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Evolvability

A Unifying Concept in Evolutionary Biology?

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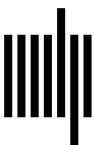
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18 Conclusion: Is Evolvability a New and Unifying Concept?

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The title of the workshop from which this volume grew asserted that the concept of evolvability is both novel and unifying. In this chapter, we consider the sense in which these assertions are true. Evolvability concepts were clearly, if sparingly, used in the last half of the 20th century, but the term only came into widespread use starting around 1990. What was new at that time was a growing awareness that inheritance should be separated from natural selection and that the properties of the inherited system themselves evolve. This pair of ideas catalyzed productive evolvability research programs that differed substantially from earlier work. The rise of the targeted study of evolvability has proved to be unifying in two senses. It emphasized connections among evo-devo, systems biology, and population biology, resulting in intellectual exchange among these subdisciplines. On a deeper level, the recognition that evolvability is a disposition, an ability only expressed when certain conditions are present, unifies different uses of the term. The diversity of contexts in which we want to quantify the disposition to evolve brings to the fore different aspects of biology that are themselves dispositions: the disposition to mutate, the disposition for mutations to have phenotypic effects, and the disposition of populations to harbor variation. The underlying unity of evolvability as a disposition to evolve is consistent with the fact that the properties that best predict evolvability will differ, depending on the context.

18.1 Introduction

As explained in the Introduction (Hansen et al., chapter 1),¹ this book is the outcome of a yearlong workshop aimed at understanding the use of the term evolvability as a label for intrinsic dispositions of organisms, genetic systems, or populations to evolve. The title of the workshop was “Evolvability: A New and Unifying Concept in Evolutionary Biology?” We want to address the implied claims in that title here: Is evolvability new? Is evolvability unifying?

Nuño de la Rosa’s (2017) bibliometric work documents the increased usage of the term evolvability starting in the 1990s (see also Villegas et al., chapter 3). More importantly, usage increased in a wide variety of evolutionary subdisciplines, and these tended to cite work from a variety of the other subdisciplines that also adopted the term. Price (1965) termed such citation networks “research fronts,” and we adopt this term as a neutral descriptor of the totality of evolvability research over the past 30 years.

1. References to chapter numbers in the text are to chapters in this volume.

Bibliometry alone, however, leaves unsettled the questions of novelty and coherence of the research itself. As documented by Nuño de la Rosa's interviews (chapter 2), many see evolvability as a fashionable relabeling of older concepts. Similarly, the unity of evolvability research is widely questioned, both by those who see value in their own restricted usage of the concept (Sterelny 2007; Pigliucci 2008; Brown 2014; Riederer et al. 2022), and by those documenting the diversity of usage (Love 2003; Nuño de la Rosa 2017).

Unsurprisingly, those participating in this project share the sense that there is something more than terminology to the rise of evolvability research, and many of us see ways in which evolvability can unify aspects of evolutionary biology. Despite this, there is no clear consensus about the answers to these two questions among us, and the chapters of this volume lay out a range of possible answers. We take up the question of novelty in section 18.2, unificatory potential in section 18.3 and highlight ongoing research in section 18.4.

18.2 Is Evolvability New?

The question of novelty is foremost one about recent history: What caused the use of the term to increase dramatically between 1990 and 2010? Nuño de la Rosa's interviews (chapter 2) probe the degree to which participants and observers in evolvability research fronts perceive it as a novel topic. With few exceptions, the interviewees identify earlier work that considered the same or related issues as current evolvability studies. These precursors are clear in the foundational population genetic work of Fisher (1930) and Wright (1932). Their conflicts over the shape of adaptive landscapes; the importance of drift; and whether genetic features, such as dominance (Mayo and Bürger 1997), are adaptations; are still actively debated by those working on evolvability today (Frank 2012). Similarly, the idea that clades (Simpson 1953; Vermeij 1987; Jablonski, chapter 17) or traits (Armbruster, chapter 15) differ in their ability to evolve is of longstanding importance in macroevolutionary studies. In evo-devo research, an important precursor to evolvability research is the European structuralist tradition exemplified by the work of Waddington (1957) and Riedl (1977, 1978). In addition, interviewees point to precursors of the effort to integrate genetics, development, and macroevolution, such as Lewontin's (1974, 12–16) conceptualization of the genotype-phenotype (GP) map as the hole in evolutionary genetics that needed to be filled by incorporation of such processes as development (e.g., Raff 1996) and biochemistry (e.g., Kacser and Burns 1981) into evolutionary thinking.

