CellPress

Opinion

Revisiting Adaptive Potential, Population Size, and Conservation

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Additive genetic variance (V_A) reflects the potential for evolutionary shifts and can be low for some traits or populations. High V_A is critical for the conservation of threatened species under selection to facilitate adaptation. Theory predicts tight associations between population size and V_A, but data from some experimental models, and managed and natural populations do not always support this prediction. However, V_A comparisons often have low statistical power, are undertaken in highly controlled environments distinct from natural habitats, and focus on traits with limited ecological relevance. Moreover, investigations of V_A typically fail to consider rare alleles, genetic load, or linkage disequilibrium, resulting in deleterious effects associated with favored alleles in small populations. Large population size remains essential for ensuring adaptation.

Trends

The importance of small population size in limiting adaptive potential is reinforced.

Estimates of genetic variance across populations tend to be imprecise.

Genomic data highlight linkage, load, and rare alleles in population size issues.

Long-term conservation maintaining adaptive potential requires large populations.

Population Size and Genetic Variation

Species and populations of conservation concern are threatened because of their inability to adapt to changes in environmental conditions as a consequence of natural processes or human activities, including habitat loss, urbanization, and invasive competing species and diseases. With ongoing climate change and expanding human populations generating stressful conditions for many species, threat levels are expected to increase and result in more populations and species being listed as threatened [1,2].

Slow evolutionary responses in threatened species may reflect a combination of low genetic variation, long generation times, and selection pressures that might be too infrequent to produce directional shifts in favored alleles. For instance, marmots may be unable to evolve the vigilance required to avoid new invasive predators due to low genetic variation for this trait [3]. Slow evolutionary responses might also occur if a long generation time means that a population declines before adaptive responses are evident.

The availability of adequate genetic variation in populations is usually measured by the **additive genetic variance**, V_A, (see Glossary) for the relevant traits, typically expressed as the **heritability** or **evolvability** of a population. Rapid selection responses require that V_A in the direction of selection on a trait is >0. One of the main factors expected to influence V_A is population size. Assuming neutrality and additive gene action, theory predicts that V_A within a population will diminish proportional to the **effective population size**, N_e [4,5]. This is due to **genetic drift**, which leads to random loss and the fixation of alleles in populations across generations. Selection on traits will also affect allele frequencies and the rate of loss of alleles. Under heterozygous advantage, selection will counter the effects of drift and maintain genetic

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variation even in small populations. However, when quantitative traits are under different forms of selection, a small population size is still expected to decrease V_A [5].

A recent meta-analysis by Wood *et al.* [6,7] (Box 1) tested the prediction that small population size is associated with low V_A. The authors quantified the relationship between evolutionary potential (h^2, the narrow-sense heritability) and census population size, and also tested the strength, direction, and form of selection in populations of different census size. Their conclusions, based on more than 80 species, were contrary to theoretical expectations; there was no evidence that adaptive potential is lower in small populations or that selective forces were consistently different between populations of different census sizes. These results, placed within the context of rapid environmental change and elevated extinction risk, provide a backdrop wherein the association between population size and adaptation needs further exploration. One important question is whether there should be less concern about situations where threatened species persist as small populations, at least from an evolutionary genetics perspective. However, we argue here that it remains important to conserve large effective population sizes, including for reasons that may not be connected to V_A.

Controlled Short-Term Studies Connect Population Size and Inbreeding to Selection Responses but Not necessarily V_A

Larger populations are expected to respond relatively more rapidly per generation to selection because they contain more alleles favored by selection, carry a reduced risk of losing favored alleles as a consequence of genetic drift, and generate relatively more novel mutations. These expectations have been confirmed experimentally in *Drosophila*, *Musca*, *Mus*, and other model animals [8]. For example, using *Drosophila melanogaster,* Jones *et al.* [9] showed that populations of larger size responded relatively faster to selection for abdominal bristle number, while Weber [10] and Weber and Diggins [11] obtained the same result for selection on wing

Box 1. Meta-Analysis of Heritability, Selection, and Population Size in the Wild by Wood *et al.*

In their recent meta-analysis on data collected on natural populations, Wood *et al.* [6] examined the relationship between population size (*N*) and narrow-sense heritability, h^2, and between *N* and the direction and form of selection. The aims were to test the assumption that small populations harbor reduced levels of adaptive genetic variation, and respond less efficiently to selection than do large populations. Contrary to theoretical expectations Wood *et al.* concluded that small populations do not have lower levels of adaptive genetic diversity compared with larger ones; they also found no evidence that selection is weaker in small, compared with large, populations (this latter conclusion is not discussed further here).

