1.2 | Scientific statements

According to philosophers of science, laws and theories are examples of *scientific statements* (Popper, 1962, p. 54, 281). Scientific *laws* are simple statements about phenomena. They are generalizations in the sense that they ignore data peculiar to individual instances of the phenomenon (Hoyningen-Huene, 2013, p. 47).

A *theory* is a set of scientific statements relating to a phenomenon (Hull, 1974, p. 2). Theories explain phenomena, often in terms of a mechanism (Rosenberg, 1985, p. 161). In the physical sciences, a theory may be a set of laws, whereas in evolutionary biology a theory can be a set of models (Beckner, 1959 p. 161; Lloyd, 1988 pp. 8–9, 37). A *model* is a bridge between a theory on one hand, and data on the other (discussed in Costa & French, 2000; Fraassen, 1989).

There are other ways of thinking about theories, laws, and models (for the many and varied perspectives on these issues, see Achinstein, 1971; Armstrong, 2016; Cartwright, 1983; Costa & French, 2000; Dhar & Giuliani, 2010; Dupré, 1993; Elgin, 2006; Feynman, 1992; Hanson, 1965; Lloyd, 1988; Lorenzano, 2006; Mayr, 1982, 2004; Murray, 2001; Pickover, 2008; Pigliucci & Muller, 2010; Rosenberg, 1985; Ruse, 1973; Smart, 1963; Fraassen, 1989; Waters, 1998; Weinert, 1995). See also the *Stanford Encyclopedia of Philosophy* for discussions of models (Frigg & Hartmann, 2020) and theories (Winther, 2020).

I now discuss a selection of scientific statements in evo-devo, and a few from evolutionary biology and developmental biology for comparison. Most relate to vertebrates.
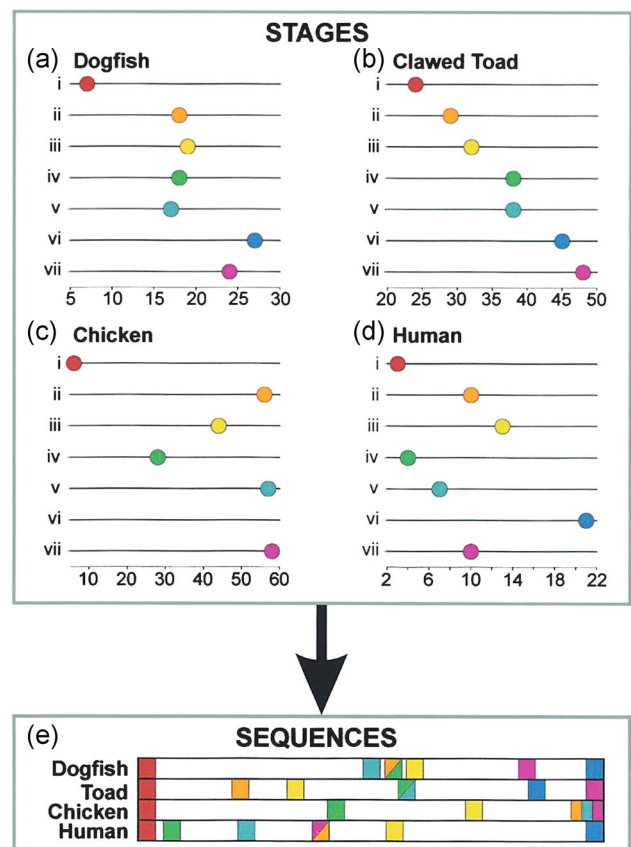

FIGURE 1 Abacus model showing sequence heterochrony in the phylotypic period. Fig. 1 in Jeffery et al., 2002, based on data in Richardson (1995). Developmental sequences in four species (a–d) are shown as abacus diagrams and the resultant developmental sequences are aligned in (e). The horizontal axis represents developmental stage and the position of the colored beads indicates the stage at which various developmental characters (i–vii) first appear. Any vertical line drawn on the abacus represents a developmental stage. No such stage can intersect all the characters in all species. The only way to achieve that is with a window or period

2 | DEVELOPMENTAL STAGES

Developmental staging is a method that segments development into a series of stages, where each stage represents a temporal cluster of morphological character states. Because of developmental variation (polymorphism) within species, each stage is a generalization. Thus, embryos of the same stage may not share *all* of the characteristics of that stage. In other words, stages are polythetic. Because development involves continuous change, the author of a staging series makes entirely arbitrary decisions on how to divide it into stages. Evo-devo research often requires stages to be compared in different species, a task that poses major problems. One of these problems, in the vertebrates at least, is heterochrony (Figure 1; Richardson, 1995). Developmental timing polymorphism within a species is another (Figure 2; Fischel, 1896; Jong et al., 2009). Yet another difficulty in comparing stages between species is character homology.
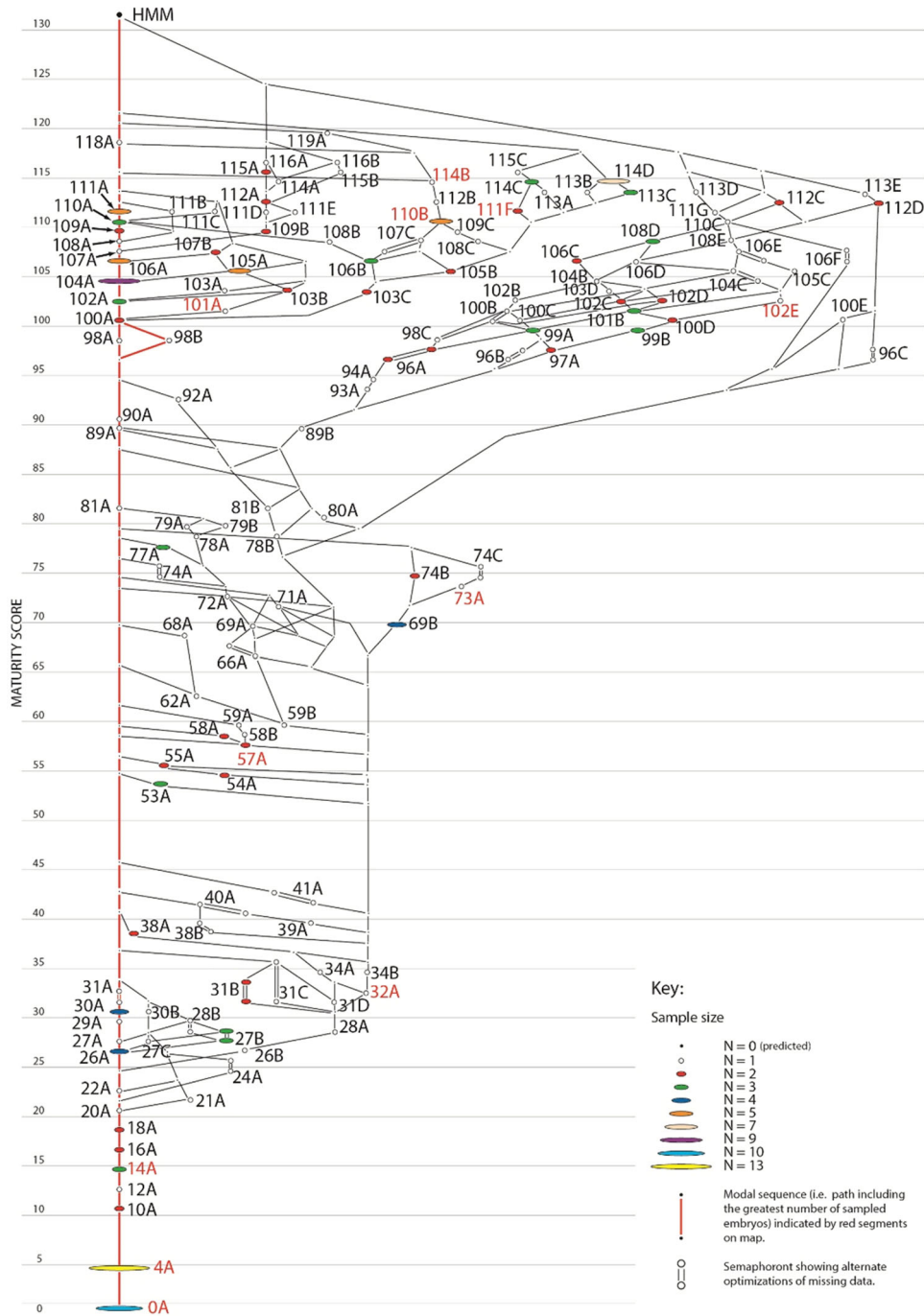
FIGURE 2 Polymorphism in the development of the cichlid *Haplochromis piceatus* shows a developmental funnel pattern. Fig. 1 in Jong et al. (2009)

For example, the Hamburger Hamilton stages for the chick (Hamburger & Hamilton, 1992) include feather tracts and the beak among its staging characters, making it difficult to apply, say, to the mouse. To address these and other issues, Werneburg (2009) developed the standard event system, a universal scheme for staging vertebrate embryos.

3 | ARCHETYPES

In evolutionary biology, an archetype is a model which represents a set of synapomorphic character states or taxic homologies (Richardson, Minelli, et al., 1998). In other words, archetypes represent homologous morphological features of a phylum, or

comparable higher taxon. von Baer's *types* are much the same thing (von Baer, 1828 pp. vii–xxii). Archetypes are generalizations because they represent all species under consideration—but none of them in particular. And, because they represent phenotypes, archetypes are often presented visually, as diagrams or illustrations.

3.1 | Body plans

> Since the rise of evo-devo as an independent field of study, the body plan concept has formed the backbone upon which much of the current research is anchored. (Willmore, 2012, p. 219).

A body plan (Ger. *Bauplan*, pl. *Baupläne*) is an archetype that supposedly represents the morphology of a single species (as in "the body plan of the zebrafish") or a group of species (as in "the vertebrate body plan"). Isaac Newton gave a list of characters to illustrate his concept of a body plan.

> Such a wonderful Uniformity in the Planetary System must be allowed the Effect of Choice. And so must the Uniformity in the Bodies of Animals, they having generally a right and a left side shaped alike, and on either side of their Bodies two Legs behind, and either two Arms … [continues list of characters] (Newton, 1718, p. 378).

More recently, some scientists have given detailed descriptions of body plans and placed them in a clear phylogenetic context (e.g., Brusca & Brusca, 1990). However, in evo-devo, the term "body plan" is often used without any real definition, as though it were more a metaphysical concept than a scientific one. And adjectives such as *fundamental*, *basic*, or *general* are sometimes prefixed to "body plan" without adding any scientific meaning (as in "the basic vertebrate body plan").

Some notion of a body plan emerged as soon as people started grouping species according to morphological and other similarities.

Aristotle made many such groupings (*Historia Animalium*, book II, 497b, 4-6 transl. Thompson, 1910). Two of them were his "animals with blood," and "bloodless animals." Lamarck, in his 1794 lectures, divided animals into those with vertebrae and those without vertebrae (as he later recalled in Lamarck, 1809, p. 118).

