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BIOLOGICAL EVOLUTION: FACTS AND THEORIES

A Critical Appraisal 150 Years After "The Origin of Species"

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THE EVOLUTION OF EVOLUTIONARY MECHANISMS: A NEW PERSPECTIVE

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1. Introduction

The Modern Evolutionary Synthesis, based on Charles Darwin's concept of natural selection in conjunction with a genetic theory of inheritance in a population-based framework, has been, for more than six decades, the dominant scientific perspective for explaining the diversity of living organisms. In recent years, however, with the growth in knowledge of the fossil record, the genetic affinities among different life forms and the roles played by non-genetic determinants of organismal shape and form, there have been challenges to the synthesis in the realms of both cellular (Margulis and Sagan 2002; Woese and Goldenfeld 2009) and multicellular (Alberch 1989; Newman 1994; Jablonka and Lamb 1995, 2005; Newman and Müller 2000; West-Eberhard 2003) evolution.

According to the eminent evolutionary biologist Ernst Mayr, "Nothing strengthened the theory of natural selection as much as the refutation, one by one, of all the competing theories, such as saltationism, orthogenesis, inheritance of acquired characters, and so forth." (Mayr 1982, 840) As I will argue below, a coherent account of the origination of the morphological motifs of multicellular organisms in fact requires bringing all three of these ideas back into evolutionary theory, though in a fashion that acknowledges their declining efficacy as evolution progresses. Put in other terms: evolutionary mechanisms themselves have evolved.

It is easy to see why the first two of Mayr's "competing theories" are antithetical to the standard picture. *Saltationism* is the idea that organismal phenotype can change from one generation to the next in a manner that is very large compared to the organism's usual range of phenotypic variation. Saltation is often associated with the concept of the "hopeful monster," a term invented by the geneticist Richard Goldschmidt to refer to novel phenotypes that might arise in a single generation by the mutation of a single broadly acting gene (a "macromutation"). Arguments developed by population geneticists such as Ronald Fisher (Fisher

1930) in the twentieth century contended that such jumps would be exceptionally rare and typically lethal occurrences not contributing significantly to the origin of species or higher taxa. But even before the Synthesis was formulated, Darwin expressed the incompatibility of saltationism with his own ideas in a statement in the first edition of *The Origin of the Species*, "[i]f it could be demonstrated that any complex organ existed, which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down" (Darwin 1859, 158).

Orthogenesis is the doctrine that organisms change in preferred directions over the course of evolution. Although this is consonant with the fact that all material systems have inherent patterns of organization that may manifest themselves rapidly (as in the transition from waves to vortices in water) or over time (as in the generation of the chemical elements), and despite the purported examples of such inherencies in organismal development and evolution provided by biologists such as William Bateson (Bateson 1909) and W. D'Arcy Thompson (1942), orthogenesis was forcefully rejected by leading architects of the Synthesis, including George Gaylord Simpson (1944) and Mayr himself (Mayr 1974).

The most disparaged of all the competing theories listed by Mayr is the third one, the inheritance of acquired characteristics, or Lamarckism. This is ironic, considering that Darwin himself became increasingly receptive to this notion in successive volumes of *The Origin*. Indeed, a role for inheritance of characters acquired during an individual's lifetime was written out of the standard theory not because it conflicted with natural selection, but because it violated the tenet of chromosomal genes as the exclusive medium of inheritance. An added barrier to the operation of Lamarckian mechanisms for animal species first emphasized by the post-Darwinian biologist August Weismann is the sequestering of the germ line from the rest of the body during development.

It is important to recognize, however, that Darwin and most of his successors concerned themselves with multicellular forms, both plants and animals, but conspicuously avoided providing any account of the origination and innovation of the morphological motifs, e.g., body plans and organ forms, that are raw material for natural selection. The focus on this missing element by the emerging field of evolutionary developmental biology (Robert 2004; Müller and Newman 2005; Müller 2007; Callebaut *et al.* 2007; Moczek 2008; Fusco and Minelli 2008) has highlighted a number of properties of developmental systems that were previously marginal to evolutionary theory. These include developmental and phenotypic plasticity and genotype–phenotype discordances (Newman 1994; Trut *et al.* 2009;

Pigliucci 2001; West-Eberhard 2003; Badyaev 2005; Badyaev *et al.* 2005; Salazar-Ciudad 2006; Goodman 2008; Vedel *et al.* 2008), determination of form by physical and epigenetic factors (Müller and Streicher 1989; Newman and Comper 1990; Newman and Müller 2000), and inheritance systems that extend beyond the gene (Jablonka and Lamb 1995; 2005).

