PERSPECTIVES

OPINION

Evo–devo: extending the evolutionary synthesis

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Abstract | Evolutionary developmental biology (evo–devo) explores the mechanistic relationships between the processes of individual development and phenotypic change during evolution. Although evo–devo is widely acknowledged to be revolutionizing our understanding of how the development of organisms has evolved, its substantial implications for the theoretical basis of evolution are often overlooked. This essay identifies major theoretical themes of current evo–devo research and highlights how its results take evolutionary theory beyond the boundaries of the Modern Synthesis.

Evolutionary developmental biology (evo–devo) emerged as a distinct field of research in the early 1980s to address the profound neglect of development in the standard modern synthesis framework of evolutionary theory, a deficiency that had caused difficulties in explaining the origins of organismal form in mechanistic terms[1,2]. Methodological advances such as techniques for gene cloning and visualization of gene activity in embryonic tissues facilitated the emergence of the new field by allowing the comparison of developmental processes of different taxa at the molecular level. Today, evo–devo research is characterized by a dialectical approach that, on the one hand, looks at how developmental systems have evolved and, on the other hand, probes the consequences of these historically established systems for organismal evolution. A further question is how evolutionary developmental interactions relate to environmental conditions (BOX 1). The pursuit of these core questions utilizes various conceptual and methodological approaches, representing branches of research that can be called 'programmes'.

Multiple research programmes

Over the past two decades, at least four major research programmes have formed in evo–devo, although there is extensive overlap among them.

The comparative embryology and morphology programme. This approach studies the morphogenetic differences that distinguish primitive and derived ontogenies. Information from extant species is increasingly combined with contributions from palaeontology, including fossilized vertebrate embryos and early stages of invertebrate development[3]. Through its characterization of the large-scale patterns of morphological evolution, palaeontology provides evidence for significant changes in developmental pathways, for example, through heterochrony[4], and the details of anatomical variation over hundreds of millions of years can be compared with the developmental patterns in extant species[5]. One recent approach has been to quantify ontogenetic shape transformations[6] and use phenotypic morphospace concepts[7] for the evolutionary interpretation of developmental data.

The evolutionary developmental genetics programme. This approach focuses on the evolution of the genetic machinery of development[8]. Rapid progress in the cloning of regulatory genes and new techniques of visualizing gene expression in embryonic tissues has made this the most productive area of empirical evo–devo today. Its foundational achievement was the discovery of extensive similarities in gene regulation among distantly related species with fundamentally different body plans[9]. The programme concentrates on the evolution of genetic toolkits and the regulatory logic that underlies organismal development; for example, the evolution of the homeotic genes through mutation, duplication and divergence. The hierarchies of gene regulatory networks and signalling pathways that regulate cell and tissue interactions are equally central[10,11]. Mapping their expression patterns and their correlation with characteristic constructional features of body architecture yields information on their possible roles in phenotypic evolution[12].

The experimental epigenetic programme. This programme examines how the dynamics of molecular, cell and tissue interactions affect evolutionary change. It looks at properties of development that are not directly genetically determined, such as self-organization or geometric and physical factors. Perturbations of cell number, cell cycle, developmental timing or inductive interactions have been shown to produce phenocopies of derived or ancestral character states[13], occasionally amounting to homeotic transformations[14]. The epigenetic approach also probes the influences of the environment on development, demonstrating that the same genotype can produce strikingly different phenotypes in response to altered external conditions[15–17].

The theoretical and computational programme. This approach concentrates on the quantification, modelling and simulation of developmental evolution, and assists the conceptual unification of evo–devo theory in conjunction with experimental research. Among its substantial tasks is relating the precise timing and topology of gene activity to actual changes in cell and tissue behaviours. This has led to the development of computational tools for the three-dimensional reconstruction and quantification of gene expression in developing embryos[18–20], and the exploration of new mathematical methodologies for the analysis of such data[21]. Multivariate analyses extend the quantitative approach to ontogenetic shape trajectories[22]. Such theoretical tools help to localize the ontogenetic

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components of phenotypic change, assist in the organization of data and link evo–devo with quantitative genetics and with the study of morphological integration[23].

