OPINION

The future of evo–devo: model systems and evolutionary theory

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Abstract | There has been a recent trend in evolutionary developmental biology (evo–devo) towards using increasing numbers of model species. I argue that, to understand phenotypic change and novelty, researchers who investigate evo–devo in animals should choose a limited number of model organisms in which to develop a sophisticated methodological tool kit for functional investigations. Furthermore, a synthesis of evo–devo with population genetics and evolutionary ecology is needed to meet future challenges.

Evolutionary developmental biology (evo–devo) investigates the evolution of developmental processes, aiming for a mechanistic understanding of phenotypic change[1,2]. Building on the analysis of model organisms in developmental biology, evo–devo has seen a fruitful expansion in the last two decades and has successfully integrated various comparative research strategies[3–7]. The investigation of several concepts, including modularity, redundancy, developmental constraints, evolutionary novelties and phenotypic plasticity, forms a framework for evo–devo. However, evo–devo suffers from a sometimes misguided selection of model organisms, often with a limited availability of technical tools[8,9] and, most importantly, poor integration with other areas of evolutionary biology[10]. In this Opinion article, I argue that the future success of evo–devo in animals depends on two major technical and conceptual aspects: first, evo–devo has to concentrate on a few well-selected model organisms to allow the development of a sophisticated analytical tool kit for functional investigations; and second, evo–devo has to enhance its connections to other areas of evolutionary biology. Specifically, synthesis with population genetics can reveal how phenotypic evolution is initiated at the microevolutionary level, and synthesis with evolutionary ecology can add an ecological perspective to these evolutionary processes.

Limiting the number of models

The principle that focusing on a few organisms can be effective is demonstrated by the fact that the initial rise of developmental genetics was largely based on two invertebrate model systems, *Drosophila melanogaster* and *Caenorhabditis elegans*. The mechanistic understanding of development in these model organisms was also one of the important starting points for 'modern' evo–devo. Initial evo–devo work, which focused mainly on the cloning and expression pattern analysis of genes homologous to *D. melanogaster* developmental control genes[11], pointed towards an unexpected conservation of developmental genes. This work was, however, largely descriptive.

In some new evo–devo model organisms, such as the insects *Tribolium castaneum*[12] and *Nasonia vitripennis*[13] and the nematode *Pristionchus pacificus*[14], researchers started to build a more sophisticated tool kit to investigate the mechanisms of evolutionary change in developmental processes (TABLE 1). However, the development of these methods — including forward genetics to allow gene knockout or knockdown, and transgenesis to allow experimental manipulation — proved challenging. Method development depends mostly on empirical optimizations, which are largely species specific, so protocols cannot be transferred from one organism to another. Large research communities can overcome these challenges, but in evo–devo, with its relatively small research communities, method development is much harder.

One reverse genetics technology that has been used extensively in evo–devo in recent years to overcome technical limitations is RNAi. Although RNAi is becoming increasingly accessible, it is not easily transferable to every organism, and even in *C. elegans*, in which it was originally described, it does not work in all cells and tissues. By definition, RNAi is biased towards candidate genes identified in model organisms and is a transient method. Both of these features influence the type of questions that can be addressed by RNAi and the accuracy of the conclusions. Two of the strongest applications of RNAi in model organisms are genome-wide RNAi screens and the generation of double mutants by performing RNAi in a mutant background, but these are not yet realistic in evo–devo systems.

Owing to the technical limitations discussed above, evo–devo has largely followed the classical strategy of comparative morphology by analysing more organisms to provide unbiased phylogenetic sampling[8]. Particularly in the animal kingdom, with its deep branches and vast diversity of form and species, one can always look at new taxa and investigate their molecular inventory. If species are selected from a phylogenetic perspective, such studies can increase our understanding of the molecular evolution of developmental control genes; this research strategy provides important insight into evolutionary patterns. However, this strategy also has a serious trade-off: because of the limited resources and small number of researchers, large phylogenetic sampling will often result in few studies per organism and a superficial understanding of each system. In addition, it has been argued that analysing species because of their phylogenetic position rather than their conceptual value could leave the discovery of law-like generalities to chance[8].

I argue that the analysis of the central concepts of evo–devo can best be achieved by the selection of a limited number of model organisms and the development of sophisticated made-to-measure tool kits: this principle has been highly successful

in developmental genetics and its application in evo–devo seems equally promising. One reason for this optimism is that most conceptual themes in evo–devo arose from developmental genetics. Phenomena such as redundancy might be observed as widespread[15], and yet their significance in developmental processes and their contribution to evolution cannot be identified by the analysis of a single species; their role in evo–devo requires comparative studies between related species of the same taxa. Classical model organisms are a valuable starting point for such studies; by comparing *D. melanogaster* with other insects, or *C. elegans* with other nematodes, one can use the mechanistic insights provided by classical models to investigate evo–devo themes.

Considerations for comparative studies. To ensure that the comparative studies introduced above will be valuable for elucidating changes in development and the influence of these changes on evolution, two factors must be considered.

First, the species that are compared should be related in such a way that distinct, but still homologous, developmental patterns can be studied. Changes in developmental processes and mechanisms can then be identified as the cause of morphological diversity and novelty. By contrast, if organisms are completely unrelated, comparisons often result in a descriptive list of their molecular inventories, thus not going much beyond the information that genome projects provide. The intellectual merit of comparative studies in unrelated organisms often rests with providing evidence for the co-option of conserved transcription factor modules and signalling networks in independent evolutionary lineages[3].