In the remainder of this chapter I will describe how our current inferences about the genetic endowment of the single-celled ancestors of the Metazoa (multicellular animals) combined with knowledge of the physical properties of viscoelastic materials (e.g., cell clusters and tissue primordia) have led to new understanding of the origination and early evolution of animal form that is simultaneously saltational, orthogenic and Lamarckian. The three erstwhile prohibited concepts converge in this revised explanatory framework precisely because the earliest multicellular animals were subject to external physical forces and effects that would have shaped and reshaped them in often nonlinear and abrupt fashions, and because the range of morphological outcomes (if not the particular outcome) emerging under these conditions were to a surprising extent physically inevitable.

We have proposed that this early period of physics-dependent morphogenesis is when much large-scale macroevolution took place (Newman and Müller 2000; Newman 2005; Newman *et al.* 2006). In particular, it was the era in which the major phyla were established. Only after extensive stabilizing and canalizing selection would the descendents of these early-diversifying organisms have settled into the mode described by the Modern Synthesis. In this current mode, gene mutation generally leads to deleterious or incremental alteration of the phenotype because generation of form is now guided by robust hierarchical programs of gene regulation. Any effects of the external environment on developmental outcomes, moreover, are either minimal or specifically incorporated into the generative program of the species (e.g., temperature-dependent sex determination in reptiles; Bowden *et al.* 2000).

2. Dynamical patterning modules vs. cell state switching mechanisms

Our concept is based on the presence of a set of molecules in certain modern unicellular organisms, the Choanozoa, and the inferred presence of the single-celled ancestors of the animals. The molecules in question (products of a subset of the genes of the "developmental-genetic toolkit"; Wilkins 2002; Carroll *et al.* 2005) were predisposed to assume novel functions in the multicellular state by mobilizing physical effects that were irrelevant to patterning on the scale of the individual cell. We refer to the joint effect of these ancient molecules and the phys-

ical processes they mobilize as "dynamical patterning modules" (DPMs). Most fundamentally, the multicellular state itself likely came into being by one class of ancestral molecules, the cadherins, forming a DPM by harnessing the physical effect of homophilic adhesion. Because of the limited set of relevant physical effects that apply to matter on the scale of cell aggregates, a set of inevitable morphological motifs arose in animal systems, constituting a deeply embedded orthogenetic principle in this class of organisms. These include the recurrent appearance of interior body cavities, multiple tissue layers, elongated bodies, segments, and appendages. The emergence of these structures thus required neither adaptationist nor incrementalist mechanisms.

Because physics can act with immediacy to shape and modify form, particularly in the developmental stages of organisms for which canalizing mechanism were not yet in place, early morphological diversification also need not have taken long periods of time. Genetic consolidation therefore likely followed, rather than accompanied, the rapid radiation of body plans referred to as the Cambrian explosion. In addition, while the limited number of physical effects that enter into DPMs are dictated by the laws of nature, the set of molecules involved in these modules is also limited, but this is just a fortuitous matter of their having been the only suitable ones present in the ancestral cells. The suggestion that the animal phyla emerged early and rapidly by means of the DPMs carries the implication that the associated molecules should be central to the developmental pathways of all extant animals, and this is borne out by the evidence.

The biosynthetic states of all cells are determined by the dynamics of transcription factor-mediated gene regulatory networks (GRNs) (Davidson 2006). Such networks, containing feedback and feed-forward loops by which the transcription factors promote and suppress their own and each other's synthesis, exhibit multistability (Forgacs and Newman 2005). The systems can thus switch among discrete states, the number of states always being much smaller than the total number of genes in the organism's genome. Since the genes that specify nontranscription factor proteins and regulatory RNAs are themselves subject to transcriptional control, the alternative stable states of the GRNs specify cell types distinguished by extensive biosynthetic differences. All unicellular organisms, be they bacteria, fungi, protists, or algae, exhibit alternative states of differentiation, both reversible and irreversible, under different conditions (e.g., Blankenship and Mitchell 2006; Vlamakis *et al.* 2008). This must also have been the case for the single-celled ancestors of the Metazoa, that is, the ancient and modern animals.

The transcription factors contained in the developmental-genetic toolkit form

GRNs that help generate distinct cell types during development. But an equally important aspect of development is the arrangement of cells into appropriately coherent spatiotemporal patterns (Salazar-Ciudad *et al.* 2003; Gilbert 2006). Unlike cell switching mechanisms, however, specific mechanisms of developmental pattern formation and tissue morphogenesis cannot have existed before multicellularity. In fact, the processes that generate spatial organization at the multicellular level are of an entirely different character from those which operate in individual cells (Newman and Bhat 2009; Newman *et al.* 2009).