While Wood *et al.* acknowledged caveats and limitations of their meta-analyses, additional, important limitations concerning statistical power apply. First, the majority of studies included in the analysis had limited power to detect significant levels of h^2. Of the 3371 h^2 estimates included (http://dx.doi:10.5061/dryad.rd5rn), 35.72% were not significantly different from zero. It was not possible to determine significance for a further 838 (24.85%) because standard errors on h^2 estimated were not reported. Thus, only 39.43% of the studies had estimates of h^2 that were significantly different from zero (Figure I). To further explore the power of this study to detect heritability, we performed correlation analysis between narrow-sense heritability and family size. Doing so revealed a significant ($P = 0.006$) but small ($r = -0.06$) negative correlation between heritability and family size. Regressing heritability against family size returned an adjusted R-square value of 0.003, confirming the conclusion that there is no real association between family size and heritability, which further speaks to limitations in the data used in their analysis.

Second, most of the traits studied were morphological (68.76%), followed by life-history traits (22%). Physiological traits, which will be critical in responding to environmental change [79,80], comprised only 0.03% of the studies.

Third, metapopulation structure (contemporary or historical) of the populations used might influence patterns of genetic diversity. This is critical, because even historical gene flow between populations within a species, or admixture between closely related species [32,78,81] can result in higher estimates of genetic diversity than expected. Furthermore, genetic diversity even in small isolated populations can take some time to decline, due to drift [81]. Inferences about the relationship between population size and point estimates of genetic diversity are challenging when made in the absence of on-going genetic monitoring and without insight into the demographic history of the population.

Glossary

Additive genetic variance (V_A): variance due to additive allelic effects in a population.
Antagonistic interactions: indicates that the fitness effect of two factors (e.g., environments) is less than the sum of the effect of the individual factors.
Associate overdominance: a mechanism that can arise by an overdominant locus being linked to neutral loci or by the presence of multiple recessive deleterious alleles across different haplotypes resulting in a large cumulative advantage of a heterozygote genotype. This mechanism has been suggested to conserve genetic variation in small populations because of strong linkage disequilibrium arising during the bottleneck coupled with disfavored homozygosity in the presence of recessive deleterious alleles.
Balancing selection: selection that works to maintain polymorphism at a given locus.
Effective population size (N_e): the size of an idealized population that would experience the same amount of genetic drift and inbreeding as the population of interest. In popular terms, N_e is the number of individuals in a population that contribute offspring to the next generation.
Evolvability: additive genetic variance standardized by the trait mean; often used as a measure of adaptive potential.
Genetic drift: the process of change in allele frequencies owing to chance events that determine which alleles are carried over to the next generation.
Genotype × environment (G×E) interactions: changes in the relative performance of different genotypes across an environmental gradient.
Heritability: a measure that explains how much variation in a phenotypic trait in a population is due to genetic differences between individuals. The narrow- (h^2) and broad- (H^2) sense heritabilities are the additive genetic variance and the total genetic variance, respectively, relative to the phenotypic variance in a population. Narrow-sense heritability is often used as a measure of adaptive potential.
Inbreeding depression: suffering from diseases, low fertility, and a

Finally, N and not N_e was used in the comparisons. The authors discussed the pros and cons of doing so; nonetheless, the use of N rather than N_e further limits interpretations, particularly when population size was not estimated on the same populations as those used in the h^2 studies.

