Chapter 1
Reflections on Model Organisms in Evolutionary Developmental Biology

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Abstract This chapter reflects on and makes explicit the distinctiveness of reasoning practices associated with model organisms in the context of evolutionary developmental research. Model organisms in evo-devo instantiate a unique synthesis of model systems strategies from developmental biology and comparative strategies from evolutionary biology that negotiate a tension between developmental conservation and evolutionary change to address scientific questions about the evolution of development and the developmental basis of evolutionary change. We review different categories of model systems that have been advanced to understand practices found in the life sciences in order to comprehend how evo-devo model organisms instantiate this synthesis in the context of three examples: the starlet sea anemone and the evolution of bilateral symmetry, leeches and the origins of segmentation in bilaterians, and the corn snake to understand major evolutionary change in axial and appendicular morphology.

1.1 Introduction

In a prescient methodological paper of the early 1990s, James Hanken argued that evolutionary developmental biology (evo-devo) must combine a model-systems (or model organisms) strategy, exemplified in developmental biology, with a comparative strategy, exemplified in areas of evolutionary biology, to study cranial development and evolution (Hanken 1993). This insight had historical precedent (de Beer 1985 [1937]) and was straightforward conceptually—evo-devo should combine aspects of developmental models and aspects of evolutionary models—but subtle to implement, in large part because these approaches to studying organisms and their traits are in tension with each other (Collins et al. 2007; Minelli and Baedke 2014). Developmental model organisms are used to establish core

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similarities exemplified by many taxa (i.e., conservation), especially with an eye toward medical application (Bier and McGinnis 2003), whereas a comparative strategy is utilized to establish significant patterns of difference (i.e., evolutionary change) manifested across a clade (Harvey and Pagel 1991). Given this tension between investigating similarities and differences of model organisms in evo-devo, it is unsurprising that researchers often discuss their status and distinctiveness (Jenner 2006; Collins et al. 2007; Jenner and Wills 2007; Milinkovitch and Tzika 2007; Russell et al. 2017), especially in calls to introduce and standardize new ones (Crotty and Gann 2009; Lapraz et al. 2013; Braasch et al. 2015; Medina Jiménez et al. 2017).

Although it is commonly recognized that evo-devo model organisms are associated with distinctive reasoning practices, much attention has been given to the lingering effects of standard model organisms from developmental biology, such as *Drosophila*, because these played a key role in touchstone studies that helped establish contemporary evo-devo (Carroll 1995; McGinnis et al. 1984). "Model organisms, in particular the big six, are conceptual carry-over from developmental biology, but their study was crucial in establishing evo–devo as a new discipline" (Jenner and Wills 2007, p. 311). The recommendations that follow from this type of concern are laudable (e.g., "judicious choice of new model organisms is necessary to provide a more balanced picture") and build on analyses showing how numerous features of standard developmental model organisms are not representative, such as rapid rates of development and high degrees of canalization (Bolker 1995). *C. elegans* embryogenesis is not representative of nematodes for pattern formation and cell specification (Schulze and Schierenberg 2011), mice do not exemplify key features of early mammalian development (Berg et al. 2011), and zebrafish fin formation is not a good proxy for the ontogeny of tetrapod appendages more generally (Metscher and Ahlberg 1999). However, these recommendations conceal an underlying logic to the combining of different modeling approaches that is suggested in Hanken's earlier discussion and was glimpsed by others at the same time (Kellogg and Shaffer 1993).

The purpose of this chapter is to reflect on and make explicit the distinctiveness of model organisms in the reasoning of evolutionary developmental research. We argue that model organisms in evo-devo instantiate a distinctive synthesis of model systems strategies from developmental biology and comparative strategies from evolutionary biology that can negotiate the essential tension between developmental conservation and evolutionary change (Collins et al. 2007; Minelli and Baedke 2014). Evo-devo model organisms are typically selected and evaluated given their potential for solving problems concerning both the evolution of development and the developmental basis of evolutionary change, as well for their experimental tractability (Sommer 2009). In condensed form, the results acquired by studying experimentally tractable model organisms in evo-devo are generalized or extrapolated to particular taxa (developmental modeling emphasizing similarities) to which other taxa are then compared phylogenetically (evolutionary modeling emphasizing differences). They fulfill Hanken's original aim of integrating both strategies to study complex phenomena like cranial development and evolution: "Solution of many outstanding problems … will require a combined approach that incorporates the technical and conceptual strengths of each" (Hanken 1993, p. 455).

