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# The alluring simplicity and complex reality of genetic rescue

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**A series of important new theoretical, experimental and observational studies demonstrate that just a few immigrants can have positive immediate impacts on the evolutionary trajectory of local populations. In many cases, a low level of immigration into small populations has produced fitness benefits that are greater than those predicted by theoretical models, resulting in what has been termed 'genetic rescue'. However, the opposite result (reduced fitness) can also be associated with immigration of genetically divergent individuals. Central to our understanding of genetic rescue are complex interactions among fundamental concepts in evolutionary and population biology, including both genetic and non-genetic (environmental, behavioral and demographic) factors. Developing testable models to predict when genetic rescue is likely to occur is a daunting challenge that will require carefully controlled, multi-generation experiments as well as creative use of information from natural 'experiments'.**

The complex interplay of gene flow, mutation, drift and selection in natural populations makes it difficult to predict which evolutionary force will be most important at any particular time or place [1]. For many years, the demographic contribution of immigrants received the primary emphasis in the literature [2–4], based on the premise that the genetic effects of small population size are less important than are other factors in determining population persistence [5]. More recently, it has been shown unequivocally that inbreeding resulting from genetic drift in small populations can depress POPULATION FITNESS (see Glossary) and increase extinction risk [6–9]. In an exciting new development, a variety of natural and experimental studies demonstrate that immigrants can effect a GENETIC RESCUE [10] of small, inbred, at-risk populations by alleviating INBREEDING DEPRESSION and boosting fitness.

Genetic rescue is generally considered to occur when population fitness, inferred from some demographic vital rate or phenotypic trait, increases by more than can be attributed to the demographic contribution of immigrants [11,12]. (In human medicine, genetic rescue is used in reference to gene therapy, but this usage lies outside the scope of this article.) Genetic rescue might play a subtle,

yet crucial role in the evolution of small natural populations and can, under some circumstances, be an effective conservation tool. Evidence that genes from a pulse of immigrants can increase population growth rate also has important implications for the study of METAPOPULATION dynamics [13].

However, immigration of genetically divergent individuals can also lead to the opposite effect: a reduction in population fitness owing to OUTBREEDING DEPRESSION. Whether immigrants increase or reduce population fitness depends upon interactions among several genetic and non-genetic factors, such as the degree of EPISTASIS, demography, behavior and environmental context. This complexity makes it difficult to predict whether any given immigration event will effect genetic rescue. Results of recent studies should help to re-focus research toward a fuller understanding of the evolutionary consequences of migration among small populations, as researchers focus more upon the complex interactions among forces that underlie the evolution of spatially structured populations.

## Fitness effects of immigrant genes

The fundamental premise of genetic rescue is that, if a local population suffers inbreeding depression, immigrants can infuse new genetic variation that increases fitness. Under this scenario, immigrants must produce descendants that are, on average, more fit than those of

## Glossary

**Epistasis:** interactions among genes at different loci that influence a phenotypic trait.

**Genetic rescue:** an increase in population fitness owing to immigration of new alleles.

**Heterosis:** elevated fitness of offspring from matings between genetically divergent individuals (i.e. hybrid vigor).

**Inbreeding depression:** reduced fitness of offspring from matings between related individuals, owing to reduced heterozygosity and/or increased expression of deleterious, recessive alleles.

**Intrinsic coadaptation:** elevated fitness caused by positive epistasis.

**Local adaptation:** increase in fitness of a local population associated with an increase in the frequency of alleles or allelic combinations favored by local selection pressures.

**Metapopulation:** a population of populations linked by migration; in the classic definition, local populations are subject to frequent extinction and recolonization events.

**Outbreeding depression:** reduced fitness of offspring from matings between genetically divergent individuals, owing to dilution of local adaptation and/or disruption of epistasis.

**Population fitness:** mean fitness measured as population growth rate or inferred from changes in reproduction or survival rates.

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residents to then raise the overall mean fitness of the local population. Ideally, genetic rescue is measured by an increase in population growth rate over multiple generations.