3. The emergence of the Metazoa

The evolutionary history of the metazoans was initiated with remarkable rapidity during the late Precambrian and early Cambrian periods and is relatively well described (Rokas *et al.* 2005; Larroux *et al.* 2008). Development in all the metazoan phyla has been mediated by the same conserved developmental–genetic toolkit regulatory molecules for more than half a billion years (Carroll *et al.* 2005). The extant metazoans have classically been divided into the Eumetazoa, organisms which exhibit true tissues, epithelia with polarized cells, cell–cell junctions, a well-defined basement membrane, and neurons and muscle cells; and the sponges (Porifera) and Placozoa, which lack these features. *Trichoplax adhaerens*, the single known type of placozoan, contains several cell types and layers, but unlike the sponges (which exhibit gastrulation-like movements during development and complex labyrinthine morphologies) (Larroux *et al.* 2006), it has a simple, flat body without internal cavities. Surprisingly, on the basis of purely genetic criteria Placozoa may have greater genetic affinity to the Eumetazoa than the earlier-diverging sponges (Srivastava *et al.* 2008).

The eumetazoans, in turn, are divided into the diploblasts, consisting of the Cnidaria (e.g., hydroids and corals) and, traditionally, the Ctenophora (e.g., comb jellies), have two epithelial body layers and true lumens. The triploblasts (chordates, echinoderms, arthropods, mollusks, etc.), in contrast, have a third, mesenchymal, body layer. Genomic analysis has suggested that rather than being in the main line of the animals, the Ctenophora are actually a sister clade of the Metazoa (Dunn *et al.* 2008).

Sheetlike and hollow spherical forms (Yin *et al.* 2007), and budding and segmented tubes (Droser and Gehling 2008), possibly the most ancient metazoans, are seen beginning about 630 million years ago in fossil beds of the Precambrian Ediacaran period. Essentially all the triploblastic metazoan body plans then emerged within the space of no more than 20 million years, beginning about 535

million years ago (Conway Morris 2006), during the well-known Cambrian explosion. It has been suggested that the first Cnidaria (corals, hydroids) may have been holdovers from the Precambrian (Erwin 2008). Modern animals, and perhaps some of the Ediacaran forms, have a common ancestry in the Precambrian along with the Choanozoa, some of whose extant members are transiently colonial (Wainright *et al.* 1993; Lang *et al.* 2002; King *et al.* 2003; Philippe *et al.* 2004; Shalchian-Tabrizi *et al.* 2008).

Many of the toolkit genes, including some which have key roles in morphogenesis and pattern formation, are found in the genome of *Monosiga brevicollis*, an exclusively unicellular choanozoan (King *et al.* 2008). A few additional genes were added to the toolkit concomitant with the emergence of the sponges, and a few more arose with the simplest eumetazoans, the cnidarians. The Cambrian explosion followed with no more significant additions to the toolkit.

Metazoan complexity was thus achieved in a rapid fashion with an essentially unchanging set of ingredients. An essential evolutionary step for multicellularity was the acquisition by single-celled antecedents of the capacity to remain attached to one another after dividing. No new genes or gene products were required to mediate this function. The genome of *M. brevicollis* contains 23 putative cadherin genes, as well as 12 genes for C-type lectins (Abedin and King 2008; King *et al.* 2008), the protein products of which mediate cell attachment and aggregation in metazoan organisms in the presence of sufficient levels of extracellular calcium ion. Rising oceanic Ca2+ levels during the period in which multicellularity was established may have recruited these ancient proteins to new roles (Kazmierczak and Kempe 2004).

4. The developmental genetic toolkit: new contexts, new roles

Metazoan embryos employ a variety of patterning and shaping processes (Salazar-Ciudad *et al.* 2003), some of which are used in all the animal phyla and others of which are used in some of them. As noted above, the first DPM, designated ADH (*Table 1*), results in the formation of a multicellular cluster. Within such a cluster, any or all of the following can occur: the local coexistence of cells of more than one type, the formation of distinct cell layers, or an internal space or lumen, elongation of the cell cluster, the formation of repeated metameres or segments, the change in state or type of cells in one region of the cluster due to local or long-range signals from another region, the change in stiffness or elasticity of a cell layer, and the dispersal of cells while they continue to remain part of an integral tissue (reviewed in Forgacs and Newman 2005).

As the Metazoa emerged, DPMs mediated all of the above transformations by mobilizing physical forces and processes characteristic of viscoelastic, chemically active materials on the spatial scale of cell aggregates and tissue primordia (100 μm – 1 mm). Such materials are referred to by physicists as "soft matter" (De Gennes 1992) which is simultaneously an "excitable medium" (Mikhailov 1990).