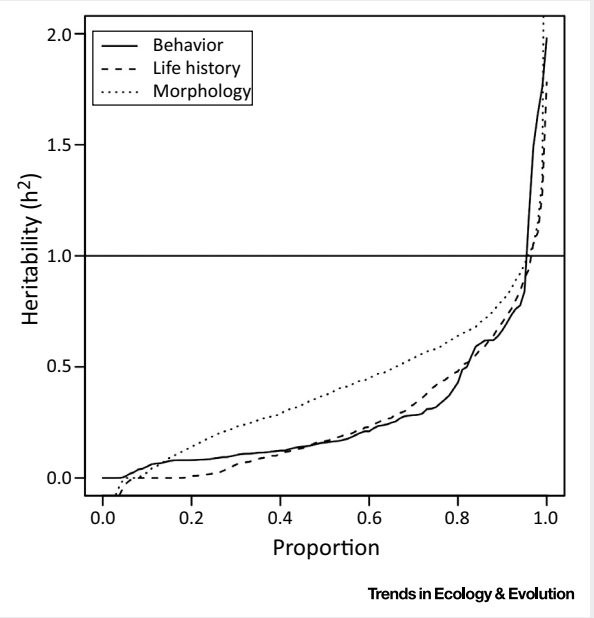

Figure I. Heritabilities from [6] Presented As Proportions for Behavioral (Solid Line), Life-History (Dashed Line), and Morphological (Dotted Line) Traits. The theoretical upper limit for heritability ($h^2 = 1$) is indicated by a solid horizontal line.

length and ethanol vapor tolerance, respectively. Specifically, populations with a census size >1000 had faster and more consistent responses to selection compared with smaller populations of ≈100 individuals.

While such studies often focus on traits with limited ecological importance (typically morphological traits with high heritability), population size-dependent responses to selection have also been shown for the ability of *Drosophila birchii* (an Australian endemic rainforest species) to evolve higher heat tolerance and avoid extinction [12]; populations with a census size of 1000 responded more to selection and had reduced extinction risk compared with populations with a census size of 20, which showed lower growth rates and higher stochasticity in those growth rates. Changes in levels of genetic variation associated with the founder populations of experimental populations have also been clearly linked to persistence and extinction risk, particularly under stressful conditions [13,14].

Evidence for inbreeding and population bottlenecks leading to intermittent inbreeding depression on adaptive responses is more inconsistent. Some laboratory experiments on *Drosophila*, butterflies, and other insects showed that inbreeding reduced V_A, heritabilities and selection responses [15–17]. For example, the realized heritability for cold resistance (chill coma recovery time) in selected inbred lines of *Bicyclus* butterflies was around 3.5% in contrast to nearly 10% in outbred lines, highlighting a loss of evolutionary potential under inbreeding [15].

However, inbreeding and bottlenecks can affect selection responses, heritability, and V_A in different ways. Low heritability estimates in highly inbred populations might reflect an increase in the environmental variance, V_E, relative to V_A under benign conditions [16,18,19]. Moreover,

general reduced fitness in offspring of consanguineous matings.
Linkage disequilibrium (LD): the non-random association of alleles at different loci.
Mutational meltdown: accumulation of harmful mutations in a small population, which leads to loss of fitness and reduced population size, and contributes to extinction risk.
Selective sweeps: the process whereby adaptive alleles and alleles positioned nearby on chromosomes, increase in frequency in a population due to natural selection.

Box 2. Effects of Bottlenecks on Heritability and Evolvability

A recent meta-analysis by Taft and Roff [20] examined 107 estimates of V_A for stress resistance, morphological, behavioral, and life-history traits from laboratory studies to better understand the effects of bottlenecks on heritability and evolvability (I_A). They showed that inbred populations with F levels <0.25 had higher V_A compared with non-inbred (F = 0) control populations [20]. However, when pooling data across inbreeding levels and traits, no effect of population bottlenecks was observed (Figure I). In addition, effects of extreme bottlenecks were mostly observed in the first generations with strong inbreeding, at relatively low inbreeding levels, and for low heritability traits [20]. Overall, the evidence from controlled laboratory studies provides little evidence that population bottlenecks are strong drivers of low heritabilities and evolvabilities, at least in the short term.

laboratory studies suggest that only low population sizes across multiple generations result in significant reductions in h^2 and V_A [20]. Where detected, reductions in V_A due to inbreeding and bottlenecks are often less than expected [20] (Box 2). This suggests that selection (e.g., **balancing selection**) or conversion of dominance or epistatic variance to V_A maintains genetic variation in small populations [20–22]. However, increases in V_A after a bottleneck might not translate into higher adaptive potential because traits for which these increases are observed typically are those also suffering the most from **inbreeding depression** [23]. One explanation is that the lethal and recessive detrimental alleles of large effect responsible for inbreeding depression also contribute to increased V_A following a bottleneck [24]. Thus, the evolutionary significance of small increases in V_A and heritabilities detected under laboratory conditions are probably minor and unlikely to influence selection responses [25].

