Evolvability

A Unifying Concept in Evolutionary Biology?

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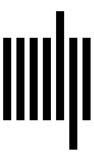

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7 The Evolution of Evolvability

Thomas F. Hansen and Günter P. Wagner

The evolution of evolvability became a topic in the 1990s, and since then, it has progressed from controversies about its radical or conventional nature to a mature research program with hypotheses motivated in evolutionary theory and theoretical population genetics. Evolvability is an outcome of a variety of organismal traits, and it evolves along with these traits. In this chapter, we first review the theoretical basis for the main modes of evolution of evolvability, including adaptation at various levels; contingent evolution based on indirect, canalizing, and congruent selection; and neutral evolution, including systems drift. We then present an overview of organismal properties that may influence evolvability and provide some selected reviews of their possible modes of evolution.

7.1 Introduction

The diversity of life testifies to the capacity of organisms to evolve into a variety of complex forms and modes of existence. On one hand, this reflects the power of natural selection to build complex adaptations. One of the main achievements of twentieth-century evolutionary biology was the theoretical and empirical demonstration of the efficacy of natural selection. Given heritable variation, selection can produce stunning changes in little time. On the other hand, the diversity of life also reflects the ability of at least some organisms to produce new variations that can fuel selection. The ability to produce and maintain potentially adaptive heritable variation is what we call *evolvability*. In their drive to demonstrate the power of natural selection, the architects of the modern synthesis took the existence of heritable variation more or less for granted. With some exceptions, variation was not seen as a property in need of explanation or studied as an evolving variable. This view started to change toward the end of the last century, when an increasing number of researchers began to study variation and the ability of organisms to produce variation. In particular, the architectural features of organisms that structure their variational properties, the genotype-phenotype map, became a subject of study (e.g., Wagner and Altenberg 1996).

What happened in evolutionary theory toward the end of the last century can be described as a case of theory expansion, in which previously external conditions and assumptions about variability became "endogenized" in the sense of being treated as something to be explained within the theory (Okasha 2021). Thus emerged the study of "the evolution of evolvability." This phrase, popularized by Dawkins (1988), refers to the evolution of the organismal or population properties that influence the ability to evolve.

As evolvability is an outcome of organismal properties, there is no mystery or paradox to its evolution. Evolvability evolves along with the traits that influence it. Such questions as "is evolvability evolvable?" and attempts to demonstrate that evolvability can evolve through simulations or experiment are therefore of limited interest. The question is not whether evolvability can evolve, but how it evolves.

In this chapter, we review principles for the evolution of evolvability and conclude that there is no simple or agreed-on answer to how this actually happens. A variety of opinions and hypotheses can be found, and the answer may depend on phylogenetic scale, what traits are considered, whether origin or maintenance is to be explained, and on whether ultimate or proximate explanation is intended. A key question is whether organisms are somehow adapted to be evolvable. Gould (2002) stated a "paradox of evolvability" as "how can something evolve that is not of immediate use?" As explained above, this is not a literal paradox, but Gould intended to challenge a perceived notion of evolvability as an individual-level adaptation, and, as selection is a population phenomenon, evolvability must materialize through population variation, making it difficult to conceive how it can be directly selected on the individual level. This problem was recognized as far back as by Dobzhansky (1937), who referred to it as the "paradox of viability."

Nevertheless, the notion that organisms are designed for evolvability is widespread and has strong antecedents. Riedl (1977, 1978) pointed to the improbability of producing functional variations through mutation in complex organisms with many interlocking parts. He inferred that organisms must be structured to vary along functional lines. Similar ideas have been expressed by Berg (1957, 1958), Waddington (1957), Olson and Miller (1958), Cheverud (1982, 1984), Conrad (1983, 1990), G. Wagner (1986, 1996, 2014), Raff (1996), Gerhart and Kirschner (1997), and A. Wagner (2005), among others. The concept of modularity has been particularly important in this line of thinking. Wagner and Altenberg (1996), for example, identified unbounded pleiotropy as a major impediment to complex adaptation and suggested that the partitioning of the organism into variationally distinct parts allowed each part to evolve in a quasi-independent manner such that adaptation in one part would not fatally interfere with adaptation in other parts. The emphasis on cis-regulatory modularity in evolutionary developmental biology (e.g., Stern 2000; Carroll 2008) reflects this idea. Because regulatory proteins function in a variety of contexts, mutations in their coding sequence have been assumed to be highly pleiotropic and therefore unlikely to improve the organism. In contrast, mutations in cis-regulatory modules may have more narrow effects due to the specificity of the regulatory modules themselves. While it is becoming clear that cis-regulatory mutations are not the only way of making modular changes in gene regulation (e.g., Lynch and Wagner 2008), modular change remains a guiding principle in evolutionary developmental biology.

Gould (2002) proposed two solutions to the paradox of evolvability. One was to give up on the idea of evolvability as a (narrow-sense) adaptation and instead view it as an exaptation, a trait that has evolved for a different purpose than its current function. In this view, evolvability may or may not be maintained as a (broad-sense) adaptation, but the focus is shifted from selection on evolvability itself to the evolution of the various traits and properties that relate to evolvability. Evolvability is likely subject to a variety of indirect selection pressures caused by adaptation in correlated traits, and these need not be related to whether evolvability is of benefit to the organism or population (Sniegowski

and Murphy 2006; Hansen 2011). In particular, evolvability may be a side effect of the ways organisms structure their development and physiology to be coordinated, robust, and/or flexible in relation to environmental conditions (e.g., Gerhart and Kirschner 1997). For example, constraints on body symmetry may evolve as adaptations to ensure a functional symmetric body in the face of developmental perturbance, but as a side effect may also structure genetic variation to be more symmetric, which will facilitate the evolvability of symmetric changes and reduce the evolvability of asymmetric changes. Selection is also not all powerful, and systems drift and other forms of neutral evolution of genetic architecture are central to the evolution of evolvability (A. Wagner 2005; Lynch 2007).

Gould's (2002) other proposed solution was that evolvability evolves as a group- or lineage-level adaptation. Among those who favor an adaptive view of evolvability and explicitly consider the level of selection, some form of higher-level selection seems to be the favored solution (e.g., Gerhart and Kirschner 1997). This even includes Dawkins (1988), who went as far as describing the evolution of evolvability as "a kind of higher-level selection." Yet it is not obvious that one needs to move beyond conventional within-population selection to solve the paradox of evolvability (e. g., Wagner 1981). In this chapter, we construct some ways in which evolvability can be said to evolve by direct individual- or gene-level selection.

In any case, our position is that evolvability is an outcome of a variety of organismal characteristics, and that its evolution must ultimately be understood in terms of the evolution of these characteristics and the various traits that influence them. As there is a varied set of relevant characteristics, most known modes of evolution are relevant, and this includes adaptation through direct selection for evolvability on various levels, contingent changes due to indirect selection on traits or properties correlated with evolvability, and neutral modes of evolution, such as systems drift and accumulation of nearly-neutral changes that affect evolvability. Many aspects of evolvability are also deeply integrated with and therefore constrained by organismal structure and life cycle, which sets up historical contingencies and major transitions in body plan or inheritance systems as relevant modes of evolution.

7.2 Modes of Evolution of Evolvability

In this section, we review the theoretical basis for the main modes of evolution of evolvability. We aim to clarify motivation, conditions, problems, and arguments more than to judge general plausibility. Plausibility of different hypotheses is better considered in relation to the evolution of particular characteristics, as illustrated in section 7.3.

7.2.1 Adaptation

The motivation for viewing evolvability as an adaptation is that organisms seem designed to be evolvable, and adaptation by natural selection is the main source of design in nature. If we accept that organismal architecture generates accurate inheritance, coordinated variability, continuity, recombination, and robustness to an unexpected degree, then, to the extent that these properties facilitate evolvability, we must infer that organismal structure facilitates evolvability to an unexpected degree. An unexpected degree of functional organization is design, and if evolvability is the function, evolvability must be an adaptation.

Leaving aside the debates as to whether organisms really are unexpectedly evolvable and whether this is due to frozen constraints with ancient origin or continuously maintained in individual lineages, the problem with the above argument is that evolvability may evolve by selection without being an adaptation. Even if organisms display complex functional order that reflects a multitude of adaptations, it does not follow that every property of the organism is an adaptation for any specific function. Adaptation for property X requires direct selection being caused by property X (Sober 1984), and in the case of evolvability, this means that evolvability must cause the selection for the properties that influence evolvability. The obvious alternative is that these properties are selected for reasons unrelated to evolvability, and that the evolvability evolves as a correlated response. In this scenario, organisms may appear designed to facilitate evolvability without evolvability being the adaptation.

