PLASTICITY, COMPLEXITY, AND THE INDIVIDUAL

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INTRODUCTION

The first half of the 20th century was a pivotal time for biology. The different branches of evolutionary biology, from genetics to paleontology, operated independently, each with its own debates and guiding theories. A major shift started in the 1930s, when theoretical and empirical work in population genetics (1) reconciled Mendelian inheritance with natural selection, (2) demonstrated that microevolution and macroevolution were compatible, and (3) elevated Darwin’s views of descent with modification and evolution by natural selection as unifying theories in biology (Mayr & Provine 1998). These achievements, now referred to as the \textit{Modern Synthesis} (Mayr & Provine 1998), enabled researchers to delineate a set of principles that could explain variation in genetic and phenotypic patterns over space and time. For example, we can understand the maintenance and spread of selfish genetic elements within the genome (e.g., transposable elements) or selfish individuals in a population (e.g., cheaters) using the same conceptual framework and principles of evolution by natural selection. Nevertheless, the \textit{Modern Synthesis}, in its original conception, was limited: its application and appeal were largely limited to branches of biology interested in population-level processes. While there were attempts to incorporate a role for individual development and physiology into this broader evolutionary synthesis by Goldschmidt (1940), Schmalhausen (1949), and Waddington (1942), such efforts remained
outside the focus of mainstream evolutionary biology. As a result, the Modern Synthesis left out areas of biology concerned with the structure and function of individual organisms, such as physiology, development, functional morphology, neuroscience, and behavior (Gottlieb 2001). These organismal branches recognized and embraced evolutionary concepts such as homology in comparative studies (Hall 2012) or how “ontogeny recapitulated phylogeny” (Kalinka & Tomancak 2012), but they largely operated outside an evolutionary framework when studying how organisms work today. Subsequently, much of biology below the level of individuals came to favor reductionism, assuming that greater deconstruction would explain best how organisms, tissues, and cells work (Bartholomew 1986; Strange 2005).

Today, however, biology finds the barriers between fields breaking down; there is an increasing integration of evolutionary principles into organismal biology (Carroll 2005; Jablonka & Lamb 2005; Harrison et al. 2012; Nesse et al. 2010; Perlman 2013; Westneat & Fox 2012), a growing appreciation that organismal function might inform evolutionary theory (Schlichting & Pigliucci 1998; Bell 2009; Flatt & Heyland 2011), and a desire to understand how complex integrated systems, such as whole organisms, function and evolve (Wagner & Altenberg 1996; Stern 2010; Strange 2005; Martin et al. 2011; Noble 2013).

The next few years may therefore become another pivotal time for biology, as technical and mathematical advances are diffusing shared approaches across biological levels of organization. Moreover, new, extended syntheses are emerging that are truly integrative in their views on interactions among environments, genomes, and phenotypes (e.g., Schlichting & Pigliucci 1998; West-Eberhard 2003; Jablonka & Lamb 2005; Davidson 2001; Pigliucci & Muller 2010). Whereas the Modern Synthesis simplified biological processes by developing a general theory grounded in mathematical models, these new approaches are playing out against the backdrop of rapid progress toward understanding the mechanisms underlying the complexity of life. In the process, we are faced with what at first glance appears as an overwhelming degree of information and contingency. Our goal here is to argue that as we begin to open the black box linking genotypes, phenotypes, and their natural environments, an evolutionary perspective of how whole organisms function is needed. In doing so, mechanistic studies of form and function will be infused and guided by evolutionary theory, evolutionary biology will incorporate an understanding of how underlying mechanisms constrain or facilitate certain ecological and evolutionary outcomes, and collectively biologists working across scales will be motivated by a shared perspective that promotes developing and testing general theory.

We feel that these goals toward an integrative organismal biology will be served best by elevating the roles of individuals in biology. Already, there is a strong tradition of research on the structure and function across levels of organization (see also Wake 2008; Satterlie et al. 2009; Mykles et al. 2010; Noble 2013). But only recently has this work started to become firmly grounded in evolutionary theory and in natural (as opposed to laboratory) contexts. In this chapter, we focus on two themes that reveal the importance of understanding individuals: (1) the concept of phenotypic plasticity, or the capacity for a given genotype to produce different phenotypes in response to different environments and (2) the concepts of complexity and integration, or how suites of interacting traits across levels of organization respond to, and evolve in response to, environmental variation. Below, we first provide a brief history of progress toward an integrative organismal biology. We then review why the concepts of plasticity, complexity, and integration have such unifying power. We end with a case study of how a focus on understanding mechanisms within individuals can influence biology across scales.
Conceputal unification occurs when disciplines come to share underlying theories and questions but use different approaches. The promise of unification is that it will reveal new insights not achievable otherwise. Conceptual unification in biology remains a work in progress, and a key barrier has been the division between wanting to understand *how* organisms work versus *why* they work one way as opposed to another (e.g., Mayr 1961; Orians 1962; Dobzhansky 1964). Mayr (1961) referred explicitly to how (functional biology) vs why (evolutionary biology) as complementary but not alternative explanations for pattern and process. In practice, asking *how* biological systems work lends to reductionism because we often assume (at least implicitly) that insight stems from decomposing wholes into parts. In contrast, evolutionary biology is based on a set of conditions; the presence of heritable variation, the historical and contemporary processes generating and acting upon that variation, and the outcomes and patterns of these processes. These conditions were first fully articulated by Darwin (1859) without any knowledge of DNA or a mechanistic understanding of how organisms were built, and they eventually became codified in the population genetic models developed during the Modern Synthesis. Yet, we now are rapidly moving into an era where the divide between functional and evolutionary biology is eroding.

