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# The significance and scope of evolutionary developmental biology: a vision for the 21st century

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**SUMMARY** Evolutionary developmental biology (evo-devo) has undergone dramatic transformations since its emergence as a distinct discipline. This paper aims to highlight the scope, power, and future promise of evo-devo to transform and unify diverse aspects of biology. We articulate key questions at the core of eleven biological disciplines—from Evolution, Development, Paleontology, and Neurobiology to Cellular and Molecular Biology, Quantitative Genetics, Human Diseases, Ecology, Agriculture and Science Education, and lastly, Evolutionary Developmental Biology itself—and discuss why evo-devo is uniquely situated to substantially improve our ability to find meaningful answers

to these fundamental questions. We posit that the tools, concepts, and ways of thinking developed by evo-devo have profound potential to advance, integrate, and unify biological sciences as well as inform policy decisions and illuminate science education. We look to the next generation of evolutionary developmental biologists to help shape this process as we confront the scientific challenges of the 21st century.

## INTRODUCTION

Evolutionary developmental biology (evo-devo) originated as the attempt to bring together developmental biology and evolutionary biology and to conceptualize evolution as heritable changes in development. Although having antecedents prior to Darwin (see Gould 1977; Friedman and Diggle 2011), evo-devo was made possible in large part by the emerging power of molecular biology to contrast gene sequences, and subsequently gene functions, across taxa (e.g., Ohno 1970; King and Wilson 1975; Jacob 1977; Bonner 1981). Since its emergence as a distinct discipline with dedicated journals and professional societies (Raff 2000), evo-devo has undergone dramatic transformations, and has now grown into a multifaceted discipline that has opened up novel and synthetic ways to address fundamental, long-standing questions across areas of biology, as well as illuminated patterns and processes in biology that other disciplines were unable to see (Hall 2012; Olson 2012). Just as the Modern Synthesis was able to unify many aspects of biology in the mid-20th century, evo-devo is now positioned to transform and unify diverse aspects of biology, one of the primary scientific challenges of the 21st century. This paper highlights the scope, power, and future promise of evo-devo as a locus of integration for a multitude of biological disciplines, which will make it possible to overcome persistent conceptual boundaries and limitations, as well as address critical and urgent questions of applied significance. Here we articulate key questions at the core of eleven biological disciplines and discuss why evo-devo is uniquely situated and equipped to substantially improve our ability to find meaningful answers to these questions.

## EVOLUTIONARY BIOLOGY

In this section, we discuss four interrelated questions of central importance to evolutionary biologists—the origins of novelty, the causes of variation, and the sources of homology and convergent phenotypic evolution—and highlight how evo-devo research has fundamentally altered the way we conceptualize and investigate these processes.

Darwin's theory of evolution is based first and foremost on descent with modification. Everything new, ultimately, has to come from something old. At the same time, we are captivated by complex novel traits precisely because they lack obvious homology to preexisting traits. How novelty arises from within the confines of ancestral homology and how natural variation can lead to the evolution of complex, novel traits therefore remain some of the most intriguing and enduring questions in evolutionary biology (Wagner 2014). Mainstream evolutionary biology has struggled to adequately address these questions, largely because it narrowly defines the evolutionary process as a change in the genetic composition of a population, and emphasizes mutations as the primary source of evolutionarily relevant phenotypic variation (e.g., Falconer and Mackay 1996; Lynch and Walsh 1998). Using approaches based on transmission genetics, evolutionary biologists have developed powerful models to describe and predict how *existing* phenotypic variation in populations and its genetic correlates are sorted and shaped by evolutionary processes, but generally have been unable to provide meaningful ways of thinking about how, and under what conditions, novel, complex phenotypic traits emerge. Contributions from evo-devo make it clear that to do so requires a phylogenetically explicit, comparative understanding of developmental mechanisms, providing a foundation for investigating the means by which genetic differences contribute to novel phenotypic variants through ontogeny (e.g., Mabee et al. 2000; Monteiro and Podlaha 2009).

By uncovering the nature and distribution of developmental processes across the tree of life, evo-devo has fundamentally altered and enriched our understanding of innovation in the living world. Specifically, evo-devo research has demonstrated that developmental evolution relies heavily on (i) *duplication* of patterns and processes, from individual genes or genome elements (Lynch and Conery 2000; Damen 2002; Locascio et al. 2002; Gompel and Prud'homme 2009; Yockteng et al. 2013; Rensing 2014) to organismal parts [e.g., appendages (Cohn 2004; Pavlopoulos et al. 2009; Hughes et al. 2011), segments (Chipman et al. 2004), leaves (Byrne 2012), and floral organs (Zahn et al. 2010)], (ii) *modification*, from expansion of specific domains (Rensing 2014) and regulatory network interactions (de Bruijn et al. 2012) to the coordinated modification of organ systems (Bloom et al. 2013), and (iii) *co-option* at multiple levels of biological organization, enabling the evolution of novel traits [e.g., butterfly wing patterns (Saenko et al. 2008), beetle horns (Moczek and Rose 2009), the turtle shell (Gilbert et al. 2007; Kuratani et al. 2011), nectar spurs (Sharma et al. 2014)], novel developmental mechanisms (Ewen-Campen et al. 2012), and novel trait characteristics [e.g., condition-dependency (Kijimoto et al. 2013); Batesian and Müllerian mimicry (Martin et al. 2012; Kunte et al. 2014)]. Rather than requiring novel genes or pathways, functionally integrated, novel phenotypes emerge

from ancestral variation through the differential combination and re-deployment of existing developmental modules. Through these discoveries evo-devo research has provided novel ways for understanding—and investigating—phenomena for which traditional evolutionary biology lacked meaningful explanations, such as the discreteness of phenotypic characters (Wagner 2014), the conservation and deep homology of characters (Shubin et al. 2009; Scotland 2010), and the causes of phenotype complexity (Monteiro and Podlaha 2009).

The origin of novel traits in evolution and development is in many ways an extreme case of a larger phenomenon central to evolutionary biology: the origin of phenotypic variation *of any kind*. Mainstream evolutionary biology (i) has traditionally focused on mutations as the only source of evolutionarily relevant phenotypic variation, which (ii) is random with respect to its effects on the phenotype. As a consequence, (iii) natural selection emerges as the only process capable of generating adaptive matches between organisms and their environment. Evo-devo research has significantly expanded all three of these axioms. Specifically, evo-devo has empirically confirmed the longstanding intuition of many biologists that developmental systems are themselves a source of *biased variation* that constrains as well as encourages the operation of natural selection in a specific manner [e.g., segment number in centipedes (Arthur 2002); sex- and nutritionally-cued dimorphisms in horned beetles (Emlen et al. 2005; Kijimoto et al. 2013); digit reduction in amphibians (Alberch and Gale 1985); beak evolution in song birds (Fritz et al. 2014)]. This biasing effect facilitates phenotypic diversification by converting random genetic variation into non-random and frequently functionally integrated phenotypes. The both *biasing* and *facilitating* nature of development thus contributes to the evolutionary process by selecting the amount and type of phenotypic variation available for evolutionary processes to act upon (Gerhart and Kirschner 2007).

At the same time, research findings coming out of evo-devo have led to a deeper appreciation of the interactions between developing organisms and the environmental and ecological conditions within which they function. Developmental plasticity—the ability of the genome to produce a range of phenotypes through its interactions with the environment—was once considered a special case observable in a subset of taxa, but is now recognized as the norm, and ecological conditions are recognized as being able to influence developmental outcomes at all levels of biological organization. Interactions between developing organisms and ecological circumstances therefore have the power to shape patterns of selectable variation available in a given population. These effects range from predisposing genes subject to environment-sensitive expression to mutation accumulation [e.g., bacteria: (Van Dyken and Wade 2010); aphids: (Brisson and Nuzhdin 2008)] to allowing initially environment-induced phenotypes to be genetically stabilized through subsequent selection on genetic modifiers [e.g., *Daphnia*: (Scoville and Pfrender 2010); cave fish: (Rohner et al. 2013); tadpoles: (Ledon-Rettig et al. 2010); *Drosophila*: (Waddington 1953; Waddington 1956); snakes: (Aubret and Shine 2009); moths: (Suzuki and Nijhout 2006)]. At the same time, we have come to realize that developing organisms themselves shape and alter their developmental environment and ecological niche, and thus bias the selective conditions that they and descendant generations may experience (see below in section on evo-devo's impact on Ecology).

