Chapter 19
Development and Evolution: The Physics Connection

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19.1 Introduction

To assert that living systems are material entities, plainly subject to the laws of physics and chemistry, has been uncontroversial since at least the beginning of the twentieth century. The veneration of Gregor Mendel (1822–1884) and Charles Darwin (1809–1882) as founding figures of modern biology is to a great extent due to their positing materialist explanations for two of the most salient features of organisms: the transmission of distinctive within-type features across generations and the transformation of types over time.

Organisms are composed of complex materials, making the variation of biological form ultimately a problem of physics. For Isaac Newton (1643–1727), who established the dominant physical paradigm of the eighteenth century, matter was inert and inertial, changing its form and position in a continuous fashion, and only when acted on by external forces. Jean-Baptiste de Lamarck (1744–1829), Johann Wolfgang von Goethe (1749–1832), and Étienne Geoffroy Saint-Hilaire (1772–1844) attempted to formulate "laws of form" based on speculative extensions of the prevailing physics. Both the chemistry and physics of middle-scale ("mesoscale") matter soon underwent major advances, however. Figures such as John Dalton (1766–1844), Joseph Louis Gay-Lussac (1778–1850), Claude-Louis Navier (1785–1836), and Sadi Carnot (1796–1832) established a scientific foundation for qualitative transformations in the composition and state of materials, which provided countless examples of abrupt transitions in the composition and form of parcels of matter. The older Newtonian picture, however, persisted as the signature of materialism through the late nineteenth into the twentieth century, not with standing advances in physics in the interim (Newman and Bhat 2011).

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Darwin's theory of evolutionary change embodied this Newtonian incrementalist materialism (see Weber and Depew 1996). The correspondence between the gradual refinements featured by natural selection and the highly successful industrial paradigm of trial-and-error fabrication of metal machine tools, dies and molds likely contributed to the theory's early acceptance. It also established an intellectual habit of avoiding the role of development in evolution because if the only relevant changes in an object's form are gradual, then how the object originated, its degrees of freedom, and the limits of its possible deformations can be side-stepped. This aspect of Darwin's theory is used to this day for impugning critics of the standard model; anyone who would not acknowledge that every complex biological character arose gradually, under adaptive selection, must be irrationally uncomprehending of the "universal acid" of Darwin's "dangerous idea" (Dennett 1995; see also Dawkins 1996).

Darwin's incrementalism could only survive its harnessing to Mendel's genetics in the Modern Synthesis by embedding them both in a populational framework that expunged the saltationism implicit in many of Mendel's experimental results (Provine 2001). The focus of the theory became alleles of small effect or quantitative trait loci. Although Darwin's doctrine of pangenesis and embrace of the inheritance of acquired characteristics provided ample space for behavioral and environmental (i.e., non-genetic) influences on variation, this was often condescendingly dismissed as the rare stumbles of a great man.

Even though embryology increasingly provided support for both discontinuities and conditionality of the phenotype-genotype relationship, the synthesis architects forged a view of organismal form on the basis of the machine-like expression of "information" contained in genomes, with small changes in this information mapping onto small changes in an organism's phenotype. By the mid-twentieth century, the new field of developmental biology—influenced by the successes of molecular genetics and the parallel rise of digital computers—came to endorse, in theory if not in practice, the information-based notion of the "genetic program" (Kay 2000).

The agenda of evolutionary developmental biology (Evo–devo), which began to assume its modern form at the 1981 Dahlem conference on evolution and development (Bonner 1982), is concerned both with the evolution of developmental mechanisms and the role of developmental processes in setting the trajectory of evolutionary change. Once this perspective, with its associated set of issues, was identified, it was bound to destabilize the Modern Synthesis for reasons related to the history outlined above. In particular, gradualism could no longer be privileged over saltationism in considering the range of variation consistent with given genotypes and small variations thereof—modern developmental biology and life history studies disclosed unforeseen complexities in genotype-phenotype mappings. And, in addition, it was no longer possible to ignore the physical forces and effects pertaining to living materials, e.g., cell aggregates and tissues. The earlier "information" model of the genome placed no constraints on biological form and function, so long as it resulted from a sequence of changes each of which met some marginally superior adaptive role. If, on the contrary, phenotypic jumps and morphological novelties resulting from developmental rerouting were possible, the actual physical processes that mold tissues and induce switching among the multidimensional biochemical

states that characterize cell types were strong candidates for major causal and constraining factors of organismal form and function.

Even before physics had advanced to the point of being able to account, in principle, for the forms and patterns of developing tissues, several prescient scientists had recognized its potential to explain the origination of morphological motifs and thus introduce a predictive component to evolutionary theory. William Bateson (1861–1926) proposed that certain tissues exhibited oscillatory excitations that could cause them to organize into segmental and other repeating patterns (Bateson and Bateson 1928; Newman 2007). D'Arcy Wentworth Thompson (1860–1948) suggested that viscous flow and environmentally induced mechanical deformation, among other physical factors, could explain the shapes of organisms and morphological transformations between different species (Thompson 1942). The embryologist E. E. Just described the animal egg as a purely physical system that was nonetheless "self-acting, self-regulating and self-realizing" (Just 1939, 237; Newman 2009). One implication of these views—that much biological form was nonadaptive—had no place in the emerging standard model, however, and these figures were relegated to the scientific margins during their lifetimes.

By the 1970s, when my colleagues and I, along with several other groups, began our attempts to integrate new findings from the cell and molecular biology of developing systems with the physics of condensed, chemically and mechanically excitable materials, mesoscale physics had advanced to a level barely imagined by Bateson, Thompson, and Just. In the following sections I will review some work in this vein from circa 1981 and the post-Dahlem period, and its influence on concepts of the evolutionary role of physical processes and mechanisms. The presentation will be divided into four phases in the development of Evo–devo, characterized by scientific themes that successively received new or intensified attention during the past four decades.

19.2 Phase I: Physical Mechanisms of Embryogenesis

19.2.1 Oscillations and Somitogenesis

One area of major progress in the 1950s and 1960s in the study of dynamical systems of the middle scale, such as chemical reaction networks, was the theory of nonlinear oscillations; chaos theory, developed in the 1970s, was just one of its many fruits (Minorsky 1962; Epstein and Pojman 1998). Oscillations could occur in any "excitable" (i.e., reactive, energy-storing) system, living or nonliving, in which there was an appropriate balance of positive and negative feedback interactions. The principles that emerged from this area of research were quickly applied to a variety of biological questions (Winfree 1980; Goldbeter 1996). Where the phenomena described were metabolic processes like glycolysis (Boiteaux et al. 1975) or pulsatile chemical signaling by the social amoeba *Dictyostelium discoidum*

(Goldbeter and Segel 1977), there was little scientific resistance since the study of metabolism had long been a province of chemistry, a field for which dynamics was integral. More controversial, since it related to morphology, was the proposal of an oscillatory mechanism for the generation of somites, paired blocks of tissue that emerge in a sequential cranio-caudal direction during vertebrate embryogenesis (Cooke and Zeeman 1976). According to this mechanism, cells in the presomitic tissue oscillate in a synchronized fashion with their periodically changing cell state (the clock) acting as a "gate" for the action of a front of potentially changed cell behavior that sweeps along the embryo's length (the wavefront). The interaction of these two factors was predicted mathematically to generate a segmental pattern.