Buffon thought that animals shared a 'primitive and general design' representing "an original plan on the basis of which they had all been conceived" (Buffon, 1753, p. 379). Appel suggests that Buffon's primitive plan influenced Geoffroy Saint-Hilaire and his vertebrate type of organization (Appel, 1987; É. Geoffroy Saint-Hilaire, 1818, p. xxxi–xxxii). In species that differ from the type of organization, Geoffroy used his *principle of connections* to reveal their homologies (his "analogies"; É. Geoffroy Saint-Hilaire, 1807). Geoffroy later extended his "unity of organic composition" to all animals (É. Geoffroy Saint-Hilaire, 1820a, 1820b). He argued, for example, that insects formed an additional class of vertebrates, their exoskeleton being analogous to the vertebral column (É. Geoffroy Saint-Hilaire, 1822a, p. 99 *et seq.*).

This suggestion led to a clash with Cuvier (reviewed by Appel, 1987) who recognized four separate branches (*embranchements*) of the animal kingdom: *Animalia vertebrosa*, *mollusca*, *articulata*, and *zoophyta* (syn. *radiata*; Cuvier, 1812, pp. 83–84). The *types* of von Baer are equivalent to these branches (Gould, 1977, p. 57).

To some scientists, morphological similarities among animals were evidence that they were created by the same supernatural entity. Owen's archetype vertebrate skeleton (Figure 3), which he considered to be a "law" (Owen, 1847, p. 93), represented to him the common plan that pleased the Creator (Owen, 1847, p. 295). Owen defined his archetype as follows: "The archetype skeleton represents the idea of a series of essentially similar segments succeeding each other in the axis of the body; such segments being composed of parts similar in number and arrangement" (Owen, 1866, pp. xii–xiii).

Darwin, by contrast, explained unity of type or body plan by unity of descent (C. Darwin, 1859 p. 206). According to Mayr, "Darwin thus replaced the archetype of idealistic morphology by the common ancestor" (Mayr, 1982, p. 465). This is not entirely true because Darwin did refer to ancestors as "archetypes" (C. Darwin, 1859, p. 435). Müller and Haeckel argued that similar embryonic morphology in different species is due to the repetition of ancestral
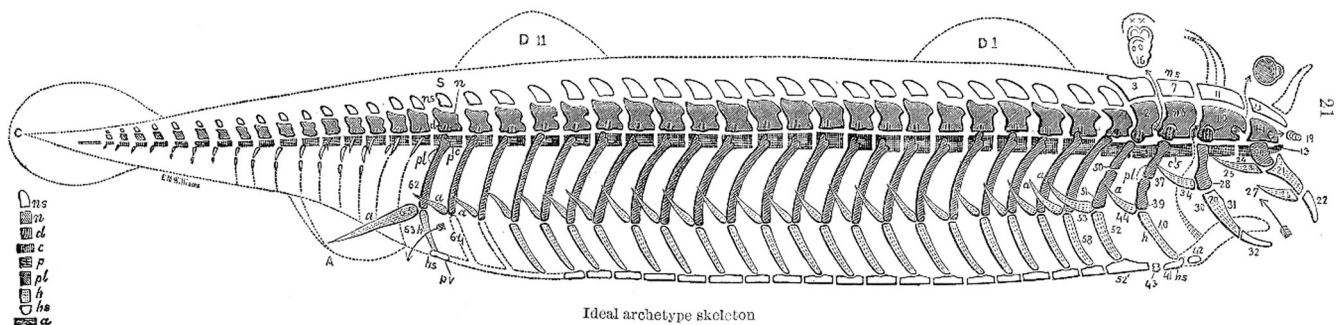

Ideal archetype skeleton

FIGURE 3 Owen's archetype vertebrate skeleton. (Owen, 1866, p. 30)

adult stages during development. With this argument, they injected archetypes into recapitulation theory (see Section 6.5).

3.2 | Developmental stages as archetypes

Many scientists have proposed that certain developmental stages are conserved among all members some or other higher taxon. These stages may even take on a life of their own, as when the Gastrula stage was thought to represent a real animal, the Gastraea. Haeckel proposed the Gastrula as a common stage in the development of many metazoans. The Gastrula, he said, was a hollow sac with a single opening and a wall consisting of two single-cell layers: an inner entoderm and an outer exoderm (Haeckel, 1873, p. 254–255). Haeckel modestly wrote: "I regard the Gastrula as the most important and significant embryonic form in the whole animal kingdom." (Haeckel, 1873, p. 254). The identical form of the gastrula in different animals suggested to Haeckel that they evolved from a common ancestor, the Gastraea (Haeckel, 1872, pp. 466–467; Engl. transl. in Haeckel, 1873, pp. 254–255; Levit et al., 2021). De Robertis and Sasai have commented: "Although simplistic, the Gastrea theory historically was very useful because it proposed that all multicellular animals were monophyletic" (De Robertis & Sasai, 1996, p. 40).

Sander defined the phylotypic stage as that stage in insect development when the *Körpergrundgestalt* appears (Sander, 1996, fig. 1). The *Körpergrundgestalt*, which translates as basic body shape or plan (of the phylum), was a concept used by Seidel (1953, p. 5); it may have originated with Alfred Kühn (according to Niklas et al., 2016). Seidel claimed that the body plan appears during vertebrate development after gastrulation (Seidel, 1953, p. 89).

The pharyngula was said to be a conserved stage in vertebrate development when the pharyngeal arches and pouches are present (Ballard, 1981 p. 392; Kimmel et al., 1995). It is difficult to identify this conserved stage precisely, at least in amniotes, because the pharyngeal arches develop in rostrocaudal sequence. Therefore, they do not appear in a single embryo simultaneously, in the same, undifferentiated state (Richardson, Allen, et al., 1998).

Another reason why it is difficult to identify conserved developmental stages in vertebrates is the rampant heterochrony in that taxon. Structures develop at different times in different species (reviewed by Richardson, 1995). This is why Duboule argued that there was no discrete phylotypic stage in the vertebrates but rather a series of stages that he called the phylotypic progression (Duboule, 1994 p. 139). My analysis confirmed this hypothesis and I used the term phylotypic period as a synonym for phylotypic progression (Richardson, 1995; see also Irie & Kuratani, 2014).

3.3 | Molecular archetypes

Urbilateria is "The hypothetical ancestral animal... (primitive bilateral animal), from which the arthropod and the chordate lineages diverged 600 million years ago" (De Robertis & Sasai, 1996; De Robertis, 2008 p. 40). It is a reconstruction of an ancestral state based on molecular and other data. The zootype (Figure 4) represents a conserved pattern of gene expression seen in most metazoans at the tailbud stage (Slack et al., 1993). This stage was said to correspond to Sander's phylotypic stage.

The proto-gnathostome pharyngeal skeleton is a model based on the expression pattern and function of *Dlx* and *Hox* genes (Depew et al., 2002; Graham, 2001). These molecular data are projected onto a proto-gnathostome head skeleton to produce a combined morphological-molecular archetype (Figure 5). While the authors acknowledge that the scheme is hypothetical, it is certainly a valuable heuristic scheme for understanding the evolution and development of a complex region.
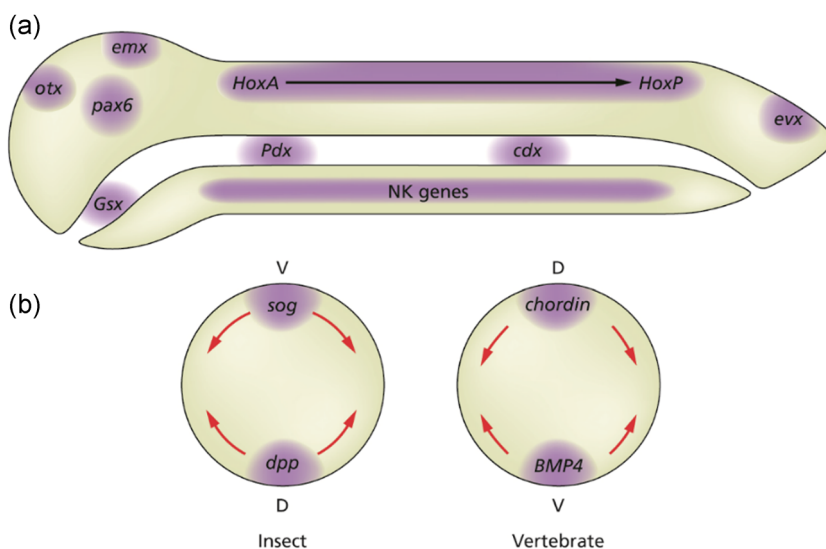

FIGURE 4 Updated zootype. From (Slack, 2012). Courtesy Prof. Jonathan Slack, permission from Wiley. The zootype is an important landmark in evo-devo and a valuable aid to understanding complex data

FIGURE 5 Proto-gnathostome head skeleton showing genes important in patterning of the pharyngeal arches. Fig. 1A in Depew et al. (2002). Courtesy of Prof. John Rubenstein, and with permission of the American Association for the Advancement of Science. Abbreviations are given in the original paper
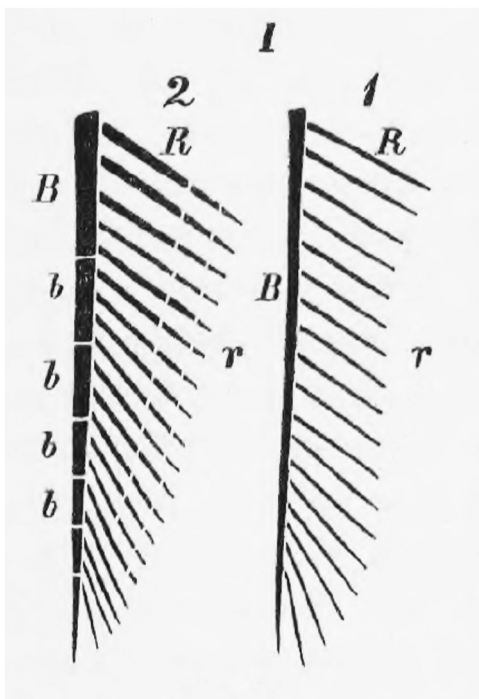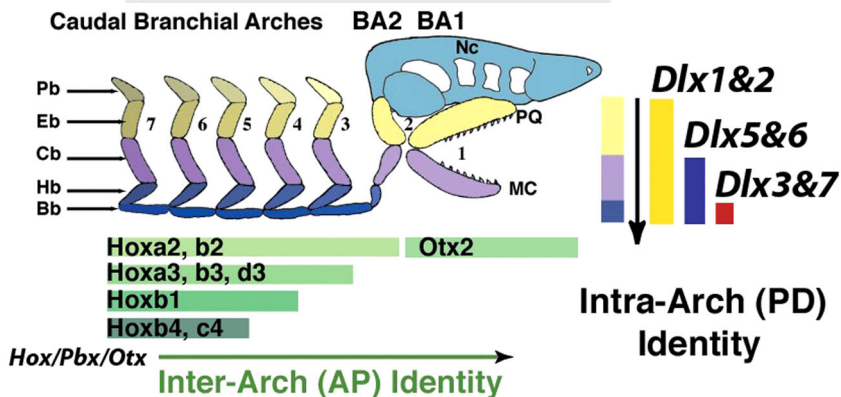

thought to represent the primitive condition for sarcopterygians. Instead, the archipterygium has been replaced with the metapterygium model (Ahlberg, 1989; Coates, 1994; Friedman et al., 2007; Stephens & Strecker, 1985).