Evo-devo has similarly provided novel ways to understand—and distinguish between—homology and homoplasy. Due to advances by evo-devo research programs, homology—considered by many as among the most important concepts of evolutionary biology—has matured from Owen's (1843) basic definition ("the same organ in different animals under every variety of form and function") to a more robust characterization of what constitutes "sameness" in developmental evolution. For example, homology is now understood to emerge differentially on different levels of biological organization (Abouheif et al. 1997), or for processes conveying character *identity* compared to those specifying character *state* (Wagner 2007, 2014). Some of the most significant advances concern homology and levels of organization: morphologically non-homologous structures may share some homology in their underlying developmental mechanisms ("deep homology;" Shubin et al. 2009), while morphologically homologous structures may retain a remarkable degree of phenotypic conservation in descendant lineages despite their underlying developmental machineries diverging dramatically ("developmental systems drift") (Weiss and Fullerton 2000; True and Haag 2001). Collectively, these insights have transformed the way we conceptualize and investigate homology, recognizing that not all aspects of development are equally variable, and that differential variational properties contain important biological information critical to understand why and how developmental evolution unfolds the way it does.

Finally, many of the same discoveries have also advanced our understanding of homoplasy, or convergent evolution. By examining the developmental genetic basis of homoplastic traits, evolutionary developmental biologists have discovered that morphological convergence or re-evolution of a particular trait can be accomplished by specific mechanisms acting during development (Wake et al. 2011), such as repeated and independent differential selection on the same genetic loci (Gompel and Carroll 2003; Sucena et al. 2003; Shapiro et al. 2004; Protas et al. 2006; Shapiro et al. 2006), repeated re-deployment (co-option) of the same genetic and developmental modules into novel positional or serial contexts (Bartlett and Specht 2010), utilization of completely distinct developmental mechanisms that yield similar morphological outcomes (Wittkopp et al. 2003; Steiner et al. 2009; Tanaka et al. 2009; Green II and Extavour 2012), or re-emergence of dormant or suppressed developmental pathways (Rajakumar et al. 2012;

Rohner et al. 2013). It is through these diverse studies that evolutionary developmental biologists have revealed that convergent evolution is itself a dynamic and heterogeneous phenomenon, and that convergence at the morphological and genetic levels can arise independently via distinct evolutionary processes (Gompel et al. 2005; Manceau et al. 2010; Losos 2011). As such, evo-devo has begun to provide novel ways to investigate the nature of both homology and homoplasy in enabling morphological, biochemical, and molecular diversification.

As evolutionary biology looks to the 21st century, one of its challenges will be to better describe the way that the variation *generating* and *biasing* mechanisms of development interact with the variation *sorting* mechanism of natural selection to produce organismal diversity and adaptation. Evo-devo research helps meet this challenge by providing powerful empirical and conceptual avenues that allow us to integrate the principles of phenotype construction with those of phenotype selection, across all levels of biological organization.

## DEVELOPMENTAL BIOLOGY

In-depth, causal-mechanistic analyses of developmental processes require a full spectrum of genetic manipulations (mutagenesis, transgenesis, clonal analysis), which is available only for a small set of model organisms. Such studies have led to unprecedented insights into the architecture of gene regulatory networks (GRNs), the molecular biology of signaling processes including the mechanisms of morphogen function, and the cellular and subcellular processes of morphogenesis (the formation of three dimensional shape and structure). Increasingly, quantitative data are available that allow computational modeling and the formulation of theories with predictive power (Jaeger et al. 2004; Manu et al. 2009; Hoyos et al. 2011; Roth 2011; Peter et al. 2012). Developmental biology has now arrived at a point where future advances will require the implementation of evo-devo approaches, addressing questions such as: how many different network structures can explain convergent or homologous phenotypic traits? Are there common regulatory principles shared among developmental processes producing similar phenotypic outputs? To what degree can network analysis and biophysics alone explain developmental properties? And, what are the relative contributions of evolutionary history, population structure and ecological contexts to development? In other words, only a comparative approach can identify which features of developmental gene regulatory networks (GRNs) are essential to achieve a certain phenotypic outcome, and which ones are free to change during evolution.

In this section, we will discuss several fundamental aspects of development, our understanding of which will increasingly depend on the successful application of evo-devo concepts and approaches: (i) the deep conservation of regulatory networks and pathways despite their deployment within highly varying developmental contexts; (ii) the opposite phenomenon—variation of developmental processes resulting in highly similar phenotypic outcomes [developmental systems drift (True and Haag 2001)]; and (iii) the mechanisms that ensure reproducibility and robustness of development (canalization).

### Deep conservation of regulatory networks

Evo-devo emerged with the realization that most molecular pathways controlling development are deeply conserved, and can be homologized across broad phylogenetic distances. The Hox cluster in animals still provides one of the most powerful examples (Pearson et al. 2005). The molecular mechanisms underlying the highly conserved collinear arrangement of Hox genes along the chromosome has been elucidated through an ingenious series of experiments in model systems (Noordermeer and Duboule 2013). This work, which has been extended to theoretical, predictive approaches (Almirantis et al. 2013), might explain why the arrangement of Hox genes is highly conserved throughout evolution. However, only through evo-devo studies did we begin to learn how the Hox cluster evolved in the first place (Gehring et al. 2009; Holland 2013), how changes in cluster structure correlate with alterations in the body plan, and how changes in Hox regulation and protein structure correlate with morphological diversity (Pearson et al. 2005; Holland 2013).

A very different example is the conservation of BMP signaling (together with a small number of extracellular modulators) in the context of dorsoventral patterning in most bilaterian animals (De Robertis 2008). Given the fact that the deployment of other signaling pathways has changed drastically throughout evolution, why is this pathway so highly conserved in the process of axis formation, which itself occurs in highly diverse developmental contexts in the various bilaterian lineages? Currently there are only a few answers to this question. The feedback between the pathway and its modulators might establish a fairly robust self-regulatory system for spatial patterning and scaling (Plouhinec and De Robertis 2009; Inomata et al. 2013), the extracellular modulators might reduce stochastic noise (Karim et al. 2012), or the downstream GRN might be highly constrained (Mizutani and Bier 2008).

These examples show that while understanding attained from model systems can provide mechanistic arguments for the evolutionary success of highly conserved developmental pathways, evo-devo studies are required to show how far developmental processes can be adapted to varying conditions and which parts may represent indispensable key components.

### Developmental systems drift

Given the vast diversity in eye morphologies, few would have predicted that orthologs of the transcription factor Pax6 would

control eye development from insects to vertebrates (Kozmik 2005). On the other hand, many may have expected that the molecular processes involved in axis determination in *Drosophila* are conserved at least within flies (St. Johnston and Nüsslein-Volhard 1992), and that early embryogenesis and vulva specification of *Caenorhabditis elegans* should be broadly conserved in nematodes (Gonczy and Rose 2005; Sternberg 2005; Schierenberg and Sommer 2013). Yet drastic changes in development were indeed observed in both instances, in spite of common, homologous final morphologies (Schierenberg 2005; Fonseca et al. 2009; Sommer and Bumbarger 2012), a phenomenon we now recognize as developmental system drift (DSD; True and Haag 2001).

The most comprehensive genetic analyses of DSD come from work on nematodes. Genetic screens in *Pristionchus pacificus* have provided an independent way for reconstructing and comparing vulval development between nematode genera, showing that the same organs can be constructed by homologous cells that are nonetheless regulated by different molecular mechanisms (Sommer and Bumbarger 2012). Within the genus *Caenorhabditis*, global comparison of the function of transcription factors between two closely related species with almost identical morphology showed that more than 25% of conserved genes had altered functions (Verster et al. 2014). Although this work significantly advances our knowledge of different developmental trajectories leading to the same morphology, it does not explain the causes for the observed evolutionary changes. Studies in insects, on the other hand, have illuminated the developmental context that enables DSD. The emergence of the anterior determinant Bicoid for head patterning, for example, is linked to a dramatic change in extraembryonic development (Lemke et al. 2010). Many aspects of axis formation, like the employment of the oocyte nucleus for defining dorsoventral polarity, oocyte-to-follicle cell signaling and the recruitment of the Toll pathway from an ancestral immune function, can be viewed as adaptations to prior key innovations in insect reproduction and terrestrial lifestyle (including, for example, ovariole structure, eggshells, early syncytial stages of yolk-rich embryos, and extraembryonic membranes) (Lynch et al. 2010; Lynch and Roth 2011). This scenario reveals the limitations of understanding developmental processes based on abstract GRN and biophysical reasoning alone. Furthermore, it highlights a trend: we will increasingly recognize variation in developmental mechanisms as the result of adaptation to—and coevolution with—the internal organismal environment that was ancestrally constructed (Moczek 2012).