Evolutionary theory provides context and explanations for patterns that functional biology cannot. For example, understanding the details of transcription and translation does not tell us why genes and proteins are conserved across related taxa, or why they predictably change in response to certain environmental pressures. Similarly, a functional biologist can study the biomechanics of how bill size influences the ability to crush a seed, but an evolutionary biologist is more likely to explain why populations of birds on different islands have larger or smaller bills. Yet, there is a desperate need for unification – because the power of functional or evolutionary biology to explain biological phenomenon is limited when they operate alone. Evolutionary theory’s ability to predict how a given population will respond to natural selection is often limited, because genotypes and phenotypes are generally black boxes, as are the developmental and physiological pathways that translate genotypes into phenotypes. Such limitations are pervasive in optimality and game theory models, where the constraints on the response to selection are simply inferred from deviations from a predicted optimum (Parker & Maynard-Smith 1990). Indeed, many evolutionary biologists would argue that a mechanistic understanding is not needed to predict evolutionary outcomes because, over time, natural selection will find optimal solutions. By contrast, others argue we need mechanism if we are to understand the trade-offs that constrain responses to selection. These constraints may be genetic in the form of pleiotropic relationships, physiological or developmental in the form allocation trade-offs between traits competing for the same pool of resources, or functional when selection on one trait or function negatively impacts another. Mechanism therefore provides insight into why one optimal solution rises to the top, and is something that optimality approaches are unable to do. For example, in their review of the regulatory mechanisms underlying polyphenisms, Zera and Brisson (Chapter 5, this volume) demonstrate how the genetic and endocrine basis of different phenotypes act via developmental modules to constrain or bias the evolution of phenotypes. Similarly, an understanding of the physiological trade-offs associated with tolerance to different environmental conditions can predict where a species lives far more effectively than a strictly ecological approach (Chapter 18, this volume). Within this framework, unification acknowledges that there is a deep reciprocity: how can inform why, and why can inform how.
A skeptic may ask: why should functional biology be integrative? Can’t it advance on its own, outside the umbrella of evolution? We feel that, ultimately, progress will be slower in nonevolutionary strands of functional biology. First, we would remind functional biologists of Dobzhansky’s (1964, 1973) dictum that “nothing in Biology makes sense except in the light of evolution.” Indeed, evolutionary theory is the only accepted unifying framework for organizing and understanding the hierarchy of life. Second, if we accept descent with modification, and all the genetic, developmental, and functional constraints that go with it, then we must recognize that even reductionist approaches to function are not divorced from the broader evolutionary context focusing on the unity of life (Hochachka & Somero 2002; Sharan et al. 2005; Carroll 2005; Gerhart & Kirschner 2007). For example, it is this evolutionary unity or conservation that serves as a key justification for using model organisms to infer general function. Indeed, most biomedical research uses model organisms as diverse as bacteria, yeast, plants, nematodes, flies, fish, and mice to better understand and improve human health precisely because all the taxa share many genes and proteins by virtue of their evolutionary history. However, despite such conservation, it is increasingly recognized that the same genes and proteins have been coopted over time to perform diverse functions. Thus, understanding the mechanism at the molecular and cellular level ultimately depends on how past selective pressures and phylogenetic history have shaped the organismal context and systems in which these processes are embedded.

A skeptic might also ask, conversely, why evolutionary biology should pay attention to mechanism, as prominent scientists have recently done (see Flatt & Heyland 2011: chapter 28 exchange with Stearns). We answer that organisms are the conduits through which genes and their products interact with each other and with their environments. Thus, knowledge of mechanism allows evolutionary theory to move beyond models of how selection acts on variation among “genotypes,” to models of how selection acts on pathways, networks, and interactions (e.g., Proulx et al. 2005). Indeed, we now know that the genotype-phenotype map, and selection’s ability to act on particular pathways, is significantly more complicated than either classic Mendelian genetics or the central dogma of molecular biology have led us to believe. In a real sense, organisms are emergent Gordian knots of complexity, all tied up by pleiotropic linkages and trade-offs that cascade in unexpected ways and at different levels of organization in response to their environments. Such integrative complexity requires thinking about evolutionary theory in a way that explicitly acknowledges the integrated character of organisms and that takes mechanism seriously. This rethinking is already underway, with progress in areas of evolutionary theory as diverse as stasis, evolvability, constraints, and the origins of complex traits (e.g., Moran 1994; Wagner & Altenberg 1996; Kirschner & Gerhart 1998; West-Eberhard 2003; Hansen & Houle 2004; Hansen 2006). We present detailed examples of these ideas below and other authors present similar arguments throughout the book (Chapters 2, 6, & 9, this volume).

