Revision of the paper “When does gene flow facilitate evolutionary rescue?”

M. Tomasini and S. Peischl

February 28, 2020

Dear Dr. Bank, dear editorial board of PCI Evolutionary Biology,

We thank you for considering our manuscript for recommendations by PCI Evol Biol. We also thank the reviewers for their detailed and critical assessment, which was extremely helpful in revising the manuscript. We also apologize for the long time it took us to resubmit our revision.

We believe that the revised manuscript has improved considerably in terms of quality and clarity. We have addressed all points raised by the reviewers and have rewritten the Supplemental Material significantly, taking into account the comments of the reviewers. Please find below the revised manuscript as well as a detailed response to each of the reviewer’s comments (in bold). The changes are highlighted in the main text in red.

Reviewer 1

The paper is interesting as it discusses many effects of gene flow on the probability of rescue in a two-deme model. The interpretations are sound and the approximations seem to behave well and capture what is going on. A better illustration of the parameter range where there is an intermediate migration rate maximizing rescue would be required to better evaluate the quality of the approximations. Another point is that all computations are made assuming some fixed values for given mutants. However, to get a realistic picture and prediction on the effect of gene flow, it would require to integrate this over the different possible type of arising mutants in any given situation. The outcome will then entirely depends on the bivariate distribution of selective effects of mutants in the two environments. If there are no mutants that confer a large benefit in the new environment, with little deleterious in the old one, then most mutants will be highly susceptible to swamping (and reciprocally, if there is little trade-off in fitness effects, gene flow will favor rescue). Hence extending this theory to ‘real’ prediction is not as straightforward as the authors explain. The effect of diploidy (and dominance) is also entirely lacking, not even discussed, which is surprising for results supposed to work best in sexual populations.

> We have now included additional figures to show how well the analytical approximation fits simulations, and when it fails to predict the outcome of simulations (see Figures 3/S5 and replies to comments below). We have also extended the discussion of the limitations of our model, including the role of diploidy (page 19, lines 526–530). We agree that extending this model to a bivariate distribution of fitness effects would be very interesting. This is however a mathematically very challenging problem and we feel that a exhaustive simulation approach of the role of the distribution of fitness effects is beyond the scope of this paper. Nevertheless, we expect that our theory can still be very useful for predictions in experimental systems (e.g., like the qualitative prediction by the reviewer in the paragraph above).

Specific comments:

• 154-89: The description is ambiguous. The text mentions that many results were already obtained then state that this is a key unanswered question. This can be improved by stating what
is known and unknown more clearly.
We have rewritten those two paragraphs with the aim of making clearer what is known and what is unknown, as well as how we will contribute to answering unresolved questions. (page 3, lines 82–91).

- l146 Explain better how these equations are obtained. The paper should be self-sufficient.
  We added a short description of how these formulas were obtained, and a reference to the original paper where the derivation is presented in full detail (page 6, lines 154–157).

- l192-200 can you show where is the limit of swamping on figure 1 if the two demes were at carrying capacity but with the two different environments? It would clarify the interpretation that the maximum occurs near the swamping limit.
  We added the formula for the swamping limit (page 8, line 228), and added a vertical line indicating it in Figure 1A.

- l204 The positive effect of migration in phase 2 is not clear in the simulations.
  We modified the text to specify that the positive effect of migration in phase 2 is only an expected behavior (page 9, line 233), and we specify later that in the simulations there are two effects that hide the expected behavior of our model: on one hand, the fact that we do not take into account the time-inhomogeneity in the selective coefficient; on the other hand, relaxed competition (Uecker et al. 2014) plays an important role for high migration rates (pages 9–10, lines 248–264).

- l225 why are you talking about space? This is a two demes, spatially implicit model. Same comment line415.
  We removed the reference to space and replaced “space” with “demes”. (page 10, line 274; page 18, line 477).

- l252 right-hand part?
  Fixed (page 12, line 315).

- l273 another reason to show swamping limits as explained above, the same comment applies to Fig 4 in the following §.
  We expanded the explanation of this point, by mentioning explicitly the condition for gene swamping and discussing it more in detail, in particular in mathematical terms. (page 13, lines 339–341 and following).

