Evo-Devo and Phylogenetics

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Abstract

The contribution of evolutionary developmental biology (evo-devo) to phylogenetics has two aspects. The first is methodological: how to partition the phenotype into independent characters, in the light of the evolvability and modularity of developing systems. Evolvability, the ability to produce heritable phenotypic variation, has taken central role in explanations of evolutionary change, together with an increasing appreciation of the complex relationships between genotype and phenotype, which are characterised by (1) pleiotropy, (2) the involvement of a large number of genes in controlling single phenotypic traits, (3) the presence of polyphenism due to the influence of external, nongenetic factors, and (4) the

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modular architecture of developing systems. This allows for the occasional manifestation of saltational evolution. The second contribution of evo-devo to phylogenetics relates to specific sources of information that can be used in phylogenetic analysis, as provided by differences in the spatial and temporal patterns of expression of developmental genes or whole gene regulatory networks and by heterochronic patterns, especially in the framework of sequence heterochrony where changes in the temporal sequence of individual developmental events are considered relative to other events in the ontogeny of the same organism. In turn, a sound understanding of phylogenetics can benefit evo-devo in the selection of new model species.

Keywords

Heterochrony · Homology · Model species · Phylogeny · Saltational evolution

Introduction

Evolutionary developmental biology, or evo-devo, emerged as an independent discipline within the life sciences in the last quarter of the twentieth century. However, to some extent its historical antecedents can be traced back to the efforts of Etienne Geoffroy Saint-Hilaire (1772–1844), who systematically looked for equivalent structural elements in the body plans of animals as different as a vertebrate, a crayfish, and a squid, and to the long, although discontinuous, tradition of studies on *heterochrony*. When Ernst Haeckel (1834–1919) first introduced the latter term, this was intended to label a deviation from Haeckel's biogenetic "law" according to which ontogeny (the development of the individual) recapitulates phylogeny (the evolutionary history of the species). Heterochrony thus referred to circumstances where the comparative study of developmental sequences of different animals cannot be straightforwardly used to infer their evolutionary relationships. In the twentieth century, these deviations from the *biogenetic law* were the subject of Gavin de Beer's (1899–1972) ground-breaking work. This author established that an animal's ontogenetic progression towards sexual maturity does not necessarily proceed in strict conjunction with the development of its nonreproductive (somatic) structures. This decoupling allows for the two processes to run at different pace and eventually to evolve via changes in the relative time of onset or offset of somatic versus reproductive development or in their relative speed. This way, heterochrony emerged as a pervasive and variegated developmental basis of evolutionary change (Gould 1977).

However, when evo-devo eventually took form in the 1980s, this discipline's focus was largely divorced from those original ties to phylogenetics. A quarter of century later, Wiens et al. (2005) could still write that up to the time the overall contribution of evo-devo to phylogenetics had been quite small. However, a growing appreciation of the mutual benefits that can derive to both evo-devo and phylogenetics from reciprocal interactions has surfaced at last in recent years.

The contribution of evolutionary developmental biology (evo-devo) to phylogenetics has two aspects. The first is methodological: how to partition the phenotype into independent characters, in the light of the evolvability and modularity of developing systems. Evolvability, the ability to produce heritable phenotypic variation, has taken central role in explanations of evolutionary change, together with an increasing appreciation of the complex relationships between genotype and phenotype. The second contribution of evo-devo to phylogenetics relates to specific sources of information that can be used in phylogenetic analysis. In turn, a sound understanding of phylogenetics can benefit evo-devo in the selection of new model species.

Evo-Devo's Contribution to Phylogenetics

The advent of evolutionary developmental biology offers indeed new opportunities to extract phylogenetic information from a comparison of developmental schedules of different species (Telford and Budd 2003; Minelli et al. 2007). Evo-devo's contribution to phylogenetics has two aspects. The first is methodological: how to partition the phenotype into independent characters; the second relates to specific sources of information to be used in phylogenetic analysis, as suggested by heterochrony or by comparative patterns of expression of developmental genes.

Partitioning the Phenotype into Individual Characters

One of the main steps in a phylogenetic analysis is filling a data matrix: the rows are the taxa (usually, species) to be compared, the columns are the characters for which the taxa are compared. A basic requirement is, to include only mutually independent characters, to avoid giving more weight to those that are instead interdependent. In practice, however, it is often difficult to determine if two characters are actually independent or to which extent.