The increase in fitness is thought to be due primarily to HETEROSIS in the offspring that result from matings between immigrants and local individuals. Heterosis occurs via two mechanisms. First, immigrant alleles can mask deleterious, recessive alleles that have achieved a high local frequency via genetic drift, which can occur when the product of population size ( $N$ ) and the selection coefficient ( $s$ ) is less than one ( $Ns < 1$ ). Second, matings between immigrants and local individuals produce highly heterozygous offspring, which are often favored by natural selection. The recent literature suggests masking of deleterious alleles is the more prevalent mechanism of heterosis [14].

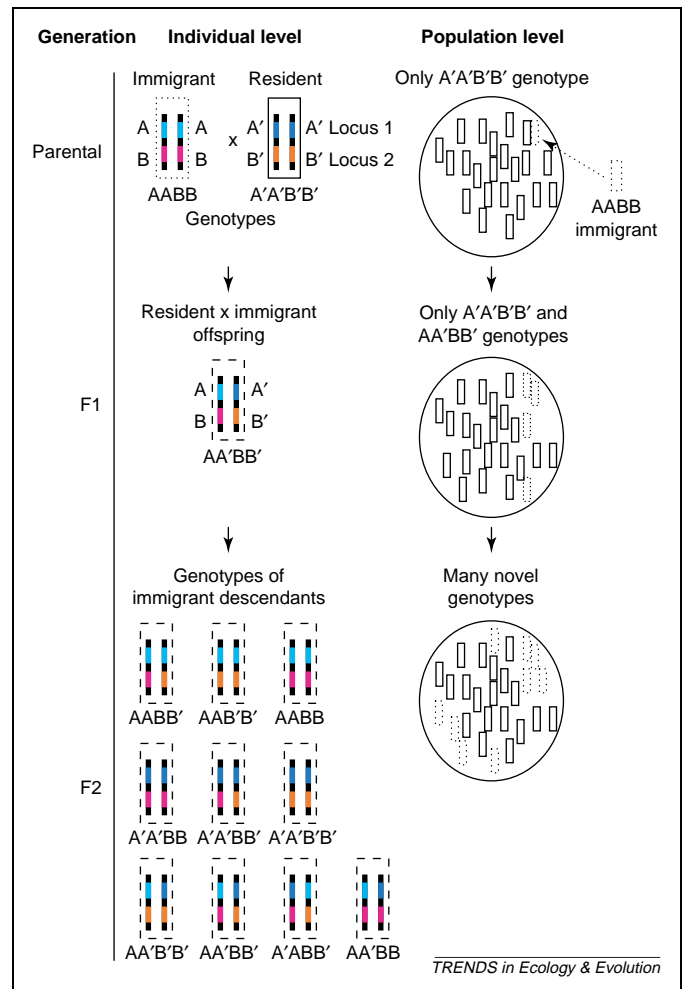
To understand how immigration can either increase or reduce population fitness, it is necessary to consider multiple gene loci over multiple generations (Figure 1). The F1 generation will have high heterozygosity (and, hence, heterosis) as a result of allele frequency differences between parental types. Positive epistasis will also be maintained because one set of chromosomes from each parental lineage remains intact. However, immigration will also decrease LOCAL ADAPTATION by diluting local alleles that make positive additive contributions to fitness. Therefore, the net fitness effects of immigration in the F1 generation can be either positive or negative, depending on whether the positive effects of heterosis more than compensate for the dilution of local adaptation.

In subsequent generations (F2 and beyond), recombination will disrupt positive epistatic interactions among parental alleles at different loci (Figure 1), thus reducing INTRINSIC COADAPTATION. If the immigration rate is high and from a genetically divergent source, population fitness can be reduced in the F2 generation and beyond as immigrants dilute locally adaptive alleles and disrupt co-adapted gene complexes. Furthermore, heterozygosity and associated heterosis peaks in the F1 generation and declines thereafter. As a consequence, descendants of immigrants often exhibit initial heterosis followed by subsequent outbreeding depression in following generations (Box 1), so whether a population is rescued genetically by immigrants largely depends on the relative importance of these opposing phenomena.

### Observational studies of genetic rescue

Several recent studies report increased fitness in response to low levels of immigration (gene flow) into populations that have suffered recent declines (Table 1). For example, immigrants apparently increased the hatching rate of imperiled prairie chickens *Tympanuchus cupido* [15] and reduced the proportion of stillborn births in a relict population of adders *Vipera berus*, while increasing molecular genetic variation, recruitment and population growth rate [16]. A single immigrant is thought to have spurred the growth of a stagnant, recently re-founded Scandinavian wolf *Canis lupus* population [17,18].

