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Eco-evolutionary extinction and recolonization dynamics reduce genetic load and increase time to extinction in highly inbred populations

Anders P. Charmouh,[1,2] Jane M. Reid,[1,3] Trine Bilde,[4] and Greta Bocedi[1]

[1]*School of Biological Sciences, University of Aberdeen, Aberdeen AB24 2TZ, United Kingdom*

[2]*E-mail: a.poulsencharmouh.19@abdn.ac.uk*

[3]*Centre for Biodiversity Dynamics, Institutt for Biologi, NTNU, Trondheim 7491, Norway*

[4]*Department of Biology, Aarhus University, Aarhus C 8000, Denmark*

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Understanding how genetic and ecological effects can interact to shape genetic loads within and across local populations is key to understanding ongoing persistence of systems that should otherwise be susceptible to extinction through mutational meltdown. Classic theory predicts short persistence times for metapopulations comprising small local populations with low connectivity, due to accumulation of deleterious mutations. Yet, some such systems have persisted over evolutionary time, implying the existence of mechanisms that allow metapopulations to avoid mutational meltdown. We first hypothesize a mechanism by which the combination of stochasticity in the numbers and types of mutations arising locally (genetic stochasticity), resulting local extinction, and recolonization through evolving dispersal facilitates metapopulation persistence. We then test this mechanism using a spatially and genetically explicit individual-based model. We show that genetic stochasticity in highly structured metapopulations can result in local extinctions, which can favor increased dispersal, thus allowing recolonization of empty habitat patches. This causes fluctuations in metapopulation size and transient gene flow, which reduces genetic load and increases metapopulation persistence over evolutionary time. Our suggested mechanism and simulation results provide an explanation for the conundrum presented by the continued persistence of highly structured populations with inbreeding mating systems that occur in diverse taxa.

KEY WORDS: **Dispersal, genetic load, genetic stochasticity, inbreeding, metapopulation dynamics, mutational meltdown.**

A key challenge at the interface of population and evolutionary biology is to understand how ecology, genetics, and resulting evolution can combine to affect long-term persistence of small populations (Gonzalez et al. 2013; Carlson et al. 2014). Small populations are common in nature and often situated within highly structured metapopulations (defined as populations of interconnected local populations [Harrison and Hastings 1996; Hanski 1998]), where costs of dispersal can be high and resulting gene flow between local populations can be very restricted. Local populations then inevitably become increasingly inbred and experience high extinction risk due to genetic and demographic stochasticity. Accumulation and fixation of deleterious mutations can then in principle lead to dramatic decreases in fitness and population size, termed "mutational meltdown" (Lynch and Gabriel 1990). Here, the decreasing census population size resulting from accumulating deleterious mutations decreases effective population size (N_e), facilitating further fixation of deleterious mutations and further reduction of population size. These feedbacks can continue until genetic and demographic stochasticity eventually lead to population extinction (Lacy and Lindenmayer 1995; Gaggiotti and Hanski 2004). Yet despite such expected intrinsic challenges, populations of many animal and plant species are known to have persisted over long evolutionary time in highly structured metapopulations, even including permanently inbred

systems with extremely low dispersal rates and hence very little gene flow among local populations (Stebbins 1957; Avilés and Purcell 2012; Busch and Delph 2017). The ongoing challenge is therefore to explain such long-term persistence of structured, inbred populations in the face of expected mutational meltdown (Lynch and Gabriel 1990; Lande 1994).

Here, the challenges, and hence the potential solutions, involve the dynamics of genetic load. In general, genetic load comprises three main components: drift load, defined as the reduction in fitness caused by deleterious mutations that are fixed in local populations (Crow and Kimura 1970; Whitlock 2002); mutation load, defined as the average reduction in fitness due to deleterious mutations at mutation-selection balance (Haldane 1937; Agrawal and Whitlock 2012); and inbreeding load, defined as the reduction in fitness caused by the expression of deleterious recessive alleles and loss of heterozygosity at overdominant loci due to inbreeding. Inbreeding depression is in turn defined as the decrease in fitness of inbred versus outbred individuals (Keller and Waller 2002; Vandewoestijne et al. 2008; Charlesworth and Willis 2009; Hedrick and Garcia-Dorado 2016). In particular, inbreeding depression and drift load can substantially increase extinction risk of small and isolated populations (Kimura et al. 1963; Lande 1994; Saccheri et al. 1998; Higgins and Lynch 2001; Nonaka et al. 2019). Extensive theoretical investigation has consequently aimed to understand if and how underlying mutations can be eradicated (i.e., purged; Bataillon and Kirkpatrick 2000; Glémin 2003; Glémin et al. 2003; Ronce et al. 2009; Lande and Porcher 2017).

Inbreeding depression and drift load are not fixed properties of populations but can evolve and are particularly influenced by N_e (Kondrashov 1985; Porcher and Lande 2016). In small populations, inbreeding increases homozygosity, exposing deleterious recessive mutations to selection and thereby decreasing inbreeding load (Agrawal and Whitlock 2012; Hedrick and Garcia-Dorado 2016). Yet, inbreeding also further reduces N_e and thereby reduces the efficacy of selection (Crow and Kimura 1970; Ewens 2004). This in turn increases the probability that deleterious mutations can drift to fixation, increasing drift load. In such situations, the balance between purging and fixation can readily shift toward fixation and, in principle, resulting mutation accumulation can dramatically decrease fitness and population size (Hedrick 1994; Wang et al. 1999; Crnokrak and Barrett 2002; Glémin 2003; Abu Awad and Billiard 2017; Caballero et al. 2017; Lande and Porcher 2017). Further, although population structure (i.e., subdivision into small local populations or demes) increases homozygosity and hence increases the efficacy of selection against deleterious recessive mutations (Whitlock 2002), strongly subdivided populations with little dispersal will be more affected by drift due to low N_e (Wright 1931; Crow and Kimura 1970; Glémin et al. 2003). Strong population structure can therefore lead to accumulation of higher drift load (Whitlock 2002; Glémin et al. 2003), increasing the extinction risk (Lande 1994). However, to date, there has been little explicit consideration of the degree to which extinction-recolonization dynamics, and variable dispersal and resulting gene flow, acting within highly structured systems can potentially prevent mutation accumulation and hence protect against mutational meltdown and metapopulation extinction.

Substantial previous work has considered the consequences of extinction-recolonization dynamics for patterns of neutral and, to some extent adaptive, genetic variation (Wright 1931; Wade and McCauley 1988; McCauley 1991; Hastings and Harrison 1994; Harrison and Hastings 1996; Pannell and Charlesworth 2000; Whitlock 2004), and for evolution of some life-history traits such as dispersal (Olivieri et al. 1990, 1995; Leimar and Norberg 1997; Olivieri and Gouyon 1997; Travis and Dytham 1998; Gandon and Michalakis 1999). Such dynamics could also be hypothesized to protect highly structured metapopulations against inevitable extinction due to large genetic loads (Fig. 1). Specifically, if dispersal and hence gene flow is initially restricted, local populations will be demographically and genetically largely independent (Olivieri et al. 1990). Different local populations will then accumulate different mutations and genetic loads, and hence experience different levels of extinction risk purely because of genetic stochasticity (Fig. 1[I]; Hanski 1998). Resulting genetically driven extinctions of local populations with higher load (i.e., local mutational meltdowns) could then facilitate overall reduction of mutation load at the metapopulation level (Fig. 1[II]). Following such genetically driven local extinctions, recolonization of empty space by dispersers originating from surviving local populations with lower load (Fig. 1[III]) could then allow demographic recovery of the whole metapopulation with reduced load, and thereby increase system persistence time (Fig. 1[IV]). This overall hypothesis (Fig. 1) implies that intertwined dynamics of genetic load, dispersal, and resulting local extinctions and recolonizations acting over long evolutionary timeframes in highly structured metapopulation systems could provide one route by which such systems can avoid, or delay, extinction in nature. Such outcomes would be manifested through substantial fluctuations in overall metapopulation size (i.e., severe decreases in numbers of individuals followed by recovery), with underlying transient dynamics of genetic load and dispersal (Fig. 1).