Adaptations can exist on different levels in the biological hierarchy. The paradox of evolvability: "How can something evolve that is not of immediate use?" is only paradoxical on the implicit assumption that the functional benefit must pertain to an individual organism. For the adaptationist, the easy way out is to assign the level of selection for evolvability to other units, such as genes, groups, or lineages. We will discuss each of these below, but first we sketch a way one may also meaningfully talk about individual-level selection for evolvability.

An episode of selection can be formally described as a mapping from a set of entities (e.g., population of individuals) to another set (Kerr and Godfrey-Smith 2009). Fitness is assigned to different types of entities to describe their expected ratio of representation after selection to representation before selection. To select *for* evolvability on the level of individuals, we need to set up the mapping in such a way that a high-evolvability type has high fitness because it has high evolvability. This is not possible if the episode of selection does not include reproduction, because there is then no possibility for the evolvability to manifest itself. It is of course possible that high-evolvability types have high fitness in this scenario, and we can have individual selection *of* evolvability, but not individual selection *for* evolvability (sensu Sober 1984). We can, however, consider a mapping from a set of adult individuals in one generation to their adult offspring in the next (or even a later) generation. In this case, a high-evolvability individual may produce a set of candidate offspring that is more adaptable (e.g., more variable in some ecologically relevant trait), and if the selection happens in an uncertain, changing, or unfavorable environment, the high-evolvability types may end up with a better representation among adults in the next generation (i.e., higher fitness), because they were more likely to produce some offspring that were well adapted to the environment they encountered.

This scenario, familiar from the literature on bet-hedging strategies and from the tangled-bank hypothesis for the evolutionary maintenance of sexual recombination, is a candidate for direct individual-level selection for evolvability. On a similar basis, candidates for individual-level adaptation for evolvability may also be found in mechanisms for stress-induced release of genetic variation in situations where the individual is likely to be maladapted. This can take the form of phenotypic expression of segregating "hidden" variation (e.g., Rutherford and Lindquist 1998) or the form of increased rates of mutation under stress (e.g., Galhardo et al. 2007).

7.2.2 Gene-Level Adaptation

Some may object that the above mechanism is selection of family groups more than of individuals, and it can also be considered in terms of selection on the level of genes. The relative stability of alleles makes it more natural to consider episodes of selection that last over more generations. Hence, if we consider a mapping from a population of alleles to a later point in time, we can see that an allele that generates more variable descendants may be better represented, because it is more likely that some of its descendants were successful in an unfavorable environment. If we consider the mapping to be composed of a series of selective episodes, the fitness over the total mapping is the product of the Wrightian fitness values of the individual episodes of selection. Formally, if W_i is the fitness of the allele in the ith episode of selection, the fitness over a sequence of episodes is $W = \Pi_i W_i$. Now consider an allele that starts out with fitness W_0 but produces offspring with variable heritable fitness. Then, by the fundamental theorem of natural selection, the mean fitness of the subpopulation carrying the allele will increase in each episode of selection with a term v that is equal to the variance of fitness divided by the mean fitness. Hence, assuming for simplicity that v stays constant over the sequence of selection episodes, the fitness of the allele over the whole sequence will be $W = \Pi_i(W_0 + iv)$. Assuming the same process operating in the population as a whole, the relative fitness of the allele after t episodes of selection will be

$$w = \frac{\prod_{i=0}^{t-1}(W_0 + iv)}{\prod_{i=0}^{t-1}(\bar{W}_0 + iV)},$$

where $\bar{W}_0$ is the intial mean fitness of the population, and V is the total variance in fitness of the population divided by the mean fitness. From this equation, and assuming also that V stays constant, we see that the allele will increase in frequency due to selection if

$$\prod_{i=0}^{t-1}(W_0 + iv) > \prod_{i=0}^{t-1}(\bar{W}_0 + iV),$$

which can be approximated as

$$\frac{v}{W_0} - \frac{V}{\bar{W}_0} > \frac{-2ln(W_0/\bar{W}_0)}{t}.$$

The left-hand side of this equation can be interpreted as the difference in evolvability between carriers of the allele and the population at large. The term v/W_0 is the initial average opportunity for selection (i.e., the variance in relative fitness) of the subpopulation carrying the allele, and the term $V/\bar{W}_0$ is the initial opportunity for selection in the population at large. The numerator on the right-hand side is the initial fitness cost of carrying the allele. A cost is to be expected due to the likely immediate deleterious effects of variation. Hence, an allele that increases the opportunity for selection on its carriers will spread if it can overcome direct fitness costs. As the number of episodes of selection (e.g., generations) increases, the more likely it is that the high-evolvability allele will increase in frequency. Wagner (1981) described a similar mechanism in terms of selection on modifiers of Malthusian fitness.

Well-known examples that may fit this description include "mutator" alleles that increase the mutation rate of their carriers, alleles that increase the recombination or outcrossing

rates of their carriers, and "modifiers" that epistatically increase the effects of other allele substitutions in the genomes in which they are situated. More generally, we can consider any allele that influences the variational properties of the organism as a putative evolvability allele, and if the variational changes caused by such an allele increase the opportunity for selection on its descendants, it may spread in the population according to the above criterion.

In this model, alleles that elevate the opportunity for selection are favored because their descendants are able to adapt in the sense of increasing their mean fitness faster than the population at large. This is direct selection for evolvability, because it is the effect of the allele on evolvability that makes the difference in the selective outcome, and the described process thus has the potential to create and maintain adaptations for evolvability. We can imagine such alleles spreading in maladapted species with more scope for changing fitness variation, and that species living in changing environments may maintain higher evolvability because they tend to be maladapted more of the time.

7.2.3 Group- or Lineage-Level Adaptation

Even if they are divided on whether adaptive evolution of evolvability occurs at all, commentators as different as Dawkins (1996), Gould (2002), and Lynch (2007) all suggest that this would require some form of higher-level selection. A shift to higher-level units with internal evolutionary processes that may differ in evolvability is indeed an obvious solution to the problem of constructing direct selection for evolvability. Populations with high evolvability will on average be better adapted to their environment, and they may tend to survive better, bud off more offspring populations, or produce more propagules of individuals that transfer the evolvability-enhancing traits to other populations.

Group selection has had a bad press, particularly when associated with naive best-for-the-species styles of argument. Evolvability may be good for the species, but this is no explanation for why species are evolvable. Nevertheless, carefully formulated models have demonstrated that group selection can be efficient in maintaining group adaptations (Okasha 2006). Although the focus of such models has been on social traits like altruism, there is also work supporting group or lineage selection as a viable hypothesis for the maintenance of sex and recombination (Maynard Smith 1978; Nunney 1989), and for emergent species-level traits and trends more generally (e.g., Lloyd and Gould 1993; Jablonski 2008).

The modern treatment of group selection is based on the Price theorem and works by splitting the evolutionary change over an episode of selection into components attributable to selection among groups and selection within groups, or from the group-selection perspective by treating lower-level selection as transmission effects (Price 1972; Okasha 2006; Frank 2012). This approach requires a recognizable group structure in which groups can be assigned a fitness based on differential contribution to the metapopulation at the end of the episode of selection. Any trait correlated with the group fitness will experience group selection, and if the correlation is causal, the trait can evolve as a group-level adaptation. There are two limitations, however, in applying this to evolvability.

The first is that group-level selection may be overcome by within-group selection. As we have seen above, the mean fitness of an evolvable population will increase with a factor equal to the genetic opportunity for selection (i.e., the evolvability of fitness) per generation. Hence, the group evolvability of fitness will be the among-group variance in the evolvability of (within-group) fitness. We do not have any estimates of group evolvability

of fitness, but we can illustrate its potential impact with a thought experiment. Let us assume a metapopulation in which half the populations have an evolvability for fitness of 1% and the other half an evolvability of 3%, meaning that selection would increase the genetic value of fitness with 1% per generation in the former and by 3% in the latter. These values are consistent with current estimates of evolvability of life-time fitness (Hansen and Pélabon 2021). If we assume that the subpopulations' contributions to the metapopulation are proportional to their final mean fitness, then we can compute that group selection will increase mean evolvability of fitness by 0.5% per generation (i.e., from 2% to 2.01%). This matches the evolvability of many quantitative traits and may thus balance many processes acting to diminish within-population evolvability. Group adaptation for evolvability is thus plausible, provided a group structure with enough variation in evolvability can be maintained.