These studies, which encompass a wide range of vertebrate taxa, suggest that immigration can increase



**Figure 1.** Genetic rescue. Genetic rescue depends upon whether selection favors the new genotypes created by immigration. The mating of a genetically divergent immigrant (homozygous for one set of alleles A and B at loci 1 and 2, respectively) with an individual from a local population (homozygous for different alleles A' and B') produces F1 offspring that are heterozygous and adds genetic variation to the population. By the F2 generation, this mating generates ten possible genotypes at two loci. In real populations, there are many more loci and novel genotypes generated by immigration events.

the fitness of small, inbred populations by restoring adaptive genetic variation. However, because each of these studies was limited to a single, unreplicated population without experimental controls, it is impossible to attribute unequivocally the fitness increases to genetic rescue rather than to other potentially confounding factors, such as benign changes in the local environment or non-genetic influences of immigrants. For example, it is possible that the Scandinavian wolves were so closely related they simply avoided breeding for behavioral reasons until the unrelated immigrant arrived [17].

### Experimental studies of genetic rescue

Other recent studies have isolated the genetic influences of immigrants by controlling for their demographic impacts, and they support the premise that immigration can increase population fitness [19–23]. The most striking example of genetic rescue is from a water flea *Daphnia magna* metapopulation inhabiting Baltic seashore rock-pools [19]. In replicate populations, the researchers mated residents with residents, residents with immigrants and

### Box 1. Heterosis and outbreeding depression

Initial heterosis, followed by outbreeding depression, has been observed recently in taxa as diverse as angiosperms [62,63], copepods [64], insects [65], birds [66] and mammals [67]. In the marine copepod *Tigriopus californicus*, Burton, Edmands and colleagues found heterosis in F1 hybrids followed by F2 outbreeding depression levels that correlated with the genetic divergence between source and recipient populations [64,68,69]. In Fenster and Galloway's studies of the partridge pea *Chamaecrista fasciculata*, F1 crosses of individuals from populations at all distances studied (0.1–2000 km) showed heterosis, thus demonstrating inbreeding depression within populations [62,63,70]. Subsequently, outbreeding depression was found in crosses from populations separated by  $\geq 1000$  km, but not until the F3 generation. Because unlinked genes begin recombining in the F2 generation, the appearance of consistent outbreeding depression only in the F3 generation demonstrates that disruption of epistasis as a result of linked genes can continue to reduce fitness beyond the F2 generation. Evidence also suggests that cytonuclear co-adaptations (i.e. the coadaptation of nuclear and cytoplasmic organelle genes) can contribute to outbreeding depression [70,71].

In a remarkable example of intrinsic coadaptation, Gharrett *et al.* found outbreeding depression in crosses of two pink salmon *Oncorhynchus gorbuscha* populations that spawn in the same location (and, hence, experience on average the same environment) but are isolated temporally because of strict even- or odd-year life cycles [72]. Inter-year crosses showed outbreeding depression in the F2 (but not F1) generation, which provides evidence for disruption of positive epistasis following recombination. These theoretical results help to explain that even the same selection pressures (on average) over many generations do not guarantee a similar genetic architecture, which, in turn, suggests that extensive mixing of populations experiencing similar selective regimes might increase fitness in real populations.

immigrants with immigrants. Repeated generations of asexual reproduction locked in place F1 genotypes. Because asexual reproduction prevented segregation of alleles, selection could act over many generations on intact resident, F1 hybrid, and pure immigrant genomes and amplify fitness differences among lineages over time. Ultimately, the hybrid F1 clonal lineages had an average fitness that was over 35 times that of resident lineages.

This study demonstrates that inbreeding depression is a biologically important phenomenon in this water flea metapopulation and that immigration can increase fitness greatly. Because entire life cycles were observed, fitness impacts were integrated over the full life history and amplified over time. By contrast, most studies infer fitness effects of experimental treatments on only one or two traits measured in a single generation. Selection intensity on individual life history traits can vary greatly over time and space, and the cumulative effects of selection on multiple traits will interact to produce overall fitness effects. This implies that short-term studies of a few traits can result in misleading conclusions. For example, Bryant *et al.* found a strong genetic rescue effect on larval emergence in experimental house fly *Musca domestica* populations, but only after an initial five-generation period in which low levels of immigration provided no detectable benefits to recipient populations [20].