DPM	Characteristic molecules	Physical principle	Morphogenetic Role
ADH	cadherins	adhesion	multicellularity
DAD	cadherins	differential adhesion	tissue multilayering
LAT	Notch	lateral inhibition	coexistence of alternative cell types
POLa	Wnt	cell surface anisotropy	lumen formation
POLp	Wnt	cell shape anisotropy	tissue elongation
OSC	Wnt + Notch	synchronized biochemical oscillation	morphogenetic fields; segmentation
MOR	TGF-β/BMP; Hh	diffusion	pattern formation
ASM	FGFs	diffusion	induction
TUR	MOR + Wnt + Notch	chemical waves	periodic patterning
ECM	collagen; chitin; fibronectin	stiffness; dispersal + cohesion	epithelial elasticity; skeletogenesis; epithelial-mesenchymal transformation

Table 1: Names, components and roles of major Dynamical Patterning Modules (DPMs)

Detailed descriptions of the properties of the major basic and combined DPMs and their developmental and proposed evolutionary roles can be found in earlier publications (Newman and Bhat 2008; 2009; Newman *et al.* 2009). Here these features will be characterized briefly. Each DPM is given a three-letter designation.

Adhesion and differential adhesion — As mentioned above, the emergence of Metazoan multicellularity depended on cadherins and C-type lectins of single-cell

ancestors taking on the new function of cell–cell adhesion (ADH). If, in addition, subsets of cells within an aggregate contain sufficiently different levels of cell adhesion molecules on their surfaces, there will be a sorting into islands of more adhesive cells within lakes of less adhesive ones (Steinberg and Takeichi 1994). This constitutes a second DPM, differential adhesion (DAD). Since cells undergo random motion, small islands of like cell types will coalesce and an interface will be established, across which cells will not intermix (Steinberg 2003). This effect, which has the same physical basis as phase separation of two immiscible liquids such as oil and water (reviewed in Forgacs and Newman 2005), leads to the formation of nonmixing cell layers, an early stage of most animal embryogenesis.

Lateral inhibition and choice between alternative cell fates – Morphologically complex organisms always employs lateral inhibition (LAT) during embryogenesis, whereby early differentiating cells signal to cells adjacent to them to take on a different fate (Rose 1958; Meinhardt and Gierer 2000). Lateral inhibition in metazoans is mediated by the Notch signal transduction pathway, specifically, interaction of the cell surface receptor Notch with members of a class of other integral membrane proteins (Delta, Serrate/Jagged, and Lag2: the DSL proteins) that act as ligands for the receptor and mediators of Notch activity (Ehebauer *et al.* 2006). This mechanism does not determine the particular fate of any cell, but only enforces the coexistence of alternative fates in adjacent cells in the same cluster or aggregate.

The most basal metazoans to contain the Notch receptor are sponges (Nichols *et al.* 2006) though related protein modules probably existed in a choanaozoan ancestor (King *et al.* 2008). Lateral inhibition would have enabled basic cell pattern formation in these organisms and more complex animals.

Apical-basal and planar cell polarity – As noted above, cell aggregates behave like viscoelastic liquid droplets (reviewed in Forgacs and Newman 2005). This means that their default morphology is topologically solid (i.e., having no lumen), and spherical. Animal embryos defeat these morphological defaults by employing cell polarization. Cells can be polarized in one of two ways. When they become anisotropic along their surfaces (referred to as apical–basal (A/B) polarization; Karner *et al.* 2006b), interior spaces or lumens can arise within aggregates. Specifically, when A/B polarization leads cells to have lowered adhesiveness on one portion of their surface, they will preferentially attach to their neighbors on their more adhesive (lateral) portions, leaving the less adhesive (basal) portions adjoining an interior space (Newman 1998). Apical–basal polarity is also important in fostering layered tissue arrangements.

Tissue elongation may occur when cells individually polarize in shape (rather

than surface properties), a phenomenon called planar cell polarity (PCP; Karner *et al.* 2006a). Planar-polarized cells can intercalate along their long axes, causing the tissue mass to narrow in the direction parallel to the cell's long axis, and consequently elongate in the orthogonal direction. This tissue reshaping is known as convergent extension (Keller *et al.* 2000; Keller 2002).

Both A/B polarity and PCP are mediated by secreted factors of the Wnt family (Karner *et al.* a,b). Which type of polarization occurs depends on the presence of different accessory proteins. The A/B- and PCP-inducing Wnt pathways are referred to, respectively, as the canonical and noncanonical Wnt pathways. In each case, the structural alterations of individual cells have novel consequences in a multicellular context, permitting multicellular aggregates to overcome the morphological defaults of solidity and sphericality. We designate the DPMs involving the Wnt pathway operating in a multicellular context as POLa and POLp (*Table 1*).

Some key intracellular components of the Wnt pathway have counterparts in fungi, where they also mediate cell polarity (Mendoza *et al.*, 2005). Their role in the shaping of metazoan embryos could only have emerged with the multicellular state, but the appearance of this new function would have been all but automatic. Sponges, which are characterized by many interior spaces, have genes for Wnt proteins and their ligands (Nichols *et al.* 2006). Such genes are also present in the placozoan *Trichoplax* (Srivastava *et al.* 2008), which despite containing only four cell types, has them arranged in three distinct layers, which is possible only if the cells are polarized.