## Mechanisms underlying developmental robustness

One of the most remarkable features of development is canalization, wherein developmental processes and the emergence of phenotypic products can be highly reproducible in spite of internal (genetic) and external (environmental) perturbations (Waddington 1942). Modeling approaches have started to yield insights into the regulatory mechanisms underlying robustness and canalization (e.g., von Dassow et al. 2000; Wagner 2005), and their role in rendering developmental systems evolvable (Draghi et al. 2010; Wagner 2011). In addition, for the first time a genetic circuit was described recently in *Drosophila melanogaster* that is dedicated to suppressing developmental fluctuations in early cell fate determination (Gavin-Smyth et al. 2013; Panfilio and Roth 2013). This genetic circuit itself is subject to rapid evolution, showing that canalization can be achieved in different ways. A *Drosophila* species was even identified that lacks canalization (of this particular aspect of development) and thus must tolerate increased embryonic lethality (Gavin-Smyth et al. 2013). This is an important result since it shows that not all features of development are necessarily canalized, placing considerable limits on modeling approaches that assume robustness of developmental processes (Eldar et al. 2002; Roth 2011). It also highlights the need for investigation of the mechanisms underlying developmental variation not only in our rather artificial lab strains, but also in wild populations. This has been done extensively for *C. elegans* and *Arabidopsis*. In *C. elegans*, for example, two partially redundant mechanisms buffer vulval development and explain variation in development among inbred lab strains as well as cryptic variation in wild populations (Felix and Barkoulas 2012). The alternative developmental trajectories found within *C. elegans* populations in part resemble the diversity fixed in different species of the genus. Genome-wide association studies in *Arabidopsis thaliana* in turn have been able to map the genetic loci responsible for variation in developmental processes like trichome patterning and flowering time (Weigel 2012). Similar to *Caenorhabditis*, this bias in intraspecific variation correlates with evolutionary differences present in other species of the genus *Arabidopsis*. As such, adding ecologically informed contrasts to studies designed initially to examine robustness and buffering of development in model species or strains has begun to facilitate a deeper understanding of the evolution of buffering and the ecological conditions that shape robustness in natural populations.

## Last but not least—getting outside the nucleus

Evo-devo has also revolutionized the nature of developmental biology by showing that internal and external environmental conditions play profound roles in the unfolding of normative development. Developmental plasticity is now considered the norm, and developmental responsiveness to diet, stress, the presence of predators, or temperature differences pervades the animal kingdom (Gilbert and Epel 2009). Moreover, as will be discussed in more detail below, normal development is predicated on the presence of persistent symbionts that are

critical in the morphogenesis of many organs (Gilbert et al. 2012; McFall-Ngai et al. 2013). Developmental biology has come a long way indeed since the 1990s, when scientists were asking whether components outside the nucleus had any role in normal development.

## PALEONTOLOGY

Explaining biodiversity demands integrating paleontology with evo-devo. Whereas paleontology aims to determine "What happened during evolution?," evo-devo tries to answer "How did it happen?" Bringing these fields together is critical. Thewissen et al. (2012) conclude that "developmental evidence enriches paleontology in formulating and assessing hypotheses of homology, character definition, and character independence, as well as providing insights into patterns of heterochrony, evolvability of features, and explanations for differential rates of evolution." This is especially true in vertebrate paleontology, where evo-devo has played significant roles in recent advances concerning the evolution of diverse traits, from teeth and limbs to turtle shells.

For example, the evolution of the turtle shell has long been one of the biggest questions in vertebrate paleontology. It has been difficult for paleontologists to reconstruct the non-shelled ancestor of turtles or to explain how a shell could come into existence. Rieppel (2001) first pointed out to paleontologists that the findings of development might help solve this problem. Recently, Lyson et al. (2013a) have proposed an "evolutionary developmental model for the origin of the turtle shell" wherein paleontological evidence suggests that a certain group of reptiles developed their ribs in the same manner as turtles (and only turtles) presently do. Other integrations of turtle evo-devo and paleontology have since explained the origins of the turtle shoulder-girdle (Lyson et al. 2013b; Nagashima et al. 2013) and the mechanism for the robustness of the scute pattern (Moustakas-Verho et al. 2014).

The last-mentioned work is especially noteworthy because of its integration of mathematical models with evo-devo approaches. A parallel effort has been similarly informative for research into the evolution of teeth. For instance, a recent study was able to "replay" the fossil record of rodent tooth development by changing paracrine factor concentrations as tooth buds developed. Starting with a "generic" tooth that lacked specific cusps and ridges, Harjunmaa et al. (2014) were able to restore the evolutionary sequence of events leading to the three-cusped molar. By varying the concentrations of paracrine factors involved in cusp formation, the authors were able to reconstitute the formation of the trigonid cusp (the first part of the molar to have evolved), and by further changing these concentrations, they brought forth the talonid cusp, which evolved more recently and is used for shearing food. This account, enabled by mathematical approaches (Kavanagh et al. 2007; Salazar-Ciudad and Jernvall 2010) and integrated into paleo-ecological models (Rodrigues et al. 2013; Luo 2014), demonstrated "how combining development and function can help to evaluate adaptive scenarios in the evolution of new morphologies" (Rodrigues et al. 2013).

Limb evolution also has been a critical success story for the integration of paleontology and evo-devo. Integrating development into the fossil record has been used to explain the origins of mammalian flight (Cooper et al. 2012), the loss of limbs in snakes (Cohn and Tickle 1999; Di-Poï et al. 2010; Mallo et al. 2010; Head and Polly 2015), cetaceans (Thewissen et al. 2006), and fish (Shapiro et al. 2004; Tanaka et al. 2005), as well as the mechanisms of marsupial forelimb heterochronies (Doroba and Sears 2010; Keyte and Smith 2010; Chew et al. 2014). The combination of paleontology and evo-devo has also helped explain the homology of digits between dinosaurs and birds (Tamura et al. 2011; Wang et al. 2011; Salinas-Saavedra et al. 2014) as well as their skulls (Bhullar et al. 2012). Moreover, combining two elements of evo-devo—developmental plasticity and comparative developmental genetics—with paleontology has given us reasonable scenarios explaining how fins could have developed into functional limbs (Shubin et al. 2006; Davis 2013; Schneider and Shubin 2013; Standen et al. 2014; Woltering et al. 2014). And, here again, mathematical modeling is playing a role in uniting evo-devo with paleontology. For example, Zhu et al. (2010) have integrated developmental mechanisms with paleontological reconstructions to show how changes in development can alter the embryological placement of digits in certain ways only, thereby demonstrating how the various digit formations seen during early amniote evolution could have evolved. These and many other examples illustrate the reciprocal relationship between evo-devo and paleontology in their common quest to reconstruct developmental evolution on our planet (see Raff 2007; Sánchez 2012).

## NEUROBIOLOGY

Neuro-genomics and neuro-transcriptomics have contributed substantially to our knowledge of the evolution of genetic networks involved in complex neurobiological processes and pathological changes. However, the ever-increasing list of candidate genes has yielded limited insight into the functional consequences of variation in genes and expression patterns (Harris and Hofmann 2014). Recent work now indicates that organisms might be primed for adult neural function and behavior during ontogeny depending on internal and external conditions (e.g., Neckameyer and Bhatt 2012). For example, changes in the expression levels of neurotransmitters during development have been associated with mental illness in humans, such as depression (Sodhi and Sanders-Bush 2004), and functional studies across various animal models are beginning to uncover a developmental role for neurotransmitters

in shaping neuronal architecture during ontogeny (e.g., Gaspar et al. 2003; Neckameyer 2010; Neckameyer and Bhatt 2012). These comparative studies highlight the utility of an evolutionary framework in addressing open questions in neurobiology, placing evo-devo in a central position to help identify principles of neural function.

Evo-devo approaches and concepts also help advance other longstanding questions in neurobiology. For example, classical behavioral selection in animal domestication showed long ago that breeds with behavioral differences from those found in the wild can be established (e.g., Darwin 1871; Belyaev et al. 1981). Analyses into the causes of this behavioral diversification have mainly focused on understanding the genomic response to artificial selection on the basis of underlying genetic variations (Trut et al. 2009). However, recent evidence of environmentally induced trait inheritance has significantly changed this traditional focus. For instance, Dias and Ressler (2014) demonstrate that parental behavioral experiences can be passed on to offspring via epigenetic imprinting and can lead to stable changes in the sensory neuronal architecture. These results raise many intriguing questions. How is information about the induced architecture stored and transmitted to the germ line? How does it instruct the neuro-developmental processes in the progeny to produce altered neuronal shape? Interestingly, the memory of an acquired environmental familiarization behavior in planarians persists through regeneration even after decapitation (Shomrat and Levin 2013), showing that behavioral information and memory can be stored in the periphery and passed on to the regenerating tissue. But which cells can store this epigenetic information? Can we identify pathways for the transmission of neural epigenetic inheritance? Tackling these questions will require a comparative analysis of neuro-developmental processes in a variety of metazoans, thus putting evo-devo approaches in a unique position to lead progress in this area of neurobiology.