We begin our discussion with a review of different categories of model systems that have been advanced to understand practices found in the life sciences. This sets the stage to comprehend how evo-devo model organisms instantiate a synthesis of different modeling strategies from both development and evolution. We illustrate this type of synthesis with three examples: the starlet sea anemone used to address questions related to the evolution of bilateral symmetry in metazoans, species of leeches used to study processes of segmentation and represent lophotrochozoans for comparison with better studied chordates and ecdysozoans, and the corn snake used to investigate the origin of increased numbers of vertebrae and the reduction or absence of limbs. In conclusion, we propose that the "judicious choice of new model organisms is necessary" in evo-devo not only to provide a more balanced picture of developmental processes but also as an ongoing methodological strategy for answering questions about the evolution of development and the developmental basis of evolutionary change.

1.2 Different Categories of Biological Model Systems

The reasoning and material practices surrounding model organisms and model systems in the life sciences are diverse. What one disciplinary approach refers to as a model organism can be quite distinct from what another disciplinary approach designates a model organism. This is exacerbated by the fact that biologists also routinely discuss "non-model" organisms, which have different contrast classes for what are supposed or assumed to be "model" organisms (e.g., Russell et al. 2017). We have no delusions of policing this semantic diversity, nor would we presume to attempt to because these ambiguities of meaning can be productive in ongoing research. Instead, to the end of characterizing the distinctiveness of evo-devo model organisms, we rehearse a variety of different categories that have been introduced to capture different facets and distinctions latent in these diverse meanings associated with "model organisms."

1.2.1 Representation and Manipulation

Biological model systems are evaluated in terms of two major criteria: representation and manipulation (Love and Travisano 2013). The former concerns what biological systems a model can represent and to what extent. The latter concerns ease of empirical examination of a model. Ankeny and Leonelli (2011) emphasize two dimensions underlying the representational role of biological model systems: scope and target. *Representational scope* describes how widely and to what biological systems the results and lessons learned by studying a model system are projected. If a research group uses zebrafish to learn about vertebrates in general, then zebrafish as a model organism is supposed to have vertebrates as its representational scope. *Representational target* indicates what biological phenomena are explored by studying the model system. If the research group uses zebrafish to explore nervous system development, then in this situation the development of the nervous system is the representational target. In many cases, the choice of representational target is connected to the representational scope. For example, the study of genetic and cellular *mechanisms* in development (representational target) and the discovery that they are widely conserved evolutionarily (representational scope) is a significant motivator for the continued use of model systems (Gerhart and Kirschner 2007; Ankeny and Leonelli 2011). Additionally, the representational target might be a higher-level *phenomenon* instead of a molecular mechanism, and either of these can be scrutinized narrowly (*specificity*) or with respect to a range of variation on the theme (*variety*) (Love and Travisano 2013).

Many different factors are relevant to the criterion of manipulation for model systems. Examples include the availability of the biological system, the cost of initiating inquiry on it, possible experimental techniques that can be applied, and how quickly one can produce data and results (Love and Travisano 2013). Although there are differences in the degree to which these factors must be present and how they are fulfilled (e.g., regular availability might be achieved through chemically preserving and storing specimens), it is widely accepted that manipulation is a crucial criterion for biological model systems. Furthermore, the criteria of representation and manipulation are interrelated. In some cases, they exhibit a trade-off relationship, such as an organism that faithfully represents organisms of interest might be difficult to experimentally manipulate or an organism that is easy to manipulate might represent a group or phenomenon of interest poorly. Biologists choose and evaluate model systems by considering these criteria jointly, giving weight to different factors in terms of what they aim to accomplish (i.e., their research purposes).

1.2.2 Model Organisms and Experimental Organisms

In addition to those already described, previous philosophical studies have introduced a number of significant distinctions about biological model systems. Ankeny and Leonelli (2011) distinguish *model* organisms from what they call *experimental* organisms. These differ in their representational scope, representational target, manipulative requirements, and purposes of research. “Model organisms” correspond to a limited number of species that have been widely used in recent biological research, such as mouse, zebrafish, fruit fly, and *C. elegans*. Studies of model organisms have various genetic, developmental, physiological, ecological, and evolutionary phenomena as their target, especially those that occur in organisms generally. Results of these studies (e.g., identified mechanisms) are generalized to a wide range of other species. Important manipulative requirements for model organisms (in this sense) are the ability to undertake genetic analysis and successful standardization to minimize confounding variation (e.g., pure lines and standard strains). They are studied for the purpose of developing “an integrative understanding of intact organisms in terms of their genetics, development, and physiology, and in the longer run of evolution and ecology, among other processes” (Ankeny and Leonelli 2011, p. 319).

