SYMPOSIUM INTRODUCTION

Perspectives on Integrating Genetic and Physical Explanations of Evolution and Development: An Introduction to the Symposium

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From the symposium "Physical and Genetic Mechanisms for Evolutionary Novelty" presented at the annual meeting of the Society for Integrative and Comparative Biology, January 4–8, 2017 at New Orleans, Louisiana.

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Synopsis In the 20th century, genetic explanatory approaches became dominant in both developmental and evolutionary biological research. By contrast, physical approaches, which appeal to properties such as mechanical forces, were largely relegated to the margins, despite important advances in modeling. Recently, there have been renewed attempts to find balanced viewpoints that integrate both biological physics and molecular genetics into explanations of developmental and evolutionary phenomena. Here we introduce the 2017 SICB symposium "Physical and Genetic Mechanisms for Evolutionary Novelty" that was dedicated to exploring empirical cases where both biological physics and developmental genetic considerations are crucial. To further contextualize these case studies, we offer two theoretical frameworks for integrating genetic and physical explanations: combining complementary perspectives and comprehensive unification. We conclude by arguing that intentional reflection on conceptual questions about investigation, explanation, and integration is critical to achieving significant empirical and theoretical advances in our understanding of how novel forms originate across the tree of life.

Introduction

> It would ... be an exaggeration to see in every bone nothing more than a resultant of immediate and direct physical or mechanical conditions ... But I maintain that it is no less of an exaggeration if we tend to neglect these direct physical and mechanical modes of causation altogether, and to see in the characters of a bone merely the results of variation and of heredity. D'Arcy Thompson (1917)

One hundred years ago, D'Arcy Thompson (1860–1948) published his landmark book *On Growth and Form* (Thompson 1917). Prescient in many ways, Thompson used different types of mathematical representation commonly found in the physical sciences to comprehend biological phenomena, specifically morphological shape and its evolution. At the time of the book's completion, the chromosomal theory of inheritance had recently been put forward and classical genetics was emerging as a promising research program (Morgan et al. 1915). Thompson explicitly sought to develop an explanatory framework that took both physical dynamics and hereditary contributions into account.

During the course of the 20th century, genetic approaches became dominant in both developmental and evolutionary biological research. Genetic approaches are characterized by appeals to changes in the frequency, distribution, or expression of genes, as well as interactions among RNA and protein products. In contrast, physical approaches appeal to processes common to nonliving materials, especially mechanical and geometrical properties of mesoscale materials (including irreversibility, self-organization, and symmetry breaking). These approaches were largely relegated to the margins of biological research and discourse, despite important advances in modeling physical modes of causation (e.g., Turing 1952;

for historical perspective, see Hopwood 1999; Maienschein 2000; Keller 2002).

Over the past two decades, there have been renewed attempts to find balanced viewpoints, something akin to what Thompson envisioned. These integrated explanatory approaches combine different kinds of causal factors into more unified accounts of complex phenomena that result from a plurality of causes. Many attempts at integration focus on the variety of interacting processes that generate the heterogeneous shapes, size, and structural features of an organism as it develops from embryo to adult. This is captured explicitly in quotes like this one by Savin et al. (2011): "there has been a renewed appreciation of the fact that to understand morphogenesis in three dimensions, it is necessary to combine molecular insights (genes and morphogens) with knowledge of physical processes (transport, deformation and flow) generated by growing tissues." Many of the efforts to combine molecular insights and physical processes concentrate on reciprocal interactions between gene expression and mechanical forces or other physical factors (e.g., Brouzés and Farge 2004), or find empirical signatures that differentiate genetic and physical explanations of traits (e.g., Milinkovitch et al. 2013). Hypotheses about the relevance of physical dynamics to the evolution of morphology (Newman 2012; Fernandez-Sanchez et al. 2015) have tracked the rise of evolutionary developmental biology with its emphasis on how features of development can bias the production of variation and thereby affect the direction or rate of evolutionary change (Love 2015). This includes the origin of qualitatively new variation at particular junctures in phylogenetic history at different levels of hierarchical organization—evolutionary novelty (Müller and Streicher 1989; Wagner 2014).