Second, comparative studies should concentrate on mechanisms rather than, for example, gene conservation and gene expression. For transcription factors and cell–cell signalling molecules this is of particular importance because studies in model organisms constantly reveal that protein function is context dependent. One well-known example is Wnt signalling, which has both β-catenin-dependent and β-catenin-independent functions[16]. Therefore, studies that rest on the analysis of expression patterns of shared components of such pathways can easily be misleading. Only functional investigations and comparisons between a developmental model system and an evo–devo 'model system' can reveal how mechanisms change during evolution to create phenotypic diversity or novelty (discussed further in the following section). Furthermore, such studies can indicate the importance of evo–devo concepts for studying the evolution of developmental processes.

Taking these two considerations together, I argue that restricting the number of model organisms would help the field of evo–devo in its search for a theory. Developing a theory is of utmost importance for any discipline. This is clearly shown in evolutionary genetics, which builds on the framework of population genetics. In the context of developing a theory, it has been argued that signalling pathways and transcription factor modules could serve as a theoretical framework for elucidating developmental changes in evolution[1]. As functional investigations of development require the generation of sophisticated methods (TABLE 1), the limitation of the number of evo–devo model organisms is a logical consequence, and is a prerequisite for the long-term success of evo–devo.

Table 1 | **Several central criteria for evo–devo model species**

Methodology or approach	Scientific aim
Forward genetics	Unbiased identification of developmental mechanisms
Reverse genetics (RNAi, small interfering RNA morpholinos)	Functional studies from gene predictions
Genome projects	Evolution of genome architecture
Transgenesis	Experimental manipulation of gene function
Phylogenetic reconstructions	Directionality of evolutionary changes
Microevolutionary comparison of different isolates of the same species	Natural variation in developmental control genes
Genome-wide association studies	
Recombinant inbred line analysis	
Evo–devo in relation to ecology	Environmental influence on developmental control genes

The need for sophisticated tools

The importance of in-depth functional studies for achieving the aims of evo–devo, and by consequence limiting the number of organisms used, can be illustrated by case studies from nematodes and insects. These two cases indicate how the use of forward and reverse genetics can provide mechanistic insights into the evolution of development.

The nematode vulva. The nematode *P. pacificus* has been developed as a model system in evo–devo for comparison with *C. elegans*[14] (TABLE 2). *P. pacificus* shares many technical features with *C. elegans*, such as a 3–4 day life cycle, simple culture and self-fertilization as mode of reproduction. Its hermaphroditic mode of reproduction makes forward genetics feasible, the *P. pacificus* genome has recently been sequenced[17] and a DNA-mediated transformation method allows genetic manipulation[18].

Although *P. pacificus* shares technical features with *C. elegans*, many aspects of its development are strikingly different. Particular attention has been given to the development of the vulva, the nematode egg-laying structure. *C. elegans* vulva formation is one of the best studied developmental processes in animals[19], providing a platform for mechanistic studies in evo–devo[20]. Two hallmarks of *C. elegans* vulva formation are the generation of a vulva equivalence group and the induction of the vulva by the gonadal anchor cell. *P. pacificus* reveals striking differences with respect to both aspects of vulva development (BOX 1). Vulva induction requires different signalling pathways, and the reduction of the size of the vulva equivalence group in *P. pacificus* involves a transcriptional module that is absent from *C. elegans*, although it is otherwise conserved among metazoans[21,22]. Recent genetic studies in just these two species have allowed the molecular and mechanistic basis for these evolutionary changes in pattern formation and induction to be identified.

Insect dorso–ventral patterning. The red flour beetle *T. castaneum* is one of a few insects that have been developed as a model organism for mechanistic investigation in evo–devo[12]. This beetle can be easily cultured, has a short life cycle and is amenable to forward genetics analysis. The genome of *T. castaneum* has been sequenced, and an RNAi technique has been developed[23]. RNAi has proved particularly powerful and efficient in this organism, providing a tool for the large-scale elucidation of gene function[23].

Table 2 | **A selection of emerging evo–devo model systems with genetic tools in the vicinity of classical model organisms**

Classical model organism	Evo–devo model	Evo–devo themes	Refs
Drosophila melanogaster (arthropod)	*Tribolium castaneum*	Segmentation, appendix formation	12,26,28
	Nasonia vitripennis	Segmentation	13
	Daphnia pulex	Response to environmental variation	58
Caenorhabditis elegans (nematode)	*Caenorhabditis briggsae*	Sex determination, convergent evolution	63
	Pristionchus pacificus	Pattern formation, induction	14,20–22
Zebrafish	*Astyanax mexicanus*	Developmental and morphological response to environmental variation	54
	Sticklebacks	Developmental and morphological response to environmental variation	64
Hydra (cnidarian)	*Nematostella vectensis*	Evolution of body plan, ecological evo–devo	53
Arabidopsis thaliana (higher plant)	*Antirrhinum* (snapdragon)	Flowering	65

In *T. castaneum* embryogenesis, posterior segments develop successively and two extra-embryonic membranes cover the egg. By contrast, in *D. melanogaster* all segments form simultaneously and extra-embryonic membranes are fused to the amnioserosa[24] (BOX 2). RNAi studies of known dorso–ventral patterning genes have shown striking differences between *T. castaneum* and *D. melanogaster* in the function of individual genes and of genetic networks (BOX 2). In particular, gene duplications and subfunctionalization are crucial for extra-embryonic membrane formation and dorso–ventral patterning[25–28].