Indeed dispersal, defined as any individual movement potentially leading to spatial gene flow (Ronce 2007), comprises one fundamental property of any dynamic metapopulation system. Previous studies have shown that dispersal can rapidly evolve in response to multiple drivers (Bowler and Benton 2005; Clobert et al. 2012) including kin competition (Comins et al. 1980), environmental stochasticity (Hanski and Gilpin 1997), and inbreeding

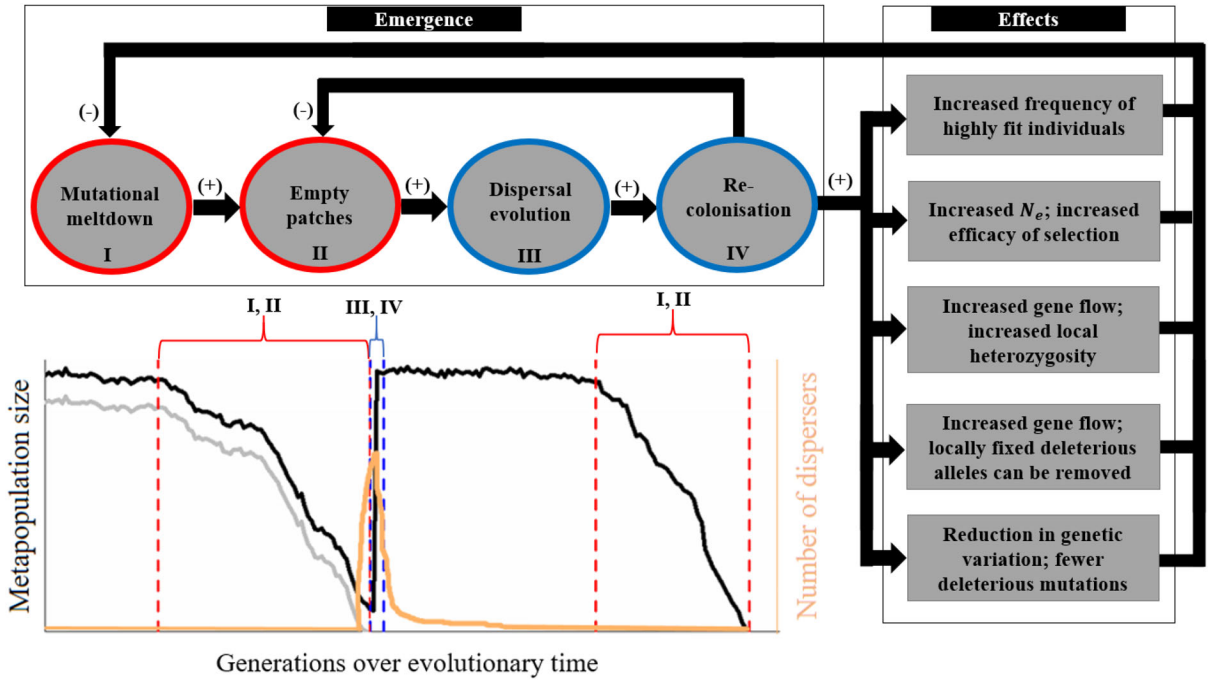

Figure 1. Schematic representation of the hypothesized mechanism by which metapopulation persistence through evolutionary time can be increased. Accumulation of genetic load can result in a mutational meltdown that makes local populations go extinct (I), resulting in empty patches (II). As a result, selection can favor evolution of increased dispersal (III), allowing empty patches to be recolonized relatively rapidly, resulting in metapopulation recovery (IV). Metapopulation size is illustrated for hypothetical cases where (black) metapopulation persistence time is increased through events I-IV by a substantial fluctuation in metapopulation size, and (gray) where the metapopulation instead directly goes extinct due to mutational meltdown (events I-II but not III-IV occur, meaning that there is no fluctuation in metapopulation size). The timeframe of the whole process may vary from hundreds to tens of thousands of generations depending on parameters such as population size and the rate at which deleterious mutations occur. The full process has several effects at the local population and metapopulation levels (right panel), which ultimately reduce the genetic load, thereby reducing the short-term risk of further mutational meltdowns and increasing metapopulation persistence time. Plus and minus symbols denote hypothesized increases and decreases, respectively. The number of hypothetical dispersing individuals through events I-IV is shown in orange.

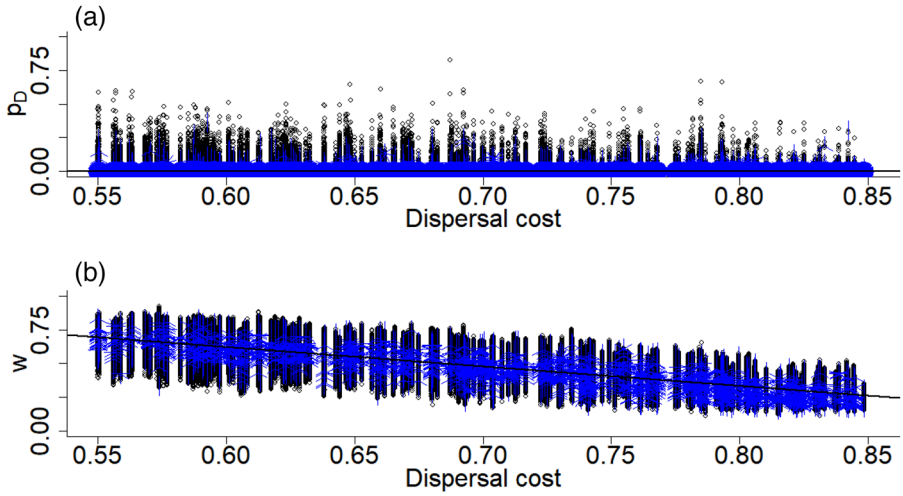

Figure 2. Distribution of (a) evolved individual dispersal probabilities p_D and (b) individual genetic fitness w before any fluctuations in metapopulation size. Results are presented after 20,000 generations, across 500 simulations with different dispersal costs ($0.55 \leq c_D \leq 0.85$). Each black point represents an individual. Blue sunflower plots depict densities of points. Black regression lines highlight that before any fluctuations, (a) selection favors $p_D \approx 0$ and (b) higher c_D is associated with lower w.

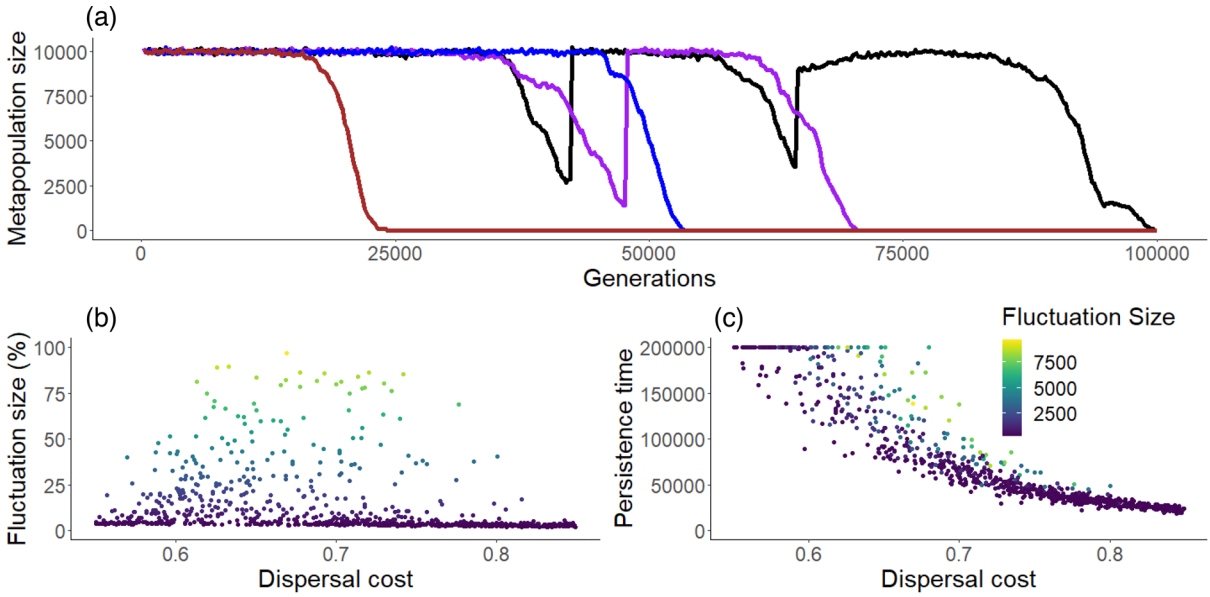

Figure 3. **Fluctuations in metapopulation size, and metapopulation persistence time. (a) Four individual simulations chosen to illustrate fluctuations (one fluctuation, purple; two fluctuations, black), or their absence (brown, blue), in metapopulation size across generations. (b) The maximum fluctuation size, expressed as the percentage of the initial metapopulation size, observed in each individual simulation as a function of dispersal cost. Each point represents one simulation (1000 in total). (c) Metapopulation persistence time, measured as the number of generations until metapopulation extinction, as a function of dispersal cost. In panels (b) and (c), colors represent the amplitude of the largest fluctuation in metapopulation size; each point represents one simulation (1000 in total).**

