Fragmentation helps evolutionary rescue in highly connected habitats

Matteo Tomasini[1, 2, 3, 4, *] and Stephan Peischl[1, 3, †]

[1]Interfaculty Bioinformatics Unit, University of Bern, 3012 Bern, Switzerland

[2]Computational and Molecular Population Genetics Laboratory, Institute of Ecology and Evolution, University of Bern, 3012 Bern, Switzerland

[3]Swiss Institute for Bioinformatics, 1015 Lausanne, Switzerland

[4]Department of Integrative Biology, Michigan State University, East Lansing, MI 48824, USA

[*]Current affiliation: Michigan State University

[†]Corresponding author: stephan.peischl@bioinformatics.unibe.ch

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Abstract

Genetic variation and population sizes are critical factors for successful adaptation to novel environmental conditions. Gene flow between sub-populations is a potent mechanism to provide such variation and can hence facilitate adaption, for instance by increasing genetic variation or via adaptive introgression. On the other hand, if gene flow between different habitats is too strong, locally beneficial alleles may not be able to establish permanently. In the context of evolutionary rescue, intermediate levels of gene flow are therefore often optimal for maximizing a species chance for survival in meta-populations without spatial structure. To which extent and under which conditions gene flow facilitates or hinders evolutionary rescue in spatially structured populations remains unresolved. We

address this question and show that detrimental effects of gene flow can become negligible in spatially structured populations subject to a gradual deterioration of environmental conditions. If the number of sub-populations is sufficiently large, we find a positive relationship between the amount of gene flow and the survival chance of the population. A counter-intuitive conclusion is that increased fragmentation can facilitate species survival in the face of severe environmental change if migration is common but limited to neighboring sub-populations.

Introduction

Recent environmental or climatic changes have severe consequences on the survival of many species [Thomas et al., 2004]. Rapid and severe environmental change might cause extinction of resident populations due to genetic maladaptation to the new environmental conditions [Cahill et al., 2013]. A population may survive such environmental change if it adapts quickly enough via standing genetic variation or *de novo* mutations, a process that has been coined evolutionary rescue [Gomulkiewicz and Holt, 1995, Alexander et al., 2014, Carlson et al., 2014]. Theoretical studies of the mechanisms that can facilitate or hinder survival of populations experiencing environmental change can provide critical insights in the context of adaption and survival in the face of global climatic change, but also in medically relevant scenarios such as the evolution of antibiotic or other treatment resistance (*e.g.* Alexander et al. [2014], Carlson et al. [2014]).

It has been demonstrated theoretically as well as experimentally that evolutionary rescue in single, isolated populations depends strongly on two factors: initial population size and standing genetic variation [Lynch, 1993, Bell and Gonzalez, 2009, Samani and Bell, 2010, Bell and Gonzalez, 2011, Bell, 2013, Ramsayer et al., 2013, Carlson et al., 2014]. Large population sizes increase the chances that a mutation that ultimately rescues a population has higher chances to arise and establish before the population goes extinct [Lynch, 1993, Gomulkiewicz and Holt, 1995, Bell, 2013]. Similarly, initially high standing genetic variation increases the chance that a mutation that can save the population may already be present in the population [Gomulkiewicz and Holt, 1995, Barrett and Schluter, 2008, Vander Wal et al., 2013].

Evolutionary rescue has been thoroughly studied in idealized laboratory conditions and key theoretical predictions have been confirmed [Carlson et al., 2014]. However, these idealized laboratory conditions

are unlikely to reflect the spatio-temporal demographics of natural populations or the intricate spatial and population structure within and across human bodies during the evolution of antibiotic or treatment resistance [Bell, 2017]. For instance, in the face of structured populations it has been demonstrated both experimentally [Bell and Gonzalez, 2009, 2011, Gonzalez and Bell, 2013] and theoretically [Uecker et al., 2013] that gene flow between sub-populations can facilitate evolutionary rescue. In a two-deme model, the conditions for when this should occur have recently been derived in Tomasini and Peischl [2020]. A critical assumption of the modelling attempts in Uecker et al. [2013] and Tomasini and Peischl [2020] is that gene flow occurs at the same rate between any pair of demes. Experimental work suggests, however, that the spatial organizations of sub-populations modulates the effect of gene flow [Bell and Gonzalez, 2011, Gonzalez and Bell, 2013] and it remains unclear how spatial structure might change our understanding of the role of gene flow during adaptation to severe environmental change.

