

*Making evolutionary predictions about the structure
of development and morphology: beyond the
neo-Darwinian and constraints paradigms*

Isaac Salazar-Ciudad

According to Darwinism, evolution occurs because, in populations, there is heritable phenotypic variation, and then ecological factors differentially affect the contribution of each of those variants to the next generation. Thus, to understand the way in which phenotypes in a population change over generations (this is the direction of evolutionary change) two questions need to be addressed: (1) which phenotypic variants arise in each generation, and (2) which of these variants are filtered out by ecological factors in each generation. In each generation, and assuming no dramatic genomic rearrangements, developmental dynamics determine which morphological variation arises from genetic and environmental variation. Developmental dynamics are currently not very well understood and thus the question of which phenotypic variants arise in each generation is not well understood either. A different emphasis is given to each of these two questions by different approaches or schools of thought in evolutionary biology.

For many evolutionary biologists, especially those close to the core of neo-Darwinism, this lack of understanding about development has not always been perceived as a limit on progress in understanding morphological evolution (Haldane 1932, Mayr 1982). For some authors (Haldane 1932) this does not derive from lack of understanding development. Instead, natural selection is seen as the main or unique force determining how the phenotype changes (Fisher 1930, Charlesworth *et al.* 1982). The question of which phenotypic variation arises and what its role is in determining how phenotypic distributions change over time is either not addressed or assumed to be unanswerable. Which variation is produced is essentially seen, according to the neo-Darwinian view, as unpredictable, other than that it should be abundant, small (gradual) and, in principle, possible in any trait.

Evolving Pathways: Key Themes in Evolutionary Developmental Biology, ed. Alessandro Minelli and Guiseppe Fusco. Published by Cambridge University Press. © Cambridge University Press 2008.

These views about the role of development and variation in evolutionary theory have found many detractors during the past century, especially since the 1980s (Alberch 1980, Goodwin 1994, Newman and Müller 2000). This research claims that development has an important effect in evolution because it produces variation that differs from the variation assumed by the neo-Darwinian view. These studies introduce concepts such as developmental constraint, developmental bias, evolutionary novelty and robustness (Müller, Chapter 1 of this book) to describe aspects of evolution that are not conveniently approached from the Modern Synthesis. Often these approaches are not perceived as an integrated or consensus alternative to the Modern Synthesis nor as being in total agreement with it. Most of this research, which will be referred to here as the constraint school, involves conceptual (Alberch 1980, Horder 1989, Goodwin 1994, Fusco 2001, Arthur 2004) and experimental embryology studies (Richardson and Chipman 2003, Newman and Müller 2005) considering how development can affect morphological evolution, but not (with some exceptions: Newman and Müller 2000) how developmental mechanisms themselves evolve.

The advances in developmental genetics towards the end of the twentieth century have been perceived (Gilbert and Sarkar 2000) as a unique opportunity to integrate development into evolutionary theory. Many of these studies are concentrated on the search for the ultimate molecular differences underlying morphological differences between species. This does not directly explain which morphological variation is possible depending on genetic variation in development (question 1). Most of the research in developmental genetics is experimentally driven. The extraction of general theoretical insights to explain which morphological variation development can produce is just at its beginning, and it is still not clear how these insights will modify evolutionary theory or the relationship between the developmental constraint school and the Modern Synthesis.

This chapter critically reviews some advantages and disadvantages of these three schools of thought, neo-Darwinism, the developmental constraints school and developmental genetics, in understanding the way in which morphology changes in evolution (as described). It will be discussed how some assumptions of neo-Darwinism contrast with what is currently known about morphological variation and its developmental bases, how the constraint school and developmental genetics share or require some neo-Darwinian assumptions, and how research agendas in developmental genetics can be slightly rephrased so that they can be more easily used in the other two schools and, in general, for the study of how development

affects evolution. A new set of concepts and studies that try to avoid these disadvantages will be explained. These will be used to argue that some aspects of the evolution of morphology and development are predictable if some information is available about development and selective pressures in previous generations. These new concepts allow us to approach questions that are not within reach for these three schools. Inferences will be made about the relative involvement of different types of developmental mechanisms in the evolution of morphology under different selective pressures. In general the aim is to explain how the study of pattern formation can help in understanding which morphological variation is possible in development (question 1) and, at the same time, how development itself evolves.

THE NEO-DARWINIAN APPROACH TO MORPHOLOGICAL EVOLUTION

Morphological variation is produced by the process of development. In order for natural selection to be the main force in determining how morphology changes it is required that (1) any small morphological variant is possible and (2) that genetic and morphological variation are linked by a simple relationship. If the first assumption does not hold true, then the direction of morphological change is also determined by which morphological variants are possible and/or more frequent. If the relationship between genotype and phenotype is not simple, then evolving from one morphology to another one that is more adaptive may not always be possible. This is either because morphologies produced by similar genotypes might be very different and then have very different fitness values, or because similar morphologies are not easily accessible through changes in development. Consequently, there is not always a path of permanently increasing fitness leading from one morphology to another.

Studies in population and quantitative genetics do not claim that any variation is possible. Instead, it is claimed that there is abundant additive genetic variation, that variation is of small magnitude and that it can be accumulated to eventually produce any trait value. These conditions are necessary but not sufficient for selection to be the only force determining the direction of evolution. For that, it is also required that any combination of trait values is possible. In other words, if the morphology of an individual can be represented as a point in a hyperspace of trait values, any point should be reachable by accumulation of small mutational steps. This implies, since traits are arbitrary, that in each generation, variation is possible in any direction (any small change in trait value combinations).

