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The Causality Horizon and the Developmental Bases of Morphological Evolution

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Abstract With the advent of evolutionary developmental research, or EvoDevo, there is hope of discovering the roles that the genetic bases of development play in morphological evolution. Studies in EvoDevo span several levels of organismal organization. Low-level studies identify the ultimate genetic changes responsible for morphological variation and diversity. High-level studies of development focus on how genetic differences affect the dynamics of gene networks and epigenetic interactions to modify morphology. Whereas an increasing number of studies link independent acquisition of homoplastic or convergent morphologies to similar changes in the genomes, homoplasies are not always found to have identical low-level genetic underpinnings. This suggests that a combination of low- and high-level approaches may be useful in understanding the relationship between genetic and morphological variation. Therefore, as an empirical and conceptual framework, we propose the causality horizon to signify the lowest level that allows linking homoplastic morphologies to similar changes in the development. A change in a system below the causality horizon cannot be generalized. In more concrete terms, homoplastic morphologies cannot be reduced to the same change in gene regulation when that change occurs below the causality horizon; rather, a higher-level mechanism should be identified.

Keywords Causality horizon · EvoDevo · Genotype–Phenotype map · Patterning

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Introduction

Different scientific fields such as evolutionary biology and developmental biology address issues related to the phenotype. Although there is some degree of overlap in the interests of these respective fields, there is also a large degree of variation in the assumptions and burdens of proofs between them. Whereas multidisciplinarity should be advantageous, it requires concepts that can cross disciplines and levels of organization in order to connect studies ranging from evolution to development.

Here we review current research approaches on which levels of developmental regulation (regulatory sequences, genes, gene interactions, gene networks, and epigenetic networks) are used to explain morphological variation between individuals, populations, species, and higher-order taxonomic categories. We discuss a conceptual barrier or "causality horizon" that limits the predictability of morphological variation (Fig. 1). We propose the use of the causality horizon as a boundary of successful, or appropriate, reductionism in development. For example, below the causality horizon, homoplastic change in morphology between two species cannot be reduced to the same change in development. In other words, below the causality horizon determining the ultimate genetic or developmental cause underlying a specific change in the phenotype in one species would not help in predicting the cause underlying a corresponding change in another species. Future work,

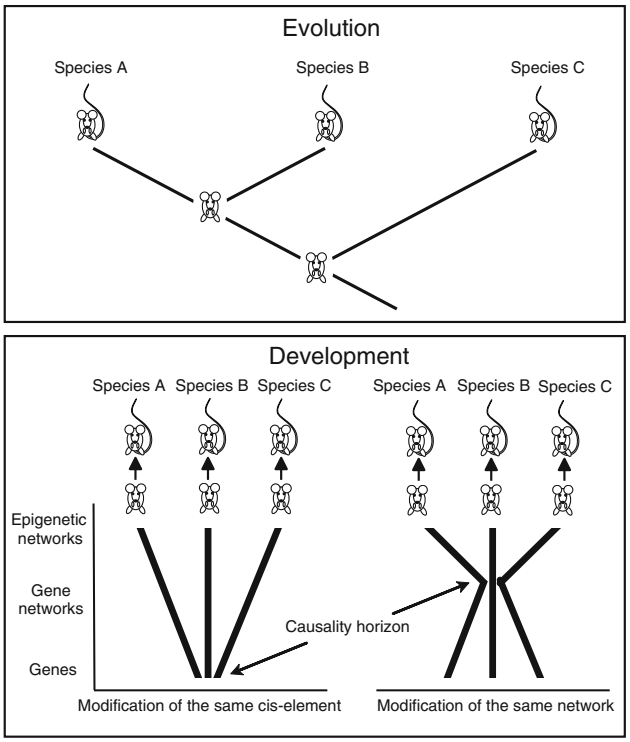

Fig. 1 Causality horizon and the limits of predictability of developmental systems. A hypothetical example of the homoplastic evolution of a tail in three species of mice (Species A, B, and C, *top*). In each species the ancestor did not have a tail. Developmentally (*bottom*), acquisition of a tail can be achieved through similar changes in the cis-regulation of the same gene (*left*). Alternatively, a tail can form through changes in the regulation of a different gene in each species (*right*). In the latter case, comparable changes in the gene network, for example, would explain the homoplastic acquisition of a tail. In the former (*left*) and latter (*right*) cases the causality horizon is at lower and higher levels of organization, respectively

especially at the population and species levels, will help to delineate the causality horizon of the genetic basis of morphological evolution.