The long-term maintenance of group differences in evolvability would require a degree of remixing of groups before within-group selection removes individually deleterious evolvability-enhancing traits. This is a serious limitation for species- or clade-level selection with little opportunity for remixing. To maintain evolvability as an adaptation on these levels, it must be constrained on lower levels. This would not work if the evolvability in question is a function of quantitative polygenic traits, which inevitably are themselves evolvable on the organismal level. But it is more plausible when evolvability is the outcome of discontinuous changes in the body plan or inheritance system that may become burdened and difficult to reverse. Indeed, many discussions of evolvability from a macroevolutionary perspective concern innovations such as the evolution of new character identities, transitions to new levels of organization, or the construction of qualitatively new niches. More generally, any historical contingency may irreversibly set new evolutionary possibilities that can be conceptualized as a change in evolvability. Species selection then emerges as a potent mechanism for preserving and proliferating clades with constrained traits that provide for richer evolutionary possibilities.

The second limitation to evolvability as a group adaptation is that group selection, just like individual selection, may be indirect. Even when there is population structure facilitating group selection, traits influencing evolvability may be (group) selected for reasons unrelated to their effects on evolvability. For example, Lloyd and Gould (1993) argued that species selection may favor genetic variability, because species with a subdivided population structure will both tend to maintain more genetic variation and be more prone to speciate. Traits that generate the subdivided population structure, such as having non-planktonic larvae, may then be considered species-level adaptations, but not for (within-species) evolvability, as the increase in genetic variation is a side effect and not a cause of increased speciation rates. In contrast, Dobzhansky (1937) argued that evolvability ("evolutionary plasticity") was selected on the species level because it reduces extinction risk by increasing the ability to adapt to environmental change. This would be direct species selection for evolvability and would act to maintain evolvability as a species-level adaptation to changing environments.

7.2.4 Contingent Evolvability: Epistasis and Trait Evolution

The most obvious situation in which evolvability is favorable is when the population is under directional selection. Under directional selection on a trait, both the rate of change in the trait and the increase in mean fitness caused by the selection are proportional to the additive genetic variance in the trait. If we take the additive variance as a measure of trait

evolvability, we can ask how the evolvability itself is likely to change in this situation. Carter et al. (2005) showed that the per generation change in the additive variance in a polygenic trait under linear selection with a selection gradient β is

$$\Delta V_A = 2\beta(C_3 + \varepsilon V_A^2) + \mathrm{o}(\beta),$$

where C_3 is the additive-genetic third cumulant of the trait, ε is a measure of directional epistasis, and $\mathrm{o}(\beta)$ designate terms that vanish under weak selection. The third cumulant is positive when there is positive skew in the distribution of genetic effects, which will happen if alleles that increase the trait tend to be rare. Hence, this term describes the leading effects of allele-frequency changes on the variance, which will increase if rare alleles tend to increase in frequency, but decrease if common alleles tend to increase in frequency. The second term describes the leading effects of epistasis. A positive ε means that allele substitutions with positive effects on the trait tend to elevate the effects of other genetic changes, and a negative ε means that allele substitutions with positive effects on the trait tend to depress the effects of other genetic changes. Hence, positive epistasis in the direction of selection will increase evolvability, while negative epistasis in the direction of selection will decrease evolvability. Note that this has nothing to do with build-up of linkage disequilibrium or hitchhiking of alleles.

An important insight from this model is that the evolution of evolvability under directional selection does not depend on whether it is favorable to the population. Whether the evolvability is increasing or decreasing under linear directional selection depends, at least to a first approximation, on the details of the variational architecture. The main factor determining whether evolvability will increase or decrease is the directionality of epistasis. This stems from the fact that directional epistasis determines the correlation between the trait and its variability. Positive directional epistasis implies a positive correlation in the sense that increasing the trait will also make it more variable. Changing a trait in a direction of positive epistasis will tend to elevate the effects of new mutations, and thus the input of new mutational variance (Hansen et al. 2006).

We can now recognize the mechanism for evolution of evolvability in this model as indirect selection. Direct selection on the trait generates indirect selection on trait variability, and this indirect selection can be positive or negative, depending on whether the correlation between the trait and its variability is positive or negative. In this light, Hansen (2011) proposed that trait evolvability mainly evolves as a correlated response to trait evolution. The argument is that such indirect selection is likely to be ubiquitous, strong, and variable, and it will tend to swamp weaker effects of alternatives, such as genetic drift and canalizing selection.

7.2.5 Adaptive, Canalizing, Conservative, and Hitchhiking Selection on Alleles

Trait selection has complex and sometimes counterintuitive effects on the underlying genes. In this section, we decompose the gene-level effects of directional and stabilizing selection on a trait into four distinct forces and discuss their interplay in the evolution of evolvability. This section is technical, and a theory-averse reader may skip to the next section. In a nutshell, we show that the effects of selection on a gene can be decomposed into (1) an *adaptive force* favoring allele substitutions that improve trait adaptation, (2) a *canalizing force* favoring alleles that epistatically reduce the effects of other alleles when

the fitness function is concave (and disfavors them when it is convex), (3) a *conservative force* that acts against rare alleles when the fitness function is concave, and (4) a *hitchhiking force* favoring alleles in positive linkage disequilibrium with other favorable alleles.

Let $z = z(a_1, \ldots, a_n, y)$ be a trait that is a function of the state of a number of loci, a_1 to a_n, as well as a focal locus, y, the effects of which we will examine. We will follow Hansen and Wagner (2001) in measuring the genotypic state of all the loci on a scale set by the phenotypic effect they will have if substituted into a given reference genotype. That is, $y = z(a_1, \ldots, a_n, y) - z(a_1, \ldots, a_n, 0)$, where all the other loci are at their reference values, which by definition are $a_i = 0$ for all i. We will take the reference values of the as to be their population means. Let the relative fitness of the phenotype, z, be $w(z)$, and consider this as a function of the state of our focal locus. In the appendix, we show that the change in relative fitness due to substituting $y = y$ for $y = 0$ in an epistatic trait architecture is

$$s \approx \beta y - \gamma^2 \left(\varepsilon_1 + \frac{1}{2}\delta_1 \right) V_A y - \frac{1}{2}\gamma^2((1+\delta)^2 + \varepsilon_2 V_A)y^2 + \beta\left(\delta + \left(\varepsilon_3 + \frac{\delta_2}{2} \right) y \right) y,$$

where β and $-\gamma^2$ are the first- and second-order selection gradients on the trait, and V_A is its additive genetic variance. The epsilons and the deltas, defined in the appendix, are measures of patterns of epistasis and linkage disequilibrium. The ε_1 is a measure of the directional epistatic contribution of the change. This is the measure of y's effect on evolvability; it will be positive if the change y tends to elevate the effects of other loci, and negative if y tends to reduce the effects of other loci. The directional epistatic ε-parameter discussed in section 7.2.4 is a weighted average of the ε_1 across all loci affecting the trait. The ε_2 is a measure of the magnitude of the epistatic modifications due to y; it will usually be positive. The ε_3 measures whether the directionality of the epistatic modifications matches the linkage disequilibrium between y and the loci it modifies. The δ is the summed linkage disequilibrium between y and the as, so that the product δy is a measure of how much carriers of the y-genotype differs from other individuals due to disequilibrium with other loci. The δ_1 and δ_2 measure how epistasis among the a-loci matches patterns of linkage disequilibrium.