Structure–function dualism. The genetic experiments in *T. castaneum* and *P. pacificus* described above, and others like them[13], indicate that the exact mechanisms by which developmental control genes work can change rapidly during the course of evolution. For example, homologous genes can assume different functions in different species so that elimination of these genes results in different phenotypes[22,28]. Also, some developmental control genes are present in one organism but not in another[21], and genes that are duplicated during the course of evolution can undergo subfunctionalization in individual evolutionary lineages[26]. Therefore, comparative studies between phylogenetically related species can reveal how induction, pattern formation and segmentation evolve and contribute to the generation of evolutionary novelty. The examples of the nematode vulva and insect embryogenesis also show how homologous characteristics — characteristics that are shared because of a common ancestry — can be uncoupled at different levels: although the cells that form the nematode vulva and the organ itself are homologous, the genes regulating the underlying molecular processes are not necessarily homologous[29,30]. This allows deBeer's proposal, that homologous structures can be built by different genes[31,32], to be tested at a molecular level[29].

Genetic experiments give insights into how the function of a homologous gene can change during evolution. Isolation of a known gene in a new species or expression studies do not allow us to identify function and potential functional alterations during the course of evolution; this requires specific tools, such as forward and reverse genetics. The genes *zerknüllt* and *Toll*, for example, are both expressed during dorso–ventral patterning in *D. melanogaster* and *T. castaneum*, but their differing functions were only revealed by genetic manipulation experiments[28]. Although this conclusion is worthy in itself, it also provides an additional argument for the selection of a limited number of evo–devo model systems and the development of functional tools in these species.

The future of evo–devo models

The *T. castaneum* and *P. pacificus* case studies show how the use of new models can give novel insights into evo–devo. Therefore, going beyond the classical model systems can be of value. *T. castaneum* and *P. pacificus* are two evo–devo models that have a sophisticated tool kit — but how many species should there be? The number of species worked on in evo–devo is constantly changing, with species being added and being removed: a recent monograph provides a detailed list of 'emerging model organisms'[33]. In some cases these organisms have received special attention because they offer the analysis of themes that have not received particular attention in classical models, such as regeneration, which can be efficiently studied in planarians and ascidians[34,35]. Similarly, some themes in evo–devo can only be studied in a particular species, or group of species. Under such circumstances, alternative models should also be used. But in the more general evo–devo context most concepts are based on widespread phenomena. For example, redundancy, phenotypic plasticity and developmental constraints are found in most organisms, and their role in evo–devo can therefore be studied in several systems if the appropriate tools are available. Thus, broad phylogenetic sampling is not a necessary prerequisite for studying the mechanisms behind important evo–devo concepts. With the two criteria identified above, namely the technical considerations and the need to compare the phylogenetic relationship of the evo–devo and the classical model organism, a realistic starting number of evo–devo model species should not be much higher than a dozen because the long-term value of a species depends on its conceptual merit (TABLE 2).

Implications for the funding of evo–devo research. Another sensitive issue for evo–devo studies is research funding. Relative to comparative morphology, one of its intellectual forerunners, research in evo–devo requires substantially more investment. An emerging consequence is, therefore, the problem of securing funding for evo–devo in the modern life sciences, which largely aim to address applied research questions. This difficulty arises when evo–devo studies are compared with mechanistically driven applied research projects. A second significant problem is obtaining the initial funding for technology development in new model organisms. I argue that evo–devo projects that focus on functional studies are the most likely to be successful in competition with other research fields. In addition, allocation of research funds for technology development, as has been seen for comparative

genomics, could further help evo–devo to succeed in a world of limited funds. Specific funding allocation could, for example, target the exploration of new species to extend the number of model systems over a longer time period. Together, seeking funding for functional studies and technology development might even result in a gain of funding for evo–devo overall.