Approaches to Link Morphology to Different Levels of Organismal Organization

From the Genes to the Phenotype

Two opposing views can be considered for the role of developmental genetics in evolution: the *master gene* view and the *micromanager* view. Hox genes have had a central role in this debate since their discovery. According to the master gene view (Gehring 1993), Hox genes and other major transcriptional factors would be among the more upstream regulators of body plans and segment identity. These genes would control segment identity through a hierarchy of downstream transcriptional factors and effectors (Gehring 1993). This master gene view stems from early studies of homeotic mutations, which uncovered the unexpected conservation of these genes and their spatio-temporal patterns of expression. There is a growing body of literature correlating gross anatomical differences between high taxonomic categories, such as orders and classes, with spatial differences in gene expression in Hox or other conserved transcriptional factors (reviewed in Carroll et al. 2001). These "macro-EvoDevo" studies are especially common in arthropods, because they possess a clear correlation between the morphological identity of a segment and Hox expression during development.

Other studies, however, have indicated that changes in Hox regulation can be implicated in more subtle morphological differences at the species level (Akam 1998). This "micromanager" (Akam 1998) view suggests that Hox genes and other major transcriptional factors may opportunistically affect development both at upstream and downstream levels. Consequently, no strict genetic hierarchy may exist in development and major morphological transitions may not require "master" genes to explain differences in body plans.

The identification of differences in gene expression underlying morphological variation leaves open the questions of how specific morphologies arise over the course of development, and how morphological diversity arises over the course of evolution. The latter issue is particularly vexing because genetic differences underlying morphological diversity between two lineages may not be indicative of the genetic variance that originally produced their differences in form (Nijhout 1990). This is because genes and genetic interactions involved in the formation of a specific morphology can evolve and change through time without concomitant changes in morphology. The more time which has elapsed between the common ancestor of two lineages, the more likely the genetic bases of morphological diversity may have changed by phenogenetic, or developmental system drift (Weiss and Fullerton 2000; True and Haag 2001; Salazar-Ciudad 2009).

Regardless of the exact developmental mechanism, macro-evolutionary differences arise first as intrapopulation variation. For this and other reasons many researchers in EvoDevo (Pennisi 2002) have turned their efforts towards the study of the developmental bases of morphological differences between closely related species or populations. Many of these studies focus on the disappearance of specific morphological structures. For example, the loss of eyes in cave populations of the fish *Astyanax mexicanus* appears to be a consequence of an expansion of the Sonic hedgehog (Shh) expression domain in the head (Jeffery 2009). Another example is stickleback fishes, many species of which have undergone independent and repeated colonization of fresh-water habitats from an originally marine population. In many cases this colonization has been

accompanied by a reduction in their dermal armor and these reductions have been linked to the *Ectodysplasin* gene in several populations (Knecht et al. 2007; DeFaverti et al. 2011). Turning from the loss to the modification of structures, differences in the width and length of the beaks of several species of Darwin finches seem to be associated with differences in Bone morphogenetic protein 4 (Bmp4) and Calmodulin expression, respectively (Abzhanov et al. 2004, 2006). At the tissue level, Bmp4 and Calmodulin produce different beak morphologies through specific spatial patterns of proliferation in the beak primordia (Wu et al. 2006). In general, since a morphological structure requires interactions between many genes, it is likely that disruptive mutations resulting in the loss of a structure occur easily in evolution. In contrast, new morphological structures or changes in existing structures may be less likely to appear during evolution. Indeed, whereas loss of cusps, the major morphological features of teeth, occurs when individual genes are experimentally manipulated in mouse molar teeth, substantial increases in cusp number (and thus in tooth complexity) occur through experimentally tinkering with a specific combination of three genes (Harjunmaa et al. 2012). This experimental result on teeth indicates that dental complexity is a polygenic trait, and an increase in complexity would be unlikely to result from evolutionary drift alone.