Two recent plant studies provide further evidence of the fitness benefits immigrants can provide to inbred populations. In experimentally inbred populations of the mustard *Brassica campestris*, one immigrant per

generation significantly increased the fitness of four out of six fitness traits in treatment populations compared with (no immigrant) controls [21]. No fitness difference was found between the one-immigrant and 2.5-immigrant treatments, which suggests that only very low levels of immigration are necessary for a fitness boost. However, greater phenotypic divergence among populations was found in the one-immigrant treatment compared with 2.5-immigrant treatment. This is interesting because it shows that lower immigration can facilitate local adaptation in spatially structured populations that are subject to variable or divergent selection pressures.

In small white campion *Silene alba* populations, gene flow increased germination success and the success of immigrant pollen correlated positively with the amount of inbreeding in recipient populations [22,24]. This work demonstrates inbreeding depression in these populations and suggests that, all else being equal, populations that are more inbred are more likely to benefit from a genetic rescue effect. Together with the *Brassica* study and others [23,25–28], this implies that very low levels of immigration could cause genetic rescue in inbred populations without greatly constraining local adaptation. Fortunately, it is increasingly possible to identify recently inbred populations using new molecular-based statistical approaches [29], and so candidate populations for genetic rescue should be easier to find.

### Rescue via other genetic pathways

Immigrants can also increase fitness via mechanisms other than heterosis [12,30]. One such mechanism is frequency-dependent selection for rare alleles. In small populations of self-incompatible plants with few alleles at the S-locus (which inhibits pollination by donors with the same S-allele type as the maternal plant), immigrant pollen with novel S-alleles can substantially increase reproductive success [31–33]. There is also evidence in Hymenoptera that frequency-dependent selection for novel sex-determining alleles introduced into bottlenecked populations by immigrants would raise colony fitness by increasing the frequency of diploid heterozygotes (females, which contribute to colony success), at the expense of diploid homozygotes (males, which drain resources) [34].

Gemmell and colleagues hypothesize that female immigrants might also benefit small populations by introducing new mitochondrial DNA (mtDNA) alleles, which are maternally inherited in most species [35]. They suggest that mtDNA alleles with negative fitness effects (e.g. on male fertility) would become fixed in small populations, because selection acts less efficiently (and differently) on mtDNA alleles, owing to their maternal inheritance, than it does on nuclear alleles [36]. In this scenario, immigrant females that pass on superior mtDNA alleles would boost population fitness with their extra-nuclear genetic contributions.

### Inferences for metapopulation conservation

The upshot of these recent studies is that genetic rescue could be crucially important to entire metapopulations by reducing local inbreeding depression or adding adaptive



**Table 1. Recent empirical studies showing genetic rescue effects<sup>a</sup>**

Species	Study type <sup>b</sup>	Context	Immigrant source <sup>c</sup>	Study length <sup>d</sup>	Primary results	Refs
Animal						
Water flea <i>Daphnia magna</i>	Exp	Field and laboratory populations	Nearby population	F1	Population growth rate many times greater in outbred than in inbred populations	[19]
House fly <i>Musca domestica</i>	Exp	Laboratory populations	Same population	F20	Pupal emergence in immigrant populations greater than controls	[20]
Fruit fly <i>Drosophila melanogaster</i>	Exp	Laboratory populations	Same population	F3	Reproductive fitness in immigrant populations twice that of the controls	[23]
Flower beetle <i>Tribolium castaneum</i>	Exp	Laboratory populations	Same population	F20	Population growth rate higher in populations receiving immigrants from high fitness (but not low fitness) populations	[41]
Adder <i>Vipera berus</i>	Obs	Isolated population	Distant population	F1	Population growth rate increased, stillborn birth rate decreased	[16]
Prairie chicken <i>Tympanuchus cupido</i>	Obs	Isolated population	Distant populations	F1	Egg viability increased	[15]
Song sparrow <i>Melospiza melodia</i>	Obs	Isolated population	Unknown population	F2	F1 fitness elevated, but F2 fitness lower	[78]
Scandinavian wolf <i>Canis lupus</i>	Obs	Isolated population	Unknown population	F2	Population growth rate increased	[17]
Plant						
Mustard <i>Brassica campestris</i>	Exp	Outdoor populations	Same population	F6	Immigrant pollen increased 4/6 fitness traits	[21]
White campion <i>Silene alba</i>	Exp	Greenhouse study of field-collected plants	Nearby populations	F1	Immigrant pollen increased germination success in peripheral populations	[11]
Scarlet gilia <i>Ipomopsis aggregata</i>	Exp	Isolated populations	Distant population	F1	In small population only, seed mass and germination increased by immigrant pollen	[25]
Yellow pitcher plant <i>Sarracenia flava</i>	Exp	Isolated populations	Distant population	F1	Plant height increased by immigrant pollen	[26]
Scurvy grass <i>Cochlearia bavarica</i>	Exp	Outdoor populations	Nearby populations	F1	Seed mass and plant size increased by immigrant pollen	[28]