Quantitative developmental data are also used for the biomorphic modelling of specific organ systems, such as tooth development (FIG. 1) or limb development[24], so as to illustrate how changes in gene activity and the self-organization of cells affect morphogenesis and the possibilities of phenotypic variation or innovation. Models help us to identify general properties of evolving developmental networks, suggesting, for instance, an evolutionary tendency to replace self-organizing 'emergent' networks with hierarchical networks[25]. This indicates that the genetically entrenched ontogenies of extant species, from which our knowledge of development is derived, constitute a stabilized and canalized condition, although greater flexibility and innovative potential might have existed in primitive systems[26].

The pluralism that is seen in today's evo–devo defies notions of a single research programme. Rather, evo–devo explores a multitude of topics at the development–evolution interface using a plethora of approaches and methods. At the same time, relatively few common theoretical themes cut across programmes and capture the consequences that evo–devo has for evolutionary theory.

Major theoretical themes

Evolution of the gene regulatory machinery is commonly regarded as a primary creative force in morphological evolution[12]. Consequently, the function and evolution of regulatory gene networks, signalling pathways and other aspects of the molecular circuitry of development have become prevalent topics of empirical research. The study of point mutations[27], transposable elements[28] and gene duplication[29] in the origin of *cis*-regulatory elements, as well as their variation[30], changes in function[31], and population dynamics[32], provides the foundation for molecular models of organismal evolution. Despite high conservation of gene regulatory elements in anatomically diverse organisms, such as Hox gene activation in vertebrates and arthropods[9], there is extensive variation in their activation patterns among individuals, populations and species. Evolutionary modifications in the segmentation and regional differentiation of major body sections are associated with shifted Hox expression domains[33,34], and changes in head and limb formation show similar shifts in Hox expression[35,36]. Given the correlations between differences in phenotype with differences in gene activation, a major line of evo–devo concentrates on developing a theory of evolving gene regulatory networks[10]. Further experimental proof will be necessary to determine the extent to which gene regulatory change has a causal role in evolution.

Viewed at the level of the phenotype, the evo–devo problem takes on a different emphasis. Here the question is how certain constructional motifs arise, how they become conserved and integrated into the body architecture, and how they are reused over and over again. Because phenotypic architecture is more robust than many of the suites of molecular and developmental interactions that are involved in its formation (BOX 2), the origin of phenotypic organization has become one of evo–devo's most salient issues. This focus necessarily includes many more factors than the evolution of gene regulation alone, notably the dynamics of epigenetic interactions, the chemicophysical properties of growing cell and tissue masses, and the influences of environmental parameters. As a consequence, several overarching theoretical themes pertaining to the explanation of phenotypic organization have emerged. Whereas an early focus was on heterochrony[37,38] and developmental constraint[39], the prominent theoretical themes today are modularity, plasticity and innovation.

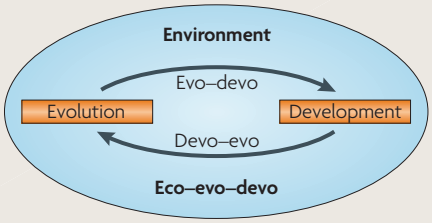
Modularity. Modular organization is pervasive at all levels of biological organization, from the genetic to the developmental, anatomical and behavioural. Modules are generally distinguished by their greater internal (intramodule) than external (intermodule) integration, by their repetitiveness and by their evolutionary persistence and reuse. The question raised by evo–devo scientists is whether certain forms of developmental modularity can be facilitators of adaptive or even non-adaptive evolution, and whether modularity represents a preferred mode of phenotypic evolution, one that is favoured by natural selection[40–42].

One way to study modularity is by the analysis of 'genotype–phenotype maps'[43]. If the correspondence between genetic variation and phenotypic variation is modular, it can be decomposed into independent maps of smaller dimension. Those modules that affect only a part of the phenotype can react to selection independently, without deleterious pleiotropic effects on other parts. The evolution of modularity as an adaptive principle, if confirmed, should enhance a population's ability to generate heritable phenotypic variation[43].