depression (Perrin and Mazalov 2000; Jaquiéry et al. 2009), but can be constrained by multiple costs that dispersing individuals may incur (Bonte et al. 2012). Further, although the level of dispersal shapes metapopulation structure, metapopulation structure can also feed back to affect dispersal evolution. This is because the availability of empty habitat patches due to local extinctions allows dispersing individuals to escape from negative density dependence acting in full habitat patches, and from local inbreeding, and therefore will influence the extent to which increased dispersal is favored by selection (Olivieri et al. 1990, 1995). Such interacting dynamics between local extinctions and dispersal evolution have been well studied for cases where local extinctions occur due to environmental and/or demographic stochasticity, where high dispersal probability is predicted to evolve (Slatkin 1977; Foley 1994; Pannell and Charlesworth 1999; Zheng et al. 2009; Travis et al. 2010). Here, frequent dispersal not only allows recolonization but also increases the overall N_e, thereby reducing accumulation of drift load (Whitlock 2002; Glémin 2003), and reducing the probability of extinction. However, when dispersal costs are high, and local extinctions occur because of intrinsic genetic stochasticity resulting from random variation in numbers and types of mutations arising in different local populations alongside inevitable demographic stochasticity, it is not yet clear whether interacting dynamics between local extinctions and dispersal could still emerge, or hence whether rapid dispersal evolution could prevent metapopulation extinction by mutational meltdown.

Accordingly, we test the overall hypothesis that intrinsic genetic stochasticity, dispersal evolution, and resulting metapopulation dynamics arising in highly structured metapopulation systems can jointly act to reduce system-wide genetic load, and thereby increase metapopulation persistence through long evolutionary time (Fig. 1). This encompasses the possibility that rapid dispersal evolution, following extinctions of local populations with higher genetic load that would create empty patches and cause strong selection for dispersal, can be a key mechanism that allows recolonization of the entire system from remnant local populations that have persisted due to lower genetic load, and thus temporarily rescue the whole metapopulation from extinction.

To fully capture the focal stochastic processes, we test our hypotheses by building and analyzing a spatially and genetically explicit individual-based model, where both genetic load and dispersal probability can evolve. We first examine whether substantial fluctuations in metapopulation size, which are one expected manifestation of our proposed mechanism (i.e., collapse and recovery; Fig. 1), can arise across a range of dispersal costs and are associated with increased metapopulation persistence time. Second, we examine whether transient dispersal evolution and changes in the magnitude and composition of the genetic

load occur and can be identified as underpinning mechanisms. Overall, we show that enhanced long-term persistence of highly structured metapopulations can in principle emerge due to combinations of genetic stochasticity and dispersal evolution and consider the circumstances under which such mechanisms can apply. We thereby highlight how explicitly linking key forms of genetic variation, life-history evolution, and population dynamic processes arising in highly structured metapopulation systems can facilitate understanding of system persistence.

Methods

Our hypothesis that genetic stochasticity and dispersal evolution can jointly act to increase metapopulation persistence time envisages strongly structured metapopulation systems where dispersal costs are high and local populations are typically isolated and consequently highly inbred. Accordingly, we model a metapopulation over a spatially explicit grid of 10×20 habitat patches. Each patch can be occupied by a local population with carrying capacity $K = 50$ individuals of a sexually reproducing, diploid species with nonoverlapping generations.

GENETIC ARCHITECTURE

Each individual's genome comprises two independent components of genetic architecture that, respectively, affect juvenile survival and determine the dispersal probability p_D. First, to model genetic effects on juvenile survival (i.e., the genetic load), each individual carries a genome comprising two homologous continuous chromosomes of length R (genome map length), on which deleterious mutations accumulate (Roze and Rousset 2009). The number of loci at which mutations can potentially occur is therefore effectively infinite (infinite site model). The number of new mutations for each newly born individual is drawn from a Poisson distribution $Pois(U_d)$, resulting in an average of U_d deleterious mutations/genome/generation. To make running a large number of simulations computationally tractable, a mutation rate of $U_d = 0.1$ deleterious mutations/genome/generation was chosen, which is on the mid to low side of typical empirical estimates (Mukai 1969; Mukai et al. 1972; Lynch et al. 1999; Haag-Liautard et al. 2007; Rutter et al. 2010; Zhu et al. 2014). To show that emerging system dynamics are not contingent on low mutations rates, we also examined a mutation rate an order of magnitude higher ($U_d = 1.0$) in an appropriate different parameter space and found qualitatively similar dynamics (Supporting Information; Figs. S1, S2).

Each deleterious mutation is characterized by its position on the chromosome, sampled from the continuous uniform distribution $U(0, R)$, a dominance coefficient (h), and a selection coefficient (s) that determines the mutational effect in the homozygous state. We model s as a random variable of the gamma distribution $\Gamma(1.0,\ \bar{s})$, where $\bar{s}$ denotes the mean selection coefficient ($\bar{s} = 0.05$; Schultz and Lynch 1997; Spigler et al. 2017). The dominance coefficient h of a mutation m depends on its selection coefficient s_m and is sampled from a continuous uniform distribution $U(0,\ e^{-k s_m})$. Here, k is defined as $-\ln(2\bar{h})/\bar{s}$, where $\bar{h}$ is the mean dominance coefficient ($\bar{h} = 0.3$). Such a relationship between dominance and selection coefficients of new mutations derives from current empirical estimates (Caballero and Keightley 1994; Lynch et al. 1999; Eyre-Walker and Keightley 2007; Haag-Liautard et al. 2007; Spigler et al. 2017). Mutational effects are multiplicative; the genetic fitness w of an individual (which affects juvenile survival) is therefore calculated as

$$w = \prod_{i=1}^{N\text{het}} (1 - s_i h_i) \prod_{j=1}^{N\text{hom}} (1 - s_j) \quad (1)$$

where N_{het} is the number of heterozygous mutations and N_{hom} the number of homozygous mutations. The number of recombination events per individual is sampled from a Poisson distribution $Pois(R)$ (meaning the recombination rate is proportional to the genome map length). The position of each new recombination site is sampled from the uniform distribution $U(0, R)$.

Second, to model genetic effects on dispersal probability, and hence allow dispersal evolution, individuals additionally carry 20 diploid loci with continuous allelic effects. The sum of the 40 allelic values determines the individual's probability of dispersing p_D. The dispersal phenotypic value is bounded such that if the sum of allelic values is less than zero, $p_D = 0$ or, if the sum of allelic values is bigger than one, $p_D = 1$ (i.e., $0 \leq p_D \leq 1$). For the dispersal loci, the number of recombination events/individual/generation is sampled from the Poisson distribution $Pois(0.1)$. Alleles experience a mutation probability of 0.001/haploid locus/generation; when a mutation occurs, a random normal deviate sampled from the normal distribution $N(0,\ 0.1/\sqrt{2 \cdot 20})$ is added to the allelic value. Mutational effect sizes are therefore very small, meaning p_D is unlikely to substantially exceed the biologically relevant bounds of 0 and 1.