Integration with evolutionary theory

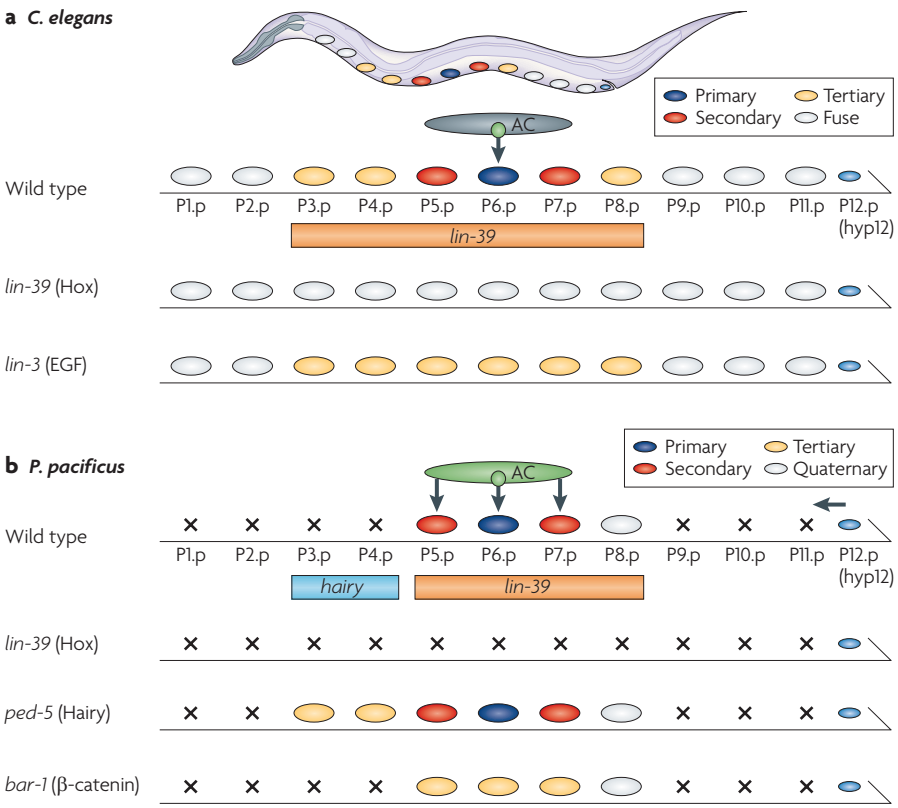
In addition to practical considerations regarding the number of model organisms and the development of appropriate analytical tools, the interaction of evo–devo with other research areas needs to be re-considered to ensure future successes in the field. Specifically, I argue that more integration with evolutionary biology would be mutually beneficial (TABLE 1). The relationship between development and evolution has changed several times in the past 150 years (discussed in REF. 36). Currently, there is growing consensus that development has to be integrated into evolutionary theory, because the evolution of form and the generation of morphological novelty are of utmost importance in a general philosophical framework of biology. However, working solely within the conceptual framework of evo–devo results in a gene-centred and development-centred perspective that lacks interrelationships with other areas of evolutionary biology. If evo–devo wants to establish itself as a part of evolutionary theory, it has to find a suitable way of incorporating evolutionary thinking and recent advances, such as genomics[10]. Specifically, I argue that a synthesis with population genetics and evolutionary ecology is required.

A synthesis with population genetics. Why are developmental control genes conserved at the sequence level, when their functions can change? This question and the original observations that led to it are important because they help to distinguish, in the evo–devo context, between the contrasting theories of neo-Darwinism and neutral evolution. In neo-Darwinism, positive (that is, directional) selection is thought to be the major mechanism driving the change of allele frequencies and it predicts that genes would not be conserved among species[37,38]. By contrast, Kimura's neutral theory of molecular evolution proposes that the majority of mutations in non-coding areas of the genome are selectively neutral or nearly neutral, whereas most mutations in genes are selectively deleterious[39]. The neutral theory predicts that in coding regions

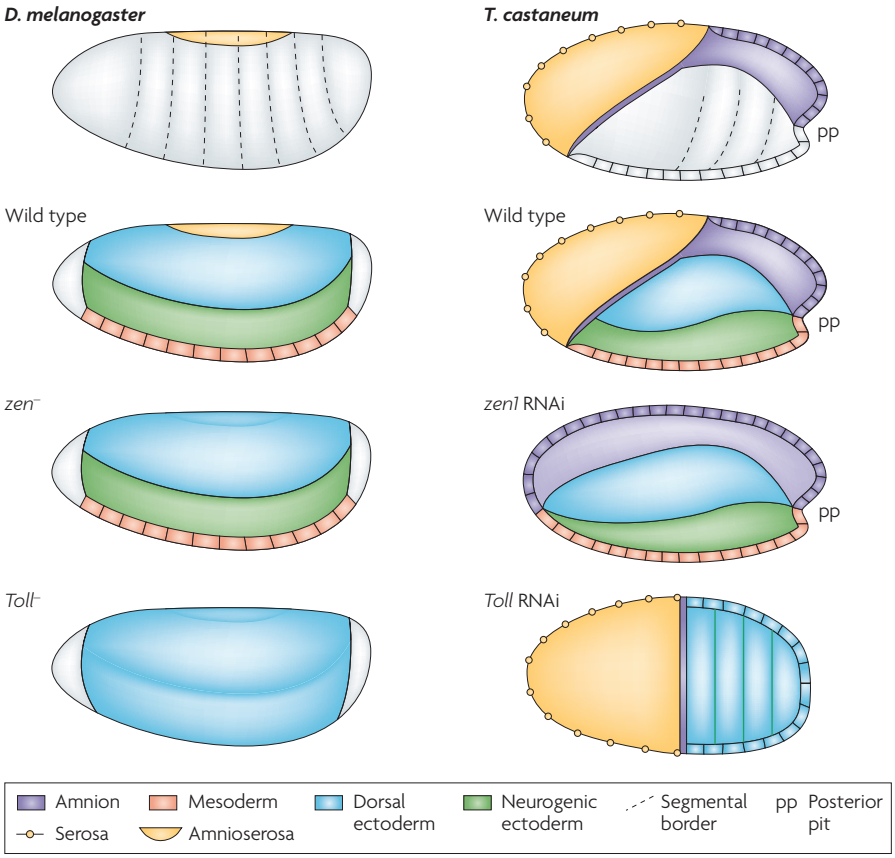
Box 1 | Vulva induction in *C. elegans* and *P. pacificus*