A different way to approach the role of modularity in evolution is through the study of the mechanistic relationship between developmental modules and units of phenotypic construction. Subsets of anatomical architecture can vary and adapt independently and, hence, qualify as modules. In the morphological tradition, such units have been called homologues, characterized by their autonomy in body-plan organization[44]. Because there is continuity in the phenotypic evolution of these modules, a correspondence with genetic modules that maintain the autonomy of the anatomical modules might be expected; however, this is not always the case. Numerous examples show that the molecular and developmental pathways can change over evolutionary time, whereas the anatomical modules (homologues) remain constant (BOX 2). The phenotypic end-states seem to have greater importance than the

Box 1 | **Questions at the interface between evolution and development**

Evo–devo questions
- How did development originate?
- How did the developmental repertoire evolve?
- How are developmental processes modified in evolution?



Devo–evo questions
- How does development influence phenotypic variation?
- How does development contribute to phenotypic novelty?
- How does development affect the organization of phenotypes?

Eco–evo–devo questions
- How does the environment interact with developmental processes?
- How does environmental change influence phenotypic evolution?
- How does developmental evolution affect the environment?

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maintenance of the pathways by which these states can be reached[40]. For this reason, the evolution of anatomical homology cannot be explained solely by continuities of gene regulation; rather, as the modularity approach suggests, it will be necessary to identify evolutionarily dissociable units of developmental systems, which might include epigenetic interaction systems as well as regulatory networks[45].

Phenotypic plasticity. Phenotypic plasticity, the capacity of a single genotype to produce different phenotypes in response to changing external conditions, emerges as another major theme in evo–devo. One way to approach the role of plasticity in evolution is through 'developmental reaction norms'[46]; that is, functions that relate the response of a genotype to a specific environmental perturbation. Although such effects eventually feed into developmental genetic pathways, the actual phenotypic change depends on epigenetic factors including diet, pH, humidity, temperature, photoperiod, seasonality, population density or the presence of predators. The physiological and metabolic processes that mediate interactions between the environment and development, such as endocrine and hormone activity, have a key role[16]. Other approaches focus on seasonal[47] or predator-induced[48] polyphenisms, changing nutrient regimes[49] and environmental regulation[50].

Developmental plasticity is important in evo–devo because it gives explicit consideration to the relationships among the variation of traits, natural selection, environmental influences and generative bias. Plasticity implies that selection can operate on various stages of ontogeny, and it provides a key to instances of rapid reaction of populations to changing environmental conditions. Studies of environment-dependent trait correlations and plastic responses across different environments show that changing conditions can be met with coordinated reactions. Selection might favour developmental systems that actually reduce integration, in order to allow adjustments of the relationships among traits in response to environmental circumstances[15,51].

Innovation. Innovation is a third area in which evo–devo makes an original contribution to evolutionary theory[52,53]. Whereas function shift, macromutation, and symbiosis were once invoked to explain the origin of phenotypic novelties, evo–devo concentrates on the contributions of development. Several gene regulatory changes were found to be associated with instances of novelty, as seen in the evolution of butterfly eyespots[54], insect wings[55], cephalopod tentacles[56], tetrapod digits[57], bird feathers[58] or the turtle carapace[59]. Most cases indicate the redeployment of existing regulatory circuits in new developmental contexts, but it is often difficult to demonstrate that such changes were actually responsible for the evolutionary origination of the novel character because we assess gene regulation by the study of extant species.

As an alternative approach, evo–devo also probes the mechanisms of epigenetic causation in morphological innovation. Developmental systems utilize several basic chemicophysical mechanisms that are common to non-living and living materials, which have thus been termed 'generic'[60], such as viscoelasticity, differential cohesivity, biochemical diffusion and oscillation, or mechanochemical excitability. In the context of evolving development, such mechanisms can give rise to 'generic forms' that are products not of deterministic genetic programmes, but of the properties of the material cell aggregates, resulting in tissue layering, lumen formation, segmentation, and other forms of three-dimensional patterning (FIG. 2). These simple morphogenetic templates, which can be exploited by further evolution, are thought to have an important role in the evolutionary origination and innovation of phenotypic characters[26,53].

Through the impact of these themes and of other evo–devo concepts[8,61], a significant change in the framing of research questions and the interpretation of results is in progress. It is now a widespread requirement in developmental biology that its models should not merely explain the extant condition, but must also be able to account for the evolutionary origination and modification of a given system[62]. By contrast, the important consequences of evo–devo for a more comprehensive theory of organismal evolution have not yet been equally appreciated.