Possibly because of the conviction that embryonic development was a programmed machine-like process that had little in common with the conditional (i.e., producing outcomes subject to physically defined parameters), environment-sensitive aggregation of *Dictyostelium*, the clock-and-wavefront model, an embodiment of William Bateson's proposed vibratory mechanism for segmentation, was similarly ignored. Then, in the late 1990s, Olivier Pourquié and his colleagues presented compelling experimental evidence for a formally similar mechanism for somitogenesis. It involved a demonstrable intracellular biochemical clock, the components of which included the transcriptional switching factor Hes1 and a wavefront consisting of a gradient of the morphogen FGF8 with its source at the embryo's tail tip (Palmeirim et al. 1997). The dynamics of interaction of these factors were somewhat different from those predicted by Cooke and Zeeman: the periodic "sweeping" effect is due to the clock, which is phase-shifted in a continuous fashion along the length of the embryo, not to the wavefront, which is relatively static. Nonetheless, it is clear, as Bateson, and Cooke and Zeeman, predicted, that a tissue-based oscillator underlies somitogenesis. That the associated developmental mechanism is a conditional physical process rather than a machine-like programmatic one is demonstrated by its ability to account for the increase in number of segments in snakes, for example, by evolutionary alterations in the ratio of parameters characterizing the interaction of the clock and wavefront (Gomez and Pourquié 2009).

19.2.2 The Turing Mechanism in Limb Development

Like several other research groups in the 1970s (Gierer and Meinhardt 1972; Kauffman et al. 1978), we were intrigued by the potential explanatory power of the reaction-diffusion mechanisms explored by the mathematician Alan Turing in his paper titled "The chemical basis of morphogenesis" (Turing 1952). Although he had some predecessors in this line of research (Kolmogorov et al. 1937; Rashevsky 1948), Turing showed in a particularly accessible fashion that a balance of positive and negative feedbacks in an open chemical system (essentially identical to networks that generate temporal oscillations), coupled with differences in the rates of diffusion of the key reactive molecules, could defy the expectation that everything

evens out under the influence of diffusion and instead (self-)organize into stable, nonuniform concentration patterns, often exhibiting periodicities.

Because a prominent aspect of the vertebrate limb is the quasi-periodic arrangement of its skeletal elements, we attempted to understand its development in terms of a Turing-type mechanism. The most widely discussed model for this phenomenon at the time was one that incorporated the physical process of molecular diffusion (Crick 1970), but relied heavily on the genetic information paradigm (Summerbell et al. 1973). In particular, all the details of the resulting skeletal pattern depended on the "interpretation" of a simple diffusion gradient based on a presumed point-by-point internal representation of the developing limb in the organism's genome (Wolpert 1971).

Our approach was to model the capacity of the limb's mesenchymal tissue to exhibit formal properties similar to Turing's chemical reaction-diffusion system. By incorporating what was known in the late 1970s about the cell and molecular biology of the formation of precartilage mesenchymal condensations, we were able to show that a succession of skeletal patterns with increasing numbers of parallel elements would be predicted to form under experimentally ascertained changes in the size and shape of the undifferentiated distal tip of the limb bud (Newman and Frisch 1979).

The relation between the actual course of development of a chicken limb and that predicted by a more recent version of our reaction-diffusion model (Zhu et al. 2010) is shown in Fig. 19.1. Isolated and dissociated limb bud tissue can reconstitute limb-like skeletal patterns in vivo (Zwilling 1964; Ros et al. 1994), and nodular patterns of

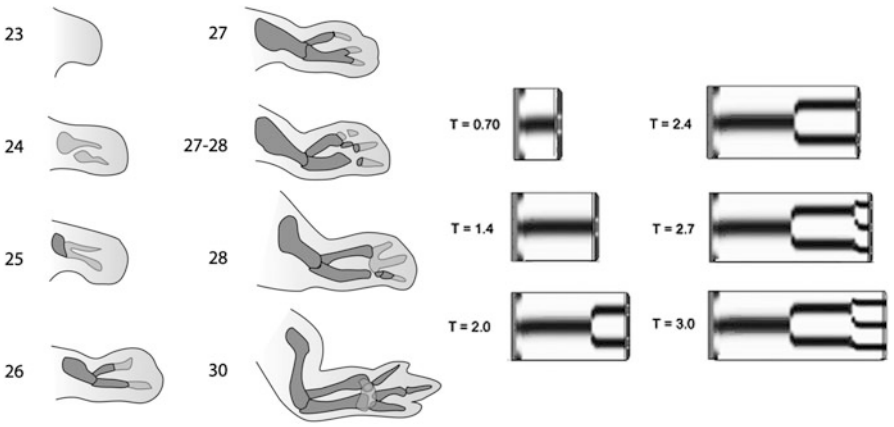


Fig. 19.1 Simulation of chicken wing development. (*Left*) Developmental progression of the chicken forelimb between days 3 and 7 of development (indicated by the corresponding Hamburger-Hamilton stages). Early cartilage, including precartilage condensations, is shown in *light gray*; definitive cartilage is shown in *dark gray*. (*Right*) A sequence of snapshots from a simulation of normal limb development based, on a Turing-type reaction–diffusion model. The transitions between different numbers of elements in successively appearing regions of the simulated limb, which occur in the development of the actual limb, are primarily the result of the changing size and shape of the spatial domain within which the reaction-diffusion system operates. Time in the simulation is in arbitrary linear units (Adapted from Zhu et al. 2010)

cartilage with similar spacing statistics in vitro (Kiskowski et al. 2004; Christley et al. 2007). These phenomena, as well as aspects of the skeletal patterns of mutant and fossil limbs, find ready explanation in the self-organizational capacity of Turing-type reaction–diffusion mechanisms (Miura et al. 2006; Zhu et al. 2010), and our predictions have been borne out in a recent study using gene manipulation in mice (Sheth et al. 2012). Studies of a variety of partly self-organizing developmental systems over the past 30 years, however, have shown that unlike purely chemical reaction-diffusion systems, which have been experimentally confirmed to form patterns by Turing's mechanism (Castets et al. 1990; Ouyang and Swinney 1991), "reaction" and "diffusion" in the developing embryo can often represent complex biosynthetic response and transport functions (Kondo and Miura 2010). While thus only formally similar to chemical reaction and molecular diffusion, these interacting processes produce patterns that resemble those of the purely chemical systems.

19.3 Phase II: "Generic" and "Genetic" Mechanisms of Development

If embryos could take form using "generic" physical processes, such as biochemical oscillations, reaction-diffusion patterning, and thermodynamically driven phase separation of differentially adhesive cell populations (Steinberg 1978), to which living tissues were susceptible in common with nonliving malleable, excitable, media, how were such forms inherited? And if genes were (and are) not the exclusive medium of the inheritance of form, what was the relationship between gene regulatory mechanisms and the physical processes highlighted above, and how has it changed over the course of evolution?

Since animal life cycles typically involve a gametic phase, it has been standard to think that what is passed on to the next generation at this reproductive bottleneck is simply DNA, and (for the more mechanistically broad-minded) patterns of methylation and organized ooplasms that influence its expression. But the physical world is also part of every organism's inheritance. Moreover, contrary to common belief, this does not affect every parcel of matter or cluster of cells in a uniform fashion (Newman 2011a). Solids do not flow and liquids do not bounce, despite existing in the same environment.

Specific gene products in the developing embryo help to mobilize different physical effects—surface tension, viscosity, elasticity, phase separation, solidification—and the evolution of developmental regulatory genes cannot be understood apart from the physical effects they directly or indirectly mobilize. Thus, gametes convey not just genes but the processes that are inescapably mobilized when the genes become expressed (Newman 2011a).

