Extinction vortices are driven more by a shortage of beneficial mutations than by deleterious mutation accumulation

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Abstract

Habitat loss contributes to extinction risk in multiple ways. Genetically, small populations can face an "extinction vortex" — a positive feedback loop between declining fitness and declining population size. There are two distinct extinction vortex mechanisms: i) ineffective selection in small populations allows deleterious mutations to fix, driving "mutational meltdown", and ii) smaller populations generate fewer beneficial mutations essential for long-term adaptation, a mechanism we term "mutational drought". To determine their relative importance, we ask whether, for a population near its critical size for persistence, changes in population size have a larger effect on the beneficial vs. deleterious component of fitness flux. In stable environments, we find that mutational drought is nearly as significant as mutational meltdown. Drought is more important than meltdown when populations must also adapt to a changing environment, unless the beneficial mutation rate is extremely high. Using simulations to capture the complex linkage disequilibria that emerge under realistically high deleterious mutation rates, we find that decreased effective population size is driven primarily by linkage disequilibria between deleterious and beneficial mutations, rather than among deleterious or among beneficials. These disequilibria modestly increase the importance of mutational drought.

Keywords: population persistence, extinction spiral, background selection, genetic hitchhiking, population genetics, census population size, evolutionary rescue

Introduction

Climate change, habitat loss, and habitat fragmentation directly cause natural populations to shrink, or in some cases go extinct. To what degree the genetics of a population might contribute to its decline and eventual demise, and how, remains an open question (Keller and Waller 2002; Spielman, Brook, and Frankham 2004; Frankham 2005; Fox and Reed 2011; Kardos et al. 2021; Kyriazis, Wayne, and Lohmueller 2021; Dussex et al. 2023). On short timescales, shrinking population sizes lead to the loss of potentially adaptive standing genetic variation, and to increased inbreeding depression from deleterious recessive alleles. Here, however, we focus on longer-term threats, on the timescale over which fixation events accumulate. A positive feedback loop known as an "extinction vortex" can occur on these longer timescales, in which declining fitness makes populations smaller, causing their fitness to fall even faster (Giplin and Soulé 1986; Tanaka 2000; Fagan and Holmes 2006). We consider two distinct mechanisms by which an extinction vortex might operate. First, ineffective selection in small populations might allow a series of deleterious mutations to become fixed, in a process of "mutational meltdown". Second, fewer individuals entail fewer opportunities for the appearance of the novel mutations required for long-term adaptation, a process we call "mutational drought".

Mutational meltdown has received the most theoretical attention of the two (Lynch and Gabriel 1990; Gabriel, Lynch, and Bürger 1993; Lynch, Conery, and Bürger 1995b; 1995a; Zeyl, Mizesko, and De Visser 2001; Shaw and Baer 2011; Coron et al. 2013; Lansch-Justen et al. 2022; Olofsson et al. 2023). Mutational meltdown is a positive feedback loop between population size N and mean fitness $\bar{W}$ (Figure 1). As a population declines in size, deleterious mutations fix more easily due to random genetic drift (Figure 1, red arrow). This decreases mean fitness $\bar{W}$, causing the population size to decline further (Figure 1, upward arrow).

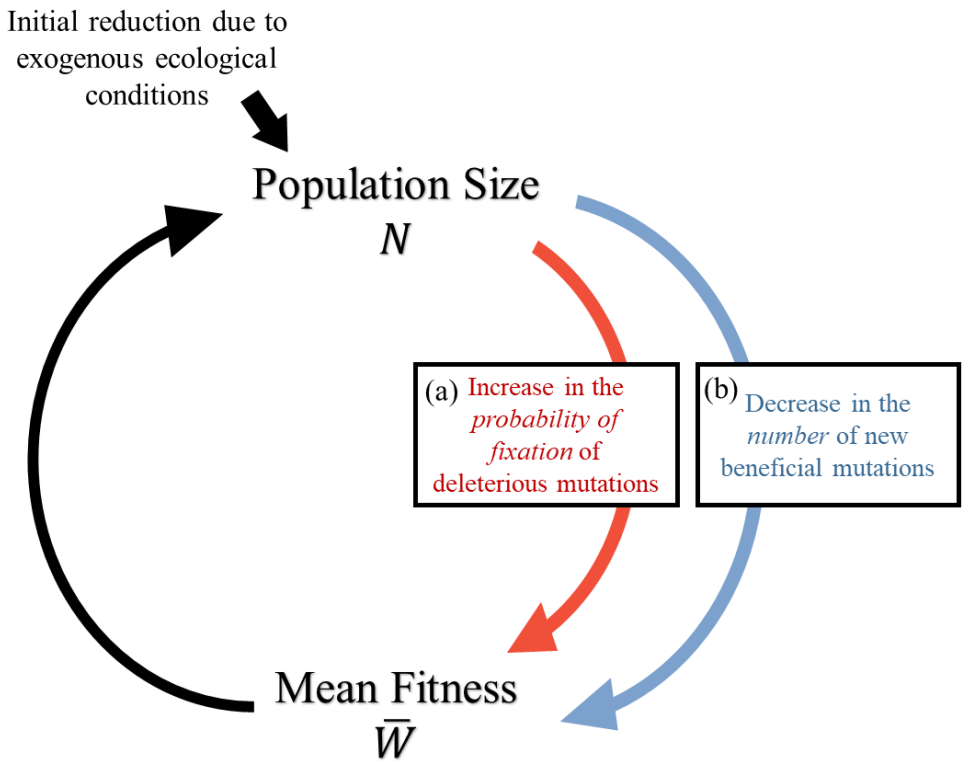

Figure 1. **An extinction vortex can be driven by the dynamics of either deleterious (mutational meltdown; red) or beneficial (mutational drought; blue) mutations**.

In the absence of beneficial mutations, even large populations melt down eventually. This is because, given a continuous distribution of deleterious selection coefficients, some are too small to be reliably purged by selection, even in large sexual populations; this has been called "Ohta's ratchet" (Ruan et al. 2020).

Schultz and Lynch (1997) and Whitlock (2000) therefore modeled a low rate of beneficial mutation, sufficient in larger populations to offset deleterious fixation events. They calculated the fitness fluxes v_d and v_b from deleterious and beneficial fixation events, respectively. Each of the fluxes is given by $UN \int p(s) p_{fix}(s) s \, ds$, where U is the genome-wide mutation rate per generation in each of the N individuals, producing selection coefficient s according to the beneficial or deleterious probability density function $p(s)$, which goes on to fix with probability $p_{fix}(s)$, changing population fitness by s.

Unlike Lande (1998), who considered only reverse mutations, treatment of full distributions for both beneficial s_b and deleterious s_d enables compensatory asymmetry, i.e. many small effect deleterious fixations can be offset by a smaller number of larger effect beneficial fixations (Poon and Otto 2000; Whitlock 2000; Matheson, Bertram, and Masel 2023).

Schultz and Lynch (1997) emphasized the critical value of U_b/U_d (i.e. ratio of genome-wide beneficial : deleterious mutation rates) that is needed to balance deleterious and beneficial fluxes, as a function of population size N and degree of outcrossing. Here we follow Whitlock (2000), who studied an essentially identical model, but inverted the relationship to instead emphasize a critical population size N_{crit} as a function of U_b/U_d. Below N_{crit}, a population crosses the threshold into an extinction vortex, i.e., a self-reinforcing process of fitness loss.

