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Predicting the Deleterious Effects of Mutation Load in Fragmented Populations

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Abstract: Human-induced habitat fragmentation constitutes a major threat to biodiversity. Both genetic and demographic factors combine to drive small and isolated populations into extinction vortices. Nevertheless, the deleterious effects of inbreeding and drift load may depend on population structure, migration patterns, and mating systems and are difficult to predict in the absence of crossing experiments. We performed stochastic individual-based simulations aimed at predicting the effects of deleterious mutations on population fitness (offspring viability and median time to extinction) under a variety of settings (landscape configurations, migration models, and mating systems) on the basis of easy-to-collect demographic and genetic information. Pooling all simulations, a large part (70%) of variance in offspring viability was explained by a combination of genetic structure (F_{ST}) and within-deme heterozygosity (H_S). A similar part of variance in median time to extinction was explained by a combination of local population size (N) and heterozygosity (H_S). In both cases the predictive power increased above 80% when information on mating systems was available. These results provide robust predictive models to evaluate the viability prospects of fragmented populations.

Keywords: extinction time, genetic structure, habitat fragmentation, metapopulation, mutation load, offspring viability

Predicción de los Efectos Deletéreos de la Carga de Mutaciones en Poblaciones Fragmentadas

Resumen: La fragmentación del hábitat inducida por humanos constituye una amenaza mayor para la biodiversidad. Los factores genéticos y demográficos se combinan para conducir a las poblaciones pequeñas y aisladas hacia vórtices de extinción. Sin embargo, los efectos deletéreos de la endogamia y la deriva pueden depender de la estructura de la población, los patrones de migración y los sistemas de apareamiento y son difíciles de pronosticar ante la ausencia de experimentos de cruzamiento. Realizamos simulaciones estocásticas basadas en individuos con el objetivo de predecir los efectos de las mutaciones deletéreas sobre la adaptabilidad de la población (viabilidad de la progenie y tiempo medio de extinción) bajo una variedad de escenarios (configuraciones de paisaje, modelos de migración y sistemas de apareamiento) sobre la base de información demográfica y genética fácil de obtener. Al combinar todas las simulaciones, una gran parte (70%) de la varianza en la viabilidad de la progenie fue explicada por una combinación de la estructura genética (F_{ST}) y la heterocigosidad intra deme (H_S). Una parte similar de la varianza en el tiempo medio a la extinción fue explicada por una combinación de la estructura genética (F_{ST}) y la heterocigosidad (H_S). En ambos casos, el poder predictor incrementó más de 80% cuando se disponía de información de los sistemas de apareamiento. Estos resultados proporcionan modelos predictivos robustos para evaluar la viabilidad potencial de poblaciones fragmentadas.

Palabras Clave: carga genética, estructura genética, fragmentación de hábitat, metapoblación, viabilidad de la progenie, tiempo de extinción

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Introduction

Human-induced habitat fragmentation constitutes a major threat for biodiversity (Frankham 1995). Consequences are, at first, demographic. Small and isolated populations suffer from increased stochasticity and limited rescue effects, which may suffice to cause local extinctions (Lande 1993; Hanski & Ovaskainen 2000). But fragmentation also has genetic consequences, which are likely to contribute significantly to extinction risks. Increased genetic drift reduces the effectiveness of selection against deleterious mutations (Kimura et al. 1963), leading to their progressive accumulation (e.g., Lynch et al. 1995), and decreases standing genetic variation and rate of fixation of beneficial mutations (Whitlock 2003), which limits the evolutionary potential of isolated populations. Although the importance of genetic relative to demographic factors is still debated (e.g., Frankham 1995; Lande 1995; Spielman et al. 2004), the 2 factors are expected to interact and feed back on each other, progressively driving fragmented populations into “extinction vortices” (Lacy & Lindenmayer 1995) or “mutational melt-downs” (Lynch et al. 1995; Higgins & Lynch 2001).

The potential effects of deleterious mutations on population fitness are often estimated from the level of inbreeding load. If one assumes there is a negative exponential relationship between fitness and inbreeding coefficient of individuals within a population (Morton et al. 1956; Kalinowski & Hedrick 1998), the slope of the regression of $\log(\text{fitness})$ against inbreeding coefficient provides an estimate of inbreeding load, or number of lethal equivalents (reviewed in Keller & Waller 2002). Inbreeding load in wild populations is commonly high (e.g., Ralls et al. 1988; Kruuk et al. 2002; Reed et al. 2007), although exceptions exist (e.g., Duarte et al. 2003).

Viability losses, however, may also come from drift load (i.e., local fixation of mild deleterious mutations hidden from selection by drift) (Keller & Waller 2002). Small populations are expected to harbor more drift load (Whitlock et al. 2000) and less inbreeding load than large ones (because individuals are genetically more similar locally; e.g., Bataillon & Kirkpatrick 2000). Local drift load is not revealed by regression of fitness on inbreeding coefficient; rather, it is revealed by heterosis effects (i.e., fitness increase of offspring from crosses among compared with within populations), and it has received wide empirical support (e.g., Coulson et al. 1998; Marr et al. 2002; Bush 2006). Because local populations may exhibit low inbreeding load but high drift loads, management decisions made on the basis of inbreeding depression only may be misleading.

Although the dramatic consequences of inbreeding and drift loads have been recognized, there is no simple way to incorporate them in the toolbox of conservation geneticists without turning to heavy experimental designs (within and between population crosses). Keller

and Waller (2002) suggest use of F_{ST} as “an index of the susceptibility of a population to the deleterious effects of drift load.” Whitlock (2002) showed that the local drift load caused by mild deleterious mutations may indeed increase with F_{ST} in an infinitely large metapopulation, depending on the mode of population regulation and mutation parameters.

Using stochastic individual-based simulations, Higgins and Lynch (2001) showed that metapopulation viability increases with the number, size, and connectivity of local demes. Theodorou and Couvet (2006) further showed that, for a given metapopulation size, fitness is higher with a few large populations than with several small ones, and that for small, isolated populations the increase in local population size has a much greater positive effect on population fitness than other parameters, such as migration or number of demes.

