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Evolvability and evolutionary rescue

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Abstract

The survival prospects of threatened species or populations can sometimes be improved by adaptive change. Such evolutionary rescue is particularly relevant when the threat comes from changing environments, or when long-term population persistence requires range expansion into new habitats. Conservation biologists are therefore often interested in whether or not populations or lineages show a disposition for adaptive evolution, that is, if they are evolvable. Here, we discuss four alternative perspectives that target different causes of evolvability and outline some of the key challenges those perspectives are designed to address. Standing genetic variation provides one familiar estimate of evolvability. Yet, the mere presence of genetic variation is often insufficient to predict if a population will adapt, or how it will adapt. The reason is that adaptive change not only depends on genetic variation, but also on the extent to which this genetic variation can be realized as adaptive phenotypic variation. This requires attention to developmental systems and how plasticity influences evolutionary potential. Finally, we discuss how a better understanding of the different factors that contribute to evolvability can be exploited in conservation practice.

K E Y W O R D S

developmental bias, gene regulatory networks, variational properties

1 | INTRODUCTION

Many species and populations are endangered as a result of environmental and ecological change. Biodiversity loss can be mitigated by restoring habitats and ecosystems to their previous states. Unfortunately, this is often impossible since anthropogenic activities can lead to irreversible changes. An alternative is to allow the endangered species to adapt to their new environment. Adaptive change through natural selection can make populations recover from a loss in numbers caused by environmental change, expand their range into previously uninhabitable regions, and even cope with inbreeding. Threatened populations and species that adapt their way out of conservation concerns are said to undergo "evolutionary rescue" (Bell, 2017). For many conservation challenges faced today, evolutionary rescue may seem like the only viable option. The flip side is that adaptive evolution can also be the source of conservation concerns. Adaptation can make harmless nonnative species invasive, enable parasites or pathogens to jump hosts, and cause pest species to overcome biocontrols. For all of these issues, assessing the risks and likely success of mitigation plans would

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be greatly improved by understanding how evolvable populations are.

Broadly speaking, the potential or disposition of a population or lineage to undergo adaptive evolution constitutes its evolvability (Brown, 2013). The disposition to evolve does not depend on one single property and the term "evolvability" refers to a family of more or less related concepts, each tailored to pick out a particular aspect of the disposition for adaptive evolution (Table 1). While this can be confusing, biologists do in fact routinely navigate multiple concepts with the same term, such as "gene" or "species" (Brigandt, 2020).

What all perspectives that address evolvability have in common is that they are concerned with the raw material-heritable phenotypic variation-that natural selection acts upon. The processes that generate selectable variation can be studied at many levels-genetic, developmental, and ecological-and the importance of particular factors or entities, like population genetic variation, may differ depending on the time scale of the analysis. Thus, what appears crucial for evolvability from one perspective may appear irrelevant from another, which creates certain "blind spots" and is a potential source of communication failure. Effective communication therefore requires that researchers are aware and respect that there are multiple causes of evolvability, and that research programs that focus on different causes chose to idealize the evolutionary process in different ways.

Rather than favouring one concept over another, our aim here is to introduce and explain some of the key facets of evolvability and discuss their applications, limitations and advantages. The coverage is not exhaustive, and we direct the reader to articles that explore these and other issues in further detail (Brown, 2013; Hendrikse et al., 2007; Payne & Wagner, 2019; Pigliucci, 2008; Wagner & Altenberg, 1996). We put particular emphasis on aspects of evolvability that may be less familiar to conservation biologists to provide a conceptual roadmap of evolvability research and an entry into the literature. We end by discussing some of the challenges that researchers face if they are to implement insights from evolvability research into conservation practice.