To address the role of gene flow for evolutionary rescue in spatially extended populations, we perform extensive simulations of evolutionary rescue when environments deteriorate gradually across space. We compare the effects of long-range migration (*i.e.* the island model [Wright, 1943], where migrants are exchanged among all demes at equal rates) and short-range migration (*i.e.* the stepping stone model [Kimura and Weiss, 1964], where migrants move only between neighboring demes) on the probability for evolutionary rescue. We find that short- and long-range dispersal can both have a beneficial effect on evolutionary rescue, but also find qualitative differences between the two scenarios. Our main result is that the probability for evolutionary rescue increases monotonically with migration rate if migration is local and the number of demes is large. This is contrasted by the island model, where too much gene flow prevents rescue via swamping of rescue mutations independently of the number of demes in the model. These findings suggest that evolutionary rescue in natural populations might be most likely in spatially extended populations composed of many small sub-populations with substantial, yet locally restricted, gene flow.

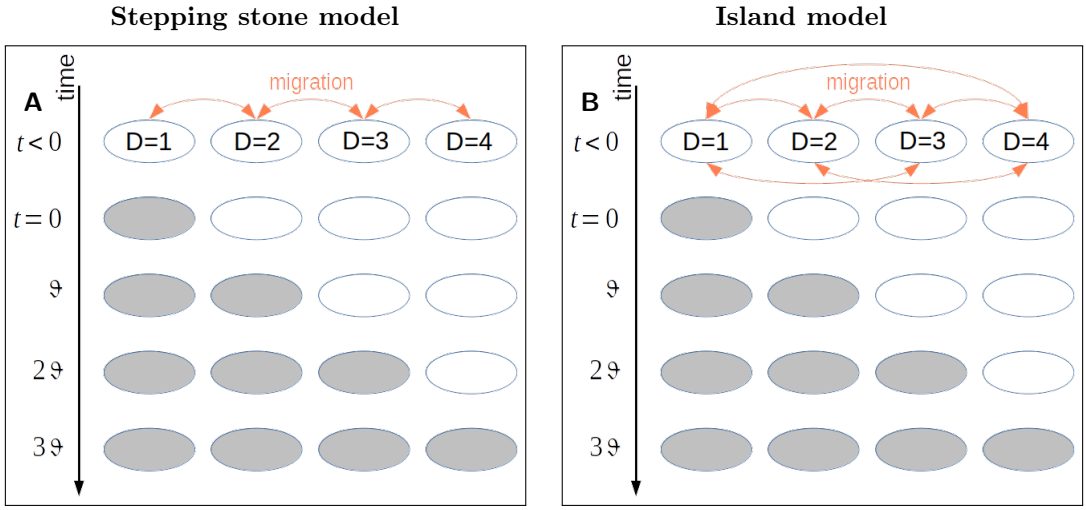

Figure 1: In panel A, a schematic of the stepping stone model (local migration), in panel B a schematic of the island model (global migration). Schematic for $D = 4$.

Methods

Model

We consider a structured population consisting of D demes organized along a one-dimensional lattice (see figure 1). Demes are labeled $i = 1, \dots, D$ and are filled with haploid wild-type individuals with discrete and non-overlapping generations. Each deme can be in one of two environmental states: the original unperturbed state (or "old" state) and the deteriorated state (or "new" state). In our model, initially the whole habitat is at demographic equilibrium in the original environment. Every θ generations the leftmost deme in the unperturbed state switches to the deteriorated state such that the whole habitat gradually deteriorates at a constant rate of one deme each θ generations. In the deteriorated part of the environment, growth rates of wild-type individuals are negative but beneficial mutation can arise and save the population from extinction by restoring positive growth rates.