The effect of connectivity was formalized by the one-migrant-per-generation (OMPG) rule, according to which one migrant per generation should suffice to protect local populations from the accumulation of deleterious mutations (e.g., Mills & Allendorf 1996; Couvet 2002; Wang 2004). Nevertheless, migration rate is notoriously difficult to assess in the field (Whitlock & McCauley 1999), and its effect may depend on other parameters, such as migration model, total metapopulation size, and mating system, that affect the purging of deleterious mutations (Glémin 2003).

We used stochastic individual-based simulations to investigate population fitness (offspring viability and time to extinction) under various metapopulation settings. The aims were to derive robust predictive models of population fitness from easy-to-collect genetic and demographic data that may account for both inbreeding and drift loads and to test the validity of the OMPG rule under different migration models and mating systems.

Methods

Life Cycle

We performed simulations in Nemo, a stochastic, individual-based, genetically explicit framework (Guillaume & Rougemont 2006). Model organisms were diploid, had separate genders or not, depending on the mating system, and lived in a structured metapopulation of d demes with local carrying capacity, N . A series of loci were subject to deleterious mutations, whereas others were neutral. We implemented the following semelparous life cycle: (1) viability selection on newly born offspring that survived with a probability derived from their deleterious mutation genotype, (2) dispersal of surviving offspring according to a specific migration model (see below), (3) random regulation of local populations, which reduced the pool of competing individuals to the

local carrying capacity (with equal sex ratios in case of separate genders), and (4) reproduction during which females were assigned a fecundity value drawn from a Poisson distribution with constant mean f and were mated as many times as indicated by their fecundity (one offspring per mating). Males were chosen according to 1 of 3 mating systems described below (random mating, selfing, or polygyny). Offspring alleles at neutral and selected loci were inherited randomly (i.e., no linkage), barring mutations. Sex was set randomly (with equal sex ratio) when genders were distinct. Adults were removed after reproduction, and the cycle started again.

Population Structure, Dispersal, and Mating System

We ran simulations under different metapopulation configurations to cover a large range of fragmentation levels. We varied independently local ($N = 4, 8, 16, 25, 50$, and 100 individuals) and total metapopulation sizes ($N_t = 200, 400, 800$, and 1600). The number of demes (d) was set by the ratio $d = N_t/N$. For each metapopulation configuration, we used 4 different migration rates ($m = 0.001, 0.003, 0.01$, and 0.1) and 2 different migration models (island and linear stepping stone) that represented the 2 extremes of a continuum of isolation by distance. Most realistic cases are likely to fall in between. The effect of systematic inbreeding induced by mating patterns was explored with 3 systems: random mating, selfing, and polygyny. Selfing rate was set to 50%; the other 50% resulted from random mating within the deme. Under polygyny only one-quarter of the males present in each population were allowed to reproduce, so successful males mated on average with 4 females.

We thus obtained a fully factorial core set of simulations exploring 576 parameter combinations (6 local population sizes, 4 total population sizes, 4 migration rates, 2 migration models, 3 mating systems). Here we refer to the 6 combinations of mating systems and migration models as data sets 1 to 6. For this core set, average fecundity f was set to 15 for females (random mating and polygyny) and 7.5 for hermaphrodites (selfing) to keep the same reproductive output per population. The effect of lowered fecundity ($f = 6$) was investigated under random mating and island migration in an additional set of simulations (data set 7).

Mutation Models

The neutral markers, used to assess the level of neutral genetic diversity within and among populations, followed a k -allele mutation model (KAM), with $k = 256$ possible allelic states over each of 24 loci and a mutation rate $u = 0.0001$.

Fitness was controlled by a set of L (fixed to 1000) independent loci carrying deleterious alleles of various strength and dominance effect. We drew the number of

new mutations occurring in a particular genome from a Poisson distribution with a mean equal to the diploid genomic mutation rate (U). Mutations affected only non-deleterious alleles, turning them into the deleterious form (reverse mutations were neglected), and acted independently on fitness so that offspring viability (v) was computed as the product of fitness at each locus i : $v = \prod_i v_i$, where v_i is 1, $1 - s_i$, or $1 - b_i s_i$ if the locus was homozygous wild-type, homozygous mutant, or heterozygous, respectively. The values used for the mean mutation effect ($\bar{s} = 0.05$) and average dominance ($\bar{b} = 0.36$) were derived from *Drosophila* studies (reviewed in Lynch et al. 1999) and are commonly used in simulations (Wang et al. 1999; Higgins & Lynch 2001; Theodorou & Couvet 2006).

For the core set of simulations, the genomic mutation rate was fixed to $U = 0.5$, and the mutant effects s were exponentially distributed among the L loci. Following Wang et al. (1999), the dominance coefficient b of a mutation with effect s was set to satisfy the relationship $b = \exp(-ks)/2$, where k is a constant chosen so that the average dominance of all mutations in the genome equals \bar{b} (Caballero & Keightley 1994). This induced an inverse relationship between the magnitude of effect of a mutation and its degree of dominance, as expected from biochemical arguments and supported by mutation-accumulation experiments (Simmons & Crow 1977; Phadnis & Fry 2005).

We also performed additional simulations under random mating and island migration to further explore the effects of genomic mutation rate ($U = 1$, data set 8) and the distributions of deleterious effects, assuming either a truncated lognormal (data set 9) or a gamma distribution (data set 10). The log normal distribution was parameterized according to Loewe and Charlesworth (2006), with log mean (SD) = -6.4 (5.3). The distribution was truncated to the right so that no $s > 1$ (and $\bar{s} = 0.05$). We took the shape parameter for the gamma distribution ($\alpha = 1.69374$) from Keightley's (1994) estimation on the Mukai et al. (1972) *Drosophila* data set and adjusted its scale so that $\bar{s} = 0.05$.