2 | EVOLVABILITY AS GENETIC VARIATION

In a population with high genetic variation, chances are that some individuals will be able to survive and reproduce even if the environment changes, or if a new pathogen or competitor arrives. Furthermore, with high genetic variation, natural selection and recombination can bring together genetic variants that result in phenotypes that are better adapted than any of the phenotypes that were originally present. All else equal, populations with high genetic variation will thus be more evolvable than population with low genetic variation. This is one reason why estimating standing genetic variation is important in conservation practice (it is not the only reason; genetic markers also allow one to estimate inbreeding or to identify lineages or hybridization events; reviewed in Shafer et al., 2015). However, without the introduction of new genetic variants, evolution would slow down. The processes that replenish genetic variation are therefore also important determinants of evolvability. Intrinsic factors that shape the introduction of new genetic variation include mutation rates, or the activity levels of transposable elements (Stapley et al., 2015). While these

TABLE 1 Perspectives on evolvability

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Main focus	Major determinant of evolvability and examples of key concepts	Case study and review
Genetic variation	Population (standing) genetic variation (e.g., allelic richness) and the introduction of novel variants (e.g., mutation rate, activity of transposable elements)	Carvalho et al. (2020); Rebollo et al. (2012)
Phenotypic variation	Population (standing) phenotypic variation (e.g., additive genetic variation; G-matrix) and the alignment of phenotypic correlations and direction of selection	Hansen and Houle (2008); Houle et al. (2017)
Phenotypic variability	Developmental interactions (e.g., gene-regulatory networks; modularity) and their influence on the phenotypic variation available for selection (as captured by the genotype-phenotype map; developmental bias)	Gerhart and Kirschner (2007); Kouvaris et al. (2017)
Phenotypic plasticity	Responsiveness of phenotypes to environmental stimuli (e.g., adaptive plasticity, reaction norms) and its impact on population persistence and phenotypic variation available to selection (environment-phenotype map; developmental bias)	Brun-Usan et al. (2020); West- Eberhard (2003)

Note: Current research on evolvability can be classified according to their main focus. This is one possible way to structure research on evolvability; for two other categorization schemes, see Brown (2013) and Pigliucci (2008).

variance-introducing factors are more difficult to quantify than standing genetic variation, they may provide useful estimates of evolvability on particular time scales (Bedau & Packard, 2003; Rebollo et al., 2012).

For all their worth, estimates of evolvability based on genetic variation will often provide limited insights into whether or not a population will actually adapt. This limitation arises because adaptation does not only require genetic variation per se, but requires that the genetic variation is relevant for the adaptive demands imposed by the environment. For instance, if the threat comes from a new parasite that infests the gut, genetic variation in coat color is likely irrelevant. Whether or not genetic variation is translated into phenotypic variation with adaptive value depends on the relationship between genotype and phenotype, and between phenotype and fitness (Coulson et al., 2011; Salazar-Ciudad & Marin-Riera, 2013). These relationships are occasionally sufficiently simple to be empirically tractable. One illustrative example is the evolution of colouration in lizards and mammals that live in habitats where either dark or pale colouration makes the animals cryptic (e.g., Rosenblum et al., 2010). Mutations in several well-known genes, such as Melanocortin-1 receptor (Mc1r) or Agouti, affect the darkness of the skin or hair largely independent of genetic background and environmental factors. In these cases, the production of melanin requires a functional Mc1r allele and, since most mutations will make the gene less efficient, alternative alleles will tend to reduce the amount of melanin available for transport and deposition. Thus, estimating the genetic variation at candidate loci for skin or hair color can provide a better estimate of the potential for adaptation to dark or light habitats than would genome-wide genetic variation.