Studies of the mechanisms of behavioral plasticity directly lead to the question of its evolutionary origin. How does neural development facilitate the emergence of plastic behavior? Recent evidence comparing feeding behavior and neural connectivity in the bacterial-feeding *C. elegans* with the predatory *P. pacificus* suggests that the generation of novel behavioral phenotypes is achieved via a massive rewiring of homologous neurons (Bumbarger et al. 2013). More studies that compare nervous system architecture or connectivity in closely related taxa are needed to address the multiple levels of neural organization at which evolutionary behavioral changes occur.

Furthermore, behavioral responses can be regulated by hormones during development and subsequently shaped by experience and/or environmental signals. Neuropeptides play dual roles in regulating behavior and sexual maturation in holometabolous insects. For example, in flies, the brain-derived prothoracicotropic hormone (PTTH), acts on light receptors to generate light avoidance behavior for finding dark places to pupate in late larval stages, while inducing steroidogenesis to regulate maturation (Yamanaka et al. 2013). Therefore, modulation of *innate behaviors* can be accomplished by hormonal action, and the evolution of new behaviors may be coupled to pleiotropic effects in development. In spite of metamorphic remodeling, larval conditioned odor aversion (i.e., memories of larval *learned behaviors*) has been shown to survive through metamorphosis in *Manduca sexta* (Blackiston et al. 2008). Understanding the precise developmental mechanisms of innate or learned behaviors has implications for evolution, as they generate behavioral variation from which reproductive isolation can emerge, and that selection can act upon, generating adaptive changes in behavior in sometimes as short as a single generation (Dias and Ressler 2014).

Additional open, critical questions in neurobiology revolve around the evolution of social behavior and cognition. Common molecular pathways seem to underlie both solitary and social behavior. For example, genes involved in feeding and reproduction in solitary species (e.g., fruit flies) have been co-opted for the division of labor in eusocial animals (Toth and Robinson 2007). This leads to the question of how conserved molecular pathways can perform their role despite major differences in brain structure and nervous system organization. Other research questions include how anatomical differences between the human brain and that of other primates are connected to the evolution of cognition, complex social behavior and emotional processing. Developmental regulatory genes have been found to be differently active in the brains of chimps and humans (McLean et al. 2011; Dennis et al. 2012). One particular trait of interest to evo-devo biologists is the prolonged phase of neuronal maturation of humans compared to other primates (Hrvoj-Mihic et al. 2013). Did this heterochronic shift facilitate anatomical changes related to human-specific neural functions?

The examples presented here demonstrate that a deep understanding of neuronal function and pathology in the context of natural environments can only be achieved through an understanding of the developmental and evolutionary dimensions of neuronal systems. Consequently, future research in neurobiology must go beyond the study of traditional model organisms—and traditional laboratory settings—and engage in the comparative analysis of ontogenetic processes and neuronal functions across various metazoans, as well as across relevant ecological contexts in natural populations. Future advances of neurobiological research will therefore be deeply rooted in the evo-devo field.

## CELLULAR AND MOLECULAR BIOLOGY

Across metazoans, early specification and determination of embryonic cell lineages occurs through a combination of invariant and regulative mechanisms. For some organisms (e.g.,

mouse and sea urchins), the timing of determination and segregation of fate potential for precursor cells can be altered in response to environmental influences, both internal and external (Smith and Davidson 2009; Sharma and Ettensohn 2011; Martinez Arias et al. 2013). Our current understanding of the evolution of stem cells and the differentiated cell types they give rise to during development has been restricted, either taxonomically by the limited number of traditional model systems amenable to functional approaches, or methodologically, by non-model systems where modern approaches are costly and time-consuming (e.g., cnidarians, spiralians, crustaceans, etc.). Fortunately, the ever-lowering cost of sequencing combined with recent advances in genome editing technologies [i.e., via CRISPR-Cas9 and TALENs (Dickinson et al. 2013; Joung and Sander 2013)] is increasingly closing the gap between non-model and model systems, positioning evo-devo to provide an evolutionary framework for questions of interest to cell and molecular biologists. Here we focus on the process of cell differentiation from pluripotent precursors and the morphogenetic behaviors these cells must execute, two of several areas in which evo-devo approaches have begun to provide major new advances to longstanding questions in cellular and molecular biology.

## Evolution of gene regulatory networks (GRNs) underlying cell differentiation

The plasticity of progenitor cell lineage decisions that result in the appearance of new cell types or structures over evolutionary timescales has been the subject of multiple studies. In the discovery of induced pluripotency, it was found that expression of four proteins could completely override the differentiated state of a cell, causing it to de-differentiate to an embryonic progenitor (Takahashi and Yamanaka 2006). Similar results have been seen with trans-differentiation, whereby one differentiated cell type is changed to another following forced expression of, in one case, a single transcription factor (Weintraub et al. 1991). These results suggest that differentiation may be best defined as a stable, robust state of gene expression that nevertheless retains the potential for reversibility, even in single cells.

Despite these advances, our understanding of how cell-type specific GRNs are established during development and how they change over evolutionary timescales is extremely limited. With the advent of more functional tools at the disposal of researchers using non-model systems, this is a question perfectly suited for an evo-devo approach. For example, recent work on sea urchin development provides insights into the execution of cell type specific GRNs, as most early embryo cell types are competent to trigger the skeletogenic GRN (Sharma and Ettensohn 2011) and comparative data from related echinoderms illuminate how these GRNs evolve (Ettensohn 2009; McCauley et al. 2010). Furthermore, dissecting the evolution of these pathways has implications for regenerative medicine because it increases our understanding of the directed differentiation of embryonic and induced pluripotent stem cells.

During metazoan embryogenesis, an important contributor to the emergence of cell lineages is changes in combinatorial gene expression profiles of transcription factors that induce spatial and/or temporal change (Davidson et al. 2002; Maduro 2006; Wray 2007). In addition, these patterns of gene expression are mediated by epigenetic processes that directly affect the accessibility of DNA by transcription factors in the nucleus (Huh et al. 2013). Mutations in non-coding RNA loci (Mattick 2007) and post-transcriptional regulation (Alonso and Wilkins 2005) can also affect the time, place, or amount of gene expression. Insight into how small RNAs affect gene expression can be aided through a comparative approach. For example, the comparison of miRNA genes across fruit fly species (Lu et al. 2008; Mohammed et al. 2013) and within the nematode *Caenorhabditis briggsae* (Jovelin and Cutter 2011) shows remarkably rapid adaptive evolution and functional diversification for newly evolved miRNAs. Therefore, miRNA and other short or long non-coding RNA loci display evolutionary signatures, and demonstrate how changes in epigenetic regulation or RNA modulation have revealed new sources of genetic and phenotypic variation of gene expression. We need to dissect how these processes interact with the *cis*-regulatory logic of GRN functionality, in order to understand how environmental signals may be selecting for developmental regulators within these new sources of variation. This will only be solved through a comparative evo-devo approach that utilizes a wide diversity of organisms.

## Morphogenesis

Following the specification of discrete cell types in the early embryo, cells must then execute a myriad of morphogenetic behaviors to attain tissue and organ-level complexity. To date, the greatest insights into these processes [e.g., epithelial to mesenchymal transition during gastrulation and neural crest migration (Smallhorn et al. 2004; Clay and Halloran 2013)] have occurred through the use of model developmental systems that allow for advanced live cell imaging techniques combined with functional perturbation in a genetic context.