Before leaving archetypes, it is worth noting that the word *phylotype* was introduced as a synonym for the phylotypic stage (Minelli & Schram, 1994; Richardson, Minelli, et al., 1998 p. 158). I now think we probably introduced an unnecessary neologism into the literature. Nonetheless, the word phylotype has taken on a life of its own, evolving into a synonym for body plan (Kuratani et al., 2020; Leroi, 1998).

4 | CONCEPTS

According to Mayr, one thing that sets biology apart from the physical sciences is that it deals with concepts (principles) rather than laws (Mayr, 1982). Mayr does not define "concept" (even in his glossary) but he does give examples, including homology, species, selection, and fitness.

4.1 | Homology

Owen defined a homologue as "The same organ in different animals under every variety of form and function" (Owen, 1843, p. 379). Serial homology was Owen's term for the similarity between repeating structures or segments in one individual (Owen, 1847 p. 175). Redefining homology in evolutionary terms, we can say that it is the correspondence between characters in different species, that reflects their origin from the same character in a common ancestor. The character in question can be any structure or attribute (Hall, 1999b). Today, a correspondence in gene expression patterns in different species is often used to address homology questions, such as the homology of avian wing digits (Vargas et al., 2008). For more on homology see Hall, (1999a) and Mayr (1982), and for the history of the term homolog, see Owen (1847 pp. 173–175).

FIGURE 6 Gegenbaur's archipterygium. On the right (1) is the archipterygium with an unsegmented, cartilaginous stem (B) to which are attached a series of unsegmented cartilaginous rays. From this, a fin skeleton can be derived by segmentation of the stem and rays (2). From Gegenbaur (1870b, p. 416). *Key:* B, Basale of the axial element; b, successive divisions of the axial element; R, Randradius (protopterygium); r, successive fin rays

3.4 | The archipterygium

Gegenbaur's archipterygium (Figure 6) is the hypothetical ancestral form of the endoskeleton in sarcopterygian paired appendages (Gegenbaur, 1870a, 1870b). The archipterygium has an axial skeletal element with a series of ray-like cartilages arranged along its length (Gegenbaur, 1870b p. 416). An archipterygium-like morphology is seen in lungfish, although this is no longer

5 | LAWS AND RULES

Laws are sometimes called "rules" or "principles," but the choice of name is arbitrary. They are empirical generalizations. In some respects, laws can be thought of as scientific one-liners, in which case Roux's epic statement that "development is change" (Roux, 1894, p. 3) could be a law (I think it is probably just a definition). Most laws of evo-devo were coined in the 19th century. At that time, many scientists believed that biology, if it were to be regarded as a proper science, needed to come up with universal, mathematically based laws, like those used in physics and chemistry. Some biologists, motivated by physics envy, did try to reform biology in the image of the physical sciences. Examples include Carl Ludwig, with his "new physiology," and Wilhelm His Sr. with his "physiological embryology" (Richardson & Keuck, 2021).

5.1 | Laws of limb evo-devo

Owen argued that distal skeletal elements are more subject to evolutionary variation than are proximal ones (Owen, 1835, p. 353). One could call this a law of variability of distal limb structures. Owen formulated it for vertebrates and it is, therefore, a lineage-specific generalization. One obvious explanation for Owen's law is that the distal limb has more skeletal elements than the proximal limb, and therefore more degrees of freedom to vary.

Morse's law states that "when the number of fingers or toes is reduced in Mammalia and Reptilia, they are always taken away from the sides of the member, the thumb first disappearing and then the little finger" (Morse, 1874, p. 153). I have argued elsewhere (Richardson, 2012a) that this generalization, first suggested by Flower (1870, p. 255), has a number of exceptions and may therefore apply to fewer taxa than Morse suggested. In any case, it is really just a lineage-specific generalization.

The primary axis of the limb (not to be confused with the primary body axis) is an empirical generalization about the sequence and spatial pattern of cartilage differentiation in the amniote limb. In whole mounts stained for cartilage, an inverted Y-shaped tissue mass is seen, with its postaxial branch passing through the fourth digit (Burke & Alberch, 1985). This pattern can be used to support hypotheses about the homology of digits in the avian wing (Wagner & Gauthier, 1999, p. 5113).

5.2 | von Baer's laws

These laws (von Baer, 1828, p. 224) describe patterns of phenotypic divergence between species during development (reviewed by Gould, 1977, pp. 52–63, 486; Abzhanov, 2013; Ospovat, 1976). They are as follows:

(1) General features of a large animal group develop earlier than specific features.

(2) From the most general morphological relations, less general ones develop, and so on until ultimately the special ones appear.

(3) An embryo, instead of passing through the stages of other animals (during development) becomes increasingly different from them.

(4) The embryo of a higher animal never resembles another animal; it only resembles its embryo.von Baer also proposed a law of differentiation (von Baer, 1828, pp. 153–155) essentially his second law. It states that the homogeneous early embryo gradually becomes heterogeneous as a result of germ-layer formation, histogenesis, and morphogenesis. Laws (1)–(3) reflect von Baer's view that there is an early, identical stage, or original form (*Urform*) in all animals: a hollow vesicle (von Baer, 1828, pp. 223–224). This view is in conflict with the hourglass pattern described by later embryologists (Section 8.4), which describes considerable diversity in early developmental stages. With its divergence from the same starting point in different species, von Baer's pattern of divergence is more of a developmental funnel than an hourglass (Section 8.3). Law 4 is an argument against recapitulation. For more on the supposed conflict between von Baer's laws and the developmental hourglass, see Section 9.4.

5.3 | Law of embryonic resemblance

This law was discussed by Darwin (1859, p. 440), who says that other scientists before him had also observed it. The law states that the embryos of different species are more alike than their respective adults (Hall, 1997; Irie & Kuratani, 2014; Irie, 2017; Richardson & Keuck, 2002). By way of illustration, Darwin quotes von Baer's anecdote (and misattributes it to Agassiz): "I have two small embryos in spirits of wine, whose details I omitted to write down, and I am now completely unable to determine which class they belong to. They might be lizards, small birds, or very young mammals" (von Baer, 1828, p. 221). I have often wondered whether von Baer's failure to distinguish between avian and mammalian embryos might be explained by his myopia (although he claimed that it actually helped him see small objects in fine detail; see Baer and Oppenheimer (1986, p. 222).

5.4 | Biogenetic law

Haeckel's version of recapitulation theory was embodied in his biogenetic law. It states that development is a rapid rerun of evolutionary history, with inheritance and adaptation as the underlying drivers (Haeckel, 1876a, p. 33; Gould, 1977; Olsson et al., 2017; see Section 6.5). Haeckel modestly adds that his law represents "the first law of development, a fundamental biogenetic law which stands or falls together with Darwinian theory itself" (Haeckel, 1872, p. 471).

5.5 | His's growth law

Wilhelm His Sr. proposed that: "the entire development of the organism can be derived from a growth law which originates as a relatively simple function of space and time" (His, 1868, p. 220). The growth law was based on the differential growth of organ-forming regions in the embryo (His, 1868, 1875). His suggested that the growth parameters of organ primordia vary between species, and that this is the mechanism underlying morphological evolution. The growth law is probably the first comprehensive model of morphogenesis and morphological evolution (Richardson & Keuck, 2021). Unfortunately, it was vaguely formulated and failed to gain traction among biologists.

5.6 | Other laws of evo-devo

The study of abnormal embryos led Geoffroy Saint-Hilaire (the elder) to the principle of the balance of organs; he called it a general law of biology (É. Geoffroy Saint-Hilaire, 1822b, p. 244 *et seq*.). His argument was that when an organ develops to an abnormally large size, other organs in that embryo will be smaller. Aristotle had made a similar statement in *De Partibus Animalium* (Ogle, 1911, book II 658a lines 35–36; Russell, 1916, p. 11). Geoffroy Saint-Hilaire (the younger) also investigated this law, citing the example of a malformed fetus in which the kidney on one side was abnormally small, and its adrenal gland abnormally large (I. Geoffroy Saint-Hilaire, 1832, p. 276).

Darwin wrote: "hence, if man goes on selecting, and thus augmenting, any peculiarity, he will almost certainly unconsciously modify other parts of the structure, owing to the mysterious laws of the correlation of growth" (C. Darwin, 1859, pp. 11–12). Haeckel discusses this concept under the name of the law of correlative adaptation: "According to this

important law, actual adaptation not only changes those parts of the organism which are directly affected by its influence, but other parts also not directly affected by it" (Haeckel, 1876b, pp. 241–242). These phenomena might today be explained in terms of compensatory growth and pleiotropy (see Sections 6.12 and 7.7).

Louis Agassiz and Augustus Gould proposed what might be called a law of function in determining developmental sequences. They wrote: "the organs of the body are successively formed in the order of their organic importance, the most essential being always the earliest to appear" (Agassiz et al., 1867, p. 336). Müller gave a persuasive counterargument: "This proposition might be characterised *à priori* as undemonstrable, since it is impossible … to establish a sequence of importance amongst equally indispensable parts. Which is the more important, the lung or the heart?—the liver or the kidney?—the artery or the vein?" (Müller & Dallas, 1869, p. 102).

A size-complexity rule was formulated by Bonner (2004). It states that an evolutionary increase in the body size of animals is accompanied by an increase in complexity, as the animal becomes subfunctionalized into more specialized cell types. Interestingly, something analogous happens in development: as Roux put it, development is "the coming into existence of visible complexity" (Roux, 1895b, p. 4).

Cuvier's principle of correlation referred to a correspondence in the form of different parts, whereby they function co-operatively to meet the trophic needs of the organism (Cuvier, 1826, p. 59; Cuvier, 1829); an organism is, therefore, a functional "ensemble" of parts (Cuvier, 1826, p. 47). As an example, he cites carnivorous land mammals in which a powerful bite needs a powerful masseter muscle, and this, in turn, requires a robust zygomatic arch for its attachment, and so forth (Cuvier, 1826, p. 48).