In *Caenorhabditis elegans* the vulva is a derivative of the ventral epidermis, which consists of 12 ectoblasts, named P1.p–P12.p according to their antero–posterior position[19] (see the figure, part **a**). In wild-type animals, the vulva is formed from the progeny of P5.p–P7.p. P6.p has the primary fate and generates eight progeny (represented by a blue oval) and P5.p and P7.p have the secondary fate and form seven progeny each (represented by red ovals). P3.p, P4.p and P8.p have the tertiary fate (represented by yellow ovals). These cells are competent to form vulval tissue, but remain epidermal under wild-type conditions. The remaining ectoblasts (light grey ovals) fuse with the hypodermis and are not competent to form part of the vulva. P12.p is a special cell called hyp12, and forms part of the rectum. The vulva equivalence group, consisting of P3.p–P8.p, is located in the central body region and is specified by the homeobox (Hox) gene *lin-39*. In *C. elegans lin-39* mutants, positional information for the formation of the vulva equivalence group is missing, and P3.p–P8.p fuse with the hypodermis. *C. elegans* vulva induction depends on a signal from the anchor cell (AC, green circle) of the somatic gonad (dark grey oval). Ablation of the AC at birth is sufficient to prevent vulva induction and mutations in the epidermal growth factor (EGF) family member *lin-3* result in a vulvaless phenotype.

As in *C. elegans*, the *Pristionchus pacificus* vulva forms from the ventral epidermis, which is generated by homologous precursor cells, P1.p–P12.p (see the figure, part **b**). In *P. pacificus*, however, P1.p–P4.p and P9.p–P11.p die of programmed cell death and reduce the size of the vulva equivalence group to four cells[20]. In contrast to *C. elegans*, P3.p and P4.p are unable to form part of the vulva in *P. pacificus* because they die early in development. P5.p–P7.p have a secondary–primary–secondary pattern, as in *C. elegans*, and P8.p is a special epidermal cell (light grey oval), which is designated a quaternary cell fate. The vulva equivalence group, although reduced in size, is also formed by positional information of the Hox gene *lin-39*. In *P. pacificus lin-39* mutants, the vulva equivalence group is not formed and P5.p–P8.p die of programmed cell death. The reduction of the size of the vulva equivalence group in *P. pacificus* involves the transcription factor *hairy*[21]. In *hairy* mutants, P3.p and P4.p survive and form a vulva equivalence group with a pattern that is reminiscent of the pattern in *C. elegans*. Genetic and biochemical studies showed that, in *P. pacificus*, HAIRY and GROUCHO form a heterodimer that downregulates the activity of *lin-39* in P3.p and P4.p. Surprisingly, there is no 1:1 orthologue of *hairy* in the *C. elegans* genome. Moreover, vulva induction in *P. pacificus* requires multiple cells of the somatic gonad instead of only one, as is the case in *C. elegans*. Mutations in the β-catenin-like gene *bar-1* in *P. pacificus* result in a vulvaless phenotype, indicating that Wnt signalling controls vulva induction. Indeed, genetic studies showed a redundant role of several Wnt ligands, which are expressed in the somatic gonad and the posterior region of the animal (arrows)[22].



Box 2 | **Dorso–ventral patterning in *D. melanogaster* and *T. castaneum***



Drosophila melanogaster is a long germ band insect that forms all body segments simultaneously during the blastoderm stage[24] (see the figure, left panel). By contrast, *Tribolium castaneum* is a short germ band insect in which posterior segments develop successively[24] (see the figure, right panel). As a result, the extra-embryonic membranes differ between *D. melanogaster* and *T. castaneum*. *T. castaneum* has two extra-embryonic membranes: the serosa, surrounding the complete embryo, and the amnion, covering the embryo proper on the ventral side. In *D. melanogaster*, both membranes are fused to an amnioserosa, which covers the embryo only at the dorsal side. Dorso–ventral patterning and extra-embryonic membrane formation require homologous genes that have divergent functions. Mutations in the homeobox transcription factor *zerknüllt* (*zen*) in *D. melanogaster* result in the replacement of the amnioserosa by ectodermal tissue[25]. *T. castaneum* contains two *zen* genes, *zen1* and *zen2*, and RNAi experiments revealed sub-functionalization of these genes[26]. RNAi against *zen1* results in the absence of the serosa and an expansion of the germ rudiment towards the anterior, indicating that *zen1* acts in antero–posterior development and specifies the border between the embryonic and extra-embryonic tissue[26]. In *D. melanogaster*, the loss of the transmembrane receptor Toll results in completely dorsalized embryos, whereas RNAi against *T. castaneum Toll* results in the absence of the central nervous system and the amnion. These differences reflect the different regulatory linkage of signalling networks in *D. melanogaster* and *T. castaneum*[28].

purifying selection dominates over positive selection and, as a result, genes should be conserved over large evolutionary time spans[39]. The evolutionary conservation of developmental control genes — as indicated by studies in evo–devo — strongly supports Kimura's neutral theory.