Small, hollow, cell clusters identified in the Precambrian Doushantuo Formation in China and referred to as "embryos" (Chen *et al.* 2004; Hagadorn *et al.* 2006; Yin 2007) may actually have been the definitive forms of the earliest metazoans and metazoan-like organisms (Newman *et al.* 2006). The origination of these hollow forms at the transition between the Ediacaran biota and those of the Cambrian explosion was plausibly based on the presence of POLa. Specifically, the presence of the canonical Wnt pathway in a multicellular context could have readily led to the aggregates developing interior spaces.

Genes specifying components of the noncanonical Wnt pathway do not appear to be present in sponges and placozoans, which correspondingly show no sign of body elongation. They are, however, present in the morphologically more complex cnidarians (Guder *et al.* 2006), which display elongated body stalks and appendages.

Oscillations in cell state – As noted earlier, cell differentiated states are determined by intracellular transcription factor-based gene regulatory networks (GRNs). Such GRNs are typically multistable, but certain arrangements of positive and negative

feedbacks will cause such systems to exhibit temporal oscillations in concentration of gene products (Goldbeter 1996; Reinke and Gatfield 2006).

In a single-celled organism, a periodic recurrence of cell state has no developmental consequences. If the oscillation involves downstream effectors of the Notch pathway (which normally enforces alternative cell fate decisions; see above), the result will be that cells will remain labile and uncommitted (Kageyama *et al.* 2008). Furthermore, if the oscillations become synchronized, the labile cell state will be coordinated across broad tissue domains, permitting concerted responses to a variety of developmental signals. Such synchronized Notch-associated oscillations have indeed been observed during early vertebrate development (Özbudak and Lewis 2008). Because of the near-ubiquity of oscillatory gene expression (Reinke and Gatfield 2006) and the inevitability of synchronization when oscillators are weakly interacting (as is typical for cells in a common tissue) (Garcia-Ojalvo 2004), we have proposed (Newman and Bhat 2009) that the oscillation DPM (OSC; *Table 1*) is at the basis of the ubiquitous but mechanistically elusive phenomenon of the "morphogenetic field" (Gilbert 2006).

Morphogen gradients and activator–inhibitor systems – While single-celled organisms can change their physiological state in response to molecules secreted into the microenvironment by other such cells (Luporini *et al.* 2006), this effect has novel developmental consequences when it occurs in a multicellular context and *gradients* can be formed. Secreted molecules that act as patterning signals in metazoan embryos by mediating concentration-dependent responses are termed morphogens (MOR; *Table 1*). Examples of morphogens are Wnt, discussed above, Hedgehog, BMP/TGF-β, and FGF (Zhu and Scott, 2004). The genome of marine sponges contains genes specifying examples of the first two of these categories of morphogens and their receptors (Nichols *et al.* 2006), whereas Placozoa contains components of the first three (Srivastava *et al.* 2008) and Cnidaria all four (Holstein *et al.* 2003; Rentzsch *et al.*, 2008).

The ability of one or a small group of cells to influence other cells via morphogens, either within a common tissue primordium, or, in a special case referred to as embryonic induction, asymmetrically across tissue boundaries (the ASM DPM; *Table 1*), enables the generation of nonuniform cellular patterns. Assuming that the function of morphogens is tied to the physical principle of molecular diffusion, Crick calculated that they would generate patterns over tens of hours on a spatial scale of 100 μm–1 mm, similarly to what is observed in embryos (Crick 1970). Building on this basic mechanism, evolution has often produced

transport processes that are formally equivalent to diffusion, but which, by using additional cell-dependent modalities, are faster or slower than the simple physical process (Lander 2007).

When morphogens are positively autoregulatory, that is, directly or indirectly stimulatory of their own synthesis in target cells, they tend not to be maintained as gradients, since all cells eventually become morphogen sources. This tendency can be held in check, however, if the positively autoregulatory morphogen elicits a mechanism of lateral inhibition (such as the LAT DPM associated with Notch signaling). In this case, a zone will be induced around any peak of morphogen activity within which activation will not spread (Gierer and Meinhardt 1972; Meinhardt and Gierer 2000). Peaks of activation in such systems will form only at distances sufficiently far from one another so that the effects of the inhibitor are attenuated. This arrangement, termed local autoactivation–lateral inhibition (LALI) (Meinhardt and Gierer 2000; Nijhout 2003; Newman and Bhat 2007), can produce regularly spaced spots or stripes of morphogen concentration (TUR; *Table 1*). In contemporary metazoans the TUR DPM (named after the mathematician Alan Turing who first investigated such pattern-forming systems; Turing 1952), has been proposed to underlie pattern formation of the vertebrate limb skeleton (Newman and Frisch 1979; Hentschel *et al.* 2004), the dentition (Salazar-Ciudad and Jernvall 2002), feather germs (Jiang *et al.* 2004), and hair follicles (Sick *et al.* 2006).