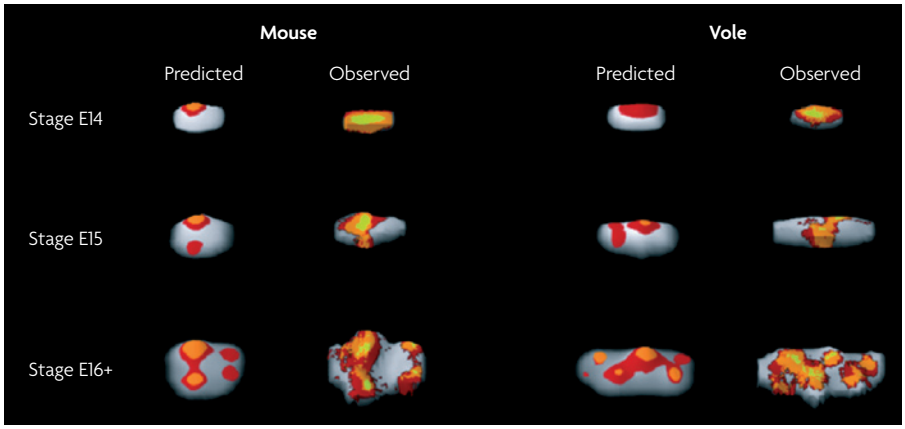

Figure 1 | **A morphodynamic model relating shape change and gene activation in the development of mammalian molar teeth.** Viewed from above, tooth crowns are characterized by a specific number and location of cusps, which arise at the sites of epithelial signalling centres called enamel knots. The model produces three-dimensional shapes of tooth crowns, and of activator and inhibitor concentrations that affect cell proliferation in enamel knot regions. The simulated shape changes during different stages of tooth growth predict areas of activator and inhibitor expression (in the left-hand columns) that can be compared with actual patterns of gene signalling that mark the enamel knots in embryonic stages of tooth development (for mice and voles, right-hand columns). In each case, the predicted concentration peaks of activator and inhibitor activity (coloured red and orange, respectively) in simulated shapes resemble the observed activity patterns of gene signalling families in natural tooth development. Coexpression domains of fibroblast growth factor 4 (*Fgf4*), sonic hedgehog (*Shh*), lymphoid enhancer binding factor 1 (*Lef1*), and *p21* (also known as *Cdkn1a*) in the cores of the enamel knots (coloured yellow) are surrounded by areas lacking *Fgf4* (coloured orange) and *Fgf4* + *Lef1* expressions (coloured red), corresponding with regions of activation and inhibition of cell proliferation. The results demonstrate that the shape of the developing tooth has a causal role in the placement of enamel knots; that is, the evolutionary variation of tooth shape will automatically lead to a change in the placement and number of cusps. Modified with permission from REF. 62 © (2002) National Academy of Sciences (USA).

Theoretical implications

Evo–devo represents a causal mechanistic approach towards the understanding of phenotypic change in evolution. In this it differs significantly from the prevailing focus in the standard theory of evolution, which is based on the correlation of phenotypic character variation with statistical gene frequencies in populations. The explanation of adaptive change as a population-dynamic event was

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Box 2 | **Examples of conserved phenotype despite altered development**

- Segmental organization is established by different morphogenetic modes in short-germ and long-germ insects, and entails different roles for homologous genes[33].
- Cell-lineage specification and gastrulation mechanisms differ in sea urchins that undergo direct development (with no larval stage) from those that undergo indirect development (including a larval stage)[78,79].
- The mode of determination of the anchor cell and its further role in vulva development differ radically in different species of nematodes[80,81].
- The cartilage precursor of the lower jaw is induced by different tissues and at different developmental stages in cyclostomes, amphibians, birds and mammals[37].
- Identical shapes of mammalian teeth can be attained by different parameter changes in morphodynamic gene networks[62].

the central goal of the Modern Synthesis. By contrast, evo–devo seeks to explain phenotypic change through the alterations in developmental mechanisms (the physical interactions among genes, cells and tissues), whether they are adaptive or not. This addresses many of the constituent features of phenotypic change, such as the generation of new structural elements (novelty), the establishment of standardized building units (modularity, homology), the arrangement of such units in lineage-specific combinations (body plans), and the repeated generation of similar forms in independent taxa (homoplasy). In addition, evo–devo aims at explaining how development itself evolves and how the control of developmental processes is brought about by the interplay between genetic, epigenetic and environmental factors. With these goals, evo–devo moves the focus of attention to the qualitative phenomena of phenotypic organization and their mechanistic causes. The major departures of evo–devo from the standard theory are characterized by the terms evolvability, emergence and organization.