In contrast, “experimental organisms” are studied to explore particular biological phenomena. They exemplify the principle proposed by August Krogh: “For a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied” (Krogh 1929, p. 202). Historical examples include sea urchins for studying fertilization or early embryogenesis and frogs for studying the role of electricity in muscle contraction. Experimental organisms are chosen to answer specific questions, which means that each one has specific phenomena as its representational targets (Burian 1993). In the case of experimental organisms, the results of the research are often (though not necessarily) generalized or extrapolated more narrowly than results derived from model organisms. They also are not as standardized and less suitable for many forms of genetic analysis. However, this is not an inherent drawback because manipulative requirements vary depending on what questions are being addressed. The giant squid axon was strategic for electrophysiological experiments to ascertain neuronal function because its size (~0.5 mm in diameter) made it possible to reliably apply voltage clamps (Hodgkin and Huxley 1952).

1.2.3 Exemplars Versus Surrogates

Another helpful distinction has been made between *exemplary* and *surrogate* models (Bolker 2009). This distinction consists in what kind of inference predominates in the research using the model system. Exemplary models are studied as examples of larger groups of organisms, such as zebrafish as a model of vertebrates or *Drosophila* as a model of animals generally. The results acquired investigating an exemplary model are generalized to a larger group of which the model species is a member. Standard developmental biology model organisms are exemplary in this sense: “The motivation for their study is not simply to understand how that particular animal develops, but to use it as an example of how all animals develop” (Slack 2006, p. 61). On the other hand, surrogate models serve as substitutes for particular biological systems. The results derived from research on a surrogate model are extrapolated to a specific target. A predominant example is the use of mouse as a model of *Homo sapiens* (e.g., Cheon and Orsulic 2011). The inference is from a proxy to a target instead of from an exemplar to other taxa more generally, as is the case for exemplary models. The different roles played by exemplary models and surrogate models arise from different investigative purposes. For exemplary models, the goal is to identify widely shared biological mechanisms or better understand evolutionary processes. As a result, exemplary models are associated with basic research. In contrast, surrogate models are used in more applied fields, such as biomedicine or conservation research, to better understand medical and ecological problems and develop potential solutions to them.

1.2.4 Model Taxa and Model Life Histories

Although most philosophical accounts have been concerned primarily with organisms of specific *species* that are used as models, there also are perspectives that focus on differently arrayed biological systems. The notion of a model *taxon* refers to a clade that is used to investigate diverse questions about genetic, developmental, physiological, ecological, and evolutionary phenomena both within the clade and with the aim of identifying generalizations applicable to other clades (Griesemer 2015). Thus, the representational scope of a model taxon is understood as taxa within and beyond the clade, with results ascertained through investigation applying differentially to individual taxa of smaller and larger sizes. Inquiry is organized around interrelated "packages of phenomena" as the representational target—rather than individual phenomena—and constitutes central features of the evolution of the taxon. For example, lungless salamanders have been studied as a model taxon and have provided explanatory insights about the evolution of anatomical features (e.g., the tongue or body size) and associated functional systems (e.g., feeding, locomotion), especially with respect to mechanisms that contribute to these patterns (e.g., miniaturization derived from changes in developmental timing or large cell size resulting from constraints of genome size) (Wake and Larson 1987; Wake 2009). Another prominent example of a model taxon used to investigate ecological and evolutionary questions is the squamate genus *Anolis*, which is composed of a large number of lizard species with good phylogenetic resolution, while also being regionally delimited and relatively accessible (Sanger 2012; Stroud and Losos 2016).

Griesemer uses the term "export" to refer to the predominant inference made from model taxa, where exportation is distinguished from inferences involving simple generalization. The latter is common in molecular biology and operates by assuming that species are instances of the same type. Exportation is based on the idea that taxa are historical individuals and in lineal relationships with one another. Although discussions of model organisms tend to focus on how particular results acquired by studying them are extrapolated, generalized, or exported, Griesemer also emphasizes additional kinds of payoffs that can be acquired by studying model taxa. These include methodological lessons about how to investigate different taxa.