The four terms in the equation illustrate four distinct forces of selection on our focal locus. The first term, βy, describes an *adaptive* force due to trait adaptation. An allelic substitution is favored if it changes the trait in the direction of selection, and as discussed above, this may generate indirect selection on evolvability. This force is likely to dominate the dynamics if the trait is not at a fitness equilibrium, and its effect on evolvability will depend on the directionality of epistasis (ε_1). The second term describes a *canalizing* force. An allelic substitution with a net canalizing effect ($\varepsilon_1 < 0$) will be favored under stabilizing selection ($\gamma^2 > 0$), while a substitution with a net decanalizing effect (i.e., increasing evolvability ($\varepsilon_1 > 0$)) will be favored if there is positive curvature ($\gamma^2 < 0$) in the fitness landscape. There is also a canalizing effect due to directional third-order fitness epistasis between y and pairs of a-loci (the δ_1 term). Under stabilizing selection, this will favor changes in a direction opposite to the direction of epistasis between loci in positive linkage disequilibrium. The third term describes a *conservative* force acting against any change under stabilizing selection ($\gamma^2 > 0$). Because it increases with the square of the effect of the change (i.e., with y^2), the conservative force will overpower the other forces when the effect size

of the mutation increases, and thus block mutations above a certain size from participating in both adaptation and systems drift under stabilizing selection. For example, ignoring linkage disequilibrium and directional selection, a canalizing mutation cannot be favorable if its phenotypic effect, y, exceeds $2\varepsilon_1 V_A$, which is quite strict. If we assume that the mean-scaled additive variance (i.e., the evolvability) is 0.1%, then a mutation with an average 10% modification of other loci would have to have a phenotypic effect less than 1% to have any possibility of being favored under stabilizing selection.

These three forces were named in Le Rouzic et al. (2013), who derived them for a general multilinear epistatic architecture but without linkage disequilibrium (see also Hermisson et al. 2003). The fourth term describes a *hitchhiking* force due to linkage disequilibrium between the focal change and favorable alleles (δ and ε_3), or favorable combinations of alleles (δ_2), at other loci. Any new mutation will necessarily appear in a particular genetic background, and its initial dynamics, and hence invasion probability, will be influenced by this association. Under free recombination, the initial association is rapidly broken down, but random linkage disequilibrium may still affect its dynamics, as in the Hill-Robertson effect (Felsenstein 1974). While these mechanisms will have indirect and haphazard effects on evolvability, we can also recognize the gene-level adaptation discussed in section 7.2.2 as deriving from this type of hitchhiking. If the focal evolvability-enhancing allele is causally involved in making its associated alleles more favorable, then the hitchhiking can be considered as direct selection for evolvability. This may happen directly through epistatic modification of the associated alleles (the ε_3 term) or through modification of mutation or recombination rates that increases the chance of the focal allele becoming associated with something adaptive. To be effective, such adaptive hitchhiking requires some mechanism for maintaining the specific association. This can come about through tight linkage, population structure, or selection. Pavličev et al. (2011) presented a model of how epistatic modifiers of multivariate genetic variation can be maintained in linkage disequilibrium with their target genotype by selection in the face of recombination, thereby generating changes in the G-matrix that match patterns of directional selection (see also Wagner and Bürger 1985).

To fully understand the evolution of genetic changes that modify evolvability, we must consider all these forces, as well as genotype-by-environment interaction and genetic drift (see sections 7.2.6 and 7.2.7 below). For example, while stabilizing selection on the trait induces canalizing selection on the underlying loci, this force is unlikely to drive evolvability to zero, because it will conflict with other forces (Hermisson et al. 2003; Le Rouzic et al. 2013). In particular, as the canalizing force weakens with reduced additive variance, while the conservative force is less affected, there will be a lower limit to the canalization that can be achieved. This lower limit will be larger if stabilizing selection is stronger, and we get the counterintuitive result that stronger stabilizing selection may lead to a less-canalized genetic architecture with larger mutational effects (Wagner et al. 1997; Le Rouzic et al. 2013).

Hence, two findings from this analysis are that evolvability in the sense of allelic (and mutational) effect sizes (1) is likely to evolve in idiosyncratic manners that depend on details of genetic architecture and patterns of selection, and (2) will be robustly maintained at a nonzero level due to haphazard indirect selection, the conservative force, and inevitable mutation bias against perfect canalization. The analysis further identifies two possible mechanisms for adaptive increase of evolvability. One is through hitchhiking with favorable alleles generated by the evolvability-enhancing mechanism (the ε_3 term), and the other is through decana-

lizing selection in a convex fitness landscape (the ε_1 term). As fitness landscapes are more likely to be concave when populations are well adapted (close to fitness peaks), the latter force may normally act to reduce evolvability through adaptive canalization, but there may be situations in changing or fluctuating environments in which the population is temporarily in convex (or less concave) areas of the fitness function, which may act to elevate evolvability relative to more stable environments (Le Rouzic et al. 2013; see also Layzer 1980).

7.2.6 Congruence

Genetic effects can also evolve due to associations with environmental variation. A paradigmatic example is Haldane's theory for dominance evolving as a side effect of selection for the wild-type allele to be robust against unusual environmental conditions (Bagheri 2006). This example has been generalized to the proposal that genetic canalization evolves as a side effect of environmental canalization (Wagner et al. 1997; Ancel and Fontana 2000; Meiklejohn and Hartl 2002; de Visser et al. 2003). This *congruence hypothesis* is based on the idea that genetic and environmental robustness may result from similar physiological mechanisms, and if selection favors robustness against environmental perturbations, then it will indirectly favor robustness against genetic perturbations (i.e., allele substitutions). In general, robustness will be favored in concave fitness landscapes, and environmental variation will then add a force of indirect canalizing selection on genetic effects similar to the (genetic) canalizing force discussed above.

7.2.7 Neutral Evolution of Evolvability

Michael Lynch (e.g., 2005, 2007) has argued that many aspects of genome architecture are determined by genetic drift and mutation pressure. The key to his argument is that weak selection is inefficient in small populations. A common rule of thumb is that fitness differences need to be larger than $1/4N_e$ to dominate genetic drift and mutation pressures. To see what this means, consider that the ratio between the fixation probabilities of an advantageous and a disadvantageous allele with a (heterozygous) fitness difference of s is approximately e^{4sNe} (Bürger and Ewens 1995). Hence, if $s = 1/4N_e$, then the ratio of the fixation probabilities is merely $e^1 \approx 2.71$, which would allow frequent invasions of the deleterious allele and not be sufficient to overcome even mild differences in mutation rate. Increasing either the fitness difference or the effective population size by an order of magnitude, however, would increase the ratio of the fixation probabilities by three orders of magnitude and make selection very powerful relative to drift. Lynch has argued that the relevant measures of N_e for many multicellular organisms, like plants and animals, are often quite small, usually less than 10,000. This means that genotypes with fitness differences below a few hundredths of a percent or so will be practically indistinguishable by selection. Even fitness differences of a percent or more may be dominated by drift, mutation, or rare migration in local populations of large-bodied organisms.

These facts limit the potential for fine-tuning genetic architecture in multicellular organisms. If we ignore linkage disequilibrium, we can rewrite the canalizing force discussed above as $2\varepsilon_1 yL$, where L $(= \gamma^2 V_A/2)$ is the load generated by the curvature in the fitness function, and $\varepsilon_1 y$ is the average modification of the effect of substitutions at other loci. If the trait generates a strong fitness load of 10%, and our substitution generates a large 10% average modification of other loci, we see that the canalizing force generates a fitness advantage of

$s = 2\%$ for the canalizing allele, which would only need $N_e = 12.5$ to generate a ratio of fixation probabilities equal to e^1 and be effective in generating canalizing adaptations with effective population sizes above 100 or so. These numbers are only realistic, however, if the focal locus can modify many loci in a consistent manner. An epistatic modification of 10% of one other locus out of say 100 affecting the trait, would make $\varepsilon_1 y = 0.001$, and $s = 0.02\%$, which would require $N_e = 1250$ just to generate a ratio of fixation probabilities equal to e^1. In practice, then, there is little room for adaptive canalization (or decanalization) on a locus-by-locus basis in multicellular organisms. If adaptive canalization of polygenic traits happens at all, it must be through systemwide modifications that allow the simultaneous change of many loci at once. This point has been argued by Proulx and Phillips (2005) based on related considerations, which they extend to other aspects of the evolution of genetic architecture, such as the evolution of dominance and the invasion of gene duplications.

According to Lynch (2007), the large, redundant, and complex genomes of multicellular plants and animals can be explained by the accumulation of mildly deleterious changes that slip under the resolution of selection. Such changes include the invasion and subfunctionalization of genes after duplication, the expansion and modularization of regulatory sites, the expansion of introns, and the proliferation of transposable elements. All these processes may facilitate evolvability. For example, the invasion and subfunctionalization of duplicated genes is likely to be slightly deleterious but sets up a potential for subdivision and specialization of function that can be used to provide more refined adaptation. The expansion of gene families and regulatory elements provides for a richer toolbox to be used for future evolution. In these cases, evolvability evolves as a contingent side effect of the changes in genome architecture, but unlike the mechanisms discussed above, this is not due to indirect selection deriving from other functions but is due to the near-neutral accumulation of slightly deleterious changes.