Defining what is a small or gradual change is relative and there has been lengthy discussion about it (Mayr 1982, Gould and Eldredge 1977). The question of the nature of morphological variation (question 1) has been directly addressed much less frequently (Alberch 1980, Goodwin 1994, Newman and Müller 2000, Salazar-Ciudad 2006b). These assumptions may be useful when studying simple univariate traits and, in fact, many artificial selection studies show that there is abundant, small, cumulative, heritable variation for these traits (Weber 1992, Bronikowski *et al.* 2004). However, when morphology is described by several measurements, the variation observed is neither isotropic nor possible for all trait combinations. For some trait value combinations, there is no variation (the traits are highly correlated) while for others, there is variation.

There is no evidence that the relationship between phenotype and genotype is simple. In fact, one of the few general perceptions acquired from the study of development, and already claimed before the advent of modern developmental biology, is that this relationship is anything but simple (Horder 1993). Most genes affect several traits in a way that depends on the environment and/or the rest of the genotype. Some small genetic changes can give rise to dramatic phenotypic effects (Kangas *et al.* 2004) whereas sometimes relatively large genetic changes (such as gene deletions) can produce no obvious phenotypic changes in laboratory conditions (Wilkins 2001). Moreover, the same new phenotype can be produced by different genetic changes (Alberch 1980, Horder 1989). As such, even when the question is only about the kinetics of replacement between morphological variants, developmental dynamics cannot be ignored. In other words, the adaptive landscape where each genotype has a fitness according to the morphology it produces is often complex because the mapping between genotype and morphology is often complex.

Studies of multivariate quantitative genetics do not rely on these assumptions about morphological variation. The relationship between genotype and phenotype is not assumed, and neither are the magnitude and nature of variation; instead, they are estimated statistically as the matrix of additive genetic covariance between traits. Again, however, the question is mainly about the kinetics of replacement between variants. Which variation appears is not explained but merely described. This approach cannot explain anything about the evolution of development or about how, and how often, G-matrices evolve. In addition, there are some methodological assumptions that are worth considering. Morphology is often measured on the basis of a set of traits that are (arguably) homologous between the individuals compared. With this approach, morphological variation

changing the features that are used to define the traits themselves is not contemplated. The same situation applies to morphological changes that have no obvious homology with previous morphologies. This problem is relevant because this kind of variation is likely to be classified as novelty (Müller and Wagner 1991), and novelty is the kind of phenomenon that has been claimed to be difficult to explain from the neo-Darwinian approach. The mathematical apparatus of quantitative genetics requires that each trait value is determined by the sum of many genes or loci of small and invariable phenotypic effect. In other words, the effect of a gene does not depend on the other genes in the genotype. Quantitative genetic models with epistasis also exist but also assume phenotypic values determined by the summation of genetic effects. In addition, since all measurements are based on variances, these methods work better when phenotypic distributions are normal and in fact, the summing up of many genes of small effect warrants normal distributions. However, these assumptions contrast with what is known about development. The coordination of the interactions of gene products during development is hardly describable as the addition of the effects of genes that are independent of the genetic background. On the contrary, the role of a gene, and which traits it affects, normally depends on the rest of genes in a genome. In other words, epistasis is more often the rule than the exception. As a result, G-matrix estimations are often variable with the genetic background (Carlborg and Haley 2004). This problem is likely to be more important for complex morphologies (Salazar-Ciudad 2006a). In fact, in those few cases in which genetic and cellular interactions have been mathematically modelled to reproduce accurately, through development, complex adult morphologies (Salazar-Ciudad and Jernvall 2002, Harris *et al.* 2005, Newman and Müller 2005) the genetic architecture of morphological variation has turned out to be totally different from the one assumed by quantitative genetic inferences (phenotypic traits are not determined by summation of fixed genetic effects).

THE CONSTRAINT SCHOOL

Many studies in the early 1980s and afterwards (Alberch 1980, Goodwin 1994, Newman and Müller 2000) have argued that, even if natural selection cannot always act on how the phenotypes are produced (Mayr 1982), understanding developmental dynamics is important because it determines which kind of morphological variation can appear from genetic variation (question 1). This is normally stated as development constraining (Maynard Smith *et al.* 1985) or biasing morphological evolution. These

concepts are devised to contrast with the previous view in which any small morphological variation is possible. However, all morphological variation is produced by development and because of development. This means that even the neo-Darwinian assumptions on variation logically require development to work in a specific way (as described in the previous section and in Salazar-Ciudad 2006a). However, the question is not whether development constrains evolution (or whether there are developmental constraints) because development is always there. In fact, contrary to what has been proposed, developmental constraints cannot be tested (Beldade *et al.* 2002; see Salazar-Ciudad 2006a for a discussion). The question is, instead, how different kinds of development affect evolution. This question should be addressed by looking at which variation each kind of development can produce (and not which imaginable variation they cannot produce): these are called here the variational properties of a type of development (Salazar-Ciudad *et al.* 2003).