A final category of biological model system is a model *life history* (Love and Strathmann 2018). These are temporal sequences that occur within the ontogeny of organisms, characterized in terms of functional and morphological properties, which are used as models of sequences within development found in other species. Marine invertebrate larvae are a primary example of a model life history (Love 2009). Unlike a model taxon, these stages of life history are not unified within a single monophyletic group; often, studies of marine larvae involve cross-clade comparisons of functional requirements for specific ecological settings that exhibit a broad but disjoint taxonomic distribution (i.e., their representational scope). The representational targets of investigations of model life histories are functional or morphological traits in ontogenetic sequences relevant to questions about developmental, ecological, and evolutionary phenomena. Some resulting generalizations revolve around particular instantiations of larval forms that exemplify a broader type (e.g., pluteus or trochophore), while others pertain to behavioral and ecological patterns, such as feeding versus nonfeeding or planktonic versus benthic. Model life histories concentrate attention on problems related to ecology, evolution, adaptation, and phylogeny and serve to coordinate research by scientists from different disciplines, often at marine stations where the availability, cost, and infrastructural prerequisites for manipulation are in place to support the relevant configuration of approaches simultaneously.

1.3 Examples of Evo-Devo Model Organisms

The reasoning strategies associated with evo-devo model organisms have distinctive features and are not sufficiently characterized by any one of the accounts of biological model systems reviewed above. One central feature is the importance of phylogenetically informed comparison. Although results and lessons acquired by studying model organisms in evo-devo are generalized or extrapolated, similar to what is seen for the use of many other model systems, this is followed by a process of comparison with taxa related by specific patterns of common descent. These processes of comparison are crucial for elucidating the origin of novel traits in a lineage, the evolution of properties of ontogeny, and dissecting the relevant influence of developmental processes on evolutionary mechanisms, all of which comprise research purposes governing the use of model organisms in evolutionary developmental research (Collins et al. 2007).

*1.3.1 The Starlet Sea Anemone (*Nematostella vectensis*)*

A good example of an evo-devo model organism is the starlet sea anemone, *Nematostella vectensis* (Darling et al. 2005; Genikhovich and Technau 2009; Layden et al. 2016). *Nematostella* has many practical advantages for experimental studies: it can be maintained easily in little space and at a low cost, adults reproduce under laboratory conditions about once a week and throughout the year, eggs are large enough for manipulation, and the generation time is relatively short (Darling et al. 2005). Resources and experimental techniques available include an annotated genome, visualization techniques such as in situ hybridization and immunohistochemical analysis, and knockdown/knockout techniques from molecular genetic analysis (e.g., Morpholinos, CRISPR/Cas9, and TALEN), as well as overexpression through mRNA injection (Layden et al. 2016).

An important problem to which *Nematostella* can contribute answers is the evolution of bilaterality. Bilateral symmetry was one of the major evolutionary novelties that originated in animals more than 600 million years ago, and evo-devo researchers have tried to reveal when and explain how the two major body axes (anterior–posterior [A–P] and dorsal–ventral [D–V]) emerged. To accomplish this requires comparing bilaterian axis formation (e.g., in *Drosophila* or mouse) with the ancestral pattern of development. *Nematostella* belongs to the phylum Cnidaria, which is an outgroup of Bilateria that includes corals, jellyfish, hydras, and sea anemones. It is expected to serve as a model of the ancestral pattern of development that basal metazoans exhibited in the past on the assumption that extant members of this outgroup have retained significant features of this pattern. Although it appears to be radially symmetrical, *Nematostella* has two body axes. The oral–aboral (O–A) axis runs from the mouth to the other end of the body; the directive axis runs across the pharynx and is orthogonal to the O–A axis. Molecular developmental studies have revealed relations between these body axes of *Nematostella* and the A–P and D–V axes of bilateria, which give clues as to how the primary and secondary axes of symmetry in animals originated.