All mechanisms of development, generic or otherwise, therefore involve organization and transformation of materials in which gene products play a prominent part. But it also became clear in the 1970s and 1980s that this was not the whole

story. A burst of research during this period enabled by the new technologies of gene cloning and sequencing, and then genetic engineering of multicellular organisms, established that animal development was accompanied, and indeed apparently orchestrated, by programmed expression of gene activity regulated according to a hierarchical logic (Davidson 1976, 1986).

Taking account of the compelling narratives emerging from both the physical and genetic lines of developmental biological research, we suggested that there was a complementarity between generic and genetic mechanisms of pattern formation and morphogenesis (Newman and Comper 1990). "Genetic" in this case did not simply mean employing genes; as noted above, all developmental mechanisms fit this description. Nor did it mean not employing physics: all biological mechanisms are subject to the laws of physics and chemistry. Rather, "genetic mechanisms" of development referred to hierarchical programs of gene expression and other ontogenetic consequences of highly intricate molecular organization that do not bear any straightforward relationship to organizational processes of nonliving materials.

Our complementarity proposal addressed an emerging paradox. Gene manipulation methods newly available in the 1980s were beginning to show that key developmental control genes, even those at the apex of regulatory hierarchies, were often dispensable (Hülskamp et al. 1989; Zimmer and Gruss 1989) or nearly so (reviewed in Shastry 1995). These findings were difficult to reconcile with the accepted incrementalist scenario for the evolution of these elaborate mechanisms, in which each piece of the puzzle was presumed to be selected for its marginal adaptive advantage. The principle that every genetic difference between related organisms makes a phenotypic difference, or at least did so at some point in evolutionary history, seemed inconsistent with findings that individual, or groups of, regulatory genes may be centrally involved in developmental processes that also occur equally well without them. Even if redundancy and compensatory action were involved, these results suggested a more fluid relationship between genes and form than that advocated by the Modern Synthesis and genetic program models.

The generic/genetic duality indicated a way out of this conundrum through a revised understanding of the relationship between genes and form (Newman and Comper 1990). The idea was that developmental mechanisms represented evolving composites of generic and genetic processes. Specifically, we suggested that the morphological motifs of body plans and organ forms were established early in evolution by generic physical mechanisms whose organizing effects were inescapable in the sense that they were inherent to the materials involved.[1] Then, over time, selective pressures to stabilize and make routine the development of generically originated forms that found success in the original or other ecological settings would lead to the accumulation of genetic circuitry and pathways that facilitated

[1] This aspect of the concept contained echoes of William Bateson and D'Arcy Thompson, as well as the anti-adaptationism of Stephen Jay Gould and Richard Lewontin (e.g., Gould and Lewontin 1979).

construction of these forms.[2] Ultimately, the developmental need for the generic physical mechanism could be partly or even largely bypassed. The physical mechanisms mobilized by the genetic circuitry in these more complex contexts would have decreasing resemblance to those of purely physical systems.[3]

One much-discussed example will illustrate this idea. The identification of regulatory genes of the segmentation pathway in embryos of the fruit fly *Drosophila melanogaster* and the visualization of their spatial expression patterns disclosed striking seven-stripe patterns of "pair-rule" gene mRNAs and proteins at the stage at which the embryo is a syncytium and the transcription factor products are in principle free to diffuse between the nuclear sites of production of their mRNAs (Carroll and Scott 1985; Frasch et al. 1987). The resemblance of these stripes to ones predicted to be formed by a Turing-type reaction-diffusion mechanism led some to initially conclude that this was precisely the basis of this early developmental step. Once it became clear, however, that individual pair-rule stripes were in some cases actually specified by dedicated promoters responsive to position-specific combinations of other factors (Goto et al. 1989; Stanojevic et al. 1991), the notion of a generic patterning mechanism for these stripes was almost universally abandoned (Akam 1989).

Our proposal of a progressive supersession of generic mechanisms by genetic ones suggests a different interpretation of the "inelegant" (Akam 1989) generation of the elegant pair-rule stripe patterns: the primordial mechanism of stripe formation in long germ-band insects such as *Drosophila* was indeed a Turing-type reaction-diffusion mechanism, but this pattern was "captured" over time (in part through promoter duplication) by the more reliable non-generic molecular hierarchy that is seen in present-day forms (Newman 1993; Salazar-Ciudad et al. 2001).

This and other plausible cases of morphologically elaborate forms originating by the action of generic physical mechanisms, and only later coming under the control of complex genetic mechanisms, implied evolutionary scenarios that ran counter to the expectations of Darwinian models. In particular, the rapid early diversification of animal phyla and the stability of morphological types once established (congruent with paleontological findings difficult to accommodate in the standard model), were readily explained by this alternative view of the relationship between genes and form (Newman 1992, 1994).

19.4 Phase III: The Autonomization of Form

Our "physico-genetic" view of the development and evolution of animal form attempted to avoid both naïve physicalism and genetic determinism. Its major features were: (i) organisms are both physical entities and repositories of genetic

[2] This aspect reflected the insights of C. H. Waddington and I. I. Schmalhausen on canalization and stabilizing selection, respectively (Waddington 1942; Schmalhausen 1949).

[3] In many cases, however, it is possible to discern the continued efficacy of the originating physical mechanisms in present-day organisms (see Forgacs and Newman 2005).

information; (ii) development, as the reorganization and transformation of living matter, makes use of the morphogenetic and pattern forming capabilities of meso-scale physics, but the more purely generic physical effects were more prominent earlier in the evolution of a body plan or organ form; and, (iii) once a functionally successful or adequate form arises, natural selection, under the premium of breeding true and developing reliably, promotes the evolution of stabilizing genetic mechanisms that protect developmental pathways against perturbations by external factors like temperature and pressure (both osmotic and hydrostatic), which might affect the outcomes of generic physical processes.

This view seems to imply that over the course of evolution organismal body plans and organ forms should tend towards the condition of "genetic machines" that late twentieth century mainstream evolutionary and developmental biology appeared to maintain they always had been (e.g., Yuh et al. 1998). But research on comparative developmental biology, particularly as it came to be informed by genomics, had more surprises to offer.

The problem of homology, for example, had puzzled morphologists (e.g., Richard Owen) well before Darwin advanced his theory of evolution. What was the relationship, for instance, between the body segments of different animals that may (humans, snakes) or may not (mice, flies) have had a recent common ancestor, or among the distinct elements of the vertebrate limb? The discovery of the pan-phyletic employment of homeobox-containing genes for similar developmental functions in the 1980s (Lobe and Gruss 1989) encouraged gene-based definitions of homology (Holland et al. 1996). These quickly led to new conceptual difficulties, not least of which were the conflation of homology with analogy and the failure to take account of the rewiring of genetic networks that occurs during evolution (Raff 1996; Bolker and Raff 1996; Minelli 1998; see Müller 2007). Nevertheless, assigning evolutionary relationships to different biological structures on the basis of a privileged set of developmental regulatory genes continues to be a popular theme in evolutionary biology under the rubric of "deep homology" (Shubin et al. 2009).

Even before the discovery of the homeobox, Pere Alberch recognized that, insofar as development was underlain by physical mechanisms, ideas of homology based solely on common descent (whether morphological or genetic) could not be sustained. This is because these notions assumed an orderliness of embryogenesis by which corresponding stages in the embryos of different species could be placed into correspondence with one another. But physical mechanisms of morphogenesis could be mobilized in different sequences in different lineages (Alberch 1985).