Another central concept in the criticisms to the neo-Darwinian approach to morphological evolution is novelty. Many definitions consider novelty (Müller and Wagner 1991) as phenotypic change that does not fit into the scheme of small quantitative changes in existing traits (for example, the appearance of new traits). It is often proposed that novelty occurs rarely, while more gradual quantitative changes occur often. Novelty research often points out that the qualitative aspects of morphological variation may be related to developmental dynamics. However, since neo-Darwinism does not consider development, nor any intrinsic patterns of morphological variation appearing from it, the distinction between rare qualitative changes and common quantitative changes may not be the best way to describe morphological variation. If what is known about the morphological variation possible by development is taken into account (Salazar-Ciudad 2006b), then there are several kinds of possible morphologies, each of them with its specific multivariate pattern of variation. In a sense, the concept of novelty is useful only as far as the gradual totipotent view of variation is accepted.

THE DEVELOPMENTAL GENETICS SCHOOL

The understanding of the genetic bases of development has increased dramatically during the past 30 years. Interest in development had not always come, as in the case of the constraint school, from the perception that there is a conflict between our current understanding of morphological variation and development and the conceptual framework of the Modern

Synthesis. The aim of the developmental genetics school of evo-devo is often perceived as the identification of the genetic bases underlying morphological differences in evolution (Wilkins 2001). Here I argue that most studies in evo-devo are not designed to address question 1.

Many researchers in developmental genetics have become interested in evolutionary issues after the discovery that many important genes in development are conserved across animals. Often, the same genes, gene interactions and similar patterns of gene expression are involved in the development of similar morphological structures in different species. Many research papers in evo-devo consist of standard research in developmental genetics with some comparative discussions at the end. By comparing developmental genetics between different species, essential data about variation in development are acquired. These studies identify differences in the patterns of expression of homologous genes (Patel 1994, Abzhanov and Kaufman 1999), differences in the target genes of homologous transcriptional or signalling pathways (Akam 1998), or even differences in the *cis*-regulatory elements of homologous genes (Carroll 2000), that correlate with morphological differences between species. These studies show correlations between genetic differences and morphological differences between species but do not show which were the original genetic changes that gave rise to these differences. This is not even the case when experimental mutations in one species produce morphologies reminiscent of the other species (Solé *et al.* 1999, Nijhout 2002). Even between closely related species the genetic structure of development may have changed since the time the morphological differences under study appeared. Then the genetic differences currently found may differ from the ones originally involved in the formation of a morphological structure. It has even been suggested that in many cases (Salazar-Ciudad *et al.* 2001a,b, Newman and Müller 2000) the developmental mechanisms underlying a specific morphology can change during evolution.

Although identifying these genetic differences may be a first necessary step, it does not in itself explain which patterns of morphological variation are produced by development or how development evolves. A gene difference, a difference of gene expression or a difference in a target gene does not explain a morphological difference unless the network of genetic, cellular and epigenetic interactions in which it is acting is causally understood. In other words, single genes or even small groups of gene interactions do not constitute mechanisms to explain morphological variation.

In fact, the problem of morphological variation can be seen, by using adequate definitions, to be the same as the problem of pattern

formation: that is, how relatively simple spatial distributions of cell types and extracellular components (hereafter called a pattern or previous pattern) are transformed, during development time, into different (normally more complex) spatial distributions of cells types and extracellular components (hereafter called a final pattern). From these definitions development can be seen as a sequence of these transformations between patterns; morphology and its variation as these patterns and their variation. Causal explanations of development require a description of (1) the network of gene interactions involved in a specific pattern transformation, (2) how these affect basic cell behaviours (e.g. proliferation, apoptosis, adhesion, signal secretion and reception, etc.), (3) how these networks and cell behaviours interact with the epigenetic information existing in the previous pattern and in other parts of the embryo (i.e. the spatial distributions of extracellular signals and components, and the spatial distribution and mechanical properties of cells) and (4) how the patterns produced will change when (1), (2) or (3) change. These networks of interactions are herein called developmental mechanisms (Salazar-Ciudad *et al.* 2003) while the pattern variations they can produce are called the variational properties of a developmental mechanism. Without an understanding of how pattern formation takes places in a morphological structure, the identification of a genetic difference underlying a morphological difference between species cannot be meaningfully interpreted. However, hypotheses about pattern formation that are based on partially known gene networks and previous patterns can be used to give tentative explanations about the morphological differences between species. These hypotheses can be refuted or refined by comparing their predictions with morphological variation between mutants and between species. This approach, here called 'variational', has been used in some previous studies (Goodwin 1994, Holloway and Harrison 1999, Salazar-Ciudad and Jernvall 2002, Harris *et al.* 2005, Jaeger *et al.* 2004, Newman and Müller 2005) and has the advantage of explaining which morphological variation is possible by development, rather than only which are the genetic changes underlying particular morphological variants.

Even if pattern formation is one of the more apparent and important phenomena in development, explicit hypotheses about the mechanisms for specific pattern transformations are rare. Even more rarely is it demonstrated how proposed hypotheses can explain the production of a pattern and its variation from previous patterns and networks of genetic and cellular interactions. For complex pattern transformations, verbal arguments are unlikely to be able to describe precisely how the patterns will change according to a given hypothesis when mutations or previous pattern changes occur.