Due to the large evolutionary distance between established model systems, increased taxonomic sampling is necessary to improve our understanding of how cells initiate and execute morphogenetic behaviors. Understanding how these behaviors evolved and whether they share a common ancestry will be accomplished only by moving beyond traditional genetic model systems. Recent work on sea urchins and ascidians is paving the way, connecting developmental GRNs to the cell biology of morphogenesis (Christiaen et al. 2008; Warner et al. 2014). Comparative research is yielding important results in this vein, including vulval morphogenesis in rhabditid nematodes

(Kiontke et al. 2007; Matus et al. 2014), neuroblast differentiation in insects (Biffar and Stollewerk 2014), bristle pattern formation in Drosophilids (McGregor et al. 2007), and melanin pigmentation in zebrafish species (Parichy 2006). These approaches have the inherent advantage of studying homologous cell types that undergo morphogenetic events. Thus, the comparative approach inherent to evo-devo research offers exciting ways to unify and extend our understanding of how precursor cells differentiate and execute morphogenetic behaviors leading to the growth and formation of both shared and lineage specific structures unique to each organism.

## QUANTITATIVE GENETICS AND PHENOMICS

Quantitative genetics focuses on short-term predictions (in natural or experimental populations) of population responses to selection as functions of both the strength of selection and available (additive) genetic variation. Recent empirical developments and theoretical contributions in evo-devo have extended this framework (Hill and Mulder 2010), in particular by demonstrating that the developmental processes underlying phenotype expression themselves influence the generation, degree and distribution of phenotypic and genetic variation (Wolf et al. 2001). In some instances, a better understanding of the mechanisms underlying trait development has enhanced our existing models of quantitative trait evolution. For instance, some studies have found that the fixation of large effect mutations modifies developmental processes by not only influencing trait means, but also by altering the pattern of genetic covariances among traits (Agrawal et al. 2001). For example, the *erecta* gene in *Arabidopsis thaliana* influences many aspects of plant and floral development, and panels of recombinant inbred lines that vary for a major effect allele of *erecta* show a substantial change in the structure of the genetic covariance matrix (Stinchcombe et al. 2009). Thus the effect of fixation of such an allele is not limited to altering trait means: it can also generate changes in developmental processes that influence the rate and trajectory of multivariate evolution.

Insights generated through evo-devo will also help guide the meaningful interpretation of the large-scale phenomics data that are increasingly being generated (Houle et al. 2010). Phenomics focuses on characterizing the nature of variation of physical and biochemical traits and their dependency on genetic and environmental properties. Even though collecting such data has become increasingly easier, developing biologically sensitive models has been difficult, even with very large sample sizes (Meyer 2009). Specifically, to date most parameter constraints imposed on models with such high dimensional data do not utilize any biological information, such as how mutations may influence development, how development influences patterns of covariation, and how environmental conditions may affect these interactions (Wolf et al. 2006). Lynch and Walsh (1998) explicitly state how quantitative genetics is ready and primed to integrate such considerations, yet evo-devo approaches are needed to generate the relevant biological information.

Our knowledge of developmental processes, how they influence observed phenotypic variation, and in turn how such processes vary, will also be increasingly important for understanding the nature of modularity and integration of biological systems (Wagner et al. 2007). It remains unclear how best to generate biologically meaningful modules from morphological or developmental data, and such attempts require an understanding of development and its influences on variation (Klingenberg and Zaklan 2000; Klingenberg 2009). Increasingly there are attempts to build *de novo* modules of covarying structures, such as from the butterfly nymphalid ground plan of wing structures (Suzuki 2013). Although this is an important first step, it has the potential to be taken much further when such methods can take into account the influence of development on observed variation (Nijhout 1991). Similarly, advances in the analysis of biological shape (geometric morphometrics) contextualized by evolutionary developmental biology has already led to profound improvements in our understanding of the evolution of trait size and shape (Klingenberg et al. 2003; Zelditch et al. 2012; Parsons and Albertson 2014).

## HUMAN HEALTH AND DISEASE

In this section we discuss three areas of central importance to our understanding of human health and disease: (i) the biology of birth defects; (ii) cancer; and (iii) the role of environment in development. We highlight how evo-devo has fundamentally altered the way we conceptualize and investigate these phenomena. We begin with a discussion of how evo-devo positively impacts our understanding of human birth defects.

Nearly one out of every 33 children in the United States is born with a birth defect, and those birth defects result in about one out of every five infant deaths within the first year of life (Mathews and MacDorman 2013). Human development cannot be experimentally manipulated, so to understand the etiology and pathogenesis of these conditions, we rely on non-human model organisms. However, evolved developmental differences between species greatly impair our ability to extrapolate what we learn about development from model organisms to humans. For instance, when genes such as *Sall1*, *Alx4*, and *Fgfr2* are deficient in humans, they cause serious limb anomalies. However, when these same genes are knocked out in mouse embryos, the resulting mice display minimal or no limb defects (Wynshaw-Boris 1996; Hajihosseini et al. 2001; Mavrogiannis et al. 2001; Nishinakamura et al. 2001).

A critical barrier to our study of human birth defects is therefore our incomplete knowledge of how normal development differs among animal species. In this, we are limited by the

fact that development has been broadly examined in only a few species. Just as the ability to study leprosy (Hansen's disease) was enhanced by our knowledge that armadillos and magabey monkeys (but not rats, dogs, or macaques) could acquire and transmit this disease (Bennett et al. 2008; Truman et al. 2011), our ability to understand and treat birth defects will be enhanced by knowledge of the diversity of developmental performances, which the field of evo-devo is uniquely positioned to advance.

A mutually beneficial relationship also exists between evo-devo and cancer biology. Cancer is a disease of altered development. The genes that promote cancers are often those that normally regulate cell cycling, cell differentiation, and cell signaling (Berman et al. 2002; Rubin and de Sauvage 2006; Song et al. 2011; Tautz and Domazet-Loso 2011). As such, comparative analyses of development in various metazoans are beginning to contribute to the identification of many cancer components. For example, the *Wnt* and *hedgehog* genes were first identified as genes controlling *Drosophila* development, and the canonical RAS pathway was identified as regulating vulval differentiation in nematodes and retina development in *Drosophila* (see Gilbert and Bolker 2001).

The notion that cancers are initiated in stem cells has further linked cancer to development and evo-devo (Lapidot et al. 1994; Krausova and Korinek 2014). The ability of certain tumors to form more readily in some organisms than others has been linked to molecules involved in cell-cell interactions during development (Tian et al. 2013), and the ability to metastasize has been similarly linked to the developmental phenomena of epithelial-to-mesenchymal transitions (Nieto 2013). Cancer and stem cell studies are also related to regeneration and aging, two areas in which evo-devo approaches have led to significant contributions (Rezza et al. 2014; Tabar and Studer 2014).

Finally, evo-devo also provides insights into the role of the environment in normal and abnormal development. For example, variation in fetal nutrition in mammals can lead to potentially adaptive phenotypes, as small bodies and slow metabolisms are thought to be favored in poor conditions (Bateson et al. 2004). Temperature alone is thought to determine sex in many reptile and fish species, and temperature also differentially affects male and female fitness (Charnov and Bull 1977; Warner and Shine 2008; Mitchell et al. 2013). Many taxa, including insects, amphibians, crustaceans, and plants, produce defenses in response to predator cues that are beneficial when predators are present, but costly when predators are absent (reviewed in Werner and Peacor 2003). Human development is also responsive to environmental conditions, and this environmental sensitivity renders us susceptible to environmental signals that may or may not be predictive of future environments. Responses to early life conditions are thought to be potentially adaptive, but the observation that early life conditions predispose humans to disease in late life—especially metabolic disease—suggests that the physiological settings achieved through developmental plasticity might be maladaptive if the environment changes too quickly (Gluckman and Hanson 2004; Gluckman et al. 2009).

Symbionts provide a second layer of environmental control over development (Gilbert and Epel 2009; McFall-Ngai et al. 2013). Some symbionts are essential for normal development. For example, the wasp *Asobara* will not form ovaries without signals from *Wolbachia* (Pannebakker et al. 2007), and mice and zebrafish do not form normal guts without symbiotic bacteria (Hooper et al. 2001; Stappenbeck et al. 2002; Rawls et al. 2004; Mazmanian et al. 2005). Colonization by developmentally critical symbionts is an entirely new research area that is likely to be essential to medicine. Recent studies of kwashiorkor, for instance, have shown that the protein deficiency underlying this disease only manifests when certain gut bacteria are present (Smith et al. 2013). The health repercussions of excluding symbionts from our bodies are also becoming clearer as we become increasingly hygienic. Rates of autoimmune disease are highest among people with the greatest sanitation practices. These practices eliminate helminthes (worm-like parasites) that are, evolutionarily, a normal part of our digestive ecology, and secrete molecules that down-regulate their hosts' immune systems (Bilbo et al. 2011). Remarkably, at least two autoimmune diseases (inflammatory bowel disease and multiple sclerosis) have been alleviated or cured in humans by reintroducing helminthes (Bilbo et al. 2011). These studies suggest that maintaining the health of the evolutionary partners that comprise our microbiome will be a major goal of human medicine.