<sup>a</sup>Only studies that show population fitness responses to treatments are included.

<sup>b</sup>Obs, observational; Exp, experimental.

<sup>c</sup>Source population for immigrant individuals. In many experiments, immigrants are recent descendants from same source as recipient populations.

<sup>d</sup>Inferred study length in generations from first immigration event, sometimes not explicitly stated in studies.

alleles that increase the probability of local population persistence. In turn, this bolstering of local populations maintains a broad geographical distribution of populations that buffers overall metapopulation extinction and provides future immigrants for other populations [10]. A genetic rescue effect can improve the likelihood of success of colonization events that might otherwise fail because immigrants can reinforce colonizing populations that often evolve from a few founders and quickly become inbred [17,22]. From a conservation perspective, this also means that genetic rescue might have an important impact in the spread of unwanted invasive species along the leading edge of invasion by supplying recently established, small propagules with adequate genetic variation to respond to selection and adapt to the new environment [37]. Therefore, a useful strategy for reducing the spread of invasive populations could be to minimize the chances for genetic rescue to occur.

Although the term 'genetic rescue' is new, the underlying concepts are not. Similar to many other useful concepts in evolution, the thread of genetic rescue can be traced back to Charles Darwin and Sewall Wright (Box 2). Recent theory has refined our understanding of genetic rescue and shown that heterosis is maximized when local population size is small, gene flow is low and selection intensity is low or intermediate [38,39]. These results are

germane, because reductions in local population size (and, hence, greater drift and less efficient natural selection) and restrictions in gene flow are two of the primary consequences of the ongoing worldwide habitat fragmentation crisis [40]. This suggests that anthropogenic influences will increase the number of cases where genetic rescue will be an important evolutionary phenomenon and effective conservation tool.

### Complicating genetic factors

In spite of these exciting results, several important caveats apply to the laboratory and field studies reporting genetic rescue that should temper the use of genetic rescue as a management tool. First, most laboratory studies have used highly inbred lines or populations. The level of inbreeding typically was equivalent to full-sib mating for two generations or more, so it is not surprising that mating with an immigrant would provide fitness benefits. It is difficult to translate these experimental results directly to natural populations in which inbreeding levels are usually unknown and unlikely to be as high.

Second, the experimental populations and immigrants are usually derived from a single source population. Given that immigrants share a common genetic architecture with the recipient population, the chances of outbreeding depression are reduced. Finally, most studies have

**Box 2. The conceptual foundations of genetic rescue**

The concept of genetic rescue was presaged by Charles Darwin, who, in his extensive surveys of empirical data to better understand evolutionary processes, noted that (i) isolated populations often suffer from inbreeding and inbreeding depression, and that (ii) immigration ('new blood') can help recover a population's fitness [73]. Although Darwin's observations are over 100 years old and report insights from husbandry that probably extend back millennia to the early days of domestications, theory to understand these observations is still being developed.

The seminal theoretical work relevant to genetic rescue was proposed by Sewall Wright, who was interested in the effects of immigration among populations linked by gene flow. He showed that one migrant per generation among populations equally linked by immigration was adequate to keep the same neutral alleles segregating in all populations, and that the relative strength of gene flow and selection determined the fate of non-neutral alleles [74,75]. Wright's

contributions remain the foundation for much of the ongoing research related to population subdivision, migration and the distribution of genetic variation in neutral and selected loci and traits.