Simulations

For each of the 960 combinations of parameters (576 for the core set plus 384 for the 4 additional sets), we first performed 30 replicates over 50,000 generations with neutral markers only (to get the required statistics for parameter values that would lead to population crashes in the presence of deleterious mutations). Next we performed 15 replicates over 5,000 generations after adding deleterious-mutations effects. At the start of simulations, we assigned neutral markers random allelic values to ensure a maximal initial variance, and fixed loci under selection to the fit allele. Statistics were recorded every

Table 1. Spearman rank correlations between the variables used as predictors of offspring viability and median time to extinction (MTE).*

	$\text{Log}(N)$	$\text{Log}(d)$	$\text{Log}(1 - F_{ST})$	$\text{Log}(H_O)$	$\text{Log}(H_S)$	H_T
$\text{Log}(N_t)$	0.003	0.58	-0.12	0.35	0.35	0.53
$\text{Log}(N)$		-0.80	0.66	0.52	0.55	-0.55
$\text{Log}(d)$			-0.60	-0.22	-0.24	0.76
$\text{Log}(1 - F_{ST})$				0.75	0.77	-0.87
$\text{Log}(H_O)$					0.97	-0.43
$\text{Log}(H_S)$						-0.44

*Key: N , local population size; d , number of demes; F_{ST} , genetic structure; H_O , observed heterozygosity; H_S , within-deme expected heterozygosity; H_T , total expected heterozygosity; N_t , total metapopulation size.

10 generations and measured from the offspring that survived the viability-selection episode.

Statistical Analyses

We computed mean F_{ST} , H_O , H_S , and H_t (Nei & Chesser 1983), first over the 30 neutral replicates (averaged over generations 20,000–50,000) and second over the 15 replicates with deleterious mutations (generations 4,500 to 5,000), together with offspring viability v (for simulations in which all 15 replicates survived) and median time to extinction (MTE) (for simulations in which more than 50% of the replicates crashed before 5000 generations).

To find the best predictors of offspring viability from the core data set, we proceeded in 3 steps. First, we transformed the potential predictors (F_{ST} , H_O , H_S , H_t , d , N , and N_t) with the functions x , $\log(x)$, $1/x$, and $1/\log(x)$, and $\log(1 - x)$ for predictors ranging from 0 to 1 and selected the transformations providing the best linear relationship with $\text{logit}(\text{viability}) (= \log \frac{v}{1-v})$. These turned out to be $\log(1 - F_{ST})$, $\log(H_O)$, $\log(H_S)$, H_t , $\log(N_t)$, $\log(N)$, and $\log(d)$.

Second, we performed linear regressions of $\text{logit}(\text{viability})$ on the transformed predictors for each mating system and migration model independently (hence, 6 partitions). The same analyses were performed on data pooled by mating system (3 partitions) and migration models (2 partitions) and on the entire data set.

Third, we combined predictors 2×2 ($y \sim ax_1 + bx_2 + c$) to find the best bivariate prediction of $\text{logit}(\text{viability})$ on the same partitions as above. The different models were then ranked on the basis of the amount of explained variance, and ranks were averaged to select the best overall model.

We used the same procedure to predict median time to extinction from the core data set (with $1/\text{MTE}$ as the dependent variable) and to analyze the additional simulations (data sets 7–10). We did not perform multiple stepwise regressions, which, owing to the high power of simulation studies, tended to retain too many variables and usually retained different ones depending on the settings (data not shown).

Results

Genetic parameters calculated on neutral markers (F_{ST} , H_O , H_S , and H_t) did not differ whether calculated in the presence or absence of deleterious mutations (correlation coefficients ranging from 0.97 to 0.99); thus, hereafter we consider only values in absence of mutation load. The F_{ST} averaged 0.68 (range 0.007–0.995), $H_O = 0.07$ (range 0.003–0.38), $H_S = 0.08$ (range 0.004–0.38), and $H_t = 0.49$ (range 0.03–0.98). Spearman rank correlation between the predictors ranged from -0.87 to 0.97 (Table 1).

Offspring Viability

Over the surviving populations from the core data set, offspring viability averaged 43%, depending greatly on the mating system and slightly on the migration model. It was highest under self-fertilization (averaging 49% and 45% for the island- and stepping-stone models of migration) but had a wide range (19–68%). Values were slightly lower under random mating (45 and 43%, respectively; range 23–59%) and lowest under polygyny (37 and 33%, respectively; range 18–56%).

Offspring viability was well predicted by $\log(H_S)$, $\log(1 - F_{ST})$, and $\log(H_O)$, with 41–67% of the variance explained depending on the partition used, but none of them ranked systematically higher (average ranking 1.7, 2.0, and 2.3, respectively). All 3 descriptors still explained at least 46% of variance when pooling data by mating system, but $\log(H_O)$ lost explanatory power when data were pooled by migration model ($R^2 < 31\%$). When pooling all 6 partitions, $\log(H_S)$ and $\log(1 - F_{ST})$ remained the best predictors ($R^2 = 46$ and 42%, respectively).

Both were also included in the best bivariate combination (Table 2), with an average rank of 1.0 (i.e., best in all cases). When pooling all 6 partitions, 70% of variance (Table 2) was explained by

$$\log \frac{v}{1-v} = a \log(1 - F_{ST}) + b \log(H_S) + c, \quad (1)$$

with $a = 0.39$, $b = 0.52$, and $c = 1.19$. The explained variance increased to 71–74% when splitting data by migration models (2 partitions), 87–92% when splitting by

Table 2. Regression models for offspring viability as a function of F_{ST} and H_S for the different data sets.^a