Serres proposed a law of symmetry (E. R. A. Serres, 1830, p. 20). He noted that the embryonic blood vessels are initially formed in
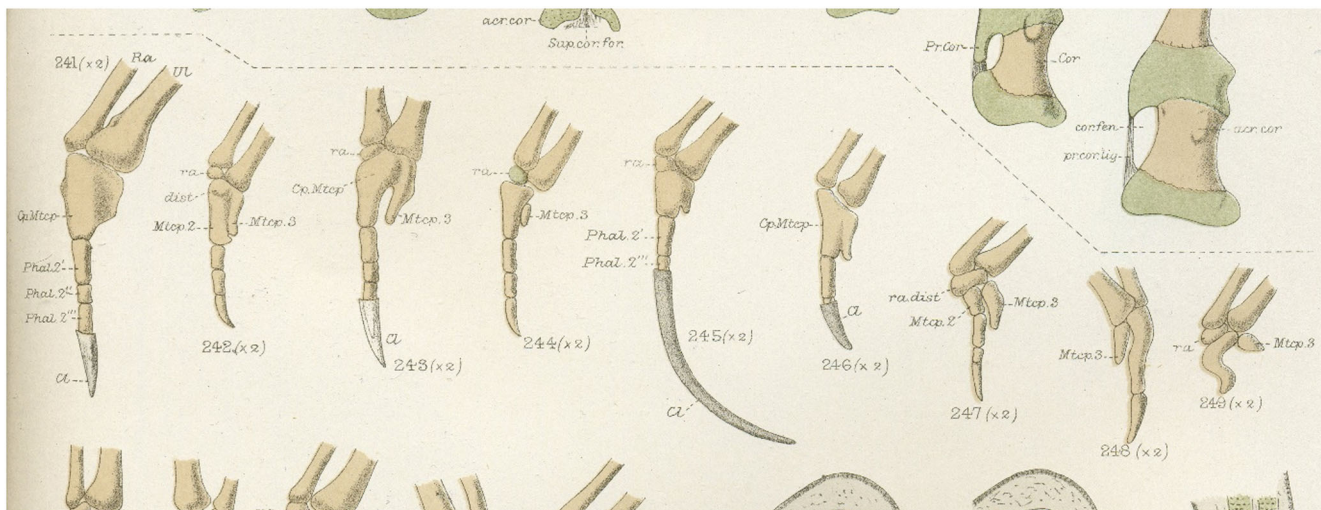

FIGURE 7 Phenotypic variation in the kiwi wing as an example of developmental instability in a rudimentary structure. Adult skeletal preparations. Detail of plate 17 in Parker (1891). *Apteryx bulleri* is shown in figs. 245–249. Note the variation in the size and presence of a claw, and the number of phalanges (which he details on p. 112)

symmetrical pairs. He also suggested that the organism consists of primordial right and left halves that become fused during development (E. R. A. Serres, 1860, pp. 80, 205–220). Russell argued that this law has some similarities with the concrescence theory of Wilhelm His (Russell, 1916, p. 206 n. 2; for concrescence, see Section 7.4). For more recent discussions of symmetry, see Desgrange et al. (2018), Grimes (2019), Lobikin et al. (2012), Monsoro-Burq and Levin (2018), and Smyth (2018).

There are various centripetal and centrifugal laws of development, stating that organs develop in a gradient toward, or away from, the center of the embryo, respectively. Serres argued that embryonic blood vessels develop from the periphery to the center (*loi de formation de la circonférence au centre* (E. R. A. Serres, 1830, p. 20). By contrast, von Baer held the centrifugal view (von Baer, 1828, pp. 158–159, 172), as did Wilhelm His Sr. (His, 1875, pp. 119–129).

Darwin (1859, pp. 131–170) discusses several laws of variation and gives a new explanation for them in terms of natural selection. Among them was the law that structures "developed in an extraordinary degree or manner" tend to be unusually variable (C. Darwin, 1859, p. 150). He got the idea from Waterhouse (1848, p. 452 n. 1; see also P. C. Darwin et al., 2009, p. 150). Darwin noted the variability of rudimentary structures (between individuals). He suggests a mechanism for this law: "their variability seems to be owing to their uselessness, and therefore to natural selection having no power to check deviations in their structure" (C. Darwin, 1859, pp. 149–150; Section 6.14; Figure 7).

6 | THEORIES

Theories are compound scientific statements, consisting of a set of generalizations about a phenomenon. In evolutionary biology, a theory is often a set of models (Lloyd, 1988). However, the theory of natural selection has been characterized as a complex hierarchy of subtheories (Tuomi, 1981). Incidentally, critics of evolution who say that "evolution is only a theory" imply that scientific theories are, by definition, speculative. They are not. In scientific usage, a theory can be proven or unproven (Dawkins, 2009).

6.1 | Preformation and epigenesis

Preformation theory holds that an organized individual is present in the early embryo, or in the gametes. Epigenesis is the theory that the embryo is formed *de novo* out of homogeneous matter (reviewed by Rádl, 1909). These two theories are usually thought to be mutually exclusive. However, Roux argues that there is no dichotomy, because neither theory is correct. He says that development is the production of visible complexity (Roux, 1895b, pp. 4–5). At earlier stages, that complexity may not yet be evident phenotypically but is there in terms of cell specification.

Preformation theory produced an icon of biology: Nicolaas Hartsoeker's illustration of a homunculus or miniature person (Figure 8). Hartsoeker never claimed to have seen such a thing; his drawing was purely hypothetical. He wrote: "if we could see the little animal [homunculus] through the skin that hides it, we would perhaps see it as represented in this figure" (Hartsoeker, 1694, pp.

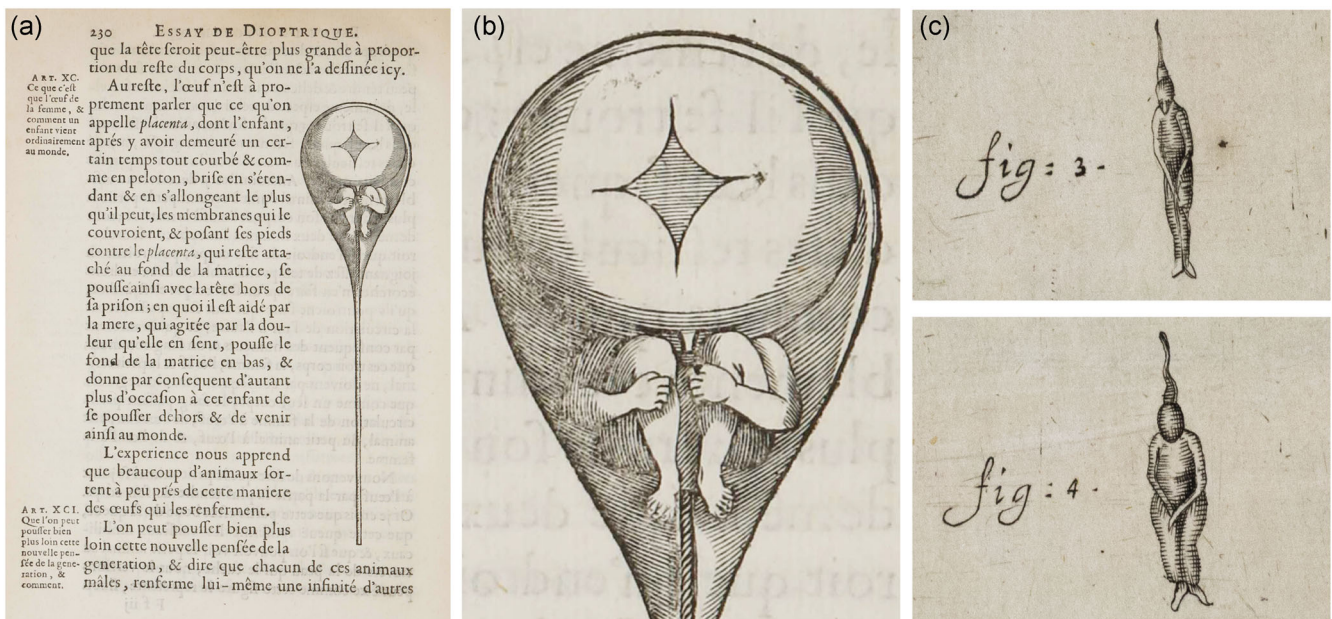**FIGURE 8** Drawings of a homunculus, one hypothetical, one satirical. Hartsoeker's hypothetical homunculus; (a) p. 230; (b) detail. From Hartsoeker (1694). The image was a speculation on what a homunculus *might* look like. (c,d) van Leeuwenhoek's reproductions of what he considered to be the bogus homunculus of Dalenpatius. (a,b) Courtesy Sophia Rare Books, Denmark. (c) Copyright, The Royal Society, London
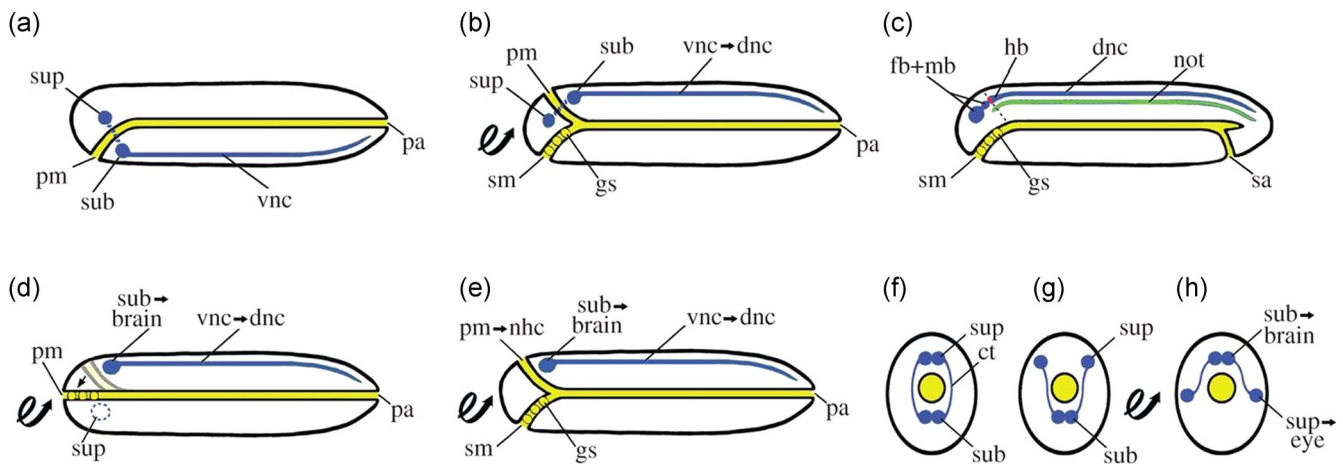
FIGURE 9 The inverted invertebrate theory of vertebrate origins (Holland, 2016, fig. 1). Courtesy Prof. Nicholas Holland. See original for key. (a) Dohrn's annelid-like ancestor; (b) transitional stage; (c) vertebrate stage; (d) Kleinenberg's scenario; (e) Beard's scenario; (f) Minot's scenario

229–230; see also Corcos, 1972; Hill, 1985). van Leeuwenhoek also depicted homunculi (Leeuwenhoek, 1699, figs. between pp. 266 and 267). They were his copies of satirical illustrations by Dalenpatius (1699); van Leeuwenhoek reproduced them only to ridicule them (Corcos, 1972; Hill, 1985; Leeuwenhoek, 1699).

6.2 | Vertebral theory of the skull

This was Oken's theory, and it was based on his observation that some skull bones have the characteristics of vertebrae. In fact, he thought "the entire human is but a vertebra" (Oken, 1807, p. 5; see also Richards, 2002). Oken's epiphany on finding a deer skull is a great story:

> In August 1806 I made a journey across the Harz Mountains with two students ... I slipped down the southern side through the forest - and lo and behold: the most beautiful skull of a female deer, bleached by exposure, lay at my feet. I picked it up, turned it around, looked at it, and that was it. It's a vertebral column! (Oken, 1818, p. 511)

Goethe claimed to have had a similar idea—when he looked at a piece of animal skull in the Jewish cemetery in Venice (Goethe, 2013 p. 126). Richards thinks this was perhaps a faulty recollection on Goethe's part (Richards, 2002). For other discussions of the vertebral skull theory and head segmentation, see Section 8.2, and Mitgutsch and Maienschein (2003) and Richards (2002).