Other studies have gone to an even lower organizational level and have been able to identify the ultimate sequence differences underlying morphological variation between populations or closely related species. Most of these studies have identified specific cis-regulatory regions underlying differences in the morphology. This kind of genetic difference has been found, for example, in the variation of thoracic bristle number and position in two species of Drosophila (Marcelini and Simpson 2006), the amount of bristles in different segment numbers in different species of Drosophila (Frankel et al. 2011), and the differences in the patterns of wing coloration in several species of Drosophila (Rebeiz et al. 2009).

From the Phenotype to the Genes

Studies in developmental biology have often treated morphological variation more as a nuisance than as an important phenomenon in its own right. Indeed, many laboratory animals are inbred in order to provide a uniform genetic background for experimental studies. In contrast, because variation is a requisite for natural selection and evolution, evolutionary biologists have been extraordinarily attentive to measuring variation. Classical (Fisher 1930; Haldane 1932), and more recent (Charlesworth and Lande 1982; Barton and Partridge 2000; Coyne 2006) models of population genetics assume abundant genetic variation for most morphological traits and a relatively simple relationship between the genotype and the phenotype. These models omit development, which has been criticized by many EvoDevo biology studies over the last quarter century (e.g., Alberch 1982; Goodwin 1994; Salazar-Ciudad 2006). On the other hand, multivariate quantitative genetics allows approaching many questions in population genetics without assuming a simple relationship between genotype and phenotype (Atchely 1987). Genetic variation and the relationship between genotype and phenotype are statistically inferred from phenotypic measurements and from information about genetic relatedness in a population. In some cases, research in multivariate quantitative genetics tries to infer the genetic basis of morphological variation or, in its own terminology, the genetic architecture of traits. In those cases the methodology uses a top-down approach in which phenotypic information is used to identify genes, or regions in the genome, with roles in producing morphological variation. Conversely, in developmental genetics interactions between genes are used to understand morphology and its variation.

Some studies also partially merge approaches in quantitative genetics with developmental genetics (Gibson and Hogness 1996; Palsson and Gibson 2000; Mezey et al. 2005; Dworkin and Gibson 2006). In these studies morphological variation arising from sets of natural or artificial alleles is studied in detail by morphometric or other methods. This approach is not restricted to quantitative genetics, because morphometric studies of mutants can uncover variational properties of complex structure such as the mouse face (Marcucio et al. 2011).

Modeling Gene Networks

As more and more developmental genes are identified and mutants described, there is a gradual and long-lasting change of research focus from the study of individual genes to the study of gene interactions and gene networks. These networks tend to be complex and include many genes. In contrast, most techniques available in developmental genetics involve the manipulation of one or few genes in a rather crude way (for example, knock-outs and overexpression gene constructs). The understanding of how genetic manipulations alter the dynamics of gene networks and developmental processes is far from straightforward. This challenge is one of the reasons why developmental studies, trying to understand how gene networks produce phenotypes and morphological variation, increasingly use gene network modeling.

The improvement in computational power and the accumulation of large amounts of data on gene network topologies involved in pattern formation and morphogenesis is facilitating a steady increase of studies that closely

integrate experiments and mathematical modeling (Shvartsman et al. 2002; Janssens et al. 2006; Sheth et al. 2012). As in most other approaches in developmental biology, these studies on gene networks aim to explain wild-type development and phenotypes. Relatively few studies using gene networks try to predict the phenotypes of mutants and other species (Shvartsman et al. 2002; Nakamasu et al. 2009; Gong et al. 2012). Eventually, the capacity of a model to predict how phenotypes change when one or a few gene functions are altered could be regarded as the best test for models.

Most developmental models, indeed most studies in developmental biology as a whole, treat patterning as a strictly bounded process in which a fixed number of relatively immobile cells exchange extracellular signals. These approaches have been quite successful in developmental systems such as Drosophila segmentation (Janssens et al. 2006), lateral inhibition by notch-delta signaling (Collier et al. 1996), and several Turing-like regular patterns (Meinhardt 1982). In development it is often the case that during signaling cells participate in intricate morphogenetic movements. This limits the general applicability of gene network models to development. Since studies on phenotypic variation during development are scarce (von Dassow and Davidson 2007; Marcucio et al. 2011) gene network models have few opportunities to be tested in explaining, for example, phenotypic variation underlying evolution. There are, thus, good reasons to expand gene network models to include morphogenetic movements, such as tissue growth, and be able to make predictions about final morphology.