Even though they are adequate determinants of form, however, physical mechanisms have difficulty accounting for important aspects of biological specificity. While a physical mechanism such as reaction-diffusion could help explain why a reduced-size limb in an evolutionary lineage would suffer the abrupt loss of a digit, it could not determine *which* digit would be lost (Alberch and Gale 1983; Alberch 1985). Such specificity is a function of a lineage's evolutionary history wherein elements became individualized and differentiated from each other, rather than (as would be generated by purely generic physical mechanisms), simply equivalent modules.

To address this inertial aspect of evolved form (referred to as "burden" by Riedl 1978), Gunter Wagner proposed a "biological homology concept" in which pathways of gene activity and interaction constrain the production of individualized parts of the phenotype (Wagner 1989). These "epigenetic traps" limit the possible phenotypic effects of genetic variation, "even though they became established by genetic variation and gene substitution in the first place" (Wagner 1989, p. 66).

Based on work summarized above on physical causation in development, Gerd Müller and I presented an extension of the biological homology concept (Müller and Newman 1999). We suggested that the evolution of the morphological phenotype proceeds in three stages: *generation*, *integration* and *autonomization*. In the first stage, novel morphological motifs are produced by the action of generic physical processes acting on multicellular aggregates or parcels of tissue. The mechanisms of innovation include generic physical determinants that are relevant to the origination of new body plans in ancient clusters of "developmentally naïve" cells (i.e., cells with no evolutionary history in a developing system; Newman and Müller 2000; Newman et al. 2006), but also that act on the "developmentally sophisticated" tissues of more evolved organisms (Müller 1990). We referred to these as *epigenetic* mechanisms, in the classical sense of mobilizing intrinsic generative properties of tissues, rather than the narrower one of chemical modifications to DNA (Müller and Newman 2003). Such epigenetic mechanisms tend to yield trends in the evolutionary trajectories of morphological outcomes which are predictable from the inherent material properties of the tissues (Newman and Müller 2005). Recurrent morphological motifs generated in this fashion would appear as "homoplasies" (Wake 1991).

During the second stage of the proposed evolutionary scenario, the adaptive utility of the novelty—insofar as it exists—places a premium on genetic variants in which the novel structure becomes generated by developmental processes that are independent of the conditionality of physical determination. This leads to the novel constructional unit becoming integrated into the developmental repertoire of the organism by what Waddington termed genetic assimilation (Waddington 1961).

In the final stage of the evolution of a morphological unit it becomes independent not only of its originating conditions, but also of the gene expression networks mobilized at the initiating step. Once the unit or element has been sufficiently well integrated into the organism's ontogeny, there is no reason why it must continue to be generated in the same manner. Autonomization arises from genetic changes and rewiring of circuits ("developmental systems drift": True and Haag 2001) that may leave a structure unchanged, or nearly so, while altering the means of its developmental realization. Striking examples of this are seen when comparing endomesoderm specification (Lin et al. 2009) and vulva development (Kiontke et al. 2007) in different nematode species, and optic vesicle formation in Medaka and zebrafish (Furutani-Seiki and Wittbrodt 2004). Once integrated and autonomized, a novelty would be less likely to undergo dramatic morphological changes as a result of changes in genetic architecture. The evolutionarily stable structure would now be susceptible to the kind of incremental fine-tuning featured in the gradualist scenarios of the Modern Synthesis (Müller and Newman 2005).

This framework provides a rational basis for homologizing structures in related lineages. The relationship between homologues is partly one of common origin and common ancestry, although sister groups that have homologous structures need not have been descended from a common ancestor that also had that structure (Alberch 1985). It is, in addition, partly one of common developmental mechanisms, although what is common to the mechanisms may have little to do with the precise genes employed.

A question posed at the beginning of this section concerned whether the proposed evolutionary trajectory away from the generic physical determination of form and towards non-generic, hierarchical modes of development led embryos to become the genetic machines or computers of some standard narratives. The answer from the perspective of autonomization is clearly no—forms, not genes, become increasingly important in determining evolutionary trajectories. Furthermore, as indicated by the conservation of morphological phenotypes in the face of gene knockouts and developmental systems drift, developmental systems retain their dynamicity over phylogenetic time scales despite the fact that genetics and physics become increasingly intertwined.

19.5 Phase IV: Dynamical Patterning Modules: Entrenched Associations Between Gene Products and Physical Processes

Beginning in the 1990s there was increasing recognition that all animal phyla implemented their developmental processes using a common set of proteins, products of what has been termed the "developmental-genetic toolkit" (see Carroll et al. 2004). These "tools" included transcription factors, some relatively specific to certain metazoan cell types and others associated with positional differences within unitary tissues, as well as molecules involved in cell-cell aggregation (cadherins, collagen) and signal transduction (Wnts, Notch, BMPs). Duboule and Wilkins suggested that the majority of these gene products were invented before the Cambrian explosion "for specialized, terminal cell differentiations rather than for the earliest steps in basic patterning" (Duboule and Wilkins 1998). This prediction was amply borne out a decade later when the genomic sequence of *Monosiga brevicollis*, a unicellular choanoflagellate representative of an extant sister clade of Metazoa, became available (King et al. 2008).

Though they did not originally evolve to mediate multicellular development, this is precisely what these molecules now do in animal embryos. Moreover, many of them perform their functions to surprisingly similar ends given the phylogenetic distances involved. For example, transcription factors Pax6 and Nkx2.5 act early in the developmental pathway of eyes and hearts, respectively, in both mice and fruit flies, and Dlx helps specify the distal ends of developing limbs in these same organisms. No one had previously thought mammalian and insect eyes or limbs

were anything but analogous, and the common ancestor of chordates and arthropods did not even bear limbs. And even if hearts could be traced to a common bilaterian ancestor, the conservation of the genes in the developmental pathway over more than a half billion years of subsequent evolution was not what the standard evolutionary narrative would have predicted (Newman 2006).

The challenge to our physical-genetic hypothesis for the generation of metazoan body plans was that it contained no implication concerning the level of molecular conservation seen in the developmental-genetic toolkit (Newman 1994). Generic physical processes such as adhesion, diffusion, lateral inhibition (i.e., the enforcement by a cell on its neighbors of an alternative cell state), and so forth, are expected to be indifferent to the specific identity of molecular components they interface with so long as those components harness the relevant physics. Cell adhesion proteins have to be sticky, morphogens have to be released and not irreversibly bind to extracellular materials, and mechanisms for alternation of cell fates require some kind of switching mechanism. For this reason (under the standard assumption that diversification of phyla took place by the accumulation of many microevolutionary steps—"phyletic gradualism"), each of the mechanisms employed in the physical-genetic model should have had many different molecular embodiments since the appearance of the Metazoa more than 600 Ma ago.

But like the cell type- and region-specific transcription factors mentioned above, and equally surprisingly, the products of the genes specifying basic multicellular morphogenetic and patterning functions (the "interaction toolkit") are highly conserved: cadherins and collagens mediate associations among cells in all animal embryos; the Wnt pathway mediates changes in the shape or surface polarity of embryonic cells of nearly all animal phyla, with emergent morphological or topological consequences at the tissue level (Newman and Bhat 2008); the Notch pathway acts (via its nuclear switching factor Hes1) to mediate segmentation in phyla as evolutionarily separated as arthropods (Schoppmeier and Damen 2005) and vertebrates (Dequéant and Pourquié 2008); secreted morphogens of the hedgehog, BMP and FGF families, and a few others, mediate nonlocal cell-to-cell communication in all animal embryos (Lander 2007).