INTEGRATIVE ORGANISMAL BIOLOGY: PROGRESS TO DATE

Despite the practical and philosophical barriers in place, the conceptual divide between functional and evolutionary biology has varied over time. During the 1950s and 1960s, the biological sciences started transitioning from the organism-based disciplines of zoology and botany to more specialized groupings of cellular and molecular biology, physiology, and ecology and evolution (Huey & Bennett 2008). Increasing knowledge of biological complexity also caused greater specialization within subdisciplines, as fields like animal physiology split into the ever more specialized topics such as endocrinology, neurobiology,
INTEGRATIVE ORGANISMAL BIOLOGY: PROGRESS TO DATE

and functional morphology (Huey & Bennett 2008). Although prominent physiologists, like George Bartholomew (1958, 1966), and evolutionary biologists, like Theodosius Dobzhansky (1964), argued against the gathering reductionism, these views found little traction. Serious erosion of the divide between functional and evolutionary biology started in the early 1980s when Arnold (1983) proposed the morphology-performance-fitness framework. This framework introduced physiologists and functional morphologists to quantitative genetics and provided the conceptual and statistical tools to study how selection acts upon variation in performance and fitness. Arnold’s (1983) framework also catalyzed the development of evolutionary physiology (Garland & Carter 1994), and enabled physiologists and evolutionary biologists to interact productively (Kingsolver & Huey 2003). Building from the foundations laid out by Bartholomew (1964), Huey and Pianka (1981) and Huey and Bennett (1986) introduced approaches that explicitly dealt with the problem of proper phylogenetic inertia in comparative studies – approaches that are now standard in comparative physiology (Garland et al. 2005). Although the importance of these evolutionary ideas was openly debated among physiologists (largely due to confusion over what the implications were for the merging of disciplines – see commentaries in Tracy et al. 1982), the inferential benefits of these approaches started to take hold. One prime example is the landmark 1987 publication New Directions in Ecological Physiology edited by Martin Feder, Al Bennett, Warren Burggren, and Ray Huey, which emphasized the importance of interindividual and genetic variation in physiological traits as the raw material for evolution – not just a source of noise (Bennett 1987; Koehn 1987; Arnold 1987). At the same time, Richard Sibly and Peter Calow published Physiological Ecology of Animals: An Evolutionary Approach (1986) and Peter Calow edited Evolutionary Physiological Ecology (1987), which were both early attempts to link physiological mechanisms to classic questions on trade-offs and life history evolution – a topic that has grown into a major area of research (see Flatt & Heyland 2011; Chapters 10 & 13, this volume). More recently, physiologists and ecologists have continued along the path of integration, as a way to understand the mechanisms underlying large-scale ecological patterns (Spicer & Gaston 1999; Chown & Gaston 2008; Lessels 2008; Williams 2008; Gaston et al. 2009; Chapter 17, this volume).

A second wave of unification between evolutionary and functional biology occurred throughout the 1990s as new molecular tools appeared. Perhaps the most prominent example was evolutionary developmental biology, or evo-devo (Goodman & Coughlin 2000; Gilbert 2003). Developmental biology was a vibrant but fairly independent field for many years (Gottlieb 2001), but in this period it began to connect with mainstream evolutionary biology, in the process revisiting early attempts at unification by Goldschmidt, Schmalhausen, and Waddington. Its first major contribution was to show that diverse body plans, across phyla, stemmed from conserved patterns of gene expression (Gilbert 2003; Carroll 2005). Since then, the incorporation of evolutionary developmental biology has expanded rapidly (Stern 2010), and can be seen in the emerging fields of ecological development (eco-devo), evolutionary medicine, and mechanistic life history theory (e.g., Gilbert & Epel 2009; Nesse et al. 2010; Flatt & Heyland 2011). Still, evolutionary thinking in other branches of functional biology remains limited to a tiny fraction of a large field of researchers.

Today, these subdisciplines, functional and evolutionary alike, are converging around two themes. The first centers on phenotypic plasticity, which attempts to understand how environmental variation interacts with genetic variation to shape the development and function of phenotypes. Plasticity has a long history in evolutionary biology and is increasingly viewed as an interesting problem in organismal biology. The second theme moves beyond
reductionism and studying traits in isolation, and instead emphasizes the complexity and integration of traits. The implications of such integration, especially how it manifests mechanistically, warrant attention at multiple levels.

