Deep Homology?

Uncanny Similarities of Humans and Flies Uncovered by Evo-Devo

Humans and fruit flies look nothing alike, yet their genetic circuits are remarkably similar. Here, Lewis I. Held, Jr. compares the genetics and development of the two to review the evidence for deep homology, the biggest discovery from the emerging field of evolutionary developmental biology (evo-devo). Remnants of the operating system of our hypothetical common ancestor 600 million years ago are compared in chapters arranged by region of the body, from the nervous system, limbs, and heart, to vision, hearing, and smell. Concept maps provide a clear understanding of the complex subjects addressed, while encyclopedic tables offer comprehensive inventories of genetic information. Written in an engaging style with a reference section listing thousands of crucial publications, this is a vital resource for scientific researchers, as well as for graduate and undergraduate students.

Lewis I. Held, Jr. is a fly geneticist who has taught human embryology for 30 years. He studied molecular biology at MIT (BS 1973), investigated bristle patterning under John Gerhart at UC Berkeley (PhD 1977), and conducted postdoctoral research with Peter Bryant and Howard Schneiderman at UC Irvine (1977–1986). *Deep Homology?* is his fifth scholarly monograph, following *Models for Embryonic Periodicity* (Karger 1992), *Imaginal Discs* (Cambridge University Press 2002), *Quirks of Human Anatomy* (Cambridge University Press 2009), and *How the Snake Lost Its Legs* (Cambridge University Press 2014).

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Uncanny Similarities of Humans and Flies Uncovered by Evo-Devo

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Preface

Given the immensity of the Universe, it is hard to imagine that Earth is the only planet teeming with living things. Some day, therefore, we will likely encounter extraterrestrial beings, provided that our own species doesn't extinguish itself first.

Fortunately, our yearning for an encounter with alien life can be sated here and now by the expedient equivalent of *Gulliver's Travels*. Geneticists have been exploring a sort of Lilliput for over 100 years, but their exploits are not well known.

Ever since Thomas Hunt Morgan started experimenting with the fruit fly *Drosophila melanogaster*, *c.* 1908 [474,1180], this tiny insect has beguiled those of us who have followed in his footsteps. Its anatomy (exoskeleton, six legs, compound eyes) looks "alien" to our own (endoskeleton, two legs, simple eyes) [363], but its behaviors are eerily humanoid. Three examples were featured in Jonathan Weiner's lyrical biography of Seymour Benzer, *Time, Love, Memory* [2404] – namely, its sleep–wake cycle, its courtship rituals, and its ability to learn.

Still, the greatest similarities between humans and flies are completely invisible to the naked eye, or even to a high-powered microscope. They are genetic. The ways in which the human and fly genomes encode anatomy are amazingly alike. What we've learned about those codes is impressive, but it is even more fascinating to contemplate what we have yet to learn in this regard. This book surveys both the Known and the Unknown and seeks to trace a boundary between them.

The terrain charted here lies in a fertile hybrid zone between the realms of evolutionary and developmental biology – an area that has come to be called "evo-devo" [1251]. Evo-devo attained notoriety in 1988 with the discovery that vertebrates share clusters of *Hox* genes with flies [128,2021]. Additional "toolkit" genes [357,2435] have since been found that are likewise involved in constructing anatomies across the animal kingdom [482,494,678,1927,2310]. The history of these epiphanies is recounted in the Introduction, *Hox* complexes are analyzed in Chapter 1, and the remaining chapters cover a variety of organs or organ systems where vertebrates and flies share deep similarities.

The time seems right for a synthesis of this kind. Evo-devo is entering its Golden Age [1505,1522] and is ripening nicely: 2017 marks the fortieth anniversary of Gould's *Ontogeny and Phylogeny* [785] and the twentieth anniversary of the term "deep homology" [2086].

