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Opinion

Purging and accumulation of genetic load in conservation

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Our ability to assess the threat posed by the genetic load to small and declining populations has been greatly improved by advances in genome sequencing and computational approaches. Yet, considerable confusion remains around the definitions of the genetic load and its dynamics, and how they impact individual fitness and population viability. We illustrate how both selective purging and drift affect the distribution of deleterious mutations during population size decline and recovery. We show how this impacts the composition of the genetic load, and how this affects the extinction risk and recovery potential of populations. We propose a framework to examine load dynamics and advocate for the introduction of load estimates in the management of endangered populations.

Highlights

The rapid loss of biodiversity requires urgent action to reduce species extinction risk. Genomic tools contribute essential knowledge to management and recovery programs of endangered species.

An increasing number of genomic studies attempt to quantify the amount of deleterious genetic variation (i.e., genetic load), which is a major threat to small populations, to predict the risk of extinction of species and to guide recovery programs.

A clear understanding of the definitions of load as well as the limitations of methods for its estimation is crucial for a better integration of genomics in the conservation toolbox.

Genetic load as a threat to small populations

In the current biodiversity crisis, anthropogenic impacts on ecosystem functioning are the primary threat to species extinction. However, **genomic erosion** (e.g., [1,2]; see Glossary) is often only noticeable many generations after the onset of the immediate threats that lead to population decline. Thus, there is a time-lag between the demographic and genomic impacts of the threats. Most deleterious mutations are initially rare and, hence, it can take many generations of drift for them to increase in frequency, in a process referred to as '**drift debt**' [3]. Only once these mutations are common enough do they become homozygous and reduce the mean population fitness. The fitness effects of recessive deleterious mutations that were initially masked as heterozygotes then become expressed as homozygotes. The **masked load** is thus converted into a **realised load** [4,5], changing the constitution of the **genetic load** [6]. Inbreeding can accelerate this process, resulting in **inbreeding depression**. Genome sequencing and bioinformatic analyses can also shed light on the severity of these threats in non-model organisms [7]. By studying the genetic load and inbreeding, we are better able to evaluate the future viability of species and devise appropriate conservation measures [5]. Since the first paper on 'load' in 1950 [8], scientists from different disciplines (e.g., quantitative geneticists, population geneticists, and ecologists) have defined the term 'genetic load' to suit their study system. Crow introduced three definitions of the genetic load relying on either population fitness or population size metrics for its estimation [9].

Subsequently, some misunderstandings have arisen around the genetic load. These stem from the fact that the genetic load can be estimated as a proportional decrease in the average fitness of a population relative to that of the optimal (maximal) genotype. In addition, the genetic load can be studied using population genetic and quantitative genetic theory [6]. In this population genetic definition, the genetic load can be estimated by summing up the selection coefficients of all deleterious mutations [i.e., **lethal equivalents (LEs)**]. Wallace covered both concepts in detail and noted this distinction in his 1970 textbook [10].

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The confusion arises because these two concepts respond differently to inbreeding. Homozygosity increases during inbreeding, which reduces the mean fitness and increases the genetic load expressed in terms of fitness. However, in terms of LEs, the genetic load does not change, unless **purging** [11] removes some of the deleterious mutations (Figure 1).

Bertorelle *et al.* [6] discussed how the genetic load can be split into two components, the realised load and the masked load. Only the realised load affects the fitness of individuals in the present generation (Figure 1). By contrast, the masked load has no direct bearing on fitness of individuals, but it can reduce fitness of individuals in future generations, for example if the population becomes more inbred. Therefore, the masked load is also referred to as the **inbreeding** load [9,11] or the potential load [12]. Splitting load into its two components helps to clarify what happens in declining populations of threatened species. Inbreeding and **genetic drift** [13] can convert part of the masked load into realised load [6]. This results in inbreeding depression and reduces fitness [14], which enables purifying selection to purge some of these deleterious mutations. In addition, some of the genetic load is lost by genetic drift (Figure 2). Although drift is a neutral process, it can incur a fitness cost by increasing the allele frequencies of deleterious mutations at some loci.