There have been attempts to accommodate these striking findings of molecular conservation to the phyletic gradualism of the Modern Synthesis; for example, perhaps it was the regulatory portions of the toolkit genes that evolved gradually (Carroll 2000). But morphological gradualism itself is no longer tenable: evidence has mounted that the abrupt appearance of disparate animal phyla in the late Precambrian and early Cambrian fossil beds (Conway Morris 2006; Budd 2008; Shen et al. 2008) is not an artifact of fossil recovery, but was truly compressed in time (Rokas et al. 2005; Peterson et al. 2008).

Certainly the outcome (with respect to the genes utilized) of the physical generation/origination of forms would have been different if phyletic gradualism had been a valid concept. But the physical-genetic hypothesis does not require gradualism. If the unicellular antecedents of the Metazoa contained most of the interaction toolkit genes, as now appears to be the case (King et al. 2008; Abedin and King 2008; Manning et al. 2008; Sebé-Pedrós et al. 2010), then,

by virtue of their entering into multicellular aggregates, their gene products would automatically mobilize physical processes and effects characteristic of the increased scale of such aggregates and the fact that they comprise discrete, independently mobile subunits (i.e., cells) (Newman and Bhat 2008).

The change to a multicellular context has numerous consequences (Newman and Bhat 2008): (i) while surface tension does not determine the shapes of individual cells, it does determine the shape of a cell aggregate; (ii) cell aggregates containing surface-polarized cells can spontaneously acquire internal lumens; (iii) aggregates containing distinct populations of cells with different adhesive strengths will spontaneously sort out into separate layers; (iv) aggregates of cells that each contain the same biochemical oscillator will spontaneously undergo synchronization, so that the cell state (with respect to the oscillating component) will be globally coordinated across the cell mass; and, (v) cells that secrete diffusible molecules, when present in an aggregate, can act as sources of gradients that pattern neighboring cells, or, when interacting with synchronized oscillating cells, control segmentation.

Physical origination processes are naturally saltational (i.e., nonlinear) and orthogenetic (i.e., similar morphological motifs are expected to occur in independent lineages). These early-established structural themes would constitute a "developmental burden" for subsequent evolution (Riedl 1978), giving them the property of "generative entrenchment" (Wimsatt 1986; Wimsatt and Schank 2004). Because the physical mechanisms involved are sensitive to external conditions, these processes are also naturally plastic. But physically based plasticity would be expected to decline as integration and autonomization, due to stabilizing and canalizing selection (Waddington 1942; Schmalhausen 1949), set in.

The capacities of the products of the ancestral unicellular counterparts to the molecules of the metazoan interaction toolkit to facilitate the mobilization of a range of distinct and relatively independent physical processes in multicellular aggregates, can been schematized into "dynamical patterning modules" (DPMs) (Newman 2010; Newman and Bhat 2008, 2009; Fig. 19.2). The most fundamental of the DPMs is *ADH* (cell–cell adhesion). Genes specifying several members of the most commonly employed cell-cell adhesion proteins are present in the non-colonial choanoflagellate *M. brevicollis* (Abedin and King 2008). What was required, therefore, in order to "invent" the corresponding DPM was a genetic or environmental change that turned the originally nonhomophilic cell surface proteins into homophilic ones. Once this occurred, *ADH*, by mediating aggregate formation, would have set in motion the early developmental-evolutionary trajectory of the Metazoa.

It is evident that these early associations of gene products and physical processes would have been among the most indispensible causal factors of animal development. If diversification happened quickly, as proposed here, the phyla would have immediately set out on their separate evolutionary paths with identical developmental-genetic toolkits (embodied in the DPMs) but different morphotypes (Newman 2011b). Over time, as the phyla's characteristic morphological motifs became integrated into body plans and organ forms, the toolkit would have become increasingly entrenched. Even as some morphological building blocks became partially unmoored from their originating conditions (autonomization), the most

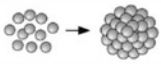
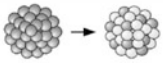
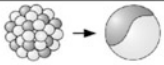
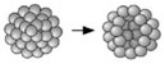
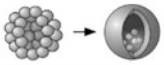
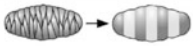
DPM	molecules	physics	evo-devo role	effect
ADH	cadherins	adhesion	multicellularity	
LAT	Notch	lateral inhibition	coexistence of alternative cell states	
DAD	cadherins	differential adhesion	phase separation; tissue multilayering	
POL_a	Wnt	cell surface anisotropy	topological change; interior cavities	
POL_p	Wnt	cell shape anisotropy	tissue elongation	
ECM	chitin; collagen	stiffness; dispersal	tissue solidification; elasticity; EMT	
OSC	Wnt + Notch	chemical oscillation	segmentation; periodic patterning	
MOR	TGF-β/BMP; FGF; Hh	diffusion	pattern formation	
TUR	MOR + Wnt + Notch	dissipative structure	segmentation; periodic patterning	

Fig. 19.2 Key dynamical patterning modules (DPMs), their respective molecular constituents and physical principles, roles in evolution and development, and schematic representations of the main morphological motif they generate. Each DPM is assigned a three-letter acronym. *ADH* cell-cell adhesion, *LAT* lateral inhibition, *DAD* differential adhesion, POL_a cell polarity (apicobasal), POL_p cell polarity (planar), *ECM* extracellular matrix, *OSC* biochemical oscillation, *MOR* morphogen, *TUR* Turing-type reaction-diffusion system. This list of DPMs is not exhaustive. DPMs that refer to individual cell functions such as the *POL*s and *OSC*, are to be understood as designating the multicellular consequences of those functions (Based on Newman and Bhat 2008. See Newman and Bhat 2008, 2009 for additional details)

plausible rewirings of developmental pathways would have involved novel deployments of DPMs, which in present-day organisms typically retain the same associations of physical effects and specific toolkit molecules on the basis of which they first came into existence.

19.6 Conclusions

The legacy of Dahlem 1981 is multifaceted, but there is general agreement that the emphasis on the role of developmental mechanisms in generating morphological variation and thus influencing the pathways of evolution was a prominent and influential theme (Love 2006). Our physico-genetic perspective on the

connection between evolution and development has led us to conclusions at odds with the Modern Synthesis, though our framework finds support from findings by investigators working within Evo–devo employing different paradigms from ours:

(i) Morphological evolution does not necessarily track genetic evolution; large-scale morphological change can occur with a minimum of genetic change, while morphology can be static despite extensive genetic change (e.g., Kuraku and Meyer 2008; Cardoso et al. 2009)
(ii) Phenotypic change can precede associated genotypic change (e.g., West-Eberhard 2003; Palmer 2004).
(iii) Macroevolutionary change can be very rapid (e.g., Rokas et al. 2005).
(iv) Saltation is an expected mode of evolution; gradualist adaptive scenarios are not needed to transition from one complex morphology to another (e.g., Erwin 2000; Minelli et al. 2009; Chouard 2010).
(v) Homoplasy is expected to be common; some morphological motifs are recurrent and even predictable, and do not necessarily arise by selection for functional adaptation (e.g., Conway Morris 2003; Seaver 2003; Grazhdankin 2004; Jaekel and Wake 2007).
(vi) Evolution is not uniformitarian; developmental mechanisms at the origin of many morphological motifs were different in kind from those of present-day organisms (e.g., Davidson and Erwin 2009).
(vii) Morphological plasticity was greater at early stages of the evolution of body plans and organ forms than at later stages (e.g., Coates and Clack 1990; Webster 2007).