To the extent that biology textbooks mention evo-devo at all, they usually include diagrams of *Hox* homologies, but those oversimplified renditions omit many of

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the intriguing nuances [551]. Indeed, the entire field of evo-devo is brimming with Gordian Knots that beckon the next crop of would-be Alexanders. Some of those brain teasers are offered here as "puzzle boxes" with enough citations (numbers in square brackets) to allow novices to conduct their own customized investigations. Those neo-evo-devo devotees are the primary audience for whom this book was written, though other fans of the field might enjoy the narrative also. The corpus of text, puzzles, and diagrams (Chapters 1–7) is just long enough to serve as a staging area for launching readers into the ocean of literature (References section). In this way I am trying to "pay forward" the priceless gift that Martin Gardner gave me and the other budding child-scientists of my generation with his marvelous "Mathematical Games" column for *Scientific American*.

The citations that infest the text are admittedly annoying, but all of them are pertinent, and some of them are gems. For example, there is one reference buried in the "neuron identity" row of Table 2.1 with the lackluster title "Opposing intrinsic temporal gradients guide neural stem cell production of varied neuronal fates" [1336]. It solves a riddle posed some 50 years earlier by the British theoretician John Maynard Smith about how cells tell time [1452]. The dueling clock genes that were identified were given the cute names *Imp* and *Syp*. The deep thinker who would be most amused by such deep homologies is Aristotle, who was fascinated by the natural world but bewildered by its inner workings.

Evo-devo terms are deftly explained in Hall and Olson's *Keywords and Concepts in Evolutionary Developmental Biology* [848], and most of the other technical terms used here should be defined in any college genetics textbook. Nevertheless, readers may still find the jargon daunting unless they are at least acquainted with the basic tenets of evo-devo. Those principles are accessible in the popular books by Sean Carroll (*Endless Forms Most Beautiful* [327] and *From DNA to Diversity* [330]), and the more advanced treatises by John Gerhart and Marc Kirschner (*Cells, Embryos, and Evolution* [742] and *The Plausibility of Life* [1164]).

How can a book that focuses on only two species offer any wider insights? Because this comparison is only a means to an end. The rationale is to use whatever clues are unearthed by the comparison to propel broader surveys of animal phyla. *Homo sapiens* and *Drosophila melanogaster* occupy such distant twigs on the tree of animal life that any similarities must indicate either (1) enduring conservation, which could allow us to deduce aspects of our last common ancestor [90,953], or (2) convergent evolution, which could allow us to discern constraints on the range of available outcomes [633,2360]. In either case this "compare and contrast" exercise should prove worthwhile.

In 1997 an exercise of exactly this sort was conducted for vertebrate versus arthropod limbs by Neil Shubin, Cliff Tabin, and Sean Carroll [2086]. They showed that vertebrate and arthropod limbs are built by similar algorithms, despite manifesting starkly different anatomies, and they argued that the simplest explanation for the genetic similarities was conservation rather than convergence. These authors coined the term "deep homology" to denote this phenomenon, and they illustrated the meaning of this term by a familiar example of wing evolution (boldface added):

> **Determination of whether two structures are homologous depends on the hierarchical level at which they are compared.** For example, bird wings and bat wings are analogous as wings, having evolved independently for flight in each lineage. However, at a deeper hierarchical level that includes all tetrapods, they are homologous as forelimbs, being derived from a corresponding appendage of a common ancestor. Similarly, we suggest that whereas vertebrate and insect wings are analogous as appendages, the genetic mechanisms that pattern them may be homologous at a level including most protostomes and deuterostomes. Furthermore, **we propose that the regulatory systems that pattern extant arthropod and vertebrate appendages patterned an ancestral outgrowth** and that these circuits were later modified during the evolution of different types of animal appendages. Animal limbs would be, in a sense, developmental "paralogues" of one another; modification and redeployment of this ancient genetic system in different contexts produced the variety of appendages seen in Recent and fossil animals. [2086]

In 2009 those same authors reprised their theme in an essay entitled "Deep homology and the origins of evolutionary novelty" [2087]. In that paper they argued that vertebrate and insect eyes are also deeply homologous. They admitted surprise at the accumulating evidence consistent with their thesis, and they offered a firmer definition of the deep homology concept (boldface added):