LIFE CYCLE

At each generation, each adult female mates with one random adult male (sampled with replacement, allowing multiple matings per male) within her local population and produces a number of offspring sampled from the Poisson distribution $Pois(F)$ such that mean fecundity is $F = 12$ offspring. Offspring sex is randomly assigned (male and female being equally likely) such that the expected primary sex ratio is 1:1. After reproduction, all adults die and offspring survive to become adults with a probability given by the individual's genetic fitness w. Surviving offspring may disperse with genotype-dependent probability

p_D. If an individual disperses, the dispersal distance is given by $-2\ln(x),\ x \sim U(0, 1]$ giving a pattern of dispersal distances as a negative exponential distribution with a mean of 2 habitat patches, whereas the direction is sampled from the uniform distribution $U(0,\ 2\pi)$. The individual is then displaced from a random position (in continuous space) within the natal patch to the new location. If the new location falls outside the grid or within the natal patch, dispersal distance and direction are resampled until the individual effectively disperses to a new patch. The cost of dispersal is modeled such that a dispersing individual has a constant probability c_D of dying during dispersal. Relaxing the assumption that c_D is independent of distance would be unlikely to substantially alter current results given that most dispersal events relatively short distance on average and very infrequent, as appropriate for a highly viscous metapopulation. After dispersal, individuals in each population are subject to negative density-dependent survival. An individual's survival probability is min(K/N, 1), where N is the total number of individuals in the local population.

SIMULATION EXPERIMENTS

We ran simulations where we varied the cost of dispersal c_D to test if a range of costs exist under which fluctuations in metapopulation size and hence the extinction-recolonization dynamics that we hypothesised would emerge and facilitate a reduction of genetic load and thereby increase in metapopulation persistence over long evolutionary timeframes (Fig. 1). Of course, even relatively small changes in metapopulation size could cause some genetic variation to be lost. To assess the effect of all fluctuations, we extracted the largest decrease and subsequent increase in metapopulation size observed over any period of 1000 generations and defined this as a fluctuation. During a defined fluctuation, recovery to the original metapopulation size always happens relatively rapidly (Fig. 3a), thus the interval of 1000 generations was sufficient. Defining a fluctuation in terms of a timespan allowed us to investigate the effects of the full range of changes in the metapopulation size. We could thereby determine whether small changes in the metapopulation size, due to demographic stochasticity, and big changes in the metapopulation size due to extinction and recolonization had distinct effects on persistence time.

To determine the parameter space within which the hypothesized dynamics occur, we randomly sampled c_D from a uniform real distribution such that $c_D \sim U(0.55,\ 0.85)$ for each individual simulation run. This range was chosen as the biological space of interest because if c_D is too low, the metapopulation effectively becomes one big panmictic population without any structure such that high levels of inbreeding do not emerge. If c_D is too high, dispersal does not evolve at all, and recolonization is no longer possible. At the beginning of each simulation, all habitat patches were initialized with K individuals and sex ratio 1:1. Each initial individual had a genome with zero deleterious mutations and alleles at the dispersal loci were sampled from the normal distribution $N(0.05/(2 \cdot 20),\ 0.1/\sqrt{2 \cdot 20})$. We ran 1000 simulations, each over 200,000 generations. This long duration was chosen to give an appropriate evolutionary timeframe over which enough mutations occur to make mutational meltdown possible over the range of dispersal costs investigated. The model was implemented in C++ and the source code is available at https://github.com/r02ap19/InbredMetapops/tree/master.

To quantify the effects of fluctuations on the genetic load, we calculated changes in mean metapopulation genetic fitness w, and in the genetic load following a fluctuation. These properties were calculated by sampling all extant local populations at 200 generation intervals within 1000 generations before and 1000 generations after the fluctuation (i.e., a total of 10 samples per simulation). The difference in each metric, denoted with Δ, was then calculated as the mean of the last five samples (post-fluctuation) minus the mean of the first five samples (pre-fluctuation). Differences between means, rather than simply point estimates, were calculated to reduce sampling variance given the highly stochastic population trajectories. To assess the effects of fluctuations on genetic variation at the local population versus the whole metapopulation levels, we created two sets of individuals that did not take part in the life cycle and were just used for calculating mean homozygosity of deleterious mutations carried on the main modeled chromosomes. In the first set, individuals were created by mating each female to a randomly sampled male from another local population, thereby allowing to calculate mean homozygosity of deleterious mutations at the metapopulation level. In the second set, individuals were created by mating each female to a random male from the same local population, thereby allowing to calculate mean homozygosity of deleterious mutations at the local population level.

Results

With high dispersal cost ($0.55 \leq c_D \leq 0.85$), dispersal probability generally evolved to $p_D \approx 0$ (Fig. 2a), such that local populations within the metapopulation were effectively isolated from each other. This caused accumulation of deleterious mutations in the genome that reduced population mean w. Although the evolved dispersal probability was very low across the range of costs, slightly higher values of p_D evolved at lower costs. These slight differences were sufficient to create differences in the level of population isolation (i.e., in metapopulation structure) and in mean population genetic fitness, such that higher w was observed at lower dispersal costs (Fig. 2b).

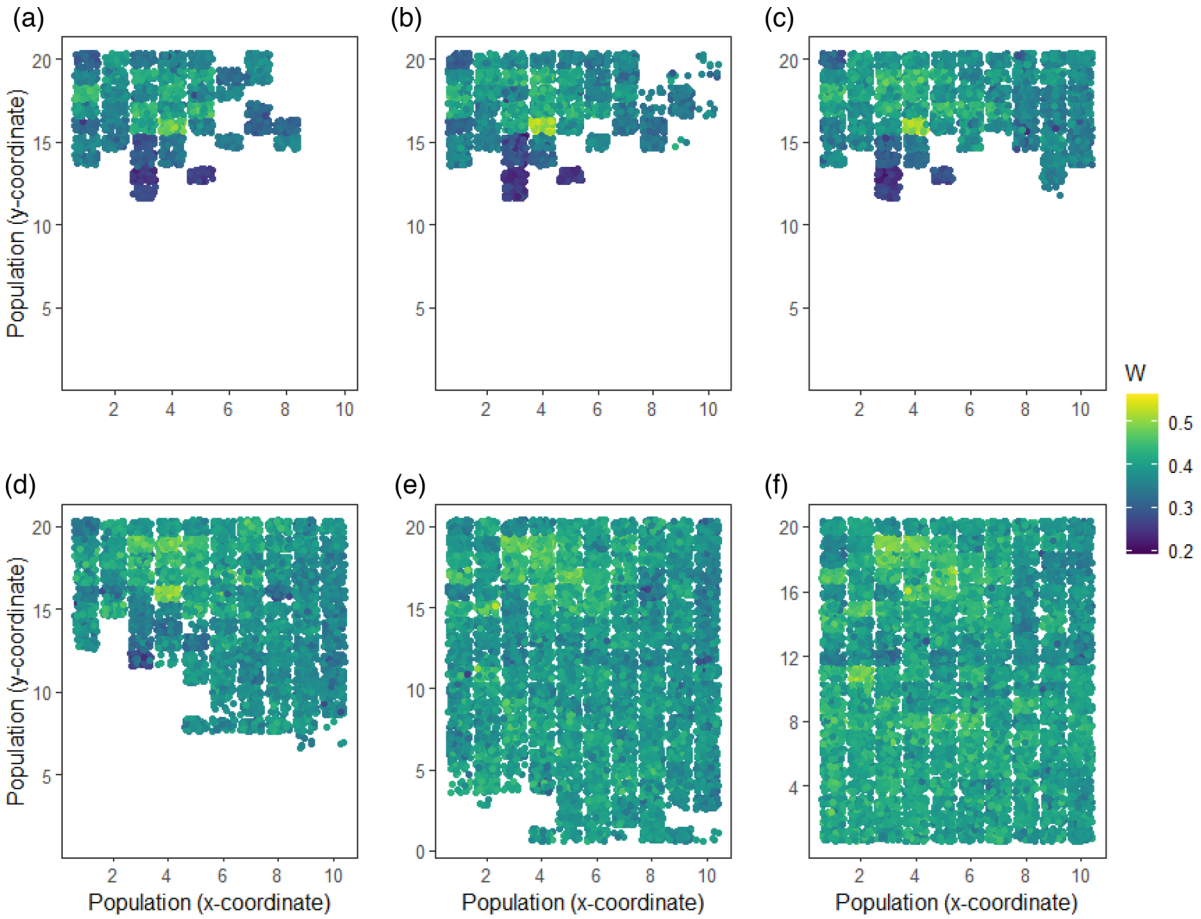

Figure 4. **Example snapshots of a typical single simulated metapopulation undergoing a substantial fluctuation in size through time, showing individual genetic fitness (*w*; colour scale). Each panel shows the entire metapopulation at time intervals of 25 generations (from a to f); each point indicates a single individual with emerging rectangles representing local populations. Starting from the point where most local populations have gone extinct, recolonization of empty patches quickly proceeds from the remnant local populations until the whole metapopulation is recolonized. Through this process, local populations with very low average fitness (dark blue dots in a-c) have disappeared. In this example, $c_D = 0.7$.**