I suggest that these observations, all of which are puzzling from the viewpoint of the Darwinian model, flow logically from the physical-genetic framework. Darwin's theory, immersed in the scientific culture of its time, committed itself to gradualism as the only acceptable form of material change under the doctrine of *Natura non facit saltum*. Though the Modern Synthesis also embraced this metaphysics, we now know much more about physical processes and their role in generating living structures than we did in the mid-twentieth century. The intellectual ferment around integrating development with evolutionary theory that Dahlem 1981 both represented and promoted is coming to fruition in a broader understanding of the causal basis of life's varied forms.

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References

Abedin, M., and N. King. 2008. The premetazoan ancestry of cadherins. *Science* 319: 946–948.
Akam, M. 1989. Making stripes inelegantly. *Nature* 341: 282–283.

Alberch, P. 1985. Problems with the interpretation of developmental sequences. *Systematic Zoology* 34: 46–58.
Alberch, P., and E.A. Gale. 1983. Size dependence during the development of the amphibian foot. Colchicine-induced digital loss and reduction. *Journal of Embryology and Experimental Morphology* 76: 177–197.
Bateson, W., and B. Bateson. 1928. *William Bateson, F.R.S., Naturalist; His essays and addresses, together with a short account of his life*. Cambridge: Cambridge University Press.
Boiteux, A., A. Goldbeter, and B. Hess. 1975. Control of oscillating glycolysis of yeast by stochastic, periodic, and steady source of substrate: A model and experimental study. *Proceedings of the National Academy of Sciences of the United States of America* 72: 3829–3833.
Bolker, J.A., and R.A. Raff. 1996. Developmental genetics and traditional homology. *Bioessays* 18: 489–494.
Bonner, J.T. (ed.). 1982. Evolution and Development. Dahlem Konferenzen, Berlin: Springer.
Budd, G.E. 2008. The earliest fossil record of the animals and its significance. *Philosophical Transactions of the Royal Society, B: Biological Sciences* 363: 1425–1434.
Cardoso, A., A. Serrano, and A.P. Vogler. 2009. Morphological and molecular variation in tiger beetles of the *Cicindela hybrida* complex: Is an 'integrative taxonomy' possible? *Molecular Ecology* 18: 648–664.
Carroll, S.B. 2000. Endless forms: The evolution of gene regulation and morphological diversity. *Cell* 101: 577–580.
Carroll, S.B., and M.P. Scott. 1985. Localization of the fushi tarazu protein during *Drosophila* embryogenesis. *Cell* 43: 47–57.
Carroll, S.B., J.K. Grenier, and S.D. Weatherbee. 2004. *From DNA to diversity: Molecular genetics and the evolution of animal design*. Malden: Blackwell.
Castets, V., E. Dulos, J. Boissonade, and P. DeKepper. 1990. Experimental evidence of a sustained standing turing-type nonequilibrium chemical pattern. *Physical Review Letters* 64: 2953–2956.
Chouard, T. 2010. Evolution: Revenge of the hopeful monster. *Nature* 463: 864–867.
Christley, S., M.S. Alber, and S.A. Newman. 2007. Patterns of mesenchymal condensation in a multiscale, discrete stochastic model. *PLoS Computational Biology* 3: e76.
Coates, M.I., and J.A. Clack. 1990. Polydactyly in the earliest known tetrapod limbs. *Nature* 347: 66–69.
Conway Morris, S. 2003. *Life's solution: Inevitable humans in a lonely universe*. Cambridge/New York: Cambridge University Press.
Conway Morris, S. 2006. Darwin's dilemma: The realities of the Cambrian 'explosion'. *Philosophical Transactions of the Royal Society, B: Biological Sciences* 361: 1069–1083.
Cooke, J., and E.C. Zeeman. 1976. A clock and wavefront model for control of the number of repeated structures during animal morphogenesis. *Journal of Theoretical Biology* 58: 455–476.
Crick, F.H.C. 1970. Diffusion in embryogenesis. *Nature* 225: 420–422.
Davidson, E.H. 1976. *Gene activity in early development*, 2nd ed. New York: Academic.
Davidson, E.H. 1986. *Gene activity in early development*, 3rd ed. Orlando: Academic.
Davidson, E.H., and D.H. Erwin. 2009. An integrated view of Precambrian eumetazoan evolution. *Cold Spring Harbor Symposia on Quantitative Biology* 74: 65–80.
Dawkins, R. 1996. *Climbing mount improbable*. New York: Norton.
Dennett, D.C. 1995. *Darwin's dangerous idea: Evolution and the meanings of life*. New York: Simon and Schuster.
Dequéant, M.L., and O. Pourquié. 2008. Segmental patterning of the vertebrate embryonic axis. *Nature Reviews Genetics* 9: 370–382.
Duboule, D., and A.S. Wilkins. 1998. The evolution of 'bricolage'. *Trends in Genetics* 14: 54–59.
Epstein, I.R., and J.A. Pojman. 1998. *An introduction to nonlinear chemical dynamics: Oscillations, waves, patterns, and chaos*. New York: Oxford University Press.
Erwin, D.H. 2000. Macroevolution is more than repeated rounds of microevolution. *Evolution and Development* 2: 78–84.
Forgacs, G., and S.A. Newman. 2005. *Biological physics of the developing embryo*. Cambridge: Cambridge University Press.

Frasch, M., T. Hoey, C. Rushlow, H. Doyle, and M. Levine. 1987. Characterization and localization of the even-skipped protein of *Drosophila*. *EMBO Journal* 6: 749–759.

Furutani-Seiki, M., and J. Wittbrodt. 2004. Medaka and zebrafish, an evolutionary twin study. *Mechanisms of Development* 121: 629–637.

Gierer, A., and H. Meinhardt. 1972. A theory of biological pattern formation. *Kybernetik* 12: 30–39.

Goldbeter, A. 1996. *Biochemical oscillations and cellular rhythms: The molecular bases of periodic and chaotic behaviour*. Cambridge: Cambridge University Press.

Goldbeter, A., and L.A. Segel. 1977. Unified mechanism for relay and oscillation of cyclic AMP in *Dictyostelium discoideum*. *Proceedings of the National Academy of Sciences of the United States of America* 74: 1543–1547.

Gomez, C., and O. Pourquié. 2009. Developmental control of segment numbers in vertebrates. *Journal of Experimental Zoology (Molecular and Developmental Evolution)* 312: 533–544.

Goto, T., P. MacDonald, and T. Maniatis. 1989. Early and late periodic patterns of even skipped expression are controlled by distinct regulatory elements that respond to different spatial cues. *Cell* 57: 413–422.

Gould, S.J., and R.C. Lewontin. 1979. The spandrels of San Marco and the panglossian paradigm. *Proceedings of the Royal Society B: Biological Sciences* 205: 581–598.

Grazhdankin, D. 2004. Patterns of distribution in the Ediacaran biotas: Facies versus biogeography and evolution. *Paleobiology* 30: 203–221.