> One of the most important, and **entirely unanticipated**, insights of the past 15 years was the recognition of an ancient similarity of patterning mechanisms in diverse organisms, often among structures not thought to be homologous on morphological or phylogenetic grounds . . . Homology, as classically defined, refers to a historical continuity in which morphological features in related species are similar in pattern or form because they evolved from a corresponding structure in a common ancestor. **Deep homology also implies a historical continuity, but in this case the continuity may not be so evident in particular morphologies; it lies in the complex regulatory circuitry inherited from a common ancestor.** [2087]

The present book grew from the seeds sown by those two seminal papers. Although the goal here is to compare humans and fruit flies, experimentation on humans is unethical, so virtually all of the data assigned to the human side of the ledger come from mice instead; mice are close enough to us genetically to serve as a proxy. Moreover, many comparisons will involve broader taxonomic levels (e.g., mammal–insect, vertebrate–arthropod, deuterostome–protostome) as we trace the similarities back through geologic time, and some contrasts will be lopsided (e.g., vertebrate–fly) due to the nature of the relevant data available in the literature.

The history of science is punctuated with epiphanies where two things which had been thought to be qualitatively different turned out to be fundamentally alike [316]. Thus, Newton compared the moon to a falling apple, Faraday united electricity with magnetism, and Einstein wedded space with time and matter with energy [261]. Now, thanks to decades of work by legions of evo-devotees, we realize that *H. sapiens* and *D. melanogaster* are not as different as we'd imagined. Rather, humans and fruit flies seem more like twins separated at birth half a billion years ago [927].

Evo-devo thus finds itself at the same sort of threshold as the one crossed by Galileo ~400 years ago when he gazed at Jupiter through a state-of-the-art, but still rather crude, telescope. There he saw what he first thought were nearby stars but soon realized were orbiting moons [2424]. That discovery astounded him and revolutionized astronomy. Even so, his telescope could not resolve Saturn's rings, which he mistook for lateral bulges [154]. Evo-devo is giving us a first glimpse of our metazoan forebears, and we are bound to draw some wrong conclusions about them (until we uncover their fossil remains), but even ghostly images are arguably better than none at all [2035]!

Discerning whether a given similarity is due to common descent (homology) or to independent evolution (convergence or parallelism) can be quite tricky [847,1350,2033], and partisans have clashed over the origins of the brain [2198], the eye [1629,1666,1787], and other organs [601]. One especially instructive debate concerns whether the chordate notochord is homologous to the annelid axochord [274].

Guidance on the homology–convergence controversy can be found in Günter Wagner's *Homology, Genes, and Evolutionary Innovation* [2363] and George McGhee's *Convergent Evolution* [1459], and in the practical checklists devised by Ehab Abouheif *et al.* [10] and Cliff Tabin *et al.* [2221]. Readers attuned to the philosophical side of science should relish the Talmudic literature that has grown up around this topic, including incisive treatises by Antonio Fontdevila [653], Stephen Jay Gould [788], Brian Hall [846], Jason Hodin [953], Gerd Müller [1572], David Stern [2184], Pat Wilmer [2439], Greg Wray and Ehab Abouheif [9,2463], and others [128,753,1667,2198,2366].

By stressing similarities over differences, this book runs the risk of being misinterpreted as endorsing the notion of deep homology as a default assumption. For that reason a question mark was included in the title to serve as a disclaimer. Even for those features where homology is implied by a preponderance of available evidence, any surmise to that effect will be subjective and must remain tentative. Any author foolish enough to enter this tangled swamp – and I do so reluctantly – must heed the warning signs. Seth Blair, for example, has pointed out the risks of unintentional "cherry-picking" (boldface added):

> Finding similarities is something of a self-fulfilling prophecy. More detailed, mechanistic information from more taxa could certainly help in this debate, especially information based on unbiased screens instead of candidate genes. If mechanisms vary greatly, however, **it will still come down to an argument about plausibility, and one scientist's homolog is often another's convergence** . . . Can some level of mechanistic similarity ever rule out convergence, or is that wishful thinking? The identity of ancestral organisms has been the subject of intense debate since the 1800s and it is interesting to think about what kind of data it would take to settle that debate. On the other hand, what fun would that be? [215]