## ECOLOGY

The fields of ecology and developmental biology have traditionally interacted very little, whereas the integration between ecology and evolutionary biology has been significant and productive in some contexts (e.g., evolutionary ecology, ecological genetics) but rather modest to non-existent in others (e.g., community and landscape ecology). The growth of evo-devo as a discipline has revealed novel opportunities to integrate ecological perspectives and concepts and, in the process, address questions of both fundamental importance and growing urgency across ecological disciplines. Below, we highlight two such areas.

### Niche construction, habitat engineering, and ecological inheritance

The preceding section highlighted our growing recognition of symbiosis as playing a critical role in defining developmental phenotypes across a wide range of organisms, and impeded symbiosis as being at the heart of many human diseases. Symbionts and hosts depend on each other to generate—through their development, metabolism and behavior—the proper

environment required for their own development. Viewed this way, symbiosis emerges as an especially important class of a much larger phenomenon—organisms' use of developmental and physiological processes to create environmental circumstances conducive for survival and reproduction, or *niche construction*.

Niche-construction theory represents a relatively recent effort to avoid false dichotomies that treat organisms as separate from their niches, and instead highlights that organisms actively construct and shape many aspects of their niches. For instance, the alteration of soil chemistry through metabolites, the construction of thermal environments through burrow building and the development of social environments through partner choice are all behavioral responses that shape an individual's niche and selective environment (Lewontin 1983; Odling-Smee 2010). By extension, an organism's phenotypic responses are not only end products of selection, but can, at the same time, constitute evolutionary processes that alter selective pressures. Because the modified components of the environment are products of organismal responses, they can also be viewed as extended phenotypes that are potentially heritable and can therefore evolve (i.e., ecological inheritance). The potential for niche construction to modify ecological and evolutionary dynamics is especially great in cases where niche construction occurs across generations; that is, where niche-modifying behaviors occurring in one generation affect the selective environments experienced by members of subsequent generations (Laland et al. 2001). Models incorporating niche construction provide strong evidence that niche construction can maintain genotypes that would otherwise be lost (Laland et al. 1996; Kerr et al. 1999; Laland et al. 1999, 2001; Silver and Di Paolo 2006; Creanza et al. 2012), significantly alter evolutionary dynamics (Laland et al. 1996, 1999, 2001; Kerr et al. 1999), facilitate the evolution of cooperative behavior, (Lehmann 2007, 2008; Van Dyken and Wade 2012), allow organisms to persist in otherwise inhospitable environmental conditions (Kylafis and Loreau 2008), and affect carrying capacities, species diversity and ecosystem robustness (Krakauer et al. 2009).

This complex exchange between individuals and their developmental environments is thought to be a common property of all organisms, and humans are no exception (e.g., Harden et al. 2008). However, even though it is clear that in many cases, niche construction modifies the ecological and evolutionary trajectory of traits, whether organisms are capable of eliciting niche constructing (or habitat engineering) behaviors in the first place, the potential influences of genetic variation in these abilities (Saltz and Nuzhdin 2014), and whether these activities will constrain or promote subsequent evolution, are largely open questions (Laland et al. 2014). The contemporary field of evo-devo is ideally situated to uncover general principles that determine the ecological prevalence and evolutionary outcomes of niche construction—indeed, any interactions between developmental systems and the ecological contexts in which they occur—due to its comparative examination of developmental mechanisms in a phylogenetic context.

## The ecology of a changing planet

The need for a better understanding of the interactions between ecological dynamics and developmental processes has never been more urgent, as rapidly increasing numbers of species are confronting swiftly changing ecological conditions, including global climate change, habitat alteration or destruction, and biological invasions. Whether populations can endure such speedy environmental transitions has been typically viewed as an ecological and evolutionary question; i.e., *do populations harbor enough standing genetic variation to adapt to rapid changes in their ecologies*? However, as we have become increasingly aware that the phenotypic variation necessary for survival is a developmental product of the interaction between genetic and environmental variation, we are also beginning to query a populations' ability to respond flexibly via developmental plasticity, species interactions (i.e., symbiosis) and niche construction. Answering these questions will be most directly achieved through the lens of evo-devo.

For example, during environmental transitions developmental plasticity can buy time for populations to evolve by mutation and recombination while keeping fitness stable. For instance, drier spring seasons in the Canadian Yukon have resulted in earlier production of white spruce cones, the primary food source for North American red squirrels. In response to this shift in resource availability, female squirrels have advanced their parturition dates by 18 days (without a loss in mean lifetime reproductive success) over only one decade, and much of this response has been due to phenotypic plasticity (reviewed in Reale et al. 2003; Reed et al. 2011). Likewise, a 47-year study of a Great Tit population suggested that plasticity in behavior allowed these birds to tightly adjust to a changing environment (specifically, increased temperatures) and maintain their fitness, although their current behavioral responses appear non-plastic (Charmantier et al. 2008). Indeed, subsequent to such initially plastic responses, if a population harbors genetic variation for plasticity, directional selection may favor induced extremes resulting in a population with reduced plasticity but a new mean phenotype (Lande 2009), a process termed genetic assimilation (West-Eberhard 2003). Even in situations where populations encountering these abrupt environmental changes have a small population size and therefore low potential for genetic variation in plasticity (reviewed in Ledon-Rettig et al. 2014), evo-devo approaches can shed light on an organism's ability to take advantage of epigenetic variation (an intrinsically developmental phenomenon), which in some instances might allow genetically depauperate populations to survive a wide variety of novel habitats (Richards et al. 2012). In short, the potential for a population to harbor genetic variation that might participate in

genotype-environment interactions (GxE) or to produce other epigenetic responses will depend on the evolutionary history and the developmental constraints of a given organism and population, falling again into the realm of questions best answered by the field of evo-devo.

At the same time, there is likely often a limit to how well plasticity can allow organisms to adjust to sudden or drastic environmental changes that might favor phenotypes beyond the range of those currently expressed in a population. Those organisms whose development is intimately connected with temperature (such as turtles, where temperature determines sexual phenotype) or those plants whose phenology is timed with the eclosion of their pollinators may be particularly susceptible to extinction (Rafferty et al. 2013). Unfortunately, the limits to adaptive plasticity in wild populations are not well understood (Snell-Rood et al. 2010). Empirical studies are needed that reveal what traits are likely to be constrained or plastic in response to environmental variation that mirrors contemporary global change. Similarly, niche construction currently lacks a framework for testing whether species' responses will sufficiently accommodate global environmental change. For instance, niche-constructing and symbiotic abilities help certain organisms (e.g., reef corals, kelp, mangroves, and sea grass) thrive in their typical environments, but the same properties might be considered liabilities if sudden environmental changes impact associated participants in their interdependent ecosystems. Evo-devo, with its focus on organisms as interacting and interdependent developmental systems, is the field from which a predictive framework could emerge.

As we are beginning to appreciate that environments, ecologies, and niches are constructed in part by organisms themselves, that selective environments experienced now are the product of organisms' choices and actions occurring in preceding generations, and that successful future development depends on the environmental legacies of development as it currently occurs, evo-devo offers empirical opportunities to elucidate the interdependencies of developmental processes and ecological conditions, and to predict their evolutionary outcomes. Such insights can only help to prioritize conservation efforts during a time of rapid environmental change.

## AGRICULTURE AND FOOD SECURITY

Domestication and agriculture have long provided important insights for understanding evolution by natural selection (Mathew 1831; Darwin 1859, 1868), and some of the most dramatic examples of rapid evolutionary change from physiology (e.g., herbicide and insecticide resistance) to morphology (e.g., teosinte to corn) come from agricultural contexts (Dermauw et al. 2013; Meyer and Purugganan 2013; Yu et al. 2013). Despite this long and productive exchange between plant and animal breeding and evolution, evo-devo has rarely been explicitly integrated into these research programs. Because of its central role in understanding how new phenotypes are generated, evo-devo is poised to become a powerful tool in agricultural research, an integration that is now more urgent than ever. By mid-century the world's population will reach nine billion (Conway and Wilson 2012). The challenges associated with providing a secure food supply for the global population are numerous, though few are likely as pressing as increasing agricultural productivity while decreasing environmental degradation. Yet, yields of many of the world major food crops have plateaued (Tester and Langridge 2010; de Bossoreille de Ribou et al. 2013; Grassini et al. 2013), suggesting an end to the "green revolution." Moreover, human induced changes to climate will require the increased use of land currently unsuitable for agriculture. The emerging interface between evo-devo and food security focuses on understanding how new phenotypes are produced, and how those phenotypes might be modified through changes in developmental properties. Historically, modification of phenotypes has been accomplished through selective breeding while taking advantage of standing variation, but evo-devo harnesses a new understanding of how variation is generated and expressed to suggest powerful new avenues of agricultural research. Future progress on multiple issues in crop and livestock improvement will thus benefit from the integration of evo-devo and agriculture, as discussed in more detail below.