We will make a case that, despite these precursors, the emergence of the evolvability research front was catalyzed by two major conceptual advances that clarified how to think about evolvability. The first is the separation of the concept of natural selection from that of inherited variation, which enabled the recognition of evolvability as a disposition to evolve should the right stimuli occur. The second is the articulation of the idea that the ability to evolve can itself evolve. Both conceptual shifts set the stage for investigation of the processes that shape evolvability. This change in perspective catalyzed new research programs, in which novel concepts were brought into play, while drawing on intellectual precursors.

Natural selection has long been confounded with inheritance. For Darwin and most of his followers, natural selection was not separated from inheritance. Endler's (1986) influential book on natural selection made the inclusion of inheritance explicit. His favored

definition of natural selection included three elements: phenotypic variation, fitness differences among phenotypes, and inheritance, and has been widely used by others (e.g., Lewontin 1970; Mayr 1982; Ridley 1998, 2002). A few previous authors, albeit influential ones (Fisher 1930; Haldane 1954; Van Valen 1965), had instead adopted definitions involving only phenotypic variation and fitness differences. Endler noted this viewpoint but explicitly rejected it by definition: “If there is no inheritance then the process of natural selection cannot occur” (Endler 1986, 13).

Two important developments, one theoretical and the other empirical, tipped the balance of thinking toward separation of selection and inheritance. The theoretical development was the Price theorem (Price 1970; 1972; Hansen, chapter 5), which expresses the change in phenotype as the sum of the effects of selection and of transmission bias that includes inheritance. The Price theorem was not widely understood or applied before the 1990s (Frank 1995), but it then became a staple of conceptual analyses of selection that allowed clarification of previously confusing debates about levels of selection and the like, which are indeed complicated when inheritance or genetics is mixed into the picture but are quite simple from the perspective of selection alone (but see Okasha and Otsuka 2020).

The empirical development was the emergence of evolutionary quantitative genetics with its operational tools for measurements of evolution, genetic variance, inheritance, and selection as separate entities. Lande (1979) first showed that the multivariate response to selection could be represented as

$$\Delta\bar{z} = \mathbf{G}\boldsymbol{\beta},$$

where $\Delta\bar{z}$ is the vector of predicted changes in trait mean values, \mathbf{G} is the additive genetic variance matrix, and $\boldsymbol{\beta}$ is the selection gradient vector. The Lande equation neatly separates selection from genetic variation and inheritance. Lande and Arnold (1983) went on to demonstrate that $\boldsymbol{\beta}$ could be estimated as the multivariate regression of relative fitness on the trait vector. These papers popularized the representation of selection separately from inheritance, and they demonstrated how to estimate selection on multiple traits from data obtained using the standard observational and experimental methods of the ecologist. This started an industry of investigations that has provided thousands of field estimates of the strength and mode of natural selection. Similarly, inheritance and genetic variation in the form of the G-matrix, which describes the heritable component of genetic variation (Hansen, chapter 5), could be studied in the lab or in the field with classical or modern genetic methods without worrying about the connection to selection.

With these advances, the modern evolutionary biologist is well primed to think about evolution by natural selection as a two-step process. The first step is the appearance of heritable variation, and the second is the action of natural selection on this variation. The term “evolvability” filled a newly created need to talk about the variational preconditions for natural selection separately from discussion of natural selection itself. Terms such as facilitated variation, evolutionary drivers, adaptability (Anpassungsfähigkeit), and adaptive versatility were used for this purpose in the 1970s and 1980s, but they never came into general use. This gain in conceptual and empirical separation of selection and inheritance also precipitated a change in emphasis from constraints as forbidden or discouraged directions of evolution to quantification of how evolvable the phenotype is in each direction using properly justified measures of evolvability (Gould 1989; Schluter 1996; Hansen and Houle 2008).