So why even try, given all the uncertainties, ambiguities, and complications in attempting to envision the so-called "urbilaterian" ancestor [484,486,601] of humans, flies, and other bilaterally symmetric animals [90,1158,2035]? The saving grace of this otherwise quixotic quest is that it does not aspire to reach any lasting conclusions, but merely to stimulate further research. Dan Nilsson has offered wise

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advice on how to proceed with regard to the study of eye evolution in particular (boldface added):

> For understanding eye evolution we are left with a number of cues from morphology and ontogenetic paths, from developmental genes and their interactions, and from physiology and effector genes. **All of these cues can be deceptive, and none is principally more important than any other.** Hypotheses on eye evolution will also have to agree with phylogenetic trees, datings of molecular divergence, and the fossil record. The best we can do is to aim for a synthesis. [1629]

This undertaking may also prove worthwhile for a more practical reason: the fly genome is a gold mine of genes whose homologs cause cancer [937,1948,2361], aging [1616,1775,1797], neurodegeneration [368,672,1466,2316], and a host of other human maladies [1719,2380,2392,2486], so some of the similarities revealed here could have broad clinical applications [204,1378,1775,1935,2444]. Indeed, ~77% of human disease-causing genes have a fly homolog [187,1889,1905]. The relevance of fly circuitry to human pathology [526,1935] even extends to neurological [1618,1679] and psychiatric [2321,2494] disorders, and detailed assays have recently been published for how to measure the behavioral parameters [1525,2312].

Utility is surely a virtue, but so is beauty, and evo-devo has dramatic and aesthetic dimensions that merit our attention as well. For example, few phyla have ever ventured onto land; two that have done so are chordates and arthropods, and both taxa have even taken to the skies [759]. We humans are rightly proud of our history, but flies can boast a heroic odyssey too. The impetus for this book is thus partly Homeric: to extol the fly's genomic exploits vis-à-vis our own. Tom Brody's *Interactive Fly* website is a terrific resource for delving into the comparative genetics of flies versus vertebrates, including the human diseases that are currently being investigated using flies as a model system. Andreas Schmidt-Rhaesa's *The Evolution of Organ Systems* [2003] treats some of the topics covered here in a more encyclopedic way in terms of animal phylogeny.

For the sake of terminological consistency, the nomenclature of fly genetics is followed. Protein names are set in roman type and capitalized (e.g., Spalt), while gene names are italicized (e.g., *spalt*) and capitalized only if the first mutation described was dominant. Abbreviations: ATP (adenosine triphosphate), bp (base pair), cAMP (cyclic adenosine monophosphate), kb (kilobases), LOF (loss of function), GOF (gain of function), mb (megabases), and MY (millions of years). Fly/vertebrate homologs are denoted by a slash mark (e.g., *eyeless*/*Pax6*), whereas the order is reversed (vertebrate/fly) in Figures 6.1 and 6.2 to conform with schematics.

Ancillary material has been exiled to tables and figure legends so as not to disrupt the flow of the narrative. The deeply conserved role of *doublesex*/*Dmrt1* in sex determination [167,1324,1822,2420,2538] is omitted entirely because I have covered this subject in a previous book [925] (cf. gonad and germ cell evolution [611,612,613]). Other topics have been excluded because the evidence for deep homology, although enticing, is preliminary: gut [282,288,885,1073,2228], liver [2312], kidney [934,2312,2400], integument [1052,2271], skeleton [1579,2242], muscle [164,700,1687], tendons [1692,2032,2125], and the recently discovered deep homology of cartilage [2245]. Finally, I have refrained from discussing the universal "machine code" of the genome unless it is germane to anatomy [2272]: microRNAs [8,386,834,1841,1941], introns [1943], enhancers [394,1383,1569,1874,2336], epigenetic tags [1294], transcription factors [567,1636], genomic ontology [2365], gene orthology [1458], and polyploidy [668].