Biologists have studied the evolution of phenotypes with a simple genetic basis in detail because they are amendable to study and useful to address particular problems (Orteu & Jiggins, 2020). However, the genetic causes of the vast majority of phenotypic traits involves multiple genes whose interactions can make the relationship between genotype and phenotype much more complex (e.g., nonlinearity introduced by epistatic or pleiotropic interactions). Without candidate "genes for" the traits of interest, researchers often resort to statistical correlations between genotypic and phenotypic variation. Genome-wide association studies (GWAS) or other "outlier scan" approaches can detect loci that associate with particular phenotypes or environments (e.g., Carvalho et al., 2020). This can provide information about alleles that are associated with local adaptation to, for example, different climates (Ferrero-Serrano & Assmann, 2019; for an example applied to conservation, see Mahony et al., 2020). In the context of conservation

biology, this can help to assess the risk for population extinction or assist restoration programs by screening individuals or populations for beneficial alleles before release into a threatened population (Kelly & Phillips, 2016).

One important lesson from GWAS studies is that sequence variation often is a poor predictor of phenotypic variation. Empirical studies show that the amount of phenotypic variation explained by genetic variation is typically very small (Boyle et al., 2017), and the statistical association between genotypes and phenotypes can be highly context-dependent and complex (both observations follow theoretical predictions; Burda et al., 2011). Therefore, statistical approaches are often unable to deliver allelic candidates that robustly convey a fitness benefit. Furthermore, adaptive change often requires simultaneous change in several traits, but detection of multi-trait correlations in GWAS requires very large sample sizes. Given these limitations, predicting the evolutionary potential of a population on the sole basis of sequence variation is often unsatisfactory, making quantification of phenotypic variation perhaps a more promising approach.

3 | EVOLVABILITY AS PHENOTYPIC VARIATION

Biologists have long recognized that development produces correlations between traits, manifesting in phenotypic integration (e.g., Olson & Miller, 1958). As a result, populations may have high genetic variation, and even high heritable variation for individual traits, but no heritable variation for the trait combinations that are fit. For instance, the size of the eyespots on the wings of some butterflies can be changed by artificial selection experiments, but the relative size of the spots between the fore- and hind-wings cannot be changed (i.e., the trait correlation exhibits no heritable variation; Beldade et al., 2002). The correlation between these traits reduces the dimensions in which phenotypes can vary. The standing phenotypic variation can therefore provide an alternative measure of evolvability because it can provide clues about the direction of adaptive change that is possible or likely. All else equal, more heritable phenotypic variation means higher evolvability. However, as with genetic variation, not all phenotypic variation contributes to adaptation as many trait combinations will simply not allow a well-functioning organism. A more refined measure of evolvability is therefore the heritable phenotypic variation, often quantified as additive genetic variation, in the direction of selection (Hansen & Houle, 2008). This quantitative genetic concept of evolvability

determines the extent to which the populations will respond to selection (i.e., adapt) from one generation to the next. Estimates of quantitative genetic evolvability typically rely on pedigrees to disentangle heritable from non-heritable variation, and long-term studies of individually marked animals have demonstrated the utility of quantitative genetics for wild populations, including for understanding their responses to climate change (Charmantier et al., 2014).

In contrast to evolvability inferred on the basis of genetic variation alone, evolvability measures based on standing phenotypic variation recognizes that it is the link between genetic variation and phenotypic variation that matters, and that selection rarely acts on a single trait independently of other traits. However, both genetic and phenotypic estimates of evolvability are restricted to the variation that exists here and now. Consequently, the accuracy and utility of predictions about adaptive change will depend on the extent to which the structure of phenotypic variation remains constant over time (e.g., Milocco & Salazar-Ciudad, 2020). Thus, it is important to know how stable trait covariances are (hence the interest in the stability of the "G-matrix" in evolutionary quantitative genetics; Arnold et al., 2008). Unfortunately, the standard assumptions in evolutionary theory do not provide much information on this issue. Yet, understanding how phenotypic variation itself varies is exactly the kind of knowledge that is required to infer if and how populations are likely to adapt beyond a few generations.