PHENOTYPIC PLASTICITY: THE LINK BETWEEN INDIVIDUALS, ENVIRONMENTS, AND EVOLUTION

A Brief History and Review

That phenotypes emerge from interactions between genotypes and their environments has long been recognized, but it was the work of Woltereck (1909), on parthenogenic lines of *Daphnia* and *Hyalodaphnia*, that first clearly revealed the distinction between genetic and environmental sources of phenotypic variation. Woltereck (1909) introduced the concept of the reaction norm, plotting how individuals from the same genetic background changed predictably in response to environmental cues. Reaction norms are visual representations of phenotypic plasticity, and they typically are depicted as continuous linear or nonlinear functions (Schlichting & Pigliucci 1998; Chapter 3, this volume). While the concept of reaction norms is widely used today, the interactions between genes, phenotypes, and the environment was a major source of confusion and controversy at the turn of the century (Schlichting & Pigliucci 1998). Indeed, the founders of the Modern Synthesis struggled with or simply ignored plasticity because they considered environmentally induced variation as nonheritable and thus irrelevant to evolutionary processes (Schlichting & Pigliucci 1998; Pigliucci 2001). Yet, other evolutionary biologists had a different perspective on such environmentally induced variation, as there was no denying that environments could significantly alter patterns of development, physiology, and behavior (e.g., Baldwin 1896; Goldschmidt 1940; Waddington 1942, 1953; Schmalhausen 1949). However, their “alternative synthesis” did not resonate with their contemporaries (Schlichting & Pigliucci 1998).

Today, environmentally induced variation – in the form of developmental plasticity, physiological flexibility, epigenetic inheritance, hidden reaction norms and release of cryptic genetic variation – is increasingly thought to influence adaptive evolution (e.g., Baldwin 1896; Waddington 1942, 1953; Bradshaw 1965; Schlichting & Pigliucci 1998; Pigliucci 2001; West-Eberhard 2003; Jablonka & Lamb 2005; Ghalambor et al. 2007; Piersma & van Gils 2011). This renaissance is a reflection both of plasticity’s ecological and evolutionary roles, but also its ability to link processes at the individual and subindividual levels (i.e., gene expression) to processes at the population level (i.e., the relative fitness of different phenotypes and the strength of selection). Indeed, developmental, physiological, and behavioral plasticity can facilitate adaptive evolution by helping populations (1) move between adaptive peaks without incurring the cost of selection, and (2) persist in new environments until an opportunity arises for directional selection to act on new mutations (e.g., Robinson & Dukas 1999; Price et al. 2003; Ghalambor et al. 2007). Conversely, adaptive plasticity can also constrain adaptation by masking heritable genetic variation and weakening the strength of selection (e.g., Huey et al. 2003; Borenstein et al. 2006; Paenke et al. 2007). Environments do not always induce beneficial changes in phenotypes; particularly in cases where the environment is novel or stressful, plastic changes can be nonadaptive (Ghalambor et al. 2007). The role of nonadaptive plasticity in evolution has received even less attention but likely results in either extinction or strong directional selection in poor or novel environments (Falconer 1990; Grether 2005; Ghalambor et al. 2007; Conover et al. 2009).
What role do organismal biologists have in answering evolutionary questions about phenotypic plasticity? An integral one! Studies of development, physiology, and behavior are often mechanistic studies of phenotypic plasticity, whether or not researchers cast their research in that context. Understanding organismal responses to temperature, nutrients, disease, or any other aspect of the environment, external or internal, can be studied within a phenotypic plasticity framework. As such, empirical studies of physiology (e.g., Lee & Peterson 2003; Lee et al. 2003; McCairns & Bernatchez 2010; Handelsman et al. 2013), morphology (e.g., Chapman et al. 2000; Losos et al. 2000; Wund et al. 2008; Badyaev 2009), development (Badyaev & Landeen 2007; Young & Badyaev 2007), and behavior (Yeh & Price 2004; Losos et al. 2006) are already playing an important role in testing the ecological and evolutionary importance of phenotypic plasticity in natural populations.

**Plasticity 101: A Q&A Session**

Despite straddling the environment-organism interface, phenotypic plasticity remains a source of confusion (Pigliucci 2001), primarily because unlike classical evolutionary theory, the dual roles played by the environment – as the source generating phenotypic variation and the filter through which selection sorts this variation (West-Eberhard 2003). Because plasticity is so integral to the role of the individual in evolutionary biology and as the bridge across scales of biology, we attempt to clarify some of the confusion by answering commonly raised questions.