While applied quantitative geneticists were already primed to regard selection as something different from inheritance due to the fact that selection is under the control of experimenter (e.g., Falconer 1981), the recognition of this critical separation was ironically hampered by the univariate breeder's equation familiar to quantitative geneticists,

$$\Delta\bar{z} = h^2 S,$$

where h^2 is the heritability, the proportion of variation that is additive genetic, and S is the covariance between relative fitness and the trait value, also known as the selection differential. Although the breeder's equation is a correct formulation of the response to selection, it invites the user to interpret h^2 as a measure of evolvability and S as a measure of selection. This interpretation is incorrect, as explained in chapters 5 and 6. Heritability is a dimensionless quantity, thus displacing all the scale information into S . Both the magnitude of genetic variance and the strength of selection affect S , thus confounding selection and inheritance. The assumption that h^2 represents what we want to know about inheritance precludes measurement of the disposition to respond to selection. Indeed, the first use of the term evolvability in the quantitative genetic literature was to make this point (Houle 1992). This misconception about the nature of h^2 persists (Hansen et al. 2011; Hansen and Pélabon 2021).

The second conceptual advance that led to the emergence of an evolvability research front was the recognition that the disposition to evolve itself has the capacity to evolve (Conrad 1983; Dawkins 1989; Pigliucci 2007; Hansen and Wagner, chapter 7). The recognition of the evolution of evolvability as a productive research area has origins in the fields of evo-devo and computer modeling of evolutionary processes. The earliest use of the phrase "evolution of evolvability" was by Dawkins (1989) in an essay on creating computer models of "artificial life." Dawkins argued that implementing open-ended evolution of computer programs under selection for increased performance required that the variation introduced fulfill special conditions, and that the existence of these conditions in biological organisms was in itself an interesting and understudied problem. Other theoreticians had previously identified the problem of what organismal features enable evolution without using the term evolvability (e.g., Lewontin 1978; Riedl 1978; Conrad 1983; Wagner 1984).

The rise of thinking about the evolution of evolvability is closely tied to the concept of the genotype-phenotype map, Lewontin's (1974) term for the set of processes by which genetic effects result in the phenotype. Alberch (1991) was among the first to explicitly associate evolvability with properties of the GP map, but the key paper that merged the study of evolvability with the GP map is Wagner and Altenberg (1996), who, like Dawkins, drew on evolutionary computer science concepts. Following ideas of Riedl (1978), they argued that evolvability could only be achieved if the effects of genes on traits could be parceled out into modules that can be changed in a quasi-independent fashion. The idea that evolvability requires modularity was paradigmatic in the emerging field of evolutionary developmental biology, evo-devo (e.g., Raff 1996). This is, for example, manifest in the emphasis on changes in cis-regulatory modules as the source of morphological evolution (e.g., Stern 2000; Carroll 2008).

A second important distinction introduced by Wagner and Altenberg (1996) is between variability and variation. While mutation was always recognized as the ultimate source of genetic variation, Wagner and Altenberg identified variability, the disposition of mutations

to produce phenotypic effects, as the property of the GP map that affects evolvability. Subsequently many have argued that the defining feature of evo-devo is the study of how evolvability is determined by the structure and evolution of the GP map (von Dassow and Munro 1999; Hendrikse et al. 2007; Brigandt 2015; Love 2015; Minelli 2017). In this view, evo-devo is a field devoted to the study of the first of the two steps in evolution by natural selection; that is, to the variational preconditions for natural selection.

Identification of variability as distinct from both mutation and the maintenance of genetic variation mirrors the identification of evolvability as the features that enable a response to selection. It is important to realize that these two related conceptions of evolvability arose essentially independently from different intellectual precursors—one from incorporating organismal processes such as development into mainstream evolutionary biology, and the other from a combination of evolutionary theory and quantitative genetics. We argue that the adoption of the term evolvability independently by these two intellectual traditions is what catalyzed the initial synthetic power of the evolvability research front (Nuño de la Rosa 2017, chapter 2; Villegas et al., chapter 3).

The degree of novelty in these advances is a matter of debate. Pigliucci (2007, 2008) featured the idea that the concept of the evolution of evolvability had no intellectual precursors in the modern synthesis prior to 1990 and used this novelty as a key argument that an “extended synthesis” of 20th-century evolutionary biology is occurring. In contrast, we prefer to treat the current work on the evolution of evolvability as a case of “endogenization” (Okasha 2021), in which the abstract principles of Darwinian mechanisms are applied to explain previously recognized but less well understood phenomena.