4 | EVOLVABILITY AS PHENOTYPIC VARIABILITY

From a developmental perspective, the starting point for adaptive evolution is the generation of phenotypes that are fitter than the phenotypes that already exist (West-Eberhard, 2003). The focus on the origin of phenotypic variation in this view includes morphological, physiological and behavioral processes that shape organisms at all life stages ("development" in a broad sense). A developmental system that imposes strong covariation between traits can therefore prevent populations from adapting to environments that demand very different patterns of covariation. Even when adaptation is possible, these developmental dependencies will determine how populations will adapt because there are typically multiple adaptive solutions to any given ecological problem (reviewed in Melo et al., 2016; Uller et al., 2018). For example, birds can track the peak of food availability in a warming climate by initiating breeding earlier in the season, by switching diet, or by shifting to a cooler

breeding habitat. Which of these alternative adaptive solutions is most likely depends not only on the (additive) genetic variation in the population at present, but also on the kinds of heritable phenotypes that will arise when the population encounters a new environment. In fact, a population may have little or no heritable variation in the current environment (i.e., low evolvability in the quantitative genetic sense), but a high potential to generate adaptive phenotypic variation in the future (i.e., high evolvability in the developmental sense).

In contrast to variation, which can be studied by measuring the phenotypes (or genotypes) in a population, inferences about variability (i.e., the propensity to vary; Wagner & Altenberg, 1996) require attention to the mechanisms of development. Perturbing development, for example by artificially inducing mutations, can reveal the phenotypes the developmental system is capable of generating. Such studies have been conducted in the laboratory (e.g., Houle et al., 2017), but experimental assessment of phenotypic variability in response to genetic perturbation is usually not an option for wild populations. Some guidance may instead be found by looking for general properties of developmental systems that make them prone to produce heritable phenotypic variation (Jimenez et al., 2015).

Creating in silico models of developmental systems allows the exploration of their variational properties (e.g., Salazar-Ciudad & Jernvall, 2002). Developmental models that explore evolvability come in different degrees of complexity and biological reality. One common approach is to represent phenotypes as the expression levels of one or several of a set of interconnected genes, a gene regulatory network (GRN; Mjolsness et al., 1991). Increasing the level of complexity requires those GRNs to be complemented by cell biomechanics or morphogen diffusion, which allows the modeling of 3D anatomical structures such as teeth or limbs (e.g., Salazar-Ciudad & Jernvall, 2002). Regardless of the level of complexity, it is theoretically possible to assess the space of phenotypic possibilities of GRNs by modifying the strength of interactions between genes, the number of genes, or how the genes regulate each other (Figure 1). Such regulatory mechanisms of evolutionary change are well supported empirically (Carroll, 2008), but GRN topology is generally considered to vary less than the strength of interactions, in part because the genetic changes are more specific or local (e.g., insertion or deletion of a transcription factor binding site). In contrast, modifications to the strength of interactions in a GRN can be affected by a large number of genes or allelic variants (Boyle et al., 2017). Accordingly, genetic variation in regulatory interactions between genes is likely to be much higher than genetic variation in network topology.



FIGURE 1 Gene regulatory networks and variability in phenotypic outcomes. The figure shows six different hypothetical populations whose individuals exhibit different values of two traits (e.g., hind- and forelimb lengths). The distribution of phenotypic variation of each population is depicted as an orange area in a two-trait adaptive landscape (where dotted lines are iso-fitness curves and the "+" sign represents the optimal fitness peak). The phenotypic variation observed in each population is underpinned by variation in the strength of interactions between genes G1, G2, and G3 in a gene regulatory network, or gene regulatory network (GRN). This is potentially influenced by allelic variation at a very large number of loci. What makes the six populations different is the topology of the GRN (e.g., activation vs. inhibition between a pair of genes). A given GRN can transition into another GRN by means of large-effect mutations (wide black arrows) that change its genetic interactions, and thus how the GRN transforms allelic variation into realized phenotypic variation. By means of these mutations, an initial population (within the orange rectangle), whose individuals cannot reach an optimal phenotype, can evolve its GRN so that newly arising phenotypes will reach the fitness peak (green rectangle at bottom right). Notice, however, that such an evolutionary sequence towards an optimal phenotypic variation may need to pass intermediate GRNs with suboptimal forms of variation (center-right panel) [Color figure can be viewed at wileyonlinelibrary.com]