Population size in deme i at time t is denoted $N_i(t)$ ($i \in \{1, \dots, D\}$, $t = 0, 1, 2, \dots$). In the original environment, density regulation is implemented such that all demes are at carrying capacity, κ, at the end of each generation. This model of instantaneous growth or culling is a good approximation to logistic density regulation if growth rates are sufficiently large relative to migration rates [Beverton and Holt, 1957, Tomasini and Peischl, 2020]. Initially all demes are at carrying capacity such that $N_i(0) = \kappa$, $\forall i$. We define the total carrying capacity of the habitat as $K_{\text{tot}} = D\kappa$. Individuals migrate to a different

deme with probability m (forward migration). We consider two modes of migration: (i) global migration, allowing an individual to migrate to any deme in the habitat (the island model, Wright [1943]), and (ii) local migration, that allows an individual to migrate only to neighboring demes (the stepping stone model, Kimura and Weiss [1964]). The boundaries of the habitat (to the left of the first deme and to the right of the last deme) are reflecting, that is, individuals cannot leave the habitat.

Fitness is determined by a single locus with two alleles: a wild-type allele and a mutant allele. We assume that each individual has Poisson-distributed offspring with the mean proportional to its fitness. In the original environment, relative fitness of wild-type individuals is set to $w_{\mathrm{wt}}^{(o)} = 1$ and the fitness of a mutant is $w_{\mathrm{m}}^{(o)} = 1 - s$, where $s > 0$ is the selection coefficient against the mutant. Mutations are therefore counter-selected in the original habitat. Absolute fitness in the original habitat is then given by $w_l^{(o)}\kappa/N_i'(t)$ ($l \in \{\mathrm{wt}, \mathrm{m}\}$), where $N_i'(t)$ is the population size after selection and migration but before density regulation. Mutations occur at rate u per generation and we ignore back mutations. Modifying the mutation rate modifies the total probability of rescue proportionally across the whole range of parameters that we study here: hence, for the rest of this work, we set $u = 1/K_{\mathrm{tot}}$ such that on average a single mutation occurs per generation in the whole habitat.

At a time $t = 0$, the first (*i.e.* leftmost) deme ($i = 1$) switches its environmental state to the deteriorated environment. In a deteriorated deme, wild-type individuals have an absolute fitness of $w_{\mathrm{wt}}^{(n)} = 1 - r$, with $r > 0$, and the resident population starts to decline. In the new environment, the mutant has an absolute fitness $w_{\mathrm{m}}^{(n)} = 1 + z$, with $z > 0$. At time $t = \theta$, deme $i = 2$ (at that point the leftmost deme in the old state) deteriorates, at $t = 2\theta$ the third deme, and so on until the whole habitat is deteriorated. We call the period between two subsequent deterioration events an epoch and θ is the length of an epoch. The deterioration of the whole habitat takes $\Theta = (D - 1)\theta$ generations (see table 1 for a full list of all parameters of the model).

Simulations

We performed population based simulations. Unless the rescue mutation is lethal in the original environment, the initial number of mutants in deme i, $N_i^{(\mathrm{m})}$, is given by mutation-selection equilibrium such that their relative frequency in the population is $f_0 = u/s$ [Gillespie, 2004], and the wild-type population

size in deme i is $N_i^{(\mathrm{wt})} = \kappa - N_i^{(\mathrm{m})}$. The mutation-selection equilibrium may not be suited for individuals with low mutation rate, as it ignores drift (*e.g.* see Hermisson and Pennings [2005]), but we use it only for comparison and our results hold in general for any f_0. At each generation, the populations of mutants (if existing) and wild types in each deme reproduce. We implement reproduction and selection by sampling from a Poisson distribution with the mean of the distribution given by the absolute fitness of wild-type and mutant individuals. After reproduction, we implement mutation as a binomial process with sampling probability $\pi = u$. In the island model, the total number of migrants is determined in each deme with a binomial process with sampling probability $\pi = m$, then the whole pool of migrants is re-distributed over all demes with a multinomial distribution. For the stepping stone model implementation, individuals migrating to the right and individuals migrating to the left are picked as a binomial process with probability $\pi = m/2$. After the whole habitat is deteriorated, we let the system evolve for 500 more generations. The expected extinction time in the absence of evolutionary rescue is much shorter than this burn-off. We consider the population rescued if the mutant population reaches $K_{\mathrm{tot}}/2$. We performed 1000 replicates for each parameter combination. Simulations were performed in Python.