Recent advances in population genetics have come through comparative genomics, with genome sequencing projects revealing an enormous amount of natural variation[10]. But is natural variation also seen in developmental control genes? How do developmental control genes change in microevolution? More generally, are non-adaptive forces important for developmental evolution? Work at the interface between population genetics and evo–devo will indicate the contribution of natural variation to the evolution of development. This requires the research portfolio of population genetics to be added to evo–devo[10,40] (TABLE 1).

The comparison of very closely related species and independent isolates of the same species can indicate to what extent developmental processes evolve at the microevolutionary level. High-resolution mapping, through genome-wide association studies or through recombinant inbred lines, combined with next-generation sequencing can identify the molecular changes that cause a particular effect. Such studies can easily be performed in any species, as long as enough natural isolates have been or can be obtained. A few inroads into the microevolution of development have been taken; for example, studies in *P. pacificus* and *C. elegans* indicate that vulva development is subject to microevolutionary change[41,42]. In *C. elegans*, several recent studies show the power of QTL analysis for other developmental and life history traits, such as copulatory plug formation and pathogen susceptibility[43,44]. Therefore, 'next-generation genetics', as recently proposed for plants[45], can be a powerful new tool when applied to evo–devo. Ultimately, such studies might indicate how natural variation contributes to macroevolutionary alterations. Neo-Darwinism assumes that macroevolutionary change results from repeated microevolutionary alterations, but there is no substantial proof for this assumption. Current population genetics lacks an in-depth consideration of developmental control genes in the same way as evo–devo lacks a serious consideration of microevolutionary processes. Therefore, a synthesis of evo–devo and population genetics would provide a substantial contribution to evolutionary theory.

A synthesis with evolutionary ecology. All processes required for phenotypic change — natural variation, selection, genetic drift and developmental change — occur in populations that live in a specific ecological context. As the environmental conditions that organisms are exposed to change, it is crucial to ask whether the environment influences development. But are the developmental response to the environment and the ecological interactions of the organism important for the evolution of new phenotypes? How do developmental processes evolve under changing environmental conditions?

Research programmes in 'ecological developmental biology' are now actively propagated[40,46]. For some evo–devo models the ecological niche is well described. For example, *P. pacificus* lives on a scarab beetle[47,48] and *T. castaneum* in dry environments, such as wheat[49]. Both species are now the subject of 'ecological evo–devo'

research[50–52]. Other evo–devo models, such as the cnidarian *Nematostella vectensis* and some of its close relatives, differ from each other in their ecological niche and tolerance, and research programmes that involve ecology-oriented studies are well underway[53]. Other models have been established largely owing to ecological considerations. For example, studies in the cavefish *Astyanax mexicanus* can indicate how the developmental networks regulating eye development have been altered in response to the dark environment in caves[54]. Phenotypic plasticity is a central concept of evo–devo and is, by definition, at the interface between evo–devo and ecology[55,56]. However, although it is a widespread phenomenon[57–59], further studies are required to reveal whether phenotypic plasticity is a common route for the generation of developmental novelty. One advocate of this idea was van Valen, who was ahead of his time when he proposed that "evolution is the control of development by ecology"[60] — a statement that is now being transferred to a highly interdisciplinary research agenda.

Conclusions

I argue that the attempt of evo–devo to understand phenotypic change and novelty requires functional investigations. This is best achieved by choosing a limited number of model organisms and by developing a sophisticated methodological tool kit in those organisms. Although such a research strategy is constrained by unbiased phylogenetic sampling, it can help evo–devo to develop its own theory and to secure funding as part of the modern life sciences. Insight into the change of developmental mechanisms provides a platform for the integration of evo–devo into evolutionary theory — the single most important requirement for the long-term success of this young discipline. The partial ignorance of evo–devo with respect to the complexity of evolutionary theory[61], and the naive assumption that all developmental patterns observed in nature are adaptive[62], is an important threat to evo–devo. A synthesis with population genetics and evolutionary ecology can help evo–devo meet these challenges, but requires new research strategies and intense consideration of evolutionary theory.