New beneficial mutations do not just offset degradation; they also create a second, distinct positive feedback loop (Figure 1, blue arrow). Declining N reduces the number of beneficial mutations entering the population, NU_b. This slows the adaptive increase in $\bar{W}$, which feeds back into lower N (Figure 1, upward arrow). The importance of this second feedback loop was previously briefly noted in the Discussion of Osmond and Klausmeier (2017) as an incidental finding, within a study focused on the effect of fitness function shape on extinction vortices in the context of a rapidly changing environment. We refer to this novel type of extinction vortex as "mutational drought." A shortage of adaptive fixations could be a problem not just to counter environmental change, but also just to offset deleterious fixations under high U_d, even in the absence of environmental change.

Here we systematically explore how much beneficial flux declines vs. deleterious flux increases as habitat loss drives a population's size down toward N_{crit}. Mathematically, we describe the sensitivities of both beneficial and deleterious fitness fluxes as their derivatives with respect to population size, $\frac{dv}{dN}$, evaluated at N_{crit}. The "drought : meltdown ratio" $\left|\frac{dv_b}{dN}\Big/\frac{dv_d}{dN}\right|_{N_{crit}}$ quantifies the degree to which

beneficial vs. deleterious mutations are more important in precipitating an extinction vortex. A ratio < 1 indicates that mutational meltdown is more important, a ratio > 1 indicates that mutational drought is more important, and a ratio equal to 1 represents equal contributions.

Whitlock's (2000) simple model of fitness flux $UN \int p(s) p_{fix}(s) s \, ds$ assumes that each mutation evolves independently. However, the independence assumption is violated by background selection caused by deleterious mutations, and by hitchhiking and clonal interference caused by beneficial mutations (Park and Krug 2007; Charlesworth and Jensen 2021). These phenomena increase the fixation probabilities of deleterious mutations and decrease those of beneficial mutations. In the process, in a finite population, both deleterious (Keightley and Otto 2006) and beneficial (Barton and Otto 2005) mutations cause linkage disequilibrium (LD), accounting for the non-independence. Importantly, LD has been shown to accelerate mutational meltdown (Lynch, Conery, and Bürger 1995a).

Background selection among unlinked sites must be accounted for in the $U_d > 1$ regime in which it is more powerful than background selection among linked sites (Matheson and Masel 2024). The evidence for high $U_d > 1$ is best established for humans. Lesecque et al. (2012) obtained a lower bound for human U_d by assuming that mutations are deleterious only in the 55% of the 6×10^9 diploid genome that is not dominated by dead transposable elements shared with chimpanzees, and that this 55% of the genome evolves 5.7% slower due to this constraint (Eőry, Halligan, and Keightley 2010). Combined with a conservative point mutation rate of 1.16×10^{-8} (Wang and Obbard 2023), this yields an estimated rate of deleterious mutations of $0.55\times6\times10^9\times0.057\times1.16\times10^{-8}=2.2$ per replication. This estimate is conservative: some mutations to transposable element regions are deleterious, 1.16×10^{-8} is the lower bound of a 95% confidence interval (Wang and Obbard 2023), and non-point mutations and beneficial mutations are neglected. Some therefore argue that the human deleterious mutation rate is as high as $U_d = 10$ (Reed 2005; Kondrashov 2017). Humans have only a modestly higher point mutation rate than most other eukaryotes (Wang and Obbard 2023), making it likely that $U_d > 1$ is common.

However, capturing the unlinked LD that is important in the U_d >1 regime requires simulating the entire genome rather than just a genomic region. This is computationally infeasible for most forward-time simulators (e.g., SLiM, Haller and Messer 2019), because the number of segregating mutations to be tracked scales with $U_d N$, which becomes too large. Here we conduct whole genome simulations using a recently developed approach (Matheson, Bertram, and Masel 2023) that assumes that recombination occurs only at hotspots; we track only a summary of each "linkage block" (region between hotspots), avoiding the need to track every segregating mutation.

Here we ask how important mutational drought is relative to mutational meltdown, as a function of three main parameters: 1) U_d/U_b, 2) the rate of environmental change, if any, and 3) the presence or absence of LD. We also ask how LD lowers both N_{crit} and the usually measured N_e (i.e. expected coalescence time of a neutral allele), and the degree to which lowering is driven by background selection vs. hitchhiking vs. clonal interference.

Methods

1. Without linkage disequilibrium (LD)

Fixation probability. Independent evolution of each site (i.e. no LD nor epistasis) enables an analytical, one locus approach. Each copy of a mutation with fitness effect x affects fitness by a factor of $(1+x)$. To facilitate comparisons with simulation results, we capture co-dominance not via a dominance coefficient $h = 0.5$, but by reducing fitness by $(1+x)^2$ for homozygous mutants. The exact probability of fixation $p_{fix}(s)$ of a new mutation under the Moran birth-death process is then

$$p_{fix}(s) = \frac{1 - e^{-2s}}{1 - e^{-4Ns}}$$

where the selection coefficient $s = \ln(1+x)$ represents the difference in Malthusian fitness. We take this from Equation 1 of McCandlish et al. (2015), adjusted for a diploid population of size N.

Deleterious fitness flux. Polymorphism data allows inference of the distribution of $2N_e x$, which we divide by $2N_e$ to obtain the unscaled fitness effect x. We use the human distribution of fitness effects (DFE), because it has been well studied, and is at least somewhat appropriate for large-bodied species commonly of conservation concern. We contrast two published DFEs: Boyko et al. (2008; α = 0.184, β = 8200) and Kim et al. (2017; α = 0.169, β = 1327.4). Both fit a gamma distribution $p_d(-2N_e x_d) = \frac{e^{\frac{-2N_e x_d}{\beta}} 2N_e x_d{}^{-1+\alpha} \beta^{-\alpha}}{\Gamma(\alpha)}$ where $\Gamma(\alpha)$ is the gamma function, α is the shape parameter, and β is the scale parameter. Selection coefficients are of larger magnitude in the Boyko et al. (2008) DFE than in the Kim et al. (2017) DFE, as can be seen by comparing the cumulative probability distributions (Figure S1).

The deleterious fitness flux, i.e. the rate of population fitness changes due to deleterious fixations, is equal to the per-generation rate of new mutations $U_d N$, times their fixation probability $p_{fix}(s_d)$, times their homozygous impact on fitness $2x_d$ once fixed:

$$v_d = U_d N \int_{-\infty}^{0} p_d(2N_e x_d) \frac{2N_e x_d}{N_e} p_{fix}\left(\ln\left(1 + \frac{2N_e x_d}{2N_e}\right)\right) d(2N_e x_d) \quad (1)$$

We integrate with respect to $2N_e x_d$ rather than x_d for convenient usage of inferred DFEs. We rescale using the inferred N_e from either Boyko et al. (2008; N_e= 25636) or Kim et al. (2017; N_e= 11823), matching the DFE used.

Beneficial fitness flux. We assume an exponential distribution with mean effect size $\overline{x_b}$:

$$p_b(x_b) = \frac{1}{\bar{x}_b} e^{-x_b/\bar{x}_b}$$

The beneficial fitness flux, i.e. the change in population fitness due to the fixation of beneficial mutations is

$$v_b = U_b N \int_{0}^{+\infty} p_b(x_b) 2x_b \, p_{fix}(\ln(1 + x_b)) \, dx_b \quad (2)$$

Critical population size. We calculated the deleterious and beneficial fitness fluxes numerically in Mathematica 14.2.0 (Supplementary Notebook), using Equations (1) and (2). We also consider

environmental change δ_{env}, as either zero or in the range δ_{env}= -[10^{-6} – $10^{-3.5}$]. We express the environmental change rate, for ease in interpretation, as the number of generations over which environmental change causes a 10% reduction in fitness; this is equal to -0.1/δ_{env} = [10^{5} – $10^{2.5}$] generations. We consider this range low because it makes deleterious fixations a larger source of fitness loss than environmental change. We envisage that coevolution, especially with parasites, makes the biggest contribution to δ_{env}, following the Red Queen hypothesis (VanValen 1973). Approximating absolute fitness as always equal to 1 at N_{crit} helps justify making the rate U_b and DFE of beneficial mutations independent of U_d and δ_{env}.