In fact, the most explicitly formulated hypotheses that exist include mathematical models that give precise morphological quantitative descriptions about the patterns produced (Holloway and Harrison 1999, Salazar-Ciudad and Jernvall 2002, Harris *et al.* 2005, Newman and Müller 2005). Research with explicit pattern formation hypotheses based on networks of gene, cell and epigenetic context interactions are relatively rare. Most of the research is more focused on identifying genes, and gene or tissue interactions (and their timing), that are required for the development of some morphological structure. Even when the focus is on pattern formation, it is rarely stated from which previous pattern a pattern appears. Moreover, the reasons for the formation of a pattern are sometimes indicated as being due to the existence of a previous pattern. Although most pattern transformations occur from spatially heterogeneous patterns, the question of pattern formation cannot be passed back to previous patterns in some kind of preformationist chain (Horder 1993). In each developmental stage some spatial information (in the form of spatial distributions of cells) is produced from the previous one. How that happens is the question of pattern formation. Inevitably the explanation of the transformation between a previous pattern and a later pattern requires a precise description of both patterns. Accurate descriptions of both final morphology and intermediate embryonic morphologies are, however, relatively rare (see for exceptions Jernvall *et al.* 2000, Streicher and Müller 2001, Kuszak *et al.* 2004). The same occurs for patterns of gene expression, even though it is well known that they change in complex ways in space and time. Somehow, in the same way that some researchers (Dobzhansky 1937) tried to reduce evolution to changes in gene frequencies, some developmental biologists see development as reducible to gene interactions, or even *cis*-regulatory regions (Carroll 2000), both at the causal level and at the level of explanation.

THE EVOLUTION OF DEVELOPMENT

For many developmental biologists there may not be any general principles for the evolution of development (Akam 1998). The claimed opportunistic nature of evolutionary change (Sander and Schmidt-Ott 2004) may be one of the reasons for that. Although for short timescales some genetic changes may seem more likely than others, evolution will, over time, use whatever genetic variation is at hand to produce adaptive variation. As a consequence, previous history about genetic changes may easily fade away over time, precluding predictions about development evolution. Moreover, it has been

suggested that, since selection cannot see how the phenotype is produced, mutations that do not alter how development works but do increase its genetic complexity may accumulate over time. This would result in the logic of development becoming more and more baroque over time (True and Haag 2001, Salazar-Ciudad 2006a). Here it will be argued, however, that precisely because of the opportunistic nature of evolution, general predictions about the evolution of development and the effect of development in evolution are possible. These predictions do not involve the exact molecular nature of changes in development but rather involve more general aspects about the logic and topology of genetic networks and how they interact within the developing epigenetic context of the embryo or intermediate phenotype.

In the same way that development can be described as a sequence of pattern transformations, it can also be described as a sequence of action of developmental mechanisms (each mechanism responsible for a specific pattern transformation). Then the evolution of development can be described as changes in the developmental mechanisms used in a lineage over time. These changes can occur because new developmental mechanisms are recruited or because existing developmental mechanisms are replaced by other ones. In this chapter two developmental mechanisms are considered to be different if their gene network topologies are different or if they affect different cell behaviours. This definition is merely a choice of convenience that reflects the fact that gene network topology is among the best-known aspects of developmental mechanisms. Moreover, topological changes have been suggested to have, on average, more dramatic effects on variational properties than other kinds of change (Salazar-Ciudad *et al.* 2000). From this perspective, the morphological outcome of development can change for two reasons: (1) because mutations (or environment) change which subset of the variational properties of some developmental mechanisms are produced, or (2) because mutations (or environment) change some developmental mechanisms (meaning topology and then, probably, variational properties).

The chances of a *de novo* formation of a developmental mechanism depend on its genetic structure. The more genes and gene interactions a developmental mechanism involves, or in other words the more base changes in more genes are required, the more unlikely a mechanism will appear through random mutation. The same applies for the number of genetic changes required to evolve one developmental mechanism from another. The likelihood of an existing developmental mechanism being recruited in a new place and time in the developing embryo depends,

instead, on the proportion of genes in the network that can lead to the activation of the whole mechanism.

Developmental mechanisms are not selected by themselves nor by their variational properties but by the specific morphology they produce in specific individuals (which is only a part of the variational properties). If the genetic and variational properties of developmental mechanisms are known, then the evolution of development can be understood by how likely it is that different developmental mechanisms appear or are recruited by mutation, and how likely it is that the morphologies they produce are adaptive in specific environments. Only a limited number of developmental mechanisms are known to that extent. However, it has been suggested on theoretical grounds that there is a limited number of types of gene network topologies that can produce pattern transformations (Salazar-Ciudad *et al.* 2000, 2003). Pattern formation capacity and opportunism (in the form of likelihood of appearance by mutation) confine the spectrum of developmental mechanisms that can possibly be involved in different situations in development and evolution. This variational approach can be useful because, at least, all developmental mechanisms can be classified into exclusive types that share some aspects of their genetic and variational properties. Predictions about the relative involvement of each type at different stages of development and under different selective pressures are then possible. The next sections offer examples of how developmental mechanisms can be classified and how this approach can give interesting evolutionary insights. This ‘variational’ approach can be used on different classifications (for example Salazar-Ciudad *et al.* 2001a) and is not dependent on the specific one presented in the next section.