Data set ^b	Parameters ^c	Mating system and migration model ^d	Intercept	Log($1-F_{ST}$)		Log(H_S)		Total R^2	Rank
				Coef.	R^2	Coef.	R^2		
1	$f = 15, U = 0.5$, exponential	IM random mating	0.903	0.543	0.41-0.54	0.442	0.36-0.49	0.90	1
2	$f = 15, U = 0.5$, exponential	IM polygyny	1.411	0.598	0.46-0.51	0.678	0.43-0.48	0.94	1
3	$f = 15, U = 0.5$, exponential	IM selfing	1.548	0.606	0.45-0.63	0.518	0.28-0.46	0.91	1
4	$f = 15, U = 0.5$, exponential	SSM random mating	1.133	0.319	0.27-0.41	0.573	0.51-0.65	0.92	1
5	$f = 15, U = 0.5$, exponential	SSM polygyny	1.877	0.380	0.31-0.40	0.903	0.57-0.65	0.97	1
6	$f = 15, U = 0.5$, exponential	SSM selfing	1.976	0.381	0.26-0.57	0.726	0.36-0.67	0.93	1
1-3	$f = 15, U = 0.5$, exponential	IM	1.114	0.529	0.32-0.45	0.468	0.25-0.39	0.71	1
4-6	$f = 15, U = 0.5$, exponential	SSM	1.414	0.322	0.19-0.40	0.629	0.34-0.54	0.74	1
1, 4	$f = 15, U = 0.5$, exponential	random mating	0.948	0.384	0.30-0.46	0.485	0.41-0.56	0.87	1
2, 5	$f = 15, U = 0.5$, exponential	polygyny	1.494	0.460	0.36-0.47	0.737	0.50-0.56	0.92	1
3, 6	$f = 15, U = 0.5$, exponential	selfing	1.645	0.454	0.33-0.59	0.585	0.30-0.56	0.88	1
1-6	$f = 15, U = 0.5$, exponential	all data pooled	1.185	0.391	0.24-0.42	0.523	0.28-0.46	0.70	1
7	$f = 6, U = 0.5$, exponential	IM random mating	0.689	0.342	0.20-0.25	0.326	0.59-0.64	0.85	5
8	$f = 15, U = 1$, exponential	IM random mating	-0.395	0.483	0.46-0.50	0.358	0.43-0.48	0.93	2
9	$f = 15, U = 0.5$, lognormal	IM random mating	0.905	0.480	0.41-0.59	0.419	0.36-0.54	0.95	1
10	$f = 15, U = 0.5$, gamma	IM random mating	0.798	0.516	0.49-0.61	0.323	0.26-0.38	0.87	1

^aAlso shown are the intercept, the regression coefficients, and the variance explained by F_{ST} and H_S , the total amount of variance explained, and the model ranking. Because order of introduction of variables in the model affects the amount of explained variance (but not the regression coefficients), partial R^2 is shown for each variable when introduced first and second. Significance levels of all coefficients and R^2 are below 0.0001.

^bEach data set is assigned a number (1-10). When regressions were performed on pooled data, the data sets used are shown.

^cShown, respectively, are the fecundity values (per female), the genomic mutation rate, and the type of distribution for the deleterious effects.

^dAbbreviations: IM, "island migration model"; SSM, "stepping-stone migration model"; "IM-random mating" means that all simulations run with random mating and island migration model were used in the regression (but with the same parameter values). "IM" means that all simulations run under island migration model with the same parameter values were pooled (independently of the mating system). "Random mating" means that all simulations run under random mating with the same parameter value were pooled (independently of the migration model). "All data pooled" means that all simulations run with the same parameters values were pooled (independently of the mating system and migration model).

mating system (3 partitions), and 90-97% when simultaneously splitting by migration model and mating system (6 partitions; Table 2). Regression coefficients were positive in all cases, but viability displayed a sharper transition from high to low values under selfing than under polygyny or random mating (Fig. 1). Simulations that collapsed because of mutational meltdown fell well within the predicted low-viability area, even though these data were not used for model fitting.

Decreasing fecundity ($f = 6$, data set 7) had no effect on offspring viability, and model 1 explained 85% of variance (Table 2). Increasing mutation rate ($U = 1$, data set 8) lowered offspring viability, but model 1 remained excellent (rank 2; $R^2 = 93\%$). The lognormal and gamma distributions of deleterious effects (data sets 9 and 10) had only marginal effects on offspring viability, and model 1 remained the best (rank 1 in both cases), with 95 and 87% of variance explained respectively (Table 2).

Time to Extinction

Extinction rate averaged 51% over the core data set (294 out of 576 simulations were extinct before 5000 generations) and was higher under polygyny (70%) than under random mating (45%) or selfing (38%). It was also higher under the stepping-stone dispersal (76%, 50%, and 43%

for polygyny, random mating, and selfing, respectively) than under the island model (67%, 40%, and 32%, respectively).

Median time to extinction (MTE) did not differ much among mating systems (averages 1079, 1118, and 1137 generations under polygyny, random mating, and selfing, respectively) with similar ranges (200-4000 generations). The $1/MTE$ correlated mainly with $\log(1 - F_{ST})$, $\log(H_S)$, $\log(H_O)$, and $\log(N)$ (with R^2 ranging from 22 to 83%), but none of these variables showed consistency among the different models. Accordingly, model ranks were very similar (2.2, 2.3, 3, and 3.2 for $\log[1 - F_{ST}]$, $\log[H_S]$, $\log[N]$, and $\log[H_O]$, respectively). After pooling all data, $\log(1 - F_{ST})$ and $\log(N)$ remained the best candidates ($R^2 = 50$ and 49%, respectively), followed by $\log(H_S)$ ($R^2 = 43\%$).

When pooling all 6 partitions, the best bivariate model for predicting extinction time combined $\log(H_S)$ and $\log(N)$:

$$1/MTE = a \log(H_S) + b \log(N) + c, \quad (2)$$

with $a = -8.36 \times 10^{-4}$, $b = -8.30 \times 10^{-4}$, and $c = 7.65 \times 10^{-4}$ ($R^2 = 68\%$; Table 3). The same model emerged when considering the average ranking over the different partitions (rank 2.2; the second-best model was $1/MTE$