Modeling Epigenetic Networks

At present, due to lack of knowledge about development and computational power, it is impossible to simulate any single individual from fertilization to adulthood. Development is, instead, partitioned into a sequence of separate pattern transformations. In these kinds of simulations, spatial distributions of cell types in one stage, or patterns, are transformed into new patterns in a later stage. Even for this limited task it is rarely the case that most of the genes involved in a pattern transformation are known. However, it is perhaps a reasonable assumption that the ultimate action of a gene or gene network is to regulate cell behavior, and that these behaviors in turn are limited in number. Cells can divide, die, secrete extracellular matrix or signaling molecules, express membrane receptors for signaling or adhesion, and move and change shape according to internal changes in the cytoskeleton (Salazar-Ciudad et al. 2003). Thus, development and pattern transformations can be understood as the collective behavior of large sets of cells. Each cell reacts to external inputs, in the form of extracellular molecular signals or incoming forces, by changing a limited number of behaviors in specific ways. These behavioral changes can also affect the material properties of cells and extracellular matrices and alter the cells' mechanical responses to pressures (Newman and Comper 1990; Beloussov 1998) and the diffusivity of extracellular signals. These kinds of integrative approaches have been proposed by many workers in morphodynamics (Salazar-Ciudad et al. 2003), in morphoregulation (Plikus et al. 2005), on the palimpsest model (Hallgrímsson et al. 2005), and on generic mechanisms (Newman and Müller 2005).

Many of the high-level studies include gene networks, and aim to explain not only the wild-type morphology but also the generation of variation and, in general, the relationship between the genotype and the phenotype. Some of these studies focus on vertebrate organs that develop in relative isolation from the rest of the body, and in which the basic genetic and epigenetic interactions are relatively well known. These models can act as devices to integrate known low-level interactions into mechanistic hypotheses that give quantitative morphological predictions. These predictions can in turn be tested against variation in nature and in the laboratory, and used to design further experiments.

Because both gene interactions and cell behaviors are incorporated into the models, there are currently relatively few examples of such models. Moreira and Deutsch (2005), for example, have been able to explain the color patterns in the skin of zebrafish from a model including local cell signaling and differential cell adhesion. A reaction–diffusion model that includes experimentally corroborated inhibition between Shh and Bmp signaling has been used to explain the branching pattern of different types of chick feathers (Harris et al. 2005), and to suggest how different types of feathers may have evolved (Prum 2005). A model of tooth morphogenesis (Salazar-Ciudad and Jernvall 2002; Salazar-Ciudad 2008) considers cell proliferation, differentiation, and adhesion, together with a gene network incorporating experimentally derived dynamics of Bmp, Shh, and Fibroblast growth factor (Fgf) signaling. A biomechanically more realistic model (Salazar-Ciudad and Jernvall 2010) of tooth development is able to capture aspects of population-level variation in tooth shapes, thus potentially bridging micro- and macroevolution.

Causality Horizon

From our discussion above it is clear that there are many different low- and high-level approaches by which the relationship between genotype and phenotype is studied. Low-level approaches are closer to the directly heritable

elements, the genes, in which mutations occur. Gene function is dependent on complex networks of interactions between genes themselves and the epigenetic context of the developing embryo. Perhaps a central question in coming years will be whether all morphological variation can eventually be understood from the genes. That is, are genes the level where morphological variation should be understood? Whereas these questions are reminiscent of epistemological debates about reductionism and synthesis (Gilbert and Sarkar 2000), the increasing number of experimental studies may provide an empirical answer to these questions.