Table 1: **List and description of all parameters**

Parameter	**Description**
D	Number of demes
$N_i(t)$	Number of individuals in deme i
κ	Carrying capacity per deme
$K_{\mathrm{tot}} = \kappa \cdot D$	Total carrying capacity of the habitat
m	Rate of migration per individual
$w_{\mathrm{wt}}^{(o)} = 1$	Fitness of a wild-type individual in the old environment
$w_{\mathrm{wt}}^{(n)} = 1 - r$	Fitness of a wild-type individual in the new environment
$w_{\mathrm{m}}^{(o)} = 1 - s$	Fitness of a mutant individual in the old environment
$w_{\mathrm{m}}^{(n)} = 1 + z$	Fitness of a mutant individual in the new environment
$0 < s \leq 1$	Disadvantage against a mutant copy in the old environment
$0 < z \ll 1$	Advantage of a mutant copy in the new environment
$0 < r < 1$	Stress against the wild-type population in the new environment
θ	Speed of deterioration of the environment, length of an epoch
$\Theta = \theta(D-1)$	Deterioration time of the whole habitat
$u = 1/K_{\mathrm{tot}}$	Mutation rate (wild type to mutant)
$f_0 = u/s$	Initial mutant frequency

Results

Figure 2 illustrates the probability for evolutionary rescue as a function of the migration rate as well as other parameters of the model. In all models a proportion m of all individuals migrates between demes. In the stepping stone model migrants move to one of the two neighboring demes, whereas in the island model all migrants are pooled and then distributed uniformly across all demes. Figures 2 A, C and E extend previous findings for a two-deme model and an island model [Uecker et al., 2013, Tomasini and Peischl, 2020] and show that intermediate migration rates are optimal whenever environmental change is sufficiently slow (large theta), environmental stress is strong (large r) or the fitness cost in the original habitat is low (small s). In contrast, Figures 2 B, D and F show that large migration rates tend to maximize the probability for rescue in the stepping stone model. Figure 2 H and I show illustrative examples that correspond to scenarios where environmental change is harsh enough so that extinction is a likely outcome in the absence of gene flow (high r) and change occurs gradually across demes (high θ). In these figures we also see that the maximum values for the probability of rescue can be significantly larger in the stepping stone model as compared to the island model.