Some limitations of the efficacy of selection are also likely to hold for unicellular and small-bodied organisms, as increasing population sizes may increase the frequency of selective sweeps that cause stochastic changes on linked loci with effects similar to genetic drift. Gillespie (2000) has referred to this as genetic draft, and it puts upper limits on the (long-term) effective population size, even when the census size is practically infinite (Lynch 2007).

Systems drift is another neutral mechanism relevant to the evolution of evolvability (e.g., True and Haag 2001; Hahn et al. 2004; McCandish 2018). If a character under stabilizing selection has a polygenic architecture, then many different genotypes may generate the same optimal character state. If the subspace formed by these genotypes is connected through genetic steps that slip under the resolution of selection, then neutral evolution can proceed in this subspace. As the different genotypes in the subspace may have different variational properties (i.e., different mutational spectra), we have the potential for evolution of evolvability without changes in the trait itself.

Many have argued that the neutral exploration of such subspaces, or neutral networks, allows evolution to find or poise itself for new innovations (Kauffman 1993; Schuster et al. 1994; A. Wagner 2005, 2008; Payne and Wagner 2014). This mechanism sets up the possibility of a positive relationship between robustness and evolvability, in that increasing robustness will decrease the phenotypic differences between genotypes, which will increase the size of near-neutral subspaces. More robust characters or genotype-phenotype maps may therefore be more evolvable in the sense of being able to better explore their genotypic

neighborhood. Systems drift is also the main mechanism for the evolution of postzygotic reproductive isolation through the Bateson-Dobzhansky-Muller process, and may thus facilitate local adaptation, speciation, and species selection by reducing gene flow between incipient species.

7.2.8 System-Level Contingency

Many aspects of evolvability are not character specific but outcomes of general organismal architecture or population properties. Species- or population-level properties, such as population density, distribution range and structure, mating system, reproductive rates, and modes of dispersal, will affect the evolvability of the whole organism, as will rates and accuracy of development, modes of reproduction and inheritance, and mechanisms of homeostasis and plasticity. The evolution of any such property will generate contingent changes in the evolvability of specific characters. We will discuss some of these properties in section 7.3, and many others are discussed in other chapters of this book. Here we just emphasize the distinction between character-specific and general evolvability. One fundamental aspect of the evolution of evolvability is the evolution of distinct characters in the first place. The emergence of a variationally quasi-independent character also implies the emergence of a quasi-independent character-specific evolvability, which is likely to be contingent on the developmental origin of the character (Wagner 2014).

Changes in the developmental or genetic system may also be instrumental in the maintenance of evolvability when they become integrated into the body plan or life cycle of the organism in ways that cannot be easily undone. Major transitions such as multicellularity; sexual reproduction; and the evolution of organizers, axes, or symmetries in the body plan are likely to get "burdened" when other traits are organized around them, and their effects on evolvability are then frozen and maintained, even if these effects by themselves become unfavorable to the individual organisms or populations carrying them. A genetic instantiation of this process is the maintenance of duplicated genes after subfunctionalization has rendered the duplicates complementary and both essential.

7.3 Organismal Properties Related to Evolvability and Their Evolution

Table 7.1 lists some properties that may influence evolvability with suggested modes of evolution. Many of these properties are discussed elsewhere in this book, and here we only provide a few selected reviews to illustrate the application of our theoretical concepts and perspectives.

7.3.1 Sex and Recombination

The realization that sexual recombination can produce new variation transcending current phenotypic ranges was perhaps the first major insight in evolvability in the modern synthesis, and it was instrumental in the acceptance of the efficacy of natural selection (e.g., Beatty 2016). Consequently, and in fact going back as far as Weismann (1889), the idea arose that the function of sexual reproduction was to generate variation for natural selection to act on (e.g., Dobzhansky 1937). Although sexual recombination is crucial for the maintenance of evolvability in multicellular organisms, this is not a sufficient explanation for its evolution. There are individual-level costs to sexual reproduction, and its maintenance

Table 7.1
Properties that influence evolvability with suggested modes of evolution of evolvability

Property	Effect on evolvability	Mode of evolution
Variation[5,6,12,13,14]	Allows selection	*G, MS, C, G*
Mutability[5,7]	Source of variation	
Mutation rate[7]		A_i, *S*, A_g
Mutation effect[7,11]		*C, K*, A_i
Mutational target[7]		*N, C*, A_i
Recombination[7]	Generates new variation. Allows complex adaptation	A_g, A_i, *S*
Mating system[12]	Affects maintenance of variation	*S*, A_g
Symmetry[7,10,15,17]	Constraint and facilitator	*S, K*
Modularity[7,8,15,17]	Facilitates quasi-independence	
Cis regulation[9]		*C, N*
Pleiotropy[8,9,10,16]		*C, K*, A_i
Char. identity[15]		*S*
Continuity/fidelity[7,15]	Allows complex adaptation	*C, S, K*
Robustness[8,11,16]	Allows systems drift and hidden variation	*G, K*
Plasticity[5,13]	Capacitance, Baldwin effect	*C*
Epistasis[7,8,9,10]	Allows evolution of gene effects	*C, K*
Individuality[16]	Transition of selection level, facilitates specialization	*S*, A_g

Notes: The letter *A* signifies evolving as an adaptation for evolvability, with A_i specifying individual or gene-level adaptation and A_g specifying group or species adaptation. Contingent evolution is indicated by *C* when the indirect selection stems from the trait in question and by *S* when the indirect selection stems from systems-level properties (including selective constraints and burden). Neutral evolution is indicated by *N*, canalizing selection by *K*, congruent selection by *G*, and mutation-selection balance by *MS*. Relevant chapters are indicated by superscripted numbers: 5 Hansen, 6 Houle and Pélabon, 7 this chapter, 8 Pavličev et al., 9 Hallgrímsson et al., 10 G. Wagner, 11 A. Wagner, 12 Sztepanacz et al., 13 Pélabon et al., 14 Voje et al., 15 Armbruster, 16 Galis, 17 Jablonski.

requires powerful selection pressures or constraints (Williams 1975). Given that obligate asexuals are rare and phylogenetically short-lived, the maintenance of sex has been called the queen of problems in evolutionary biology (Bell 1982). Despite much research and a multitude of hypotheses, no complete consensus has appeared (Hartfield and Keightley 2012).

The many hypotheses for the evolution of sex and recombination span most modes of evolution that we have discussed above. The most direct link to evolvability is found in the Red Queen hypothesis, which in its original formulation explains the maintenance of sex as a group- or species-level adaptation for evolvability in a changing biotic environment (Maynard Smith 1978). The hypothesis subsequently has become more focused on sex as an adaptation to deal with arms races with evolving parasites that tend to adapt to common genotypes, thus giving an advantage to rare and novel genotypes. In some of these formulations, the advantage is more on the individual than on the population level, and they would have been better labeled as cases of the tangled-bank hypothesis than as cases of the classic Red Queen hypothesis. According to the tangled-bank hypothesis (Ghiselin 1974; Bell 1982), sex is maintained as an adaptation for producing variable offspring to increase the chances that some are successful in an uncertain environment. We have outlined how this could be constructed as an individual- or gene-level adaptation for evolvability, but note that some related individual-advantage hypotheses for sex, such as reducing local or sibling competition, do not locate the advantage in evolvability, which would then evolve as a

side effect. Nevertheless, some form of higher-level selection remains a plausible mechanism for the maintenance of sex (e.g., Nunney 1989). Furthermore, sex and recombination as adaptations for evolvability on some level is supported by their tendency to be more frequent in, and sometimes being induced by, stress and environmental degradation.

Some hypotheses for the maintenance of sexual recombination are based on advantages to breaking up linkage disequilibrium (Felsenstein 1974; Otto 2009; Hartfield and Keightley 2012). These advantages may include reduction of the mutation load in the presence of synergistic epistasis among deleterious alleles (the deterministic-mutation hypothesis), a reduction of the fixation load (Muller's ratchet), or a reduction of selective interference between advantageous alleles (the Fisher-Muller hypothesis). In each case, some form of group-level advantage seems plausible. For the Fisher-Muller hypothesis, the population advantage is in terms of elevated evolvability, which is then maintained as a group adaptation. For the other hypotheses, the link to evolvability is less obvious, but one can view the proposed advantages as facilitating the maintenance of complex adaptations, and to the extent that allowing the maintenance of complex adaptations is seen as an aspect of evolvability, the deterministic-mutation and Muller's-ratchet hypotheses also explain the maintenance of sex as an adaptation for evolvability. The tendency for sex to be less common in marginal environments can also be seen in this light as an adaptation to protect local adaptations from dilution due to external gene flow.