Although exclusively genetic or exclusively physical explanations of development and (by implication) evolution are *prima facie* implausible, there remains a question about how exactly they should be integrated to increase understanding of the origin of evolutionary novelties. It is unlikely that there is only one way to integrate these types of explanations, and part of the conceptual work required is to identify legitimate conceptions of integration. In the next section, we describe the contributions to the symposium motivated by this question, and we highlight how the contributions advance our understanding of integrating genetic and physical explanations. We also discuss in more detail the evolutionary origin of digits as a case study for integration. Subsequently, we describe two different theoretical frameworks that studiously avoid the exclusive

extremes of approaches that are only genetic or only physical: (1) integration through combining complementary perspectives from different approaches; and (2) integration through comprehensive unification of genetic and physical approaches. The authors of this paper do not fully agree on whether these different perspectives are equally viable. Nevertheless, there is consensus that this type of reflective endeavor is a critical part of ongoing inquiry. In conclusion, we suggest that further reflection on conceptual questions about how we approach the investigation and explanation of biological phenomena, including how these approaches are combined in different ways, is critical to achieving significant empirical and theoretical advances in our understanding of how novel forms originate across the tree of life (Love 2008).

Symposium contributions and exemplars of integration

To explore how genetic and physical approaches can be integrated, a symposium entitled "Physical and Genetic Mechanisms for Evolutionary Novelty" was held at the SICB Annual Meeting 2017. The organizers' aim was to assemble a group of researchers that would tackle the question of how novelty originates with an eye to synthesizing genetic and physical approaches. The intent was not to reach consensus on a definition of evolutionary novelty (Brigandt and Love 2012), and the diverse opinions on how to articulate this concept can be seen in the contributed manuscripts. Rather, the goal was to bring together investigators who were engaging a common conceptual challenge and confronting systems in which both biophysical and developmental genetic considerations are important for understanding system dynamics and their evolution. Study systems ranged from plants to cephalopods, and from beetles to dinosaurs. Research on each system gives insight into how integration can occur.

Tsutumi et al. (2017) explore tissue interdependence, wherein genetic changes to a particular tissue type result in non-genetic changes in the morphology and function of other associated tissues. They argue that this property is crucial for maintaining the functionality of complex phenotypes during the evolution of evolve new, qualitatively distinct forms (e.g., the evolution of the bat wing and jerboa hindlimb). In this paper, integration occurs by analyzing the hierarchy of genetic and physical causes within ontogeny. These arguments are complemented by the Vargas and colleagues, who analyze the effect of embryonic muscular activity on limb evolution

(Vargas et al. 2017). This paper usefully emphasizes how physical forces generated within an organism affect morphogenesis, and it highlights instances where mechanically induced phenotypes have been modified secondarily by the evolution of transcription factor gene activity. Thus, one way that integration occurs in this analysis is through hypothesizing how genetic and physical effects are ordered over evolutionary time scales.

Zimm and colleagues, like Vargas et al., discuss the effects of physics on development. However, here the relevant physical causes are external to the organism. Zimm et al. (2017) show how temperature has an impact on patterning the turtle carapace. They argue that variation is non-random and can be explained by reaction–diffusion dynamics predicted to pattern the carapace. In their treatment, integration occurs by considering and discriminating between genetic and non-genetic causes of morphological variation and developmental bias. The contribution by Young (2017) extends the discussion of how physical processes can result in the biased generation of morphological variation. Young scrutinizes macroevolutionary patterns of limb skeletal evolution and highlights a surprising result: segmentation processes can determine the relative variability of repeated elements (e.g., the middle segment of a series is often more conservative than those at the terminal ends). This achieves integration by inserting considerations relevant from physical processes into the context of traditionally genetic explanations of morphogenesis.