Evolvability. Evolvability, the intrinsic potential of a given lineage to produce heritable phenotypic variation, is traditionally explained by the amount of genetic variation that is achieved through mutation, recombination or drift. Indeed, the variations of colour patterns in vertebrates[63] and insects[64] demonstrate that single-gene mutations or relatively few regulatory changes can result in a wide range of variant patterns. Selection acting on such loci can translate directly into colour variations, but for more complex phenotypic traits the polygenic and pleiotropic conditions make the relationship between genotype and phenotype far less direct. Evo–devo argues that the variational capacities of genomes are functions of the developmental systems in which they are embedded, for example, through their modular organization, the dynamics of their mechanistic interactions and their non-programmed physical properties. Evolvability can now be analysed and interpreted in terms of developmental variation and plasticity. Whereas such interactions would usually be seen as constraining the variational capacity of a phylogenetic lineage[39], evo–devo suggests that development might actually reduce constraints on change and thus facilitate new variational potential[51,65]. The correlation of data from ecology with physiological parameters, developmental reaction norms and gene regulatory pathways enables new modelling strategies in evo–devo[66] and includes the possibility of linking population genetics with plasticity research[15,17,67].

Emergence. Whereas evolvability addresses the contribution of development to generating phenotypic variation, emergence refers to phenomena outside the scope of variation, in particular to the modes of origination, innovation and novelty in phenotypic evolution. The gene-centric perspective of the Modern Synthesis glossed over the innovation problem by tacitly assuming that genes are the sole variable determinants of structure and that they act in linear fashion. It was sufficient to focus on the dynamics of alleles in populations, assuming the prior existence of the phenotypic entities to which they correspond. No feedback between genes, gene products, the material properties of developmental systems and their environments was taken into account. Yet the capacities for emergence lie precisely in these interactions. In evo–devo, development is regarded not merely as an effector of genetic variation, but also as a potent locus of innovation.

A theory of emergence complements the theory of adaptation through its account for the appearance of phenotypic novelties in evolution. An important starting point for this new approach is the recognition that novelties represent a particular class of phenotypic change, distinct from variation and not a direct consequence of natural

Glossary

Canalization
The developmental buffering of phenotypic traits against genetic and environmental perturbations.

Generative bias
A tendency in the production of phenotypic variation or innovation that is caused by the properties of the developmental system.

Generic form
Biological forms that result from the autonomous interactions within and among cell aggregates, based on their physical properties, without a programme-like genetic control.

Genotype–phenotype map
A mathematical characterization of the correspondence of a set of genotypes with a set of phenotypes.

Heterochrony
Evolutionary changes in the timing of developmental events, such as the onset, offset or tempo of a process.

Homeotic transformation
The change of one body part into another, caused by a genetic or epigenetic perturbation of development.

Morphospace
A three-dimensional matrix of possible morphologies that is larger than the set of actual morphologies that are realized in nature.

Modern Synthesis
The prevailing theoretical framework of evolution that resulted from a combination of genetics, systematics, comparative morphology and palaeontology in the 1930s and 1940s. Also called Evolutionary Synthesis or Synthetic Theory.

Mechanochemical excitability
The capacity of cells to respond to physical and chemical stimuli.

Ontogeny
The course of individual development of an organism from the fertilized egg to the adult.

Phenocopy
An epigenetically induced phenotypic character that resembles a genetically determined character.

Polyphenism
Alternative phenotypes that arise from a single genotype as a result of differing environmental conditions.

Viscoelastic
Materials, such as cell masses, that have both viscous and elastic properties when they respond to strain.