Crop and livestock improvement, like all evolutionary processes, requires variation; a source of novel traits or trait combinations. During domestication, however, genetic variation is often reduced. Only a subset of the genes segregating in the progenitor populations is retained in crop varieties and livestock breeds (Godfray et al. 2010). Introduction of traits from wild relatives via conventional crosses and selective breeding is one method to introduce additional genetic variation. Transgenics is another potentially powerful approach, but most successful introductions of transgenically modified organisms in agriculture have involved the incorporation of only one or a few genes (Godfray et al. 2010) . However, it is likely that new phenotypes require the modification of suites of interacting genes and modification of developmental processes, a goal not yet achieved by transgenic approaches. Evo-devo studies provide the critical insight that agricultural breeds and varieties may harbor as yet "untapped" sources of potentially selectable phenotypic variation, including the reemergence of traits that appeared to have been lost during artificial selection. Rajakumar and Abouheif's (2014) review of "reversions," or the expression of ancestral traits in natural and agricultural populations of animals, suggests that such atavisms are common and these individuals are neither hopeless monsters nor freaks of nature. Rather, they are rich sources of raw materials for selection to act upon. This conclusion has important consequences for animal and plant breeding. Evo-devo can show how ancestral developmental features, such as large size, drought resistance,

etc. could be "released" developmentally from the genome and integrated into domestic stock through a process of genetic accommodation (West-Eberhard 2005; Braendle and Flatt 2006; Crispo 2007; Pfennig et al. 2010).

A related source of potential variation comes from studies of phenotypic "capacitors," such as chaperones like HSP90 (Tirosh et al. 2010; Ruden 2011; Takahashi 2013) that mask standing variation (Schlichting and Wund 2014). Stressors that exceed the buffering ability of these capacitors could release phenotypic variation for selection. For example, in a landmark study, Rutherford and Lindquist (1998) showed that mutant or pharmacologically impaired HSP90 releases a broad spectrum of novel morphological variants in lab and wild fruit fly populations, a subset of which could subsequently be selected to fixation. This demonstrates the potential of releasing cryptic variation when phenotypic capacitors are no longer able to maintain robustness of the developmental system, a phenomenon whose importance for the evolution of novel phenotypes has recently been powerfully demonstrated in natural cavefish populations (Rohner et al. 2013). Together, these examples show that improvements in productivity may therefore involve overcoming entrenched regularities in developmental interaction networks to generate new variation for selection to act upon (Hallgrimsson et al. 2009; Watson et al. 2014). Conversely, understanding how development is canalized (see section on *Mechanisms underlying developmental robustness*) could assist in the creation of crops and livestock that are more robust to impending environmental stresses.

Evo-devo also suggests that phenotypic variation can be generated via the interaction of domesticated plants and animals with microbes. The plants and animals that we consume interact with potential symbionts and pathogens, and the phenotypic outcome of interactions between hosts and microbes depends on the genomes and developmental potentials of all of the participants, as well as on the environmental context (Lau and Lennon 2011; Lundberg et al. 2012). For example, plants often rely on associated soil microbes for critical nutrients (e.g., fixed nitrogen), phytohormones that influence growth [e.g., ethylene; (Hardoim et al. 2008)], and protection from the elements (e.g., heat, salt and drought; (Rodriguez et al. 2008; Yang et al. 2009). Furthermore, *Brassica rapa* (cultivated as a source of cooking oil) grown in association with an experimentally simplified soil microbial community were far less fecund than controls and selection for aboveground biomass was much stronger in these treatments (Lau and Lennon 2011). Soil microbes may also be pathogenic, and recent studies of multiple *Arabidopsis thaliana* ecotypes show that the particular community of microbes that form beneficial relationships with plants vs. those that are excluded from the rhizosphere are specific to both plant genotype and soil characteristics (Bulgarelli et al. 2012; Lundberg et al. 2012). Plant pathogens can account for approximately 15 percent of yield losses worldwide (Dangl et al. 2013). Not only is this loss typically combatted with chemicals that could potentially damage surrounding ecosystems, much of this crop loss takes place after the freshwater required to grow the plants has been used, thereby compounding the environmental impact of crop disease. Understanding how plants and animals attract or repel certain microbes, and how these microbial communities in turn influence phenotypes across different host genotypes, soil types, and climate conditions could unleash novel sources of variation and thus improve global food security while at the same time reducing use of chemicals for the control of disease and nutrition.

Once new variants are produced, how do we predict which of these have the potential to contribute to enhanced productivity? Currently, successful introduction of new crops and livestock breeds relies on extensive field trials and evaluation of new variants in multiple conditions, often at great expense and resulting in substantial delays (Kalaitzandonakes et al. 2007). Because evo-devo ultimately seeks to understand how organisms "make themselves" (Coen 2000; Moczek 2012), evo-devo provides the critical link from genome to phenotype and even to performance that could greatly enhance our ability to predict how organisms will grow and produce in a wide range of biotic and abiotic environments without the delay imposed by extensive field trials and evaluation. Evo-devo has shown that phenotypes that have evolved repeatedly and independently in different populations and species often do so through similar developmental mechanisms (Gompel and Carroll 2003; Sucena et al. 2003; Shapiro et al. 2004, 2006; Protas et al. 2006; Rajakumar et al. 2012). This pattern of parallel evolution is nearly universal across the tree of life (Conway-Morris 2003; McGhee 2011; Wake et al. 2011). Developmental plasticity and highly conserved developmental pathways are both general properties of traits that promote parallel evolution through the recurrent appearance of phenotypic variants in a population when it encounters recurrent environmental cues (West-Eberhard 2003). The appearance of recurrent phenotypic variants that mimic repeatedly and independently evolved phenotypes are good candidates for enhancing productivity because they have been repeatedly "tested" in the evolution of a particular group. Such recurrent phenotypic variants have been environmentally induced or documented in several taxa, including butterflies (Nijhout 2003), ants (Rajakumar et al. 2012), toads (Ledon-Rettig et al. 2008), and plants (Darwin 1868). Thus, the key for successful artificial selection of recurrent variants is familiarity with both the extant and phylogenetic history of traits in the group of interest, insights most readily acquired through evo-devo approaches.

Enhanced agricultural productivity in the face of changing climate and land use will require integration across multiple fields of biological research. Agricultural research has a long history of integration with population genetics, and more recently, with developmental genetics. Evo-devo, with its fresh perspective on new sources of variation and ability to

understand how that variation might be expressed at the critical level of organismal phenotype and performance, should be an engaged and informed partner in agricultural research.

## SCIENCE EDUCATION

As biological research increasingly relies on and requires the integration of different concepts and methods, educators face new challenges in training students to become skilled practitioners and knowledgeable consumers of the "New Biology" (Council 2009). In 2011, four leading science agencies in the United States (NSF, AAAS, HHMI, and NIH) collaborated on a Vision and Change in Undergraduate Biology Education report (Woodin et al. 2010) that identifies five core concepts and six core competencies that provide a framework for improving undergraduate biology education in the US. The integrative nature and diversity of research approaches employed in evo-devo, combined with the subject matter itself, make it perfectly suited for achieving these goals (Love 2013). Here, we illustrate how principles and findings from evo-devo can be used to teach three core concepts and three core competencies identified in the report.

### Core concept: evolution

Development is the product of evolution and evolutionary change occurs in the context of developmental systems, yet evolution and development are usually taught separately. Connections between these two fields are often relegated to the end of a course or textbook. Incorporating evo-devo more fully into the standard biology curriculum will improve student understanding of evolutionary processes responsible for the diversity of organisms found in nature. Students who learn that evolution results from mutations generating phenotypic diversity and selection preferentially retaining the fittest genotypes can mistakenly think that all phenotypic possibilities have been explored and that species are optimally adapted to their surroundings. Evo-devo challenges this misconception by emphasizing the "arrival of the fittest" (Fontana 1993; Gilbert 2003) and showing how the existing developmental program can bias the range of phenotypes generated by new mutations (Brakefield 2011). A rich collection of case studies now exists demonstrating how phenotypic diversity has resulted from the duplication, rearrangement, and redeployment of existing developmental processes. Many of these studies involve species and traits that are interesting to students (Fenster et al. 2004; Cooper et al. 2012).