Holland, L.Z., P.W. Holland, and N.D. Holland. 1996. Revealing homologies between distantly related animals by in situ hybridization to developmental genes: Amphioxus versus vertebrates. In *Molecular zoology*, ed. J.D. Ferraris and S.R. Palumbi, 267–295. New York: Wiley-Liss.

Hulskamp, M., C. Schroder, C. Pfeifle, H. Jackle, and D. Tautz. 1989. Posterior segmentation of the *Drosophila* embryo in the absence of a maternal posterior organizer gene. *Nature* 338: 629–632.

Jaekel, M., and D.B. Wake. 2007. Developmental processes underlying the evolution of a derived foot morphology in salamanders. *Proceedings of the National Academy of Sciences of the United States of America* 104: 20437–20442.

Just, E.E. 1939. *The biology of the cell surface*. Philadelphia: P. Blakiston's Son and Co.

Kauffman, S.A., R.M. Shymko, and K. Trabert. 1978. Control of sequential compartment formation in Drosophila. *Science* 199: 259–270.

Kay, L.E. 2000. *Who wrote the book of life? A history of the genetic code*. Stanford: Stanford University Press.

King, N., M.J. Westbrook, S.L. Young, A. Kuo, M. Abedin, J. Chapman, S. Fairclough, et al. 2008. The genome of the choanoflagellate *Monosiga brevicollis* and the origin of metazoans. *Nature* 451: 783–788.

Kiontke, K., A. Barriere, I. Kolotuev, B. Podbilewicz, R. Sommer, D.H. Fitch, and M.A. Felix. 2007. Trends, stasis, and drift in the evolution of nematode vulva development. *Current Biology* 17: 1925–1937.

Kiskowski, M.A., M.S. Alber, G.L. Thomas, J.A. Glazier, N.B. Bronstein, J. Pu, and S.A. Newman. 2004. Interplay between activator-inhibitor coupling and cell-matrix adhesion in a cellular automaton model for chondrogenic patterning. *Developmental Biology* 271: 372–387.

Kolmogorov, A., L. Petrovsky, and N. Piskunov. 1937. An investigation of the diffusion equation combined with an increase in mass and its application to a biological problem. *Bulletin of the University of Moscow Ser Int* A1(6): 1–26, in Russian.

Kondo, S., and T. Miura. 2010. Reaction-diffusion model as a framework for understanding biological pattern formation. *Science* 329: 1616–1620.

Kuraku, S., and A. Meyer. 2008. Genomic analysis of cichlid fish 'natural mutants'. *Current Opinion in Genetics and Development* 18: 551–558.

Lander, A.D. 2007. Morpheus unbound: Reimagining the morphogen gradient. *Cell* 128: 245–256.

Lin, K.T., G. Broitman-Maduro, W.W. Hung, S. Cervantes, and M.F. Maduro. 2009. Knockdown of SKN-1 and the Wnt effector TCF/POP-1 reveals differences in endomesoderm specification in *C. briggsae* as compared with *C. elegans*. *Developmental Biology* 325: 296–306.

Lobe, C.G., and P. Gruss. 1989. Mouse versions of fly developmental control genes: Legitimate or illegitimate relatives? *New Biology* 1: 9–18.

Love, A.C. 2006. Evolutionary morphology and Evo–devo: Hierarchy and novelty. *Theory in Biosciences* 124: 317–33.

Manning, G., S.L. Young, W.T. Miller, and Y. Zhai. 2008. The protist, *Monosiga brevicollis*, has a tyrosine kinase signaling network more elaborate and diverse than found in any known metazoan. *Proceedings of the National Academy of Sciences of the United States of America* 105: 9674–9679.

Minelli, A. 1998. Molecules, developmental modules, and phenotypes: A combinatorial approach to homology. *Molecular Phylogenetics and Evolution* 9: 340–347.

Minelli, A., A. Chagas-Junior, and G.D. Edgecombe. 2009. Saltational evolution of trunk segment number in centipedes. *Evolution & Development* 11: 318–322.

Minorsky, N. 1962. *Nonlinear oscillations*. Princeton: Van Nostrand.

Miura, T., K. Shiota, G. Morriss-Kay, and P.K. Maini. 2006. Mixed-mode pattern in doublefoot mutant mouse limb—Turing reaction-diffusion model on a growing domain during limb development. *Journal of Theoretical Biology* 240: 562–573.

Müller, G.B. 1990. Developmental mechanisms at the origin of morphological novelty: A side-effect hypothesis. In *Evolutionary innovations*, ed. M. Nitecki, 99–130. Chicago: University of Chicago Press.

Müller, G.B. 2007. Evo–devo: Extending the evolutionary synthesis. *Nature Reviews Genetics* 8: 943–949.

Müller, G.B., and S.A. Newman. 1999. Generation, integration, autonomy: Three steps in the evolution of homology. *Novartis Foundation Symposium* 222: 65–73.

Müller, G.B., and S.A. Newman. 2003. Origination of organismal form: The forgotten cause in evolutionary theory. In *Origination of organismal form: Beyond the gene in developmental and evolutionary biology*, ed. G.B. Müller and S.A. Newman, 3–12. Cambridge, MA: MIT Press.

Müller, G.B., and S.A. Newman. 2005. The innovation triad: An evo-devo agenda. *Journal of Experimental Zoology (Molecular and Developmental Evolution)* 304: 487–503.

Newman, S.A. 1992. Generic physical mechanisms of morphogenesis and pattern formation as determinants in the evolution of multicellular organization. In *Principles of organization in organisms*, ed. J. Mittenthal and A. Baskin, 241–267. Boston: Addison-Wesley.

Newman, S.A. 1993. Is segmentation generic? *Bioessays* 15: 277–283.

Newman, S.A. 1994. Generic physical mechanisms of tissue morphogenesis: A common basis for development and evolution. *Journal of Evolutionary Biology* 7: 467–488.

Newman, S.A. 2006. The developmental-genetic toolkit and the molecular homology-analogy paradox. *Biological Theory* 1: 12–16.

Newman, S.A. 2007. William Bateson's physicalist ideas. In *From embryology to evo–devo: A history of evolutionary development*, ed. M. Laubichler and J. Maienschein, 83–107. Cambridge, MA: MIT Press.

Newman, S.A. 2009. E.E. Just's "independent irritability" revisited: The activated egg as excitable soft matter. *Molecular Reproduction and Development* 76: 966–974.

Newman, S.A. 2010. Dynamical patterning modules. In *Evolution: The extended synthesis*, ed. M. Pigliucci and G.B. Müller, 281–306. Cambridge, MA: MIT Press.

Newman, S.A. 2011a. The developmental specificity of physical mechanisms. *Ludus Vitalis* 19: 343–351.

Newman, S.A. 2011b. Animal egg as an evolutionary novelty: A solution of the embryonic "hourglass" puzzle. *Journal of Experimental Zoology (Molecular and Developmental Evolution)* 316: 467–83.

Newman, S.A., and R. Bhat. 2008. Dynamical patterning modules: Physico-genetic determinants of morphological development and evolution. *Physical Biology* 5: 15008.

Newman, S.A., and R. Bhat. 2009. Dynamical patterning modules: A "pattern language" for development and evolution of multicellular form. *International Journal of Developmental Biology* 53: 693–705.

Newman, S.A., and R. Bhat. 2011. Lamarck's dangerous idea. In *Transformations of Lamarckism: From subtle fluids to molecular biology*, ed. S. Gissis and E. Jablonka, 157–169. Cambridge, MA: MIT Press.