Theoretical Predictions of Loss of Quantitative Genetic Variation in Small Field Populations Are Not Well Supported

While natural populations of small size often have reduced levels of molecular genetic variation [26], there are numerous exceptions to this; and studies on fragmented and wild populations that are periodically small often reveal unexpectedly high levels of molecular genetic variation [27,28]. Furthermore, levels of quantitative genetic variation in wild populations as measured by V_A and h^2 are often not lower in small compared with larger populations [6] (Box 1). This may reflect the fact that natural populations are typically not inbred to the degree investigated in experimental laboratory populations [28], that recent admixture with related species or populations has occurred [29], and/or that there is a poor connection between N, the census size of a population, and N_e, its effective size .

One challenge in conservation genetics and/or genomics is to pinpoint whether genetic variation is adaptive and reflects either remnants of high genetic diversity in ancestral populations [30–33] or the accumulation of deleterious alleles in small populations as a consequence of genetic drift and weakened selection [32], which contribute to overall genetic diversity but are nonadaptive. **Associative overdominance** provides one mechanism where segregation of recessive deleterious alleles prevents the loss of variation in small populations, whereas, in large populations, the impact of these alleles is too small to cause deviations from neutral expectations [34]. Although challenging, the genomic toolbox for non-model species is rapidly developing, and the identification and quantification of genetic load or variation under selection are now possible [32,35].

A population of the Channel Island fox (*Urocyon littoralis*) has been stable despite a small N for >1000 years [32]. Genomic studies provided evidence of reduced molecular genetic variance and high levels of deleterious mutations in this species. However, the population has also maintained heterozygosity hotspots in parts of its genome, which might represent adaptive genomic regions. A similar example is the highly inbred Chillingham cattle breed, which does not suffer from inbreeding depression despite having low genetic variability [36]. Purging and heterozygosity hotspots non-randomly distributed across the genome are likely to be involved.

Thus, genetic variation of adaptive significance better predicts the long-term success of populations than does genetic variation overall.

Despite a few good field examples of low V_A and h^2 in populations with small population sizes, studies providing a direct link between inbreeding or drift and genetic variability remain rare. At population sizes and inbreeding rates relevant to most natural populations, where some migration between populations is typical, inbreeding levels are often low [37,38], so it is perhaps not surprising that variation in V_A and h^2 is rarely detected across populations, notwithstanding the issues of accurately measuring these parameters.

Comparing Quantitative Genetic Variation across Populations Is Challenging, Particularly for Low Heritability Traits

Heritability and evolvability estimates are prone to a high level of measurement error and, thus, low repeatability; this may be because some traits are inherently noisy and subject to the impact of minor environmental variability [39]. However, even where traits have high repeatabilities (e.g., many morphological and physiological traits) or are measured across entire life stages (e.g., many life-history traits), V_A and h^2 estimates still often have large standard errors (SEs) irrespective of whether Bayesian or frequentist approaches are used in their estimation [40]. In the Appendix to a survey of heritabilities and evolvabilities in [41], SEs on h^2 and evolvabilities were large and often overlapped with zero. This mostly reflects the small sample sizes used to estimate genetic variance in traits; the relatedness of individuals must be known to estimate V_A for traits, and this is often only available for a small subset of individuals. The problem is exacerbated when traits of interest have low heritabilities that are often impossible to estimate accurately unless several thousand individuals are scored within pedigrees. Another issue is that variation in many life-history traits is not normally distributed, resulting in estimates of genetic variance that are difficult to interpret [36]. While normality for such traits might be restored through transformation, this in turn creates issues of biological interpretation. Reliable estimates of genetic variance for traits with low heritabilities are often only available for livestock, where thousands of individuals are phenotyped through herd development [42]. In small natural populations, estimates can be improved if pedigreed phenotypes across multiple generations are available and this can be aided by high-density molecular markers to establish relatedness, but even then SEs can remain large [29].

Unfortunately, low evolvabilities and heritabilities for traits (Box 3) are common [41,43]. For instance, there is evidence of stress-response traits with low V_A failing to evolve despite intense artificial selection [44] or reaching a selection limit relatively quickly [45]. There are several reasons why traits may have low genetic variance (Box 3). Those traits with low variances may be among the most interesting from a conservation perspective; low heritabilities may point to traits that limit further adaptation that would allow a threatened population to evolve and overcome its current predicament. This can either reflect a history of directional selection on a trait that fixes favored alleles, and/or simply an ecological limit that cannot be overcome by generating beneficial mutations. Comparisons of heritability across populations are typically carried out without considering ecological relevance; the majority of comparisons in [6] are for morphological traits whose fitness connections are often unclear and that tend to have relatively higher heritabilities [41,42].