MORPHODYNAMIC MECHANISMS VERSUS POSITIONAL INFORMATION

One widespread view about how pattern formation takes place is positional information (Wolpert 1989): cells in a territory acquire information (positional information) about their fate (or differentiation state) according to the specific concentration of a diffusible signal they receive from a source at the border of a territory. In that sense two diffusible signals (morphogens) can establish a two-dimensional coordinate system according to which cells determine their positional values. These morphogens determine the genetic program that a cell undertakes. From this view the exact spatial distribution of the morphogens is not important (provided that each cell or group of cells receives different concentrations). What is important is how this

positional information is interpreted inside the cells. Originally it was even proposed that the differences in morphology among species would simply arise from different interpretation of a universal coordinate system (this idea has since been discarded). This perspective could explain how the fate of cells in a territory is determined, but not how the form of the territory can change. Morphogenetic movements are proposed to occur later as part of the interpretation of positional information (Wolpert 1989). How positional information is interpreted has not been described by these authors. Then the whole concept simply states that cells make developmental decisions according to signal concentration differences. The rest of pattern formation is relegated to the as yet unexplained interpretation of these differences. In practice, most developmental biologists use positional information just to state that cells in different places have different fates because they receive different signals or combinations of signals.

Nowadays it is well known that cells often communicate while they are engaged in morphogenetic movements. In addition, communication between cells is often reciprocal. Cells respond to received signals by sending other signals, expressing signal receptors, changing their adhesive properties (and then moving or changing shape), proliferating, dying, secreting extracellular matrix, etc. This results in a constant complex dynamic change in the position of cells and patterns of gene expression. This gives limited applicability to the positional information metaphor, even for the systems where it was first proposed: the chick limb (Hinchliffe and Horder 1993) and *Drosophila* segmentation (Jaeger *et al.* 2004). In spite of that, this metaphor can be used as an extreme from which to exemplify how the variational approach can be used to compare developmental mechanisms. Precise signal concentration sensing can be done, as in early dorso-ventral patterning in *Drosophila* (Markstein *et al.* 2004), by having enhancers of different affinity (or different number of enhancers) for the same transcriptional factor in the promoter regions of different genes (if there is a molecular pathway transducing signal concentration into active transcriptional factor concentration). At least one distinct enhancer is required for any different fate choice based on morphogen concentration. By having two non-spatially overlapping sources of different morphogens, any distribution of cell type can be produced in a given two-dimensional spatial distribution of cells (three sources of different morphogens are required in three dimensions). This is because in this condition every cell receives a unique combination of concentrations of each morphogen (Figure 2.1) and then by appropriate combinations of enhancers of differential affinity any pattern can be produced. The number of different enhancers required increases by

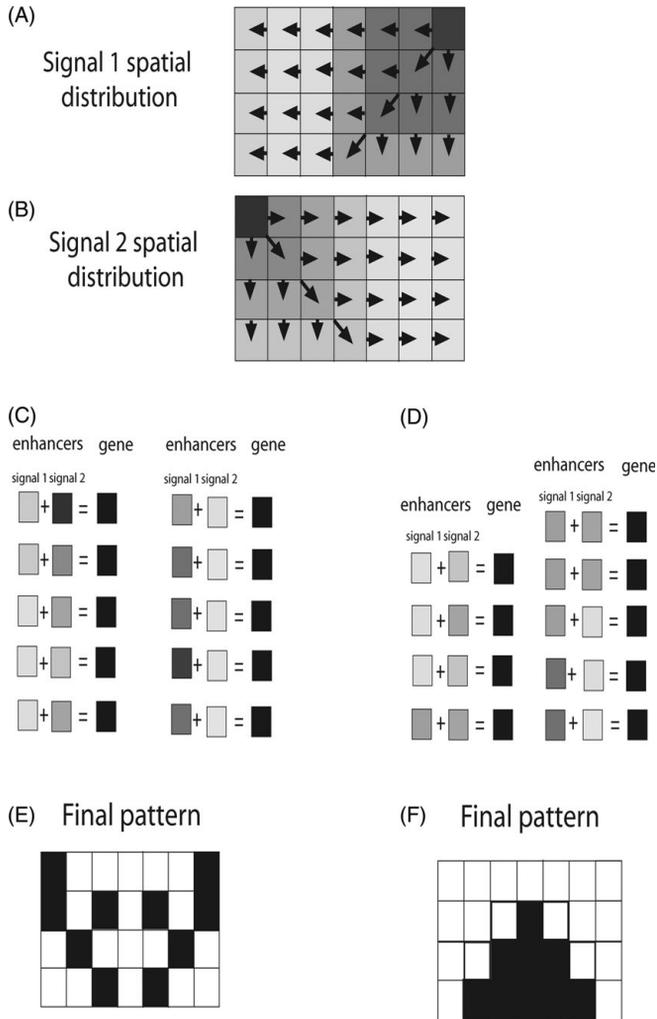


Figure 2.1 The diagram exemplifies the morphodynamic mechanism described in the text. In A and B the same field of cells is represented with the grey tones representing the concentrations of two signals. Signal 1 in A and signal 2 in B. Each cell represents a cell. The spatial distribution of the signals is idealised (it should be more curved). In C and D a schema shows how different combinations of each signal concentration cause a cell to differentiate to black type. The interpretation in C gives rise to the pattern in E and the interpretation in D to the pattern in F.

at least one with the number of cells having a state other than the default (not to be confused with the number of different cell states; Figure 2.1). Thus, a large genetic complexity is required to produce complex or large patterns. Parts in a pattern can change independently by genetic mutation only if they do not share an enhancer. In general, genetic variation is likely to produce relatively gradual pattern changes. In other words, the morphological variation produced and its relationship with genetic variation is consistent with the neo-Darwinian view.