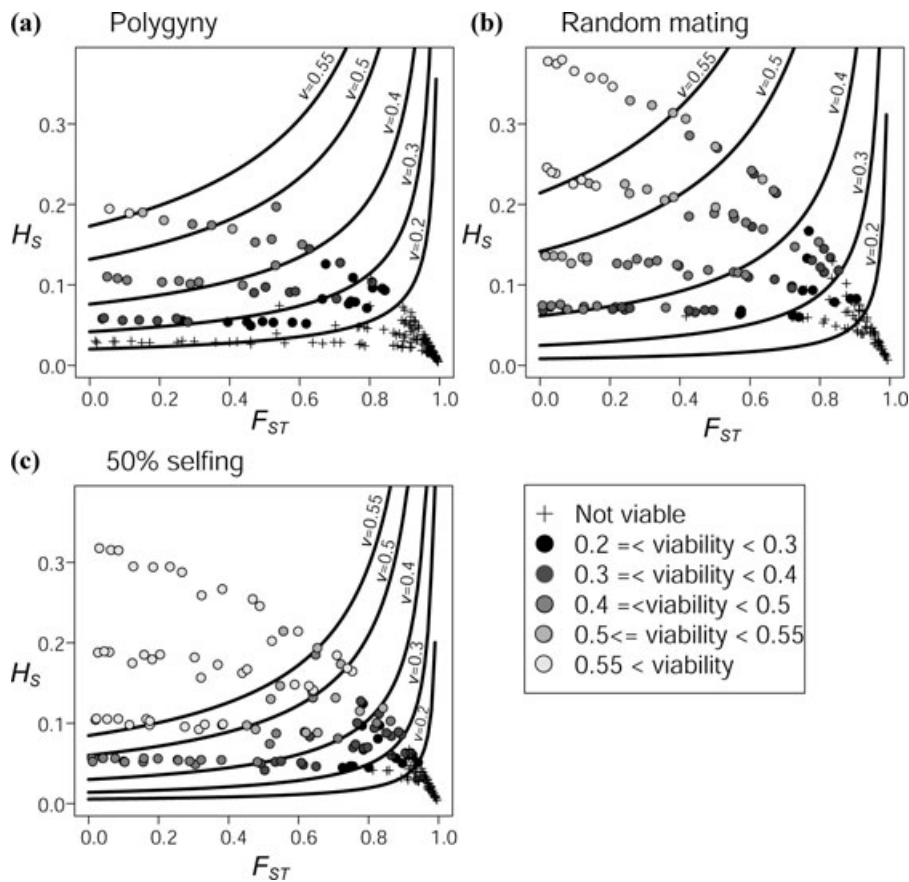


Figure 1. Offspring viability as a function of genetic differentiation (F_{ST}) and within-population heterozygosity (H_s) for simulations performed under (a) polygyny (data sets 2 and 5), (b) random mating (data sets 1 and 4), and (c) selfing (data sets 3 and 6). Dots indicate viable metapopulations, and the lighter the symbol the higher offspring viability. The expected isoclines for viability (lines) are calculated from the regression models in Table 2. Crosses represent simulations that crashed before generation 5000. Data points corresponding to the same total metapopulation size are aligned on the different curves.

$\sim \log[N_t] + \log[H_0]$ with rank 2.8). The explained variance reached 66–81% when splitting data by migration models (2 partitions), 81–86% when splitting by mating system (3 partitions), and 79–97% when simultaneously splitting for migration model and mating system (6 partitions; Table 3). Regression coefficients were negative in all cases (Table 3 & Fig. 2). Metapopulations still viable at generation 5000 fell well within the predicted viable area, even though these data were not used for model fitting. Model 2 was also good at predicting median time to extinction in simulation runs with $f = 6$ and $U = 1$ and with lognormal or gamma distribution of deleterious effects (average rank about 3); 73–94% of the variance was explained (Table 3).

Inbreeding and Purge of the Genetic Load

The ratio of offspring viability under selfing or polygyny relative to random mating was used to assess the extent of the purge in either of these mating systems. The ratio consistently exceeded unity in selfing populations (mean [SD] = 1.167 [0.136]), which thus had purged part of their mutational load. Polygynous populations underwent a higher rate of accumulation of deleterious mutations than populations under random mating (mean [SD] = 0.656 [0.168]), inducing the higher extinction rates

noted above. Nevertheless, F_{IS} was not retained as a good predictor of offspring viability or time to extinction in the regression analyses (data not shown).

One-Migrant-Per-Generation Rule

For both random mating and selfing, one migrant per population per generation was enough to allow metapopulation persistence under our core settings (Figs. 3b & 3c). None of the simulations where effective migration rate (N_m) exceeded 1 went extinct, and there were only a handful for N_m values between 0.1 and 1 (4 under selfing and 9 under random mating) that occurred under small local population sizes ($N = 4$ to 16) and low connectivity (stepping-stone dispersal). Under polygyny, by contrast, extinctions occurred for N_m values exceeding 1 but only at small metapopulation sizes ($N_t = 200$). Lower fecundity values ($f = 6$, Fig. 3d) did not affect offspring viability but increased the threshold value below which populations are at risk. Extinctions occurred for N_m values exceeding 1 but only when both total and local population sizes were small ($N_t = 200$ and $N < 100$). A higher genomic mutation rate ($U = 1$, Fig. 3e) decreased offspring viability so that extinctions occurred for N_m values exceeding 1 but only for small metapopulation sizes ($N_t = 200$).

Table 3. Regression models for median time to extinction as a function of H_s and local population sizes for the different data sets.^a

Data set ^b	Parameters ^c	Mating system and migration model ^d	Log(H_s)		Log(N)		Total R^2	Rank	
			Intercept	Coef.	R^2	Coef.			R^2
1	$f = 15, U = 0.5$, exponential	IM random mating	2.40×10^{-03}	-8.83×10^{-04}	0.13-0.46	-1.42×10^{-03}	0.38-0.71	0.84	3
2	$f = 15, U = 0.5$, exponential	IM polygyny	2.21×10^{-03}	-8.41×10^{-04}	0.9-0.31	-1.17×10^{-03}	0.49-0.70	0.79	3
3	$f = 15, U = 0.5$, exponential	IM selfing	-1.08×10^{-03}	-1.09×10^{-03}	0.39-0.76	-6.64×10^{-04}	0.17-0.54	0.93	2
4	$f = 15, U = 0.5$, exponential	SSM random mating	-5.75×10^{-04} NS	-1.20×10^{-03}	0.25-0.83	-8.51×10^{-04}	0.12-0.70	0.95	2
5	$f = 15, U = 0.5$, exponential	SSM polygyny	-1.11×10^{-03}	-1.23×10^{-03}	0.26-0.79	-6.76×10^{-04}	0.14-0.67	0.93	1
6	$f = 15, U = 0.5$, exponential	SSM selfing	-2.66×10^{-03}	-1.15×10^{-03}	0.50-0.94	-2.89×10^{-04}	0.3-0.46	0.97	2
1-3	$f = 15, U = 0.5$, exponential	IM	1.30×10^{-03}	-8.73×10^{-04}	0.16-0.30	-9.85×10^{-04}	0.36-0.51	0.66	1
4-6	$f = 15, U = 0.5$, exponential	SSM	-1.34×10^{-03}	-1.15×10^{-03}	0.32-0.70	-5.61×10^{-04}	0.10-0.48	0.81	2
1, 4	$f = 15, U = 0.5$, exponential	random mating	2.16×10^{-03}	-7.71×10^{-04}	0.13-0.52	-1.29×10^{-03}	0.32-0.71	0.84	3
2, 5	$f = 15, U = 0.5$, exponential	polygyny	1.43×10^{-03}	-8.55×10^{-04}	0.13-0.48	-9.83×10^{-04}	0.34-0.68	0.81	2
3, 6	$f = 15, U = 0.5$, exponential	selfing	-1.06×10^{-03}	-8.95×10^{-04}	0.36-0.73	-5.72×10^{-04}	0.13-0.50	0.86	2
1-6	$f = 15, U = 0.5$, exponential	all data pooled	7.65×10^{-04}	-8.36×10^{-04}	0.19-0.43	-8.30×10^{-04}	0.25-0.49	0.68	1
7	$f = 6, U = 0.5$, exponential	IM random mating	8.53×10^{-03}	-5.95×10^{-04}	0.04-0.08	-2.49×10^{-03}	0.65-0.69	0.73	3
8	$f = 15, U = 1$, exponential	IM random mating	4.47×10^{-03}	-1.43×10^{-03}	0.12-0.35	-1.91×10^{-03}	0.38-0.61	0.73	4
9	$f = 15, U = 0.5$	IM random mating	5.56×10^{-04}	-3.59×10^{-03}	0.21-0.51	-4.88×10^{-04}	0.38-0.68	0.89	3
10	$f = 15, U = 0.5$, gamma	IM random mating	3.82×10^{-03}	-7.49×10^{-04}	0.09-0.45	-1.75×10^{-03}	0.49-0.85	0.94	3