In some simulations, the accumulation of deleterious mutations caused a mutational meltdown leading to metapopulation extinction before any large fluctuation occurred (Fig. 3). However, in a proportion of simulations (which depended on c_D; Fig. S3), substantial fluctuations in metapopulation size emerged (Fig. 3). In such cases, a steep decrease in size was followed by rapid recovery to approximately the original total of ~10,000 individuals (Fig. 3a). Fluctuations in metapopulation size varied in amplitude, with the largest representing a ~97% change in size (Fig. 3b,c). Such large fluctuations were primarily observed at intermediate values of c_D within the examined range; lower or higher c_D were associated with reduced fluctuation size and frequency (Fig. 3b). A proportion of simulations with low values of c_D persisted for the full 200,000 generations after which point the simulation was terminated (Fig. 3c). Although higher c_D led to overall shorter metapopulation persistence time, individual simulations in which larger fluctuations occurred were associated with a longer persistence time than otherwise similar simulations where no large fluctuation occurred (Fig. 3c).

Because fluctuations in metapopulation size result from stochastic events, the timings and magnitudes of such fluctuations differ greatly between simulations. Therefore, rather than analyzing the temporal dynamics of all simulations together, we first illustrate the underlying mechanisms that cause fluctuations and increase metapopulation persistence time (as hypothesized in Fig. 1) by showing details of one example simulation where such dynamics occurred (Figs. 4, 5). Here, due to genetic stochasticity, some local populations go extinct much earlier than others as they happen to accumulate higher genetic load, resulting in empty habitat patches in the landscape (Fig. 4a). Despite the high dispersal cost, increased dispersal probability is then temporarily favored by selection (Fig. 5). This is because offspring of dispersing individuals, which colonize empty or low-density patches, will benefit from higher survival compared to

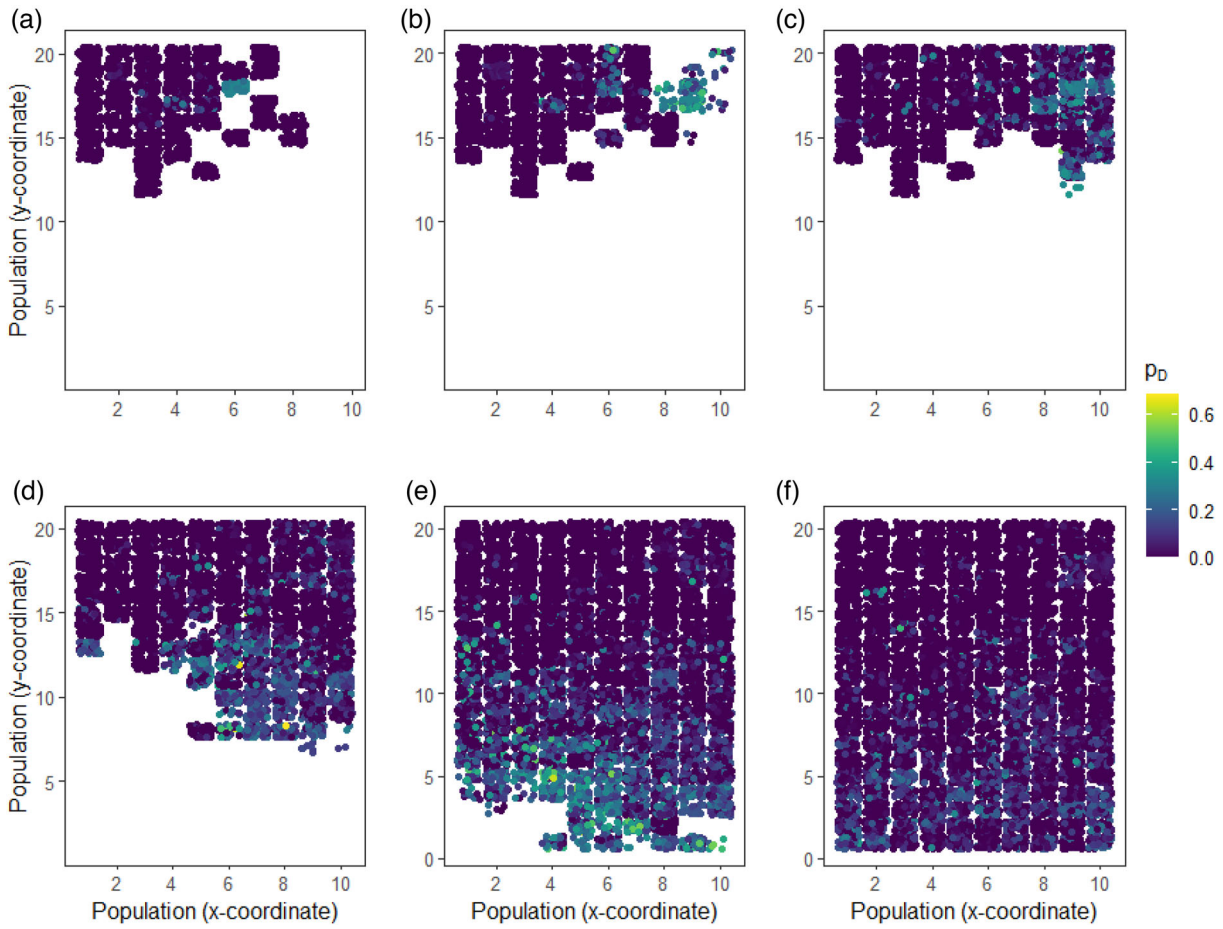

Figure 5. Snapshots of the same example metapopulation, at the same time points, as in Figure 4, showing individual dispersal phenotypic values (p_D; colour scale). Each panel shows the entire metapopulation at time intervals of 25 generations (from a to f); each point indicates a single individual with emerging rectangles representing local populations. Starting from the point where most local populations have gone extinct, recolonization of empty patches quickly proceeds from the remnant local populations until the whole metapopulation is recolonized. As empty patches appear in the metapopulation, individuals with higher p_D are favored. As the recolonization proceeds, dispersal probability quickly decreases in colonized patches. In this example, $c_D = 0.7$.

offspring of nondispersing individuals remaining in high-density patches.

Moreover, within a local population, genetically fitter individuals (i.e., high w) have their offspring production limited by density dependence to a larger extent than individuals with lower genetic fitness w (i.e., with higher genetic load), as they have proportionally more offspring surviving viability selection and thus going through density-dependent regulation. Thus, on average, because local populations with higher mean genetic load are most likely to have gone extinct, and because individuals with lower genetic load are most likely to benefit from dispersing into empty patches as their offspring are temporarily released from density dependence, new local populations are founded by relatively fitter individuals (Supporting Information S3). The mean genetic fitness at the metapopulation level consequently increases (Fig. 4). Because of the high fecundity, newly colonized patches quickly reach carrying capacity (Figs. 4b-f, 5b-f). Once all patches are recolonized, dispersal ceases to be sufficiently advantageous to compensate for the high cost, and selection quickly removes highly dispersive phenotypes from the population (Fig. 5).