The MOR DPM is used in conjunction with the OSC DPM in vertebrate *somitogenesis*, the process by which blocks of tissue, the primordia of vertebrae and associated muscles, form in a progressive spatiotemporal order along the central axis of vertebrate embryos. In the presomitic plate of vertebrate embryos, the expression of certain genes (including mediators of the Notch pathway, as discussed above) undergoes temporal oscillation with a period similar to the formation of the somites (Dequéant *et al.* 2008). These oscillations then become synchronized across the plate (Giudicelli *et al.* 2007; Kageyama *et al.* 2007; Riedel-Kruse *et al.* 2007). In conjunction with an FGF morphogen gradient with its source at one end of the extended embryo, a subset of the periodically expressed molecules provides the basis for the generation of somites in vertebrate embryos (Dequéant *et al.* 2008). The OSC DPM may have an analogous role in the segmentation of some arthropods (Salazar-Ciudad *et al.* 2001; Damen *et al.* 2005; Pueyo et al 2008).

Extracellular matrices – The DPMs ADH and DAD mediate the formation of "epithelioid" tissues and tissue layers, which are composed of cells that are directly

attached to each other. In these tissues physical properties such as viscosity, elasticity, and cohesiveness are determined by the strength of cell-cell attachment and the rheology of the cytoplasm.

The other major cell aggregate or tissue type, "mesenchyme," is composed of cells that are embedded in a secreted macromolecular microenvironment, the extracellular matrix (ECM; Comper 1996; *Table 1*). In mesenchymal tissues physical properties are largely determined by the ECM, making them subject to a range of physical processes not seen in epithelioid tissues. The ECM molecules and the physics they mobilize thus constitute a novel DPM.

Metazoan ECMs consist largely of glycosaminoglycans (a category of polysaccharide) which are typically attached to proteins in the form of proteoglycans, and various fibrillar collagens, which occupy the interstitium between mesenchymal cells and the cells of more mature connective tissues. Metazoans also produce a network-type collagen and laminin, which are components of the basement membrane that attaches epithelial sheets to mesenchymal and connective tissues.

Genes specifying a variety of interstitial and basement membrane ECM proteins and cell surface receptors for ECMs are found in the *M. brevicollis* genome (King *et al.* 2008). It is unclear what function these molecules perform in the single-celled organism, or would have performed in its common ancestor with the Metazoa, but they have clearly been recruited to new roles in the multicellular context.

Sponges contain both epithelial-like and mesenchymal cells, which reside upon and within an ECM called the "mesohyl" (Wimmer *et al.* 1999). These organisms actively remodel the branched skeletal structures defined by their ECM by the continuous movement of their cells (Bond 1992), thus exhibiting environment-dependent morphological plasticity (Uriz *et al.* 2003), but only a limited array of morphological themes. It is only the triploblasts (arthropods, annelids, echinoderms, mollusks, chordates), which contain true epithelial and mesenchymal tissue types, that collectively exhibit the entire spectrum of DPM-generated motifs (Newman and Bhat 2009) (*Figure 1*).