^aAlso shown are intercept, regression coefficients, explained variance by H_s , local population size (N), total amount of variance explained, and model ranking. Because order of introduction of variables in the model affects the amount of explained variance (but not the regression coefficients), partial R^2 is shown for each variable when introduced first and second. Significance levels of slope coefficients and R^2 are below 0.01. For the intercept, p values < 0.025, except in one case noted with NS (not significant).

^bEach data set is assigned a number (1-10). When regressions were performed on pooled data, the data sets used are shown.

^cShown, respectively, are the fecundity values (per female), the genomic mutation rate and the type of distribution for the deleterious effects.

^dAbbreviations: IM, "island migration model"; SSM, "stepping-stone migration model"; "IM-random mating" means that all simulations run with random mating and island migration model were used in the regression (but with the same parameter values). "IM" means that all simulations run under island migration model with the same parameter values were pooled (independently of the mating system). "Random mating" means that all simulations run under random mating with the same parameter value were pooled (independently of the migration model). "All data pooled" means that all simulations run with the same parameters values were pooled (independently of the mating system and migration model).

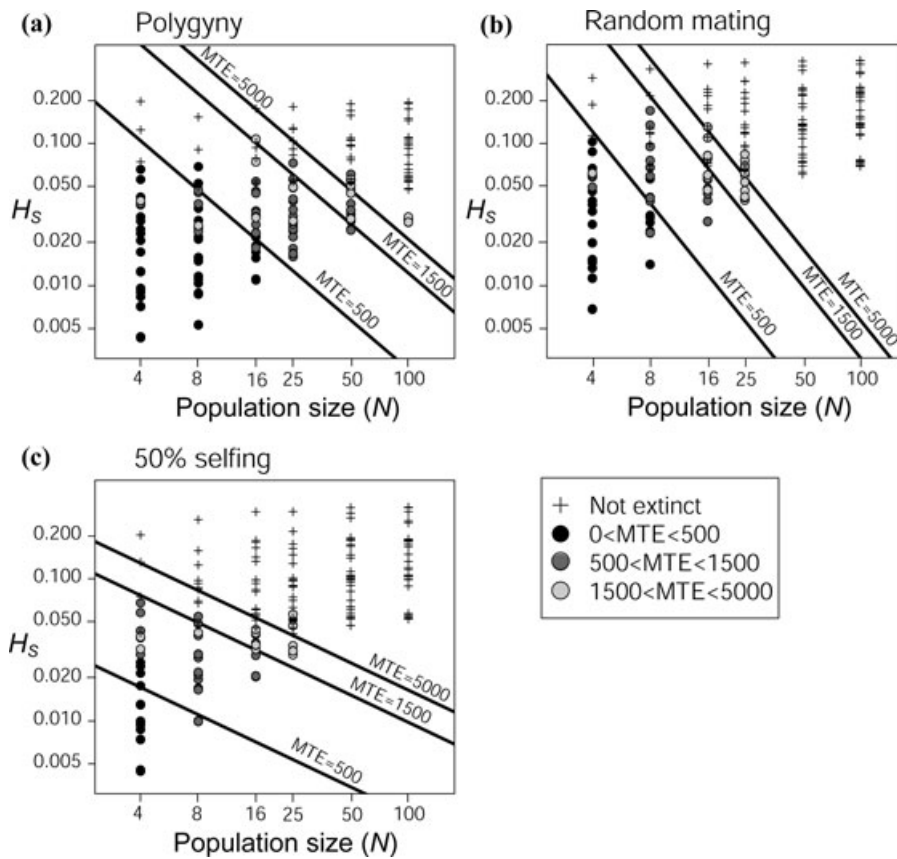


Figure 2. Median time to extinction (MTE) as a function of within-population heterozygosity (H_S) and population sizes (N) for simulations performed under (a) polygyny (data sets 2 and 5), (b) random mating (data sets 1 and 4), and (c) selfing (data sets 3 and 6) (x - and y -axes are log transformed for graphical presentation). Dots indicate metapopulations that collapsed, and the lighter the dot the longer is time to extinction. The expected isoclines for MTE (lines) are calculated with the coefficients of the regression models in Table 3. Crosses represent simulations that survived at least until generation 5000.