We then solve for N_{crit} as the value of N for which $v_{net} = v_b + v_d + \delta_{env} = 0$. We then calculate the drought : meltdown ratio as $\left|\frac{dv_b}{dN}/\frac{dv_d}{dN}\right|_{N_{crit}}$. With linkage equilibrium, the effective population size is equal to the census population size.

2. With LD

Simulation setup. Our forward time simulation method is described in detail elsewhere (Matheson, Bertram, and Masel 2023). Briefly, each genome consists of two haplotypes, divided into 23 chromosomes, further segmented into unrecombining 'linkage blocks'. The fitness impact of all mutations i = 1,2, … within a given allele of linkage block j is summarized as $l_j = \prod_i(1 + x_i)$. The fitness of an individual combines the effects of all linkage blocks L as $w = \prod_{j=1}^{L}(l_{j,1}) \prod_{j=1}^{L}(l_{j,2})$ where $l_{j,1}$ and $l_{j,2}$ refer to the two copies of linkage block j in a diploid. We employ a Moran model with a constant population size N, where individuals are chosen to reproduce based on their fitness.

Recombination occurs only at hotspots between adjacent linkage blocks. We simulated two recombination events per chromosome per meiosis (Pardo-Manuel de Villena and Sapienza 2001). We used 100 linkage blocks per chromosome for computational efficiency, which previous work found to be more than sufficient (Matheson, Bertram, and Masel 2023).

We sampled the numbers of new deleterious and beneficial mutations from Poisson distributions with means U_d and U_b, respectively. We sampled selection coefficients from the distributions described in the previous section, rescaling in the case of x_d.

Simulations ran for $100N$ generations. Because we initialized simulations with a monomorphic population, we excluded a burn-in phase when measuring fitness flux. Following Matheson et al. (2023), we ended the burn-in phase 100 generations after a linear regression of the variance in fitness over the last 200 generations produced a slope less than an arbitrary small value of $0.07/N$. Net fitness flux v_{net} was estimated post burn-in as the slope $\hat{v}_{net}$ of log mean population fitness over time, without decomposition into v_d and v_b.

Critical population size. N_{crit} is defined as the value of N for which $v_{net} = 0$, but $\hat{v}_{net}$ estimation is too noisy to find N_{crit} using purely deterministic root-finding methods, especially for small values of N_{crit}. After using a standard root-finding approach to choose a set of points near N_{crit} at which to evaluate $\hat{v}_{net}$, we therefore estimated N_{crit} as the root of a fitted linear regression, to cancel out the noise. Specifically, we first bracketed N_{crit}, with N = 1500 and 6000 as initial guesses, progressing outward by a factor of two as needed until we had $\hat{v}_{net}$ values both above and below zero. Then we iterated the secant method until $\hat{v}_{net}$ changed by < 15% in the last iteration. Then we fitted a straight line to all evaluated $\{N, \hat{v}_{net}\}$ data points for which N was within a factor of 3 from the final evaluated value. We estimated N_{crit} as the zero for this fitted line.

<u>Drought : meltdown</u> ratio. To calculate the drought : meltdown ratio in our simulations, we needed to partition the net fitness flux v_{net} into its deleterious and beneficial components, such that $v_{net} \sim v_b - v_d$. We estimated v_d and v_b from the set of mutations whose time of final fixation lay between the end of the burn-in phase and the end of the run. Tracking fixations does not exactly track mean population fitness due to fluctuations caused by polymorphisms. For computational efficiency, the simulations described so far summarize the fitness of many mutations per linkage block, making

information about individual fixed mutations inaccessible. We make them accessible by using tree sequence recording (Kelleher et al. 2018), which succinctly encodes the complete history of genetic lineages within a population. In simulations intended to estimate the drought : meltdown ratio, we used tree sequencing recording to track all non-neutral mutations, including their time of fixation. We calculated $v_d = \frac{\sum_{i=1}^{n_d} 2\ln(1+x_{d_i})}{G^*}$ and $v_b = \frac{\sum_{i=1}^{n_b} 2\ln(1+x_{b_i})}{G^*}$, where G^* equals generations elapsed since the burn-in phase ended, and n_d and n_b represent the numbers of deleterious and beneficial mutations that fixed during this time.

We numerically estimated the derivative of each fitness flux component, $\frac{dv_b}{dN}$ and $\frac{dv_d}{dN}$, as

$$\frac{dv}{dN} = \frac{v(N_{crit} + \varepsilon) - v(N_{crit} - \varepsilon)}{2\varepsilon},$$

where we chose $\varepsilon = 150$ individuals as a balance between reducing noise and avoiding curvature in v.

Results

Without LD, where $N_e = N$, Whitlock's (2000) choice of $U_d/U_b = 1000$, combined with the deleterious DFE that Kim et al. (2017) inferred for humans, and with a conservatively low $\bar{x}_b$ = 0.001, yields $N_{crit} \simeq 1834$ (Figure 2A, solid blue and red lines intersecting at dotted red vertical line). Whitlock's (2000) Equation (9) produces a substantial underestimate: $N_{crit} \cong \sqrt[3]{\frac{U_d}{64\,\bar{x}_b{}^2|\bar{x}_d|U_b}} = 1181$. Whitlock's approximation assumes an exponential DFE for deleterious mutations, with a coefficient of variation (CV_d) equal to 1, in order to simplify the Equation 3 expression for v_d in Whitlock (2000). However, the coefficient of variation is ~2.4 for the empirically inferred deleterious DFEs of both Kim et al. (2017) and Boyko et al. (2008). If we instead use Whitlock's full Equation (3), we obtain $N_{crit} \simeq 1967$, closely matching our full numerical analysis of the independent sites case. Figure S2 illustrates similar results across the range of U_d/U_b values. In qualitative agreement with Whitlock's (2000)

approximate equation, $\bar{x}_b$ is much more important to N_{crit} than $\bar{x}_d$ is (Figure S3). We note that N_{crit} values of Whitlock's are intended to represent N_e not census N.