### Core concept: structure and function

Evo-devo aims to understand how changes in DNA sequence affecting gene expression and/or protein function ultimately lead to novel phenotypes. Studies of natural variation within a species or divergence between species complement developmental biology studies of mutations isolated in the laboratory. Evo-devo also fills a critical gap in linkage mapping and association studies by showing how associated genetic changes alter development to produce phenotypic variation. For example, many regulatory changes underlying biodiversity have been described that can be used to illustrate the power of regulatory changes to alter phenotypes in other (e.g., medical) contexts (Wray 2007; Wittkopp and Kalay 2011). Case studies from evo-devo remind students that structure-function relationships are often deeply conserved and shared among diverse organisms (Becker et al. 2000; Parsons and Albertson 2009; Gehring 2011), but also exhibit variation even within closely related species or populations (Romano and Wray 2003; Wessinger and Rausher 2012; Kijimoto et al. 2013).

### Core concept: systems

Evo-devo offers opportunities to teach systems biology–"quantitative understanding of complex biological processes through an elucidation of the dynamic interactions among components of a system at multiple functional scales" (Woodin et al. 2010)–by connecting genetic changes with their (i) molecular, developmental and phenotypic consequences, (ii) effects on fitness in particular ecological contexts, and (iii) longer-term evolutionary fate. A number of "metamodels" (Kopp 2009) have been dissected in sufficient detail to facilitate this type of teaching strategy. For example, the genetic, molecular, and developmental mechanisms underlying divergent pigmentation have been elucidated in flies, butterflies, mice, fish, and plants (Kronforst et al. 2012), as have the ecological interactions that cause changes in pigmentation to affect fitness (Wittkopp and Beldade 2009; Hubbard et al. 2010).

### Core competency: ability to use modeling and simulation

Computational models and simulations allow researchers to represent and explore complex processes by integrating findings from multiple studies, allowing the impact of different parameters to be explored *in silico*. In evo-devo, computational models of developmental processes have been used to test evolutionary hypotheses and predict morphological consequences of genomic changes to regulatory networks (Ingolia 2004; Salazar-Ciudad and Jernvall 2010). For example, a model of inflorescence development in plants suggested that certain phenotypes are likely not found in nature because of developmental constraints and predicted associations between inflorescence shape, life history, and environmental conditions that are indeed found among natural populations (Prusinkiewicz et al. 2007). Students can learn to manipulate these models in computer labs and make their own predictions about

development and evolution, similar to the pedagogical use of models from population genetics and phylogenetics.

### Core competency: ability to tap into the interdisciplinary nature of science

Evo-devo began with the integration of evolution and development as its core aim and put special emphasis on comparative studies of development. Contemporary evo-devo retains this perspective, but also incorporates theory, methods, and data from fields such as paleontology (Shubin et al. 2009), population genetics (Jones et al. 2012), ecology (Gilbert and Epel 2009) neurobiology (Weber et al. 2013), quantitative genetics (Rieseberg et al. 2002; Wills et al. 2010), microbiology (Moran et al. 2008), molecular biology (Airoldi et al. 2010), molecular ecology (Lexer et al. 2003), phylogenetics (Minelli 2009), and genomics (Richards et al. 2012). Most college biology courses focus on a single discipline, leaving students to integrate information from different approaches on their own (if at all). In contrast, evo-devo is inherently interdisciplinary (Love 2013); it demonstrates how information can be shared and interpreted across disciplinary boundaries in a variety of ways. For example, interdisciplinarity can be taught by focusing on a single meta-model (Kopp 2009) and examining it from multiple perspectives: classical and quantitative genetics can be used to identify the genetic changes underlying a divergent phenotype, molecular and experimental methods of developmental biology can be used to determine how the identified genetic changes impact the phenotype, and ecological and evolutionary theory can be used to examine the impact of the phenotypic change on the species of interest.

### Core competency: ability to communicate and collaborate with other disciplines

The interdisciplinary nature of evo-devo naturally fosters the ability to communicate and collaborate. This core competency can be taught by having students work in teams to explore the evolution and development of a particular trait. For example, each student can be assigned a different role in a hypothetical evo-devo research team (geneticist, developmental biologist, population geneticist, ecologist, paleontologist, or phylogeneticist) and asked to find information from their disciplinary vantage point, working with their peers to assess how the different types of information fit together. Such an activity would reflect the reality of evo-devo research in which interdisciplinary projects are advanced despite individual researchers having primary training in only one or two disciplines. Students would quickly learn that making the most of everyone's individual skills and perspectives requires the ability to communicate clearly by translating key terminology into new domains and finding ways to explain important technical issues that are often overlooked when traversing disciplinary boundaries.

In summary, evo-devo provides an outstanding platform for teaching biology because it integrates multiple core concepts and provides opportunities to develop core competencies. At the same time, it offers powerful exemplars of how escaping programmatic boundaries and integrating data from diverse disciplines results in novel and transformative discoveries.

## EVOLUTIONARY DEVELOPMENTAL BIOLOGY ITSELF

Evo-devo in the 21st century is encountering its own frontiers in a number of ways. Here we highlight three of these areas. First, the search for deep homologies and an understanding of the nature of evolutionary constraints, whether at the level of body plans, gene families, or cell types, has been limited in large part by sparse taxon sampling. For example, non-eudicots in plants, and most protostomes in animals, have been relatively understudied at the cellular, developmental and genomic levels. Evo-devo has partly inherited this bias from developmental biology and molecular genetics, which had cultivated a limited number of model organisms of exceptional experimental accessibility. Progress towards correcting this bias, however, is underway; in the recent past, research in evo-devo has added an impressive number and diversity of increasingly accessible emerging model systems to the taxonomic portfolio of biologists. At the same time, advances in next-generation sequencing have made genomic and transcriptomic data generation possible for nearly any organism of interest, and the taxonomically widespread utility of reliable gene function assays and genome editing tools have leveled the experimental playing field considerably, permitting increased linkage between sequence, gene expression and function over an increasingly wider taxonomic range. These developments position 21st century evo-devo to facilitate a increasingly deeper and more comprehensive understanding of how—and why—developmental evolution on our planet has unfolded the way it has.

A second related problem is to understand exactly what forces shape phenotypic variation in natural populations, and the mechanisms generating organism-environment matching, or adaptation. Traditional evolutionary biology has emphasized natural selection as the primary mechanism by which adaptations can evolve, and evo-devo has provided many examples of how variations in specific developmental mechanisms can give rise to phenotypes that we believe to be adaptive. However, precisely how these specific morphological changes lead to explicit fitness advantages is much less well understood. Research in evo-devo has made clear that the nature of development biases phenotypic variation, and does so through reciprocal interaction with ecological conditions, e.g., through the processes of developmental plasticity and niche construction (Moczek 2015). Exactly how natural selection,

developmental bias, and the condition-responsive nature of development interact to shape organismal variation is a wide open question, but one that evo-devo is well suited to address due to its inherently interdisciplinary nature and explicitly phylogenetic approach.

From this follows a third major challenge, not just to evo-devo, but to the life sciences of the 21st century as a whole: the problem of emergent properties and predictability. Specifically, we need to understand the emergence, dynamics and interaction of evolutionarily conserved modules, how these modules interact to produce emergent properties in developmental networks, and how these networks result in phenotypic outcomes in specific environments through the process of evolution. This challenge will require both a systems-level integration of information and a unification of central concepts across the broadest swath of biological levels, undertakings that evo-devo is uniquely poised to execute. As modern approaches are extended to the 20 million non-model organisms, meeting this challenge will also require an integration of meaningful computational methods of analysis. A bioinformatics infrastructure that could unite and integrate genetic, developmental, phenotypic, biodiversity, environmental, and phylogenetic data is still in its infancy, but evo-devo thinking is its core and guide.

## CONCLUSIONS

The tools, concepts, and ways of thinking that have been formulated and deployed by evolutionary developmental biologists are providing powerful new approaches to resolve long-standing questions across diverse biological disciplines. Beyond advancing biological sciences as a whole, results and insights generated through the application of evo-devo practices have the potential to inform policy decisions as well as to enrich and illuminate science education. Evo-devo as a discipline has grown tremendously in recent decades and established interfaces with diverse disciplines to reach its current integrative state. We expect this transformation to escalate as evo-devo extends into still more areas, and through its insights further transforms disciplines with which it has already formed longstanding relations.

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