*If I don’t study genotypes, can I still study phenotypic plasticity? – Yes.* Phenotypic plasticity has been classically defined as the capacity of a given genotype to produce different phenotypes in response to changes in the environment. However, in practice the “genotype” can be any distinct grouping (e.g., a set of clones, recombinant inbred lines, a group of full or half-siblings, different individuals, genetically differentiated populations, or even species) about which some genetic relationships exist. Obviously the more one can control and replicate the genetic background of the groups being compared, the more strongly one can infer how the same set of genes responds to environmental variation. For laboratory-based studies, this is most easily achieved by generating genetic groups through controlled crosses (e.g., by considering siblings to be a genetic group). In natural populations, genetic control can be incorporated into studies via the use of pedigrees, or by repeatedly measuring the same individual (see Chapter 2, this volume). Repeated measurements of flexible traits in the same individual over time or space is also referred to as phenotypic flexibility (Piersma & van Gils 2011), as a means of distinguishing it from nonreversible developmental plasticity.

*Is all environmentally induced variation phenotypic plasticity? – No.* Phenotypic plasticity represents a repeatable phenotypic response to a given environmental cue by a genetic group. Plasticity can therefore be distinguished from “developmental noise” or other non-repeatable and unpredictable responses to the environment (Woods 2014).

*What do I measure if I’m studying plasticity? – Any* phenotypic trait of the same genetic group in more than one environment. At the suborganismal level, plasticity can be measured by quantifying changes in gene expression (e.g., Aubin-Horth & Renn 2009), patterns of alternative splicing (e.g., Marden 2008) or of protein synthesis (e.g., Tomanek & Somero 2000), or at whole-individual changes in metabolic rates, stress responses, growth rates, or immune profiles (e.g., Kingsolver & Huey 1998; Handelsman et al. 2013; Chapters 11, 12, & 14, this volume), morphology (e.g., Kingsolver & Huey 1998; Torres-Dowdall et al. 2012), life history orientation (Stearns & Koella 1986; Chapter 2, this volume), or behavior (Ghalambor et al. 2010; Chapter 4, this volume). Indeed, the list of phenotypes is limited only by our ability to measure them.
Can plasticity evolve in response to natural selection? – Yes. Plasticity is both an attribute of a trait (i.e., how its expression changes in response to different environments), and a trait in and of itself, therefore capable of evolving. Furthermore, selection experiments have shown that plasticity can evolve independently of trait means (Scheiner & Lyman 1991; Murren et al. 2014), and that such evolutionary changes can be rapid (e.g., Handelsman et al. 2013). Indeed, genetic groups commonly respond to environmental variation in different ways. Such variation is referred to as a genotype × environment interaction (G × E), and it reflects the amount of genetic variation for plasticity.

Collectively, the many facets of phenotypic plasticity give it profound ecological and evolutionary significance. Specifically, when we consider the dual role of the environment – as a source of plasticity within generations but a source of natural selection between generations – we find common ground between functional and evolutionary biology.

Same Wine, New Bottle: Shifting to a Reaction Norm Perspective

Functional biologists often embrace the influence of environmental variation on the traits they measure, or try to eliminate it outright through carefully controlled experiments. For example, physiologists have long been interested in the influence of temperature on traits ranging from metabolism to running speed to rates of enzyme-mediated reactions, and they quantify such changes in ways that are comparable across species or populations (e.g., Q_{10}). However, by considering such responses as thermal reaction norms (Angilletta 2009), comparisons between groups focus on changes in slopes and shapes of functions (see also Chapter 3, this volume). Here we illustrate the usefulness of reaction norms across a range of contexts. We begin with a hypothetical example that considers how the phenotypes of three populations raised in a common garden change as a function of three environmental treatments. In this example the trait of interest could be any phenotype, and the treatment could be any environmental condition. A traditional way of representing these results is shown in Figure 1.1a, where we observe that populations differ in their trait values and that the environment influences the expression of the trait. Now consider the same data represented as reaction norms (Figure 1.1b). In Figure 1.1b, we see that whereas all three populations increase their trait values in response to increases in the environmental treatment, population 3 is most plastic (i.e., has the steepest slope). Divergence in the slope of reaction norms measured under common garden conditions on populations of known relatedness provides evidence that plasticity has evolved. Models for the evolution of plasticity predict that the amount of plasticity should increase when populations are exposed to predictably more variable environments (e.g., Levins 1968; Moran 1992). Thus, if the focal trait was metabolic rate and the treatment was temperature, one testable hypothesis is that population 3 comes from a more variable thermal environment (see also Angilletta 2009). A final approach is to visualize variation within each population (Figure 1.1c). Here, we see a new pattern within the data; population 2 has less genetic variation than the others (Figure 1.1c). The major conclusion would be that population 2 lacks significant genetic variation (G × E), and thus would evolve more slowly in response to selection.

Where will Reaction Norm Thinking Lead?