The above studies focus on physical processes operating at the anatomical scale. Bartlett's contribution on the evolution and diversity of floral morphologies presents a useful contrast. The paper teases apart a classic genetic problem, ABC models of floral organ identity, and analyzes how processes dependent on physics at the molecular level (i.e., protein–protein interactions and the binding specificity of transcription factors) are involved in the evolution of morphological novelty (Bartlett 2017). In this case, the explanatory integration of genetics and physics operates at a lower level of organization and makes it possible to understand in greater detail how novel floral morphologies originate and diversify.

Finally, Nijhout and McKenna (2017) argue that novelty can evolve via the emergence of novel allometric relationships between structures. The analytic technique developed here is applicable to allometric relationships that have either a genetic or physical basis (e.g., scaling of cortical bone thickness). This technique promotes integration by making it possible to analyze the various causes of character origination and evolution within a common scheme.

Although D'Arcy Thompson attended closely to the effects of physical forces on limb bone structure, he did not scrutinize the vertebrate limb *per se*. The development and evolution of the vertebrate limb, featured in several presentations at the symposium, is a fruitful place to explore the power of combined genetic and physical approaches. Great progress has been made in dissecting genetic mechanisms operative during pattern formation and morphogenesis of the limb (reviewed in Petit et al. 2017). Additionally, much progress has been made on elucidating physical mechanisms that operate in parallel and contribute to these same processes (e.g., Sheth et al. 2012; Raspopovic et al. 2014). One area of research that was on display in four of the symposium talks (although it is not represented by an accompanying paper) illustrates these themes concretely: the evolutionary origin of digits.

Digits are segmented and non-branching endoskeletal elements organized in parallel at the distal tip of the limb. They develop in a domain of the limb bud that is demarcated by late phase expression of *Hoxa13* and *Hoxd13* (Fromental-Ramain et al. 1996) as well as by the exclusion of *Hoxa11*, which is expressed more proximally in the limb bud (Haack and Gruss 1993). Previously, fins were thought to lack this late phase expression and digit origin was attributed to the evolution of a new gene regulatory state in distal mesenchyme cells (Woltering and Duboule 2010). However, studies of gene expression patterns in diverse taxa have revealed an expression pattern in the distal domain of developing paired fins similar to what is observed in limbs (Davis et al. 2007; Johanson et al. 2007; Ahn and Ho 2008), which is driven by conserved regulatory elements (Gehrke et al. 2015). Most recently, experiments have demonstrated that the rays of paired fins are produced by a population of distal mesenchymal cells homologous to those that form digits (Nakamura et al. 2016). Thus, the origin of digits did not necessarily involve a new kind of cell-type population marked by a unique gene regulatory state, but rather could have emerged from altered differentiation and patterning in an existing distal compartment of fin mesenchyme.

Other recent work has explored how the physical mechanisms that pattern digits in the autopod originated (Bhat et al. 2016; Onimaru et al. 2016). Digits form as mesenchymal condensations by a process regulated by reaction–diffusion pattern formation (Bhat et al. 2011; Sheth et al. 2012; Glimm et al. 2014; Raspopovic et al. 2014). Reaction–diffusion

systems, like those described by Turing (1952), are a class of dynamical systems that can be used to model a wide range of phenomena, including digit formation. Turing showed how a balance of positive and negative feedback in an open chemical system, if coupled with differences in diffusion rates of the reactive molecules, can lead to stable and non-uniform concentration patterns with spatial periodicity. These insights have been applied to the vertebrate limb for some time (e.g., Newman and Frisch 1979), though at least two distinct Turing-type mechanisms have been proposed recently to explain digit patterning and origin. In mouse, three factors constitute a "substrate-depletion" Turing-type process, which has been named the Bmp–Sox9–Wnt (BSW) network (Raspopovic et al. 2014). In chick, two members of the galectin family of carbohydrate-binding proteins (Gal1a and Gal8) interact and constitute a "reaction–diffusion–adhesion" Turing-type process of multiscale pattern formation for the limb skeleton (Bhat et al. 2011). The evolutionary origination of digits could then be accounted for in terms of the origination of one of these Turing-type processes. For example, Onimaru et al. (2016) experimentally investigated the localization of BSW components in embryonic pectoral fins of the catshark and computationally modeled the effects of the BSW network under different conditions. Modulation of the BSW network parameter values can produce morphologically dissimilar structures, which suggests that this conserved patterning system could have been recruited to pattern digits.