Newman, S.A., and W.D. Comper. 1990. 'Generic' physical mechanisms of morphogenesis and pattern formation. *Development* 110: 1–18.

Newman, S.A., and H.L. Frisch. 1979. Dynamics of skeletal pattern formation in developing chick limb. *Science* 205: 662–668.

Newman, S.A., and G.B. Müller. 2000. Epigenetic mechanisms of character origination. *Journal of Experimental Zoology (Molecular and Developmental Evolution)* 288: 304–317.

Newman, S.A., and G.B. Müller. 2005. Genes and form: Inherency in the evolution of developmental mechanisms. In *Genes in development: Re-reading the molecular paradigm*, ed. E. Neumann-Held and C. Rehmann-Sutter, 38–73. Durham: Duke University Press.

Newman, S.A., G. Forgacs, and G.B. Müller. 2006. Before programs: The physical origination of multicellular forms. *International Journal of Developmental Biology* 50: 289–299.

Ouyang, Q., and H. Swinney. 1991. Transition from a uniform state to hexagonal and striped Turing patterns. *Nature* 352: 610–612.

Palmeirim, I., D. Henrique, D. Ish-Horowicz, and O. Pourquié. 1997. Avian hairy gene expression identifies a molecular clock linked to vertebrate segmentation and somitogenesis. *Cell* 91: 639–648.

Palmer, A.R. 2004. Symmetry breaking and the evolution of development. *Science* 306: 828–833.

Peterson, K.J., J.A. Cotton, J.G. Gehling, and D. Pisani. 2008. The Ediacaran emergence of bilaterians: Congruence between the genetic and the geological fossil records. *Philosophical Transactions of the Royal Society, B: Biological Sciences* 363: 1435–1443.

Provine, W.B. 2001. *The origins of theoretical population genetics*. 2nd ed. Chicago: University of Chicago Press.

Raff, R.A. 1996. *The shape of life: Genes, development, and the evolution of animal form*. Chicago: University of Chicago Press.

Rashevsky, N. 1948. *Mathematical biophysics*. Chicago: University of Chicago Press.

Riedl, R. 1978. *Order in living systems: A systems analysis of evolution*. New York: Wiley.

Rokas, A., D. Kruger, and S.B. Carroll. 2005. Animal evolution and the molecular signature of radiations compressed in time. *Science* 310: 1933–1938.

Ros, M.A., G.E. Lyons, S. Mackem, and J.F. Fallon. 1994. Recombinant limbs as a model to study homeobox gene regulation during limb development. *Developmental Biology* 166: 59–72.

Salazar-Ciudad, I., R. Solé, and S.A. Newman. 2001. Phenotypic and dynamical transitions in model genetic networks. II. Application to the evolution of segmentation mechanisms. *Evolution and Development* 3: 95–103.

Schmalhausen, I.I. 1949. *Factors of evolution*. Philadelphia: Blakiston.

Schoppmeier, M., and W.G. Damen. 2005. Suppressor of hairless and presenilin phenotypes imply involvement of canonical notch-signalling in segmentation of the spider *Cupiennius salei*. *Developmental Biology* 280: 211–224.

Seaver, E.C. 2003. Segmentation: Mono- or polyphyletic? *International Journal of Developmental Biology* 47: 583–595.

Sebé-Pedrós, A., A.J. Roger, F.B. Lang, N. King, and I. Ruiz-Trillo. 2010. Ancient origin of the integrin-mediated adhesion and signaling machinery. *Proceedings of the National Academy of Sciences of the United States of America* 107: 10142–10147.

Shastry, B.S. 1995. Genetic knockouts in mice: An update. *Experientia* 51: 1028–1039.

Shen, B., L. Dong, S. Xiao, and M. Kowalewski. 2008. The Avalon explosion: Evolution of Ediacara morphospace. *Science* 319: 81–84.

Sheth, R., L. Marcon, M.F. Bastida, M. Junco, L. Quintana, R. Dahn, M. Kmita, J. Sharpe, and M.A. Ros. 2012. *Hox* genes regulate digit patterning by controlling the wavelength of a Turing-type mechanism. *Science* 338: 1476–1480.

Shubin, N., C. Tabin, and S. Carroll. 2009. Deep homology and the origins of evolutionary novelty. *Nature* 457: 818–823.

Stanojevic, D., S. Small, and M. Levine. 1991. Regulation of a segmentation stripe by overlapping activators and repressors in the *Drosophila* embryo. *Science* 254: 1385–1387.

Steinberg, M.S. 1978. Specific cell ligands and the differential adhesion hypothesis: How do they fit together? In *Specificity of embryological interactions*, ed. D.R. Garrod, 97–130. London: Chapman and Hall.

Summerbell, D., J.H. Lewis, and L. Wolpert. 1973. Positional information in chick limb morphogenesis. *Nature* 244: 492–496.

Thompson, D.A.W. 1942. *On growth and form*. Cambridge: Cambridge University Press.

True, J.R., and E.S. Haag. 2001. Developmental system drift and flexibility in evolutionary trajectories. *Evolution and Development* 3: 109–119.

Turing, A.M. 1952. The chemical basis of morphogenesis. *Philosophical Transactions of the Royal Society, B: Biological Sciences* 237: 37–72.

Waddington, C.H. 1942. Canalization of development and the inheritance of acquired characters. *Nature* 150: 563–565.

Waddington, C.H. 1961. Genetic assimilation. *Advances in Genetics* 10: 257–293.

Wagner, G.P. 1989. The biological homology concept. *Annual Review of Ecology and Systematics* 20: 51–69.

Wake, D.B. 1991. Homoplasy: The result of natural selection or evidence of design limitations? *American Naturalist* 138: 543–567.

Weber, B.H., and D.J. Depew. 1996. Natural selection and self-organization. *Biology & Philosophy* 11: 33–65.

Webster, M. 2007. A Cambrian peak in morphological variation within trilobite species. *Science* 317: 499–502.

West-Eberhard, M.J. 2003. *Developmental plasticity and evolution Oxford*. New York: Oxford University Press.

Wimsatt, W.C. 1986. Developmental constraints, generative entrenchment, and the innate-acquired distinction. In *Integrating scientific disciplines*, ed. W. Bechtel. Dordrecht: Nijhoff.

Wimsatt, W.C., and J.C. Schank. 2004. Generative entrenchment, modularity and evolvability: When genic selection meets the whole organism. In *Modularity in evolution and development*, ed. G. Schlosser and G.P. Wagner, 359–394. Chicago: University of Chicago Press.

Winfree, A.T. 1980. *The geometry of biological time*. New York: Springer.

Wolpert, L. 1971. Positional information and pattern formation. *Current Topics in Developmental Biology* 6: 183–224.

Yuh, C.H., H. Bolouri, and E.H. Davidson. 1998. Genomic *cis*-regulatory logic: Experimental and computational analysis of a sea urchin gene. *Science* 279: 1896–1902.

Zhu, J., Y.T. Zhang, M.S. Alber, and S.A. Newman. 2010. Bare bones pattern formation: A core regulatory network in varying geometries reproduces major features of vertebrate limb development and evolution. *PLoS One* 5: e10892.

Zimmer, A., and P. Gruss. 1989. Production of chimaeric mice containing embryonic stem (ES) cells carrying a homoeobox *Hox 1.1* allele mutated by homologous recombination. *Nature* 338: 150–153.

Zwilling, E. 1964. Development of fragmented and of dissociated limb bud mesoderm. *Developmental Biology* 89: 20–37.