Environmental Effects Further Confound Population Comparisons of Heritable Variation

Effects of environmental conditions on heritability and evolvability can often be dramatic and lead to low estimates under some conditions. For instance, terrestrial isopods (*Porcellio laevis*) exposed to different diets and tested for size showed heritabilities of 0.61 ± 0.39 under high-protein conditions but this dropped to 0.08 ± 0.36 under high-carbohydrate conditions [46].

Box 3. Factors Contributing to Low Heritability in Traits

There are a variety of reasons for low h^2, and some important ones are discussed here.

Directional selection depletes additive genetic variance, following on from arguments in Fisher [82]. This explanation proposes that directional selection has depleted V_A for fitness traits and that the traits are subject to large environmental variance; the combined effect giving rise to low heritabilities.

Based on the directional selection hypothesis, lifetime fitness would be expected to show a low heritability and evolvability when compared with other types of trait. Lifetime fitness has now been studied in natural populations of collared flycatchers, red deer, great tits, red-billed gulls, house sparrows, Soay sheep, and North American red squirrels (see Table 1 in [83]). Results provide support for the directional selection hypothesis with low heritability estimates (<0.09) observed in five of these species, with the majority not being significantly different from zero [84].

A low V_A might reflect an ecological limit in a trait that cannot easily be exceeded, even though genetic variance due to dominance might persist in a population at a limit. Potential limits in traits might prevent the expression of genetic variation due to biophysical constraints [85]. The notion that traits have biophysical limits underlies current mechanistic approaches for understanding the distribution and abundance of organisms, where a set of equations reflecting physical constraints around energy metabolism and assimilation are placed within environmental contexts [86]. While mechanistic models do not preclude evolutionary change through some traits, there are assumed to be fundamental constraints that apply across species that cannot be easily altered because they are related to properties of, for example, circulatory systems or membranes, as well as limits to biochemical flux rates.

Physical constraints can place limits on the rate of development of organisms given nutritional sources, and on the running speed and other performance measures of organisms under particular conditions. Development rate and performance speed are traits that can have a low heritability, as in the case of developmental rate in meerkats [87] and frogs [88] and sprint speed in skinks and lizards [89,90]. One way of exploring whether traits are at genetically determined limits is to undertake selection experiments that aim to push traits beyond their current limits. The response to selection at least in the short term should be related to the realized heritability of a trait and its evolvability. If traits fail to respond, this can indicate a limit, although it might also reflect a general loss of genetic variation as a consequence of small effective population sizes, or trade-offs among traits.