In principle, for morphology to be predictable from low-level approaches it is required that every morphological change is uniquely attributable to a specific genetic change. To conceptualize this principle, we develop a causality horizon concept coined by Nebot et al. (1994) in connection to modeling system behavior. Basically, a low causality horizon implies that a low-level link, such as a specific gene, is involved in a specific change in morphology (Fig. 1). An example would be the involvement of Ectodysplasin in the homoplastic reduction of stickleback armor plates (Knecht et al. 2007). Conversely, a high causality horizon implies that a high-level link, such as modification of gene network topology, underlies a homoplastic change in morphology. Moreover, this modification does not need to involve the same gene in every case, such as is the case of wing polyphenism in different ant species (Abouheif and Wray 2002). Even if in every individual species one can identify that a specific gene or regulatory region corresponds to a similar change in morphology, these low-level changes would provide little power to predict the underlying gene in new species.

Although identifying "similar" morphological changes is far from a trivial task in practice, a few predictions can be made based on the discussion above (Fig. 2). First, whereas the acquisition of new characters, which can be seen as an increase in complexity, may be hypothesized to involve changes at higher levels, losses of characters can often be explained by single gene changes. Second, because development itself evolves, similar morphological changes in phylogenetically distant species are more likely to involve higher-level changes. Third, most of the studies that indicate a low causality horizon consider only two or few independent occurrences of a morphological transition. As more examples of each transition get studied, we may actually be able to place a probability value on the causality horizon. For example, because comprehensive population inventories of the genetics in the loss of stickleback armor plates are being carried out (Leinonen et al. 2012), sticklebacks may become one of the first examples in which a causality horizon can be placed with an estimate of probability.

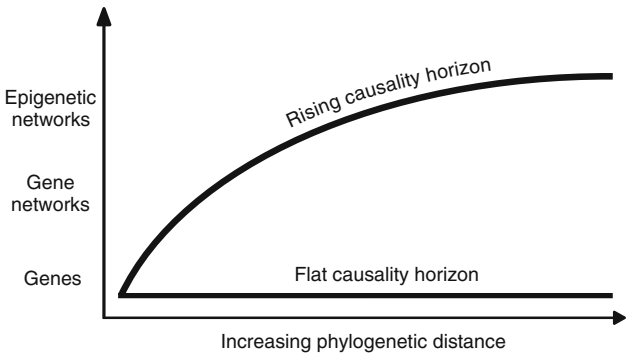

Fig. 2 The shape of causality horizons can be empirically determined by studying multiple examples of homoplastic (parallel and convergent) changes in the phenotype. The causality horizon may be expected to rise with increasing phylogenetic distance, but, for example, Hox genes may provide examples of flat causality horizon. Furthermore, gain and loss of morphological characters, or an increase and decrease in complexity may have different causality horizons

In summary, there is an ongoing transition in the field of EvoDevo to examine evolutionary changes at all levels of development, from genes to gene networks and epigenetic networks. This expansion in the research program co-occurs with a change of focus from comparisons between distantly related species to closely related species, and to the population level at which microevolution occurs. The changing research focus should be accompanied by a stronger attention to the description of subtle morphological variation occurring in mutants and other experimental manipulations of development. In this way EvoDevo can help to provide models of the relationship between the genotype and the phenotype. Eventually we may know when the causality horizon is low and genes matter more, and when the causality horizon is high and we have to focus more on gene networks and cellular behaviors to explain morphology.

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References

Abouheif E, Wray GA (2002) Evolution of the gene network underlying wing polyphenism in ants. Science 297:249–252

Abzhanov A, Protas M, Grant BR, Grant PR, Tabin CJ (2004) Bmp4 and morphological variation of beaks in Darwin's finches. Science 305:1462–1465

Abzhanov A, Kuo WP, Hartmann C, Grant BR, Grant PR, Tabin CJ (2006) The calmodulin pathway and evolution of elongated beak morphology in Darwin's finches. Nature 442:563–567

Akam M (1998) Hox genes: from master genes to micromanagers. Curr Biol 8:R676–R678

Alberch P (1982) Developmental constraints in evolutionary processes. In: Bonner JT (ed) Evolution and development. Dahlem Konferenzen. Springer, Heidelberg, pp 313–332