How might these genetic and physical approaches to the evolutionary origin of digits be integrated? Ahn and Ho (2008) proposed a scenario in which loss of the apical fin fold resulted in a population of "spare" cells in the distal fin bud. These cells, with a distinct developmental identity and a predisposition to form periodic parallel ossifications, would become the digits. Nakamura et al. (2016) confirmed key predictions of this hypothesis by demonstrating homology between cells that normally migrate into the fin fold and cells that form digits. One can predict that following the loss of the apical fin fold in pectoral and pelvic appendages of stem tetrapods, these spare cells formed endoskeleton patterned by the galectin network and that the BSW network was recruited to reinforce and autonomize a digit patterning network, modulated by *Hox* gene expression (Sheth et al. 2012).

Overall, the talks and contributed papers of the symposium yielded three important points. First, attempting to synthesize genetic and physical approaches is a difficult endeavor because these approaches often rely on distinct methods. Computational modeling is common in exploring the significance of Turing-type processes but experimental genetic manipulation is the norm for understanding the effects of changes in gene regulation. Navigating the different expertise and associated evaluative standards for these methods is necessary for bringing both together into a more unified explanatory perspective. Second, and more positively, important insights for genetic and physical features relevant to the origin of novelties have been discovered by comparing empirical results across taxa. The investigation of these different developmental properties in a phylogenetic framework is critical. This is especially significant for putative physical mechanisms where the generality of their operation might be presumed. Third, and more prospectively, there is not just one kind of integration strategy manifested in these different studies. In fact, the diversity of ways that genetic and physical approaches are marshaled suggests that broader reflection on how we might think about integration is warranted. How can we synthesize the genetic properties of living systems with their physical properties in order to comprehend their combined explanatory significance?

Integrating complementary perspectives

Organisms are material systems and, whether it is their development or behavior, they must operate within the constraints of physics. However, the laws of physics also are the modalities by which organisms take form and operate. In this sense, life processes need to be understood as physical processes, and physics is an integral aspect of biological explanations of development and evolution. This has long been recognized, and research programs that assign a central role to physics in the explanation of development are not new. In fact, they were predominant in the period prior to Thompson's (1917) publication and the rise of classical genetics. Embryologists such as Wilhelm His (1831–1904) favored explanations of developing chick embryos based on analogies with mechanical phenomena exhibited by non-living materials, such as the folding of rubber tubes, rather than hereditary (or genetic) factors (Hopwood 1999, 2000). This approach eschewed phylogenetic appeals to hereditary factors to account for the origin of morphology, as was famously exemplified in the work of Ernst Haeckel, who stated: "I depart fundamentally from the explanatory path of His. I turn to phylogeny to clarify

the historical origin of the different forms of growth and seek their completely sufficient explanatory foundation in the mutual causality of inheritance and adaptation" (Haeckel 1875, translated in Richards 2009). Another example from the mid-20th century is Erich Blechschmidt (1904–1992), who explained the existence of pharyngeal pouches in terms of folding that resulted from bending in the embryonic head. This explanation in terms of a mechanical behavior that causes differential growth in parts of the brain (Blechschmidt 1970) stands in contrast to more recent views of pharyngeal pouches as genetically-fixed, ancestral characters (Grevellec and Tucker 2010).