Sexual recombination is fundamentally integrated with organismal architecture. There are associations with meiosis, replication and DNA repair on the cellular level, and with dispersal and life-cycle stages on the organismal level. The evolution of evolvability may be constrained by all these factors. In some cases, this may result in absolute constraints or a "burden" that maintains sex and evolvability in the face of short-term costs on the individual level. The fact that there are no known asexual mammals may reflect a particularly severe constraint against parthenogenetic development in this clade (perhaps due to gamete-specific imprinting). Increased recombination may also evolve through near-neutral expansions of genomes rendering more complex, larger-bodied organisms more evolvable than microorganisms with leaner genomes (Lynch 2007).

7.3.2 Coordinated Variation (Continuity, Modularity, Symmetry)

Lewontin (1978) suggested that adaptive evolution requires two preconditions that he called continuity and quasi-independence. Continuity "means that small changes in a characteristic must result in only small changes in ecological relations" (i.e., fitness). Quasi-independence "means that there is a great variety of alternative paths by which a given characteristic may change, so that some of them will allow selection to act on the characteristic without altering other characteristics of the organism" (i.e., modularity). These two properties can be seen as manifestations of a more general property, which we call coordinated variation. The key point is that biological organisms are so complex and multidimensional that their variations must be organized, partitioned, and channeled to be usefully selected. Selection cannot optimize thousands of parts, genes, and traits simultaneously, and the potential for selective interference grows multiplicatively with increasing complexity. The only way to optimize many parts without eliminating variation altogether is to organize the variation along a limited number of functional lines (Wagner and Altenberg 1996). How this comes about is perhaps the most difficult question in evolvability

research. The many contingent modes of evolution render it almost paradoxical, and we regard this problem as substantially unsolved.

Riedl (1978) suggested that complex organisms are evolvable because their variational and functional interdependencies are congruent rather than in conflict. He called this principle the "immitatory epigenotype," because the developmentally integrated parts of the organism (the "epigenotype") "imitates" functional interdependencies among the parts. This leads to the question of whether direct selection for evolvability is responsible for the correspondence between functional and variational constraints. This question has been explored in the context of the evolution of modularity. Variational modularity is a statement about the distribution of environmental and genetic perturbations on a set of traits. A variational pattern is said to be modular if there are sets of traits that more likely vary together and quasi-independently from other traits. From the genetic point of view, modularity can be seen as a pattern of pleiotropy, in which certain genes primarily affect a subset of phenotypic traits and others less. The nature and distribution of pleiotropic effects are themselves genetically influenced and therefore evolvable, which raises the question of what evolutionary forces shape the pattern of pleiotropy (Pavličev and Cheverud 2015). Wagner (1996) proposed that functional modularity could emerge from a combination of stabilizing and fluctuating directional selection. Later, many studies have found that pleiotropy or mutational variation can potentially evolve to align with patterns of selection/function (e.g., Hansen 2003; Kashtan and Alon 2005; Jones et al. 2007, 2014; Draghi and Wagner 2008; Pavličev et al. 2011; Melo and Marroig 2015). The generality of such results is unclear, however. The evolution of pleiotropy is a special case of the evolution of gene effects and thus subject to all the forces we have discussed above. Due to the conservative force discussed in section 7.2.5, strong stabilizing selection may block canalization, and the relationship of mutational canalization to strength of stabilizing selection is nonlinear with a minimum at intermediate strengths of selection (Wagner et al. 1997; Hermisson et al. 2003; Le Rouzic et al. 2013). As a result, we expect a nonlinear relation of evolvability to strength of stabilizing selection across directions in morphospace. In the presence of directional selection, the evolution of multivariate evolvability will be determined by multivariate patterns of directional epistasis, which makes a simple alignment with patterns of selection unlikely. In many models of the evolution of modularity, the outcome is as much influenced by internal constraints or biased sets of alternatives as by the pattern of selection acting on the phenotype (Gardner and Zuidema 2003; Hansen 2011; Guillaume and Otto 2012).

Body symmetries and metamerisms are examples of structural features coordinating variation and thus facilitating evolvability in some dimensions while constraining it in others (e.g., Jablonski 2020). Such symmetries may evolve for functional reasons, which may cause the evolution of functionally organized evolvability by indirect selection. For example, variation along a left-right axis could become canalized due to selection for increased developmental robustness if left-right differences are largely deleterious in an elongated moving organism. A likely side effect is an "immitatory" canalization of genetic and mutational effects, which will symmetrize and facilitate evolvability. A related example emphasized by Gerhart and Kirschner (1997) involves tissue organization, in which the ability of a growing organ to recruit vascularization to ensure an adequate supply of oxygen and nutrients according to need is functional in terms of allowing growth and accommodating size differences in the organ. Selection for such recruiting mechanisms will then

indirectly select for evolvability, as they allow evolutionary changes in the size of the organ without the need for genetic changes in vascularization. We can recognize these examples as instances of congruent evolution, and note how congruence may allow organization of genetic variability along functional lines by means of indirect selection. Conversely, congruence may also reduce evolvability along functionally important axes due to canalizing selection in these directions.

As for the continuity or smoothness of the genotype-phenotype map, it is clear that the evolution of complex adaptations requires a supply of small-effect modifications that combine at least partly additively. Although it is an empirical fact that many genotype-phenotype maps are continuous and order-preserving in this sense (e.g., Gjuvsland et al. 2011), it is unclear why they have these properties. Kauffman (1993) argued that these properties are not expected in complex random interaction networks and inferred that some level of developmental and gene-regulatory order was necessary for evolvability. Based on the above theory, it seems likely that this would require systematic canalizing selection. Some studies have also found that epistatic interactions, and thus the ruggedness of the genotype-phenotype map, tend to be canalized under selection, thus favoring the evolution of a degree of additivity (Hermisson et al. 2003; Hansen et al. 2006; Le Rouzic et al. 2013). Continuity is also a function of the fidelity of inheritance, and it is thus preconditioned on the establishment of an accurate replication mechanism.

7.3.3 Mutability

While segregating variation in sexual populations normally holds potential for change far outside the original range, there comes a point at which new mutations are needed for further change. The amount of mutational input is variable across traits and taxa (Houle 1998) and may change either through changes in the phenotypic effects of new mutations or through their rate of appearance.

The evolution of mutational effects, as opposed to rates, is a special case of the evolution of allelic effects and is largely determined by patterns of epistasis. When the genetic background is changing, effects of new mutations will change in accordance with their epistatic relation to the genetic background (e.g., Hansen et al. 2006). A more specific mechanism for the evolution of mutational effects (including pleiotropy) is in terms of "inherited allelic effects" (Hansen 2003, 2006, 2011). This is a form of intralocus epistasis in which subsequent mutations on the same allele inherit the variational properties established by previous mutations. For example, a mutation establishing a new cis-regulatory module may not only cause expression of the gene in a novel context but may also change the mutational spectrum to make subsequent mutations in the same allele more likely to have effects in this novel context. In this case, there is an automatic association between trait effects and mutability, which facilitates the evolution of evolvability and may even lend itself to gene-level adaptation for evolvability, as outlined in section 7.2.2. The adaptation is not automatic, however, and favorable trait changes may also be achieved through elimination of regulatory elements, which may reduce evolvability.

The evolution of mutation rates is perhaps the best-studied case for potentially adaptive evolution of evolvability (Good and Desai 2016). From microbial systems, there is evidence for elevated mutation rates in stressful or novel environments (Cox and Gibson 1974; Radman et al. 1999; Metzgard and Wills 2000; Caporale 2003; Galhardo et al. 2007;

Diaz-Arenas and Cooper 2013). The extent to which this is an evolved adaptation for evolvability or just a side effect of stress on replication fidelity is debatable (e.g., Sniegowski and Murphy 2006), but our criterion for adaptive evolution can apply to modifiers of mutation rate, because a hypermutator allele will directly cause and (in bacteria) stay linked to elevated mutation rates and may thus be favored in situations in which evolvability is advantageous.