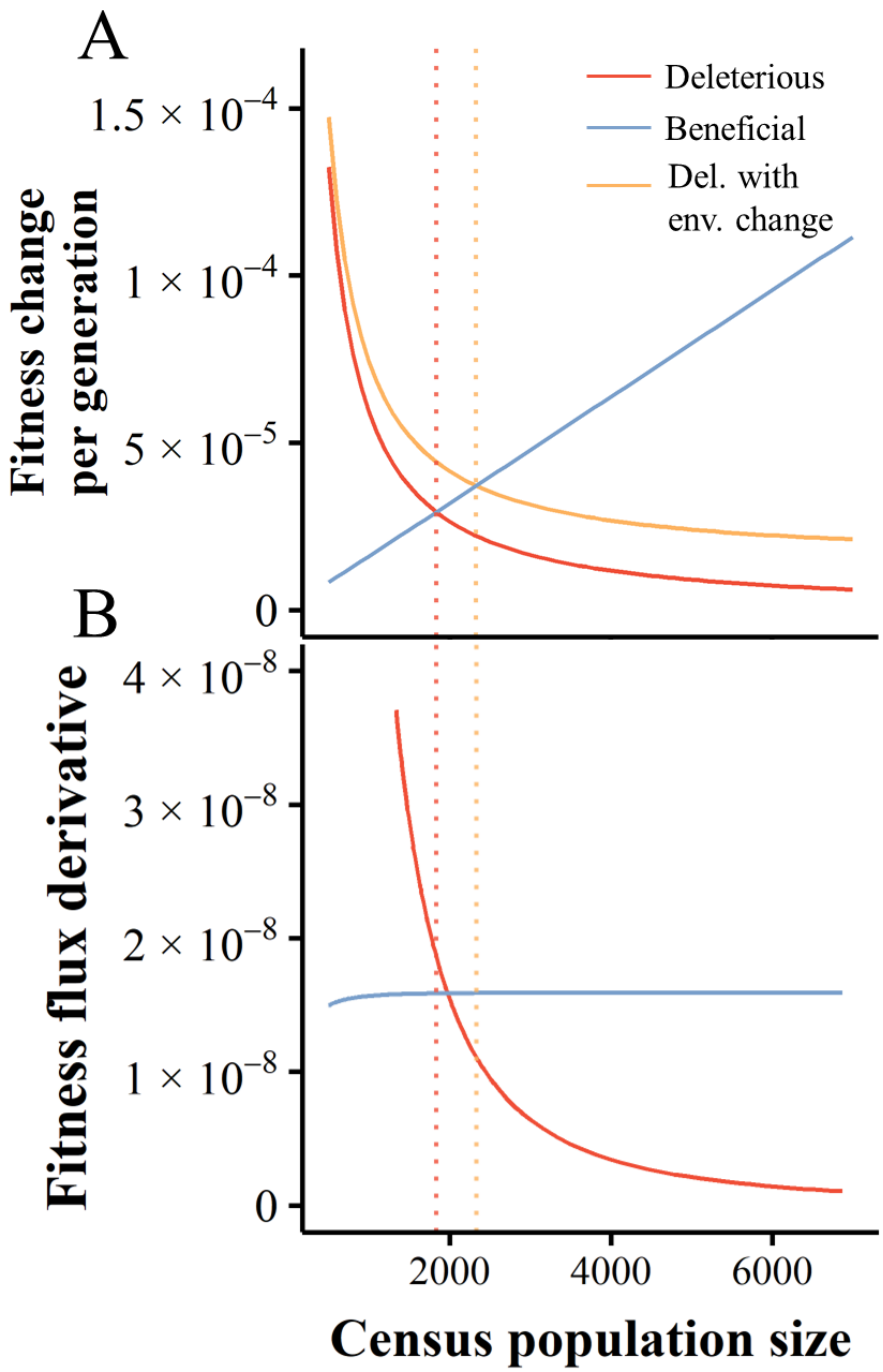

Figure 2. **Extinction vortices can be driven as much or more by mutational drought as by mutational meltdown.** Vertical lines indicate N_{crit}, defined by the intersection in (A) of beneficial mutation fitness flux (blue) with deleterious mutation fitness flux (red), or with deleterious mutation plus environmental (orange) fitness fluxes. Environmental degradation adds a constant δ_{env} = -1.5×10^{-5} per generation (corresponding to orange starred point in

Figure 3) to deleterious flux in (A) and hence does not change the red line representing slope in (B). Continuous lines are analytical results given linkage equilibrium. U_d = 2, $U_d/U_b = 1000$, $\bar{x}_b$ = 0.001, and $\bar{x}_d$ = -0.009 via the DFE from Kim et al. (2017).

At N_{crit} in the absence of environmental change (dotted red vertical line in Figure 2B), declining N has 85% of the impact on beneficial flux as it has on the deleterious flux that is normally assumed to be the sole cause of an extinction vortex according to mutational meltdown theory. When adaptation must counter environmental change in addition to deleterious fitness flux, larger populations are vulnerable to the extinction vortex, i.e. N_{crit} is higher. Fig. 2A illustrates environmental change reducing fitness by 10% over ~6,000 generations, where the orange line intersects with the blue solid line to produce dashed vertical line at $N_{crit} \simeq 2330$ (Figure 2A orange vertical dotted line). In this scenario, the impact of declining N on beneficial flux is larger than that on deleterious flux (blue line is above red along dashed vertical line in Figure 2B). In other words, environmental change makes mutational drought more important than mutational meltdown.

More broadly, the drought : meltdown ratio is > 1 with $U_d/U_b = 1000$ when slow environmental change causes fitness to decline by 10% over as many as ~20,000 generations (Figure 3A, right grey dot-dashed vertical line). When U_b is 10 times higher, faster environmental change is needed to drive drought : meltdown ratio > 1 (Figure 3A, left blue dotted vertical line, ~4000 generations for fitness to decline by 10%). We interpret both these rates of environmental decline as rather slow because they correspond to only 0.19× and 0.28× the rates of fitness decline due to deleterious fixations for U_d = 2 (Figure 3B, color-matched intersections with vertical lines). A drought : meltdown ratio > 1 does not require excessively elevated N_{crit} (Figure 3C steep rise in N_{crit} occurs well to the left of the color-matched vertical line).

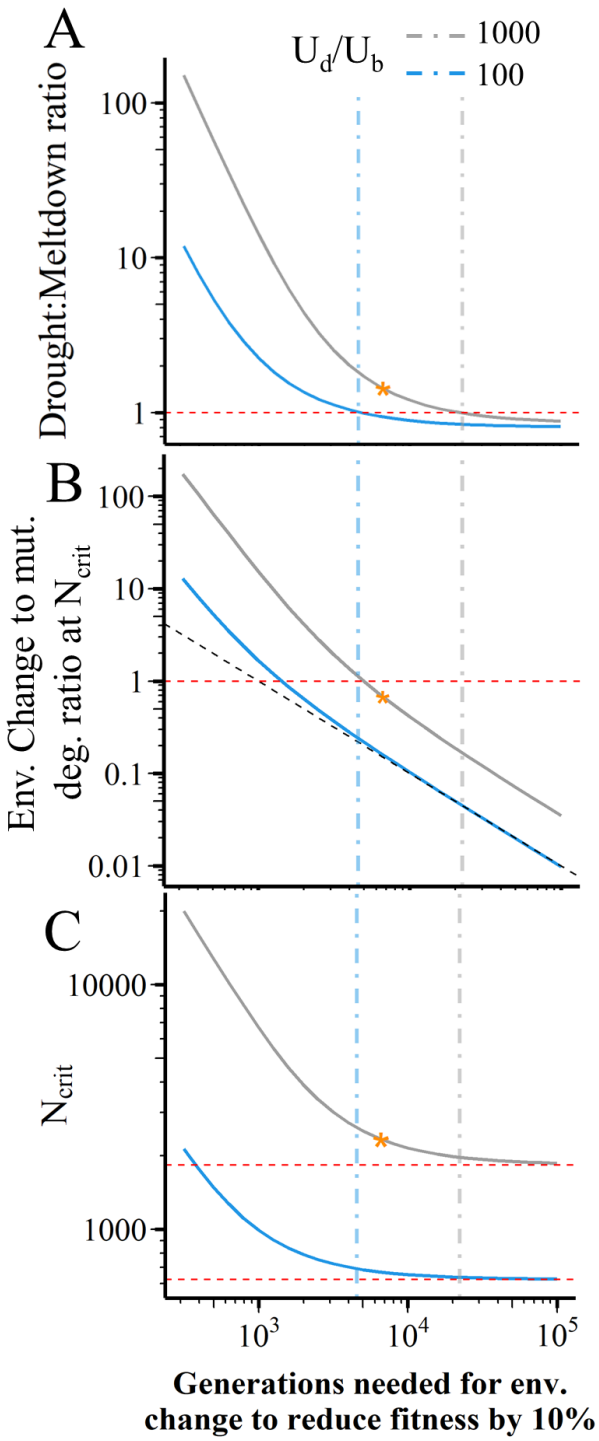

Figure 3. **Slow environmental degradation is sufficient to make mutational drought more important than mutational meltdown.** $\bar{x}_b$ = 0.001, U_d = 2, $\bar{x}_d$ = -0.009 via the DFE from Kim et al. (2017). The orange star indicates the example of environmental change shown in Figure 2. Vertical lines represent where the drought : meltdown ratio = 1. (B) We consider environmental change to be relatively slow below the red dashed line, where mutational degradation makes a bigger contribution to fitness decline. Diagonal black dashed line in (B) represents proportionate change in the x-axis and y-axis; departure from this indicates

increased deleterious flux in the face of rapid adaptation. Red dashed lines in (C) indicate the asymptotes, i.e. no environmental change.