For example, Wnt/β-catenin signaling is known to play a crucial role in A–P axis specification across bilaterians (Petersen and Reddien 2009). Thus, the function of Wnt/β-catenin signaling in O–A axis specification in *Nematostella* has been examined. In many bilaterian species, Wnt/β-catenin signaling is differentially activated at certain stages of embryonic development and in different locations of the embryo. During early embryogenesis, the side of the embryo with a high Wnt/β-catenin signaling activity develops into the posterior end, while the side with lower signaling activity becomes the anterior end (Petersen and Reddien 2009). In *Nematostella*, from the mid-blastula stage, Wnt gene expression exhibits a demarcated, staggered expression within the oral half of the embryo (Kusserow et al. 2005). Furthermore, overactivation of Wnt/β-catenin signaling promotes oral identity, while inhibition of Wnt/β-catenin signaling leads to expanded expression of aboral markers and reduction of oral marker expression (Röttinger et al. 2012). These results point toward a role for Wnt/β-catenin signaling in primary axis specification that existed before the separation of Bilateria and Cnidaria (Petersen and Reddien 2009). They also suggest a potential correspondence between bilaterian anterior and cnidarian aboral sides, on the one hand, and between bilaterian posterior and cnidarian oral sides, on the other (Layden et al. 2016), though this remains unclear (see below).

Relationships between the bilaterian D–V axis and the directive axis of *Nematostella* have also been examined. In bilaterian embryogenesis, BMP signaling plays a crucial role in the specification of the D–V axis. For example, BMP and its antagonists (e.g., Chordin) are expressed at opposite sides of the body in vertebrates and insects. Their interactions lead to a gradient of BMP signaling that helps to specify the D–V axis (De Robertis 2008). In *Nematostella*, homologs of BMP pathway genes and Chordin are asymmetrically expressed along the directive axis around and after gastrulation (Finnerty et al. 2004; Matus et al. 2006), and BMP signaling is required for directive axis formation (Saina et al. 2009). However, unlike vertebrates and insects, these genes are expressed on the same side of the body (Rentzsch et al. 2006). Additionally, they seem to constitute, along with other genes, a signaling network of different topology than is found in many bilaterians (Saina et al. 2009). Therefore, although bilaterians and *Nematostella* use common molecular signaling mechanisms in axis specification, it is unclear whether the directive axis of *Nematostella* is homologous to the D–V axis of Bilateria (Rentzsch et al. 2006; Layden et al. 2016). More recent work demonstrates that the directive axis of *Nematostella* is under the control of an axial Hox gene code—a developmental characteristic of the metazoan A–P axis—which indicates that molecular signaling pathways from both primary and secondary axis specification mechanisms in bilaterians are present in directive axis specification (He et al. 2018). This suggests that there is no straightforward homology relationship between the O–A and directive axis of *Nematostella* and the A–P and D–V axes of bilaterians.

*1.3.2 Leeches (*Helobdella*) and Corn Snake (*Pantherophis guttatus*)*

Let us briefly consider two more examples of evo-devo model organisms. Leeches of the genus *Helobdella* have played an important role in research into the evolutionary history of segmentation (Martindale and Shankland 1990; Weisblat and Kuo 2014; Kuo and Lai 2019). Each of the three superphyla of Bilateria (Deuterostomia, Ecdysozoa, and Lophotrochozoa) includes both segmented and unsegmented taxa, which prompts a question about how many times segmentation has evolved in bilaterian lineages (Davis and Patel 1999; Minelli and Fusco 2004). Comparing segmentation mechanisms of different superphyla is crucial to answering this question. However, unlike the other two superphyla that include standard model organisms, our knowledge about developmental mechanisms within Lophotrochozoa has been limited. A major motivation to study *Helobdella* as a model organism is to provide information about segmentation mechanisms of Lophotrochozoa for comparison with the other superphyla (Weisblat and Kuo 2009, 2014; Kutschera and Weisblat 2015).

Another example of an evo-devo model organism is the corn snake *Pantherophis guttatus*, which has been studied as a model for morphological evolution in modified body plans (Guerreiro and Duboule 2014). An increased number of vertebrae and the loss of limbs are characteristic in snakes. Hence, evo-devo researchers have been interested in how such an “extreme body plan” evolved (Woltering 2012), especially because a similar body plan has evolved independently in other lineages, such as in limbless anguids (slow worms or glass lizards) and caecilians (limbless amphibians). Again, as with other evo-devo model organisms, comparison of developmental mechanisms between taxa is an important step in elucidating how such radical morphological changes have occurred. The corn snake together with several other species have contributed to this research by providing details of vertebral formation and the reduction or elimination of appendage formation in snake embryogenesis (Castoe et al. 2013; Cohn and Tickle 1999; Head and Polly 2015; Woltering et al. 2009). This makes it possible to execute informative, phylogenetic comparisons with the development of other tetrapods to answer questions about the evolution of developmental features contributing to the extreme axial and appendicular morphology of snakes (Gomez et al. 2008; Guerreiro et al. 2016; Kvon et al. 2016).