Independence between two characters means that changes in one of them are not necessarily accompanied by changes in the other. On one side, this lack of correlation can be due to a lack of functional coupling, on the other side it reveals the autonomy of the developmental processes on which each character depends, a circumstance that in principle corresponds to the expression of different genes, or at least to spatial, temporal, or quantitative differences in the expression of the same genes. Here is an area where evo-devo can positively contribute to a phylogenetic analysis. To see how, we must refer to two key concepts of evolutionary developmental biology: evolvability and modularity.

With the advent of evolutionary developmental biology, *evolvability*, i.e., the ability to produce heritable phenotypic variation (Hendrikse et al. 2007) has taken central role in explanations of evolutionary change, together with an increasing appreciation of the complex relationships between genotype and phenotype (the so-called genotype → phenotype map; Pigliucci 2010; Wagner and Zhang 2011).

This complexity has many causes, among which (1) *pleiotropy*, i.e., the fact that the expression of one gene has commonly an effect on many phenotypic traits, (2) the involvement of a large number of genes in controlling the developmental processes culminating in the production of a single phenotypic trait, (3) the influence of external, nongenetic factors (discussed in a later section of this entry), and (4) the *modular architecture* of developing systems.

To some extent at least, a developing organism can be described indeed as a system of local units, or *modules*, dominated by specific developmental dynamics, such as those generating a leaf primordium in a plant or those responsible for the production of segments in an insect.

Evolutionary changes are also often modular, affecting individual characters that emerge as hot points of morphological evolution. In many rapid radiations, the explosion of phenotypes is essentially restricted to large variation in a well-circumscribed module. This is the case with the copulatory structures of a great number of insect groups, with the chewing structures (mastax) of rotifers, and with the stamens or the petals in flowering plants.

Even within a series of homologous parts do individual elements, or group of elements, often behave as partly independent modules. Examples in the animal kingdom are found, e.g., among the teeth of mammals (incisors, canines, premolars, molars) and the segments of arthropods (e.g., in insects, thoracic segments with legs versus abdominal segments without legs). In plants, examples of developmentally independent modules are the nectariferous petals of *Delphinium* (Ranunculaceae) and the individual petals and stamens of *Bauhinia* (Fabaceae): in this genus there are species like *B. blakeana*, with five petals and three fertile stamens, alongside species like *B. divaricata*, with two petals and one functional stamen only.

In phylogenetic analyses, understanding or at least estimating the modularity of the developmental processes underlying the morphological traits of species or lineages to be compared is important also when the evolutionary changes in developmental processes have been *systemic*, affecting many dimensions and body parts in integrated way. Systemic, that is, nonmodular change may conceal the actual relationships between phylogenetically related taxa. This is one of the contexts in which morphological evidence must be used most cautiously, and we must definitely acknowledge its subordinate importance in respect to comparative molecular data. A fitting example is provided by the duckweeds, long considered to form an easily diagnosable plant family, but eventually reduced to a subfamily of the Araceae (Henriquez et al. 2014). The systemic evolution the duckweed lineage has undergone has completely cancelled the modular architecture of the other Araceae and, indeed, of the overwhelming majority of plants, only leaving behind a thallus-like blob of green matter, sometimes (but not always) accompanied by simple roots and occasionally producing a rudimentary stamen or carpel, all that remains of a typical flower.

Genes Versus Environment and the Genotype → Phenotype Map

One of the reasons why an organism's phenotype cannot be fully predicted from the genotype is the frequent occurrence of alternative phenotypes in the absence

of genetic differences: this occurs when specific environmental cues are "interpreted" by the developing system as a switch between alternative pathways. This phenomenon is known as *phenotypic plasticity* and the multiplicity of resulting phenotypes is described as a case of *polyphenism* (reviewed in Fusco and Minelli 2010). Environmental influences are often due to differences in the relative length of day and night, a result of which is the seasonal polyphenism of some butterflies, e.g., the European *Araschnia levana*, with two generations per year (a spring and a summer one), dramatically different in their wing color patterns to the extent that they were originally described as different species. The temperature at which the embryo is exposed during incubation is involved instead in the environmental determination of sex in the American alligator, many turtles, and other reptiles, while in *Schistocerca gregaria* and other grasshoppers mechanical stress due to exceedingly frequent contacts of juveniles with theirs conspecifics results in the production of gregarious and migratory adults rather than solitary and sedentary ones.