Every effort has been made to ensure literal accuracy by soliciting expert scrutiny. David Hillis verified my template for bilaterian phylogeny. Jason Hodin checked Figure 1.3 and shared his vast PDF collection to expand it. Volker Hartenstein approved Figure 2.3. Dan Nilsson vetted Figure 3.3 and furnished additional unpublished data. Other scholars generously critiqued sundry drafts of the Preface and Introduction (Michael Akam, John Gerhart, and Volker Hartenstein), Chapter 1 (Michael Akam, Richard Campbell, Joseph Frankel, John Gerhart, Jason Hodin, Thurston Lacalli, and Arnaud Martin), Chapter 2 (Alain Ghysen and Thurston Lacalli), Chapter 3 (Gordon Fain, Markus Friedrich, Roger Hardie, Sönke Johnsen, Thurston Lacalli, Ivan Schwab, and Jeff Thomas), Chapter 4 (Daniel Eberl, Gordon Fain, Alain Ghysen, and Martin Göpfert), Chapter 5 (John Carlson and Alain Ghysen), Chapter 6 (Peter Bryant, Susan Bryant, and Vernon French), and Chapter 7 (Richard Cripps, Volker Hartenstein, and Eric Olson). To all of these luminaries I am grateful. I owe an even greater debt of gratitude to Ellen Larsen and Marc Srour, who read the entire manuscript in serial installments. Despite this feedback, errors may remain for which I take responsibility.

A few colleagues asked why all the drawings of humans in this book are male. They are all versions of da Vinci's Vitruvian Man, but no gender bias entered into my decision to use this icon to represent humans, mammals, vertebrates, or chordates, depending on the context. I had to redraw Leonardo's original because he sketched *two* pairs of arms and legs to show the metrics called for by the Roman architect Vitruvius [2340], while I needed only *one* pair of each to make my points. Also, he rendered a *frontal* view, but I needed *side* views in some cases, so I ordered a sculptural facsimile of Vitruvian Man from a collectibles catalog, took a picture of it from the side, imported the image into Adobe Illustrator, and traced it for that purpose. The "Vitruvian Fly" took me a week to trace from a montage of scanning electron micrographs. One last disclaimer: in a previous book [925] (Figure 6.3f), I attributed a drawing of a human–fly chimera to William Blake, based on a caption in Claudio Stern's 1990 paper [2182], and I planned to use it again here. When I wrote to inquire about copyright permission, Claudio told me that he had drawn the man with a fly's head in the style of Blake as a prank.

Marc Srour and Ruth Serra-Moreno graciously translated quotes from Geoffroy St.-Hilaire and Ramón y Cajal, respectively, in the Introduction. Several anonymous reviewers critiqued key aspects of my initial plan during the proposal process and helped refine the eventual focus of the book. Dominic Lewis, life sciences editor at Cambridge University Press, backed this (admittedly offbeat) project from its conception, and Jade Scard, content manager, nursed the manuscript through the various stages of production. I also thank Hugh Brazier, the copy-editor who

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deftly edited my last monograph, for magically polishing the rough edges of this book's prose as well.

Many undergraduates unwittingly served as guinea pigs to "beta-test" this material as a source for term-paper topics in an evo-devo seminar I've taught for a few years. One of the assignments is to pick a favorite gene from *D. melanogaster* and explain what's interesting about it from a clinical standpoint. If I were forced to play this game I'd probably choose *Dscam*, which encodes a cell adhesion molecule associated with Down syndrome (cf. Puzzles 2.7–2.10). *Dscam* is a lovely example of the gadgetry that evolution has cobbled together [258], and the experiments that have been conducted to dissect its modes of action (e.g., [2554]) are not only masterpieces of detective work; they are also great didactic vehicles for showcasing the subtle power of the genetic approach [849].

Robert Frost once mused that his goal in life was "to unite my avocation and my vocation as my two eyes make one in sight." My exploits as a fly geneticist over the past ~40 years have been so enjoyable that they seemed like a hobby, while my teaching of human embryology to premedical students over the past ~30 years was more of an assigned job, though not really a chore. Imagine my delight, therefore, when these two realms started merging at the dawn of the genomic era. Never in my wildest dreams did I think that humans and flies would turn out to be so much alike at the genetic level. My aim here is to share some of that shock and awe.