1.4 Evo-Devo Model Organisms as a "Synthesis"

The examples of evo-devo model organisms in Sect. 1.3 illustrate unique features of experimentally tractable model systems that represent a synthesis of the generalization or extrapolation of developmental mechanisms and phylogenetic comparison to answer questions about the evolution of development and the developmental basis of evolutionary change. In this section, we characterize reasoning strategies associated with evo-devo model organisms using the conceptual tools provided by previous philosophical accounts (detailed in Sect. 1.2) and contrast the features of model organisms in evo-devo with other categories of biological model systems to demonstrate their distinctive status.

1.4.1 Not Model Taxa or Model Life Histories

Evo-devo model organisms are typically one species rather than other collectives or units, which makes them distinct from model taxa and model life histories. To use a model taxon, one studies multiple species in the clade with the aim of exporting the lessons learned to other members of the same clade or to different clades. In contrast, an evo-devo model organism is a specific species that is used to produce results that can be generalized or extrapolated to another species rather than across the entire clades. For example, increased Wnt/β-catenin signaling in *Nematostella* promotes oral identity in the establishment of the O–A axis (Röttinger et al. 2012), which can be generalized to primary axis specification in a representative ancestral metazoan species extant prior to the split between Bilateria and Cnidaria hundreds of millions of years ago (Petersen and Reddien 2009). Additionally, leeches from the genus *Helobdella* qualify as model *organisms* rather than a model *taxon* because researchers select some species from the genus and study them as, for example, models of segmentation in other lophotrochozoan species (Kutschera and Weisblat 2015). The entire genus is not studied thoroughly in terms of packages of phenomena; only a few selected species of the genus are studied in terms of individual phenomena (e.g., segmentation). By parallel reasoning, evo-devo model organisms are distinguished from model life histories because the latter category is applied to specific temporal sequences within development. This does not mean that model life histories cannot help to address evolutionary developmental questions. The crucial point is that they do so in a different fashion, such as by generalizing particular functional requirements of dispersal or feeding for larval forms during ontogeny in specific ecological settings.

1.4.2 Sometimes Exemplar, Sometimes Surrogate

An evo-devo model organism can serve as an exemplar of a larger class of species or as a surrogate of a particular species. The former applies when one or a few species belonging to a particular clade are studied to elucidate how traits characteristic of that clade have evolved. Inquiry into the evolution of axial and appendicular morphology in corn snake falls under this category (Guerreiro and Duboule 2014). Evo-devo model organisms also are studied as exemplars of species in a taxon that has been underrepresented in developmental research; information about developmental mechanisms of species in this taxon is required to elucidate the evolution of widely distributed (though not necessarily homologous) traits. *Helobdella* leeches in the investigation of segmentation are exemplary models in this way. Researchers expect them to provide information about segmentation processes in Lophotrochozoa to facilitate answering questions about the origins and evolution of segmentation in Bilateria (Weisblat and Kuo 2009).

On the other hand, the role that *Nematostella* plays as a model organism in evo-devo appears slightly more complicated. In some cases, *Nematostella* is regarded as an exemplar of anthozoan cnidarians or cnidarians in general or even as an exemplar of animals that exhibit developmental processes such as asexual fission and regeneration (e.g., Burton and Finnerty 2009). In other cases, such as studies related to the evolution of bilaterality, *Nematostella* serves as a surrogate model of extinct basal metazoans. *Nematostella* is likely to have retained ancestral features of basal metazoan axis specification and thus has potential to be a surrogate of the last common ancestor of Bilateria and Cnidaria to study how bilaterality evolved. This is indicated in the ways that biologists discuss the representational roles of *Nematostella* in the context of research on the origins of bilateral symmetry: "many ancestral traits have been preserved in *Nematostella* … this makes *Nematostella* a very attractive model system among the representatives of *basal* metazoan lineages" (Genikhovich and Technau 2009, emphasis added). Importantly, *Nematostella* does not have to represent basal metazoans with respect to all traits in order to serve as a surrogate model. What is required in this context is that it represents the last common ancestor of Bilateria and Cnidaria *with respect to body axis specification*. Usefulness as a surrogate can vary depending on which trait is of interest.