- l285 explain why there is little dependencies of $s$ on swamping.
  We expanded the explanation of this point, see previous comment. (page 14, lines 353–354).

- l286-294: it would be better to show regions of parameter space where Eq12 works versus simulations. Here, two examples are singled out, but this is not really checking the quality of the approximation.
  We added a figure (figure 3) showing comparison between analytical model and simulations for multiple combinations of parameters to show the good quality of the approximation. Furthermore, we added a figure in the supplemental material (figure S5) to show a range of parameters where the approximation does not work.

- l335-338 Illustrate better the quality of Eq 16 vs simulations. Two examples are not providing a clear idea of the quality of the approximation.
  We added a figure in the supplementary material showing a comparison between simulations and theoretical expectation for more than one combination of parameters (supplemental material, figure S8, appendix D).
• 1466 But haploid. Most sexual species are diploid, aren’t they? Dominance plays a very strong role in the conditions of polymorphism. For rescue, there may be the added difficulty that if the mutant beneficial effect (in the new environment) is not dominant enough to rescue as a heterozygote, gene flow may have effects directly on the frequency, beyond the swamping effect. 

We have added a short discussion about when and how our results can be carried over to diploid organisms. (page 20, lines 529–533).

Reviewer 2

Summary

Tomasini & Peischl apply the key findings of one of their recent papers to ask which features control the probability of evolutionary rescue in a non-uniformly deteriorated habitat. In concordance with other papers in the literature, they find that p rescue is maximized at intermediate migration rates which act to balance the migration-positive effects of the non-deteriorated population as a source and the migration-negative effects of gene swamping. They describe conditions when a small amount of gene flow is detrimental for evolutionary rescue, and examine how choices of asymmetry in population size, migration rates and density regulation can be important in driving these relationships. Overall, I enjoyed reading this paper, and it got me thinking excitedly about the many directions the authors could explore in the future. I especially liked their handling of the non-instantaneous growth dynamics/density regulation. However, I felt that the authors could do a better job contextualizing their findings with existing literature, and helping the reader understand their key findings.

Major comments

Better delineate the differences from Uecker et al 2014

This paper could do a better job emphasizing what differentiates itself from previously written literature, namely Uecker’s Am Nat paper (minor - my saved reference for that Am Nat paper is 2014, not 2013. Worth double checking?). This paper seems like it’s addressing fundamentally the same questions, and little time is spent on what exactly makes it different. For example, in the sentence contextualizing their paper, the authors write

Although both theoretical and experimental advances have been made to understand the role of dispersal in metapopulation models of evolutionary rescue, the interactions between the speed and the severity of environmental change, and the amount and mode of dispersal are not well understood.

However, this is from the abstract of Uecker:

Specifically, we study the influence of population structure and density-dependent competition as well as the speed and severity of environmental change. We also determine the relative contribution of standing genetic variation and new mutations to evolutionary rescue.

What parts of the speed and severity of environmental change is Uecker’s paper not understanding that remain to be elucidated? I ask this not to be difficult, but because it’s genuinely unclear to me from the introduction and context. The paper presents a model similar to Uecker’s, which finds similar qualitative behavior with respect to intermediate migration rates. Again, while the authors are doing something different than Uecker et al 2014, it would be useful to readers to state it much more explicitly: “We make certain simplifications of Uecker’s model (two demes, time homogeneity to compute fixation probabilities) in order to explore additional phenomena Uecker et al did not consider: namely, 1) when does a small amount of migration facilitate gene flow? 2) How does asymmetry of migration rates and population sizes among demes impact fixation probabilities? 3) etc.”

> We now explain better how our work is different from previous work. In particular, we
highlight that our goal is to identify conditions for when gene flow facilitates evolutionary rescue as compared to a structured population without gene flow. This is complementary to the work by Uecker et al. (2014), who considered a larger class of models (Levene model, island model, etc.) but did not provide closed form solutions for the probability of evolutionary rescue, or analytical conditions for when the gene flow increases the chance for evolutionary rescue (page 3, lines 82–91). We also added a direct comparison of the two models in the supplemental material (figure S2).