The divide between environmentally controlled polyphenism and genetically determined polymorphism, however, is not necessarily strong. How easily this divide can be crossed is shown by the pea aphid (*Acyrthosiphon pisum*), a species where males as well as females occur in two different morphs, winged and wingless, respectively. The mechanisms responsible for the presence versus absence of wings are different in the two sexes: the male morphs represent a genetic polymorphism, whereas the female morphs depend on the photoperiod. However, the developmental pathways leading to these alternative phenotypes are nearly the same in both sexes: the product of the gene locus (*aphicarus*) controlling wing development in the male is also involved in the polyphenic response of the female.

There is growing evidence that populations harbor variable amounts of *cryptic variation*, that is, of variation that is not expressed under the environmental conditions under which the population currently lives; a change of external conditions, however, may uncover this variation and cause the expression of novel phenotypes. This can be of consequence in phylogenetic analyses. On the one hand, the previously unobserved phenotypes may wrongly suggest a phylogenetic distance quite higher than eventually demonstrated by molecular studies; on the other, the newly expressed phenotypes can offer new targets to selection and thus accelerate evolutionary divergence and perhaps the emergence of evolutionary innovations (Moczek et al. 2011).

Saltational Evolution

Before the advent of evo-devo, a serious obstacle to reconstructing phylogeny was the nearly universally (although mostly tacitly) accepted principle, that evolution necessarily proceeds by progressive accumulation of small changes; as a consequence, species differing in very conspicuous aspects could hardly be acknowledged to be phylogenetically close relatives. The strength of this preconception has been strongly reduced by evo-devo. Several lines of evidence concur indeed in demonstrating that the changes in developmental processes necessary to obtain a new,

strongly divergent phenotype are not necessarily proportional to the morphological distance between the old and the new phenotypes. On the other hand, in many evolutionary lineages, some hypothetical phenotypes differing from those occurring in nature only in minor detail do never occur because of internal constraints in the developmental processes by which the phenotype is produced. As a consequence, the actual distribution of phenotypes within a clade may reflect developmental constraints (inequalities of evolvability in different directions) rather than phylogenetic affinities, thus inviting caution in the course of phylogeny reconstructions. Segment number in centipedes offers a case in point.

All adult specimens of all centipede species have an odd number of leg-bearing segments. This number is fixed and identical in all species of some subgroups (e.g., it is always 15 in all of the ca. 1000 species of lithobiomorph centipedes described to date) but variable in others, often even within a brood issued from the same parents, for example, between 51 and 59, but limited to the odd values: specimens with 52, 54, 56, or 58 pairs of legs simply do not occur. Thus, moving from a "permitted" number, e.g., 57, to one of the arithmetically closest values (56 or 58) is not possible. Nevertheless, a much larger change, i.e., sudden and likely very recent duplication of the number of leg pairs has been observed in a lineage of scolopendromorph centipedes. Most of the *ca*. 700 species belonging to this clade have a fixed number of 21 pairs of legs, although several have 23, with a single species (*Scolopendropsis bahiensis*) including specimens with 21 leg-bearing segments along with others with 23. A duplication of the whole set of trunk segments has been suggested (Minelli et al. 2009) to account for the origination of the closely related *Scolopendropsis duplicata*, a newly discovered species where leg-bearing segments are either 39 or 43. This species has likely diverged from *S. bahiensis* quite recently, as the dramatic increase in segment number is the only obvious difference between the two *Scolopendropsis* species. It has been hypothesized that the duplication of trunk segment number, a phenotypically major leap, was very likely the effect of a minor genetic and developmental change.

Developmental Genes and Phylogenetic Inference

The most conspicuous body of information generated thus far within evolutionary developmental biology is about the so-called "developmental genes," i.e., genes demonstrably involved in the control of specific ontogenetic events or in the shaping of specific traits of body architecture. Data spans from the mere identification of these genes and of their nucleotide sequence, to the temporal and spatial patterns of expression, and the mechanisms by which the expression of these genes is modulated and the way by which, in turn, their products modulate the spatial or temporal expression of other genes.