When beneficial mutations are scarce (higher U_d/U_b), the relative importance of mutational drought is higher, with the drought : meltdown ratio saturated by the U_d/U_b~1000 value (Figure 4A) used in Fig. 2. Lowering U_b has two opposing effects. First, it proportionately lowers the beneficial fitness flux v_b and its derivative $\frac{dv_b}{dN}$ (i.e. it reduces the slope of the blue line in Figures 2A and consequently reduces the height of the blue line in Figure 2B). Second, lower v_b moves the intersection N_{crit} to the right, i.e. towards larger values of N, which lowers $\left.\frac{dv_d}{dN}\right|_{N_{crit}}$ without substantially changing $\left.\frac{dv_b}{dN}\right|_{N_{crit}}$ (Figure 2B, red and blue lines, respectively). The flat drought : meltdown ratio to the right of Figure 4A shows that when beneficial mutations are scarce at high $U_d/U_b \geq 1000$, these two effects cancel each other out.

Using the higher mean deleterious effect size $\bar{x}_d$ of Boyko et al. (2008) only slightly decreases the relative importance of mutational drought at higher $\bar{x}_d$, primarily when beneficial mutations are common (Figure 4A, difference between lines is largest at low U_d/U_b). Larger beneficial effect sizes only slightly increase the relative importance of mutational drought, again with a slightly larger effect when beneficial mutations are more common (Figure 4B).

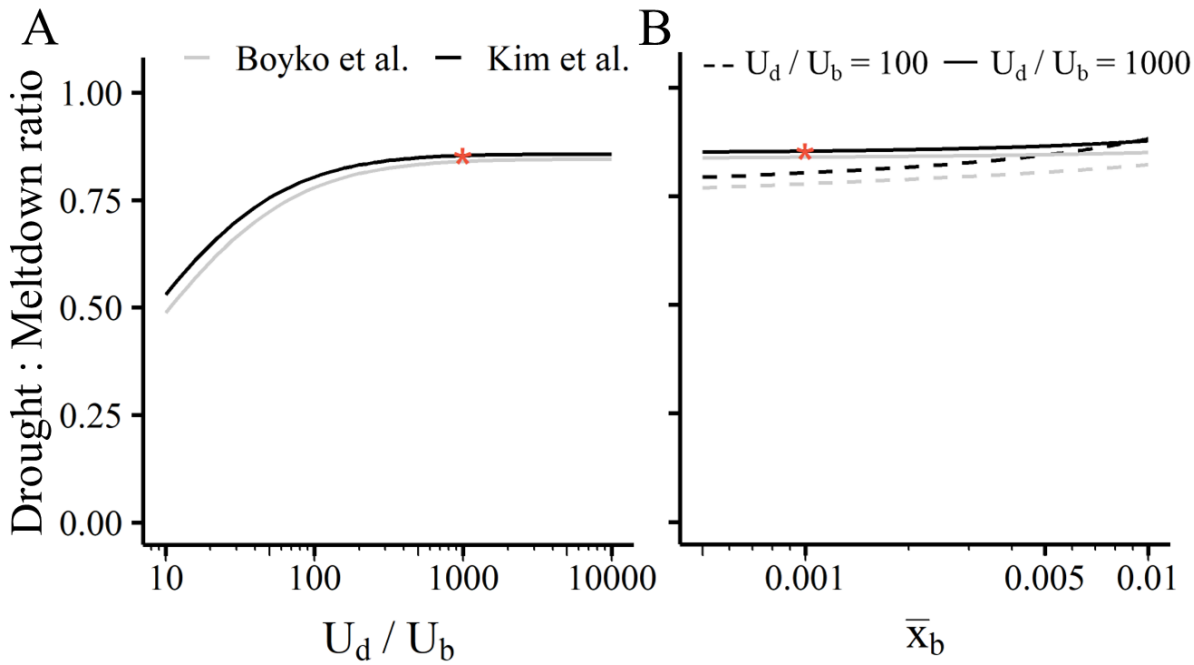

Figure 4. **The mean sizes of (A) deleterious and (B) beneficial selection coefficients have negligible impact on the relative importance of mutational drought versus mutational meltdown.** (A) Mutational drought becomes somewhat less important when beneficial mutations are abundant (low U_d/U_b). Analytical results are shown for the independent sites model, with no environmental change. $\bar{x}_b$ = 0.001 in (A). U_d = 2 throughout, but results for different U_d are superimposable. The red star indicates the example shown in Figure 2 with no environmental change.

With environmental change, dependence on U_d and U_b does not simplify to dependence on their ratio, as in Figure 4A. We illustrate this in Figure 5 for two environmental change scenarios: for the dashed lines, environmental change is swamped by deleterious mutation accumulation, whereas for the dotted lines, environmental change is more substantial albeit never exceeding mutational degradation (Fig. 5B and 5E). When faster environmental change and more scarce beneficial mutations push the drought : meltdown ratio above 1 (Figures 5A and 5B), lower U_d makes mutational drought more rather than less important (Figure 5A). The drought : meltdown ratio only falls substantially below 1 under the slower environmental change scenario, and only when U_d/U_b is small (Figure 5A, left portion of dashed blue). This corresponds to exceptionally small N_{crit} (Figure 5C). Under realistically high U_d, high drought : meltdown ratios are found when beneficial mutations are scarce (Figure 5D, solid lines to right), making N_{crit} high (Figure 5F), and

thus environmental change at N_{crit} relatively fast in comparison to a correspondingly slower rate of deleterious fixations (Figure 5E).