In the more integrative approach we envision, functional biologists will play key roles in describing the actual mechanisms that underlie plasticity (Cossins et al. 2006). Ultimately, integrative organismal biology will likely become the study of individual plasticity in gene expression, physiology, development, endocrinology, neuroscience, behavior, and other organismal properties, but in the context of evolutionary theory. Although that
shift is already underway, the real synthesis will come into view when evolutionary theory is extended to incorporate mechanisms at multiple biological levels. For example, understanding mechanism may lead to models that can predict when plasticity should and should not evolve, which traits are more likely to be plastic, or how plasticity in multiple complex interacting traits influences fitness (e.g., Ricklefs & Wikelski 2002; Hau 2007; Marden 2008; McGlothlin & Ketterson 2008; Ketterson et al. 2009; Martin et al. 2011; Chapter 5, this volume).

THE PROBLEM OF COMPLEXITY

Toward the end of the 17th century, when van Leeuwenhoek developed microscope lenses that allowed him to see microorganisms and other small objects, the apparent complexity of the living world suddenly increased. Since then, our tools and ability to describe and study the building blocks of life have only improved, as has their apparent complexity. Complex biological systems pose a dilemma for evolutionary theory. Although it is obvious that organisms adapt, how variable, viable phenotypes develop from and evolve a diversity of redundant pathways and levels of interacting systems is exceedingly difficult to understand. Nevertheless, organismal and evolutionary biology are converging on a shared theory for mapping genomes to phenotypes and for explaining the evolvability of complex systems.
A Brief History of Biological Complexity

The founders of the \textit{Modern Synthesis} knew that organisms had many genes, and that interactions and correlations among genes could cause patterns of inheritance and trait values to deviate from what simple additive models would predict (e.g., Moore & Williams 2005; Stearns 2010). The founders also knew that organismal phenotypes often evolved as integrated sets of covarying traits rather than as single traits in isolation (Huxley 1932). However, the theory, quantitative descriptions, and mechanisms connecting genetic architecture to integrated “multivariate” phenotypes did not take shape until the late 1950s. Olson and Miller’s (1958) influential book, \textit{Morphological Integration}, put forward an explicitly multivariate statistical approach to the study of traits; it also emphasized a holistic view of organismal structure and evolution that considered the genetic, developmental, and functional connections within individuals. They (Olson & Miller 1958) described a method that created groups of traits that were biologically and functionally integrated and could be distinguished using statistical correlations (i.e., pF-groups), and quantitatively compared across species. One of their key insights was that patterns of morphological integration could constrain evolutionary trajectories; because certain traits had to be inherited as groups, organismal functions could not be optimized. They argued that functionally or developmentally related traits would also be more likely to be controlled by the same genes to prevent the breakup of covarying traits. For example, crushing and grinding food requires intimate, mechanistic support from other traits, such as teeth, jawbones, and muscles. Olson and Miller’s (1958) point was that evolutionary change in tooth length could not happen without related changes in jaw and muscle traits. Their ideas are conceptual cousins to more modern gene and physiological regulatory networks that coordinate gene expression throughout development (Davidson 2001; Cohen \textit{et al.} 2012) and concepts like symmorphosis (Weibel \textit{et al.} 1991), which seek to understand how multiple parts of a pathway interact to perform a function.

Around the same time, plant biologists were also investigating trait integration. Clausen and Hiesey (1960) were interested in how trait correlations changed among ecotypes, and they conducted breeding experiments to investigate the mechanisms of inheritance underlying what they called “character coherence.” They were particularly concerned with how selection acted on constellations of genes and how the tension between character coherence and variation was resolved in natural populations. In a similar vein, Berg (1960) resurrected the concept of “correlation pleiades” to describe patterns of modularity and trait correlations within flowers, and argued for the importance of correlational selection favoring the evolution of integrated floral traits. Today, patterns of trait correlation, and the ways in which selection shapes them, are commonly studied in a quantitative genetic framework (Lande 1979; Hansen 2006).

Collectively, these early ideas laid the foundation for modern views of how interactions of suborganismal factors (e.g., genes, hormones, morphologies) contribute to phenotypic integration and modularity at the individual level and among-individual variation at the population level (e.g., Lande 1979; Cheverud 1982, 1996; Mezey \textit{et al.} 2000; Wagner & Altenberg 1996; Wagner \textit{et al.} 2007; Klingenberg 2008; Martin \textit{et al.} 2011; Wagner & Zhang 2011). This new directive of how genes map to phenotypes, however, poses an evolutionary dilemma: if traits are developmentally and functionally integrated, they will need to evolve as genetically integrated units, or in other words be under strong pleiotropic control. If correlational selection favors integration to maintain function, how do new beneficial mutations and selection act on variation without compromising performance? Breaking up tightly linked groups seems highly unlikely. These
issues fall under the umbrella of “evolvability,” a concept that comprises how complex traits arise, how selection acts on variation within complex systems, and how constraints and trade-offs bias evolution.