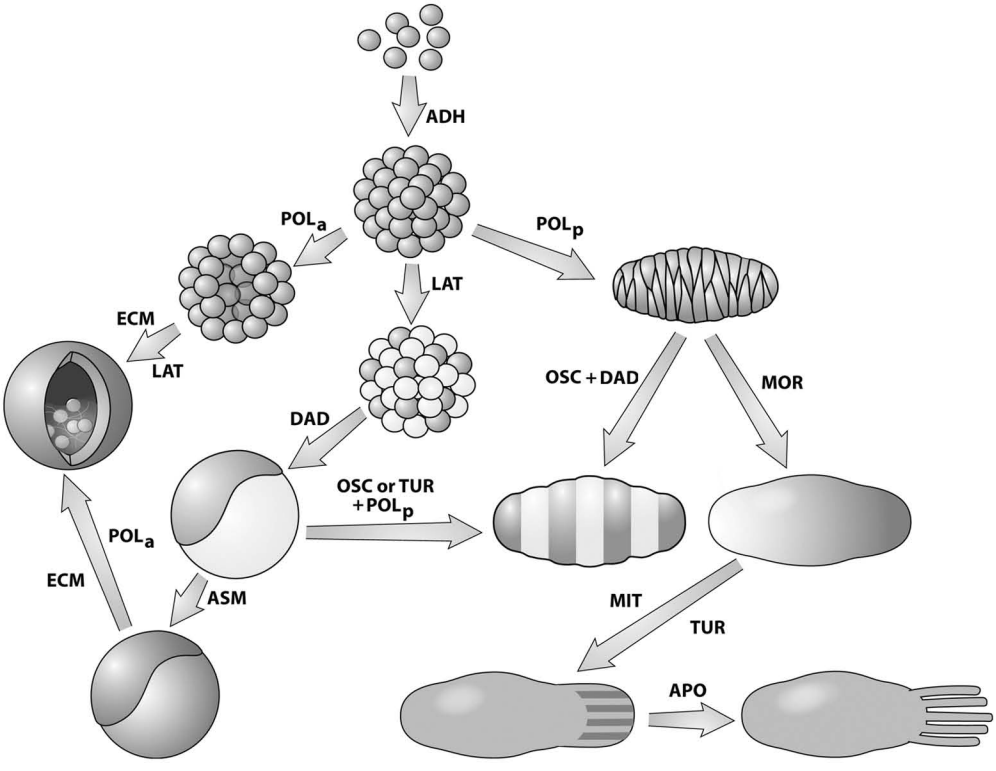

Figure 1. Schematic representation of single and combinatorial action of dynamical patterning modules (DPMs) in the generation of potential metazoan forms. Cells are represented individually in the upper tiers of the diagram, while the middle and lower tiers are shown at the scale of tissues. Beginning at the top, single cells form cell aggregates by the action of the ADH (adhesion, e.g., cadherins, lectins) module. The POL (polarity: Wnt pathway) module has two versions, apical-basal (POLa) and planar (POLp) polarity. POLa causes cells to have different surface properties at their opposite ends, leading to structurally polarized epithelial sheets and lumens within cell aggregates. POLp, in contrast, causes cells to elongate and intercalate in the plane, which leads to convergent extension and elongation of the cell mass. The LAT (lateral inhibition: Notch pathway) module transforms an aggregate of homotypic cells into one in which two or more cell types coexist in the same aggregate, while the expression of ADH molecules in different amounts lead to sorting out by the action of the differential adhesion (DAD) module. Production of diffusible molecules by cells capable of responding to these same molecules leads to morphogen (MOR, e.g., TGF-β/BMP, hedgehog) gradients, whereas morphogens can also act inductively and asymmetrically (ASM, e.g., FGFs) by being produced by one type of tissue and affecting a different type. Synchronous biochemical oscillation (OSC) of key components of the Notch and Wnt pathways, in conjunction with the DAD module, can generate segments. Appropriate feedback relationships among activating and inhibitory morphogens can lead to patterns with repetitive elements by Turing-type reaction-diffusion processes (TUR). The action of the MAPK signaling pathway in the context of multicellular aggregate containing morphogen gradients leads to nonuniform growth by the mitogenesis (MIT) module, whereas the apoptosis (APO) module leads to differential cell loss. The secretion of extracellular matrix (ECM, e.g., collagen, fibronectin) between cells or into tissue spaces creates novel mechanical properties in cell sheets or masses, or new microenvironments for cell translocation. (Adapted from Newman and Bhat, 2009, which can be referred to for additional details, including DPMs not discussed in the text.)

5. Niche construction and genetic accommodation

Models based on the ideas of the Modern Synthesis would predict that morphologically aberrant subpopulations brought into being by DPMs would be poorly adapted to the ecological niches inhabited by the originating species. But niches are not preexisting slots in the natural environment passively occupied by organisms that have the right set of characters. They are explored, selected by, and in many cases constructed by their inhabitants (Levins and Lewontin 1985; Odling-Smee *et al.* 2003). When novelties arise, particularly (as could be the case with DPM-based innovation mechanisms) in multiple members of a population, there is no requirement for the new forms to remain at their sites of origin.

If saltation inescapably implied maladaption we would expect invasive species to be less prevalent than they actually are (Carroll 2007; Stohlgren *et al.* 2008), and would not anticipate phenomena such as "transgressive segregation" in plants, whereby hybrids exhibit phenotypes that are extreme or novel relative to the parental lines wind up founding and colonizing new niches (Rieseberg *et al.* 1999; 2003). At early stages of a lineage's history, before a high degree of organism-niche coadaptation had evolved, the possibility of organisms "bolting" from their niches and setting up elsewhere would have been even greater than in present-day species.