Discussion

On the basis of our results, the effects of deleterious mutations on population fitness can be largely accounted for by a few basic genetic and demographic measurements. Offspring viability increased with genetic diversity within demes (H_S) and decreased with differentiation among them (F_{ST}), in line with both analytical treatments (Kimura et al. 1963; Whitlock et al. 2000; Whitlock 2002) and empirical observations (e.g., Madsen et al. 1996; Newman & Pilson 1997; Saccheri et al. 1998). On its own, F_{ST} explained 42% of the variance in offspring viability over our core data set, corroborating Whitlock's (2002) analytical results under infinite-island settings and supporting Keller and Waller's (2002) suggestion that F_{ST} be used as "an index of the susceptibility of a population to the deleterious effects of drift load." The positive role of diversity (H_S), on the other hand, more likely resulted from the deleterious effect of inbreeding load. A combination of both H_S and F_{ST} accounted for both loads and thus explained a large part of the variance in offspring viability ($R^2 > 85\%$ for a given mating system).

The median time to extinction also increased with diversity within demes (H_S), but the best bivariate regression included local population size (N) rather than F_{ST} , in addition to H_S (with $R^2 > 80\%$ for a given mating system). This point underlines the importance of both

demographic and genetic effects during the process of mutational meltdown, in line with both analytical models (Lande 1994; Lynch et al. 1995) and empirical observations (e.g., Saccheri et al. 1988). Small population sizes are known to enhance both demographic and genetic stochasticity, with positive feedbacks. Populations collapsed at offspring viability values below 0.2 for $f = 15$ (and below 0.4 for $f = 6$; Fig. 3), corresponding to effective reproductive rates exceeding unity, which, in absence of stochasticity, should allow positive growth rate and population persistence. This illustrates the initiation of extinction vortices by the interplay between demographic and genetic factors as soon as the system enters a critical state in terms of population size and mutation load.

Local population size was not retained in offspring viability models, contrasting with empirical support for a positive correlation between population size and fitness (reviewed in Reed 2005; see also Reed et al. 2007). Local size certainly affects a population's ability to resist drift, but our simulations also included other factors that drastically affect local genetic diversity (mating system, migration rate, and total metapopulation size). Population fitness and genetic diversity should depend more on local *effective* size, which may present only weak correlations with *census* size when such interacting factors are varied. Mating systems also had an effect of their own in

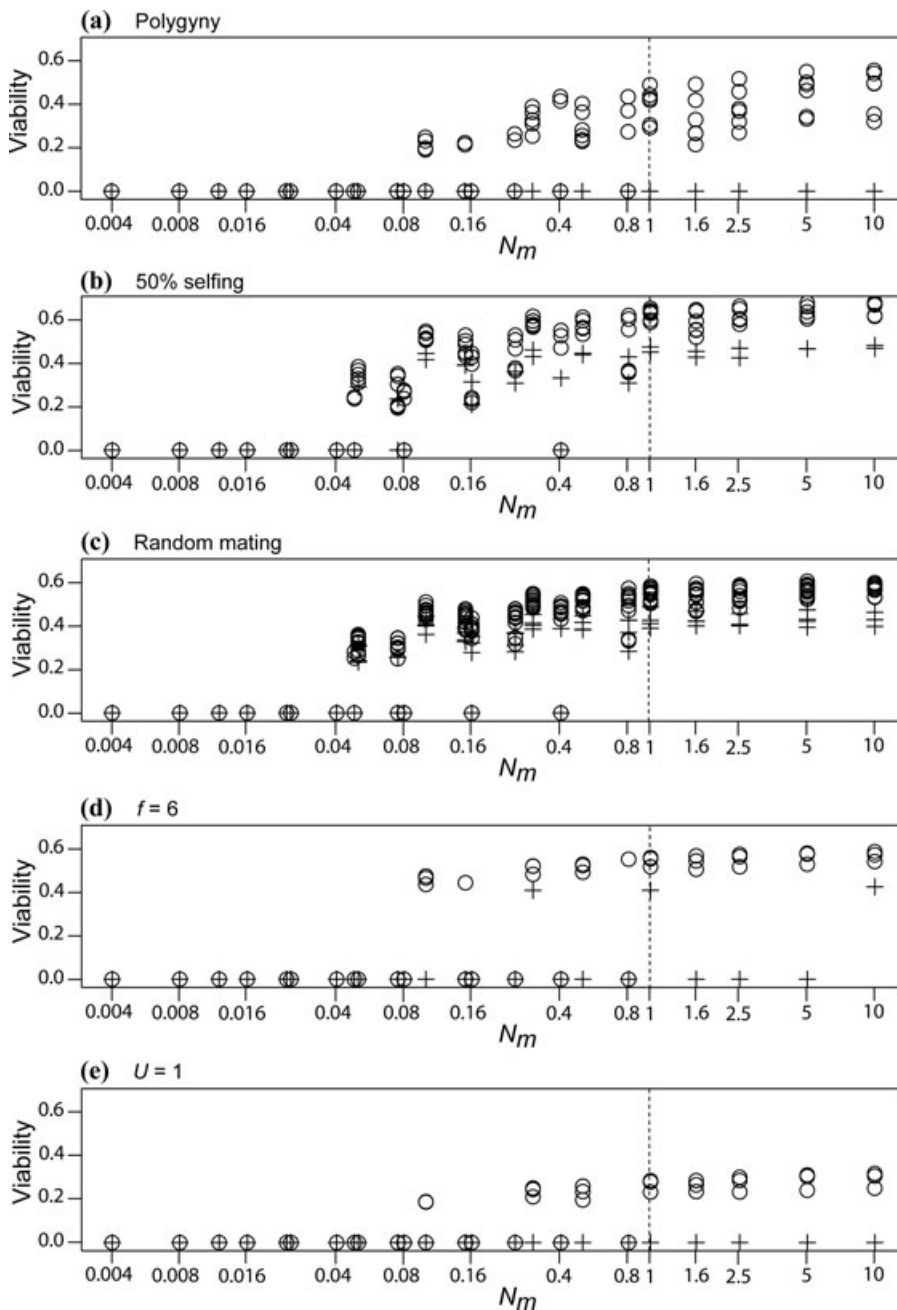


Figure 3. Offspring viability as a function of effective migration rate N_m (log scale) for (a) polygyny (data sets 2 and 5), (b) selfing (data sets 3 and 6), (c) random mating, pooling all 3 distribution models for deleterious effects (data sets 1, 4, 9, and 10), (d) random mating with lowered fecundity ($f = 6$, data set 7), and (e) random mating with increased genomic mutation rate ($U = 1$, data set 8). A viability of zero is assigned to simulations that crashed, which occurred whenever viability decreased below a threshold value (about 0.2 for $f = 15$ and 0.4 for $f = 6$). When effective migration rates exceeded 1 (vertical line), extinctions occurred only at low metapopulation sizes ($N_t = 200$, crosses) but never at larger sizes (open circles).

lowering the relationship between population size and offspring viability because selfing, which reduces effective size, increased fitness by purging the genetic load. Selection is more efficient at removing deleterious mutations under such mixed systems than under random mating owing to increased variance in individual fitness and inbreeding coefficients (see Glémin [2003] for an analytical treatment). Under polygyny, by contrast, both the effective population size and variance in inbreeding were reduced, leading to a greater rate of mutation accumulation and population extinction.