This mechanism does not make use of the form of the spatial distribution of signals (it is enough that each cell receives a different concentration). In contrast, there are other developmental mechanisms that can use this spatial information opportunistically to produce relatively complex patterns without requiring many mutational changes and complex genetic properties. These involve simple gene networks where cells directly respond to signals by sending other signals (Figure 2.2). In that way, additional and more complex spatial distributions of signals are produced by combining the spatial distributions of several signals from sources in the previous pattern. If in addition cells are changing their location while signalling (in what has been called morphodynamic mechanisms) additional spatial distributions of signals or cells can be produced. This is because signals can be sent and received from groups of cells that have the forms possible by morphogenetic movements (rods, invaginations, condensation nodes, etc.; Newman and Müller 2000, Salazar-Ciudad 2006b). Essentially a larger spectrum of forms of groups of cells and signals can be combined to produce a pattern. This does not allow the production of more patterns but the production of more complex and more diverse patterns from the same amount of genetic variation (Salazar-Ciudad and Jernvall 2004, Salazar-Ciudad 2006b). What is important is not only signal interpretation but also the spatial distributions of signals and the collective dynamic behaviour of groups of cells.

This positional information mechanism is an example of hierarchic (Salazar-Ciudad *et al.* 2000) morphostatic mechanism (in which morphogenetic movements happen after and because of signalling; Salazar-Ciudad *et al.* 2003). Simulations of both kinds of mechanisms have shown that morphodynamic mechanisms do indeed produce patterns that are more complex, more distinct and related in more complex ways to genetic variation (Salazar-Ciudad and Jernvall 2004).

This has led to suggestions that morphodynamic mechanisms are more often involved in the formation of a pattern the first time it appears in evolution (Salazar-Ciudad and Jernvall 2004). This is because many more

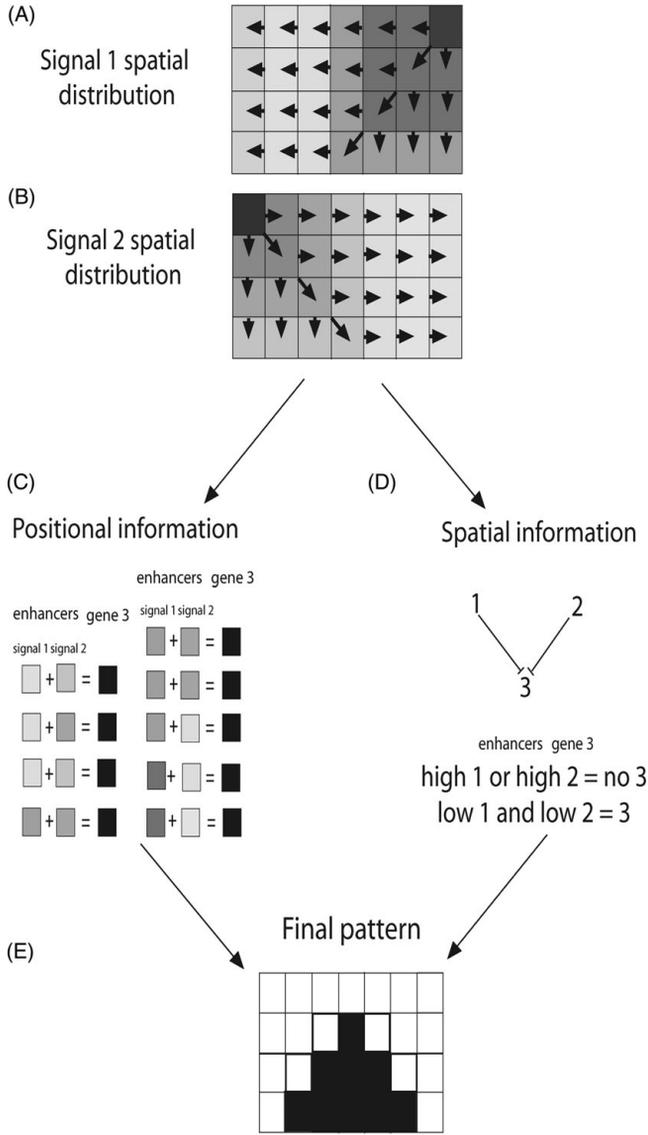


Figure 2.2 A and B as in Figure 2.1, and C as D in Figure 2.1. The interpretation in C of the signals in A and B gives rise to the pattern in E. In D it is shown how the same final pattern (in E) can be produced by gene 3 (expressed in black cells in E) being repressed where signal 1 or 2 has high concentration and active anywhere else.

patterns easily appear by random mutation in morphodynamic mechanisms (while both mechanisms are equally likely to appear). Thus, evolution may often proceed opportunistically by first recruiting morphodynamic mechanisms. Over time, some of these mechanisms may be replaced by morphostatic mechanisms for the production of the same patterns because they allow more gradual variation and a simpler relationship between phenotype and genotype. This allows, depending on selective pressures, a faster and more efficient adaptation. Note that this is not opposed to the abovementioned baroque trends in the evolution of development because a morphostatic mechanism that can replace a morphodynamic mechanism necessarily involves many more genes and gene interactions. If new patterns are more likely to be added in later development, then morphodynamic mechanisms should be more frequent in later development (Salazar-Ciudad and Jernvall 2004).