Atchley WR (1987) Developmental quantitative genetics and the evolution of ontogenies. Evolution 41:316–330
Barton N, Partridge L (2000) Limits to natural selection. BioEssays 22:1075–1084
Beloussov LV (1998) The dynamic architecture of a developing organism: an interdisciplinary approach to the development of organisms. Kluwer, Dordrecht
Carroll SB, Grenier JK, Weatherbee SD (2001) From DNA to diversity: molecular genetics and the evolution of animal design. Blackwell, Malden
Charlesworth B, Lande R (1982) Morphological stasis and developmental constraint–no problem for Neo-Darwinism. Nature 296:610
Collier JR, Monk NA, Maini PK, Lewis JH (1996) Pattern formation by lateral inhibition with feedback: a mathematical model of delta-notch intercellular signalling. J Theor Biol 183:429–446
Coyne JA (2006) Comment on "Gene regulatory networks and the evolution of animal body plans." Science 313:761
DeFaveri J, Shikano T, Shimada Y, Goto A, Merilä J (2011) Global analysis of genes involved in freshwater adaptation in threespine sticklebacks (*Gasterosteus aculeatus*). Evolution 65:1800–1807
Dworkin I, Gibson G (2006) Epidermal growth factor receptor and transforming growth factor-beta signaling contributes to variation for wing shape in *Drosophila melanogaster*. Genetics 173:1417–1431
Fisher RA (1930) The genetical theory of natural selection. Clarendon Press, Oxford
Frankel N, Erezyilmaz DF, McGregor AP, Wang S, Payre F, Stern DL (2011) Morphological evolution caused by many subtle-effect substitutions in regulatory DNA. Nature 474:598–603
Gehring WJ (1993) Exploring the homeobox. Gene 135:215–221
Gibson G, Hogness DS (1996) Effect of polymorphism in the Drosophila regulatory gene *Ultrabithorax* on homeotic stability. Science 271:200–203
Gilbert SF, Sarkar S (2000) Embracing complexity: organicism for the 21st century. Dev Dyn 219:1–9
Gong Z, Matzke NJ, Ermentrout B, Song D, Vendetti JE, Slatkin M, Oster G (2012) Evolution of patterns on Conus shells. Proc Natl Acad Sci USA 109:E234–E241
Goodwin BC (1994) How the leopard changed its spots. Weidenfeld and Nicolson, London
Haldane JBS (1932) The causes of evolution. Longmans, London. Reprint: Princeton University Press, Princeton (1990)
Hallgrímsson B, Brown JJY, Hall BK (2005) The study of phenotypic variability: an emerging research agenda for understanding the developmental-genetic architecture underlying phenotypic variation. In: Hallgrímsson B, Hall BK (eds) Variation: a central concept in biology. Academic Press, New York, pp 525–551
Harjunmaa E, Kallonen A, Voutilainen M, Hämäläinen K, Mikkola ML, Jernvall J (2012) On the difficulty of increasing dental complexity. Nature 483:324–327
Harris MP, Williamson S, Fallon JF, Meinhardt H, Prum RO (2005) Molecular evidence for an activator-inhibitor mechanism in development of embryonic feather branching. Proc Natl Acad Sci USA 102:11734–11739
Janssens H, Hou S, Jaeger J, Kim AR, Myasnikova E, Sharp D, Reinitz J (2006) Quantitative and predictive model of transcriptional control of the *Drosophila melanogaster* even skipped gene. Nat Genet 38:1159–1165
Jeffery WR (2009) Regressive evolution in Astyanax cavefish. Annu Rev Genet 43:25–47
Knecht AK, Hosemann KE, Kingsley DM (2007) Constraints on utilization of the EDA-signaling pathway in threespine stickleback evolution. Evol Dev 9:141–154
Leinonen T, McCairns RJS, Herczeg G, Merilä J (2012) Multiple evolutionary pathways to decreased lateral plate coverage in freshwater threespine sticklebacks. Evolution 66:3866–3875
Marcellini S, Simpson P (2006) Two or four bristles: functional evolution of an enhancer of scute in Drosophilidae. PLoS Biol 4:2252–2261
Marcucio RS, Young NM, Hu D, Hallgrimsson B (2011) Mechanisms that underlie co-variation of the brain and face. Genesis 49:177–189