This sequence of stochastic extinctions and selection for dispersal, which generates substantial fluctuations in metapopulation size, does not occur when c_D is either too low or too high (Fig. 3b). At low c_D, a higher mean dispersal probability evolves due to kin competition and inbreeding depression. Consequently, the metapopulation becomes more genetically homogenous and all local populations will go extinct at approximately the same. Conversely, when c_D is too high, even the presence of empty patches in the metapopulation is not enough to generate selection

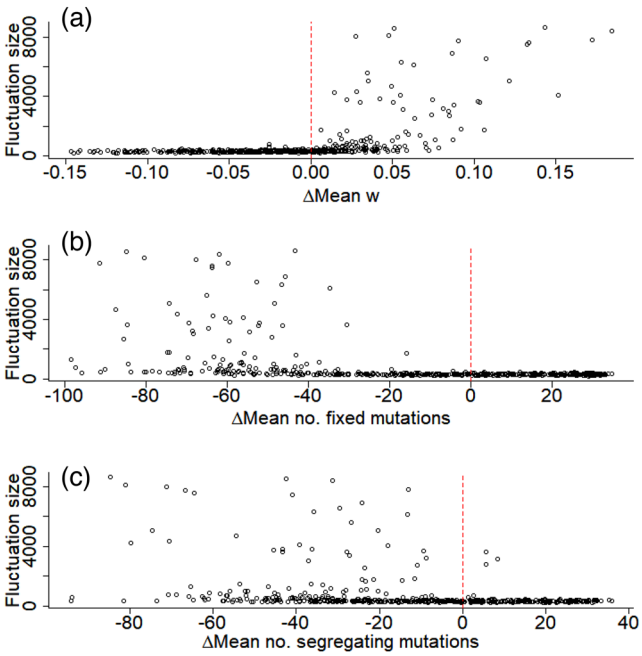

Figure 6. **Changes (Δ) in mean metapopulation genetic fitness *w*, and components of the genetic load, measured before and after a fluctuation event, as a function of the fluctuation size (change in total number of individuals in the metapopulation). (a) Change in mean metapopulation genetic fitness *w*; (b) change in mean number of fixed mutations of local populations (drift load), so that a negative difference corresponds to a decrease following the fluctuation; (c) change in mean number of segregating mutations local of populations (segregating load). Each point represents a single simulation (to make storage and analysis of output tractable, 500 simulations in total are shown). The red dashed line marks no change.**

for dispersal, thus effectively impeding evolution of dispersive phenotypes and recolonization, and leading to shorter metapopulation persistence time (Fig. 3c).

Fluctuations in metapopulation size led to an overall increase in mean genetic fitness w (Fig. 6a), translating into increased overall metapopulation persistence time (Fig. 3), with a positive association between fluctuation size and the increase in fitness and persistence time. This results from multiple mechanisms (Fig. 1). First, during the decrease in metapopulation size due to progressive extinction of local populations, many deleterious mutations are lost, resulting in lower genetic load in the metapopulation (Figs. 6b,c, 7). Second, the transient increase in p_D, and hence in gene flow among local populations, increases the N_e, which in turn increases the efficacy of selection. Very weakly deleterious mutations now become more efficiently removed, which contributes to decreasing the total number of mutations (Fig. 6). Third, in extant local populations, the increased mean p_D increases genetic variation as new alleles arrive from other, previously isolated populations (Fig. 7a). This decreases the drift load because locally fixed alleles are now exposed to selection, which can efficiently remove them (Fig. 6b). The increased gene flow also decreases the expression of deleterious recessive alleles as heterozygosity increases. Combined with fewer mutations, this increases the mean w of local populations (Fig. 6a).

Although the above processes led to an increase in local genetic variation (measured as a decrease in local homozygosity of deleterious mutations; Fig. 7a) following a substantial fluctuation in metapopulation size, overall, these dynamics led to metapopulations becoming increasingly genetically homogenous. This is shown by a large increase in homozygosity at the metapopulation level following a fluctuation in metapopulation size, and by the positive relationship between the size of the fluctuation and the increase in homozygosity of deleterious mutations in offspring derived from mating between individuals originating from different local populations (Fig. 7b).

Discussion

Understanding how systems of small and largely isolated local populations can persist through evolutionary time, despite the detrimental effects of accumulating deleterious mutations, is important because such systems occur naturally and are predicted to become more common due to anthropogenic habitat fragmentation. We show that persistence of highly structured and hence inbred metapopulations can be substantially prolonged due to episodes of local population extinctions driven by genetic stochasticity (i.e., differential accumulation of genetic load in each local population and therefore different times to local extinction), followed by recolonization made possible by transient evolution of increased dispersal. This combination of processes causes large fluctuations in metapopulation size, resulting in loss of a portion of current mutation and drift loads, and consequently an increase in mean genetic fitness. Overall, the combined effects of population structure, genetic stochasticity, and dispersal evolution generate an eco-evolutionary mechanism (Fig. 1) that we show can facilitate a reduction of the genetic load at the metapopulation level, and thereby postpone extinction.

THE ROLE OF STRONG POPULATION STRUCTURE

Our model assumes small local populations with a strong metapopulation structure and a constant high cost of dispersal. Inbreeding and stochastic spatially structured buildup of mutation and drift load and resulting asynchronous local population extinctions consequently emerge as properties of the model. Highly structured and inbred systems have arisen multiple times across the animal and plant kingdom (Avilés and Purcell 2012; Settepani et al. 2017). The most prominent and studied example is the frequent evolution of selfing mating systems in plants (Wright et al. 2013). Other examples include insects (e.g., thrips, socially

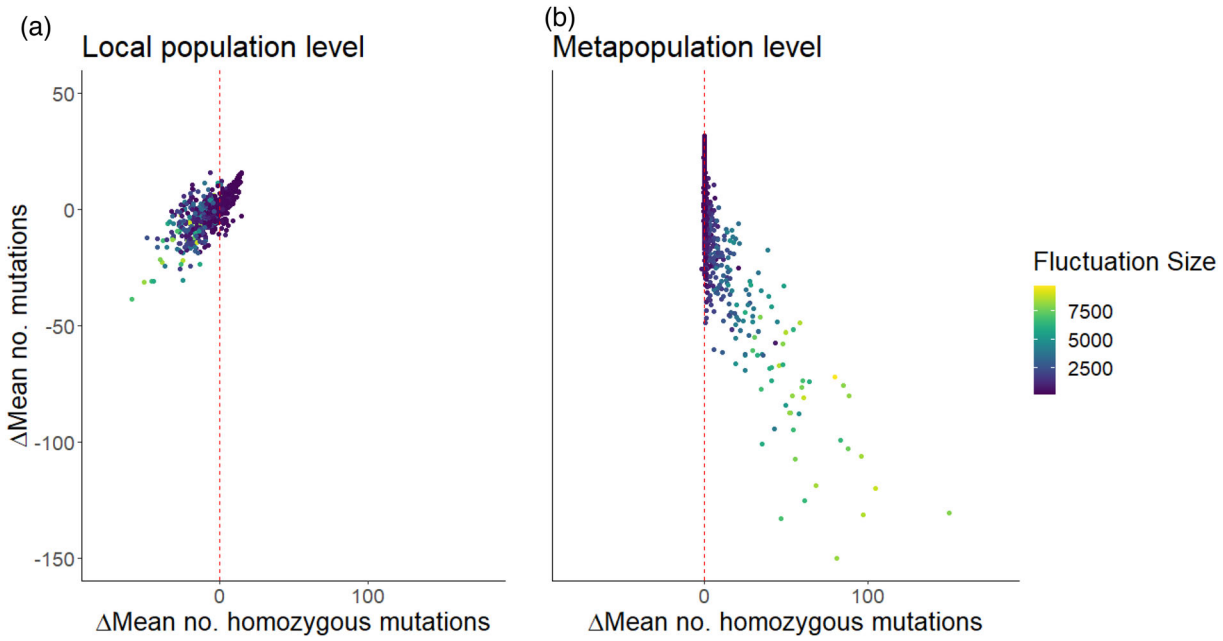

Figure 7. Changes (Δ) in the total number of deleterious mutations before and after a metapopulation fluctuation as a function of the change in the number of deleterious homozygous mutations, and of the size of the fluctuation (colour). Although a fluctuation generally decreases the amount of genetic variation in the metapopulation, a fluctuation will generally increase the level of genetic variation in extant local populations. Each point represents a single simulation, and 1000 simulations are shown. (a) Changes in individuals produced by parents from the same local population (within population random mating). (b) Changes in individuals produced by parents from different local populations (between local populations random mating). The red-dashed lines mark no change. Both panels are shown on the same *x*- and *y*-axis scale to facilitate comparison between the genetic changes at the local population versus the metapopulation level.