Theoretical models of development have revealed several features of developmental systems that influence evolvability. One of these features is modularity, or the extent to which the regulatory system is divided into semiautonomous subroutines that have their own dynamics (von Dassow & Meir, 2004). Without modularity, it would be difficult to adaptively change some parts of a phenotype without negatively affecting others. A second feature of GRNs that appears to enhance evolvability is the duplication of subroutines (Wagner, 1994). The biological equivalent is co-option of developmental pathways into new contexts, which is the basis for many phenotypic innovations (e.g., beetle horns; Hu et al., 2019). Finally, because of the nonlinear mapping between the genotype and the phenotypes, GRNs often produce the same phenotype across a range of conditions. This behavior allows the systems to accumulate allelic variation that does not affect the phenotype in the present environment, but may do so in more extreme environments, thereby delivering the fuel for adaptive change ("cryptic genetic variation"; Paaby & Rockman, 2014; Payne & Wagner, 2019).

As with the other evolvability measures, what matters to developmental evolvability is not only how much phenotypic variation that can be generated by a given developmental system, but also how well aligned this variation is with adaptive demands (Uller et al., 2018). Evolvability is high if the phenotypes that are accessible through genetic change (the "developmental lines of least resistance") are also those that are likely to have adaptive value. For example, consider that the homologous bones of fore- and hindlimbs in tetrapods have a shared developmental genetic regulation. Because of this, variation in the shape and length of limbs is biased towards phenotypes with a positive correlation between the elements of fore- and hindlimbs (Young et al., 2010). Arguably, this positive correlation between limbs is generally advantageous, but there also exist some evolutionary solutions that require very different proportions between limb bones. This happens, for instance, in tetrapods with very unusual types of locomotion (e.g., humans). Such adaptive phenotypes, which were before impossible to reach, become accessible only if organisms rewire the

Box 1 Evolvability and developmental constraint

Biologists interested primarily in natural selection are inclined to view developmental biases, like the correlation between bones in the vertebrate limbs or between butterfly eyespots, as constraints or limits on potential adaptation. The logic of this constraint-view is that development prevents the emergence of some hypothetical phenotypes that in principle could have high fitness. Thus, the constraint interpretation is like comparing the adaptive potential of an actual developmental system with that of an imagined "unconstrained" one that readily produces the necessary phenotypic variation that allows natural selection to find the optimal solution (Salazar-Ciudad, 2006; Uller & Kampourakis, 2020; Uller et al., 2020). In practice, of course, no real developmental system will produce all phenotypes, nor will all possible phenotypes be produced with equal probability. This means that the mechanisms of development can make adaptive change either unlikely (if the phenotypes it can generate include few useful variants), or very easy (if the phenotypes it can generate are well aligned with adaptive demands). Thus, whether or not development constrains or facilitates adaptive change depends on the point of view; that is, against which alternative developmental system or alternative selective pressure the focal system is compared (Uller et al., 2020). A developmental system that looks like a constraint on adaptation from one perspective can look like an opportunity for adaptation from another perspective.

developmental biology of their limbs (Box 1; Young et al., 2010).

What are the evolutionary origins for such changes in evolvability? The capacity to generate phenotypic variation is rarely directly selected for since the fitness benefits of generating phenotypic variation that may be beneficial in the future are low (i.e., natural selection is only concerned with actual, realized variation, and blind to potential, unrealized variation). Rather, selection affects evolvability indirectly, by favouring some developmental outcomes over others. Theory suggests that selection for particular trait combinations will tend to modify regulatory interactions between genes such that developmental bias becomes aligned with the direction of selection (Hansen, 2006; Kouvaris et al., 2017; Watson et al., 2014). Over evolutionary time, this raises the possibility that genetic change is prone to generate phenotypic variants that resemble past adaptations (Watson et al., 2014). If so, populations may be surprisingly able to adapt to challenges that have been encountered by their ancestors, even if the frequency of adaptive alleles is low. It remains to be seen how general this result is, and if it applies not just to models but also to actual organisms.