CONCLUDING REMARKS

The previous examples show how evolutionary considerations (in the form of expectations about the likelihood of origin by genetic variation) can produce expectations about which competing hypothesis for developmental mechanisms is more likely for specific pattern transformations (for example the one in Figure 2.2). In the same way it has been explained how consideration of the genetic and variational properties of developmental mechanisms allows predictions about the evolution of morphology and development in different situations and stages. These inferences are modest in scope because relatively little is yet known about developmental mechanisms. This is likely to change soon. In general, this chapter advocates for the unique role of pattern formation and related concepts as a bridge to relate what is known in the different schools and in evolution and development in general. In that sense the concept of variational properties offers a definition of how hypotheses about how development functions should be tested and, at the same time, a basic conceptualisation of how different developmental mechanisms variously affect morphological evolution. The tandem genetic/variational properties, on the other hand, are used to infer ways in which development can evolve. These concepts help in explaining morphological change not only by selective arguments but also on the basis of which morphological variation is more likely to appear. Overall, these concepts aim to help give more explicit theoretical grounds for the gradual switch in evolutionary theory from selective explanations to explanations based on the interplay between selective forces and developmental capacities.

ACKNOWLEDGEMENTS

I thank Jukka Jernvall, Alistair Evans, Kathy Kavanagh and an anonymous referee. This work was supported by the Academy of Finland.

REFERENCES

- Abzhanov, A. & Kaufman, T. C. 1999. Homeotic genes and the arthropod head: expression patterns of the *labial*, *proboscipedia*, and *Deformed* genes in crustaceans and insects. *Proceedings of the National Academy of Sciences of the USA* **96**, 10224–10229.
- Akam, M. 1998. Hox genes: from master genes to micromanagers. *Current Biology* **24**, 676–678.
- Alberch, P. 1980. Ontogenesis and morphological diversification. *American Zoologist* **20**, 653–667.
- Arthur, W. 2004. The effect of development on the direction of evolution: toward a twenty-first century consensus. *Evolution & Development* **6**, 282–288.
- Beldade, P., Koops, K. & Brakefield, P. M. 2002. Developmental constraints versus flexibility in morphological evolution. *Nature* **416**, 844–847.
- Bronikowski, A. M., Rhodes, J. S., Garland, T. *et al.* 2004. The evolution of gene expression in mouse hippocampus in response to selective breeding for increased locomotor activity. *Evolution* **58**, 2079–2086.
- Carlborg, S. & Haley, C. S. 2004. Epistasis: too often neglected in complex trait studies? *Nature Reviews Genetics* **5**, 618–625.
- Carroll, S. B. 2000. Endless forms: the evolution of gene regulation and morphological diversity. *Cell* **101**, 577–580.
- Charlesworth, B., Lande, R. & Slatkin, M. 1982. A neo-Darwinian commentary on macroevolution. *Evolution* **36**, 474–498.
- Dobzhansky, T. 1937. *Genetics and the Origin of Species*. New York: Columbia University Press.
- Fisher, R. A. 1930. *The Genetical Theory of Natural Selection*. Oxford: Clarendon Press.
- Fusco, G. 2001. How many processes are responsible for phenotypic evolution? *Evolution & Development* **3**, 279–286.
- Gilbert, S. F. & Sarkar, S. 2000. Embracing complexity: organicism for the 21st century. *Developmental Dynamics* **219**, 1–9.
- Goodwin, B. 1994. *How the Leopard Changed its Spots, the Evolution of Complexity*. New York: Charles Scribner's Sons.
- Gould, S. J. & Eldredge, N. 1977. Punctuated equilibria: the tempo and mode of evolution reconsidered. *Paleobiology* **3**, 115–151.
- Haldane, J. B. S. 1932. *The Causes of Evolution*. London: Longmans. Reprinted by Princeton University Press (1990).
- Harris, M. P., Williamson, S., Fallon, J. F., Meinhardt, H. & Prum, R. O. 2005. Molecular evidence for an activator-inhibitor mechanism in development of embryonic feather branching. *Proceedings of the National Academy of Sciences of the USA* **102**, 11734–11739.