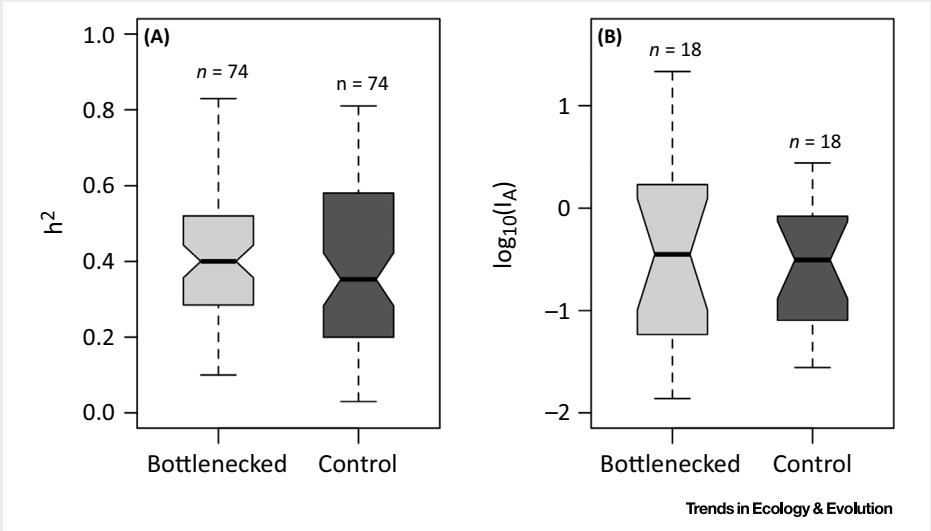

Figure I. Estimates of h^2 (A) and I_A (Log_{10} Transformed) (B) Obtained from Papers Used to Assess Bottleneck Effects on Additive Genetic Variances in [20]. Boxes represent the interquartile range (IQR), horizontal lines within the boxes represent medians, and whiskers extend to maximum and minimum values. Bottlenecked (inbred) populations were kept at low population sizes for one or more generations and estimated inbreeding coefficients in these populations vary between 0.02 and 0.73. Control lines are assumed to have F = 0, and *n* equals the number of traits assessed for h^2 and I_A, respectively. Inbreeding coefficients, traits and estimates of h^2 and I_A (and V_A) are presented in Table S1 in the supplemental information online.

Similarly, in a recent study of two natural populations of *D. melanogaster* performed under seminatural conditions, h^2 for egg-to-adult viability under cold conditions were 0.57 and 0.42 (95% CIs of 0.51–0.64 and 0.36–0.47), respectively, but this decreased at warm temperatures to 0.18 for both populations (95% CIs of 0.12–0.24 and 0.12–0.21, respectively) [47].

The fact that environmental effects on heritable variation are so common highlights the importance of characterizing V_A under conditions where selection occurs. This has been an important issue in agricultural studies for many years, where it is recognized that, because of **gene × environment (G × E) interactions**, production improvements may not occur across all environments. If the expression of heritable variation is low under periods of intense selection, trait means may not change despite selection pressures, as in the case of birth weight in wild sheep [48].

Adaptive Responses Not Captured by V_A: Mutational Meltdown

Although much of the focus in conservation genetics remains on levels of genetic variation in populations, other factors linked to mutation and **linkage disequilibrium** (LD) influence the impact of population size on evolutionary adaptive capacity (Figure 1).

Perhaps the most well known of these relates to **mutational meltdown** [49–52], where accumulating mutations interact with environmental effects to cause greater stochasticity in population size and further exacerbate the deleterious effects of mutations [49,52]. These factors increase extinction risk in persistently small populations. However, extinction risk is reduced if population size varies randomly across time [53].

The importance of mutational meltdown in small populations is rarely mentioned in practical conservation efforts. The role of genetic factors versus environmental and demographic factors in extinction risk is difficult enough to evaluate in threatened species without considering the specific components of the genetic risk factors themselves (i.e., mutation accumulation versus loss of genetic variability, inbreeding, etc.). Estimates of the rate and impact of deleterious

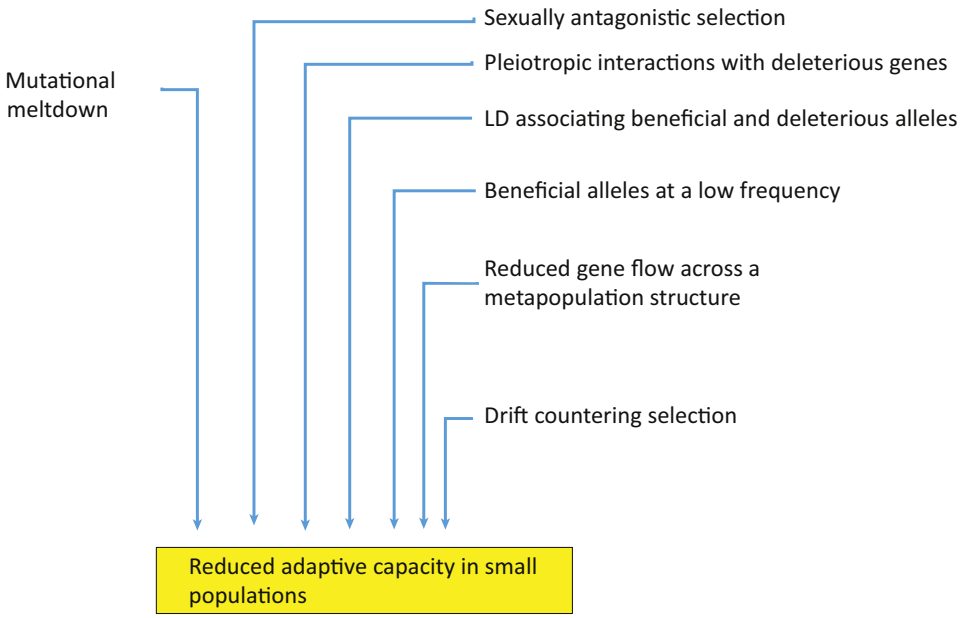

Figure 1. Why High Additive Genetic Variance (V_A) Does Not Necessarily Correlate with Adaptive Potential (Realized Heritability and Evolvability). Abbreviation: LD, linkage disequilibrium.