Meinhardt H (1982) Models of biological pattern formation. Academic Press, London
Mezey JG, Houle D, Nuzhdin SV (2005) Naturally segregating quantitative trait loci affecting wing shape of *Drosophila melanogaster*. Genetics 169:2101–2113
Moreira J, Deutsch A (2005) Pigment pattern formation in zebrafish during late larval stages: a model based on local interactions. Dev Dyn 232:33–42
Nakamasu A, Takahashi G, Kanbe A, Kondo S (2009) Interactions between zebrafish pigment cells responsible for the generation of Turing patterns. Proc Natl Acad Sci USA 106:8429–8434
Nebot A, Medina S, Cellier FE (1994) The causality horizon: limitations to predictability of behavior using fuzzy inductive reasoning. Proc Conf Model Simul 3:492–496
Newman SA, Comper WD (1990) "Generic" physical mechanisms of morphogenesis and pattern formation. Development 110:1–18
Newman SA, Müller GB (2005) Origination and innovation in the vertebrate limb skeleton: an epigenetic perspective. J Exp Zool B Mol Dev Evol 304:593–609
Nijhout HF (1990) Metaphors and the role of genes in development. BioEssays 12:441–446
Palsson A, Gibson G (2000) Quantitative developmental genetic analysis reveals that the ancestral dipteran wing vein prepattern is conserved in *Drosophila melanogaster*. Dev Genes Evol 210:617–622
Pennisi E (2002) Evolutionary biology: evo-devo enthusiasts get down to details. Science 298:953–955
Plikus MV, Zeichner-David M, Mayer JA, Reyna J, Bringas P, Thewissen JG, Snead ML, Chai Y, Chuong CM (2005) Morphoregulation of teeth: modulating the number, size, shape and differentiation by tuning Bmp activity. Evol Dev 7:440–457
Prum RO (2005) Evolution of the morphological innovations of feathers. J Exp Zool B Mol Dev Evol 304:570–579
Rebeiz M, Pool JE, Kassner VA, Aquadro CF, Carroll SB (2009) Stepwise modification of a modular enhancer underlies adaptation in a *Drosophila* population. Science 326:1663–1667
Salazar-Ciudad I (2006) Developmental constraints versus variational properties: how pattern formation can help to understand evolution and development. J Exp Zool B Mol Dev Evol 306:107–125
Salazar-Ciudad I (2008) Tooth morphogenesis in vivo, in vitro, and in silico. Curr Top Dev Biol 81:341–371
Salazar-Ciudad I (2009) Looking at the origin of phenotypic variation from pattern formation gene networks. J Biosci 34:573–587
Salazar-Ciudad I, Jernvall J (2002) A gene network model accounting for development and evolution of mammalian teeth. Proc Natl Acad Sci USA 99:8116–8120
Salazar-Ciudad I, Jernvall J (2010) A computational model of teeth and the developmental origins of morphological variation. Nature 464:583–586
Salazar-Ciudad I, Jernvall J, Newman SA (2003) Mechanisms of pattern formation in development and evolution. Development 130:2027–2037
Sheth R, Marcon L, Bastida MF, Junco M, Quintana L, Dahn R, Kmita M, Sharpe J, Ros MA (2012) Hox genes regulate digit patterning by controlling the wavelength of a turing-type mechanism. Science 338:1476–8140
Shvartsman SY, Muratov CB, Lauffenburger DA (2002) Modeling and computational analysis of EGF receptor-mediated cell communication in Drosophila oogenesis. Development 129: 2577–2589

True JR, Haag ES (2001) Developmental system drift and flexibility in evolutionary trajectories. Evol Dev 3:109–119

von Dassow M, Davidson LA (2007) Variation and robustness of the mechanics of gastrulation: the role of tissue mechanical properties during morphogenesis. Birth Defects Res C Embryo Today 81:253–269

Weiss K, Fullerton SM (2000) Phenogenetic drift and the evolution of genotype–phenotype relationships. Theor Popul Biol 57:187–195

Wu P, Jiang TX, Shen JY, Widelitz RB, Chuong CM (2006) Morphoregulation of avian beaks: comparative mapping of growth zone activities and morphological evolution. Dev Dyn 235:1400–1412