5 | EVOLVABILITY AS A FUNCTION OF PLASTICITY

As discussed in the previous section, developmental perspectives on evolvability are often studied in terms of the relationship between genetic and phenotypic variation (the "genotype-phenotype map"; Hansen, 2006; Jimenez et al., 2015). However, the capacity for adaptive evolution is not only affected by developmental responses to genetic change, but also by responses to environmental change (West-Eberhard, 2003). The relationship between plasticity and adaptive evolution is complex and remains poorly understood (recent reviews of different aspects include Levis & Pfennig, 2020; Parsons et al., 2020; Uller et al., 2020). Plasticity can facilitate survival in new or stressful environments by 'buying time' or by increasing variation via forms of bet hedging. Particularly important are mechanisms of plasticity, such as exploratory processes or learning, that allow organisms to not just increase phenotypic variation, but also use developmental processes to find adaptive solutions to new problems (Snell-Rood et al., 2018). These mechanisms increase the chances that advantageous phenotypes become established in a population (Chevin et al., 2010; Seebacher et al., 2015), allowing them to subsequently be refined by selection on genetic variation (West-Eberhard, 2003). For example, many urban reptiles, birds, and mammals were able to colonize our cities because of their ability to adaptively change their behaviors (Sol et al., 2013), behaviors that occasionally may be passed on to others through social learning (Whiten, 2019). Without some degree of flexibility, there would have been no blackbirds in our gardens or foxes in our cities. However, since the urban environment imposes demands that cannot be solved by behavioral plasticity alone, many urban populations inevitably evolve genetically, including in the traits that promoted colonization of cities in the first place (e.g., boldness; McDonnell & Hahs, 2015). The result is adaptation as we know it, but an adaptation whose initial success and subsequent outcomes are guided by developmental, physiological or behavioral plasticity (Figure 2).



FIGURE 2 The role of plasticity in adaptation to novel environments. The plots show phenotype distributions and phenotypic optima for a hypothetical example of a population from a rural environment that is colonizing an urban habitat. We assume that there are two traits that can be adaptively adjusted to life in the city: boldness and crypsis (representing alternative adaptive peaks). The ancestral, rural population scores low on both traits (orange area shows the phenotype distribution of individuals in this hypothetical 2D trait space). When shifting into urban habitat, the fitness surface changes, and individuals may respond plastically (e.g., through behavioral innovation; green solid arrow). The new, plasticity-driven phenotypic distribution in the urban habitat is represented by the solid orange areas in the right hand panels. If the main axis of variation of this new phenotypic distribution is oriented such that it is highest in the direction of the initial plastic response, natural selection may readily move the population towards the adaptive peak of high boldness (situation A). In contrast, if the maximum trait variation is not aligned with the initial plastic response (situation B), this peak can be difficult to reach, and natural selection may guide the population towards an alternative adaptive peak (here high crypsis and low boldness). Thus, the phenotype distribution that results from the initial plastic responses of individuals biases the variation that is available to natural selection, thereby making some evolutionary trajectories more likely than others [Color figure can be viewed at wileyonlinelibrary.com]

That phenotypic responses to novel environments pave the way for genetic adaptation may be quite common (West-Eberhard, 2003), but it is perhaps especially prevalent in organisms that have evolved in a variable environment and therefore been selected on their ability to respond plastically. For example, when exposed to drought, some plants may grow smaller leaves with a thicker cuticle to reduce transpiration, while others may grow longer roots and modify the osmotic pressure to increase water uptake (Sultan, 2015). The plants respond adaptively because selection has favored a correlation between those dry environments and the responses that make individuals drought resistant. Once evolved, these responses ensure particular directional, and often functional, responses to even drier environments. Thus, the evolved plasticity determines the phenotype distribution upon which natural selection can act, and plasticity can therefore put the population on one evolutionary trajectory rather than another (Figure 2). As a result, locally adapted phenotypes should tend to resemble the environmentally induced phenotypes of their ancestors.