6.3 | The leaf as the fundamental organ of plants

Wolff argued that organ development in animals is comparable to "vegetation"—the development of leaves and floral organs in

flowering plants (Wolff, 1768, 1769; transl. in Wolff, 1812, pp. 68–69). He also suggested that the calyx, petals, and fruit capsule of flowering plants are all modified leaves (Wolff, 1812, pp. 59–60). Two decades later, Goethe suggested something similar (Richards, 2002). "The organ that expanded on the stem as a leaf, assuming a variety of forms, is *the same organ* that now contracts in the calyx, expands again in the petal, contracts in the reproductive apparatus, only to expand finally as the fruit" (Goethe & Miller, 2009, Eng. transl. of Goethe, 1790, pp. 81–82, whence the italics). Goethe does not cite Wolff's earlier work, perhaps because he was unaware of it (Roe, 1979, p. 6, n. 12).

These old theories have recently found some support. Molecular-genetic studies suggest that an ancestral patterning system for vegetative shoots was co-opted during angiosperm evolution in order to pattern flowers (Lohmann et al., 2001). Furthermore, misexpression of MADS-domain transcription factors can transform leaves into floral organs (Honma & Goto, 2001). The putative homologies that are now proposed are between leaves and floral organs; and between vegetative shoots and flowers (Detlef Weigel, personal communication).

6.4 | Germ layer theory

This is the theory that three layers of cells are formed in the vertebrate embryo, that give rise to all tissues and organs (Hertwig, 1906a; Oppenheimer & Hamburger, 1976). Germ layers are often said to have been hinted at by Wolff, although that is a bit of a stretch. Wolff did suggest that the gut was formed by the folding of a membrane (Wolff, 1768, p. 448), but did not notice that the blastoderm was layered (Baer & Oppenheimer, 1986, p. 209). That fact was discovered by Pander who wrote of the blastodermal layers (*Keimhautblätter*; Pander, 1817, p. 22). von Baer thought of the germ layers as primitive organs that develop into definitive organs by folding or rolling-up (von Baer, 1828,

pp. 168–169). Remak gave them the name germ layers (*Keimblätter*; Remak, 1855, pp. 2–3). An interesting development in germ layer theory is the suggestion that the neural crest might constitute a fourth germ layer, which would mean that vertebrates are not triploblastic but quadroblastic (Hall, 2000).

6.5 | Recapitulation theory

This theory holds that development is a re-run (recapitulation) of evolutionary history (Haeckel, 1866a, p. 7; de Beer, 1951; Gould, 1977; Kuratani et al., 2020; Levit et al., 2021; Olsson et al., 2017; Rádl, 1909; Richardson & Keuck, 2002; Russell, 1916). Meckel and Serres were early proponents of recapitulation (Meckel, 1811, p. 3; M. Serres, 1827, p. 82–85; E. R. A. Serres, 1860, p. 401; reviewed by Gould, 1977; Jahn, 2002). One consequence of recapitulation is the supposed parallel between the data of embryology, comparative anatomy, and paleontology, noted by Agassiz (1857, pp. 135–136) and called the three-fold parallelism by Gould (1977).

Müller framed recapitulation in Darwinian terms (F. Müller, 1864, transl. in Müller, 1869) as did Haeckel (1866a, 1866b). Recapitulation was rejected by von Baer (Section 5.2). Recently, Abzhanov (2013, fig. 2) has suggested that there is indeed a parallelism between the evolution and development of at least some characters. A good example is the apparent recapitulation of an ancestral heterocercal stage during caudal fin development in teleosts (reviewed by Gould, 1977, p. 67).

6.6 | Inverted invertebrate theory

This theory of chordate origins has a long history. Geoffroy argued that a crayfish, turned on its back, has the same arrangement of organs as higher vertebrates (Appel, 1987; É. Geoffroy Saint-Hilaire, 1822a, p. 113). He says that, from the animal's point of view, dorsal and ventral surfaces are not defined anatomically, but according to which surface the animal habitually faces toward the sky or the soil (É. Geoffroy Saint-Hilaire, 1822a, p. 107). Semper suggested that the ventral structures of annelids correspond to the dorsal structures of vertebrates. (Semper, 1874, p. 547). And Dohrn wrote: "… I mostly agree with Geoffroy Saint-Hilaire the elder [Étienne] when he refers to insects as vertebrates that walk on their backs — to the extent that his statement expresses the morphological agreement between the dorsum of vertebrates and the ventral structures of arthropods" (Dohrn, 1875, p. iii). More recently, developmental gene expression patterns have provided support for a dorsoventral inversion early in chordate evolution (Figure 9; Arendt & Nübler-Jung, 1994, 1997; see also De Robertis & Sasai, 1996; Holland, 2016).

6.7 | Parablast theory

This theory of evolution and development was proposed by Wilhelm His Sr. (His, 1875, pp. 41–44). He proposed that the embryo has a dual genetic origin, part maternal, part zygotic. The maternal contribution consists of "parablast" cells that migrate from the ovary into the embryo via the yolk. Those cells make a major contribution to the mesoderm. The parablast theory drew much criticism and was difficult to reconcile with new ideas about gastrulation (Richardson & Keuck, 2021). For example, Kölliker's theory of chicken gastrulation, the basis of the modern view, was that the mesoderm was a purely zygotic tissue derived from the primitive streak (Kölliker, 1880, pp. 22–23).

6.8 | Theories of gastrulation in the telolecithal egg

Balfour coined the term telolecithal for eggs that have a massive accumulation of nutrient yolk at one pole (Balfour, 1880, p. 90). These eggs undergo partial or meroblastic cleavage because, he argued, cytokinetic forces are too weak to split the massive yolk (Balfour, 1880, pp. 84–90). Roux suggested an alternative explanation: meroblastic cleavage may allow the embryo to grow unimpeded while the remaining yolk is kept aside as a nutrient reserve (Roux, 1895a, p. 31).

6.9 | Germ plasm theory

Weismann proposed that there is a continuous lineage of living, hereditary substance, the germ plasm, that persists down the generations, giving rise to somatic cells during development (Weismann, 1892). According to this theory, information never flows from somatic cells to the germ plasm; the Lamarckian inheritance of acquired characters is therefore impossible (Weismann, 1893, p. 395). The current view is that, in some species, part of the oocyte cytoplasm, the germ plasm, becomes localized in a few blastomeres that become the primordial germ cells; in other species, the primordial germ cells are specified from somatic cells by induction (Nguyen et al., 2019).

6.10 | Theories of vertebrate limb evo-devo

According to the fin-fold theory, the paired limbs are remnants of ancestral, continuous lateral fin folds (Balfour, 1878, p. 102; Mivart, 1879, p. 480; Thacher, 1877, p. 298). A related theory was based on gene expression in catfish and lamprey embryos (Freitas et al., 2006). It proposes that the potential for fin and limb development evolved first in the midline, and was then co-opted or redeployed to the lateral plate. For reviews of the fin-fold theory, see Diogo (2020) and Don et al. (2013).

Gegenbaur noted similarities in chondrichthyans between the branchial skeleton and the primordial fin skeleton or archipterygium (Section 3.4). He wrote: "By this approach one can imagine the formation of the skeleton of the limbs from a formation similar to the skeleton of the gill arches" (Gegenbaur, 1872, p. 181). This branchial

theory of limb evolution was only a tentative suggestion that Gegenbaur relegated to a footnote (Thacher, 1877, p. 296; see also Diogo, 2020; Don et al., 2013).

Theories of limb-genital developmental homology suggest a link between limb buds and the genital primordia, partly because they are both patterned by posterior hox genes (see Kondo et al., 1997). It has been suggested that in snakes, evolutionary shifts in the position of the cloaca, an inducer of the genital tubercle, recruited new cell populations to genital development (Tschopp et al., 2014, p. 394; see also Sanger et al., 2015). Interestingly, there is evidence of the shared *cis*-regulation of some developmental genes in the limb buds and genital primordia (Infante et al., 2015).

The most anterior digit (MAD) theory states that the transcriptional landscape of digit I and the wrist and ankle constitutes a single, low-hox zone (Woltering & Duboule, 2010). The MAD may have evolved from low-hox tissue which gained *Hoxa13* expression, and reinforced *hoxd13* expression, as a result of evolutionary changes in gene regulation (Woltering & Duboule, 2010). The model was in part an alternative to the frameshift hypothesis (Wagner & Gauthier, 1999). The frameshift is a postulated change in positional values in the lineage leading to birds, that transformed digit "identities" in the avian wing from I-II-III to II-III-IV. A more limited frameshift has been proposed (Stewart et al., 2019) as has a model of digit homology that denies the existence of a frameshift entirely (Bakker et al., 2021, in press).

Sordino and colleagues suggested that the tetrapod digital plate evolved through changes in hox gene regulation, that led to prolonged cell proliferation in the fin bud (Sordino et al., 1995). A new, distal territory, the digital pate, thereby evolved as a neomorph. In line with this scenario, tetrapods show one or more late phases of hox gene expression not seen in the zebrafish.

6.11 | Positional information theory

This is Wolpert's theory of what he called pattern formation—the spatial organization of cell differentiation (Wolpert, 1969). Cells in the embryo, he argued, become specified according to their position, and this specification constitutes positional information. The specification takes place in a positional field, typically 1 mm in extent, which can be modeled as a coordinate system (Wolpert, 1969). One important but overlooked consequence of positional information is non-equivalence: "cells that look alike to the histologist but are in different positions in the body may have different intrinsic characters; they may have positional information, making them non-equivalent" (J. H. Lewis & Wolpert, 1976, p. 479).

Wolpert also used positional information to explain what he called the French flag problem, a model of size-independent pattern regulation (illustrated in Richardson, 2009). One of Wolpert's mechanisms of positional information involved gradients of diffusible morphogens. Evidence for gradients includes the role of *sonic hedgehog* in patterning the anteroposterior axis of the chicken limb (Riddle et al., 1993), and of *bicoid* in patterning the anteroposterior axis in the *Drosophila* egg (Driever & Nusslein-Volhard, 1988).

Wolpert later questioned whether diffusible gradients were actually sufficient to explain pattern formation (Richardson, 2009).

6.12 | Modularity theory

> The concepts of modularity and integration are central to the discourse on evolution and development. Modules are a subset of features of a given organism that are more integrated with each other than they are with the rest of the features of that organism. (Sánchez, 2012, p. 40).

Sánchez argues that integration(a mechanistic coupling between the development of different primordia) is closely related to various laws of the correlation of organs (Section 5.6). One mechanism for integration is pleiotropy, whereby functional disruption of one gene affects more than one organ system. Another is colinearity (Section 7.6), which might lead to integration because it locks the transcriptional activation of multiple patterning genes into a dependent sequence (Duboule, 1994).

The tooth-jaw module (reviewed by A. S. Tucker & Fraser, 2014) is a concept relating to the evolution of dentitional phenotypes under the influence of a set of patterning genes. The expression patterns of these genes constitute a combinatorial odontogenic homeobox code in the dental lamina (A. Tucker & Sharpe, 2004). An important consequence of modularity is that it may facilitate an increase in complexity (Carroll, 2001, p. 1102; see also: Esteve-Altava, 2017; Gilbert et al., 1996; Goswami, 2007; Redies & Puelles, 2001; Rucklin & Donoghue, 2015; Wagner, 1996).