**Understanding of $dP_{dn}/dm$ at $m = 0$**

One of the major contributions of this paper is equation (11)/(12)/(16) – effectively all the $dP_{dn}/dm$ equations. They delineate when a small amount of gene flow should enhance the probability of evolutionary rescue above a situation with no gene flow. My primary issue here is not when, but why. I feel like I did not understand where this result came from - the supplemental material in Appendix B was too brief, and the intuitive explanation could also use more exposition.

> We extended the supplemental material to make it more clear. We fixed several inconsistencies and double-checked all definitions. The new supplemental material is now much clearer and provides more details on the derivations.

For example, I am having a difficult time grasping why $\theta$ is important – is it because the amount of migrants from the non-deteriorated deme is proportional the $\theta$, but the amount of migrants lost to migration is mostly independent of $\theta$ as long as it’s not too small? This leads me to a more fundamental question: how exactly would a small amount of migration from/to a non-deteriorated environment not facilitate rescue? Is there an intuitive argument that can be made here about where mutants are coming from that could help us better understand equation 12? Put another way: what are the major costs of migration? Moving mutants from the deteriorated environment out of that environment. What are the benefits of migration? Adding new WT individuals to the population in the deteriorated environment so it declines less slowly and (maybe?) adding in mutants migrating from the new population. How many mutants are lost before $\theta$ to migration? How many mutants are gained directly via migration before $\theta$? How many mutants are gained due to a larger WT population that can then mutate before $\theta$? As long as the mutants gained (via mutation then migration or migration then mutation) are greater than the mutants lost, gene flow should help, and presumably this should work out to be what you computed in equation 12. Can the authors frame the question as mutants gained/lost instead/in addition to just taking the derivative with respect to $m$? For example, the authors’ discussion of equation 20 is very clear, and provides a practical foothold as to why this inequality leads to diverging behavior. Given how central equations 11/12/16 are, it would be very helpful to the reader to provide a similar argument, if possible.

> We added a verbal explanation of equations 11/12/16 (page 10, lines 275–286; page 11, lines 300–301). In the discussion about equation 11, we also discuss the gains and losses of mutant migrants due to their change of fitness between the two demes. The positive effect of adding wildtype individuals to deme 1 from deme 2 is described in the Introduction and in the section “Probability of rescue if mutations are lethal in the old environment”.

**Time homogeneity assumption seems to be a major shortcoming**

Comparison between stochastic simulations and analytics suggests that for certain ranges of $m$, the analytics don’t really describe the behavior of stochastic simulations. The authors were fairly upfront about the time homogeneity assumption being an issue, which I appreciated. However, there were two things related to this that I would have liked to have seen addressed:
Crash point for $p_{\text{rescue}}$? A feature in common between all of the figures is a crash of the rescue probability at a certain migration rate. $P_{\text{rescue}}$ then begins to increase again above that critical migration rate. What determines where this crash point occurs? Presumably it stems from the max in equations 3 and 4, but I don’t feel like I have an intuitive grasp on the major factors that determine where it is. Why is it so steep on the left-hand side? Is there any combination of analytics and intuition that can help us understand the shape of this curve, that might also help us understand why this range of migration rates tends to match stochastic simulations (relatively) poorly?

The crash for $P_{\text{rescue}}$ occurs because at high migration, gene swamping occurs. This prevents establishment of mutations during phase 1. Beyond a certain limit migration rate, only phase 2 contributes to rescue. Following suggestions by you and reviewer 1, we added a discussion about gene swamping and when it occurs (page 13, lines 339–341, and supplemental material, Appendix A, page 3, lines 57–64).