Another reason for the confusion pertains to how the fitness effects of mutations determine the dynamics of load. Although purifying selection is expected to purge highly deleterious mutations

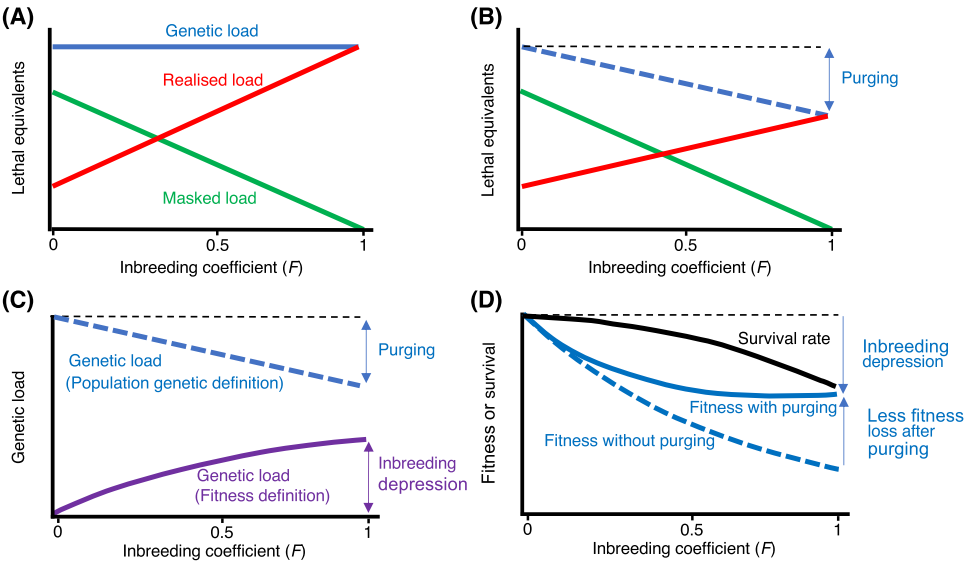

Figure 1. Conceptual figure showing the genetic load components, fitness, and survival rate as a function of the inbreeding coefficient (*F*) with and without purging. (A,B) The genetic load is the sum of the realised and masked loads. The realised load is also larger than zero in non-inbred populations (F=0) because deleterious mutations are not completely recessive and some mutations will be homozygous by chance. The masked load is converted into realised load during inbreeding as homozygosity increases. (A) Without selection, the genetic load is not affected by inbreeding and there is no purging. Nevertheless, with inbreeding, the masked load decreases, and the loss in the masked load is exactly the same as the increase in realised load. (B) If selection operates against individuals that show inbreeding depression, some of the realised load is then purged. This attenuates the increase in the realised load during inbreeding and it reduces the total genetic load. The masked load and realised load do not necessarily change linearly with *F* (see [67]). (C) Although purging reduces the genetic load (i.e., expressed in lethal equivalents), it also results in inbreeding depression (e.g., a reduction in fitness). (D) Selection during inbreeding is due to mortality (or failed reproduction) of individuals that suffer from inbreeding depression. Such inbreeding depression leads to purging, which reduces fitness and causes a momentary increase in the genetic load (i.e., in the fitness sense). However, purging ultimately reduces the number of lethal equivalents. See [67] for the analytical predictions of the inbreeding-purging model.