parasitic ants, and beetles; Buschinger 1989; Chapman et al. 2000; Domingue and Teale 2007), arachnids (e.g., spider mites and spiders; Bilde et al. 2005; Saito 2010), and even mammals (e.g., naked mole rat; Reeve et al. 1990). In some cases, such as the social spider *Stegodyphus dumicola*, systems of small and very highly inbred local populations are estimated to have persisted over millions of years (Settepani et al. 2016). Although the question of whether such systems are evolutionary "dead ends" is still open and largely debated (Stebbins 1957; Wright et al. 2013), their existence raises questions of how these species can persist despite the continuous action of genetic drift and accumulation of genetic load. The mechanism that we demonstrate may help answer such questions.

Interestingly, the observed inbreeding mating systems often occur in environments where costs of dispersal are very high (Henschel et al. 1995; Schneider et al. 2001). For example, in the social spider *S. dumicola*, high dispersal costs have been hypothesized to have caused complete loss of premating dispersal, driving the transition toward a chronically inbred system (Bilde et al. 2005). This species exists in highly structured metapopulations, where local populations (or family nests) frequently go extinct, and new patches are periodically colonized by single already-mated females (postmating dispersal). Although the causes of local population extinctions are not yet known and our model does not include postmating dispersal nor social behaviors or traits, the spider system dynamics share a lot of properties with our model, making our proposed mechanism a candidate for explaining the long-term persistence of this and similar systems. A testable prediction emerging from our proposed mechanism and model is that persisting systems are expected to have relatively recent (in evolutionary time) divergence among lineages. This is because metapopulations with extinct patches that are recolonized by descendants of a subset of individuals would show a more recent common ancestor. For example, a study that characterized the population genetic structure of *Stegodyphus sarasinorum*, a social spider distributed across the Indian subcontinent, found divergence times between lineages to be recent (in evolutionary time), with homogeneous genetic diversity across large distances, despite contemporary gene flow being extremely low or even absent (Settepani et al. 2014). This is consistent with the long-term extinction-recolonization dynamics and metapopulation homogenization over large geographical scales shown in our model (Settepani et al. 2014). Similar patterns have been found in other species (e.g., *Daphnia*; Walser and Haag 2012; Settepani et al. 2014), suggesting that this pattern may be found in different systems.

In our current model, density-dependent regulation within each local population affects offspring survival but not fecundity. Applying density dependence to fecundity would likely not change the qualitative dynamics; fewer offspring would be produced but a larger proportion would survive, thereby generating similar number of adults. However, different dynamics may result if density dependence (affecting survival or fecundity) was applied before selection. Selection would then act across fewer individuals, reducing efficacy and increasing accumulation of drift load, potentially leading to earlier extinction. Indeed, because it generally matters when during the life cycle selection is applied (Pincheira-Donoso and Hunt 2017), examining the effect of density dependence and selection acting on different stages of the life cycle would be an interesting future development.

The dynamics emerging from our model are likely to apply to inbred systems that have already gone through the hurdle of purging much of their inbreeding load. If high costs of dispersal were suddenly applied to a previously outbred system (i.e., due to sudden fragmentation that impedes dispersal) that had accumulated genetic load, including inbreeding load, the system would have the extra challenge of overcoming a sudden reduction in fitness due to expression of inbreeding depression. System extinction, rather than fluctuation and recovery (as in our current simulations), might then be more likely. How such inbreeding depression is purged, and how the processes that we describe could potentially facilitate system transition from outbreeding to inbreeding mating systems, remains an open and interesting question (Bilde et al. 2005; Wright et al. 2013).

THE ROLE OF TEMPORALLY VARIABLE GENE FLOW AND DISPERSAL EVOLUTION

Dispersal evolution is key to the dynamics that emerge in our simulations. The imposed high dispersal cost initially selects for extremely low dispersal probability, which in turn causes strong metapopulation structure, similar to what has been conceptualized as a "nonequilibrium" metapopulation (Harrison and Hastings 1996). Subsequent local extinctions and opening-up of empty habitat patches create selection for increased dispersal (Olivieri et al. 1995; Olivieri and Gouyon 1997), leading to recolonization and increasing metapopulation persistence time. This process of variable dispersal evolution stemming from contrasting forces of within- versus between-local population selection has previously been highlighted as potential mechanism rescuing metapopulation from extinction following habitat fragmentation or local extinctions due to environmental and/or demographic stochasticity (Leimar and Norberg 1997; Travis and Dytham 1999; Heino and Hanski 2001; Parvinen et al. 2003). Evolution of dispersal can thereby rescue metapopulations from what has been termed "evolutionary suicide" (Gyllenberg et al. 2002), where selection drives evolution of very low dispersal probability, although the whole metapopulation would persist for longer if individuals evolved higher dispersal probability. Here, we show that genetic stochasticity can also generate conditions under which high dispersal probability is temporarily favored, despite its high cost. Dispersal evolution can therefore also play a major role in facilitating a reduction of genetic load at the metapopulation level and thus increasing metapopulation persistence time.

With a model designed to study purging during range expansions, Marchini et al. (2016) found that inbreeding combined with periodic gene flow can lead to efficient purging of genetic load and accelerated rates of range expansions. Although the effect on purging through variable gene flow is similar to what we show, in Marchini et al. (2016)'s model, dispersal is not evolving. Rather, individuals are assumed to disperse and colonize empty patches every second generation, and only if exceeding an arbitrary fitness threshold of 0.9. Thus, only individuals with very high fitness disperse, and dispersal occurs at a somewhat fixed rate. In contrast, in our model, the dispersal rate and the fitness of successful dispersers are emergent properties of the selective environment emerging from periodic local extinctions due to genetic stochasticity and high costs of dispersal.

The existence of genetic variation in dispersal traits is essential for this mechanism to work, as selection cannot cause rapid evolution of increased dispersal unless dispersal propensity has at least some additive genetic or otherwise heritable component (Leimar and Norberg 1997). In general, there is evidence for heritable genetic variation affecting dispersal probability (Saastamoinen et al. 2018), which is to be expected because it is now clear that most dispersal traits are highly polygenic quantitative traits. Indeed, recent studies on invasive cane toads (*Rhinella marina*) in Australia show that increased dispersal in natural populations can quickly evolve (Rollins et al. 2015), and examples of heritable parental effects have also been shown in two-spotted spider mites (*Tetranychus urticae*) (Bitume et al. 2014). Although dispersal evolution is intrinsic to the dynamics emerging in our current model, similar dynamics could potentially emerge through plasticity in individual dispersal phenotypes, whereby individuals may disperse in response to some environmental or social cues indicating the availability of empty habitat patches. Such plasticity in dispersal has been documented across invertebrates, vertebrates, and plants (Arendt 2015). Most theoretical models that explicitly consider dispersal have modeled this trait without plasticity (Johnson and Gaines 1990; Payne et al. 2011) but some studies have modeled dispersal as being partially or entirely plastic (Arendt 2015; Marchini et al. 2016).