6.13 | Privileged embryo

The idea that midembryonic stages are not open to natural selection has been one of the dominant concepts in evo-devo since 1859. This idea is implicit in the hourglass and phylotypic stage/period/progression theories. Darwin wrote:

> ... I shall attempt to show that the adult differs from its embryo, owing to variations supervening at a not early age, and being inherited at a corresponding age. This process, whilst it leaves the embryo almost unaltered, continually adds, in the course of successive generations, more and more difference to the adult (C. Darwin, 1859, p. 338, my italics).

Wolpert's take on this was that the embryo is evolutionarily privileged because "It need not, for example, seek food or mate, and so is not in direct competition for ecological niches. Its primary function is to develop reliably and this reliability is the main feature on which selection will act" (Wolpert, 1994, p. 83). The privileged embryo concept is also an explanation of the law of embryonic resemblance (Section 5.6).

6.14 | Developmental stability

Developmental stability is a state reached when "the evolved or adaptive developmental trajectory is achieved despite environmental and genetic perturbations during development" (Thornhill & Furlow, 1998, p. 321; see also Beardmore, 1960; Juarez-Carreño et al., 2018; Mather, 1953). A good example of developmental *instability* is the wide individual variation in the skeleton of the vestigial wing of the flightless kiwi (Figure 7).

Another example of instability is fluctuating asymmetry (reviewed by Lens et al., 2002) which consists of "nondirectional deviations from bilateral symmetry" (Palmer & Strobeck, 1986, p. 391), and which may reflect "the inability of individuals to buffer their development against small, random perturbations of cellular processes ('developmental noise')" (Lens et al., 2002, p. 28). Developmental instability may lead to a reduction in robustness and precision. Robustness is the stability of a patterning mechanism in the face of disturbance, and precision is the ability to specify accurately the boundary between different cell types (Kerszberg & Wolpert, 2007).

6.15 | Complexity theory

There are many kinds of complexity. Morphological complexity is a function of the number of different parts (Carroll, 2001, p. 1104). Béclard talked about 'the multitude of varieties or of degrees of complication' of organs (Béclard & Togno, 1830, p. 32). Carpenter noted that evolution and development both involve an increase in complexity or "complication" of form and function (Carpenter, 1839, pp. 170, 357). Many others have commented on the increase in complexity during development (Bonner, 2004; Maynard Smith, 1983, p. 33; M. Serres, 1827, pp. 82–85; Roux, 1895b, p. 4).

6.16 | Constraints

Constraints are factors that limit the scope of evolutionary change, by canalizing that change along certain trajectories (reviewed by Furusawa & Irie, 2020; Richardson & Chipman, 2003). Constraints are implicit in the "why only five fingers?" question of C. J. Tabin (1992). Tabin's answer to that question was that pentadactyly is linked to the existence of five (and only five) expression domains of posterior HoxD genes in the limb bud (Izpisua-Belmonte, Tickle, Dolle, et al., 1991). More recently, Tabin (2009, p. 730) has concluded that "Hox genes don't work like that."

Raff expressed skepticism about constraints (Raff, 1996, pp. 295–303). I share this skepticism, at least when the logic of constraints is as follows: (i) some phenotype (a forbidden morphology) does not exist; (ii) therefore, there must be something (a constraint) preventing it from coming into existence. To me, this scenario is untestable and metaphysical, and depends on an expectation that a hypothetical phenotype *ought* to be able to exist. On the other hand, the concept of constraints is meaningful when it considers known phenotypes. For example, it is reasonable to ask "why only five fingers," given that some fossil species did have more than five (Coates & Clack, 1990).

7 | MECHANISMS

The explanatory element of a theory is usually a mechanism. In developmental biology, a mechanism is a sequence (pathway) of causal events (Sander, 1991, p. 2).

7.1 | Heterochrony

Heterochrony is an evolutionary change in developmental timing. One manifestation of heterochrony is a change in the sequence of developmental events during evolution, a phenomenon known as sequence heterochrony (See Abacus Model, Section 8.7). Heterochrony is the subject of another review in this special issue; see also (Keyte & Smith, 2014; Klingenberg, 1998; Maxwell & Harrison, 2009).

7.2 | Resegmentation

Remak proposed that the somites in the chicken embryo undergo a resegmentation [*neue Gliederung*] as they develop into vertebrae (Remak, 1855, p. 42). As a result, the adult vertebra is derived from the adjacent halves of two neighboring somites. This means that the relationship between somites and adult vertebrae is not segmental but parasegmental. A revised "re-segmentation-shift" model for somites has been proposed by (Ward et al., 2017).

7.3 | Terminal addition

One mechanism of recapitulation is terminal addition, whereby new developmental stages are added to the end of the ancestral sequence (reviewed by Olsson et al., 2017). Müller wrote: "Descendants therefore reach a new goal, either by deviating sooner or later whilst still on the way towards the form of their parents, or by passing along this course without deviation, but then, instead of standing still, advance still farther" (F. D. Müller & Dallas, 1869). The neomorph theory of tetrapod digits (Section 6.10) is an example of terminal addition.

7.4 | Concrescence

Wilhelm His Sr. proposed a developmental mechanism that became known as concrescence (His, 1875, p. 198; Richardson & Keuck, 2021). It involves the fusion of left and right halves of the embryonic

germ ring (in teleosts and chondrichthyans) so that the trunk is formed by something like the zipping-up of the two halves in the midline. This mechanism is reminiscent of Serres' view that the left and right halves of the body have separate developmental origins (Section 5.6). Concrescence was found also in some "invertebrates" (reviewed by Kopsch, 1904).

Rabl described concrescence as "one of the most important developmental theories about the structure of the vertebrate body..." (Rabl, 1897, p. xii); and even Kopsch, who was skeptical about concrescence, argued that: "the epoch–making significance of His's concept consists in the extraordinarily simple way in which the embryonic development of vertebrates and invertebrates can now be explained by the same processes" (Kopsch, 1904, p. 4). Unfortunately, subsequent cell-marking studies were not consistent with concrescence and the theory fell out of favor (Richardson & Keuck, 2021).

7.5 | Clock mechanisms

Several clock mechanisms have been identified in embryos. Evolutionary changes in the parameters of such clocks might, in principle, underlie some examples of phenotypic evolution (Richardson & Oelschlager, 2002; Richardson et al., 2004). The progress zone mechanism was proposed to explain proximodistal patterning in the tetrapod limb. It involved cells counting cell divisions: the more cell divisions, the more distal the positional information of the cell (Summerbell & Lewis, 1975; Summerbell et al., 1973). The cyclical expression of *hairy2* in the limb is consistent with a clock model (Pascoal et al., 2007). The original experiments supporting the progress zone model may also suggest a quite different model, one in which skeletal elements are specified early, then differentiate later (Dudley et al., 2002).

The segmentation clock model of somite development is based on a molecular oscillator that drives the cyclical expression of FGF, Notch, and Wnt genes (Gomez et al., 2008). These findings were interpreted on the basis of the earlier clock-and-wavefront model (Cooke & Zeeman, 1976) and can be used to explain the evolution of serpentiform animals (Gomez et al., 2008; Vonk & Richardson, 2008). The term hox clock describes the sequential activation of hox genes according to their location along the chromosome (Noordermeer et al., 2014). It has been suggested that the hox and segmentation clocks are mechanistically linked, and that both clocks are activated during the phylotypic period (Duboule, 1994). For more on clock models, see Andrade et al. (2005).

7.6 | Other mechanisms involving homeobox genes

One way in which Hox genes may influence pattern formation is through combinatorial codes. Such codes are based on multiple, partially overlapping domains of developmental gene expression, and provide a series of discrete positional values (E. B. Lewis, 1978). Examples include the hox code in the vertebrate limb (Izpisua-Belmonte, Tickle, Doll, et al., 1991, p. 588; C. J. Tabin, 1992), the ontogenic homeobox code in the dental lamina (see: Modularity), and the Dlx code that patterns the pharyngeal apparatus (Figure 5). However, expression domains may be a lot more complex than those implied by a simple code. For example, single-cell sequencing of limb bud mesenchyme shows a mosaic expression pattern of HoxD genes within the same expression domain (Fabre et al., 2018). An interesting suggestion about the mechanism of hox gene function is that each hox cluster functions as a metagene, such that a set of information is encoded as a single unit (Duboule, 1994).

Related to these mechanisms is the concept of spatial colinearity. This is the phenomenon whereby the order of homeotic genes along the chromosome correlates with their spatial expression along the primary body axis: "The wild-type and mutant segmentation patterns are consistent with an anteroposterior gradient in repressor concentration along the [*Drosophila*] embryo and a proximo-distal gradient along the chromosome in the affinities for repressor of each gene's *cis*-regulatory element" (E. B. Lewis, 1978, p. 565).

Another correlation is between the chromosomal location of homeotic genes and the timing of their activation during development—both along the primary body axis, and along the proximodistal and anteroposterior axes of the tetrapod limb (Dollé et al., 1989; Izpisua-Belmonte, Falkenstein, et al., 1991, p. 2280). These phenomena are known as temporal colinearity.

One mechanism of colinearity involves competition among posterior hox genes for a remote enhancer (Kmita et al., 2002). For the history of colinearity, see Gaunt (2015). The Einbahnstraße (one-way street) concept states that "the patterning system [in the limb] progresses from early to late, from anterior to posterior, from proximal to distal" (Duboule, 1994, p. 137).

7.7 | Regulatory evolution

Mutations in the coding sequences of developmental genes may affect not one but several organ systems. For example, mutations in HOXA13 may produce malformations in both the urogenital tract and in the limbs (F. R. Goodman et al., 2000). In such examples, pleiotropy may act as a constraint because it multiplies the potential fitness costs of the mutation. Tissue-specific regulation can break that constraint by limiting the impact of a mutation to a single organ or region. Evidence for tissue-specific regulation comes, for example, from studies of the regulatory changes in *shh* expression that underlie limb loss in snakes (Kvon et al., 2016; Leal & Cohn, 2016).