Physicalist interpretations of development and evolution are generally marginalized in comparison with predominant genetic schools of thought. For example, see Davidson and Peter (2015): "Developmental complexity is the direct output of the spatially specific expression of particular gene sets and it is at this level that we can address causality in development." This kind of argument can be unpacked as follows. Physical processes in living systems must be executed under the guidance of hereditary information encoded in the genome. Therefore, a "proper" explanation of development must be based on mechanisms of gene regulation. Only genetic mechanisms explain why an alligator egg gives rise to an aquatic predator, whereas an emu egg gives rise to a flightless bird. Physical approaches alone would be inadequate for this explanatory task. And yet the agreement among biophysicists and geneticists that organisms are physicochemical systems suggests that genetic mechanisms alone do not account for ontogeny or its evolution.

One can conceptualize developmental genetic and physical approaches as studying living systems from distinct perspectives. Each is explanatory, and they answer different kinds of questions. Research perspectives are critical for limiting the complexity of biological phenomena in order to get empirical traction and achieve explanatory success. In part, this is accomplished by circumscribing the primary scientific question. Research perspectives are not only conceptual; they include an inventory of experimental practices that encourage asking questions and obtaining answers of a particular sort. Communities of investigation then focus on these types of questions and their possible answers as legitimate avenues of research, which yields a logic of research questions (Lloyd 2015). The way questions are asked helps to constrain and determine what answers are sought and found acceptable.

Genetics is a science focused on explaining differences (Waters 2004). If two conspecific individuals differ in eye color, the geneticist asks for the cause of the difference in eye color. Standardized protocols have been developed to establish whether the difference is due to environmental or intrinsic factors, and, if the difference is genetic, what mode of genetic determination is involved (e.g., sex linked, autosomal, dominant or recessive, or polygenic). Evolutionary biology finds a natural partner in genetics because it starts with a description of differences between populations and species and then seeks to explain these differences. Just as in classical genetics, researchers can establish whether phenotypic differences are due to genetics or the environment via standardized experiments. Overwhelmingly, the differences between species and populations are genetic. Thus, explaining biodiversity or disparity concentrates on finding the genetic causes responsible for these (small or large) phenotypic differences between species (Carroll et al. 2004).

By contrast, classical mechanics is a science of process, where motion and changes in motion are explained by forces. In biology, this type of approach has a natural affinity within embryology, which is (in part) a descriptive science of the processes of transformation occurring during development. Early stages of development reflect dramatic transformative processes, such as gastrulation, neurulation, or gut formation, and the causes of these transformations must include physical forces. For example, to understand the folding of ectoderm into a neural tube, we need to understand how forces are generated that bend the epithelia into a neural groove. A mirror image of this argument can be made for morphological evolution. If morphological shape and structure is generated by physical forces in the embryo, then new forms originate in evolution by similar physical processes, and appeals to genetic causes need not be invoked.

Each of these research perspectives is partial and incomplete. Initially, genetics succeeded by explaining differences among individuals and ignoring the fact that these individuals are the result of a dynamical process. Development played little to no role in the practices of classical genetics though Morgan himself, as an embryologist and experimental developmental biologist, was fully aware of the phenomena. This was an intentional strategy for reducing the complexity of the research task: look at differences among individuals in standardized genetic and environmental backgrounds to find genetic differences that explain phenotype differences. The result is a causal explanation of a biological phenomenon.

Similarly, the initial success of a physics of development was in understanding specific physical transformations of the embryo, such as neurulation, while ignoring the fact that there are animals without neural tubes. The reduction in complexity is achieved by focusing on the dynamic, material aspects of development, putting aside the fact that species differ in their characters—look at species that exhibit the character and ask how embryos of these species manage to accomplish the relevant transformations.

The developmental genetic perspective leaves its home territory when it starts to make claims about processes and not just differences. Similarly, the physicalist orientation steps outside of its home territory when it attempts to establish the basis for differences—differences between flatworms and cows, and between flies and centipedes—rather than material transformations of the embryo. In the study of developmental evolution, explaining differences and explaining processes are not the same task.