Wagner and Altenberg (1996) partly solved these problems, arguing that genes mapped to phenotypes in highly modular ways. Parcellation of traits into functional modules would offset the negative effects of mutations and pleiotropy on traits belonging to different modules. Thus, the evolution of modularity in otherwise integrated organisms decouples the correlated response to selection. Decoupling also increases evolvability by allowing genetic and phenotypic modules to change independently without compromising function (Wagner & Altenberg 1996). These ideas have been transformative, especially in light of our increasing knowledge about the complex ways genes interact to influence the development of phenotypes (Wagner et al. 2007; Wagner & Zhang 2011; Pavličev & Wagner 2012, Chapters 5 & 6, this volume).

The utility of modularity can be seen with a simple caricature of a complex system. In Figure 1.2a, we see a pattern where the symbols could represent any set of characters, genes, molecules, or functional traits. In this caricature of a complex system, traits are able to function and evolve independently. In Figure 1.2b, each character is connected to others by an interaction and correlational selection means that the efficacy/efficiency and evolvability of some traits (and the system generally) is impacted strongly by linkages among elements. Figure 1.2b is therefore a caricature of a highly-integrated complex system, much like the floral and feeding traits described above. Figure 1.2c represents a possible resolution to problems of trait correlations (as well as within generation matching of phenotypes to environments; West-Eberhard 2003; Monaghan 2008; Martin et al. 2011); modularity enables traits to evolve as collectives and only those elements with functional connections to others experience correlated responses to selection. In other words, components of modules are highly integrated, but modules are minimally connected to other modules. Such thinking dominates much of systems biology, and the ideas are applicable to all levels of biological investigation.

What role does modularity have in the present volume? A major one. In his 2006 book, The Music of Life: Biology Beyond the Genome, Denis Noble claims that the field of systems biology is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different.... It means changing our philosophy, in the full sense of the term.

We agree, as it is through the integrated, individual organism that genetic variation is translated into phenotypic variation (Pavličev & Wagner 2012, Chapter 6, this volume).

EMBRACING THE INDIVIDUAL AND THE UNION OF FUNCTIONAL AND EVOLUTIONARY BIOLOGY

This chapter has focused on two emerging themes in organismal biology: phenotypic plasticity and biological complexity. Because these concepts describe properties of individuals, they collectively describe how environmental variation acts on genetic variation to shape phenotypes. We see these and other topics as progress toward a theory of the individual (see also Chapter 19, Conclusions to this volume), a theory whereby mechanistic understanding at different levels of biological organization informs, and is guided by, broader
Figure 1.2. A visual caricature of complex systems. (A) A complex system of different symbols, where each symbol could represent genes, traits, or any other set of characters that are independent of each other. (B) An integrated complex system of characters, where the lines connecting the symbols represents correlations and interactions between characters. (C) A modular complex system, where each large circle represents a module containing a highly integrated set of characters.
embracing the individual and the union of functional and evolutionary biology

Evolutionary theory. We feel that biologists embracing such a perspective are poised to move beyond statistical descriptions of gene–trait relationships to a more realistic understanding of how environments interface with genetic, developmental, and physiological networks to influence organismal function and performance.

We anticipate skepticism from both functional and evolutionary biologists. For example, in an exchange among Thomas Flatt, Andreas Heyland, and Stephen Stearns (2012), Flatt and Heyland argued that mechanism might force changes in life history theory. Stearns disagreed, claiming that although the study of mechanism has shed some light on trade-offs, it has not fundamentally altered life history theory. On this point, we (and others – e.g., Pigliucci & Muller 2010) side with Flatt and Heyland. To illustrate the importance of mechanism to the development of evolutionary theory, consider the example of organismal responses to heat stress. Functional and evolutionary biologists are interested in the mechanisms of thermal tolerance and adaptation to temperature and climate, but they approach the problem with different motives. The convergence of these interests rests on the highly conserved gene family from bacteria to vertebrates that produce a group of protein chaperones; heat shock proteins (hsps). Initially, as their name implies, the expression of heat shock proteins was viewed in the context of acute thermal stress, but we now know that hsps stabilize and refold unfolded proteins even in benign contexts and are thus involved in diverse processes ranging from gene expression to chromatin remodeling (Lindquist & Craig 1988; Rutherford et al. 2007). Not surprisingly, evolutionary biologists and ecologists are often interested in adaptive hsp differences between populations and species in response to different thermal environments, whereas cellular and molecular biologists often seek to understand the mechanisms regulating hsp expression and the resulting functional consequences (Lindquist & Craig 1988; Moseley 1997; Hoffmann et al. 2003; Sorenson et al. 2003; Fangue et al. 2006). As with most phenotypic traits, heat shock proteins are plastic, have the capacity to evolve, and are highly integrated with other systems to perform diverse functions.