Glossary

Drift debt: time-lag between a demographic decline and the change in genome-wide diversity.
Genetic drift: stochastic process leading to a change in allele frequencies and loss of genetic diversity due to random sampling of alleles in small populations over generations.
Genetic load: in terms of fitness, the genetic load has been classically defined as the fraction by which the population mean differs from a reference genotype (i.e., the genotype with the maximum fitness). In terms of the mathematical expression, the genetic load = realised load + masked load, and is equal to the sum of the selection coefficients of all deleterious mutations [6].
Genomic erosion: genetic threats to small populations, including loss of genome-wide diversity, increase in genetic load, maladaptation (i.e., mismatch between adaptations and environment), and genetic introgression after hybridisation (i.e., noncompatible or maladapted alleles) [6].
Inbreeding: consanguineous mating leading to a greater increase in homozygosity than expected from panmixia and which can be more frequent in small populations.
Inbreeding depression: reduction in individual fitness due to an increase in expression of (partially) recessive deleterious alleles in homozygous state; enables purging of recessive deleterious variants, but can also reduce the viability of the population.
Lethal equivalent (LE): sum of selection coefficients of all deleterious mutations that reduce the survival or fitness of individuals if expressed [6]. For example, ten mutations that reduce fitness by 10% each are equivalent to $10 \times 0.1 = 1$ LE. The fitness effects of these mutations are assumed to act multiplicatively across loci. The survival probability of an individual that expresses 1 LE equals: $(1 - 0.1)^{10} = e^{-1} \approx 0.37$. Selection coefficients of recessive deleterious mutations that are in heterozygous loci also contribute to lethal equivalents, but they form part of the masked load and do not reduce fitness.
Loss of function (LoF): genetic change leading to partial or complete inactivation of a gene and caused by single mutations (e.g., stop codons-introducing, splice site-disrupting),

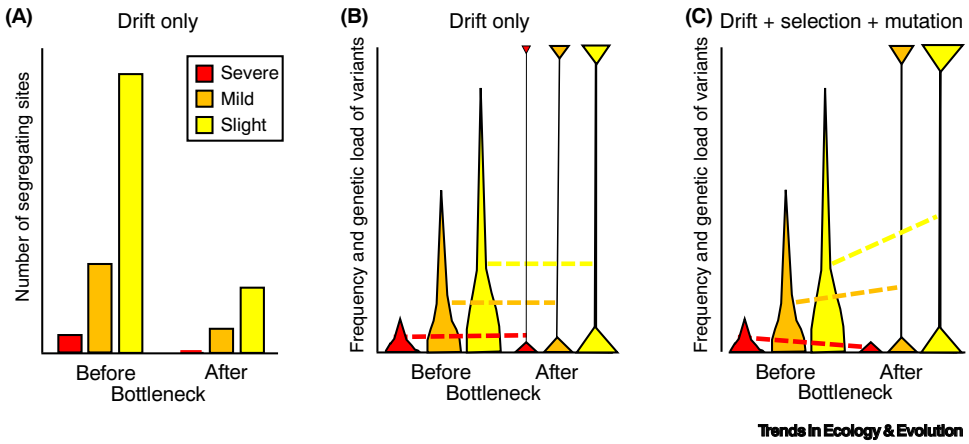

Figure 2. Conceptual diagram showing the evolution of the genetic load across a population bottleneck, and the changes in severely, mildly, and slightly deleterious mutations. (A) Genetic drift reduces the number of segregating sites (i.e., the number of loci with genetic polymorphisms). (B) Without selection, drift does not change the mean allele frequency of deleterious variants, but it does increase homozygosity. (C) In combination with purifying selection and *de novo* mutations, the mean frequency of mutations and the genetic load changes during a bottleneck in a complex way. Partially recessive deleterious mutations with severe effects ($s > 1/4N_e$) segregating in the ancestral population are likely to decrease in frequency due to purging [68], when purifying selection removes individuals that are homozygous for such mutations. Although this is associated with an initial loss in fitness, purging reduces genetic load of severely deleterious mutations after the bottleneck. By contrast, deleterious mutations (with $s \leq 1/4N_e$) drift like (nearly) neutral alleles. This too raises the level of homozygosity and increases the realised load. Furthermore, given the continuous input of new mutations, the number of loci with mildly and slightly deleterious mutations also increases. Consequently, both the genetic load and the realised load of these classes of mutation increase during and after a bottleneck.

(with $s > 1/4N_e$, where N_e is the effective population size), overwhelming drift allows for the accumulation of mildly deleterious mutations (with $s < 1/4N_e$ [9]). During prolonged bottlenecks, the increased frequency of such mildly deleterious mutations at many loci can lead to a substantial increase in load and reduction in fitness, which may threaten population persistence [15] (Figure 2). Thus, the genetic load of mildly deleterious mutations (with $s \sim 1/4N_e$) might pose a more significant threat to small populations compared with severely deleterious mutations. Recent approaches divide deleterious variation into categories (i.e., 'high', 'moderate', 'low' impact; Box 1) allowing the discovery of distinct dynamics for different categories of deleterious mutations. While we still lack information on dominance (h) and selection (s) coefficients, separating mutations into discrete categories remains necessary.