This is the final book of an evo-devo trilogy [925,928] that has entertained me, in the writing thereof, for more than a decade. The journey has at times felt as daunting as Frodo's trek to Mordor, but, like Frodo, I've been assisted along the way by wise wizards and faithful friends, some of whom are listed above. With all due respect to Professor Tolkien and his mastery of mythology, the field of evo-devo offers at least as much adventure for the hobbit-child in all of us as his fabulous world of Middle Earth.

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May 2016

Foreword

Deep Homology? is the final installment in Lewis Held's grand trilogy concerning the field of evolutionary developmental biology (evo-devo). This book follows his *Quirks of Human Anatomy* and *How the Snake Lost its Legs*. Overall, this trilogy makes the excitement and promise of evo-devo accessible to a broad readership. Let me first put Held's latest book into context. As Held puts it, "evo-devo has come into its Golden Age;" there are four specialized journals and many books dedicated to evo-devo, and just in the last few years a new evo-devo society – the Pan-American Society for Evolutionary Developmental Biology (www.evodevopanam.org) – held its inaugural meeting at the University of California, Berkeley, and its sister the European Society for Evolutionary Developmental Biology (http://evodevo.eu) held sold-out meetings in Vienna and Uppsala. These societies, meetings, journals, and publications show that evo-devo is on track to living up to its promise not only to understand how developmental processes and organismal body plans originate and evolve, but also to enrich evolutionary theory and enhance its predictive power. Indeed, evo-devo has already begun to provide critical insights into medicine, biodiversity conservation, agriculture, and animal breeding.

What sparked this rejuvenation and success was the discovery that animals as diverse and distantly related as flies and humans share a similar set of highly conserved genes and interactive gene networks that regulate their development. In *From DNA to Diversity*, Sean Carroll and colleagues called these highly conserved regulatory genes the "genetic toolkit" for animal development [5]. An early example of this toolkit comes from Walter Gehring and colleagues, who stunned our field with their discovery that the gene *eyeless*, which regulates eye development in the fruit fly *Drosophila melanogaster*, has a counterpart in mice called *Pax6*. Misexpressing mouse *Pax6* in developing fruit fly tissues leads to growth of fruit fly eyes on wings, legs, antennae, and head [11]. Conversely, misexpressing fruit fly *eyeless* in developing frog tissues leads to the development of frog eyes on different parts of the frog body [6].

This discovery was immediately met with both excitement and controversy, because it touched the core of the most important concept in comparative biology – "homology." The homology concept, which is most often defined as a trait in two species that evolved from the same trait in their most recent common ancestor, is notoriously difficult to define [3]. An analysis of eye anatomy across a wide range of animals by Salvini-Plawen and Mayr led them to conclude that the compound

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eyes of insects and the camera eyes of vertebrates are not homologous as functional image-forming eyes because eyes were absent in the most recent common ancestor of insects and vertebrates [14]. Yet, Gehring and colleagues had shown that these independently evolved or "convergent" eyes are regulated by the same homologous gene: the most recent common ancestor of flies and vertebrates possessed the *Pax6* gene. What triggered controversy was their interpretation of this remarkable discovery: because *Pax6* is homologous, the compound eyes of insects and camera eyes of vertebrates are also homologous.

This controversy gave way to broader discussion about how to reconcile the discovery of homologous toolkit genes and their networks regulating non-homologous (novel) morphologies. In a famous essay, Sir Gavin de Beer had presciently recognized that homology at the level of genes does not equate homology at the level of morphology and vice versa [7]. Bolker and Raff (1996), Abouheif *et al.* (1997), Abouheif (1997), and Wray and Abouheif (1998) further proposed that homology at the level of genes should be considered separately from homology at the level of morphology, and that one should also always specify the level at which they are assessing homology [1,2,4,16]. Abouheif [1] and Wray and Abouheif [16] took this one step further and demonstrated that a "hierarchical approach to homology," where all levels of biological organization (genes, gene expression, embryological origin, and morphology) are considered separately yet simultaneously in the framework of a phylogenetic tree, can uncover important features of the evolutionary process. In the case of eyes, it reveals that *Pax6* was likely "co-opted" to facilitate the independent evolution of image-forming eyes in insects and vertebrates. This hierarchical approach emphasizes homology at distinct levels of biological organization and co-option of developmental regulatory genes.