This pattern of "plasticity-led" evolution appears to hold up rather well in plants (Radersma et al., 2020), but it remains to be seen how common it is elsewhere. Sometimes, plasticity is likely to be of little significance, but at other times it can be directly harmful and such responses can also have implications for how evolution proceeds (e.g., Ashander et al., 2016). For example, a new diet, exposure to toxins, or other environmental stressors can reduce absolute fitness to the extent that it prevents

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populations from adapting. Even when individual responsiveness to the environment has been selected, plasticity can reduce fitness if there is a mismatch between environmental cue and the fitness benefits of responding to this cue. This can make, for example, birds that use day length to time their breeding season more mismatched to their local ecology than those that rely on temperature as a cue (see discussion in Bonamour et al., 2019). Adaptive evolution in the former case may result in a change in cue use, with the result that the locally adapted phenotypes eventually bear little or no resemblance to the environmentally induced phenotypes of their ancestors.

6 | MAKING EVOLVABILITY MATTER TO CONSERVATION BIOLOGY: THEORETICAL AND EMPIRICAL CHALLENGES

Can insights into evolvability be of use in conservation biology? Since harnessing the evolvability of a threatened population or lineage may prevent extinction, the answer has to be "yes." Insights from theoretical and empirical studies of evolvability may help to refine strategies for population rescue, habitat restoration, rewilding, pest or disease control and other concerns that preoccupy conservation biologists (Catullo et al., 2019). However, the utility of evolvability research to a large extent remains to be demonstrated. Here we briefly outline some key questions motivated by the four perspectives on evolvability discussed above.

"How well does genetic variation reflect adaptive potential?" Like virtually any area of biology, conservation programs adopt increasingly refined measures of genetic variation (e.g., Ekblom et al., 2018). However, it remains poorly understood how well estimates of genetic variation (molecular and statistical) actually capture adaptive potential of wild and threatened populations (for a recent experimental study see Ørsted et al., 2019). One possibility that is increasingly discussed is that populations at threat from climate change could be rescued by introducing individuals from other populations that carry allelic variants that are identified as being locally adapted to more extreme conditions (Carvalho et al., 2020; Kelly & Phillips, 2016). The controversy over translocation aside, this assumes that genome-wide association studies can identify allelic variants that are not only causal, but also have sufficiently robust phenotypic effects to achieve the desired outcome in the threatened population. Given that genomic signals of local adaptation commonly are weak and context-dependent it is not obvious that this approach is promising. However, there is a large and rapidly growing literature in population genomics on adaptation that arguably could be harnessed to refine this strategy (Ahrens et al., 2018).

"Why do populations fail to respond to selection pressure?" Biologists are surprised to find that populations that experience selection and exhibit heritable variation commonly fail to respond as predicted (Pujol et al., 2018). One possible explanation for the poor fit to theoretical models is that not enough attention has been paid to trait correlations and their adaptive significance. However, it remains poorly known to what extent standing phenotypic variation (including correlations between traits) actually predicts the adaptive potential of natural populations. Recent theoretical models provide a link between quantitative genetic and developmental aspects of evolvability (Milocco & Salazar-Ciudad, 2020), and the extensive literature on plant and animal breeding may provide opportunities for identifying circumstances under which the desired trait change can be achieved and when and why it fails (Kristensen et al., 2015).