These genes can be studied at different levels for their potential phylogenetic signal.

A first step is to use the gene sequences to reconstruct the phylogeny of the organisms from which the genes have been isolated. In the case of animals, several authors have looked at the *Hox genes* as to privileged genes supposed to carry

important phylogenetic signal because of their roles in controlling key aspects of the animal's body architecture such as the orderly sequence of organs along the animal's antero-posterior body axis. There are studies, for example, where Hox gene sequences are used in reconstructing the relationships among the bilaterian phyla or the major clades within the Arthropoda.

The next step is to search for homologies at the level of gene expression patterns. This way, largely accepted homologies between body regions of distantly related arthropod taxa, such as insects and arachnids, have been traced by comparing the expression patterns of *Hox* genes.

These patterns are nevertheless subject to evolution, because of *gene duplication* followed by functional divergence of the *paralogous* copies thus obtained, or by *changes in the gene's regulatory sequences*, not to mention *gene loss*. As a consequence, we observe changes in the spatial extent or in the timing or level of gene expression.

Examples of the different way in which a morphological trait can be modified by changes in the regulation of the expression of the same genes are provided by the pattern of dorsal bristles on the thorax of Diptera, which is controlled by the expression of the gene *scute*. Changes in the spatial expression of *scute* account for the differences between more distantly related taxa, such as *Ceratitis capitata*, *Drosophila melanogaster*, and *Calliphora vicina*, whereas differences in the timing of this gene's expression underlie the differences in the bristle pattern of *Calliphora vicina* compared to another calliphorid, *Protophormia terranovae.* Changes in the expression level of just two genes (*bone morphogenetic protein 4* and *calmodulin*) are instead responsible for the conspicuous differences in beak shape among Darwin's finches (*Geospiza*).

With the rapidly increasing knowledge on gene control cascades, attention has shifted from individual genes to whole gene regulatory networks. An exceptional example of the evolvability of developmental gene networks has been revealed in a comparison of notochord development in the pelagic urochordate *Oikopleura* and the ascidian *Ciona intestinalis*. In the latter, some 50 genes are known to be activated downstream of *Brachyury*, but 24 of them do not have a homologue in the small, very compact genome of *Oikopleura*. Some of the latter have undergone a lineage-specific duplication, but less than a half of them are apparently expressed in the context of notochord formation.

However, the different components of a gene regulatory network do not necessarily evolve at the same pace. For example, within the gene regulatory network controlling the specification of the endomesoderm in nematodes, evolution is most rapid for some genes involved in the specification of blastomere identity, as suggested by a comparison between the genomes of *Haemonchus contortus* and *Brugia malayi* (Maduro 2006).

Evolving Gene Functions

In animals as distantly related as are squids, insects, and vertebrates, the morphogenesis of the eye is controlled in part by the lineage-specific homologues of the

same genes. The best known and arguably the most important of these genes is *Pax6* (also known as *eyeless* in *Drosophila*). The widespread involvement of *Pax6*/*ey* homologues in eye morphogenesis has suggested a common (monophyletic) origin of all animal eyes (Gehring and Ikeo 1999), despite the gross morphological differences between ciliary-type eyes, as are those of vertebrates, and rhabdomeric-type eyes, as are those of insects, a large structural difference that would instead suggest that eyes originated at least twice independently.

However, its involvement in building eyes is not necessarily the original developmental role of *Pax6*. First, the expression of *Pax-6* is not restricted to the eyes. For example, in the squid, *Pax6* expression extends to the brain and the arms; in vertebrates, to a large part of the nervous and sensory systems, including nasal placodes, diencephalon, latero-ventral hindbrain, and the spinal cord; in *Drosophila*, its homolog *ey* is expressed, other than in the eye, also in the brain and the ventral nerve cord. Second, *Pax6* homologues are also present in eyeless animals, for example, in the roundworms (nematodes) and in the sea urchins. In the latter, a *Pax6* homolog is expressed in the tube feet. A likely conclusion is that *Pax6* was a patterning gene, originally expressed in the head, which has been co-opted several times in the regulation of eye development.