Both genetic and physicalist approaches deliberately simplify biological reality, and each are justified by the explanatory successes achieved with these strategies. However, the way research questions are asked by a physicist do not always make sense to a geneticist, especially because variation and differences are sometimes placed in the background. The answers that geneticists give to questions about physical transformations in development, such as neurulation happens due to the expression of particular genes, appear inadequate to the physicist since genes alone do not create forces that can explain the material transformation of the embryo. Yet a kind of integration can be discerned from this situation. It involves seeing complementary research perspectives as analogous to a particular modeling strategy.

Modeling complex biological phenomena always involves abstraction—the intentional omission of detail—and idealization—the deliberate misrepresentation of detail. Both are strategies to simplify our representations of complex phenomena. A realistic representation of a cell and all of its myriad constituents and interactions would be impractical and unilluminating (even if possible, in principle). Multiple-model idealization (Weisberg 2013) involves constructing multiple, related-but-incompatible models that capture distinct aspects of the causal structure of a complex system. It does not aim to produce a single best model. Instead, understanding derives from comparing and contrasting different models. Although new knowledge can be added to individual models, there is no expectation that the idealizations will be progressively removed or that the need for multiple models will fade over time.

Integrating complementary perspectives is directly analogous to multiple-model idealization. Genetic and physicalist approaches both involve deliberate misrepresentation in the service of simplification. These simplification strategies have been enormously productive individually in deciphering different kinds of causal relationships in living systems. However, these viewpoints are partial and incomplete and therefore must be compared and contrasted in order to achieve a deeper understanding of both development and evolution. This additional task of jointly evaluating the results of genetic and physical approaches yields a more integrated perspective than would otherwise be available when each orientation is only taken in isolation. Recent work on avian gut development exemplifies this integrative approach: to comprehend both how stereotypical morphology is generated and how it might evolve, researchers are combining the physical modeling of materials under compressive forces (Savin et al. 2011) with analyses of genetic pathways that can modulate buckling (Nerurkar et al. 2017).

Integration through comprehensive unification

To assert that living systems are material entities has been uncontroversial since at least the beginning of the 20th century. Given that organisms are composed of complex materials, understanding morphological shape and structure is a problem of physics. For the predominant physical paradigm of the 18th century, matter was inert and inertial, changing its form and position in a continuous fashion and only when acted on by external forces. However, the chemistry and physics of middle-scale (mesoscale) matter has undergone major advances during the interim, especially in understanding qualitative transformations in the composition and state of materials. Several prescient scientists recognized this explanatory potential. William Bateson (1861–1926) proposed that certain tissues exhibited oscillatory excitations that could cause them to organize into segmental and other repeating patterns (Bateson 1928). D'Arcy 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 1917). The embryologist Just (1939)

described the animal egg as a physical system that was "self-acting, self-regulating and self-realizing".

Subsequent advances during the 20th century in the physics of condensed, chemically and mechanically excitable materials have provided astounding resources that are applicable to the cell and molecular biology of developing systems. One area of progress is the theory of nonlinear oscillations in the study of dynamical mesoscale systems. Oscillations can occur in any "excitable" (i.e., reactive, energy-storing) system, living or nonliving, in which there is an appropriate balance of positive and negative feedback interactions. A famous application was the proposal of an oscillatory mechanism for the generation of somites (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.

Compelling experimental evidence for a formally similar mechanism emerged two decades later and involved an intracellular biochemical clock consisting of *Hes1*, a transcriptional switching factor, and a wavefront derived from a gradient of the morphogen *Fgf8* with its source at the posterior end of the embryo (Palmeirim et al. 1997). Evolutionary alterations in the ratio of parameters that characterize the interaction of the clock and wavefront account for the increase in the number of segments in snakes (Gomez and Pourquié 2009).