Conversely, in some instances, the goal is to prevent a population from evolving. Good examples are the control of pests by pesticides, the treatment of germs by antibiotics, or the use of fertilizers in agriculture. In the case of antibiotics, developing drugs that target essential components of bacteria that are not evolvable holds the promise to mitigate antibiotic resistance, a major threat to human health. This appears to be a particularly promising application of evolvability research, given that GRN models are well suited for modeling metabolic phenotypes, such as drug resistance (Barve et al., 2012), and that developmental concepts of evolvability may be particularly applicable on longer time scales (i.e., many generations).

"Can the adaptive potential of populations be predicted from past evolutionary history?" One insight from theoretical models is that past evolutionary history molds developmental systems in ways that structure phenotypic responses to genetic change (reveiwed in Uller et al., 2018). A possible consequence of this is that adaptive phenotypes that the lineage has explored in the past will be surprisingly easy to re-evolve (Kouvaris et al., 2017; Watson et al., 2014), which could result in a naturally occurring evolutionary rescue. A more general prediction is that lineages with a rich history of environmental change might generally be more evolvable than a lineage that experienced a more static environment (Brun-Usan et al., 2020; Draghi & Whitlock, 2012). However, theory is still in its infancy and there is limited empirical evidence that this is the case (albeit mostly because of a lack of studies).

The challenges of predicting how organisms will evolve are particularly acute for nonnative species and

for conservation programs (e.g., rewilding) that aim to restore the ecosystem's functionality by re-introducing key species (e.g., apex predators in Europe; Torres et al., 2018). Since these species will experience a new ecological context, it is difficult to predict the success of these introductions in the long-term, or how they will shape the ecosystem, without further understanding of the relationship between past evolutionary history and adaptive potential.

"How much does plasticity tell us about the evolutionary potential of a population?" It is widely recognized that plasticity is important to understand how populations respond to environmental and ecological challenges in the short term. It is also well established that some forms of plasticity, including developmental selection or exploratory behaviors, are more likely to improve the adaptive fit of individuals compared to other, more context-specific mechanisms (Snell-Rood et al., 2018). It remains poorly known, however, if plasticity also influences the rate and direction of adaptive evolution (see references in the previous section). Theoretical work suggests that it should (Brun-Usan et al., 2020; Draghi & Whitlock, 2012), but there are few empirical studies that specifically and quantitatively address this issue (Noble et al., 2019; Radersma et al., 2020). Major knowledge gaps include the relationship between plasticity and standing genetic variation, between plasticity and the genotype-phenotype map, and how plasticity mediates evolutionary rescue via its effect on population persistence or population size. Other open questions include whether or not plasticity increases evolvability, and if the rate and direction of adaptation can be predicted from plastic responses. The literature on adaptation in nonnative species provides particularly good opportunities to address these challenges (Lee, 2002).

7 | FUTURE CHALLENGES

There is a growing literature on the different aspects of evolvability, and it is increasingly recognized that estimates of genetic variation often will be unsatisfactory for assessing if and how populations will evolve. One of the main challenges in translating the insights from the diverse research on evolvability into conservation practice lies in their generalization. Every conservation concern has its unique set of problems—population size, habitat destruction, competitors, inbreeding, and many others. To rescue populations from extinction will always require knowledge of the nature of their specific threats, and ensuring evolutionary rescue may simply best be served by conservation strategies (e.g., habitat protection) that do not require assessment of evolvability per se. However, this does not imply that insights from evolvability research cannot be harnessed. Conservation biology has benefitted in the past from experimental work on the genetics of adaptation, inbreeding depression and the role of gene flow, even when this study was not designed with the aim of addressing conservation concerns. Importantly, however, conservation challenges have motivated specific questions and experiments, including those designed to address the relationship between standing genetic variation and evolutionary rescue (Carlson et al., 2014; Gonzalez et al., 2013). While the laboratory settings of these studies may seem distant from the conservation problems in the real world, we anticipate that this approach can be useful also for other aspects of evolvability. Thus, experimental studies of evolvability should help to determine which properties of a population that are crucial, and which can be largely ignored, to predict the prospect of evolutionary rescue.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

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