Some have argued (Prud'homme et al., 2007) that regulatory changes are the dominant mechanism of morphological evolution because they can produce relatively small or spatially localized changes with few or no fitness costs:
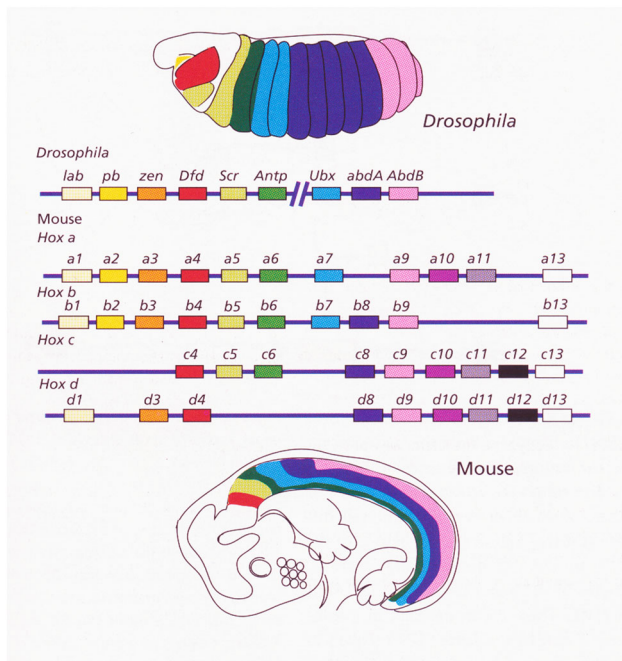
FIGURE 10 Scheme of functional and expression domains of hox genes in the embryos of *Drosophila* and the mouse. From Martinez Arias and Stewart (2002). Courtesy of Professor Alfonso Martinez Arias; permission of Oxford University Press

regulatory evolution: (i) uses available genetic components in the form of preexisting and active transcription factors and [*cis*-regulatory elements] to generate novelty; (ii) minimizes the penalty to overall fitness by introducing discrete changes in gene expression; and (iii) allows interactions to arise among any transcription factor and downstream CRE [*cis*-regulatory element] (Prud'homme et al., 2007, p. 8605).

7.8 | Genetic toolkit

The genetic toolkit for development is the set of genes involved in pattern formation (Carroll et al., 2005; Knoll & Carroll, 1999). Changes in the expression or functioning of these genes can lead to phenotypic change. The toolkit comprises transcription factors and secreted, diffusible peptides and proteins that function as short-range signalling molecules, and other genes.

8 | MODELS

One of the most memorable models in evo-devo shows the conservation of homeobox gene expression and function between *Drosophila* and mammals (Figure 10). Like other models, it forms a link between theories on one hand, and the phenomena that they address on the other.

8.1 | ABC model of flower development

This is a model (Figure 11) of the development of organs from the floral meristem (Bowman et al., 2012). The letters ABC come from: "… the three overlapping fields, named A (APETALA2 gene function, AP2), B (APETALA3 and PISTILLATA, AP3/PI), and C (AGAMOUS, AG). AP2 was proposed to function in whorl 1 to define sepals, and AG in whorl 4 to control carpel identity" (Bowman et al., 2012, p. 4095). The model is based on the study of mutant alleles in the flowering plant *Arabidopsis thaliana* (Bowman et al., 1991; J.L. Bowman et al., 2012; Coen & Meyerowitz, 1991). In these studies, different parts of the flower were found to be affected by mutations in different MADS box genes. See Smyth (2018) for a review of floral patterning.

8.2 | Head segmentation models

The idea that the head and the brain have a segmental (metameric) plan was implicit in Oken's vertebral theory of the skull (Section 6.2). There have been many efforts to understand head and brain segmentation, including the *Cranioscopie* of Carus (-Figure 12). The prosomeric model of the brain (Section 8.9) envisages distinct segmental domains of gene expression and morphology common to all vertebrates (Figure 13).

The branchial region in vertebrates embryos has a segmental organization (Kuratani, 2005) as do the rhombomeres (Depew et al., 2002; Kiecker & Lumsden, 2005). The segmentation of the pharyngeal arches is known as branchiomery (Graham, 2001). The head cavities of elasmobranch embryos, and the somitomeres, have been described as pseudo-segmental (reviewed by Kuratani, 2005; Mitgutsch & Maienschein, 2003).

8.3 | Developmental funnel

von Baer argued that the embryos of all animals start their development as a hollow vesicle that is identical in all species. From this identical starting point, the embryos of different species becomes more divergent in phenotype as they develop (von Baer, 1828, pp. 223–224). This early stage or vesicle was characterized by von Baer as a primitive form. Haeckel later equated this vesicle with his "blastula" (Haeckel, 1877, p. 153). The pattern of divergence in animal development described by Baer (early similarity followed by progressive divergence) has been called the developmental funnel (Abzhanov, 2013; Figure 14c). A funnel-like pattern has been described in the development of the cichlid *Haplochromis piceatus* (Figure 2, here; Jong et al., 2009). In that study, we were looking at polymorphisms in developmental sequences and found an invariant early developmental sequence, with a progressive increase in polymorphisms.
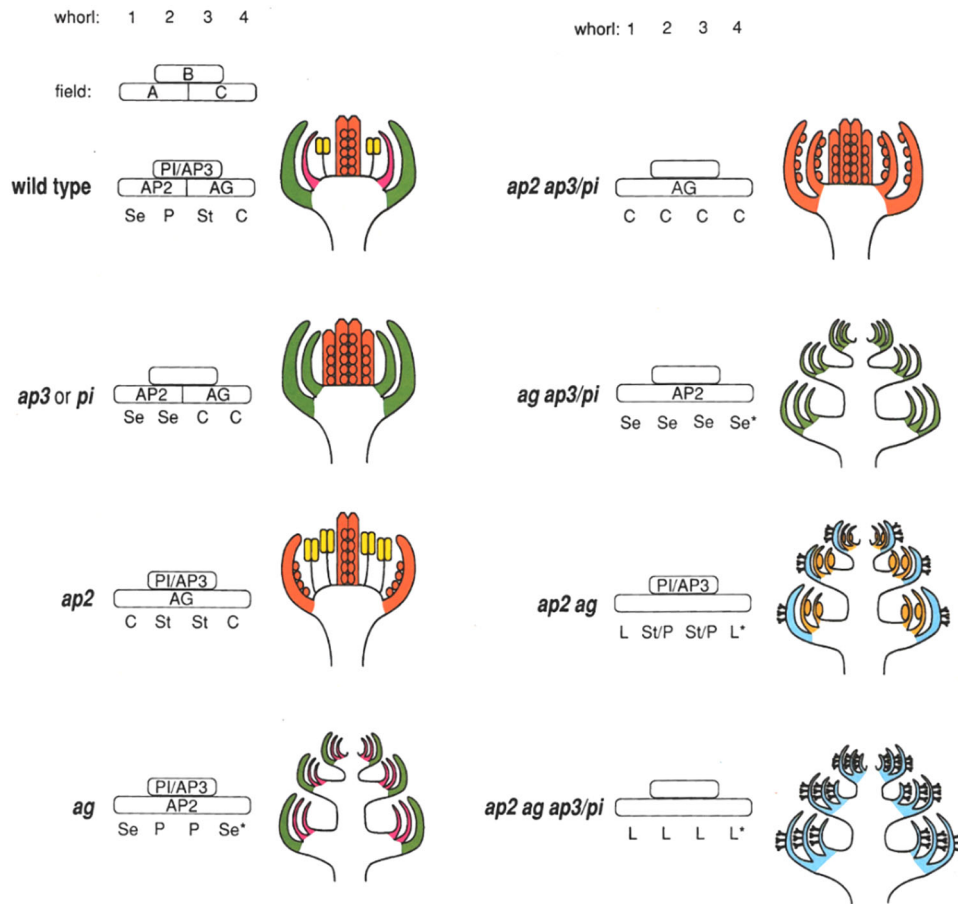
FIGURE 11 The ABC model of floral development. From fig. 9 in Bowman et al. (1991). Courtesy of Professor Elliot Meyerowitz, and with permission of The Company of Biologists, Ltd. See text Section 8.1 for details

FIGURE 12 Carus's segmented skull hypothesis. Carus, 1841. Plate I detail (fig. III) in Carus (1841). From the library of the Royal College of Surgeons of England, with permission

8.4 | Developmental hourglass or phylotypic egg-timer

This is a model of phenotypic divergence between species during development (Figure 14a; Raff, 1996, p. 208–210; Duboule, 1994; Irie, 2017). The hourglass pattern was described by His, and by Keibel, in the vertebrates (His, 1875, pp. 190–191; Keibel, 1906, p. 172); and by Müller in arthropods:

> ... it sometimes happens that the greatest similarity occurs in the middle of the development. The most striking example of this is furnished by the Cirripedia and Rhizocephala, whether we compare the two orders or the members of each with one another; from a segmentation [cleavage] quite different in its course ... proceed different forms of Nauplius, these become converted into exceedingly similar pupae, and from the pupae again proceed sexually mature animals, differing from each other *toto coelo*. (F. D. Müller & Dallas, 1869, p. 105).
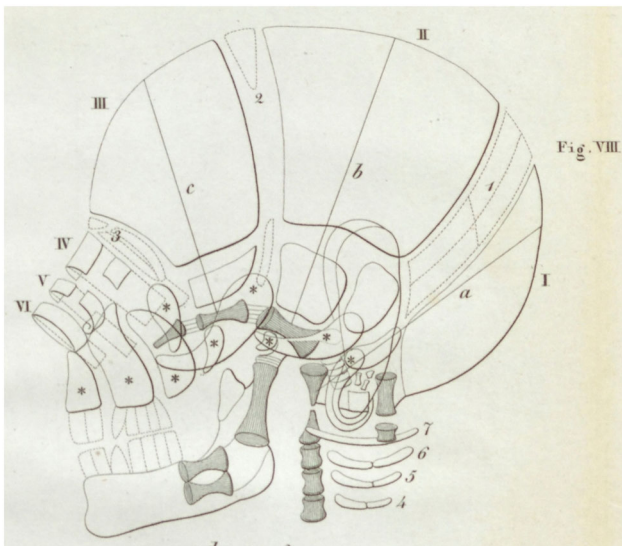
FIGURE 13   The updated prosomeric model of brain development (Puelles, 2018, fig. 8; Nieuwenhuys and Puelles (2016, fig. 9). Courtesy of Professors Luis Puelles and Rudolf Nieuwenhuys

FIGURE 14   The developmental hourglass or phylotypic egg-timer. The horizontal gray rectangle represents the phylotypic period. (a) Fig. 3 in Duboule (1994). Transcription of hox genes is sequentially activated over an extended period, the phylotypic progression, in the middle of the hourglass. Image courtesy Prof. Denis Duboule, and with permission from the Company of Biologists, Ltd. (b) Model suggesting that the earliest stages of development are part of the maternal phenotype (red) not that of the embryo (blue). Original idea in Abzhanov (2013). (c) Purely hypothetical developmental funnel which ignores early divergences belonging to the maternal phenotype. In this model, the phylotypic period already shows some phenotypic divergence, consistent with (Richardson, 1995, 1999; Richardson, Allen, et al., 1998; Richardson et al., 1997)

The hourglass is supposed to reflect the stage-specific action of natural selection. It is related conceptually to the law of embryonic resemblance (Section 5.3) and the privileged embryo theory (Section 6.13). In the middle of the hourglass sits the phylotypic period (Section 3.2). Interestingly, Abzhanov (2013) has suggested that stages of development before the maternal-zygotic transition are not relevant to the hourglass model because they are part of the maternal phenotype (Figure 14b).