If embryos could take form using physical processes (e.g., biochemical oscillations, reaction–diffusion patterning, and thermodynamically driven phase separation of differentially adhesive cell populations), then what might the relationship be between gene regulatory mechanisms and these physical processes? Gene products in the developing embryo help to mobilize different physical effects (e.g., surface tension, viscosity, elasticity, and phase separation) and the evolution of developmental regulatory genes must be understood in conjunction with the physical effects they mobilize. All processes of development involve the organization and transformation of materials in which gene products play a prominent part. A complementarity between genetic and physical mechanisms of pattern formation and morphogenesis suggests a way to comprehensively integrate both physical and genetic lines of research (Newman and Comper 1990). Development consists of evolving composites of genetic and physical processes

(Fernandez-Sanchez et al. 2015; Forgacs and Newman 2005; Newman 2016).

This comprehensive integration of genetic and physical mechanisms has two major components. The first is an account of systematic associations between gene products and physical processes. Physical processes, such as adhesion, diffusion, or lateral inhibition (i.e., the enforcement by a cell on its neighbors of an alternative cell state), are indifferent to the specific identity of molecular components involved, as long as the relevant physics is harnessed. However, the products of genes that specify basic multicellular morphogenetic and patterning functions are highly conserved (e.g., the *Wnt* pathway mediates changes in the shape or surface polarity of embryonic cells of nearly all animal phyla). The capacities of gene products to facilitate the mobilization of distinct and relatively independent physical processes in multicellular aggregates can be schematized into types of "dynamical patterning modules" (Newman and Bhat 2009). These include cell–cell adhesion involving cadherins, cell surface anisotropy involving WNTs, and Turing-type processes involving Hedgehog, TGF-β, BMP, and Notch (Table 1). Through evolutionary time, the introduction of new physical materials occurred in association with the introduction of novel genes, such as galectins or fibronectin (Newman 2016). Importantly, dynamical patterning modules are distinct from gene regulatory networks that underlie differentiation and cell identity (Wagner 2014).

The second component of this comprehensive integration is an evolutionary scenario (see Newman et al. 2006). Novel morphological motifs or themes (e.g., multiple cell layers, lumens, segments, and appendages) are initially produced in evolution by physical processes acting on multicellular aggregates or parcels of tissue (Newman and Bhat 2009). Such epigenetic mechanisms bias the evolution of morphology and are predictable from the inherent material properties of the tissues (Newman 2016). Next, the adaptive utility of a novelty places a premium on genetic variants that allow the structure to be generated more reliably in ontogeny apart from the conditions related to its original physical determination. This can facilitate the genetic assimilation of the feature. Finally, in some cases, the morphological unit evolves to become independent of the gene expression networks that initially stabilized it within a developmental trajectory, thereby accounting for the phenomenon of "developmental systems drift" (True and Haag 2001).

Overall, this integrated picture of developmental evolution takes seriously that organisms are both

Table 1 A representation of systematic associations between gene products and physical processes alongside their respective roles in developmental evolution

Dynamical patterning mechanism	Molecules	Physics	Evo–devo role
Cell–cell adhesion	Cadherins; lectins	Adhesion	Multicellularity; tissue formation
Lateral inhibition	Notch pathway	Lateral inhibition	Coexistence of alternative cell types
Differential adhesion	Cadherins; lectins	Differential adhesion; phase separation	Tissue multilayering
Multicellular apicobasal polarity	Catenin-associated Wnt pathway	Cell surface anisotropy	Topological change; internal cavities
Multicellular planar cell polarity	Catenin-independent Wnt pathway	Cell shape anisotropy	Tissue elongation
Multicellular extracellular matrix	Chitin; collagen	Stiffness; dispersal	Skeleton formation; elasticity
Multicellular oscillation	Hes+Notch; Wnt	Synchronization of cell state	Developmental fields; periodic spatiotemporal patterning
Morphogen	Hh; TGF-β/BMP	Diffusive transport	Spatial patterning
Asymmetric interaction	FGFs and FGFRs	Reciprocal binary interaction	Induction
Turing-type reaction–diffusion process	Hh; TGF-β/BMP+Notch	Dissipative structure	Periodic spatial patterning
Multicellular mitogenesis	MAPK	Mass increase	Tissue growth
Multicellular apoptosis	TNF; TNFR; Bcl-2; SMACs	Mass decrease	Tissue loss