Display of stochastic simulations In several instances, stochastic versus analytical comparisons are put in the supplement. This makes it harder for the reader to interpret the appropriateness of modeling assumptions. For example, the extent to which the analytics do not fit the simulations at high migration rates, while stated in the text, is much more evident from the figures in the supplement. This actually makes the point that mutations arriving before $\theta$ and lasting through the epoch change are likely critically important for rescue at high migration rates - this is interesting! Looking at figure S3, for example, to my eye, $p_{\text{rescue}} = 0.75$ for $s = 0.1$, whereas the model not accounting for the switch in environments suggests that $p_{\text{rescue}}$ should be 0.1. This unmodeled effect accounts for almost 90% of rescues among mildly deleterious alleles at high migration rates? Cvijovic et al, PNAS 2015 may be an interesting citation to check out with respect to the fate of a deleterious mutation undergoing an environmental switch and becoming beneficial. According to Figure S4 and S5, there is interesting behavior of fixation probabilities with respect to balanced $\beta$ at high $m$. Namely, more skew ($\beta = 0.1$) is not always greater than balanced carrying capacities in terms of $p_{\text{fix}}$ - a behavior that is not at all predicted by the model. What causes this? The figure caption directs us to Appendix A, which talks only about the temporal inhomogeneity in selection strength. In short, I feel like placing nearly all of the stochastic simulations in the supplement doesn’t really allow most readers to understand when the model fails and masks multiple interesting departures that should be studied further in the future. Why not replace Figure 4A/B with Figures S4A/B and overlay simulations throughout Figure 3?

> We added the new Fig. 3 to show a more detailed comparison between simulations and theory. We also extended the discussion in the main text about the role of time-inhomogeneity and when our models fails to predict the behavior for large migration rates (pages 9–10, lines 248–258, as well as new Figure S6 in the supplemental material).

Schematic? A schematic similar to the sketch below would have helped me in reading the manuscript:
We added a figure (Figure 1) to represent the schematics of our model.

Minor comments

All the typos, parsing problems, etc., suggested by the reviewer were corrected and are hence removed from this document.

- In some but not all plots, \( m \) goes up to 1. Is this useful to show? Limits of \( m \) could be consistent across plots.
  We fixed this. Now all the plots go up to \( m = 0.5 \), except for figure 5, that shows notable differences between the different lines for \( m > 0.5 \).

- What are the constraints on the selection strength? Based on \( p_{est} = 2z \) and description in Tomasini & Peischl 2018, selection cannot be too strong, right? Worth discussing the selective regimes in which these approximations are appropriate (the authors do a nice job discussing the importance of other parameters on their approximations).
  We mentioned the constraints on the model (in particular relative to selection strength) (e.g. page 4, section Model) and specified in Table 1 the values allowed for the parameters.

- Equations 3, 4, 7: Is \( ) \) a more conventional exclusive range delimiter than \( [ \)?
  From our knowledge, there is not a set preference for one range delimiter or the other. In our opinion, using \( [ \) makes it visually clearer that the delimiter is not included (page 6, line 161).

- Line 167: The authors didn’t vary \( K_{tot} \). It’s worth commenting on the how changes to \( K_{tot} \) might alter results.
  We now mention why we do not vary \( K_{tot} \) or \( u \), as well as how these parameters alter results. (page 7, lines 193–194).

- Figure 2: Is \( f_0 \) assumed to be mutation-selection balance here? Mention in figure caption.
  We mentioned the assumption in the caption (figure 2).

- Line 252: Right-hand? This is confusing as written.
  Indeed, we meant right-hand (page 12, line 315).

- Line 318: Can you explain the vice versa here?
  We added a sentence to explain the vice versa (page 15, line 379).

- The notation between equations 16/17 and the supplements should be consistent.
  The notation was fixed (supplemental material, Appendix B).
• Line 331: in which population does not declines - something is off about this sentence. We reformulated the sentence (page 15, lines 393–394).

• Line 338: This could do a sentence or two of interpretation in words. We added a verbal interpretation for equations 11 and 12 (page 10, lines 275–286; page 11, lines 300–301).

• Supplemental Line 32: It would be useful if a Mathematica notebook be made available. Unfortunately, we no longer have access to Mathematica and can therefore not provide a notebook with the analysis.

• In general, I found the explanation in Appendix B insufficient to follow the progression. The supplemental material was extended, and in particular Appendix B has been restructured (supplemental material, page 3, lines 69-78).