Recent models by Whitlock and colleagues have expanded Wright's work to include heterosis in immigrant offspring [38,39]. These efforts demonstrate that, as small isolated populations diverge, they become fixed for different deleterious alleles at different loci. As a result, immigrants bring in alleles that mask local deleterious alleles, immigrant offspring show higher fitness than local offspring, and the effective immigration rate (i.e. gene flow) is elevated over that expected from neutral theory as immigrant alleles increase rapidly in frequency owing to selection. These results help to explain some of the recent remarkable results from the laboratory and field, even though they are based upon simple single-locus population genetic models and do not include heterozygote advantage or other genetic mechanisms that might increase fitness.

followed results only through the F1 generation, where heterosis is maximized and outbreeding depression is often not yet expressed.

Still, although there is no doubt that immigration from a maladapted source can reduce fitness and constrain local adaptation [41–43], the idea that limited immigration can play a more positive role in evolution has received renewed attention [41,44–46]. A key to resolving the general importance of genetic rescue is understanding the relative importance of interactions among genes versus the additive effects of individual genes in determining the fitness of populations – a debate that dates back to Fisher and Wright and remains an area of active research. Some recent experimental results suggest that, if favored alleles are added to a population, they will spread because selection can efficiently choose advantageous alleles regardless of the genetic background [47]. This implies that gene interactions might not be as important as single locus, additive contributions to fitness and that, under some circumstances, at least, selection can take care of things if given enough time and a few copies of adaptive alleles to act upon. Thus, immigrants can provide useful alleles that, over long timescales, contribute to increased population fitness even if the immediate descendants of immigrants do not.

**Complicating non-genetic factors**

Given that individuals are not boxes of genes, demographic, behavioral and environmental factors can profoundly influence the fitness contributions of immigrants (Box 3). Demographic theory has predicted, and empirical studies have demonstrated, that individuals of particular ages or life stages can have disproportionate effects on the trajectory of a population. Using standard demographic data and analyses [48,49], one can predict the relative impacts of immigrants by estimating their future reproductive potential. For example, immigrants have little chance of providing genetic rescue if they are immature and have a low chance of survival to reproductive age, or are too old and have little chance of future reproduction. Joint consideration of demography and genetics in a single theoretical framework can sharpen predictions of optimal conditions for genetic rescue [50,51]. However, subtleties of how demography is incorporated into population genetic

models can alter conclusions, so careful examination of assumptions is necessary [52,53].

Even a rigorous investigation of genetic and demographic factors might be insufficient to predict reliably whether genetic rescue will occur, because important behavioral subtleties such as mate choice, dominance hierarchies and infanticide, can also influence the evolutionary impact of immigrants. For example, female mice *Mus domesticus* prefer genetically dissimilar males, which would favor immigrant males and facilitate genetic rescue. However, they also assess male quality, in addition to genetic dissimilarity, in choosing among potential mates [54], which complicates predictions of how well immigrant males might reproduce.

Furthermore, in some species, a successful male immigrant might kill existing juveniles, as occurs, for example, with immigrant adult male brown bears *Ursus arctos* following removal of local adult males by hunters [55]. In general, immigrants could have widely varying reproductive success depending upon interactions with local individuals. Thus, they could provide either no, or a great deal, of gene flow, which makes tenuous studies uninformed by behavioral or mating system data [56].

Immigrants might also serve as vectors for disease-causing parasites and pathogens, thus leading to the opposite of a rescue effect [57,58]. Little empirical evidence is available to indicate under what conditions the genetic rescue benefits of low levels of immigration outweigh the increased risk of disease transfer.

From the above considerations, it is clear that, even if one considers only biological consequences for the species of interest, evaluating and predicting the consequences of a genetic rescue attempt is exceedingly complex. In a conservation context, biological theory can provide insights, but broader considerations are also likely to be relevant. For example, genetic rescue efforts for some at-risk species have economic, social, legal and political ramifications. Integrating these types of consideration into an overall cost-benefit analysis will be challenging but necessary [59].