Still, there are more deleterious than advantageous mutations, and therefore selection to improve replication fidelity and reduce rates of mutation could be effective. Such canalizing selection will not drive mutation rates to zero, however, as the supply and effect of antimutator alleles must decrease with increasing canalization and hit a balance with increasing mutation bias toward increased rates (Lynch 2008). Mutation rates are also influenced by physiology and genome architecture, which expose them to indirect selection that may overwhelm direct selection for evolvability. The large patterns in the evolution of mutation rates are therefore likely to be contingent side effects of other changes. For example, transposable elements may increase mutation rates, and although it has been argued that transposable elements are maintained to favor evolvability (McClintock 1984), it is difficult to rule out alternatives, such as the elements acting as genomic parasites replicating for their own benefit and causing mutations as a side effect (Sniegowsky and Murphy 2006; Lynch 2007). This possibility is also supported by the existence of evolved systems (e.g., pi-RNAs and possibly methylation) to suppress such elements (Zemach et al. 2010; Kofler 2019). Although such systems could possibly be exapted into capacitors that could release dormant elements to boost evolvability in times of stress, it seems likely that their primary adaptive function is to suppress the elements.

The major determinant of trait-specific mutation rates may be the number of genes or genomic positions that potentially affect the trait. Houle (1998) put forward the hypothesis that trait differences in standing additive variation are largely determined by the mutational target size of the trait. This hypothesis goes a long way toward explaining why complex traits, such as fitness, life-history, and behavior, are more evolvable than simple morphological traits, and it suggests that the recruitment and elimination of genes affecting a trait are crucial to the long-term evolution of its evolvability. Genes may be recruited or eliminated by regulatory evolution, gene duplication, subfunctionalization, and pseudogenization, which are all subject to contingent changes unrelated to evolvability. For example, the maintenance of duplicated genes may depend less on future evolvability than on accidental subfunctionalization that renders both copies necessary (Force et al. 1995).

The impact of mutations on evolvability depends on how well they are maintained in the population. Selection acts on standing variation, and the relationship of standing variation to mutation is complicated and the subject of a huge literature, which we will not review here. Standing variation in mutation-selection balance not only depends on the mutation rate but also on genetic architecture in the form of mutational effect sizes, number of loci, epistasis, dominance, and pleiotropy. It is further influenced by external factors, such as the mode and strength of selection, population size and structure, recombination rates, mating system, and environmental variation. All these are prone to change for reasons unrelated to evolvability, which sets up contingent change as a major factor in the evolution of population evolvability as captured by the G-matrix.

7.4 Conclusion

After research on the evolution of evolvability started in earnest some 30 years ago (see Nuño de la Rosa 2017, and chapters 2 and 3[1]), there have been many advances in terms of hypotheses, concepts, and mathematical formalism. The field has progressed from loose verbal models and computer simulations with tenuous connections to biological facts to theory well grounded in mathematical population genetics, evolutionary theory, and molecular biology. This research has shown that there is nothing paradoxical about the evolution of evolvability and that it does not require any special higher-level selection to work. It is possible for the evolution of evolvability to proceed by conventional within-population selection at the gene or individual level. This does not exclude group- or lineage-level selection, however, which remains relevant in many specific cases (see table 7.1). It has further become clear that evolvability is susceptible to various forms of indirect selection and contingencies, and the degree to which organisms are adapted for evolvability is unsettled. Systems drift and other forms of (nearly) neutral evolution may also be important. Many aspects of evolvability are fundamentally integrated with organismal body plans and life cycles. They are thus subject to deep constraints and major transitions that must be considered for a full understanding of the subject. Finally, the genotype-phenotype map has emerged as the focal determinant of evolvability, and it has been made clear that epistasis controls the evolution of evolvability on the proximate level.

Empirical research is lagging, however. There has been progress in the empirical understanding of patterns, determinants, and consequences of evolvability through research on the developmental, physiological, and molecular basis of the genotype-phenotype map, on the quantification of genetic and mutational variation, and on molecular changes in experimental evolution. But there has been less research that directly addresses the evolution of evolvability. We only have anecdotal information about actual evolution of evolvability in nature, and selection experiments have rarely been used—and almost never set up—to test hypotheses about the evolution of evolvability (but see A. Wagner, chapter 11). There is a shortage of relevant information on crucial parameters, such as patterns of epistasis and pleiotropy. We also lack quantitative comparative studies of evolvability, which would be essential to test the theory.

7.5 Appendix

Let the relative fitness of a genotype $\{a_1, \ldots, a_n, y\}$ with phenotype z be $w(z(a_1, \ldots, a_n, y))$. The marginal fitness of the genotype y at the focal locus is then $\mathrm{E}[w(\mathrm{z}(a_1, \ldots, a_n, y)\,|\,y]$, where the expectation is taken over the values of the vector $\mathbf{a} = \{a_1, \ldots, a_n\}$. Let the variance matrix of this vector be $\mathbf{A}$, and take the mean of the a_i as reference genotype. For simplicity, assume that $\mathbf{A}$ does not depend on y, but we allow the possibility of the change y being in linkage disequilibrium with the a-vector by assuming $\mathrm{E}[\mathbf{a}\,|\,y] = \mathbf{b}_{\mathbf{a}y}y$, where $\mathbf{b}_{\mathbf{a}y}$ is the vector linear gradient ("regression") of $\mathbf{a}$ on y. By a second-order Taylor approximation around the reference value of $\mathbf{a} = 0$, we get

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

$$\begin{aligned}\mathrm{E}[w(z(\mathbf{a},y)\,|\,y] &\approx w(z(\mathbf{0},y)) + \left(\frac{\partial w(z(0,y))}{\partial \mathbf{a}}\right)^T \mathrm{E}[\mathbf{a}\,|\,y] + \frac{1}{2}\,\mathrm{E}\left[\mathbf{a}^T \frac{\partial^2 w(z(0,y))}{\partial \mathbf{a}\,\partial \mathbf{a}^T}\,\mathbf{a}\,|\,y\right] \\ &= w(z(\mathbf{0},y)) + \left(\frac{\partial w(z(0,y))}{\partial \mathbf{a}}\right)^T \mathbf{b}_{\mathbf{a}y} y + \frac{1}{2}\mathrm{Tr}\left(\frac{\partial^2 w(z(0,y))}{\partial \mathbf{a}\,\partial \mathbf{a}^T}\mathbf{A}\right) \\ &\quad + \frac{1}{2}\mathbf{b}_{ay}^T \frac{\partial^2 w(z(0,y))}{\partial \mathbf{a}\,\partial \mathbf{a}^T}\mathbf{b}_{ay} y^2,\end{aligned}$$

where Tr is the trace function, and $\frac{\partial^2 w(z(0,y))}{\partial \mathbf{a}\,\partial \mathbf{a}^T}$ is the Hessian matrix of $w(z(\mathbf{a}, y))$ with respect to $\mathbf{a}$ evaluated at $\mathbf{a} = 0$. A second-order Taylor approximation of fitness with respect to y around $y = 0$ now gives

$$\begin{aligned}\mathrm{E}[w(z(\mathbf{a}, y)\,|\,y] &\approx \mathrm{w}_0 + \frac{\partial w}{\partial y} y + \frac{1}{2}\frac{\partial^2 w}{\partial y^2} y^2 + \left(\frac{\partial w}{\partial \mathbf{a}}\right)^T \mathbf{b}_{\mathbf{a}y} y + \left(\frac{\partial^2 w}{\partial y\,\partial \mathbf{a}}\right)^T \mathbf{b}_{\mathbf{a}y} y^2 \\ &\quad + \frac{1}{2}\mathrm{Tr}\left(\left(\frac{\partial^2 w}{\partial \mathbf{a}\,\partial \mathbf{a}^T} + \frac{\partial^3 w}{\partial y\,\partial \mathbf{a}\,\partial \mathbf{a}^T} y + \frac{1}{2}\frac{\partial^4 w}{\partial y^2\,\partial \mathbf{a}\,\partial \mathbf{a}^T} y^2\right)\mathbf{A}\right) \\ &\quad + \frac{1}{2}\mathbf{b}_{ay}^T \frac{\partial^2 w}{\partial \mathbf{a}\,\partial \mathbf{a}^T}\,\mathbf{b}_{ay} y^2 + \, o(y^2),\end{aligned}$$