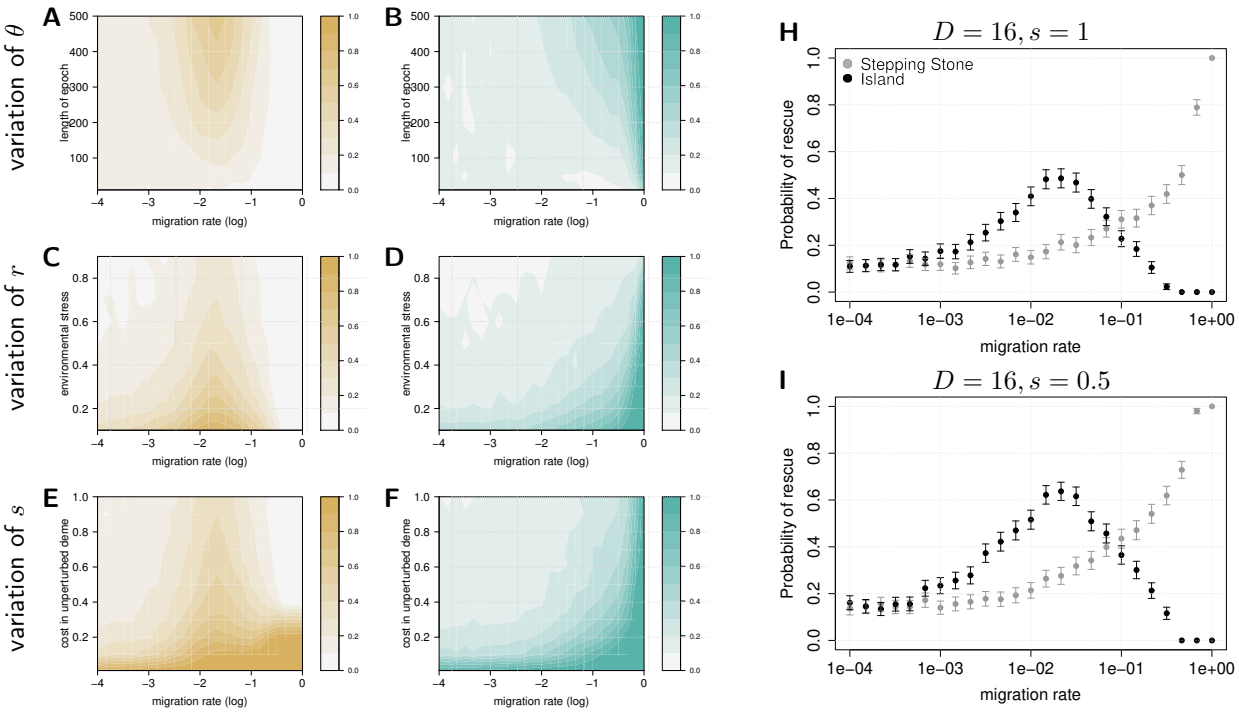

Figure 2: (A – F): contour plots of (A, C, E) the probability of rescue for the island model and (B, D, F) the probability of rescue for the stepping stone model as a function of the migration rate m. The three rows correspond to variation of different parameters: (A-B) the length of an epoch θ, (C-D) the harshness of environmental change r, (E-F) the cost s of the mutation in the unperturbed environment. Other parameters are $D = 16$, $z = 0.02$, and when not varying, $\theta = 200$, $r = 0.5$ and $s = 1$. (H-I) Comparison between stepping stone and island model. We show the probability of rescue as a function of migration rate for (H) $D = 16$, $s = 1.0$, (I) $D = 16$, $s = 0.5$. Other parameters: $r = 0.5$, $z = 0.02$, and $\Theta = 4800$.

In the island model, intermediate migration rates maximize the chances of survival due to two contrasting effects of migration [Uecker et al., 2013, Tomasini and Peischl, 2020]. On the one hand, increasing the migration rate m slows down extinction of demes with declining population size and hence increases chances for rescue [Uecker et al., 2013]. On the other hand, if migration rates are too high, rescue mutations are unlikely to establish because they are outcompeted in the original environment [Tomasini and Peischl, 2018] (i.e., gene swamping occurs [Bulmer, 1972, Lenormand, 2002]). The conditions for when intermediate migration rates increase the probability of rescue in a two-deme model can be found in Tomasini and Peischl [2020]. Uecker et al. [2013] showed that the number of demes has a negligible impact on the probability of rescue in an island model (see also figure S5B), hence we expect that the conditions derived in Tomasini and Peischl [2020] should also hold in the multi-deme island model. The stepping stone model shows a very different relationship between the probability for evolutionary rescue and the migration rate. In particular, we find that the chance for evolutionary rescue (i) is monotonically

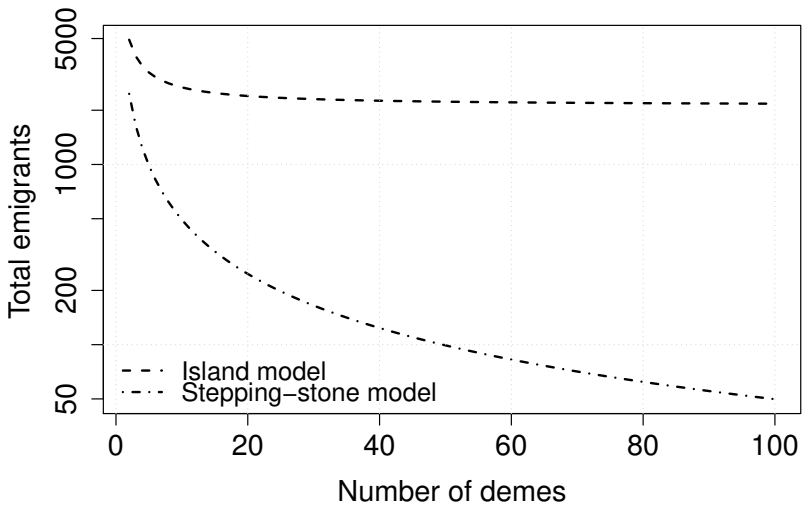

Figure 3: Total number of emigrants from the deteriorated to the non-deteriorated deme per generation, as a function of the number of demes. We keep the total population and the time to deteriorate the whole habitat constant, $K_{\text{tot}} = 20000$ and $\Theta = (D-1)\theta = 4800$. Other parameters are $r = 0.5$ and $m = 1.0$. See details in the supplementary material for derivation of the two lines, appendix A.