• Equation S6 - In the natural order of reading, the reader is directed to this equation before \( \beta \) and \( \zeta \) are introduced. It’s worth redefining them here. See comment above (supplemental material, page 3, lines 69-78).

• Supplemental Line 45: Beverton-Holt citation? The citation was added (supplemental material, page 4, line 82).

• Figure S5 caption: “We can see that at \( m = 0 \) expectations are different than simulations” - at \( m = 0 \)? Typo? We agree that we never show graphically what happens at \( m = 0 \). We changed this with \( m \to 0 \) (supplemental material, figure S7).

Reviewer 3

In their work, Tomasini and Peischl present a model for evolutionary rescue of two separated populations which interact through migration. Their main goal is to show that, under certain conditions, gene flow can favour evolutionary rescue in endangered species. Both the populations are threatened by environmental changes at two different times. The so-deteriorated environments are no longer suitable for the wild-type individuals, which are so doomed to the extinction. Their model, through a deterministic approach, describes the probability of evolutionary rescue of the endangered populations, as a function of the migration of individuals between the two regions. Their main achievement is to able to derive mathematical conditions under which the gene flow is beneficial to evolutionary rescue. The authors give a nice introduction to the topic, explaining motivations and, through a clear description of the state of art, they nicely illustrate the open problem underlying their work, motivating the study in a satisfactory way. Throughout their manuscript, they address the research questions proposed in the introduction, starting from the simplest case, which is described by symmetry in migration and carrying capacities, to more general cases with asymmetries in migration rates and carrying capacities. In general, I find the bulk of this work interesting and I think it has potential to be recommanded in the community. However I have some questions and comments which I hope could be stimulating and improve the quality of the manuscript. Before starting with the specific comments, in general, while reading the manuscript, I often had the feeling that evolution theory is used as a primary explanation for the behaviour of the model. I would have find the manuscript easier to understand if the primary explanation was based on the mathematics. Trying to be more clear: since the solutions of the model depend on the equations, their behaviour can be explained only through mathematical analysis. On the other side, I appreciate the references to previous known results, which clearly support the consistency of the model. The following comments are often extension of what just said.

Comments

1. Table 1: Is there a particular reason for choosing \( u = 1/K_{tot} \)? This value used in the simulations, however, as a matter of generality, why not leaving it general, as done for example with the other
parameters reported in the table?

We have now added an explanation of why we keep \( u \) and \( K_{\text{tot}} \) fixed (page 7, lines 193–194).

2. (a) In section Population dynamics (page 6) the authors present the equations describing the evolution of the population size. I think it might be worth to stress out that \( N_{i}(t) \) is not the overall population size, but represents only the size of the wild-type population. Also, I think it would be beneficial to the reader to have the initial conditions \( N_{1}(0) = k_{1}, N_{2}(0) = k_{2} \) stated in this section, for example after equation (10).

Done. (page 7, line 182).

(b) I think it might be worth to highlight the fact that the evolution of the mutant populations is never explicitly considered. Initially this was not very clear to me. For example, in line 229 the sentence “...high migration to be too efficient in removing mutations from deme 1” might be a bit misleading, and instead of “removing mutations” I would use “preventing establishment of mutations”.

We highlighted that mutants are not explicitly considered in the computation of population dynamics (page 7, lines 175–177). We also modified the discussion following equation (11) (where the sentence that you mention was previously found) (page 10, lines 275–286).

(c) Still regarding the modelling of the population sizes, I have a question for the authors: I understand \( k_{1} \) and \( k_{2} \) are the maximal number of individuals “allowed” in each deme. Hence, let us assume that one mutant appears, for instance, in deme 2 during phase 1 (when the population is constantly kept at \( k_{2} \) wt individuals): does this not break the “carrying capacity rule”? Or is the carrying capacity meant to hold only for wild type individuals?

The appearance of a mutant is always a substitution of a wild-type existing in the preceding generation. As such, it always replaces an individual. In any case, the parameters \( \kappa_{1} \) and \( \kappa_{2} \) (carrying capacities of deme 1 and deme 2) are not a hard deterministic bounds of a population and overshooting is possible as our simulation model is stochastic. Last, in our model mutants are rare enough that we do not have to explicitly calculate their influence on demography. This is of course an approximation, and we added a mention in the text (page 7, lines 175–178).