- Hinchliffe, J. R. & Horder T. J. 1993. Testing the theoretical models for limb patterning. In H. G. Othmer, P. K. Maini & J. D. Murray (eds.) *Experimental and Theoretical Advances in Biological Pattern Formation*. New York: Plenum Press, pp. 105–119.
- Holloway, D. M. & Harrison, L. G. 1999. Algal morphogenesis: modelling inter-specific variation in *Micrasterias* with reaction–diffusion patterned catalysis of cell surface growth. *Philosophical Transactions of the Royal Society of London, Series B* **1382**, 417–433.
- Horder, T. J. 1989. Syllabus for an embryological synthesis. In D. B. Wake & G. Roth (eds.) *Complex Organismal Functions*. New York: John Wiley, pp. 315–348.
- Horder, T. J. 1993. The chicken and the egg. In H. G. Othmer, P. K. Maini & J. D. Murray (eds.) *Experimental and Theoretical Advances in Biological Pattern Formation*. New York: Plenum Press, pp. 121–148.
- Jaeger, J., Blagov, M., Kosman, D. *et al.* 2004. Dynamical analysis of regulatory interactions in the gap gene system of *Drosophila melanogaster*. *Genetics* **167**, 1721–1737.
- Jernvall, J., Keranen, S. V. E. & Thesleff, I. 2000. Evolutionary modification of development in mammalian teeth: quantifying gene expression patterns and topography. *Proceedings of the National Academy of Sciences of the USA* **97**, 14444–14448.
- Kangas, A., Evans, A. R., Thesleff, I. & Jernvall, J. 2004. Non-independence of mammalian dental characters. *Nature* **432**, 211–214.
- Kuszak, J. R., Zoltoski, R. K. & Tiedemann, C. E. 2004. Development of lens sutures. *International Journal of Developmental Biology* **48**, 889–902.
- Markstein, M., Zinzen, R., Markstein, P. *et al.* 2004. A regulatory code for neurogenic gene expression in the *Drosophila* embryo. *Development* **131**, 2387–2394.
- Maynard Smith, J., Burian, R., Kauffman, S. A. *et al.* 1985. Developmental constraints and evolution. *Quarterly Review of Biology* **60**, 265–287.
- Mayr, E. 1982. *The Growth of Biological Thought*. Cambridge, MA: Harvard University Press.
- Müller, G. B. & Wagner, G. P. 1991. Novelty in evolution: restructuring the concept. *Annual Review of Ecology and Systematic* **22**, 229–256.
- Newman, S. A. & Müller, G. B. 2000. Epigenetic mechanisms of character origination. *Journal of Experimental Zoology* **288**, 304–317.
- Newman, S. A. & Müller, G. B. 2005. Origination and innovation in the vertebrate limb skeleton: an epigenetic perspective. *Journal of Experimental Zoology B (Molecular and Developmental Evolution)* **304**, 593–609.
- Nijhout, H. F. 2002. The nature of robustness in development. *BioEssays* **24**, 553–563.
- Patel, N. H. 1994. The evolution of arthropod segmentation: insights from comparisons of gene expression patterns. *Development* **94** (supplement), 201–207.
- Richardson, M. K. & Chipman, A. D. 2003. Developmental constraints in a comparative framework: a test case using variations in phalanx number during

- amniote evolution. *Journal of Experimental Zoology B (Molecular and Developmental Evolution)* **296**, 8–22.
- Salazar-Ciudad, I. 2006a. Developmental constraints vs. variational properties: how pattern formation can help to understand evolution and development. *Journal of Experimental Zoology B (Molecular and Developmental Evolution)* **306**, 107–125.
- Salazar-Ciudad, I. 2006b. On the origins of morphological disparity and its diverse developmental bases. *BioEssays* **28**, 1112–1122.
- Salazar-Ciudad, I., Garcia-Fernandez, J. & Solé, R. V. 2000. Gene networks capable of pattern formation: from induction to reaction–diffusion. *Journal of Theoretical Biology* **205**, 587–603.
- Salazar-Ciudad, I. & Jernvall, J. 2002. A gene network model accounting for development and evolution of mammalian teeth. *Proceedings of the National Academy of Sciences of the USA* **99**, 8116–8120.
- Salazar-Ciudad, I. & Jernvall, J. 2004. How different types of pattern formation mechanisms affect the evolution of form and development. *Evolution & Development* **1**, 6–16.
- Salazar-Ciudad, I. & Jernvall, J. 2005. Graduality and innovation in the evolution of complex phenotypes: insights from development. *Journal of Experimental Zoology B (Molecular and Developmental Evolution)* **304**, 619–631.
- Salazar-Ciudad, I., Jernvall, J. & Newman, S. A. 2003. Mechanisms of pattern formation in development and evolution. *Development* **130**, 2027–2037.
- Salazar-Ciudad, I., Newman, S. A. & Solé, R. V. 2001a. Phenotypic and dynamical transitions in model genetic networks. I. Emergence of patterns and genotype–phenotype relationships. *Evolution & Development* **3**, 84–94.
- Salazar-Ciudad, I., Solé, R. V. & Newman, S. A. 2001b. Phenotypic and dynamical transitions in model genetic networks. II. Application to the evolution of segmentation mechanisms. *Evolution & Development* **3**, 95–103.
- Sander, K. & Schmidt-Ott, U. 2004. Evo-devo aspects of classical and molecular data in a historical perspective. *Journal of Experimental Zoology B (Molecular and Developmental Evolution)* **15**, 69–91.
- Solé, R. V., Salazar-Ciudad, I. & García-Fernandez, J. 1999. Landscapes, gene networks and pattern formation: on the Cambrian explosion. *Advances in Complex Systems* **2**, 313–337.
- Streicher, J. & Müller, G. B. 2001. 3D modelling of gene expression patterns. *Trends in Biotechnology* **19**, 145–148.
- True, J. R. & Haag, E. S. 2001. Developmental system drift and flexibility in evolutionary trajectories. *Evolution & Development* **3**, 109–119.
- Weber, K. E. 1992. How small are the smallest selectable domains of form? *Genetics* **130**, 345–353.
- Wilkins, A. S. 2001. *The Evolution of Developmental Pathways*. Sunderland, MA: Sinauer Associates.
- Wolpert, L. 1989. Positional information revisited. *Development* **107** (supplement), 3–12.