increasing with increasing migration, and (ii) reaches a maximum that is much larger than the maximum chance for evolutionary rescue in the stepping stone model. Strikingly, in our example in Figure 2H and I, the probability of rescue increases from approximately 0.2 for very small migration rates to certain survival if migration rates are very large. The initial increase of the probability of rescue with increasing migration rate is slower in the stepping stone model. The reason is that more distant demes cannot exchange migrants within a single generation in the stepping stone model and thus larger levels of gene flow are necessary to overcome isolation by distance and increase genetic variation. Thus, we find that evolutionary rescue can become much more likely as compared to an island model, provided migration rates are sufficiently high. In a spatially structured population with short distance migration only, the negative effects of large migration rates seem to disappear, leading to a monotonic increase in the probability of rescue if migration rates between neighboring demes increase (figure 2H and I). In the island model, large migration rates increase the chance that rescue mutations end up in the wrong habitat, effectively preventing rescue. To better understand the role of gene flow in the stepping stone model, we computed the average number of individuals that move from the deteriorated to the non-deteriorated environment during a single generation (see Appendix A in supplemental material for the derivations). We treat this number as a proxy for the negative effect of gene flow on evolutionary rescue. Figure 3

shows that while the amount of individuals migrating out of the deteriorated habitat initially decreases with increasing number of demes in the island model, it saturates quickly and remains constant if the number of demes increases further. This is in line with, and further corroborates, the finding that the number of demes has a negligible effect on the probability of rescue in the island model. In the stepping stone model, however, we find that the total number of individuals leaving the deteriorated habitat does not saturate and continues to decrease with increasing number of demes, hence showing that the negative effect of gene flow diminishes with increasing spatial structure. This is because emigration from the deteriorated part of the habitat can only occur from the deme that deteriorated last, and hence increasing the number of demes reduces the net population affected by emigration to another deme (see Appendix A in the supplemental material for details on the computation, and Figure S3 in supplemental material).

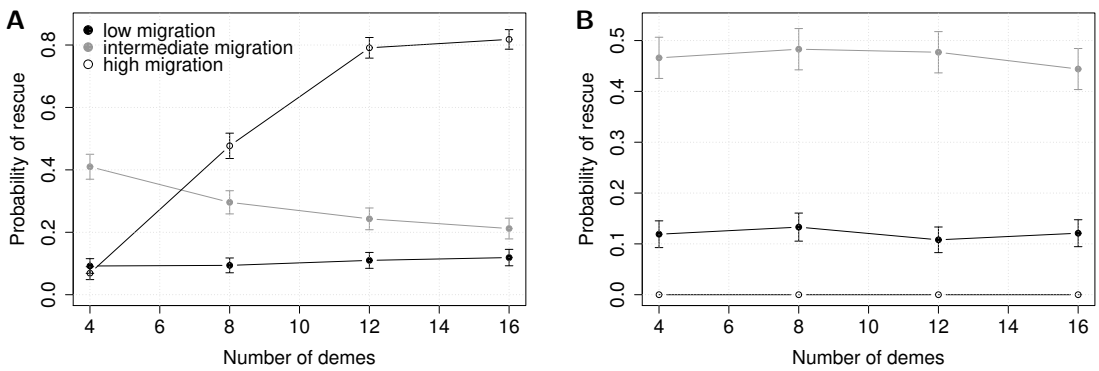

Figure 4: Probability of rescue as a function of the number of demes, for low ($m = 3.2\times10^{-4}$), intermediate ($m = 2.154 \times 10^{-2}$) and high ($m = 6.8129 \times 10^{-1}$) migration rate. (A) Stepping stone model (B) Island model. In both figures, $s = 1.0$, $r = 0.5$, $z = 0.02$, $\Theta = 4800$.