Understanding the impact of timescale is also relevant in studies of genetic load. For instance, while the realised load affects individual fitness in the current generation, both the realised and masked loads could affect the fitness and viability of the whole population in future generations. This is particularly relevant because inbreeding remains high after a bottleneck in a slowly recovering population (e.g., pink pigeon, *Nesoenas mayeri* [1]; kākāpō, *Strigops habroptilus* [2]). After a bottleneck, selection acts against deleterious mutations that have drifted to high frequencies, thereby reducing the effective population size. This might explain the massive loss of genome-wide diversity during population recovery of the pink pigeon [1]. Although its demographic recovery resulted in its down-listing in the Red List, genomic erosion remains severe. Since the goal of conservation actions is to increase long-term population viability [16,17], the focus of small population management should aim to reduce both the realised load (e.g., by limiting inbreeding) and masked load (e.g., by selecting individuals with the lowest masked load for captive breeding or translocations). Most importantly, it is critical to maintain a large effective population size to ensure efficient natural selection.

insertion/deletion (indel) variants or large deletions removing parts of a protein-coding sequence.

Masked load: component of the genetic load (in terms of LEs) the fitness effects of which are not expressed due to deleterious recessive mutations being in heterozygous state [6]; also referred to as the 'inbreeding load' or 'potential load'.

Purging: reduction in genetic load by purifying selection operating against recessive deleterious variants exposed in a homozygous state due to inbreeding in small populations, through population fragmentation or under positive assortative mating.

Purifying selection: type of selection that removes deleterious mutations.

Realised load: component of the genetic load (in terms of LEs) representing the sum of selection coefficients of all deleterious mutations that are partially expressed in heterozygotes (if dominance $h > 0$), and fully expressed in homozygous genotypes [6]. If the fitness effects of mutations act multiplicatively across loci, and if these mutations affect survival, the survival probability of an individual with a realised load of k lethal equivalents is e^{-k}.

Box 1. Estimating and simulating the genetic load

Individual genetic load is routinely estimated in genomic studies as a proxy for population fitness and to compare the relative fitness among individuals. However, these methods vary in terms of the data required and their link to fitness. Two main approaches have been developed so far. Moreover, simulations improve our understanding of the evolution of the genetic load under different conditions (e.g., past demography, life-history traits, etc.).

Coding regions

Coding regions include LoF and missense variants (e.g., VEP [58], SNPeff [59], and VIVID [60]).

Pros: individual load estimate can be used as a proxy for impact on relative fitness. The functional effect and deleteriousness of these mutations can be further assessed based on physicochemical properties of amino acid changes (Miyata score [61] or Sneath's Index [62]) or alignment-based scores (PROVEAN [63]).

Cons: require high-quality gene annotations; impact of mutations on fitness is often unknown; some LoF/missense variants can have an adaptive advantage or no apparent effect [64].

Ultra-conserved elements (UCEs)

UCEs are variants in regions of varied degrees of conservation among species (e.g., GERP scores [65]). Positions that are highly conserved receive high GERP scores and are considered to be under strong purifying selection. Variants at such sites are assumed to be deleterious.

Pros: do not require an annotated reference genome; ideal for non-model species because orthologous regions can be aligned across diverged species (including both model and non-model species).

Cons: unknown impact on fitness (unless conserved regions are annotated); changes in selection coefficients over time affect the link between conservation scores and strength of selection [66]; some substitutions in UCEs may represent lineage-specific adaptations, which can be ascertained using comparative genomics.

Genome-informed simulations

Computer models (e.g., SLiM [56]) complement genome analyses because they can evaluate contrasting demographic scenarios inferred from the empirical genome data. Empirically validated simulation approaches can also be used to inform species-specific assessments of conservation status and extinction risk (e.g., [22,23]).

Pros: can model complex demographic scenarios, including various mating systems and life-history traits, dominance (h), and selection (s) coefficients, impact of deleterious variants. No need to model complete genomes, given that a subset of genomic regions (e.g., hundreds to thousands of genes) is often sufficient.