mutation accumulation are restricted to model organisms, such as yeasts, where they are evaluated over multiple generations [54]. Comparative genomics can also identify deleterious mutation loads, as in the comparison of genomic variation in wolves and dogs, where the higher load in dog breeds likely reflects ongoing bottlenecks [55]. In model systems, meltdown effects are expected to vary within a species depending on whether genotypes already carry deleterious genes [56]. Nevertheless, theory and simulations point to potential effects of meltdown in small populations particularly when populations are already stressed both genomically (e.g., inbreeding) and environmentally; these effects will not be captured by comparisons of V_A across populations.

Adaptive Responses Not Captured by V_A: Deleterious Mutations and Linkage Disequilibrium

In addition to causing mutational meltdown, deleterious mutations coupled with LD can affect the adaptive capacity of small populations unrelated to V_A. Selection responses in both natural and experimental populations can reach a plateau after several generations, even when substantial V_A persists [57]. Under experimental evolution, where populations are maintained under different conditions, the expected directional response in a trait does not occur [58,59] and, in natural populations, there is often no response to directional selection despite V_A for selected traits [60]. In fact, natural populations are often static, failing to evolve in the expected direction even when there is V_A in a trait. Breeding time and clutch size in the collared flycatcher (*Ficedula albicollis*) represent prime examples [60].

In situations where heritabilities and evolvabilities are significant and substantial, the realized heritability of a trait may still approach zero. This may be because of interactions between traits, sex-specific effects, maternal effects, or other factors. For instance, **antagonistic interactions** between the sexes where alleles favored in one sex are selected against in the other sex occur in *D. melanogaster* and other species, although the nature of the alleles remains elusive [61,62]. Antagonistic sex effects have also been described in natural populations of red deer, where high-fitness males produce daughters with a relatively low fitness [63].

When deleterious alleles accumulate in small populations via drift and affect traits under selection, both antagonistic interactions and selection limits can be affected. Deleterious alleles may directly contribute to the expression of V_A in traits but nevertheless reduce a response to selection or result in an asymmetrical and low response towards increased fitness [64]. Deleterious alleles can also curtail selection in small populations by being in LD with alleles under selection. LD is stronger in relatively small populations, providing an effective method for estimating effective population size, especially in small populations of conservation concern [65]. However, strong LD caused by small population size means that deleterious alleles are more likely to be linked to loci under selection, which in turn shapes responses to both purifying and directional selection [66,67]. Results from simulations indicate that adaptation is constrained when beneficial alleles are linked to deleterious mutations [68], and recent genomic comparisons of selection responses highlight the involvement of large haplotype blocks when populations adapt to new conditions [69]. Therefore, deleterious alleles influence adaptation not only by accumulating in small populations through drift, but also by preventing beneficial alleles increasing when these are in LD with deleterious alleles. Such constraints are not captured by comparisons of V_A across populations.

Adaptive Responses Not Captured by V_A: Allelic Combinations and Low-Frequency Alleles

Heritability and V_A estimates are dominated by the effects of alleles at intermediate frequencies, yet genomic analyses of selection responses in populations of model organisms highlight the complexity of genetic changes in adaptive responses [69–71]. When *Drosophila* populations

are exposed to new thermal conditions, the selection response involves not only some alleles that start at intermediate frequencies, but also many alleles that start at a low frequency and then sweep through populations or stop at intermediate frequencies [72]. In small sexual populations, alleles commonly sweep from a low to high frequency, whereas the behavior of alleles in large populations is more diverse [70]. Such subtle but important differences in the genomic basis of selection responses are not detected in comparisons of V_A.