Although the distinction between exemplary and surrogate models is useful to capture some of the representational roles played by evo-devo model organisms, other details of how this distinction is characterized are not readily applicable. For example, Bolker (2009) states that a major aim of using exemplary models is to elucidate widely conserved mechanisms. This is not primarily the case for evo-devo model organisms. They are studied to elucidate developmental mechanisms characteristic of species in a taxon to compare with corresponding developmental mechanisms of species in other taxa. Discovering that these mechanisms are widely conserved is not the purpose of investigation; instead, the aim is to uncover how these developmental mechanisms changed (i.e., evolved). Bolker also holds that the central aims of using surrogate models are to understand disease etiology, identify possible therapies, and conserve threatened species. These features of surrogate models are not typically applicable to evo-devo model organisms, though in some cases this is relevant, such as comparative studies of axis specification established by *Hox* gene expression bearing on patterns of human vertebral pathology (ten Broek et al. 2012). The use of *Nematostella* as a surrogate model of basal metazoans is more typical and motivated by an interest in evolutionary history, especially the origin of bilateral symmetry.

1.4.3 Neither Model Organism, Nor Experimental Organism

Evo-devo model organisms are not model organisms in the sense of Ankeny and Leonelli (2011) because they are not intended to have a wide range of species as the representational scope and diverse phenomena as the representational target. The category of experimental organism appears better suited to evo-devo model organisms. As is expected for experimental organisms, an evo-devo model organism represents a limited range of taxa (e.g., Lophotrochozoa in the case of *Helobdella*) and extrapolation or generalization focuses on specific biological phenomenon (e.g., segmentation). However, the characterization of experimental organisms is not adequate to understand evo-devo model organisms either because the latter involve several unique features. One is that the relationship between the choice of an evo-devo model organism and the research questions being asked is more complex than what is found in cases of experimental organisms. The role of an experimental organism is to be a convenient system for studying specific developmental, physiological, genetic, or behavioral phenomenon. Thus, if a species exhibits the phenomenon of interest and satisfies relevant manipulation criteria, it can be a satisfactory experimental organism. On the other hand, exhibiting particular phenomena is only part of the representational requirement for a species to be an evo-devo model organism; its phylogenetic location in the evolutionary tree is also critical (see below).

1.4.4 The Distinctive Synthesis of Evo-Devo Model Organisms

The generalization or extrapolation of experimental results from an evo-devo model organism is followed routinely by a comparison between the taxa in which the generalization or extrapolation applies and other taxa where it does not. Such a comparison is crucial to elucidate the evolution of the traits under scrutiny. Therefore, the goal of using an evo-devo model organism is not to examine mechanisms underlying a particular developmental, physiological, genetic, or behavioral phenomenon. Rather, the examination of these mechanisms is a means to the end of answering broader evolutionary questions. Consider again *Nematostella*. A major motivation for studying it is to address the problem of how bilateral symmetry evolved in the lineage of Bilateria (Darling et al. 2005; Layden et al. 2016). This evolutionary problem is composed of many lower-level questions, such as how the different mechanisms that establish primary and secondary axes in bilaterians operate. Scientific problems constitute hierarchical structures; broad problem domains are composed of many different but related questions (Brigandt and Love 2012; Love 2008, 2014).

To account for the origin and evolution of bilateral symmetry, we have to examine many different but related questions, such as how and in what different ways the A–P axis is determined during bilaterian embryogenesis and how and in what different ways the D–V axis is determined during bilaterian embryogenesis. If *Nematostella* serves successfully as a surrogate model of the last common ancestor of Bilateria and Cnidaria, then mechanisms of its axis specification can be extrapolated to the ancestral metazoan. Researchers can then compare the (hypothetical, extinct) ancestral patterns of axis specification with those in extant bilaterian models. This comparison is a crucial step to help account for the evolution of bilaterality. The same kind of hierarchical organization of questions operates in the other two cases. For example, segmentation is a complex developmental process that requires answers to many distinct questions about the initiation, spatial arrangement, and number of segments. These questions are addressed by investigating segmentation mechanisms in *Helobdella* species and then generalized to Lophotrochozoa for broader comparison with segmentation mechanisms in Arthropoda and Chordata. This broader comparison is a means to the end of addressing the problem of how segmentation has evolved within Bilateria.