Around the same period, Bolker and Raff (1996) and Shubin *et al.* (1997) introduced another term, "deep homology," to describe the scenario in which homologous toolkit genes and their networks regulate non-homologous morphology [4,15]. In contrast to the hierarchical approach, which clearly separates levels of homology, deep homology blurs these levels, and by doing so draws greater attention to the roles these highly conserved genes and their networks played in the ancestor of two distantly related species. In the case of eyes, deep homology suggests that *eyeless*/*Pax6* may have played a role in specifying a "light-sensing" organ in the ancestor of insects and vertebrates, and that image-forming eyes would have been independently elaborated in insects and vertebrates from this light-sensing organ. However, the concept of deep homology is open to the possibility that insect and vertebrate eyes are actually homologous because they evolved from the same cell types regulated by *eyeless*/*Pax6* in the ancestor. Deep homology is also open to the possibility that *eyeless*/*Pax6* did not regulate a light-sensing organ in the ancestor, but was co-opted to facilitate the *de novo* evolution of *eyeless*/*Pax6*. Deep homology and the hierarchical approach highlight the potentiating role of the conserved genetic toolkit and its interactive networks in the evolution of novel morphologies between closely and distantly related species.

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It is hard to imagine the field of evo-devo before Nüsslein-Volhard and Wieschaus [13] discovered the genetic toolkit in fruit flies and McGinnis *et al.* [12] provided the first evidence that this toolkit was highly conserved – they showed that the binding motif in developmental regulatory genes called the homeobox was conserved in a broad range of animals. The Modern Synthesis, which integrated genetics with Darwinian evolution, has been the predominant paradigm within evolutionary biology for much of the twentieth century [8]. Architects of the modern synthesis predicted that natural selection as the primary engine of evolution should erase any homology at the genetic level between the 35 animal phyla, including arthropods and chordates [10]. At this scale of evolutionary time, natural selection would have "recrafted" the nucleotide sequences of each gene in the genome through the constant accumulation of beneficial and neutral mutations during the process of adaptation of each organism to a constantly changing local environment [10]. During this same period, experimental embryologists were searching and struggling to find "grand homologies" or conserved embryological features between animals, such as the three germ layers shared by all bilaterian animals or the cleavage patterns shared by flatworms, annelids, and molluscs [9]. Therefore, the discovery of deep homology was a major surprise for evolutionary biology and a major triumph for experimental embryologists [9,10].

Yet, the deep homology concept has not been fully grasped and incorporated into evolutionary theory, or into other areas of biology, including ecology, medicine, and agriculture. Like its predecessors, this latest book in Lewis Held's trilogy will help lay the foundation for such a synthesis. This book is the first to provide an updated and detailed analysis of several cases of deep homology in one place, allowing the reader to vividly see the concept applied to different developmental processes and different organ systems. By doing this, the reader begins to realize that deep homology may be the rule, not the exception. Held's book is timely, as evo-devo is rapidly changing and incorporating approaches from many fields of study, including genomics, ecological and quantitative genetics, developmental plasticity, ecology, paleontology, cell and systems biology, theoretical biology, behavior, and population genetics. While integrating this long list of subdisciplines is a recipe for success, the central tenet of evo-devo, deep homology, sometimes gets lost in the flood of data from so many different directions. Therefore, his enjoyable writing style, which makes deep homology accessible to a broad range of scientists, is crucial for proper integration of these subdisciplines into evo-devo.

Finally, and I never understood why, but many great book and movie trilogies seem to be written or produced in reverse order. To understand *how the snake lost its legs* and why there are so many *quirks of human anatomy*, we should probably first try to fathom the depths of *deep homology.* So read all three books, but start here and work your way backwards!

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