Comparisons of V_A are also unlikely to capture many situations where adaptation involves novel alleles starting from a low frequency. When these alleles spread, they will be detected as hard **selective sweeps**, decreasing genomic variation around the alleles under selection. Studies in *Drosophila* have shown how parts of the genome are altered due to hard sweeps imposed by laboratory directional selection for desiccation resistance [73] and natural selection imposed by low temperatures during range expansions [74]. Selective sweeps are involved in many adaptive responses to stresses such as diseases and toxins, where population size initially sharply declines followed by recovery in some populations, as documented in natural amphibian populations [75]. Signatures of selection associated with disease are particularly well known from human populations, where population expansion has resulted in encounters with new pathogens [76].

As already mentioned, from a conservation perspective, variation in traits linked to ecological limits is important in adaptive responses. Such traits can show low heritability in the direction of selection. Evolutionary constraints imposed by low V_A or trait interactions might only be resolved following rare novel changes in the genome starting from a low frequency, such as tandem duplications. These simply will not occur in populations that are small [77]. Thus, surprisingly high levels of V_A found in some small populations may not translate into a high evolutionary potential; despite weak associations between population size and h^2 and V_A estimates, there are strong genetic arguments why population sizes should be kept high to reduce extinction risks.

Concluding Remarks and Where to Next?

Wood *et al.* [6] highlighted that, while small population size is reflected in reduced molecular variation, it remains challenging to detect effects at the quantitative genetic level. We have outlined likely reasons for this, including a lack of power, particularly when it comes to low-heritability traits. Experimental studies emphasize that population size influences responses to directional selection and extinction probabilities. While rapid short-term decreases in population size might not have much impact on V_A unless there are repeated bottlenecks, such events will have other impacts on many species of conservation concern, particularly through the combined effects of deleterious alleles and LD. In addition, many adaptive changes depend on mutations that occur very rarely in small populations. However, a number of questions remain to be answered (see Outstanding Questions).

With a renewed emphasis on large population size as a way of maintaining adaptive potential, what should managers focus on? There is a need to continue to measure genetic variation within and between populations and species, which is becoming easier and more robust as genomic technologies mature [35], allowing accurate relatedness measurements to improve estimates of genetic components [28,78]. Based on data from genomic studies of model systems, it appears that using genomics to track specific adaptive changes is challenging. However, much can be achieved with high-density markers in terms of mapping genetic diversity across landscapes, and understanding the relative importance of evolutionary processes, such as genetic drift and migration (gene flow), in driving population dynamics. Genomic markers can also be used to understand the extent to which introgression and local adaptation shape genetic diversity. Finally, small natural and domestic

Outstanding Questions

To what extent does LD with deleterious alleles limit selection responses in small populations?

How often do rare alleles in experimental and natural populations contribute to adaptive responses and what is their impact?

When should genetic variation be increased through combining populations versus maintaining discrete populations?

Can genomic studies help to identify populations likely to show a boost in adaptive response as a consequence of introducing genetic variation?

Box 4. Management of Small Populations

While the importance of large population size is re-emphasized here, many natural and domestic populations are already small. In addition, there are well-documented examples of populations that prosper despite a long history of low N_e (e.g., [32,36]). Therefore, a relevant question from a conservation point of view is how these populations should be managed. A more detailed discussion of this issue appears elsewhere [91–93].

Perhaps the most important issue is when efforts should be directed at building up genetic variation through combining small populations versus maintaining discrete small populations [94–97]. In that way the potential for adaptive changes can be maintained even if such benefits are not easily measured, at least in the short term; such decisions must occur within a risk assessment framework. A renewed focus on the importance of genetic distance between populations used in genetic rescue programs can be used to guide management decisions [98].

Populations that have successfully persisted at a small size are likely to have undergone cycles of purging and/or balancing selection, combined with having experienced stable and favorable environmental conditions. These conditions may change and, therefore, such populations should be closely monitored. Where fitness starts to decline, the introduction of new genetic material ('genetic rescue') combined with improvements and/or enlargements of habitats may help these populations persist in the short term (examples in [92]). Obviously genetic rescue is not a long-term solution by itself and potential genetic and ecological reasons for failure are manifold [92], pointing to the importance of proper planning of such management practices.

populations can prosper despite low N_e, and management options are available for small populations (Box 4).

Acknowledgments

We thank Mads F. Schou, Kristian Trøjelsgaard, and Andrew R. Weeks for discussions on the topic and for providing comments on previous versions of this work.

Supplemental Information

Supplemental information associated with this article can be found online at http://dx.doi.org/10.1016/j.tree.2017.03.012.

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