Evo-devo model organisms are chosen and evaluated on the basis of their potential contributions to answering research questions about the evolution of development and developmental basis of evolutionary change. Answering such questions involves comparisons of developmental patterns and mechanisms found in different lineages. Therefore, the precise location of a species within the evolutionary tree is a critical factor for an evo-devo model organism. As a consequence, evo-devo model organisms and experimental organisms (sensu Ankeny and Leonelli 2011) are distinct in an important respect. Unlike experimental organisms, evo-devo model organisms are not chosen simply because they are experimentally tractable and exhibit interesting biological phenomena. They have to occupy appropriate phylogenetic positions, as well as exhibit particular phenomena, so that effective comparisons can be made to answer important questions that comprise the research problems of evo-devo, such as the properties underlying evolvability or the origin of novel traits (Jenner 2006; Collins et al. 2007; Jenner and Wills 2007; Milinkovitch and Tzika 2007; Sommer 2009; Minelli and Baedke 2014).

Evo-devo model organisms instantiate a distinctive synthesis of model systems strategies from developmental biology and comparative strategies from evolutionary biology. Regarding the former, they are experimentally tractable species that act as exemplars or surrogates. The results acquired by studying them can be extrapolated to a specific species or generalized to a larger group of species. Regarding the latter, evo-devo model organisms depend heavily on what phylogenetic comparisons they make possible. The purpose of studying them is to answer different questions about the evolution of development and the developmental basis of evolutionary change. Strategic comparisons between taxa is an essential step in this methodology, which means the “judicious choice of new model organisms is necessary” as an ongoing strategy. Overall, evo-devo model organisms, illustrated in the cases of *Nematostella*, *Helobdella* leeches, and corn snake, navigate the essential tension between developmental conservation and evolutionary change by uniquely integrating model systems and comparative approaches to study complex phenomena at the intersection of development and evolution.

1.5 Conclusion

Our analysis herein has concentrated on the core reasoning strategies that underlie the selection and evaluation of most evo-devo model organisms. A number of important conceptual questions have been neglected as a consequence. For example, material practices associated with the laboratory maintenance and manipulation of model organisms for reproducible research involves the idealization of variation exhibited by developmental mechanisms (Love 2010; Minelli and Baedke 2014). These practices make it difficult, if not impossible, to study particular kinds of phenomena, such as phenotypic plasticity, which are relevant to developmental evolution (e.g., Moczek et al. 2011). The nature of these practices and various strategies for negotiating among their inherent trade-offs to address questions about the evolution of development and the developmental basis of evolutionary change requires a separate discussion (Love 2010; Minelli and Baedke 2014). Additionally, we have focused exclusively on animal models in evolutionary developmental research. Although many of our claims about core reasoning strategies are transferable, an explicit treatment of models in other domains is warranted, especially for plant evo-devo (Plackett et al. 2015; Vandenbussche et al. 2016; Yuan 2019) and for anatomical units like the vertebrate limb (Collins et al. 2007; Zuniga 2015).

Answering central questions in evo-devo requires both intensive experimental examination of developmental mechanisms in selected species—a common strategy in developmental biology—and phylogenetic comparison of different species within and across taxa—a common strategy in evolutionary biology. We have argued that model organisms in evo-devo instantiate a distinctive synthesis of these two strategies. Evo-devo model organisms are experimentally tractable species that serve as either exemplars or surrogates. The results acquired through their study are generalized or extrapolated to a larger group or a particular species, to which other species are compared in order to solve evolutionary problems. *Nematostella vectensis* is studied as a surrogate of extinct basal metazoans to which Bilateria is compared to answer questions about the evolution of bilateral symmetry, leeches of the genus *Helobdella* serve as an exemplar of Lophotrochozoa to which Deuterostomia and Ecdysozoa are compared to elucidate the origins and evolution of segmentation, and *Pantherophis guttatus* is an exemplar of snakes to better understand the developmental mechanisms behind their extreme changes in axial and appendicular morphology. The involvement of phylogenetic comparison as an essential part of evo-devo research makes these model organisms a distinctive category that deserves special methodological consideration.

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