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selection[53]. Selection cannot set in until there are entities to be selected. This conundrum of the standard model disappears when selection is regarded as a general and unspecific background condition, whereas the actual morphological outcome, novelty, results from the specific dynamics of the developmental system that is under modification[17,26]. Empirical research in evo–devo has begun to concentrate on these issues[53], and the role of emergence in evolutionary theory is gaining crucial support[2,68]. The power of natural selection as a unique guiding force of evolution is thus challenged by evo–devo.

Organization. Evo–devo makes it possible to address the characteristic organizational features of phenotypic evolution, such as modularity, homology, homoplasy and body plans. This was not the case with a population-genetic approach and, as a consequence, these topics had been sidestepped by the Synthetic Theory[69,70]. Following the discovery of profound homologies in the regulatory genomes of anatomically diverse organisms, gene-based definitions of morphological homology had emerged[71], but were soon found to be inadequate[72,73]. Although the most notoriously conserved developmental control genes, the homeotic genes, exhibit non-homologous expression domains in the embryos of different phylogenetic lineages, the reverse also applies: homologous structures can be specified by non-homologous genes[74] (BOX 2). By contrast, evo–devo-based concepts of homology emphasize the commonalities of developmental pathways[75] and the modularity of developmental processes[73]. Another characteristic property of homology is seen in its organizing role in the genetic and epigenetic integration of developmental systems[44]. Epigenetic integration leads to the hierarchization of regulatory networks and to the fixation of the patterns of phenotypic construction in spite of changes in their individual molecular and developmental composition[25]. In this sense, increasingly elaborate gene regulatory systems serve to reproduce morphological templates. The close mapping between genotype and morphological phenotype can then be interpreted as not the cause but a consequence of evolution[26]. Thus, evo–devo recognizes in phenotypic organization not only an outcome of evolution, but also a feature that, in turn, has profound effects on further evolution, a claim that is supported by experiment[76] and modelling[62].

With its contributions to evolvability, emergence and organization, evo–devo addresses several issues that were neglected by the standard theory. The theoretical framework of the modern synthesis rests on a population genetics core that describes how the relationships between genetic variation, heredity and reproduction affect population dynamics. By contrast, evo–devo theory establishes how the relationships between genes, cells and developmental interactions affect the evolution of phenotypes. Hence, evo–devo does not invalidate the formal framework of the Modern Synthesis, but adds another level of explanation. The reach of evolutionary theory is expanded in that evo–devo accounts not for what kinds of variation are going to be maintained through natural selection, but also what kinds of variation can possibly arise from specific developmental systems. In this, evo–devo introduces a shift of emphasis regarding the role of natural selection in phenotypic evolution. Whereas in the Modern Synthesis framework the burden of explanation rests on the action of selection, with genetic variation representing the necessary boundary condition, the evo–devo framework assigns much of the explanatory weight to the generative properties of development, with natural selection providing the boundary condition. When natural selection is a general boundary condition, the specificity of the phenotypic outcome is determined by development. Thus, evo–devo moves the focus of evolutionary explanation from the external and contingent to the internal and inherent. It posits that the causal basis for