Dramatic functional changes have been recorded in the evolution of two members of the Hox gene family in some arthropod lineages. Hox genes, as mentioned above, are best known to specify positions along the main body axis of bilaterian animals. In the arthropods, however, one of these genes (re-named here *fushi tarazu*) is involved instead in the segmentation of the trunk and also (limited to the insects) in neurogenesis. Another Hox gene (*zerknüllt*, shortly *zen*) is involved in dorso-ventral patterning. In the flies (Diptera), a duplication of *zen* has given rise to a new functionally divergent gene, *bicoid*. In *Drosophila*, *bicoid* is required for the normal development of head and thorax, and in another dipteran, the scuttle-fly *Megaselia abdita*, it is also required for the development of four abdominal segments.

These examples show that major changes in gene functions do not necessarily determine an acceleration of morphological evolution. In other terms, homology at the level of genes, and genes expression patterns, does not necessarily suggest homology of morphological features and vice versa.

The Phylotypic Stage

The independence of developmental modules is limited by constraints, more evident at specific times along the ontogeny: specifically, largely invariant stages shared by (most of) the members of a large group such as vertebrates, or insects, can be often recognized. These stages do not coincide with the earliest embryonic stages, which are dramatically affected by conditions such as the amount and spatial distribution of the yolk in the egg, which is sometimes very different between closely related species. For example, the sea urchin *Heliocidaris tuberculata* produces small eggs, with a modest amount of yolk, which develop into a typical pluteus larva, but the very closely related species *H. erythrogramma*, barely distinguishable from

H. tuberculata in the adult stage, produces instead much larger eggs, full of yolk, from which a juvenile develops directly, bypassing the conventional larval stage. The initially divergent developmental trajectories converge however towards a later, much more conserved stage (Richardson 2012). This stage, which is called the *phylotypic stage*, is sometimes recognizable as characteristic for a whole phylum, although it must be acknowledged that often, rather than a point in development, what is conserved is instead a *phylotypic period*. This term refers to a more or less extended segment of the developmental trajectory, within which the traits shared by the members of a phylum are more or less faithfully conserved among a smaller or larger number of species. As expected, gene expression is maximally conserved around the phylotypic stage or period.

Phylogenetic Signal from Heterochronic Patterns

From the old-fashioned perspective of Haeckel's recapitulation principle (ontogeny recapitulates phylogeny), heterochrony was nothing but noise obscuring the potential contribution of a detailed knowledge of ontogeny to the reconstruction of phylogeny. Subsequent studies, however, have shown that heterochrony per se can be informative about affinities, that is, in technical language, that heterochrony may contain phylogenetic signal.

The traditional approach to heterochrony focused on developmental changes in size and shape relationships: in terms of *growth heterochrony*, two major patterns were distinguished, *paedomorphosis* and *peramorphosis*, according to whether maturation is anticipated or delayed and/or the growth period is shortened or extended, respectively.

Recognizing these evolutionary patterns of change in the developmental sequences of the species to be compared can be dramatically important to avoid serious pitfalls in the reconstruction of phylogeny. A good example is provided by salamanders. Several lineages of salamanders have evolved via paedomorphosis, that is, they retain throughout their life larval traits such as the presence of external gills. This has serious consequences on a phylogenetic analysis based on morphology. Lineages that have independently evolved by paedomorphosis will likely cluster together, irrespective of their actual affinities. In some phylogenetic analyses, most paedomorphic families (Amphiumidae, Dicamptodontidae, Sirenidae, Proteidae) cluster indeed in a single clade, including also individual paedomorphic representatives of the Plethodontidae and Ambystomatidae. This obscures the actual affinities of these lineages. To uncover the latter, it is not necessary to rely on molecular rather than morphological evidence. The same result is obtained by excluding from the data matrix of morphological data those traits that are affected by paedomorphosis, which have been acquired independently by these different lineages, accompanied by the loss of lineage-specific traits retained instead by their nonpaedomorphic relatives (Wiens et al. 2005).