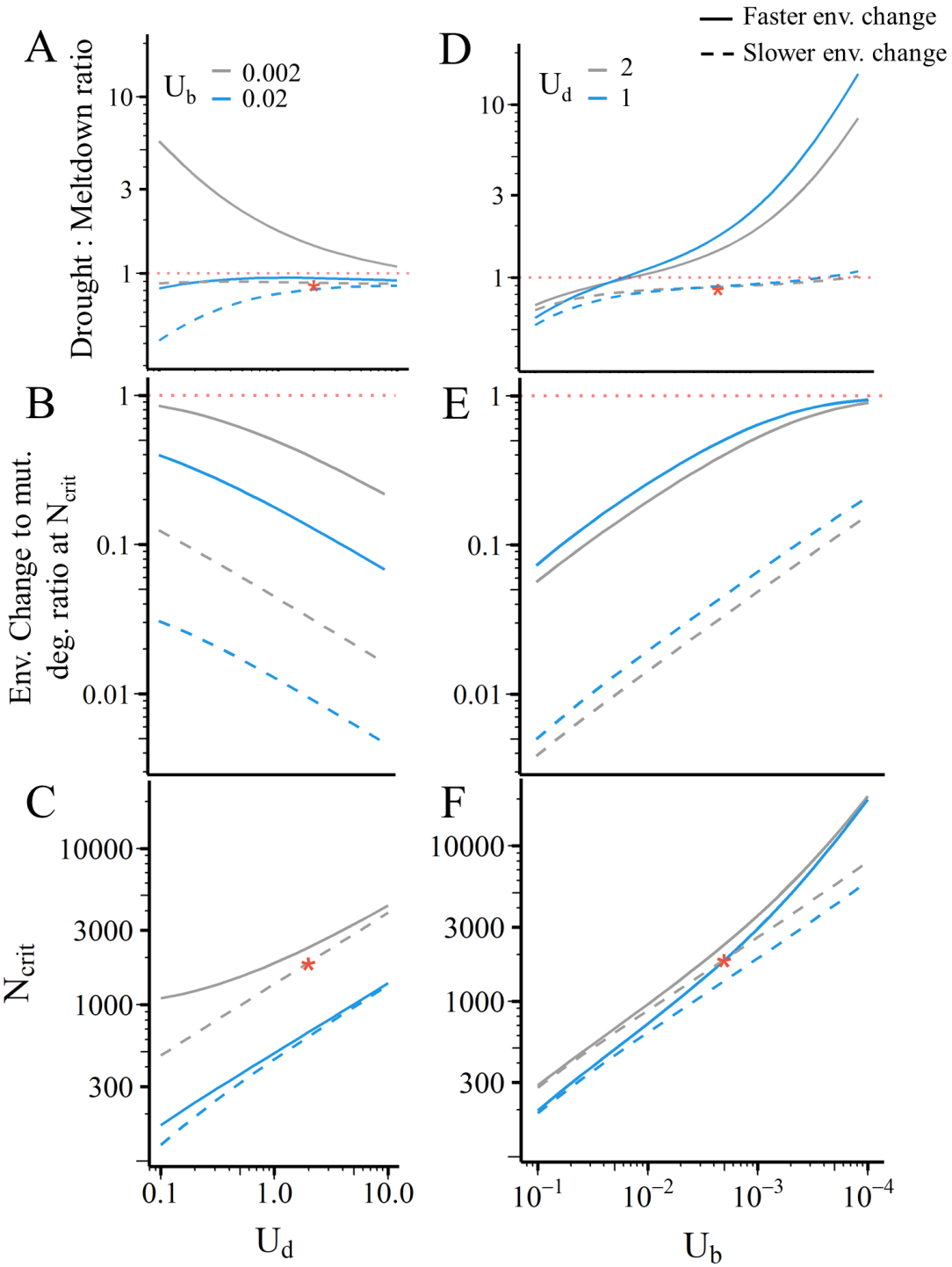

Figure 5. (A) Faster environmental degradation makes mutational drought more rather than less important for lower U_d. (A) and (D) can be compared to the no-environmental change case in Figure 4A, where only the ratio U_d/U_b matters; reverse scaling of the U_b x-axis

is used in (D) to facilitate comparison. The red star indicates the example shown in Figure 2 with no environmental change. The solid lines represent a fitness reduction of δ_{env}= -1.5×10^{-5} per generation, matching the example in Figure 2, and dashed lines represent δ_{env} = -10^{-6}; impact relative to deleterious flux is contextualized in (B) and (E). Analytical results are shown for the independent sites model with $\bar{x}_b$ = 0.001 and $\bar{x}_d$ = -0.009 via the DFE from Kim et al. (2017). Larger magnitude deleterious selection coefficients give drought : meltdown ratios a little further from 1 (Figure S4).

The presence of LD given U_d = 2 produces a modest 8% increase in the drought : meltdown ratio, from 0.85 to 0.92, as beneficial flux becomes slightly more sensitive to N (Figure 6D, blue points are above blue line). LD moves the $v_d = v_b$ intersection slightly higher in Figure 6C, corresponding to higher mean fitness and larger fitness fluxes.

LD raises N_{crit} from 1834 to 4403 (Figure 6A, solid dots; Figure S5). The shifts in both beneficial and deleterious flux curves are well captured by rescaling to express results in terms of $N_e = N\frac{\text{analytical } N_{crit}}{\text{simulated } N_{crit}}$, as seen by the close match between analytical lines and simulated points when the x-axes of Figures 6A and 6B are rescaled to produce Figures 6C and 6D.

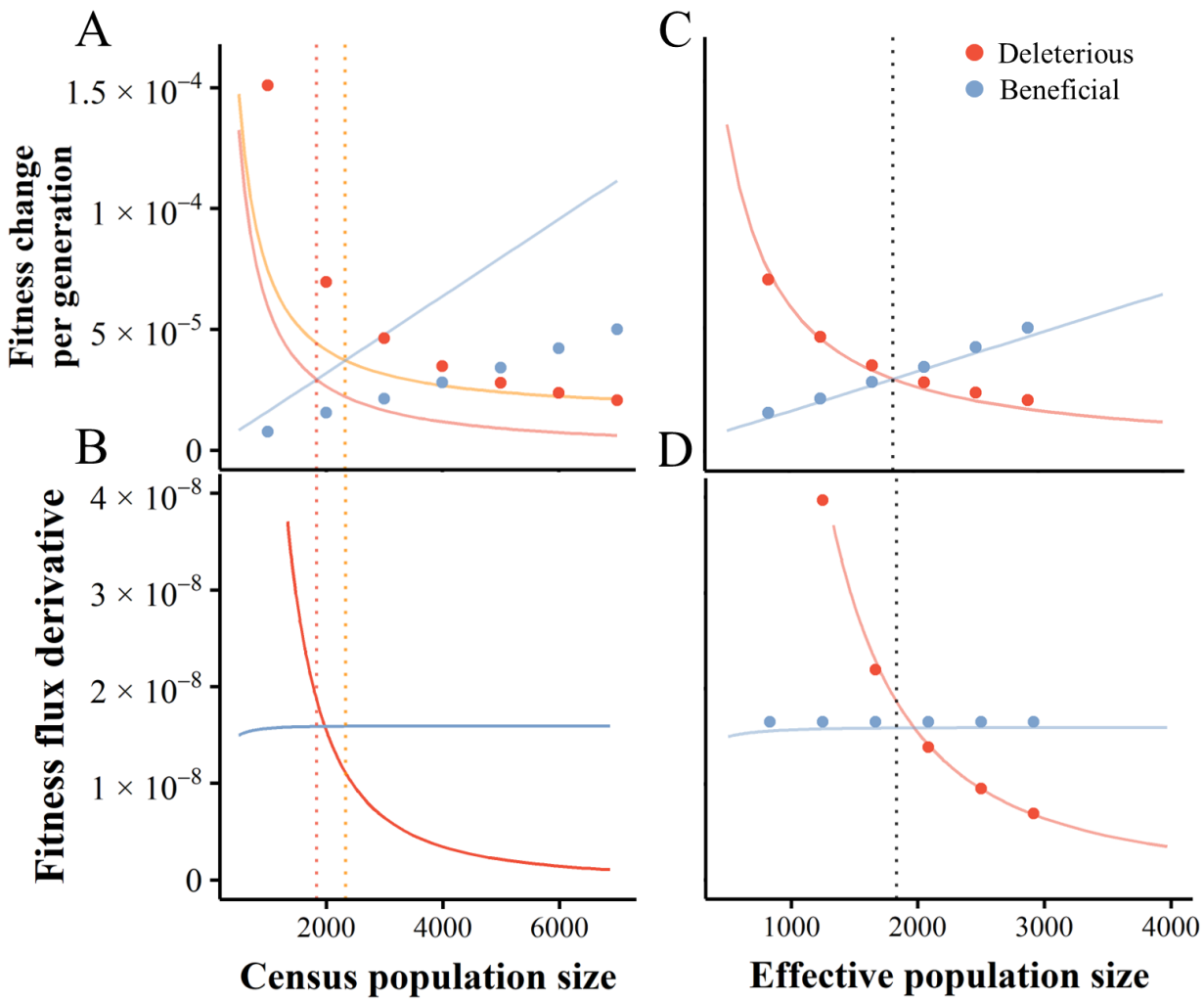

Figure 6. Linkage disequilibrium makes the role of mutational drought slightly more important compared to the linkage equilibrium case. Continuous red and blue lines are analytical results given linkage equilibrium, while dots are simulation results with LD. (A) and (B) are the same plots in Figure 2 with simulation results added in (A). In (C) and (D), the x-axis for simulation results is scaled such that the lines intersect at the same "effective" N_{crit}. U_d = 2, U_d/U_b = 1000, $\bar{x}_b$ = 0.001, $\bar{x}_d$ = -0.009 via the DFE from Kim et al. (2017). We note that the beneficial-fitness-flux-effective population size and the deleterious-fitness-flux-effective population size behave similarly to one another (C and D).