In our envisaged system, both the occurrence of metapopulation fluctuations and their impact on persistence times are likely to be affected by the model of dispersal. Wade and McCauley (1988) showed that assumptions regarding how exactly dispersal

takes place (e.g., who disperses to colonize new patches, and how many individuals disperse at once) affect the amount of neutral genetic variation segregating in the metapopulation and the extent to which local populations will differ genetically (Slatkin 1977; McCauley 1991). Specifically, they showed that if recolonization is enacted by many dispersing individuals coming from many different local populations, then extinction-recolonization dynamics will hinder genetic divergence of local populations. On the other hand, if recolonization occurs from dispersing individuals coming from a few source populations, extinction-recolonization dynamics will increase local genetic divergence. This is important for the resulting patterns of the genetic load at the local and metapopulation level (see below). In nature, whether individuals disperse is unlikely to be a result of either a genetically hard-wired phenotype or a plastic response determined solely by environmental cues. Rather, the dispersal behavior of individuals is likely to be a result of some combination of both (Roff 1999; Imbert and Ronce 2001; Clobert et al. 2012; Saastamoinen et al. 2018). Therefore, a next useful step would be to include the evolution of context-dependent dispersal, wherein individuals could also disperse in response to environmental cues, such as being able to disperse in response to high local densities. If this would affect the pattern of gene flow throughout the metapopulation, it would also likely affect the genetic effects of fluctuations on metapopulation composition and hence persistence time (Arendt 2015). Further work could consider the potential effects of sex-biased dispersal (Li and Kokko 2019) on genetic effects of fluctuations, which will likely depend on the mating system and hence whether sex-biased dispersal could result in mate finding Allee effects during recolonization. Given premating dispersal, sex-biased dispersal could reduce the probability of females and males arriving simultaneously to a new patch and thereby slow the rate of recolonization compared to our current model. In contrast, postmating female-biased dispersal (as occurs in *S. dumicola*; Schneider et al. 2001) could facilitate recolonization, which would simply require arrival of a single pregnant female, potentially facilitating the dynamics shown with our model.

THE GENETIC BASIS OF THE GENETIC LOAD

The specific architecture of the genetic load has the potential to influence the dynamics that emerge in our simulations. Another difference between our model and Marchini et al. (2016) is that they examined a limited range of selection coefficients for the deleterious mutations underlying genetic load and assumed complete recessivity of such mutations. This leaves open the question of whether purging would work assuming a distribution of selection and dominance coefficients similar to that emerging from empirical estimates (Crow and Temin 1964; Mukai et al. 1972; Simmons and Crow 1977; Caballero and Keightley 1994).

Further complexity could also be added to our currently assumed distribution of mutational effects. Our current model only considers deleterious mutations. Thus, no mutations are beneficial, and back mutations never occur, which is unlikely to hold for natural populations (Eyre-Walker and Keightley 2007; Allen Orr 2010; Loewe and Hill 2010). As a result, our simulated metapopulations inevitably go extinct at some point, and continuous cycles of decreases in genetic load through fluctuations and bottlenecks are not possible. In simulations where fluctuations occurred, we most often observed one and sometimes two to three fluctuations before extinction. If beneficial and/or back mutations were included, perpetual cycles of escapes from mutational meltdowns through fluctuations could potentially occur. Consequently, a more advanced model of mutational effects might reveal the mechanism we describe to have an even stronger buffering effect on the persistence time of real metapopulations than our current results indicate. Increasing the number of patches in the modeled metapopulation would likely increase the probability of observing fluctuations. With many patches, the probability of at least one patch experiencing the right conditions for dispersal evolution (i.e., a patch of surrounded by empty patches) will increase. Thus, the buffering mechanism we describe may be increasingly relevant for highly structured metapopulations with numerous patches.

Although experimental evidence indicates that a fraction of mutations is lethal or very strongly deleterious (Eyre-Walker 2002; Sanjuán et al. 2004; Eyre-Walker et al. 2006), our model does not explicitly include any lethal mutations but a distribution of mutational effects that will most often give rise to weakly or moderately deleterious alleles. Explicitly adding a class of recessive lethal mutations to the model would necessarily increase selection for dispersal, which could also make fluctuations more likely to occur. The presence of local adaptation across a heterogeneous environment could further shape outcomes. Increased dispersal following local extinctions might then be less beneficial for metapopulation persistence time because maladaptation of colonizers may hinder successful recolonization, and/or subsequent recombination could break locally adapted haplotypes and therefore further reduce fitness in remnant populations (e.g., Andrade-Restrepo et al. 2019). The net effect of local adaptation on metapopulation rescue might then depend on the balance between the degree of maladaptation (or strength of local adaptation) and the magnitude of genetic load that is unconditional on the local environment.

LOCAL INCREASE IN HETEROZYGOSITY VERSUS GENETIC HOMOGENIZATION OF THE METAPOPULATION

Substantial fluctuations in metapopulation size are associated with a decrease in genetic load partly because they facilitate a

local increase in heterozygosity due to increased dispersal, and hence increase gene flow between local populations that were previously almost completely isolated. This results in a genetic "rescue effect" (Brown and Kodric-brown 1977), by which extant local populations are saved from mutational meltdown by alleles arriving via immigrants from other local populations. Interestingly, our results also highlight that the heterozygosity of local populations can increase despite the size of the metapopulation going through a large decrease, equivalent to a bottleneck event. The local increase in heterozygosity is important, because when population structure is strong, selection will operate at the local population level, rather than the metapopulation level (Glémin et al. 2003). As the efficacy of selection is dependent on both the level of genetic variation and the effective population size (Crow and Kimura 1970), and the influx of immigrant into local populations will increase both of these, the net result is a decreased risk of mutational meltdown.

Although following a major fluctuation in metapopulation size heterozygosity increases within extant and newly established local populations, at the metapopulation level heterozygosity decreases. This increase in homozygosity at the metapopulation level can be compared to what Gilpin (1991) called the coalescence of the metapopulation (Pannell and Charlesworth 2000). Although a fluctuation does not represent a true coalescent event (i.e., the whole metapopulation is not necessarily re-founded by a single individual during a fluctuation), much of the metapopulation will share a very recent common ancestor. When considered together with the well-known fact that a bottleneck reduces genetic diversity (Nei et al. 1975; Harrison and Hastings 1996), this explains why a large fluctuation in metapopulation size is correlated with a large increase in the between-population homozygosity, measured as the homozygosity of deleterious mutations in offspring produced by parents from different local populations. This effect had already been shown for neutral genetic variation (Slatkin 1977; Wade and McCauley 1988), and here we show it applies also to the genetic load. Our results therefore illustrate how the extremely low levels of genetic diversity observed in systems such as *S. dumicola* (Johannesen et al. 2007; Leffler et al. 2012; Settepani et al. 2016, 2017) may result from metapopulation dynamics characterized by local extinctions followed by rapid recolonization events (Settepani et al. 2014), such that most of the metapopulation shares a quite recent coalescent event.

Conclusion

Overall, we have shown an eco-evolutionary mechanism that can facilitate reduction of the genetic load at the metapopulation level, through the action of extinction-recolonization dynamics, dispersal evolution, and the effects of drift and selection (Fig. 1). This mechanism has potential to explain the persistence through evolutionary time of highly structured metapopulations, or even of species with inbreeding mating systems (Avilés and Purcell 2012). Future developments could assess the robustness of our proposed mechanisms to the genetic architecture of the load, to different modes of dispersal including evolutionary versus plastic responses, to different life histories, and, importantly, to rapidly changing environments and consequent adaptations (or lack thereof due to genetic homogenization at the metapopulation level). Our model yields the testable prediction that inbred and structured populations maintained by the mechanism we propose are expected to show recent divergence time among lineages despite extremely low contemporary dispersal rates among local populations. This has already been found for some inbred and structed metapopulations (e.g., Settepani et al. 2014) suggesting the mechanism we describe may be highly relevant in natural populations.

AUTHOR CONTRIBUTIONS

All authors conceived the study. GB developed the model. APC conducted simulations, analyses, and data visualization and wrote this article with substantial input from GB, JMR, and TB.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA ARCHIVING

The model is implemented in C++ and the full source code is available at [https://github.com/r02ap19/InbredMetapops/tree/master]. Summary data for plots are available at https://doi.org/10.5061/dryad.hhmgqnkk5.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

S1. The effect of fluctuations on persistence time in different parameter space
S2. Proportion of simulations where a fluctuation was observed
S3. Joint selection for high fitness and high dispersal probability