Next we investigate the effect of increased habitat fragmentation in more detail. By increasing fragmentation we mean increasing the number of demes over which a population is distributed, while keeping the total population size (and the time it takes such that the whole habitat is deteriorated) constant. In other words, we split a large, well mixed population into an increasing number of smaller sub-populations, allowing only movement between two neighboring demes. Fig. 4 shows the probability of rescue as a function of the habitat fragmentation for three different rates of migration (low, intermediate and high) for the stepping stone model (4A) and for the island model (4B), in the case of mutations lethal in the old environment ($s = 1$). For low migration, fragmentation does not have an effect in either model.

With $m \to 0$, demes evolve independently and rescue is the sole result of evolution in D isolated subpopulations.

Because the total carrying capacity in the whole habitat is kept constant, the number of individuals in each deme decreases with increasing fragmentation. A critical factor for evolutionary rescue is the total number of individuals moving between the non-deteriorated and the deteriorated area of the environment. The number of individuals migrating between the two environments does not depend on the number of demes in the island model, whereas in the stepping stone model individuals can move between the two environments only at the border between the two. Thus, with higher fragmentation, in the stepping stone model a higher migration rate is necessary to recover the same flow of individuals between the environments, as compared to the island model. Large migration rates are therefore necessary to ensure a demographic rescue effect for deteriorated habitats.

We find that in the stepping stone model the negative effects of gene flow on evolutionary rescue vanish with increasing fragmentation. Rescue mutations in the deteriorated environment are much less likely to migrate into the old habitat, where these mutations would be detrimental. The higher the migration rate, the farther individuals can migrate from the border between old and new environment, effectively preventing gene swamping. Large migration rates thus facilitate evolutionary rescue by demographic persistence in the deteriorated environment, followed by prevention of gene swamping due to isolation by distance – which arises naturally when migration is localized [Wright, 1943].

Discussion

In this paper we analyzed the effects of spatial structure and fragmentation on evolutionary rescue. We compared the island model and the stepping stone model with environmental conditions deteriorating over space and time (figure 2). Our main focus is on the interactions between fragmentation and gene flow, and how these interactions influence the chances of evolutionary rescue. For the island model, we recovered and extended previous results by Uecker et al. [2013], Tomasini and Peischl [2020]. In the island model, the probability of rescue is often maximized for intermediate migration rates, while high migration rates hinder rescue via gene swamping [Bulmer, 1972, Lenormand, 2002] (figures 2A, C and E). The conditions for when migration facilitates rescue were derived in Tomasini and Peischl [2020] for

a habitat with two demes. Increasing fragmentation, that is, increasing the number of demes in the metapopulation, has only a negligible effect on the probability of rescue in the island model (see figure 4B as well as Uecker et al. [2013]). This suggests that the conditions for when gene flow facilitates evolutionary rescue in two-deme models Tomasini and Peischl [2020] can be extended to the multi-deme case. A main insight from our study is that the spatial structure of the habitat and migration patterns play a critical role (figure 2B, D and F). In the stepping stone model, we found that the probability of rescue is strongly affected by the degree of fragmentation (figure 4A). Our main result is that the chances of evolutionary rescue are maximal in a highly fragmented habitat, where neighboring demes are highly connected (*i.e.* high local migration rates). This is because spatial structure and fragmentation increase the effects of isolation by distance [Wright, 1943], effectively preventing gene swamping [Bulmer, 1972, Lenormand, 2002] and hence also the negative effects of high migration rates on evolutionary rescue observed in island models (figure 3). Our results, if confirmed experimentally, could lead to improvement of conservation strategies of fragmented habitats. The way in which the environment deteriorates also plays a role. Our results are valid for an environment that deteriorates gradually across space; if the demes in the environment were to deteriorate in a random order, we would not expect isolation by distance to protect *de novo* mutations. In a highly fragmented stepping stone model, gene flow always improves the chances of evolutionary rescue, as suggested in laboratory studies [Bell and Gonzalez, 2011, Bell, 2013]. In general, the presence or absence of spatial structure leads to different ranges of migration rates maximising the chance for rescue (see figure 4). Our comparison focused on the differences between global migration and local migration in a one-dimensional lattice. Exploring different geometries of space (such as two- and three-dimensional lattices) could also yield a better understanding of the role of isolation by distance, as these geometries are arguably more general than one-dimensional lattices. However, the general conclusions of our study are not expected to change significantly in two- or three-dimensional habitats, as causes of the effects we see (shrinking deme populations, isolation by distance) are not unique property of a one-dimensional lattice.