3. I think it would be helpful if the authors could spend few more words on equation (1), regarding the probability of rescue (it would be enough to do it in the supplementary material). (a) In particular, regarding the time limits (\(-\infty, +\infty\)): I have the feeling that evolutionary rescue would have sense only if it happens in a finite time \( T < \infty \). I would like if the authors can clarify this point, explaining why the product in (1) is until \( t = +\infty \).

We now explain this in the main text. (page 5, lines 134–137).

(b) From equation (2) it seems that

\[
\prod_{t=0}^{0} (1 - uN(t)p(t)) = 1 - P_{\text{sgv}} \quad \text{and} \quad \prod_{t=0}^{\infty} (1 - uN(t)p(t)) = 1 - P_{\text{dn}}
\]

I think it would be clearer to split (2), stating explicitly these two equations. I also would spend few more words about \( \prod_{t=-\infty}^{0} (1 - uN(t)p(t)) \). For instance, equation (5) describes \( P_{\text{sgv}} \) as a function of \( p^{(1)} \) and \( p^{(2)} \). But \( P_{\text{sgv}} \) in (2) seems to depend on \( t \in (-\infty, 0) \), while \( p^{(1)} \) and \( p^{(2)} \) are defined only for positive time.

We feel that explicitly splitting equation (2) in the way that you propose would make the main text heavier with mathematical details that are not necessarily helpful for the reader. However, we added to the main text an explanation of why we use equation (5) to describe \( P_{\text{sgv}} \). (page 6, lines 162–165).
4. (a) The formulas (3) and (4) of the probability of establishment of the mutation depend on $m$ for $t \in [0, \theta)$. However $m$ has not been previously defined. Later $m$ is used when $m_{12} = m_{21}$, as $m = 2m_{12} = 2m_{21}$, so I imagine this is its meaning. I think it would be useful to state this before equations (3)-(4).

We added a sentence with the definition of $m$ with respect to $m_{ij}$ (page 6, line 156–159).

(b) Moreover, how are (3) and (4) defined when $m_{12} \neq m_{21}$?

The full definition of equations (3) and (4) in the case of asymmetric migration is found in Tomasini & Peischl (2018). It has been now added to the supplemental material (supplemental material, page 1, lines 21–25).

5. In section Simulation model (page 6), stochastic simulations are proposed for testing the model given in equations (2)-(10).

(a) It does not look very clear to me in which way the simulations reduce the population size in the deteriorated demes. From lines 171-172: “Individuals in each deme reproduced, mutated and migrated, followed by density regulation”. I have the feeling that the authors forgot to state that there is also a mortality rate (in that sentence, the only possible reduction I see is given by the mutation of wild-type individuals, since migration does not reduce the overall population between the 2 demes).

We now mention in the main text that generations are discrete and non-overlapping. Thus, there is no mortality rate because the parental generation is replaced by the offspring each generation. (page 4, line 107).

(b) With respect to these simulations, the proposed equations (9)-(10) seem to describe an opposite behaviour, as no birth rate is present and both the populations decline exponentially in phase 2, as it comes out by calculating $N_1'(t) + N_2'(t)$ using (10).

See comment above.

(c) The simulations are used to validate the analytical findings of the continuous model (line 166) and, indeed, the solutions of the two are always compared. However I do not understand for which reasons we should trust the simulations more than the continuous model. If simulations of this kind are well-established in literature, some references should be provided. Otherwise one could also argue that the model (2)-(10) should be used to validate the discrete simulations and not the other way round. I think a clarification about this is necessary.

In our case the simulation model is biologically more realistic as compared to the analytical model, which makes several simplifying assumptions. For example, our model does not modify reproduction directly, but relies on deterministic modelling of the population dynamics, while in the simulation reproduction is represented by a Poisson process. Thus, we find it appropriate to use the simulation model to check our analytical approximations. We now mention this (page 7, line 189).