Adopting the idea that the process of endogenization is a key form of novelty, suggests a mechanism for separating “mere historical precedence” from novel intellectual traditions of the kind implied by Nuño de la Rosa’s bibliometric work. We point to three additional areas of endogenization in evolvability research currently being explored: the direct studies of the evolution of GP maps (Pavličev et al., chapter 8; Hallgrímsson et al., chapter 9), the role of robustness in evolution (A. Wagner, chapter 11), and the roles of plasticity and environmental interactions in determining evolutionary direction and rate (West-Eberhard 2003; Laland and Sterelny 2006; Paenke et al. 2007; Scott-Phillips et al. 2014), a topic regrettably underrepresented in this volume.

A rather different kind of novelty in the evolvability research front is the explicit use of measurement theory (Houle et al. 2011, Houle and Pélabon, chapter 6) to justify particular choices of both empirical measures of evolvability and the theoretical constructs that they represent. These arguments feature in the justification of the separation of natural selection and evolvability (Hansen, chapter 5; Houle and Pélabon, chapter 6). A second example of the use of measurement theory is in linking conceptions of genetic variation of the GP map to the measurement of epistasis, the interactions of alleles at different genetic loci in determining phenotypes. Hansen (chapter 5) lays out the conceptual basis for this change in viewpoint. Pélabon et al. (chapter 13) and G. Wagner (chapter 10) discuss empirical situations in which directional epistasis is expected to lead to a correlation between evolvability and trait mean.

A final novel element to evolvability studies is the incorporation of the concept of dispositions into the consciousness of biologists. Some of the earliest proponents of evolvability recognized that it was a disposition (Wagner and Altenberg 1996; Hansen 2006),

but perhaps more important to the introduction of dispositional concepts was that biological dispositions like evolvability attracted attention from philosophers (Love 2003; Sterelny 2007; Brown 2014; Brigandt et al., chapter 4). For biologists, this engagement clarifies the separation between the causal basis for the capability of evolution, and the stimuli that may actually convert capability into change (Prior et al. 1982). This clarification helps generalize the concept of evolvability by incorporating stimuli other than natural selection, including exceptionally rare changes, such as those leading to evolutionary novelties such as new body plans (Galis, chapter 16).

18.3 Is Evolvability Unifying?

This volume addresses a wide variety of phenomena related to evolvability from different perspectives. Observers of the evolvability research front have frequently expressed frustration at the diversity of phenomena to which the term is applied, and they have suggested that it should be restricted to some subset of current usage (Pigliucci 2008) or expanded to be more comprehensive (Brown 2014). Consequently, evolvability researchers are primed to consider the question of whether there is a unified basis to evolvability studies. We see several kinds of unity at work in the evolvability research front.

Nuño de la Rosa (2017) has suggested that evolvability studies can be seen as an intellectual “trading zone” (chapter 9 in Galison 1997; Winther 2015). This idea draws an analogy between locations where individuals from different human cultures exchange goods and intellectual arenas where individuals from multiple scientific subcultures find it worthwhile to engage. The key idea is that the meaning and value of the “goods” exchanged can vary from culture to culture and yet still contribute value on both sides of the exchange.

Villegas et al. (chapter 3) foreground the diversity of roles that concepts such as evolvability can play in scientific activities, including setting a research agenda, characterization, explanation, prediction, and control. For example, the idea that evolvability is correlated with mutational robustness (A. Wagner, chapter 11) can be used as a tool for prediction of evolvability, or as a target in studies that assess the strength or cause of the correlation. Villegas et al.’s catalog of roles that evolvability can play in research expands the variety of goods potentially exchanged in the evolvability trading zone, where one scientist’s explanation is used for prediction by another researcher.

This evolvability project was assembled as an instantiation of a trading zone. Its attractiveness to a diverse array of biologists exemplifies the value of the evolvability trading zone to practicing scientists. It attracted effort at least partly because it promised intellectual interchange among scientists working in different specialties. This accepting attitude to diverse work on evolvability was fostered by the philosophers and historians of science in this project, who have explicitly valued their roles as observers and documenters of, rather than judges of, scientific practice (Love 2003; Brigandt and Love 2012; Nuño de la Rosa 2017). This inclusive approach to evolvability is to be expected in a trading zone, and it represents a kind of unification of evolvability studies.