Cons: computationally intensive; risk of oversimplification of scenarios; unknowns about distributions of h and s coefficients; unknowns about the role of pre- and postzygotic selection; interpretation issues when simulations and empirical data are not congruent. Simulations should remain as an exploratory tool until they can be empirically validated to generate predictions.

Genetic load dynamics illustrated through simulations

Individual-based simulations of a large population undergoing a severe decline followed by a modest recovery illustrate the dynamics of purging and accumulation of the genetic load (Figure 3). As inbreeding increases in a declining population (even under random mating [14]), (partially) recessive deleterious mutations are more readily expressed and, thus, purged more easily [11,18,19]. The genetic load (masked + realised load; Figure 3A) and the number of deleterious variants (Figure 3B; see also Figure 2C) are reduced during the bottleneck through drift and purging [18]. Purging acts more efficiently on highly deleterious mutations [e.g., **loss of function (LoF)**], which are expected to be recessive (Figures S1–S4 in the supplemental information online). However, since drift makes **purifying selection** less efficient [14,20], some of the less deleterious mutations ($s < 1/4N_e$) increase in frequency (Figures S1–S4 in the supplemental information online). Together with the input of *de novo* mutations, this increases the realised load. Furthermore, although drift does not change the mean frequency (q) of mildly deleterious mutations ($s \sim 1/4N_e$), the variance in allele frequency does increase. While many mildly deleterious variants are lost, the