Notes: See text for discussion. Key for molecules: Hh = hedgehog; TGF-β = transforming growth factor-β; BMP = bone morphogenetic protein; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; MAPK = mitogen activated protein kinase; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor; Bcl-2 = B-cell lymphoma 2 apoptosis regulator; SMAC = second mitochondria-derived activator of caspases.

physical entities and repositories of genetic information. It also combines developmental pathways that make use of mesoscale physics with genetic assimilation mechanisms that stabilize ontogenetic outcomes and protect them from perturbations by external factors (e.g., temperature and pressure) that could change the outcomes of physical processes (Vargas and colleagues, this symposium; see also Grimes et al. [2016] on fluid flow and spinal curvature, and Tibblin et al. [2016] on temperature and vertebral number). Since morphogenesis involves the rearrangement and reorganization of materials, there needs to be a source of materials (genetic) and source for their rearrangement (physics). Since variation underlies evolutionary change, genetic changes that alter the material available for physical reorganization are essential to the process. However, insight into the pertinent dynamics derives from physical approaches to biological systems.

Conclusion and future prospects

The two general theoretical frameworks for integrating genetic and physical explanations described here—combining complementary perspectives, and comprehensive unification—are by no means uncontroversial. For example, although "combining complementary perspectives" maps tightly onto the structure of current biological research, it makes it much easier for those who have adopted an exclusively genetic orientation to ignore physical approaches and their significance (e.g., Petit et al. 2017). Similarly, the evolutionary scenario proposed in the "comprehensive unification framework" is not a consensus view among biologists and faces both conceptual and empirical challenges (Love and Lugar 2013). Combining complementary perspectives is anchored in successful research strategies, but each distinct orientation might be misleading when taken in isolation (e.g., computational physical models that ignore genetic parameters, or gene regulatory network models that ignore the geometric arrangement of materials in the embryo). A framework of comprehensive unification affirms the explanatory value of completeness, but it might be problematic in how either the genetic or physical aspects are conceptualized (e.g., whether earlier periods of evolutionary history differ from later ones).

The authors of this paper are not in agreement about which framework is preferable and even have advanced other alternatives for understanding the integration of genetic and physical explanatory approaches (Love 2017). Preferences for one framework over another are anchored in distinct evaluative standards about whether particular types of data are sufficiently incorporated, whether the data

currently available better support one or the other perspective (or neither), and whether it is best to focus on differences or processes (or both) when explaining development and evolution. The nature of these disagreements is conceptual and, therefore, requires a different strategy than just accumulating more data. For example, it will be important to be explicit about vocabulary (e.g., when is a genetic explanatory model of digit formation not physical?) and when identifying what kinds of boundaries exist between these frameworks (e.g., how flexible are these frameworks and could they be wholly or partially integrated in some fashion?).

However, the authors of this paper are in agreement that setting forth these broader interpretations of how genetic and physical explanatory approaches might be integrated serves to make explicit particular assumptions and localize disagreements among researchers. These assumptions about what is being explained (e.g., differences vs. processes) or disagreements about whether the genetic properties of living systems behaved differently early in evolution should be made explicit. Only then can they be discussed and debated to determine what effect they might have on the methodologies adopted (e.g., the kinds of data collected or the value of computational modeling or mathematical representation), the interpretation of the results derived from these methodologies (e.g., whether the evolutionary origin of digits involved recruiting a Turing-type process), and the integrated explanations that are produced from these endeavors. We recognize that this task of conceptual reflection is a genuine challenge, and that it will not be accomplished without novel conceptual and experimental innovations. Perhaps most important among the possibilities will be changes to graduate training so that students are exposed to the necessary methods, concepts, and examples of integrated explanatory approaches. Regardless, the task is worthy—achieving a more comprehensive understanding of development and evolution. One hundred years after Thompson's landmark publication, we are well-positioned to find balanced viewpoints that integrate genetic and physical explanatory approaches into more unified accounts of complex biological phenomena.

Acknowledgments

Funding

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