We believe that there is also a deep conceptual unification in the concept of evolvability. In particular, the recognition of the idea of evolvability as a disposition (Wagner and Altenberg 1996) provides a basis for recognizing common elements in different usages of the term. What unites the different uses of the term evolvability is, first, the recognition

that each describes a disposition to evolve intrinsic to the organism or population (e.g., Brown 2014). Second, these organismal and populational uses of evolvability are themselves linked to other dispositions. Wagner and Altenberg's (1996) made the distinction between variability, which is the propensity of a genetic system to yield variants that affect the phenotype; and evolvability, the propensity to evolve should the relevant cause, such as natural selection, occur. They assumed that the supply of adaptive variants limits the rate of evolution, a situation under which variability of a typical individual is the direct cause of evolvability. The quantitative genetic conception of evolvability focuses on the potentially adaptive variation in populations (Houle 1992; Hansen and Houle 2008). These two dispositions are directly linked, because variation at the population level would not exist without the ability of individuals to generate that variation. Similarly, we can identify the disposition of genomes to undergo mutation as an even more fundamental disposition that underlies both variability and variation. Consequently, the study of variability is intimately linked to the study of variation (Lewontin 1974; Houle et al. 1996; Houle 1998; Houle and Fierst 2013). Thus, there are several dispositional steps in a causal chain, and different notions of evolvability focus on different links in this chain.

Houle and Pélabon (chapter 6) use this logic to argue for a unified definition of evolvability as a disposition to evolve that can be applied in specific instances by drawing on different aspect of this linked set of dispositions. They note that there are many different aspects of organisms that could evolve, different stimuli that might trigger evolution, and different time scales of interest to biologists, for which Houle and Pélabon adopt the phrase *Of, Under, and Over*. Villegas et al. (chapter 3) point out that this unifying proposal carries over to two separate roles. First, it points to definitional unification. As long as research addresses a disposition to evolve, we have a study of evolvability. More important in their view is that this provides a basis to identify a research agenda based on the concept of evolvability. Houle and Pélabon's figure 6.1 (chapter 6) and Villegas et al.'s figure 3.3 (chapter 3) diagram different versions of this agenda.

18.4 What Is Ahead

In section 18.3, we emphasized those novel features of evolvability studies that originally catalyzed the evolvability research front. Current research focuses on important unsolved issues that we are optimistic will yield further advances in our understanding of evolvability. We highlight four specific areas in which progress is foreseeable: Modeling genotype-phenotype maps, phenomics, measurement of evolvability, and comparative evolvability.

18.4.1 Increasingly Realistic Genotype-Phenotype Maps

The genotype-phenotype (GP) map was arguably proposed to highlight the lack of attention by evolutionary biologists to how genes make phenotypes (Lewontin 1974). Since then, evolutionary biologists have enthusiastically joined in the effort to incorporate the GP map into the field, as reviewed by Pavličev et al. (chapter 8) and Hallgrímsson et al. (chapter 9). These trends are particularly apparent in the rise of studies of the role of GP maps in the evolution of development, featured in this volume and in evolutionary systems biology (Soyer and O'Malley 2013). With the metaphor of the GP map now firmly entrenched as a target of research, we can look forward to progress on several fronts.

The first of these is that the actual description of the pathways between genotype and phenotype is rapidly becoming more complete due to basic research in every area of biology, from molecular genetics and developmental biology, through physiology and behavior. Although this progress is most apparent for model organisms and humans, it also enables research on the GP map in a wider variety of systems. Basic research emphasizes the use of manipulations to test hypotheses about causal links between genotype and various functions. These data are increasingly being used to build detailed models of the genotype to phenotype relationships. Particularly promising is the trend toward causally-cohesive genotype-phenotype (cGP) models (Rajasingh et al. 2008; Houle et al. 2010; Omholt 2013; Pavličev et al., chapter 8) that relate the effects of variation through a biologically motivated and explicit network of processes that extend, with varying degrees of realism, from genotypes to phenotypes. It is important to recognize that even the most sophisticated of such models is, and is likely to remain, limited to a small portion of the total GP map. Although we cannot hope to build detailed GP maps of all phenotypes, the development and validation of a modest number of such maps, instantiated as cGP models, should be sufficient to reveal whether we can expect to discover generalizations about the relationship between GP maps and evolvability.

The second trend is the increasingly sophisticated use of genome-wide association studies (GWAS) that generate hypotheses about the potential causes of genetic variation in the phenotype. The many inferential challenges of naïve GWA studies are gradually being overcome by increasingly sophisticated statistical approaches, and by the existence of larger and larger data sets, driven by both more complete and cheaper genotyping, and by increased phenotyping capacity.