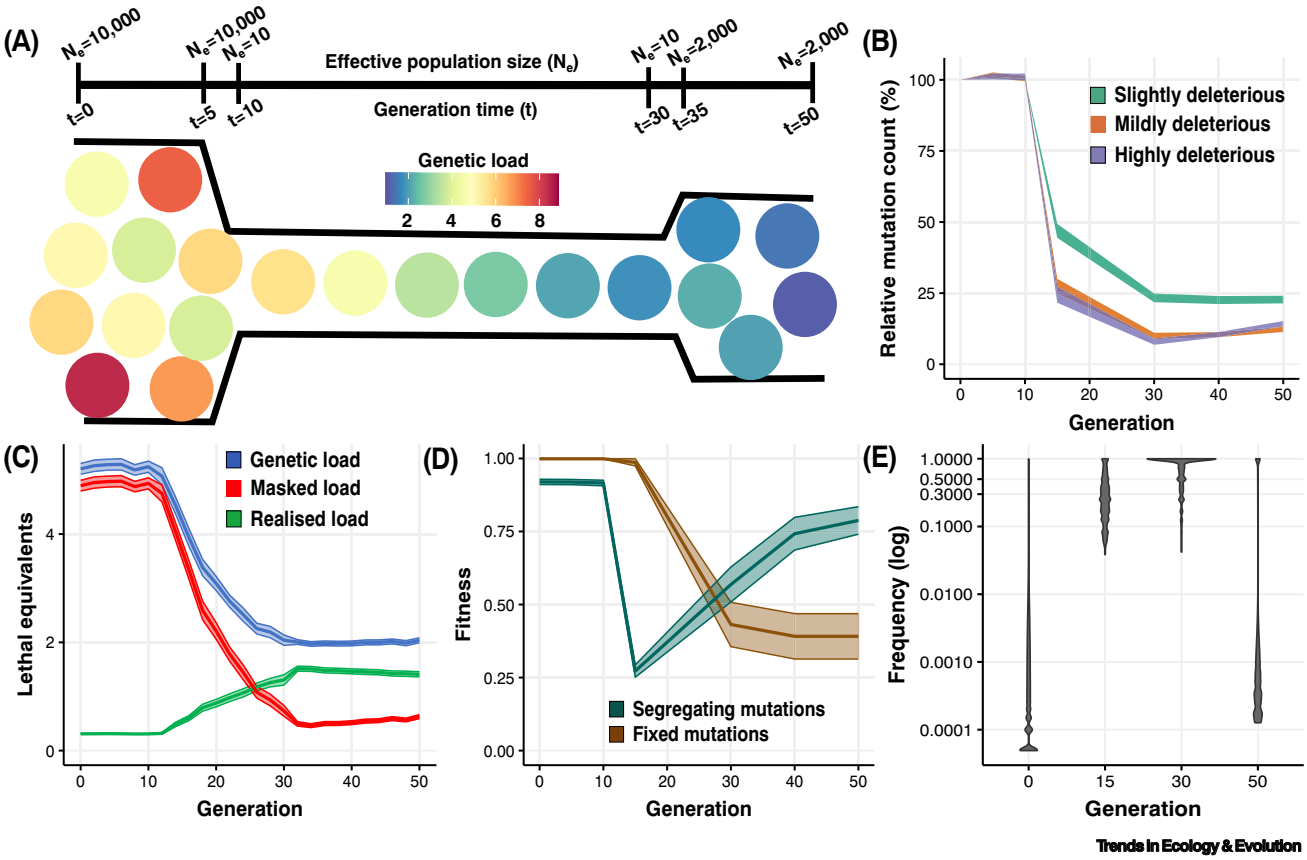

Figure 3. Purging and accumulation of genetic load in small populations. (A) An ancestral population [effective population size (N_e) = 10 000] in mutation–drift equilibrium undergoes a bottleneck (N_e = 10) followed by a recovery (N_e = 2000). The (total) genetic load is heavily reduced in response to the bottleneck due to random loss of deleterious variants and purging. (B) The count of derived mutations relative to the ancestral population decreases considerably during the bottleneck, particularly of highly and mildly deleterious mutations. (C) The total genetic load reduces during the bottleneck and the masked load is converted into realised load. (D) A large drop in fitness is caused by the homozygosity of medium- and high-frequency mutations at the start of the bottleneck (generations 10–15). Despite purging, some of these mutations become fixed, resulting in a permanent fitness loss. (E) Elevated rates of inbreeding and genetic drift increase the frequency of deleterious mutations and realised load, resulting in inbreeding depression and purging. Genetic drift overwhelms natural selection, and some variants escape purging, causing persistent realised load in the post-bottleneck population. Curves depict the mean and confidence intervals across 40 replicates. Simulations were performed in SLiM3 [56] for 10 000 genes of 500 base pairs with a recombination rate r = $1e^{-4}$ (no recombination within genes), and a per base mutation rate m = $5e^{-8}$. Deleterious mutations were sampled from a gamma distribution (mean = –0.05; shape = 0.5), a 5% tail of lethal mutations, and a negative dominance (*h*) and selection coefficient (*s*) relationship, as in [24]. See also Figures S1–S4 in the supplemental information online.

rise in frequency of a few others increases their overall homozygosity. This converts the masked load into a realised load (Figure 3C), resulting in inbreeding depression and a loss of individual fitness (Figure 3D; e.g., [21]). When the population size increases, natural selection becomes more efficient at removing deleterious variation. Purging is facilitated by the fact that deleterious mutations are more likely to be homozygous after the bottleneck. However, many slightly and mildly deleterious mutations remain at high frequency (Figure 3E), illustrating the long-term effects of population decline. Furthermore, mutations that become fixed cannot be removed by selection even if the population recovers (Figure 3E), and this can lead to a permanent loss in fitness and population viability. Moreover, *de novo* deleterious mutations will arise and, hence, the initial purging only leads to a transient reduction in deleterious variation (e.g., [21]).

Recent studies that used biologically informed simulations suggest that long-term purging could make species less vulnerable to the effects of recent bottlenecks or less vulnerable to inbreeding

depression [22,23]. However, while such populations will have less segregating deleterious variation, they will also likely have less adaptive potential from reduced genetic diversity [24–26]. Moreover, comparative analyses suggest that similar demographic histories lead to completely different outcomes, either due to stochastic effects or the complex interacting forces that determine the extinction risk of a species, such as life-history traits (e.g., fecundity, reproductive mode, or longevity [27]).