The reduction in N_e could be due to beneficial mutations interfering with each other (clonal interference decreasing beneficial flux), and/or hitchhiking (beneficial mutations increasing deleterious flux), and/or background selection (deleterious mutations both decreasing beneficial flux and increasing deleterious flux). In Figure 6 without environmental change, background selection from deleterious mutations on deleterious or neutral mutations (using eq. (4) in Matheson and Masel 2024) predicts a ratio of $N_e/N = 0.82$, but we see a ratio of $\frac{\text{analytical } N_{crit}}{\text{simulated } N_{crit}}$ = 0.42. A model of deleterious mutations alone thus accounts for only (1 – 0.82)/(1 – 0.42) = 30% of the reduction in effective N_{crit}. When we measure N_e the usual way, as the expected coalescent time, the factor reduction in N_e (Figure 7, blue triangles) matches the reduction in fitness fluxes and hence N_{crit} (Figure 7, black circles), but not that predicted by deleterious mutations alone (Figure 7, red squares).

If low N_e were due to clonal interference, then the reduction in N_e should be stronger for high U_b; but the (very weak) trend is in the opposite direction (Figure 7A). Since neither beneficial mutations alone (clonal interference) nor deleterious mutations alone can explain our results, this points to an interaction between deleterious and beneficial mutations. There are two kinds of interaction: beneficial mutations increase the fixation probability of deleterious mutations (Charlesworth 1994; Peck 1994), and deleterious mutations decrease the fixation probability of beneficial mutations (Good and Desai 2014, 201; Pénisson et al. 2017). From Figure 6, we deduce that both happen to the same degree. This interpretation explains greater N_e reduction for large U_d (Figure 7B). It is also compatible with slightly less N_e reduction for larger U_b (Figure 7A), where there is more competition between less-loaded vs. more-loaded beneficial lineages.

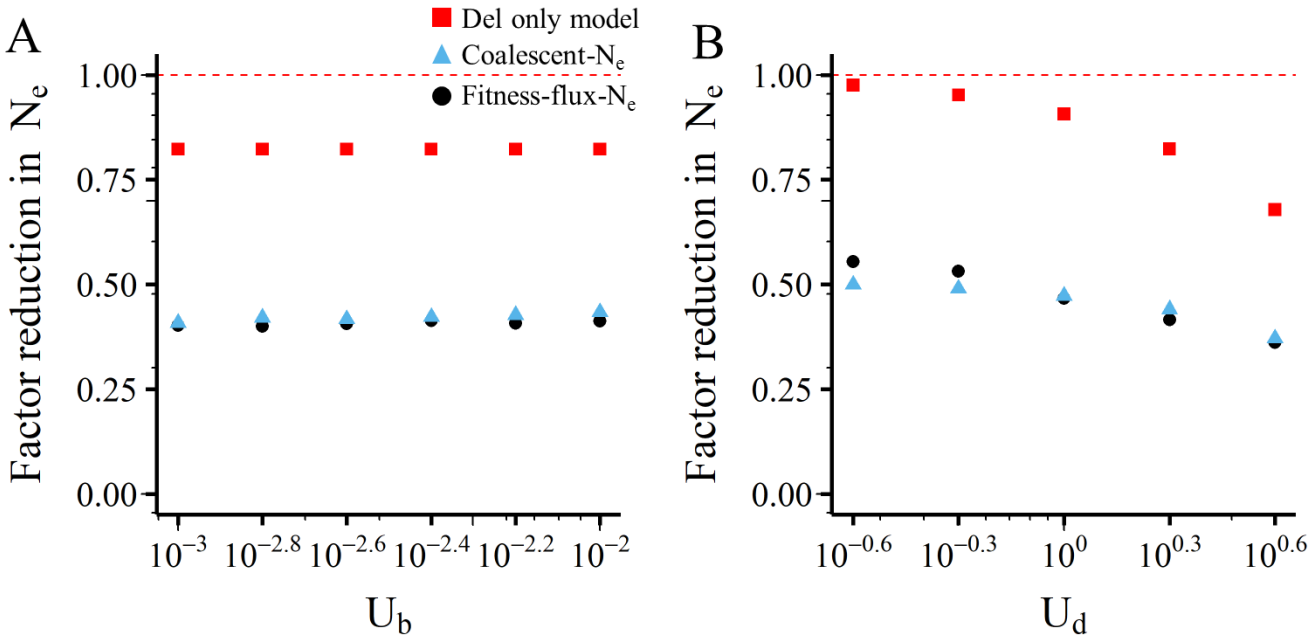

Figure 7. **The degree to which effective population size is reduced below census size is more sensitive to the deleterious than to the beneficial mutation rate.** $\frac{\text{analytical } N_{crit}}{\text{simulated } N_{crit}}$ serves as an estimate of N_e/N. $\bar{x}_b$ = 0.001, U_d = 2 (in A), U_b = 0.02 (in B), and $\bar{x}_d$ = -0.009 via the DFE from Kim et al. (2017). Model of deleterious mutations alone is from Equation 4 in Matheson and Masel (2024).