The development of GP map concepts reveals how important it is to estimate pleiotropic and epistatic effects in GWAS. Pleiotropy was largely unaddressed in the initial phases of mapping, and then addressed only indirectly (Pitchers et al. 2019). Similarly, the statistical challenges of detecting particular epistatic interactions are formidable, calling into question the validity of findings based on P-values. By transferring our attention to higher level aggregate properties, such as directional epistasis or modularity of genetic effects, we can expect more robust inferences about those aspects of pleiotropy and epistasis that shape evolvability.

Merging the basic information about organismal function with detailed GWAS data has the potential to transform our understanding of GP maps. When a cGP model is paired to data on the effects of both experimentally-induced and natural variation, we can anticipate a virtuous cycle, where researchers can predict the effects of genetic variation using systems models and then test those predictions using experimentally validated information. Where the predictions fail, the model can be improved.

18.4.2 Phenomics, Natural Selection, and Fitness

Phenomics is the laudable aspiration to comprehensively study the phenotype as a whole (Houle et al. 2010). Adaptation by natural selection depends on both the fitness consequences of an unknown number of traits subject to selection, and on the pleiotropic effects of the variants that cause variation in all those unknown traits. To be sure, there are striking examples where the genotype-phenotype-fitness relationships seem satisfyingly simple (e.g., Linnen et al. 2013), but these may be unusual, rather than typical cases. Only by broadening our

attention to include a more comprehensive view of phenotypes can we investigate this possibility.

Current genetic studies of evolution are by and large carried out on a handful of phenotypes; thus they can only address a few phenotypic dimensions. Even studies that characterize organisms with highly multivariate data are almost always limited to one sort of phenotype, such as gene expression (Aguet et al. 2017), morphological shape (McGlothlin et al. 2018), or abundance of biomolecules (Chenoweth and Blows 2008).

Limited phenotyping hampers the study of pleiotropy. Although there have been some fairly large-scale attempts to assess pleiotropy (Wagner and Zhang 2011), these are hard to generalize due to their reliance on statistical testing to infer pleiotropic effects and on the study of gene knockouts that are not representative of natural variation (Paaby and Rockman 2013). As a result, contradictory views about pleiotropy remain viable. Is pleiotropy a by-product of evolution, incapable of responding to natural selection (Wagner et al. 2007), or a key target of selection that has been shaped to maximize evolvability or robustness (Wagner and Altenberg 1996)? Is pleiotropy a source of evolutionary constraint (Orr 2000; Hansen and Houle 2004), or is it so variable that organisms can respond to any selective pressure (Pavličev and Hansen 2011; Pavličev and Wagner 2012)? Is pleiotropy “universal,” so that most mutations affect all traits to some extent (Paaby and Rockman 2013; Boyle et al. 2017), or modular, restricted to a few related traits (Wagner et al. 2007; Wagner and Zhang 2011)? The continued viability of these alternatives reveals profound ignorance about pleiotropy and its role in evolution.

The significance of properties that are clearly important to evolvability, such as pleiotropy, modularity (Pavličev et al., chapter 8), and robustness (A. Wagner, chapter 11), depend on the full range of phenotypic effects that a variant has. Equally important is that the evolutionary impact of properties such as modularity and robustness on evolvability depend on how selection affects multiple traits simultaneously (Houle and Rossoni 2022). The same modular structure that promotes the response to selection aligned with the modules will hamper responses to selection in other directions (Hansen 2003; Welch and Waxman 2003; Houle and Pélabon, chapter 6). Similarly, the potential advantages to evolvability of nearly neutral networks depends on the variety and accessibility of phenotypes at the edges of that network, and whether those particularly accessible phenotypes enhance the response to actual selection pressures (Mayer and Hansen 2017).

Technical advances in several areas are expanding our ability to phenotype individuals. Chief among these is the ever-expanding ability to measure gene expression, the causal foundation of much phenotypic variation (Aguet et al. 2017). Coupled with better knowledge of GP maps (section 18.4.1), this ability could allow more sophisticated predictions about phenotypic consequences, guiding further phenotyping efforts toward variants and traits with consequential effects on fitness. The range of high-throughput phenotyping platforms is increasing. Image processing approaches can now rapidly extract a variety of measurements of morphological features from images of any taxon (Martins et al. 2015; Porto and Voje 2020). Specialized high-throughput phenotyping has been implemented for model and economically important species, including crop plants (Yang et al. 2020) and *Drosophila* (Medici et al. 2015).