8.5 | Inverted hourglass

Some animals show a pattern of development opposite to the hourglass model:

> In other instances, the courses which lead from a similar starting-point to a similar goal, separate widely in the middle of the development, as in the Prawns
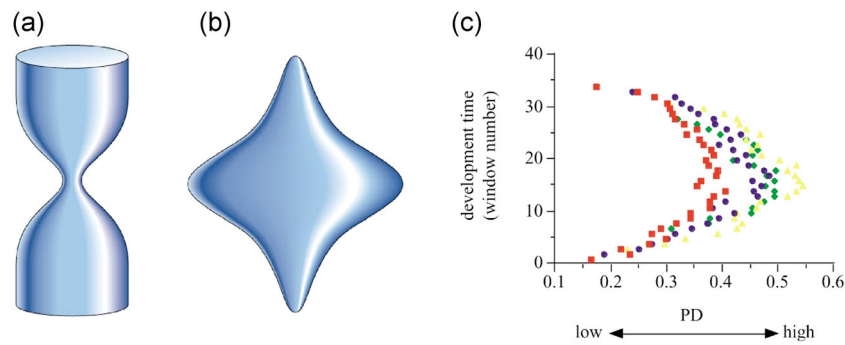
FIGURE 15   The inverted hourglass or spinning top. (a) The developmental hourglass; (b) the inverted (inverse) hourglass or spinning top, based on (c), a quantitative analysis of phenotypic divergence (PD) based on sequence variation in vertebrates, plotted against developmental time (Bininda-Emonds et al., 2003, fig. 2C). Sequence variation is maximal in mid-embryonic stages

with Nauplius [larvae] already described (F. D. Müller & Dallas, 1869, p. 105).

Our quantitative analysis of developmental sequences showed that timing shifts reached a maximum in midembryonic stages. We called this pattern the inverted hourglass or spinning top (Figure 15). I invoked an inverted hourglass pattern to suggest that midembryonic stages are likely to be accessible to natural selection because these are stages when pattern formation in underway in numerous developmental fields (Richardson, 1999). An inverted (inverse) hourglass has also been used to summarize interphylum transcriptional divergence: "Comparing a set of species of distinct phyla, the mid-developmental transition shows the most gene expression changes" (Yanai, 2018; Levin et al., 2016, fig. 4; see also Hejnol & Dunn, 2016 for a critique of that model).

8.6 | Transcriptional (phylotranscriptomic) hourglass

As the body plan is largely laid down during the middle phases of embryo development in plants and animals, then it is perhaps not surprising this stage represents the narrow waist of the hourglass where the gene regulatory networks are the oldest and most robust and integrated, limiting species diversity and constraining morphological space (Cridge et al., 2016, p. 833).

Several recent transcriptomic analyses support the developmental hourglass model. They show that conserved developmental genes are relatively highly expressed during mid-embryonic stages compared to earlier and later stages. This pattern (the phylotranscriptomic hourglass) has been confirmed in several plant and animal taxa (Cridge et al., 2016; Drost et al., 2015; Marlétaz et al., 2018; Quint et al., 2012; Tena et al., 2014; Yanai, 2018; reviewed by Richardson, 2012b). In plants, a transcriptional hourglass is repeated in post-

embryonic stages (Drost et al., 2016). The existence of transcriptomic hourglass patterns in both animals and plants suggests that those patterns evolved convergently (Quint et al., 2012).

8.7 | Abacus model

This model (Figure 1) compares developmental sequences and shows how they can change during evolution—a phenomenon known as sequence heterochrony. The first incarnation of the abacus model (Richardson, 1995) aimed to show how heterochrony makes it impossible to define a vertebrate phylotypic stage, but possible to define a more extended phylotypic period (Richardson, 2012b). The abacus model is universal in the sense that developmental sequences from any species can be compared, provided the characters are homologous.

8.8 | Prosomeric model of the vertebrate brain

The rhombencephalon (hindbrain) is an obviously segmental region of the head: "Compartition, together with segmentally reiterative neuronal architecture and the nested expression of *Hox* genes, indicates that the hindbrain has a truly metameric organization" (Kiecker & Lumsden, 2005, p. 553). Gene expression, fate mapping, and morphological analysis have led to the updated prosomeric model of brain organization (Nieuwenhuys & Puelles, 2016; Puelles, 2018; Rubenstein et al., 1994). This model (Figure 13) sees the brain as divided into longitudinal zones and a number of transverse segments or neuromeres in all vertebrates.

8.9 | Maternal-zygotic transition

This transition is a period (Figure 14b) during which maternal transcription is downregulated, maternal proteins are degraded, and development comes under the control of the zygotic genome, when

zygotic transcription is activated by maternal transcription factors (reviewed by Rengaraj et al., 2020). In the zebrafish, this takes place gradually, beginning at cleavage stages, although maternal transcripts continue to exert a significant influence on gastrulation events (Solnica-Krezel, 2020). In the chicken, and at least some mammals, there are successive waves of zygotic transcriptional activation beginning at cleavage (Rengaraj et al., 2020).

9 | ANALYSIS

In this section, I pick up on some of the key points that emerged in this review article.

9.1 | Scientific statements in evo-devo

Some of the scientific statements used in evo-devo are difficult to classify according to the various schemes proposed by philosophers of biology (Section 1.2). What, for example, is a developmental stage? It is not a theory, model, or law. It is perhaps one of Mayr's "concepts." I suspect that most biologists do not worry too much about such questions, and take instead a pragmatic view: laws, theories, models, and concepts are tools for solving scientific problems (Azzouni, 2014).

9.2 | Thinking in archetypes

Why are evo-devo researchers so inordinately fond of archetypes such as the body plan and phylotypic stage? One explanation may lie in the sheer multidimensional complexity of evo-devo questions. Such questions address the three spatial dimensions of the embryo, the expression patterns and functions of multiple developmental genes, how these parameters change over developmental time, and how they differ between species. Given this complexity, archetypes such as the zootype and the proto-gnathostome pharyngeal skeleton are helpful heuristic devices that provide a simplified view of the data. The danger, of course, is that one loses sight of the actual data completely.

Another reason why we think in archetypes is that it comes naturally to us. Cognitive psychology tells us that humans and some other animals show perceptual categorization. This is the tendency to partition the environment into smaller sets of objects sharing certain features. These categories may be structured around "natural prototypes" (Rosch, 1973).

9.3 | The problem with embryonic resemblance

There have always been widely divergent opinions on the extent of embryonic resemblance among vertebrates. Advocates of strong embryonic resemblance include Chambers (Anon, 1844, p. 212), Darwin (1859, p. 440), and Haeckel (1879, p.18). Scientists who have

emphasized significant differences among vertebrate embryos include Vogt (1858, p. 169, n. 1.) Wilhelm His Sr. (His, 1875, p. 201; Sedgwick, 1894, p. 36) and Richardson et al. (1997).

How can scientists hold such divergent views? My answer is that we have often done little more than eyeball a group of embryos, then make a subjective judgment about their degree of similarity or dissimilarity. This is akin to a phenetic comparison—the grouping of organisms based on their overall similarity (Cain & Harrison, 1958, 1960; Rossello-Mora & Amann, 2001; Sneath & Sokal, 1962; Vernon, 1988). This kind of comparison is just as problematic as the discredited "feature comparison" techniques used in some forensic sciences (Holdren & Lander, 2016). The way to address embryonic resemblance more scientifically may be to use character-based or quantitative analyses.

9.4 | A new light on von Baer and the hourglass

A common narrative is that von Baer's first three laws were incredibly interesting and important—but false. And they were false because von Baer thought that all animals had a common early stage, a vesicle, from which they diverged as they developed. That pattern of divergence looks like a funnel, and not like our current hourglass model.

However, Abzhanov (2013) notes that the earliest stages, before the maternal-zygotic transition, are actually part of the maternal phenotype (Figure 14). If so, then the earliest stages are no more divergent than the corresponding zygote stripped of its maternal characters. If this is the case, then the true pattern of phenotypic divergence might indeed be more like a funnel than an hourglass (Figure 14c). This might be an interesting area of inquiry in the future.

9.5 | Laws

> ... Zoology [has] its dogmas, which are as universally acknowledged, as they are disregarded in practice (F. D. Müller & Dallas, 1869, pp. 105–106).

Van Valen argued that it is valid to propose laws of evolutionary biology; he even proposed one of his own, relating to extinctions (Van Valen, 1973). Rensch also proposed evolutionary laws—quite a large number of them. He admitted that most of his laws of evolution were valid only in certain lineages (Rensch, 1960, p. 103), and I think that this caveat applies also to the laws of evo-devo I have covered in this review.

Van Valen and Rensch were both confident in the validity of their laws. Today, however, a common view is that biological systems cannot be described using laws because: (i) they are too complex; (ii) they show emergent properties; and (iii) they are subject to evolutionary change. This last fact means that any laws proposed by biologists can potentially be broken by natural selection (Beatty, 1995, pp. 51–52, p. 61).

In any case, biologists no longer need to feel that they have to formulate laws to prove that biology is proper science. The truth is, science is not defined by its laws. Nor is it defined by its formulation of falsifiable hypotheses or its use of a hypothetico-deductive method. In fact, the most compelling recent definition of science is that science is highly systematic when compared to other bodies of knowledge on the same subject (Hoyningen-Huene, 2013). This is the "systematicity" definition of science. If we accept this definition, we can finally lay "physics envy" to rest.

9.6 | Universality

In the physical sciences, laws are universal when they are assumed to apply everywhere in time and space (Smart, 1963, p. 53; Lloyd, 1988, p. 5). This is presumably what Newton had in mind when he wrote: "the Proposition will hold good of all bodies universally. Q.E.D." (Newton, 1729, p. 294).

In biology, the word universal does not have that meaning at all. In molecular biology, for example, a universal statement can be one that applies to all molecules of a particular class (Mannige, 2017). In evolutionary biology, the word universal has a phylogenetic meaning, as in the universal (standard) genetic code, supposedly used by all organisms. But there is a problem here: the universal genetic code is not universal: codon reassignments have evolved in several lineages (Table 2 in Sengupta & Higgs, 2015, table 2; Koonin & Novozhilov, 2017, fig. 1; Osawa et al., 1990).

Lewis Wolpert's positional information theory was intended to be universal in its application to all species (Wolpert, 1969, p. 44). The word "universal" appears 22 times in Wolpert's foundational paper (Wolpert, 1969). I remember that when I was a PhD student with Wolpert, I wrote a manuscript for submission to *Nature*, entitled "A universal positional field in the feathers of birds." It was based on transplant experiments that Amata Hornbruch and I had done, and which suggested that quail neural crest cells could reproduce a quail-like pigment pattern in chicken feathers. Unfortunately, closer inspection showed that this was not the case (Richardson et al., 1989, 1991). Lewis, therefore, abandoned the idea of submitting the manuscript to *Nature*—much to my disappointment at the time.

The idea of universal developmental mechanisms is attractive because it provides common ground for scientists studying different model animals; it also gives legitimacy to the use of animal models in studying human disorders (Richardson et al., 2001). But the reality is that organisms evolve, and so *nothing* in biology is universal—except those things which constitute your definition of "life" (e.g., cellularity, DNA, RNA, proteins, accessibility to natural selection, metabolism, etc.).

9.7 | The future of evo-devo

In the future, a major challenge will be to develop new evo-devo models and theories to accommodate the wealth of new data from high-throughput technologies. One example of these technologies is single-cell sequencing, which is beginning to be applied to evo-devo (Fabre et al., 2018; Post et al., 2020). To cope with massive datasets, evo-devo researchers are using in silico analyses, such as those that underlie the "transcriptomic hourglass" model (Section 8.6). Whether the old archetypes and models of evo-devo will survive in this new era of "big data" remains to be seen.

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