where we have simplified the notation and all differentials are evaluated at the reference genotype $\{\mathbf{a}, y\} = \{\mathbf{0}, 0\}$. The change in marginal fitness due to substituting a $y = y$ for a $y = 0$ genotype is then

$$\begin{aligned}\Delta w &= \mathrm{E}[w(z(\mathbf{a},y)|y] - \mathrm{E}[w(z(\mathbf{a},0)|y=0] \\ &\approx \frac{\partial w}{\partial y} y + \frac{1}{2}\frac{\partial^2 w}{\partial y^2} y^2 + \left(\frac{\partial w}{\partial \mathbf{a}}\right)^T \mathbf{b}_{\mathbf{a}y} y + \left(\frac{\partial^2 w}{\partial y\,\partial \mathbf{a}}\right)^T \mathbf{b}_{\mathbf{a}y} y^2 \\ &\quad + \frac{1}{2}\mathrm{Tr}\left(\left(\frac{\partial^3 w}{\partial y\,\partial \mathbf{a}\,\partial \mathbf{a}^T} y + \frac{1}{2}\frac{\partial^4 w}{\partial y^2\,\partial \mathbf{a}\,\partial \mathbf{a}^T} y^2\right)\mathbf{A}\right) + \frac{1}{2}\mathbf{b}_{ay}^T \frac{\partial^2 w}{\partial \mathbf{a}\,\partial \mathbf{a}^T}\mathbf{b}_{ay} y^2.\end{aligned}$$

The relevant partial derivatives of fitness evaluated in the reference genotype are

$$\frac{\partial w}{\partial y} = \frac{\partial w}{\partial z}\frac{\partial z}{\partial y} = \frac{\partial w}{\partial z} \equiv \beta,$$

$$\frac{\partial^2 w}{\partial y^2} = \frac{\partial^2 w}{\partial z^2}\left(\frac{\partial z}{\partial y}\right)^2 + \frac{\partial w}{\partial z}\frac{\partial^2 z}{\partial y^2} = \frac{\partial^2 w}{\partial z^2} \equiv -\gamma^2,$$

$$\frac{\partial w}{\partial \mathbf{a}} = \beta \mathbf{1}, \qquad \frac{\partial^2 w}{\partial y\,\partial \mathbf{a}} = -\gamma^2 \mathbf{1} + \beta\frac{\partial^2 z}{\partial y\,\partial \mathbf{a}}, \qquad \frac{\partial^2 w}{\partial \mathbf{a}\,\partial \mathbf{a}^T} = -\gamma^2 \mathbf{J} + \beta\frac{\partial^2 z}{\partial \mathbf{a}\,\partial \mathbf{a}^T},$$

$$\frac{\partial^3 w}{\partial y\,\partial \mathbf{a}\,\partial \mathbf{a}^T} = \frac{\partial^3 w}{\partial z^3}\mathbf{J} - \gamma^2\left(\frac{\partial^2 z}{\partial \mathbf{a}\,\partial \mathbf{a}^T} + \mathbf{1}^T\frac{\partial^2 z}{\partial \mathrm{y}\,\partial \mathbf{a}} + \left(\frac{\partial^2 z}{\partial \mathrm{y}\,\partial \mathbf{a}}\right)^T \mathbf{1}\right) + \beta\frac{\partial^3 z}{\partial y\,\partial \mathbf{a}\,\partial \mathbf{a}^T},$$

$$\frac{\partial^4 w}{\partial y^2 \partial \mathbf{a} \partial \mathbf{a}^T} = \frac{\partial^4 w}{\partial z^4}\,\mathbf{J} + \frac{\partial^3 w}{\partial z^3}\left(\frac{\partial^2 z}{\partial \mathbf{a}\partial \mathbf{a}^T} + 2\,\mathbf{1}^T \frac{\partial^2 z}{\partial \mathrm{y}\partial \mathbf{a}} + 2\left(\frac{\partial^2 z}{\partial \mathrm{y}\partial \mathbf{a}}\right)^T \mathbf{1}\right)$$
$$-\gamma^2\left(2\frac{\partial^3 z}{\partial y \partial \mathbf{a}\partial \mathbf{a}^T} + 2\left(\frac{\partial^2 z}{\partial y \partial \mathbf{a}}\right)^T \frac{\partial^2 z}{\partial y \partial \mathbf{a}} + \mathbf{1}^T \frac{\partial^3 z}{\partial y^2 \partial \mathbf{a}} + \left(\frac{\partial^3 z}{\partial y^2 \partial \mathbf{a}}\right)^T \mathbf{1}\right)$$
$$+\beta \frac{\partial^4 z}{\partial y^2 \partial \mathbf{a}\partial \mathbf{a}^T},$$

where $\mathbf{J}$ is an $n \times n$ matrix of ones, and $\mathbf{1}$ is a $1 \times n$ vector of ones. As illustrated in the first two equations, we have used the fact that all first derivatives of z with respect to $\mathbf{a}$ and y are unity when evaluated in the reference genotype. For further simplification, let us ignore the third- and fourth-order selection gradients and assume bilinear epistasis, which implies that the only nonzero derivatives of the trait are with respect to linear and bilinear combinations of the y and the a_i. Using this and feeding back into the above equation yields

$$\Delta w \approx \beta y + \beta \mathbf{1}^T \mathbf{b}_{\mathbf{a}y}\, y - \frac{1}{2}\gamma^2 y^2 - \frac{1}{2}\gamma^2 \mathrm{Tr}\left(\left(\frac{\partial^2 z}{\partial \mathbf{a}\partial \mathbf{a}^T} + \mathbf{1}^T \frac{\partial^2 z}{\partial y \partial \mathbf{a}} + \left(\frac{\partial^2 z}{\partial y \partial \mathbf{a}}\right)^T \mathbf{1}\right)\mathbf{A}\right) y$$
$$-\frac{1}{2}\gamma^2 \mathrm{Tr}\left(\left(\left(\frac{\partial^2 z}{\partial y \partial \mathbf{a}}\right)^T \frac{\partial^2 z}{\partial y \partial \mathbf{a}}\right)\mathbf{A}\right) y^2 + \frac{1}{2}\beta\, \mathbf{b}_{ay}^T \frac{\partial^2 z}{\partial \mathbf{a}\partial \mathbf{a}^T}\, \mathbf{b}_{ay} y^2 - \frac{1}{2}\gamma^2 \mathbf{b}_{ay}^T \mathbf{J} \mathbf{b}_{ay} y^2$$
$$-\gamma^2 \mathbf{1}^T \mathbf{b}_{\mathbf{a}y}\, y^2 + \beta\left(\frac{\partial^2 z}{\partial y \partial \mathbf{a}}\right)^T \mathbf{b}_{\mathbf{a}y} y^2.$$

Define the following composite parameters:

$$\varepsilon_1 = \sum_i \frac{\partial^2 z}{\partial y \partial a_i}\frac{\sum_j A_{ij}}{V_A}, \qquad \varepsilon_2 = \sum_i \sum_j \frac{\partial^2 z}{\partial y \partial a_i}\frac{\partial^2 z}{\partial y \partial a_j}\frac{A_{ij}}{V_A}, \qquad \varepsilon_3 = \sum_i \frac{\partial^2 z}{\partial y\, \partial a_i} b_{a_i y},$$

$$\delta = \sum_i b_{a_i y}, \qquad \delta_1 = \sum_i \sum_{j \neq i} \frac{\partial^2 z}{\partial a_i \partial a_j}\frac{A_{ij}}{V_A}, \quad \delta_2 = \sum_i \sum_{j \neq i} \frac{\partial^2 z}{\partial a_i \partial a_j}\, b_{a_i y} b_{a_j y},$$

where, as shown in Hansen and Wagner (2001), $V_A = \sum_i \sum_j A_{ij}$ is the additive genetic variance (including "hidden" variation due to linkage disequilibrium). Fitting these parameters into the above equation yields

$$\Delta w \approx \beta y + \beta\left(\delta + \left(\varepsilon_3 + \frac{\delta_2}{2}\right) y\right) y - \gamma^2\left(\varepsilon_1 + \frac{1}{2}\delta_1\right) V_A y - \frac{1}{2}\gamma^2 (1 + \varepsilon_2 V_A + 2\delta + \delta^2) y^2,$$

which is rearranged to obtain the equation in the main text with the notation $s = \Delta w$.

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