Some of the uncertainties that pleiotropy poses for inferences about evolvability could be resolved with estimates of fitness, rather than comprehensive phenotyping. For example,

if fitness is included in the set of phenotypes in a GWAS, one could compare how much variation in fitness is explained by a specific variant, and how much is explained by the effects of the variant on the measured phenotypes. Similarly, with replicated genotypes, one could measure the proportion of fitness variation explained by the measured phenotypes relative to the variation in genotypic fitnesses. Close correspondence would suggest that the traits important to fitness have been measured. Unfortunately, measuring fitness in a manner relevant to evolution of natural populations is itself a challenging task.

Until this problem of unmeasured traits receives attention from experimentalists, theorizing about aspects of evolvability that depend on pleiotropy will remain speculative.

18.4.3 Development and Measurement of Evolvability Parameters

One of the important products of the evolvability research front is the expansion of our roster of measurable features that we can relate to evolvability. Thirty years ago, these included mutation (Kimura 1967), genetic variance (Falconer 1981), integration (Olson and Miller 1958), and modularity (Raff 1996; Wagner 1996; Wagner and Altenberg 1996). In the intervening years, the relevance of new concepts has been developed, including plasticity, niche construction, and regulatory evolution. We focus here on three for which the relationship to evolvability is quantifiable: robustness, directional epistasis, and conditional evolvability.

Robustness is the tendency for DNA mutations to have no phenotypic consequences (A. Wagner, chapter 11). Andreas Wagner and others (Wagner 2005; Masel and Trotter 2010) note evidence that effect sizes of particular mutations change, depending on the genotype in which they occur. Genotypes that are more robust then give rise to mutants with different spectra of descendant genotypes than less robust ones. Some models predict that selection will often push genotypes to regions of genotype space that are more robust. The consequences of this can either enhance or suppress evolvability, depending on the genotype-fitness relationships (Wagner 2008; Mayer and Hansen 2017). Clever experimental work has revealed the causes and evolutionary consequences of robustness in viruses and bacteria, in which spectra of mutational effects can be rapidly screened (A. Wagner, chapter 11). This work suggests that robustness of individual biomolecules to random events, such as misfolding, reliably predicts their ability to produce adaptive variation when their function is challenged in a novel way. The challenge is to generalize these results to robustness of more complex systems and more complex organisms.

Hansen and colleagues have focused attention on changes in the average properties in the GP map as a function of the position of a genotype in phenotype space. This is reflected in *directional epistasis*, where variants that change the phenotype in one direction have systematic epistatic effects that increase or decrease the average effect sizes (Carter et al. 2005; Hansen et al. 2006). There has been relatively little experimental work on directional epistasis, although methods to estimate it are available (Álvarez-Castro and Carlborg 2007; Le Rouzic 2014). This is beginning to change (Pélabon et al., chapter 13), and we expect a great deal more experimental work on the relationship between phenotypic means and genetic effects in the near future.

Conditional evolvability measures evolvability of one trait while holding other traits constant (Hansen 2003; Hansen et al. 2003; Hansen and Houle 2008; Hansen, chapter 5). The ratio of conditional to unconditional evolvability provides a dimensionless measure of integration and modularity in the context of a particular set of selection pressures.

Although conditional evolvability is readily calculated given a \mathbf{G} matrix (Hansen and Houle 2008), even when we have an empirical estimate of the direction of selection, we often lack information on the traits that may be subject to stabilizing selection, and always lack a complete inventory of traits potentially correlated with the focal trait under selection. Useful empirical work on conditional evolvabilities awaits advances in phenotyping and the measurement of fitness landscapes.

The usefulness of these new measures of evolvability, as well as more familiar ones, will continue to increase as biologists consider the scale on which parameters are measured, i.e., interpret the meaning of measurements with explicit reference to their units. The case for doing so has been laid out on numerous occasions (e.g., Houle et al. 2011; Hansen, chapter 5), and yet many studies and reviews attempt to address quantitative questions about evolvability with quantitatively uninterpretable summary measures, such as heritabilities and correlation matrices, or P-values as substitutes for effect sizes.

We hope that the relatively new measures of evolvability that we have mentioned here are not the last to be developed. For example, some believe that organisms vary in their ability to generate novel phenotypes, a feature not captured by the measures of evolvability we have in hand.