Empirical evidence for purging and accumulation of load

An increasing number of studies have examined the dynamics of load in small or declining populations using various genomics and simulation approaches (Box 1). Accumulation of genetic load and potential reduction in fitness have often been considered the most likely outcome in the wild [4,5] and have been supported by several empirical studies (e.g., Scandinavian wolf, *Canis lupus* [28,29]; adder, *Vipera berus* [30]; Florida panther, *Puma concolor coryi* [31]; Arctic fox, *Vulpes lagopus* [32]; Chatham Island black robin, *Petroica traversi* [33]; kākāpō [34]; Channel Island fox, *Urocyon littoralis* [35]; and Soay sheep, *Ovis aries* [36]). However, new genomic data suggest that purging occurs more often than previously thought (e.g., gorilla, *Gorilla beringei beringei* [37]; kākāpō [2]; Indian tiger, *Panthera tigris tigris* [38]; Alpine ibex, *Capra ibex* [21]; Montezuma quail, *Cyrtonyx montezumae* [12]; rattlesnake, *Sistrurus catenatus* [39]; Chinese crocodile lizard, *Shinisaurus crocodilurus* [40]; and Iberian lynx, *Lynx pardinus* [41]). Several studies found evidence for long-term small effective population size before human disturbance [22,23,42] and suggested that ancestral purging rendered the species less vulnerable to the effects of recent bottlenecks and of inbreeding depression.

Consistent with theoretical predictions and simulations, many of these studies found evidence for both accumulation and purging in the same system. Indeed, purging of the most deleterious mutations appears to have occurred while a few highly deleterious and several mildly deleterious ones accumulate through drift (e.g., [21,38]; Figure 3). This paradox clearly illustrates the false dichotomy between accumulation and purging of load and has been made apparent in recent genomic studies examining the fate of mutations of varying degree of deleteriousness (e.g., [21,38,41]).

Inferring the fitness effect of mutations is challenging when relying on genomic data alone due to annotation quality and the unknowns about the *h* and *s* coefficients of mutations or without any candidate genes with prior link with a given fitness trait (e.g., dwarfism in Californian condor [43], or sperm quality in kākāpō [34] or mountain lions [44]). Nevertheless, future research using cross-species comparisons could explore whether the masked load (estimated with genomic tools, Box 1) can be used as a proxy for the likelihood of future fitness reduction. This could be useful especially in species that are likely to experience inbreeding (e.g., kākāpō, Sumatran rhinoceros, or pink pigeon). By contrast, comparing the realised load among populations or individuals may be more relevant in the short term (e.g., selection of fittest breeding individuals in management programs).

A framework for future analyses on purging and accumulation of load

Many challenges remain in studies on genetic load in endangered species. First, only few study systems combine phenotypic (fitness) and genomic data [45]. Such systems are crucial to gain insights into the effect of genetic load on individual fitness. However, intensive management programs (both in captive and noncaptive conditions) provide a unique opportunity to combine such data. Husbandry and pedigrees provide data on the heritability of fitness-associated traits. Such pedigree data can also be used in ‘gene drop’ simulations to identify non-neutrally transmitted variants [46]. While speculative, an interesting possibility would be to link the selection coefficients

of variants estimated from gene drop simulations to their mutation-impact scores [e.g., Genomic Evolutionary Rate Profiling (GERP) scores], which might allow us to estimate the fitness effects of mutation-impact scores. Furthermore, gene expression and epigenetic analyses (e.g., methylome [47]) and genome-wide association studies (GWAS) could contribute to a better understanding of the link between putatively deleterious variants and fitness [36,48,49].

Second, we still lack information on the relationship between the *h* or *s* coefficient, and the genetic architecture of a trait. For a discussion on estimating the distribution of fitness effects from genetic data, see [50,51] and the supplemental information online. Nevertheless, even without such information, estimates of the genetic load can be used as a proxy for the future trajectory of this load. Furthermore, while the link between fitness effects and GERP scores has not yet been explored, comparisons of load inferred from GERP scores among species could be useful to assess their vulnerability to the deleterious effects of inbreeding.

Third, distinguishing deleterious from adaptive or 'tolerated' deleterious variation remains challenging, even with predictors of changes in biochemical properties, and it may require complementary approaches, such as outlier tests of selection or genotype–environment association approaches [52].