An increasing appreciation of the modularity of developmental processes has fostered a new approach to heterochrony, termed *sequence heterochrony* (Smith

2001), focused on the changes in the temporal sequence of individual developmental events relative to other events in the ontogeny of the same organism. Given two events A and B in a developmental sequence, these can occur in one of the following orders: (i) A occurs before B, (ii) A and B are simultaneous, or (iii) A occurs after B. Translated into numerical codes, these timing relationships are assembled in a matrix which is subsequently subjected to phylogenetic analysis according to the current methods.

In the flowering plants, heterochronies in the production of individual floral parts can be responsible for conspicuous and phylogenetically informative differences. For example, a number of clades in the legume family (Fabaceae) are characterized by heterochronies such as the anticipation or retardation in the production of a whole whorl with respect to another (e.g., stamens vs. petals) or of a single organ (e.g., a sepal or a petal) with respect to the other elements of its whorl.

In vertebrates, the relative times at which the fore and hind limbs differentiate are characteristic of different clades (Bininda-Emonds et al. 2007). In the primitive condition, as seen in cartilaginous and bony fishes, forelimbs develop earlier than the hind limbs. In the frogs (anurans), hind limb development precedes instead the differentiation of the anterior pair of appendages. In most of the remaining vertebrates, the development of the two limb pairs is nearly synchronous.

A study of sequence heterochrony involving numerous characters has proved effective in fixing the phylogenetic position of the turtles in the phylogeny of amniotes (Werneburg and Sanchez-Villagra 2009).

Phylogenetics to the Benefit of Evo-Devo

Selecting New Model Species

Despite the pervasive comparative attitude that differentiates evo-devo from many other disciplines in the life sciences, most of the experimental results thus far contributed by evolutionary developmental biology have been obtained on a small number of model species. The list of evo-devo's choice model organisms includes animals such as mice (*Mus musculus*), chicken (*Gallus gallus*), zebrafish (*Danio rerio*), the sea squirt (ascidian) *Ciona intestinalis*, a few sea urchin species such as *Heliocidaris tuberculata* and *H. erythrogramma*, the fruitfly *Drosophila melanogaster*, and a tiny nematode worm (*Caenorhabditis elegans*), plants as the thale cress (*Arabidopsis thaliana*), tomato (*Lycopersicon esculentum*), snapdragon (*Antirrhinum majus*), and rice (*Oryza sativa*) plus the moss *Physcomitrella patens*. Except perhaps for *Ph. patens*, all these organisms were selected only because of practical advantages, such as short generation time and easy adaptation to artificial environment. Of recent, however, most suggestions for new entries to be added to the list of model organisms advocate the phylogenetic position of a species as anticipating its value in future comparisons (Milinkovitch and Tzika 2007). However, there are no scientific reasons to expect that the topology of the phylogenetic tree will inform us unambiguously about historical changes affecting characters

other than those that have been used to build the tree. Unfortunately, there are no macroevolutionary laws suggesting strong consistent trends in character variation across the different branches of the tree.

Attention has been primarily targeted towards "basal" representatives of a smaller or larger branch of the tree of life (i.e., organisms belonging to lineages that are considered to have branched off early from the common ancestor): the expectation is that a "basal" branch will be a good proxy for the unknowable common ancestor of a major clade. However, time (thus, opportunity to change) has run to the same length for all branches stemming from the same common ancestor, irrespective of their branching order; in other terms, a "basal" species is not necessarily a more conserved model of an ancestor, that is, a repository of primitive character states (Jenner 2006; Minelli and Baedke 2014).

The inadequate concern hitherto demonstrated by evo-devo researchers for comparisons within a suitable phylogenetic context is also shown by the fact that many of the popular model species belong to taxonomically small or very small genera, e.g., *Arabidopsis* (12 species), *Ciona* (9), *Heliocidaris* (6), *Caenorhabditis* (4), *Gallus* (4), and *Physcomitrella* (2). From this perspective, a welcome new entry is the scarab beetle genus *Onthophagus*, with about 2000 species, some of which are emerging as evo-devo models for the study of the developmental genetic basis of evolutionary novelties, their head and thoracic horns.

Cross-References

- ▶ Developmental Homology
- ▶ Developmental Plasticity and Evolution
- ▶ Evolvability
- ▶ Heterochrony
- ▶ Methods and Practices in Paleo-Evo-Devo
- ▶ The Developmental Hourglass in the Evolution of Embryogenesis

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