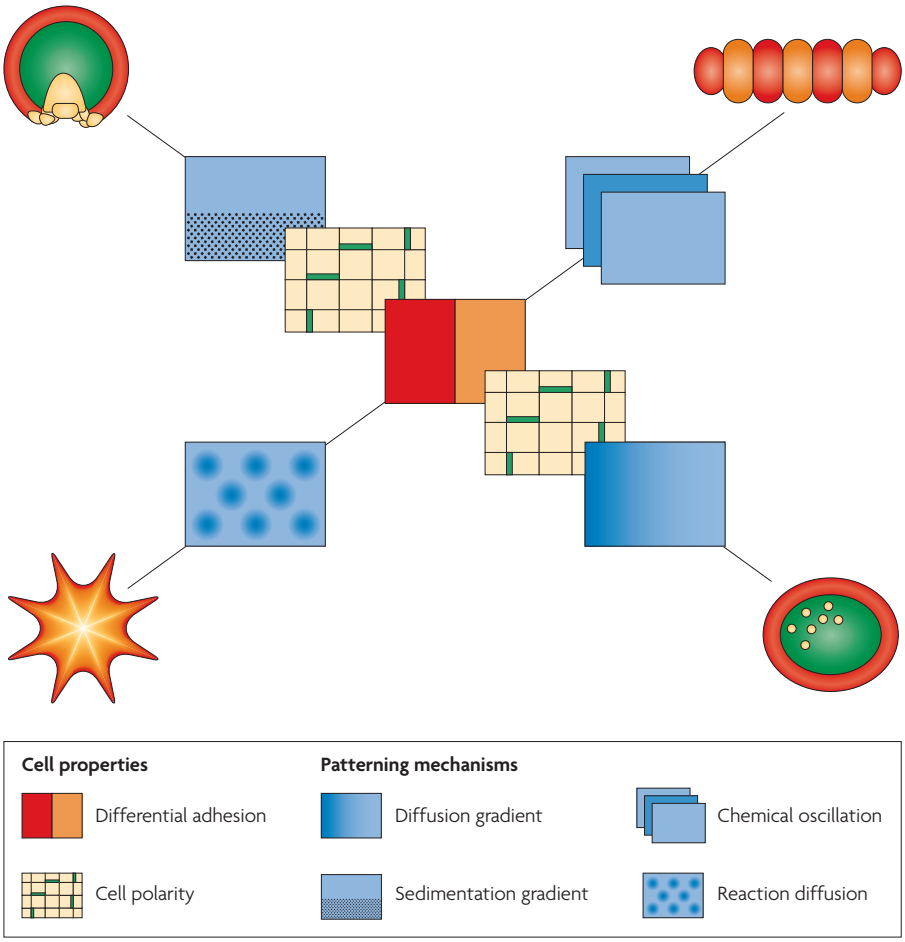

Figure 2 | **Generic forms that result from the interaction of basic cell properties with different pattern-forming mechanisms.** Differential adhesion and cell polarity (centre boxes), when modulated by different kinds of physical and chemical patterning mechanisms (blue boxes), lead to standard organizational motifs. On the upper left to lower right axis, differential adhesion properties and their polar distribution on cell surfaces lead to hollow spheres when combined with a diffusion gradient, and to invaginated spheres when combined with a sedimentation gradient. On the lower left to upper right axis, the combination of differential adhesion with a reaction-diffusion mechanism generates radially periodic structures, whereas a combination with chemical oscillation results in serially periodic structures. Early metazoan body plans represent an exploitation of such generic patterning repertoires Modified with permission from REF. 82 © (2006) UBC Press.

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phenotypic form resides not in population dynamics or, for that matter, in molecular evolution, but instead in the inherent properties of evolving developmental systems.

Challenges ahead

Evo–devo has stimulated biological research enormously, both empirically and theoretically, and its various programmes will continue to yield new data on the developmental mechanisms that underlie organismal evolution. However, several challenges lie ahead. One is whether and, if so, how the emerging new concepts can be tested empirically. How, for instance, will it be possible to ascertain that differences in gene expression or gene regulation, as observed in closely related but phenotypically diverse taxa, have actually been causal in the origin of the phenotypic change? New techniques of genetic manipulation and the increased use of non-model organisms expand the range of experimental possibilities to approach these questions. At the same time, the mechanisms of self-organization, generic tissue induction, developmental plasticity, environmental factors and so on include non-genetically programmed aspects of development that must be tested by even more demanding experimental setups. Although theoretical results from evo–devo point to the evolutionary importance of these epigentic factors, the formulation of research projects and funding strategies still needs to catch up with these requirements.

A second major challenge arises in the realm of the theoretical integration of evo–devo with the formal framework of evolutionary theory. Because the prevailing Synthetic Theory is focused on population dynamics, an inclusion of information from developmental systems will be difficult to achieve, as current evo–devo does not generate data that can be easily entered into population-dynamic algorithms. Although obtaining such data is not excluded in principle, and new tools for quantifying gene regulatory and morphogenetic variation open up exciting possibilities towards this goal, it will require an additional effort to develop suitable formalizations that enable theoretical integration. Quite conceivably, the population-theoretical framework will coexist, at least for some time, with the mechanistic models of phenotypic evolution that are derived from evo–devo. Alternative conceptions, such as epigenetic inheritance systems[77], will also need to be explored with regard to their capacity to integrate with evo–devo theory.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene
Cdkn1a | *Fgf4* | *Lef1* | *Shh*

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