Since DPMs by definition incorporate physical mechanisms and effects, the results of their action depend on externalities — ionic composition, temperature, pressure and so on. As long as DPMs were the major determinants of form, consistency of development outcome would thus require stability of the relevant environmental inputs. The niche to which a novel form would initially be best maintained would thus be the one that provided the conditions for its existence. The most effective way a phenotypically plastic organism can assume a morphotype independent of environmental lability, however, is via "consolidating" genetic or epigenetic change. Selection for persistence of an environmentally induced phenotype, variously termed stabilizing selection (Schmalhausen 1949), genetic assimilation (Waddington 1961), or genetic accommodation (West-Eberhard 2003), can convert body plans and morphological characters that started out as dependent on intrinsic physical properties of tissues and external conditions into products of lineage-specific developmental programs (Newman 1994; Newman and Müller 2000).

6. Conclusion: Darwinism as a limiting case

I have argued here that evolutionary mechanisms have themselves evolved. This analysis has involved positing roles for features that have been relegated to the

margins, or worse, in the standard accounts of evolution associated with the Modern Synthesis: saltation, orthogenesis and inheritance of acquired characters. These features are all natural consequences of considering biological systems to be material, i.e., physical, systems.

To take them in order: the possibility of saltational change in an organism's phenotype arises from the propensity of virtually all complex physical systems to exhibit nonlinear behaviors and changes in state. Phase transitions, such as melting or vaporization, or bulk transformations, such as the change from undulatory to vortical motion, are examples that present themselves if we just confine our attention to water. Living tissues of course have many more latent possibilities.

Orthogenesis is just a reflection of the fact that any physical system will assume a limited set of characteristic forms based on its inherent dynamics or modes of behavior. Liquid water can be still, or form waves or whirlpools; it can break up into drops or form rivulets on a surface. It cannot form elongated or branched structures in three-dimensions, or enclose hollow spaces.

Inheritance of acquired characters is a bit more complicated, since the typical physical system does not reproduce and therefore does not exhibit inheritance in the biological sense. This property is based on *plasticity*, the propensity of any physical system to assume alternative forms based on its inherent properties and its external conditions. No organism, no matter how under the influence of its genes, is immune from some degree of phenotypic plasticity. That is to say, organisms are not unwavering implementations of rigid genetic programs. And if an organism undergoes development as all multicellular forms do, plasticity will be manifested at nearly all stages of its ontogeny.

Developmental processes, being functions of dynamical patterning modules, will necessarily exhibit combinations of the associated morphological motifs — multiple tissue layers, lumens, segments, appendages, rod- and nodule-like cell condensations and cells dispersions. These are also the motifs that appeared in the course of metazoan evolution, hence the orthogenic character of the early stages of this process. The physical nature of the DPMs ensured that development of the earliest multicellular animals was plastic and saltational. Their molecular-genetic nature guaranteed that developmental pathways were inheritable and could evolve. If the quantity and quality of the gene products change (by mutation, for example), this will not alter the basic material nature of cell aggregates and tissues but can influence which of their inherent structural modes they will assume.

Evolution of the DPM-associated and other genes can restrict, channel, and render increasingly stereotyped, the morphological outcomes of developmental

processes. This would suppress the tendency of organisms to deviate dramatically in form from their progenitors, render variation incremental, with no obvious preferred directions, around canalized phenotypic norms that will exhibit little developmental plasticity. In other words, organisms would eventually evolve into entities whose further evolution will be largely non-saltational, non-orthogenic and non-Lamarckian.

Uniformitarianism is the supposition Darwin adopted from the geologists James Hutton and Charles Lyell, that similar forces drive morphological change at all stages of transformation (Gould 1987). It is clear from the previous discussion that the framework presented here is not uniformitarian. From our viewpoint, indeed, the Darwinian mode of microevolution is a late product of a more comprehensive process that at its earlier, more "physical" stages was generative of macroevolutionary, i.e., phylum-scale, transitions.

It should not be surprising that Darwin's mechanism would come to be seen as a special case of a broader theory of organismal change. Darwin (and Alfred Russel Wallace, the co-originator of natural selection), of necessity, based their evolutionary hypothesis on the properties of present-day organisms — Galapagos finches, domesticated animals, orchids — that are hundreds of millions of years removed from their phylogenetic origins. Not only, as invariably noted by historians of biology, were the mechanisms of inheritance unknown to Darwin and Wallace, but so were the mechanisms of development. Embryogenesis in animals and most plants lead to defined outcomes. The only readily observable inherited variations within populations are small ones. Selection based on adaptive advantage exerted over vast periods of time was thus an inspired guess for how large-scale morphological differences could be generated. Darwin's and Wallace's radically materialist theory of evolution was thus formulated as a uniformitarian and incrementalist one.

Our current understanding of the physical-molecular modules that constitute developmental mechanisms, including recognition of their pre-phylum origination and prolific dynamics, permits us to take a longer view than was available to Darwin and Wallace, while holding fast to their materialist philosophical perspective. Although present-day organisms are indeed subject to microevolution by natural selection, our new outlook suggests that their prodigious variety can only have been produced in a world that is largely lost to the distant past.

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