Fourth, genetic load estimation will depend on the genomic data used (Box 1). Even though thousands of genome assemblies are available for non-model organisms and with the potential of generating species-wide genomic data for endangered species (e.g., kākāpō [53]), many assemblies and gene annotations for endangered species are still missing. Annotation quality is also crucial to reduce the risk of spurious calls of deleterious mutations. Conversely, if the annotation is from an individual suffering from genomic erosion and already containing variants indicative of genetic load (e.g., premature STOP codon), true positives could be missed either through pseudogene filtering or if resequenced individuals contain the same variant, thus leading to an overall underestimation of load. Therefore, an alternative could be to map resequenced data to an ancestral genome, a closely related and non-inbred genome or a pangenome [54].

Fifth, temporal approaches based on a comparison of pre- and post-bottleneck genomes from ancient/historical and modern samples represent a robust experimental design and could become the gold standard to evaluate changes in load of bottlenecked populations [55]. When ancient/historical specimens are not available, comparisons of populations with different demographic histories could be valuable to examine the dynamics of load (e.g., [12]). Alternatively, if a species survives as a single population, a multispecies comparative approach could allow the comparison of the effect of life-history traits and different demographic histories on load (e.g., [21,27]).

Finally, computer simulations are likely to become instrumental in quantifying and predicting the impact of the genetic load on the fitness of individuals and viability of populations. Computer simulations can also evaluate the merit of different management scenarios by incorporating a wide variety of biologically realistic parameters [56].

Concluding remarks

A better understanding of the dynamics of genetic load can be gained by considering the impact of population bottlenecks on its two components (i.e., masked and realised load). Empirical studies and simulations illustrate how the combined impact of mutation, drift, and selection during population decline and recovery can lead to purging, inbreeding depression, and genetic load accumulation. How these processes influence the future viability of the population or species (along

Outstanding questions

How can we combine genomic, transcriptomic, and phenotypic data to quantify genetic load more accurately and to examine the genomic basis of inbreeding depression in small populations? How can genomic and fitness-related estimates of load be used to mitigate the negative impacts of load in small populations?

How do life-history traits, magnitude and timing of a bottleneck, population structure, and relationship between *h* and *s* affect the dynamics of purging and accumulation of load in declining populations and ultimately impact the long-term survival of species?

How do management efforts and speed of demographic recovery affect the dynamics of load? Could proactive management, at the early stage of a decline, prevent the accumulation of genetic load? Could investing conservation resources in a rapid population rebound (e.g., through intensive predator control or habitat protection) favour purifying selection and be sufficient to counteract the accumulation of mildly and slightly deleterious mutations in the medium to long term?

How can we reduce the risk of introduction of new genetic load in populations affected by genomic erosion? While natural gene flow or translocations can inject new beneficial genetic diversity in small and captive populations (i.e., genetic rescue), it will be essential to balance and manage the effects of introduction of beneficial (i.e., adaptive) and detrimental (e.g., LoF) variation.

Which genetic load metrics are more relevant to conservation programs and how could these be aligned with IUCN Red Lists and Green Status of Species? Should a relative change in genetic load estimated in a temporal genomics framework be used to allow for comparable estimates among species?

with direct or indirect human impacts) largely determines the future viability of the population or species, which is invaluable in conservation and species recovery programs.

Genomic erosion assessment is an essential component of genomics-informed conservation. Advances in whole-genome sequencing and bioinformatics enable us to quantify genetic load, diversity, and introgression, as well as evolutionary potential, which will help to improve species conservation and recovery programs. Furthermore, we advocate for a multidisciplinary approach combining a variety of empirical data, ideally fitness data, as well as genome-informed simulations.

Nevertheless, several challenges remain (see Outstanding questions) to further understand the genomic basis of inbreeding depression, its dynamics in various systems, and how to reduce it to maximise the chances of long-term survival of species. Ultimately, an increase in the amount of genomic data, combined with fitness data whenever possible, will contribute to a better understanding of the relationship between inbreeding, purging of genetic load, and genetic rescue. Furthermore, it will represent an unprecedented opportunity to align genetic metrics with the assessment of species extinction risk in International Union for Conservation of Nature (IUCN) Red Lists and Green Status of Species [57].

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Declaration of interests

No interests are declared.

Supplemental information

Supplemental information to this article can be found online at https://doi.org/10.1016/j.tree.2023.05.008.

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