We have assumed that migration is either between all demes, or only between neighboring demes. These are two extreme scenarios and an interesting extension would be to consider models where individuals disperse according to a distribution of migration distances. A better suited framework to explore such

a model would be continuous space models (*e.g.* like in Barton [1987], Kirkpatrick and Peischl [2013]). For a narrow migration kernel, we expect to recover our results even in continuous space. As we increase the width of the kernel (*i.e.* the distance traveled by migrants) we would expect this model to be more similar to the island model, and for high migration rates the probability of rescue should decrease again. But since we do not expect gene flow to be isotropic in natural systems, because *e.g.* of physical barriers over the habitat and habitat range limits, it is difficult to predict whether chances of evolutionary rescue would increase or decrease when widening the migration kernel, due to the effects on evolutionary rescue when gene flow is not isotropic (see Tomasini and Peischl [2020] for a discussion of asymmetric gene flow). Another mode of migration that will be worth considering in the future is density-dependent migration: in fact, that would cause a higher immigration rate in demes that are severely depleted because of environmental deterioration, and lower emigration rate from the same demes, thus increasing the chances of rescue [Tomasini and Peischl, 2020].

In our study, we considered single rescue mutations, thus ignoring multi-step rescue [Uecker and Hermisson, 2016] or the effect of the distribution of fitness effects and the fitness-landscape [Anciaux et al., 2018, Osmond et al., 2020]. It would be interesting to study the interactions of genetic architecture and spatial structure on evolutionary rescue, which would require to include recombination rates and other effects (*e.g.* clonal interference, Gerrish and Lenski [1998]). Our results should however be a good approximation for populations that reproduce sexually with strong recombination, such that rescue mutations evolve independently. We do not expect our model to be predictive for organisms reproducing with low recombination rates if multiple rescue mutations are required for restoring positive growth rates, as we neglected competition between beneficial mutations [Osmond and de Mazancourt, 2013]. It has been shown that the shape of the distribution of fitness effects as well as the recombination rate between loci harbouring rescue mutations can have important effects [Uecker and Hermisson, 2016, Anciaux et al., 2018, Osmond et al., 2020].

Evolutionary rescue is still difficult to observe in natural populations [Carlson et al., 2014] with only a few recent observations (*e.g.* Epstein et al. [2016] and Clayton and Spicer [2020]). Direct comparison of our results to observed cases of evolutionary rescue in natural populations is therefore challenging. Laboratory model systems with automated dispersal show that gene flow can have different effects on

evolutionary rescue, depending on whether dispersal is implemented locally or globally [Bell, 2013]. Such systems provide exciting opportunities to validate our theoretical results. Indirect evidence for our observation that antibiotic resistance should evolve more easily in populations with strong spatial structure comes from biofilm producing bacteria, in which antibiotic resistance is particularly widespread and difficult to control (see *e.g.* Vasudevan et al. [2019]). Furthermore, loss of flagellar function can confer a fitness advantage in the presence of an antibiotic in *Pseudomonas aeruginosa* [Rundell et al., 2020], suggesting further interactions between the evolution of antibiotic resistance and dispersal related traits. Our model could hence shed light on the difficulties to avoid the evolution of treatment resistance in spatially structured populations such as biofilms. In conclusion, a better understanding of the role of spatial structure and the mode of dispersal would be helpful not only for conservation strategies of fragmented natural populations, but also in the context of public health and the evolution of antibiotic resistance.

Authors contributions

MT and SP designed the project. MT and SP did analytical work. MT did all the simulations, figures, and wrote the first draft of the manuscript. MT and SP contributed to writing the manuscript.

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Data archiving

The code used to perform simulations and generate figures, as well as the supporting information for this article can be found on github: https://github.com/mtomasini/EvoRescueFragmentation.

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