What gives hsps to the power to force revisions to evolutionary theory is their ability to act as capacitors, particularly Hsp90. Like other molecular chaperones, Hsp90 assists in proper protein folding and protein degradation in normal cells and during heat stress. However, it also acts on signal transducers to keep unstable signaling proteins ready for activation. Hsp90 thus lies at the interface of many cellular, physiological, and developmental pathways (e.g., Rutherford & Lindquist 1998; Rutherford 2000; Rutherford et al. 2007; Taipale et al. 2010). In this capacity, Hsp90 acts at the hub of many regulatory circuits and thus masks or compensates for mutations that would otherwise have potentially deleterious effects on the phenotype (Taipale et al. 2010). This key insight was made when Hsp90 expression was altered across a range of different genetic backgrounds in Drosophila and Arabidopsis; previously silent mutations were revealed with substantial phenotypic consequences (e.g., Rutherford & Lindquist 1998; Queitsch et al. 2002; Milton et al. 2003). In other words, although substantial genetic variation existed within different genetic backgrounds, Hsp 90 covered up this variation under typical environments and effectively hid genetic variation from natural selection (e.g., Rutherford et al. 2007; Jarosz et al. 2010).

The evolutionary implications of these results are significant. In times of environmental stress, when Hsp90’s protein clients become destabilized and the buffering capacity of Hsp90 is strained, cryptic genetic and phenotypic variation may be revealed (Rutherford & Lindquist 1998; Queitsch et al. 2002; Milton et al. 2003; Rutherford 2000; Rutherford et al. 2007; Jarosz & Lindquist 2010; Jarosz et al. 2010; Rohner et al. 2013). This buffering capacity and potential for releasing variation for selection to act on has been referred to as evolutionary capacitance. Importantly from the perspective of this volume, many
suborganismal mechanisms may act in a similar way. Indeed, capacitance is a general feature of complex gene networks and a form of epigenetic inheritance (e.g., Bergman & Siegal 2003; Dickins & Rahman 2012) and has been argued to act similarly at physiological (Chapter 9, this volume; Cohen et al., 2012, Martin et al., 2011) and behavioral levels (Duckworth 2009; Ledón-Rettig et al. 2013; Snell-Rood 2013). Other capacitors, such as the yeast prion [PSI+] also exist, and both empirical and theoretical work is revealing a role for capacitors in various traits from cancer (Whitesell & Lindquist 2005; Feinberg et al. 2006; Feinberg 2007) to the evolvability of populations (e.g., Cowen & Lindquist 2005; Wagner 2008; Masel & Trotter 2010; Jarosz & Lindquist 2010). Thus, capacitors serve as an example of how a mechanistic understanding has led to the development of a new model for evolutionary change. Similar contributions are likely to increase in the future as the barriers between functional and evolutionary biology erode.

CONCLUSION

Integrative Organismal Biology can be envisioned as an exercise in opening, or at least shrinking, the black box in which genetic and environmental variation come together to shape the phenotype. The major impediment to the Modern Synthesis was the difficulty of partitioning genetic and environmental variation. Biologists often forget that R.A. Fisher, Sewell Wright, and others laid the foundation for modern statistics mostly because the tools to quantify variation did not exist. In the process, the contributors to the Modern Synthesis took the first steps toward a cohesive theory of biology. We are now in the midst of a new synthesis that is using a new set of tools. This new synthesis embraces, rather than simplifies, the nature of plastic, yet integrated, organisms. However, we argue that part of what is holding us back is, ironically enough, the very things that have driven so much progress over the past century: reductionism and theory. Reductionism has driven massive progress in many fields but, at the same time, has conceptually extracted genes from the whole organism and their natural environments. Likewise, theory proliferated to shed light on how different environmental conditions shape the evolvability of different lineages, fluctuations in population sizes, rates of speciation, the distribution of species, the emergence of infectious diseases, and other important biological phenomena, but without an understanding of the mechanisms operating at the individual level. By contrast, an integrative biological philosophy that embraces complex systems might profoundly shift how we approach questions, ultimately catalyzing genuine synthesis across biological disciplines. Such a philosophy would embrace not only the complexity of organisms, but also their complex interactions with environments (i.e., plasticity). Indeed, the causal arrows spanning genes and proteins are now appreciated as multidirectional and inseparable from the environmental context in which they occur (West-Eberhard 2003; Noble 2006, 2013). Again, the environment serves two biological roles: it regulates phenotypic variation through gene function, genetic regulatory networks, and interacting developmental and physiological systems, but it also sorts this variation at the population level through selection. It is therefore only in the natural, ecological context of the organism that integration across levels of biological organization is truly possible. Noble (2013) echoed these ideas in his claim that, “Physiology is rocking the foundations of evolutionary biology.” What we think he meant (and what the chapters of much of this volume emphasize) is that we will make great strides in biology by augmenting reductionist approaches with studies of the interactions and integration of genetic, developmental and physiological pathways that comprise whole organisms in real environments.
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