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1. Wilkins, A. *The Evolution of Developmental Pathways* (Sinauer Associates, Sunderland, Massachusetts, 2002).
2. Rudel, D. & Sommer, R. J. The evolution of developmental mechanisms. *Dev. Biol.* **264**, 15–37 (2003).
3. Raff, R. *The Shape of Life* (Chicago Univ. Press, Chicago, 1996).
4. Gerhard, J. & Kirschner, M. *Cells, Embryos and Evolution* (Blackwell Science, Oxford, 1997).
5. Minelli, A. *The Development of Animal Form* (Cambridge Univ. Press, Cambridge, 2003).
6. Carroll, S. B. *Endless Forms Most Beautiful* (Norton & Comp., New York, 2005).
7. Harvey, P. H. & Pagel, M. D. *The Comparative Method in Evolutionary Biology* (Oxford Univ. Press, Oxford, 1991).
8. Jenner, R. J. & Wills, M. A. The choice of model organisms in evo–devo. *Nature Rev. Genet.* **8**, 311–319 (2007).
9. Rieppel, O. Development, essentialism, and population thinking. *Evol. Dev.* **10**, 504–507 (2008).
10. Lynch, M. *The Origin of Genome Architecture* (Sinauer Associates, Sunderland Massachusetts, 2007).
11. Akam, M., Holland, P., Ingham, P. & Wray, G. (eds) *The Evolution of Developmental Mechanisms. Development Supplement* (The Company of Biologists, Cambridge, 1994).
12. Roth, S. & Hartenstein, V. Development of *Tribolium castaneum*. *Dev. Genes Evol.* **218**, 115–118 (2008).
13. Lynch, J. A., Brent, A. E., Leaf, D. S., Pultz, M. A. & Desplan, C. Localized maternal *orthodenticle* patterns anterior and posterior in the long germ wasp *Nasonia*. *Nature* **439**, 728–732 (2006).
14. Hong, R. L. & Sommer, R. J. *Pristionchus pacificus*: a well-rounded nematode. *BioEssays*, **28**, 651–659 (2006).
15. Cooke, J., Nowak, M. A., Boerlijst, M. & Maynard-Smith, J. Evolutionary origin and maintenance of redundant gene expression during metazoan development. *Trends Genet.* **13**, 360–364 (1997).
16. Veeman, M. T., Axelrod, J. D. & Moon, R. T. A second canon: functions and mechanisms of β-catenin-independent Wnt signaling. *Dev. Cell* **5**, 367–377 (2003).
17. Dieterich, C. *et al.* The *Pristionchus pacificus* genome provides a unique perspective on nematode lifestyle and parasitism. *Nature Genet.* **40**, 1193–1198 (2008).
18. Schlager, B. *et al.* Molecular cloning of a dominant Roller mutant and establishment of DNA-mediated transformation in the nematode model *Pristionchus pacificus*. *Genesis* (in the press).
19. Sternberg, P. W. Vulva development. *Wormbook* [online], <http://www.wormbook.org/chapters/www_vulvaldev/vulvaldev.html> 25 Jun 2005 (doi:10.1895/wormbook.1.6.1)., ed.
20. Sommer, R. J. & Sternberg, P. W. Apoptosis limits the size of the vulval equivalence group in *Pristionchus pacificus*: a genetic analysis. *Curr. Biol.* **6**, 52–59 (1996).
21. Schlager, B. *et al.* HAIRY-like transcription factors and the evolution of the nematode vulva equivalence group. *Curr. Biol.* **16**, 1386–1394 (2006).
22. Tian, H; Schlager, B., Xiao, H. & Sommer, R. J. Wnt signaling by differentially expressed Wnt ligands induces vulva development in *Pristionchus pacificus*. *Curr. Biol.* **18**, 142–146 (2008).
23. *Tribolium* Genome Sequencing Consortium. The genome of the model beetle and pest *Tribolium castaneum*. *Nature* **452**, 949–955 (2008).
24. Roth, S. in *Gastrulation: From cells to embryos* (ed. C. Stern) 105–122 (Cold Spring Harbor Laboratory Press, 2004).
25. Rushlow, C. & Levine, M. Role of the *zerknüllt* gene in dorsal-ventral pattern formation in *Drosophila*. *Adv. Genet.* **27**, 277–307 (1990).
26. van der Zee, M., Berns, N. & Roth, S. Distinct functions of the *Tribolium zerknüllt* genes in serosa specification and dorsal closure. *Curr. Biol.* **15**, 624–636 (2005).
27. Stathopoulos, A., Van Drenth, M., Erives, A., Markstein, M. & Levine, M. Whole-genome analysis of dorsal-ventral patterning in the *Drosophila* embryo. *Cell* **111**, 687–701 (2002).
28. da Fonseca, R. N. *et al.* Self-regulatory circuits in dorsoventral axis formation of the short-germ beetle *Tribolium castaneum*. *Dev. Cell* **14**, 605–615 (2008).
29. Wagner, G. The developmental genetics of homology. *Nature Rev. Genet.* **8**, 473–479 (2007).
30. Sommer, R. J. Homology and the hierarchy of biological systems. *BioEssays*, **30**, 653–658 (2008).
31. de Beer, G. R. *Embryos and Ancestors* (Claredon Press, Oxford, 1958).
32. de Beer, G. R. *Homology: An Unsolved Problem* (Oxford Univ. Press, Oxford, 1971).
33. Behringer, R. *et al.* (eds) *Emerging Model Organisms. A Laboratory Manual* (Cold Spring Harbor Laboratory Press, 2009).
34. Reddien, P. W. & Sanchez, Alvarado, A. Fundamentals of planarian regeneration. *Annu. Rev. Cell Dev. Biol.* **20**, 725–757 (2004).
35. Tiozzo, S., Brown, F. D. & De Tomaso, A. W. in *Stem Cells From Hydra to Man* (ed. Thomas Bosch) 95–112 (Springer, Heidelberg, 2008).
36. Amundson, R. *The Changing Role of the Embryo in Evolutionary Thought* (Cambridge Univ. Press, Cambridge, 2005).
37. Dobzhansky, T. *Evolution, Genetics and Man* (Wiley, New York, 1955).
38. Mayr, E. *Animal Species and Evolution* (Harvard Univ. Press, Cambridge, Massachusetts, 1966).
39. Kimura, M. *The Neutral Theory of Molecular Evolution*. (Cambridge Univ. Press, Cambridge, 1983).
40. Zauner, H. & Sommer, R. J. in *Evolving pathways: Key Themes in Evolutionary Developmental Biology* (eds Minelli, A. & Fusco, g.). 151–171 (Cambridge Univ. Press, Cambridge, 2008).
41. Zauner, H. & Sommer, R. J. Evolution of robustness in the signaling network of *Pristionchus* vulva development. *Proc. Natl Acad Sci. USA* **104**, 10086–10091 (2007).
42. Milloz, J., Duveau, F., Nuez, I. & Felix, M.-A. Intraspecific evolution of the intercellular network underlying a robust developmental system. *Genes Dev.* **22**, 3064–3075 (2008).
43. Palopoli, M. F. *et al.* Molecular basis of the copulatory plug polymorphism in *Caenorhabditis elegans*. *Nature* **454**, 1019–10222 (2008).
44. Reddy, K. C., Andersen, E. C., Kruglyak, L. & Kim, D. H. A polymorphism in *npr-1* is a behavioral determinant of pathogen susceptibility in *C. elegans*. *Science* **323**, 382–384 (2009).
45. Nordborg, M. & Weigel, D. Next-generation genetics in plants. *Nature* **456**, 720–723 (2008).
46. Gilbert, S. F. & Bolker, J. A. Ecological developmental biology: preface to the symposium. *Evol. Dev.* **5**, 3–8 (2003).
47. Herrmann, M., Mayer, E. W. & Sommer, R. J. Nematodes of the genus *Pristionchus* are closely associated with scarab beetles and the Colorado potato beetle in western Europe. *Zoology* **109**, 96–108 (2006).
48. Herrmann, M. *et al.* The nematode *Pristionchus pacificus* (Nematoda: Diplogastridae) is associated with the Oriental beetle *Exomala orientalis* (Coleoptera: Scarabaeidae) in Japan. *Zool. Sci.* **24**, 883–889 (2007).
49. Sokoloff, A. *The Biology of Tribolium* (Oxford Clarendon, Oxford, 1972).
50. Hong, R. L., Svatos, A., Herrmann, M. & Sommer, R. J. The species-specific recognition of beetle cues by *Pristionchus maupasi*. *Evol. Dev.* **10**, 273–279 (2008).
51. Hong, R. L., Witte, H. & Sommer, R. J. Natural variation in *P. pacificus* insect pheromone attraction involves the protein kinase EGL-4. *Proc. Natl Acad. Sci. USA* **105**, 7779–7784 (2008).
52. Jackowska, M. *et al.* Genomic and gene regulatory signatures of cryptozoic adaptation: loss of blue sensitive photoreceptors through expansion of long wavelength-opsin expression in the red flour beetle *Tribolium castaneum*. *Front. Zool.* **4**, 24 (2007).
53. Darling, J. *et al.* Rising starlet: the starlet sea anemone *Nematostella vectensis*. *BioEssays* **27**, 211–221 (2005).
54. Jeffery, W. R. Cavefish as model system in evolutionary developmental biology. *Dev. Biol.* **231**, 1–12 (2001).
55. Pigliucci, M. Evolution of phenotypic plasticity: where are we going now? *Trends Ecol. Evol.* **20**, 481–486 (2005).
56. West-Eberhard, M. J. *Developmental Plasticity and Evolution* (Oxford Univ. Press, Oxford, 2003).
57. Saenko, S. V., French, V., Brakefield, P. M. & Beldade, P. Conserved developmental processes and the formation of evolutionary novelties: examples from butterfly wings. *Philos. Trans. R. Soc. Lond., B* **363**, 1549–1555 (2008).
58. Laforsch, C. & Tollrian, R. Embryological aspects of inducible morphological defense in *Daphnia*. *J. Morph.* **262**, 701–707 (2004).