18.4.4 Comparative Evolvability

A final important research area is characterization of the variation in evolvability in a wider array of taxa. We currently have few well-estimated \mathbf{M} matrices and a slightly larger variety of \mathbf{G} matrices, supplemented by a relatively large number of \mathbf{P} matrices. Similarly, the GP map properties that underly variability and variation have only been studied in a handful of model organisms. Broadening these studies to include more populations and in particular a wider taxonomic diversity would allow us to generalize what we know about evolvability.

Another productive direction to expand evolvability studies would be to integrate studies of GP maps and contemporary evolvability statistics with paleontological data. Paleontological data provide unique information on evolutionary rates and directions over very long periods. The key to making use of such data is to find opportunities to distinguish between natural selection and evolvability as a cause of variation in evolutionary rate (Jablonski 2017, chapter 17; Jackson 2020). Love et al. (2021) outline three different research programs that could potentially uncover an evolvability signal in paleontological data by drawing on neontological research in development, quantitative genetics, and comparative biology.

The combination of comparative and quantitative genetic data has already suggested that such signals exist. Voje et al. (chapter 14) outline the strong and consistent evidence that the variation within single populations predicts the rates of evolution in the clade in which it resides. This observation leads to the striking prediction that the variational properties of diverging populations must be conservative. Armbruster (chapter 15) makes the case that such conservative patterns of variability in vegetative and floral traits shape the evolution of flowering plants. This correspondence between evolvability and evolutionary rates is surprising, because we know that the population processes discussed by Sztepanacz et al. (chapter 12) and Pélabon et al. (chapter 13) can lead to large changes in within-population genetic variation over fairly short time scales. Furthermore, a correspondence between variation and the rate of evolution is not expected under any of the simple models that are currently available (Bolstad et al. 2014; Houle et al. 2017; Voje et al., chapter 14).

Performing such analyses in taxa with an informative fossil record would deepen our understanding of the strength and longevity of these patterns.

Hansen and Wagner (chapter 7) point out that a wide variety of non-exclusive hypotheses exist for what drives the evolution of evolvability. These broadly fall into adaptive explanations (in which evolvability is the direct target of selection) and non-adaptive explanations, in which evolvability emerges as a by-product of other evolutionary forces. Although there has been little empirical work aimed at distinguishing between adaptive and non-adaptive hypotheses, we see opportunities to do so by investigating how evolvability changes under natural or artificial selection or following experimental alterations of mean phenotype. For example, evolve and resequence experiments could be used to infer the identity of haplotypes that increase in frequency under particular selective regimes. Then the variability of variants on favored and non-favored backgrounds could be compared by engineering specific variants into both backgrounds. An adaptive hypothesis is that persistent directional selection would increase variability regardless of the direction of selection. A non-adaptive hypothesis predicts that variability would be a monotonic function of the trait mean, regardless of the form of selection.

18.5 Conclusion

We have made the case that evolvability research is both novel and unifying, albeit with some qualifications.

The events that triggered an evolvability research front and rendered it interdisciplinary were the independent arrival of similar concepts of evolvability in different fields. This convergence generated connections between different intellectual traditions, resulting in the research documented in this volume. As we have argued in section 18.4, evolvability research continues to generate groundbreaking research. There is reason to hope that the research set in motion by the individuation of the evolvability concept will precipitate answers to the many questions about evolvability that this book identifies.

We believe one of the reasons that evolvability research has been and will continue to be productive is that it has provided a theme that unites disparate fields. The strong version of this unifying influence lies in the realization that evolvability depends on a set of linked dispositions—the disposition to mutate, the disposition of mutations to produce phenotypic variation, and the disposition of the populations carrying that variation to evolve under a variety of stimuli. This unity serves to explain the disposition of geneticists, developmental and systems biologists, and paleontologists to exchange ideas about evolvability.

The ultimate goal of research into evolvability and variability is to develop a theory to explain and predict the linked dispositions that is on par with our well-developed theory of how natural selection acts on the manifest variation. We are aware of formidable challenges that stand in the way of a full realization of the promise of evolvability theory. Until we can better characterize phenotypes and their inheritance, the form of natural selection on them, and improve our ability to measure fitness, it will be difficult to apply concepts such as robustness, conditional evolvability, and directional epistasis in a grounded way. In addition, the study of longer-term differences in evolvability as they apply to rare but critical events in the history of life, such as the origin of novelty, remains speculative.

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