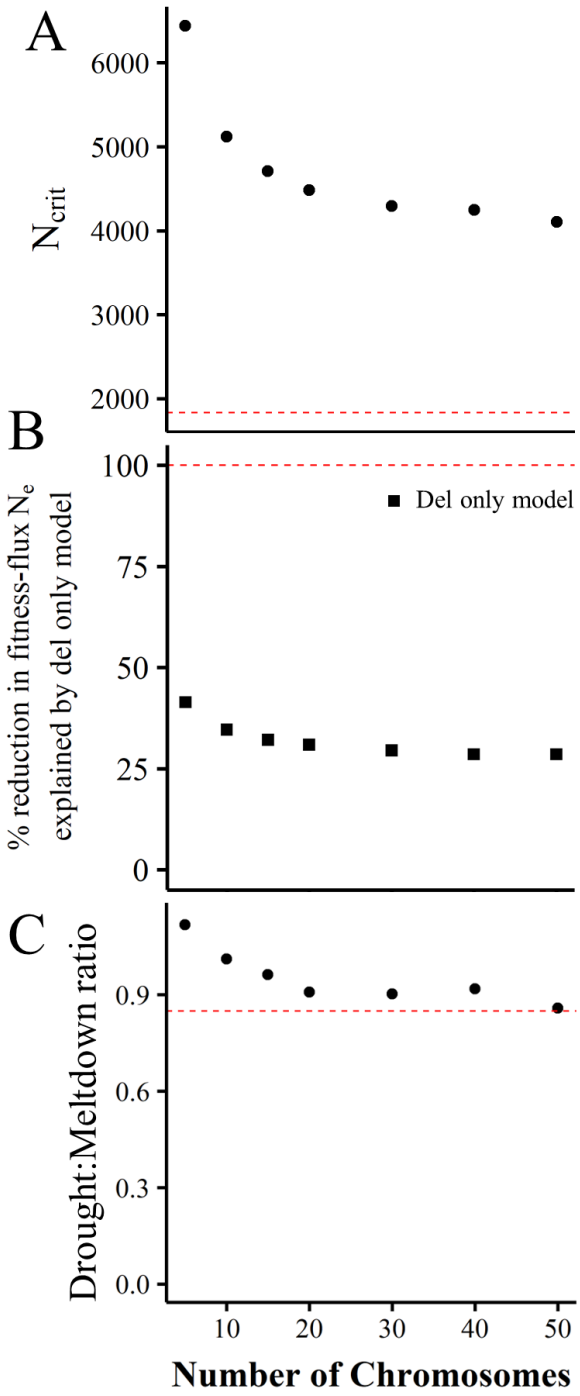

Figure 8. **More recombination does not make N_{crit} converge to the expectation for independent loci (A), but this does not affect the drought : meltdown ratio (C).** (B) More recombination makes the model of deleterious mutations alone a slightly worse fit. $\bar{x}_b$ = 0.001, U_b = 0.002, U_d = 2, $\bar{x}_d$ = -0.009 via the DFE from Kim et al. (2017), L = 100 per chromosome. Red dashed lines show analytical expectations in the absence of LD. Model of deleterious mutations alone in (B) is from Equation 4 in Matheson and Masel (2024).

We manipulate the amount of recombination in our simulations of LD by changing the number of chromosomes, given two crossover events per chromosome plus independent segregation. More recombination lowers N_{crit}, but realistic numbers of chromosomes are not sufficient to converge on the value expected without LD (Figure 8A). However, 50 chromosomes, each with 100 linkage blocks, are sufficient to obtain a drought : meltdown ratio in line with independent-sites expectations, with more LD causing only a modest increase in the relative importance of mutational drought (Figure 8C). Our model of deleterious mutations alone, which poorly describes the effect of LD on N_{crit}, becomes somewhat worse given more recombination (Figure 8B).

Discussion

Mutational meltdown describes an extinction vortex in which small populations cannot purge slightly deleterious mutations, whose fixations handicap the population, making it still smaller. Here, we find that a shortage of beneficial mutations appearing in smaller populations creates mutational drought, a distinct kind of extinction vortex. Mutational drought is only slightly less significant than mutational meltdown in the absence of environmental change, and becomes more important in the more realistic scenario of a changing environment. Mutational drought is modestly more significant if there is LD, and much more significant if we assume that beneficial mutations are rare. Beneficial mutations are thus either common, or else their population-size-dependent scarcity is critical – in neither case can population genetic models ignore beneficial mutations. Near the critical census population size, the reduction in effective population size is best explained by interactions between beneficial and deleterious mutations.

The role of beneficial mutations in population persistence studied here plays out over much longer timescales than processes of “evolutionary rescue” in previous population genetic (discrete) models, although in line with the broader use of the term in the context of quantitative genetics models (see Osmond and Klausmeier 2017). In the broad sense, evolutionary rescue refers to scenarios where genetic adaptation struggles to keep up with ongoing environmental change, over an indefinitely long period of

time (Gomulkiewicz and Holt 1995; Gonzalez et al. 2013; Alexander et al. 2014; Carlson, Cunningham, and Westley 2014; G. Bell 2017). When using the narrow sense of the term, population genetic models consider a population whose birth rate is initially less than its death rate, e.g. following a single abrupt environmental change that can be remedied by one or several beneficial mutation(s) (Orr and Unckless 2008; Martin et al. 2013; Orr and Unckless 2014; Uecker, Otto, and Hermisson 2014; Uecker and Hermisson 2016; Wilson, Pennings, and Petrov 2017). Here we use a population genetic model to consider evolutionary rescue in the broad sense more commonly treated by quantitative genetic models, across an indefinitely long series of beneficial and deleterious fixations. Given ongoing environmental change, we find that mutational drought, not mutational meltdown, is the dominant process driving the extinction vortex. We furthermore find that mutational drought is nearly as important, even in the absence of any environmental change.

Conservation management and species recovery programs assess the 'minimum viable population' (MVP) and the factors influencing it (Shaffer 1981; Lacava and Hughes 1984; Reed et al. 2003; Traill, Bradshaw, and Brook 2007). We follow Nabutanyi and Wittmann (2022) in defining N_{crit} as the lowest population size that avoids an extinction vortex. This is a different kind of MVP to the usually considered empirical predictor of probability of persistence after a specified period of time, e.g. 1000 years (Nunney and Campbell 1993; Traill, Bradshaw, and Brook 2007). Our N_{crit} concerns the ability to resupply the population with new beneficial mutations to balance both the accumulation of deleterious mutations, and ongoing environmental change, to achieve long-term viability. N_{crit} is the gateway to the extinction vortex below which some combination of mutational meltdown and mutational drought contribute. Our N_{crit} is relevant over the long timescales of multiple sweeps making our results applicable more clearly to species than to populations, reliant on mutation rather than migration as source of new variants.

The reduction from N to N_e is primarily caused by LD between beneficial and deleterious mutations, with a smaller contribution from LD among deleterious mutations. A model of background selection among linked deleterious mutations alone, capturing only the smaller component (Matheson and Masel 2024) of the smaller effect, is sometimes considered as the best explanatory model of genetic diversity patterns (Johri, Charlesworth, and Jensen 2020; Murphy et al. 2022; Buffalo and Kern 2024), e.g., via one-locus models that use the B parameter to rescale N_e (B is the ratio of the effective population size under background selection to the neutral value; Charlesworth 2013). Our results here suggest that such a model will underestimate the degree to which LD reduces N_e and N_{crit} in the parameter value regime of interest to species of conservation concern.

The assessed extinction risk of several classes of vertebrate species in the Anthropocene (IUCN 2024) includes assessed long-term risks to environmental conditions (Pacifici et al. 2015). Current conservation efforts often focus on emergency revitalization programs with tools that might only achieve short-term persistence (e.g., Santidrián Tomillo et al. 2021), potentially creating trade-offs between long-term and short-term objectives (Rout, Hauser, and Possingham 2007). Short-term goals may be problematically prioritized under triage from restricted budgets (Bottrill et al. 2008; Vucetich, Nelson, and Bruskotter 2017) over achieving long-term sustainable populations (Willis and Birks 2006; Barnosky et al. 2017).

Some conservation geneticists advocate genetic rescue, whereby gene flow from a few introduced individuals helps small fragmented populations (Whiteley et al. 2015; Frankham et al. 2017; D. A. Bell et al. 2019). The genetic rescue paradigm aims to maximize genetic diversity to reduce the risk of extinction (Whiteley et al. 2015; Ralls et al. 2018; 2020). However, gene flow from large, outbred populations may introduce too many recessive deleterious alleles to be easily purged, with deleterious effects that might quickly have devastating consequences within a small inbred population (Bijlsma et al. 2010; Kyriazis, Wayne, and Lohmueller 2021; Pérez-Pereira, Caballero, and García-Dorado 2022).

Abandoning the genetic rescue paradigm might limit the risk of deleterious accumulation in the short term, but might still be a mistake over longer timescales if a shortage of adaptive mutations later poses an extinction risk. Fortunately, according to simulations, the benefits of genetic rescue can be obtained while minimizing harm by steadily introducing migrants from other small inbred populations from which recessive deleterious mutations are already purged (Kyriazis, Wayne, and Lohmueller 2021; Pérez-Pereira, Caballero, and García-Dorado 2022), as has occurred naturally in Florida scrub-jays (Chen et al. 2016).

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Data Availability

Analytical results conducted in Wolfram Mathematica. Simulation code written in C, and graphs produced with R. Simulation code and scripts are available on GitHub at https://github.com/MaselLab/MutationLoad/tree/mutational-drought

Conflict of interest

All authors declare no conflicts of interest.

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