59. Abouheif, E. & Wray, G. Evolution of the gene network underlying wing polymorphism in ants. *Science* **297**, 249–252 (2002).
60. Van Valen, L. Festschrift. *Science* **180**, 488 (1973).
61. Hoekstra, H. E. & Coyne, J. A. The locus of evolution: evo devo and the genetics of adaptation. *Evolution* **61**, 995–1016 (2007).
62. Lynch, M. The frailty of adaptive hypotheses for the origins of organismal complexity. *Proc. Natl Acad Sci. USA* **104**, 8597–8604 (2007).
63. Hill, R. C. *et al.* Genetic flexibility in the convergent evolution of hermaphroditism in *Caenorhabditis* hermaphrodites. *Dev. Cell* **10**, 531–538 (2006).
64. Shapiro, M. D. *et al.* Genetic and developmental basis of evolutionary pelvic reduction in threespine sticklebacks. *Nature* **428**, 717–723 (2005).
65. Corley, S. B., Carpenter, R., Copsey, L. & Coen, E. Floral asymmetry involves an interplay between TCP and MYB transcription factors in *Antirrhinum*. *Proc. Natl Acad Sci. USA* **102**, 5068–5073 (2005).

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DATABASES

Entrez Genome: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome
Caenorhabditis elegans | *Drosophila melanogaster* | *Nasonia vitripennis* | *Nematostella vectensis* | *Pristionchus pacificus* | *Tribolium castaneum*

FURTHER INFORMATION

Ralf Sommer's homepage: http://www.eb.tuebingen.mpg.de/departments/4-evolutionary-biology/department-4-evolutionary-biology
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