Total population size (N_t) also played a significant role in our simulations because the dynamics of local

genetic diversity within demes also depends on inputs from the metapopulation reservoir. Depending on the mating system, 53–78% of the variance in H_S was explained by $\log(N_t)$. Furthermore, in small metapopulations ($N_t \leq 800$) deleterious mutations may get fixed at the global scale and have long-lasting consequences on population fitness via drift load but not contribute to inbreeding depression or heterosis (Whitlock 2002). Metapopulations of 200 individuals were often too small to persist, owing to dramatically low offspring viabilities, whatever the connectivity (Figs. 1 & 3). These effects have been poorly investigated until now, mainly because analytical treatments usually assume infinite or very large

metapopulations (e.g., Whitlock 2002) and previous simulation studies have not addressed variance in this parameter (Higgins & Lynch 2001; Theodorou & Couvet 2006).

Our results rejoin the results of these 2 latter studies with respect to the effects of fragmentation. For the same total number of individuals (and no environmental stochasticity), one big population was better than several small ones. Doubling the number of populations was much less efficient than doubling the size of local populations. Increasing connectivity was quite efficient, provided the total population size was not too small (>500) and local populations were smaller than 100 individuals. We thus emphasize the importance for persistence of connecting isolated populations to a reservoir of genetic diversity.

Our results also provide some validation for the OMPG rule, with some caveats. As shown in Fig. 3, populations did not collapse for effective numbers of immigrant exceeding 1 under most parameter values. Exceptions occurred only for very small metapopulation sizes ($N_t = 200$) and only in conjunction with other negative effects such as polygyny (Fig. 3a), low fecundity (Fig. 3d), or high genomic deleterious mutation rate (Fig. 3e).

Migration rates and population sizes were deliberately set to low values in order to simulate endangered populations, usually characterized by small global sizes (<2500 individuals, World Conservation Union 2001) and reduced connectivity. As a result, about half of the simulations collapsed as a result of mutational meltdown (whereas the persisting ones presented a large range of viability values), and population structure (F_{ST}) sometimes reached values close to unity. This obviously exceeds the values usually documented in natural situations because most situations fall within the range of 0–0.2 (Morjan & Rieseberg 2004). Nevertheless, endangered populations frequently display F_{ST} values exceeding 20% (e.g., Rowe et al. 2000; Eckstein et al. 2006; Kawamura et al. 2007). Moreover, the F_{ST} values measured for most of the recently fragmented and/or bottlenecked populations are likely to be underestimates because these populations usually have not had enough time to reach genetic equilibrium (Whitlock 1992; Wang 2004). We thus covered a wide panel of population genetic structures within which most endangered species are expected to fall.

One important point to emphasize is that our results must not be considered in quantitative (absolute) terms but only in qualitative (relative) terms, owing to the specificity of several assumptions underlying our simulations. This caveat obviously applies to our life-history assumptions. Lower fecundities, in particular, increased the viability threshold under which extinctions occurred (Fig. 3d), even though models 1 and 2 still held qualitatively. In addition, the genetic variance at neutral markers depends not only on effective sizes but also on mutation rates, which might be species specific and difficult to

estimate precisely. Similarly, the mutation model and parameter values used in our core simulations came from accumulation experiments performed on a single model organism, *Drosophila* (Simmons & Crow 1977; Lynch et al. 1999). Although our conclusions seem quite robust regarding the distribution of deleterious mutations (Fig. 3c), parameter values may vary among species. The genomic mutation rate in particular quantitatively affected expectations (Fig. 3e), even though models 1 and 2 still held qualitatively. Therefore, our results can best be used in a comparative context (e.g., to rank the effects of different management strategies for a given endangered species). The conservation value of different scenarios can be evaluated on the basis of their effect on a set of very few key genetic and demographic parameters (H_S , F_{ST} , and N). More specific questions might also be addressed with the same simulation framework (Nemo; Guillaume & Rougemont 2006) or, if empirical data are available, by directly evaluating regression coefficients of offspring viability on the relevant variables (i.e., H_S , F_{ST} , and N).

Our approach also bears a series of important advantages. First, it provides robust predictive models with which to assess the viability prospects of fragmented populations, which might usefully complement the OMPG rule (e.g., Frankel & Soulé 1981; Mills & Allendorf 1996; Wang 2004) because assessing migration rates in nature is still a major challenge in ecology (Whitlock & McCauley 1999), which often precludes its effective use. Second, predictive power is large even without specific information on the mating system or dispersal model (R^2 approximately 70% on pooled data) and increases with additional information on the mating system ($R^2 > 80\%$). Third, no lab breeding or controlled crosses are needed to estimate inbreeding or drift load, which are both difficult or impossible to carry out on threatened species. The genetic information required is readily obtained from neutral loci (e.g., microsatellites, now easily available for many species) and can be sampled noninvasively (e.g., from shed hair or feces, Taberlet & Luikart 1999; Broquet et al. 2007). The only demographic information required is the size of local populations, which can be obtained through basic field (e.g., mark-recapture) observations. Finally, the negative effects of both drift load (fixed deleterious mutations) and inbreeding load (segregating deleterious mutations) are accounted for, whereas empirical methods relying on estimation of the number of lethal equivalents (Morton et al. 1956) only consider the latter. Given that small populations might already be inbred to some degree, they are likely to have lost part of their standing variation and fixed part of their mutation load. We hope our results will help clarify the effects of spatial structure and connectivity on viability prospects of fragmented populations and provide additional tools to evaluate extinction threats for endangered populations.

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