**Future studies**

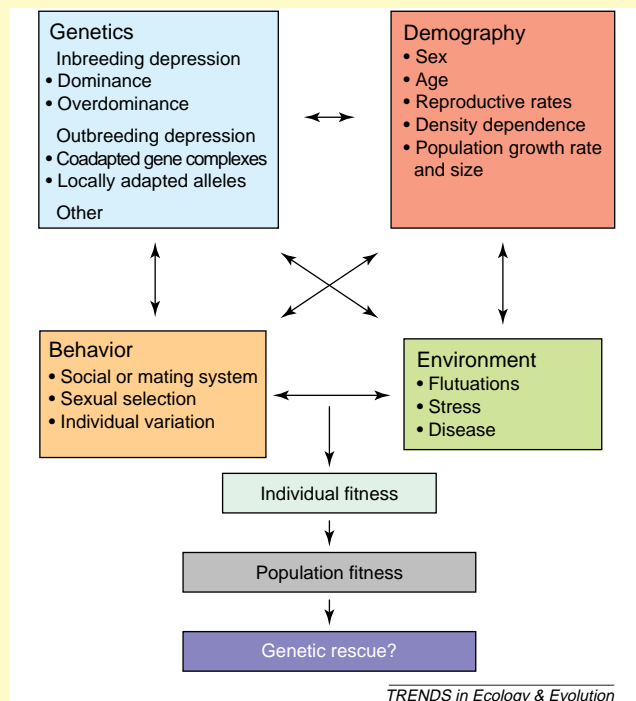
A nagging limitation is how little we know about the joint impacts of inbreeding and outbreeding depression in

### Box 3. The biological context of genetic rescue

In applying the concept of genetic rescue to wild populations, much information is needed. Ideally, detailed behavioral, demographic, environmental and genetic information would be available to provide a comprehensive framework for understanding when rescue might be achieved (Figure 1). First, it is important to know how much a population suffers from inbreeding depression and how susceptible it is to outbreeding depression. This will determine the optimal level of immigration to effect a fitness increase. However, the balance between these two considerations in wild populations is difficult to ascertain because it depends upon many usually unknown factors.

Conservation efforts on behalf of the endangered Florida panther *Felis concolor*, which has shown strong putative inbreeding depression, have attempted to integrate some of these factors. Hedrick used simple population genetics models to show that a brief period of high gene flow followed by subsequent generations of low gene flow could effect genetic rescue by reducing the frequency of deleterious alleles without substantially reducing the frequency of locally adaptive alleles [76]. Knowledge of panther behavior suggested that only females should be used as immigrants because males were likely to precipitate mortal combat with resident males, risking not only local population decline, but also the failure of immigrants to reproduce. It was also known that females readily establish territories and begin breeding after their first year.

These behavioral, genetic, and demographic considerations were incorporated into Florida panther recovery management actions and preliminary evidence suggests that the initial target level of introgression has been achieved and that at least one important fitness trait, the number of descended testicles per male, has increased [77]. Several generations of monitoring will be necessary to see if this attempted genetic rescue is successful in boosting population growth.



**Figure 1.** Some of the important biological factors that interact to determine whether genetic rescue will occur.

natural populations, except that they probably occur frequently and simultaneously [60]. A key evolutionary question is whether the heterotic effects of a few successful immigrants will outweigh reductions in fitness owing to outbreeding depression. Susceptibility to these two factors

varies considerably among taxa and specific circumstances, including population history and recent inbreeding levels, degree of local adaptation and genetic divergence between immigrants and recipient populations. Given the paucity of data addressing this issue for wild or experimental populations, it is difficult to predict with any certainty whether the net genetic effects will be positive or negative for any unstudied system. This is a sobering truth for applied conservation efforts. However, empirical data do demonstrate that low levels of immigration can provide considerable fitness benefits to recently isolated, inbred populations, and recent molecular-based statistical advances will help to identify these populations efficiently [29,61].

A daunting challenge is to develop a general theory of rescue effects that incorporates genetics, in addition to demography, behavior and disease ecology; all factors that can be shown to be of preeminent importance in specific cases. The crux of the challenge is formulating theories that are simple enough to be tested empirically and that are useful beyond only narrow conditions. There is a vital role for multi-generation experiments in developing this theory, as well as for creative uses of meta-analyses to distill collective insights from numerous imperfectly controlled laboratory and natural 'experiments'.

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