(d) One or two plots describing the stochastic evolution of the populations would be nice to see.

We added a schematic showing the typical population dynamics of the model (Figure 1).

6. (a) In line 13 of Supplemental Material, $s$ is reported to be negative, while in the main text, $s \in (0, 1)$. The authors should keep the consistency with the main text.

The supplemental material was extended as suggested, keeping consistency with the main text (supplemental material, appendices A and B).

(b) In page 4, the authors do not specify the range in which $r$ and $z$ can vary: they seem to be both positive (this is clearly truth for $r$), but is there a maximum value they can reach? If not, I think reporting $r > 0$, $z > 0$ and $0 < s < 1$ in table 1 would give more clarity to the text.

As suggested, and also following comments by reviewer 2, the constraints on the parameters were added to Table 1 (page 4).

7. Lines 195-200, from “The existence of . . . ”: (a) the explanation of the reasons behind the existence of a critical migration rate is very nice, but I think it might be helpful to first explain it
using the mathematics (this could also be done only in the supplementary material) and then
give the biological interpretation. Indeed, solving equation (9) one gets the explicit solution
(S4), which can be rewritten as

\[ N_1(t) = \left( k_1 - \frac{m_{21}k_2}{r + m_{12}} \right) e^{-(r+m_{12})t} + \frac{m_{21}k_2}{r + m_{12}}. \]

If one considers \( m_{12} = m_{21} = m/2 \) and \( \theta = 500 \), then for big times \( t < \theta \) one could approximate
\[ N_1(t) \approx \frac{m}{2r + m} k_2. \]

Therefore the number of wild-type individuals in the deteriorated deme increases as a function
of the migration rate.

**Thank you for this interesting insight. We added this derivation to the supplemental
material.** We chose to not include it in the main text because we want to make the
manuscript accessible to a broad range of readers. However, we do agree that a
mathematical treatment of the model will increase the quality of the supplemental
material and satisfy the avid mathematical reader (Appendix A, pages 2–3, lines
35–52).

(b) On the other hand, I had to spend some time for understanding the sentence “too much
migration between demes prevents rescue mutations from establishing despite being positively
selected in one of the two demes, a process called gene swamping” (lines 198-200). Surely I think
that this sentence should be used as a confirmation of the consistency of the model with respect
to the evolutionary theories. However, the solutions of the model should be explained using the
mathematics. Indeed, using the parameters \( z = 0.02 \) and \( s = 1.0 \) reported in the caption of
Figure 1, during phase 1 the function \( p^{(2)} \) is always zero for any \( m > 0 \) (and this is consistent
with the fact that the mutation is lethal in the old environment), and the function \( p^{(1)} \) is non-zero
only for very small values of \( m \). Therefore, from (7), for bigger values of \( m \), one gets \( \pi_{dn} = 0 \).
This is the reason why “for large migration rates, rescue can only occur during phase 2” (line
201). I think it might be helpful to remark this, and it might be enough to just plot \( p^{(1)} \) versus
the migration rate.

*We added a discussion of this to the supplemental material (see Appendix A, page
3, lines 57–64).*

8. Figure 1B, page 7: Is the probability of rescue represented with filled dots calculated as (number
of rescues) / (number of total simulations), where number of total simulations = 2000?

*Yes, we added a line about this in the description of the simulations (page 8, lines
210–211).*

9. In section “When does intermediate migration favors rescue?” (page 8) (and also in Appendix
B), the condition under which intermediate migration is beneficial to evolutionary rescue is
proposed (and derived). This is done by showing that \( P_{\text{rescue}} = P_{\text{rescue}}(m) \), seen as a function
of \( m \), increases at \( m = 0 \). This means that even a very small migration would have a more
beneficial effect as compared to the no migration case. However, in principle, this does not
necessarily imply that intermediate migration has a better impact with respect to the maximal
migration case. Indeed, in order to prove that \( P_{\text{rescue}} \) is maximal if migration is intermediate,
I would either check if there is a maximum in \((0,2)\) or, checking continuity of \( P_{\text{rescue}}(m) \), it
would also be enough to see that \( P_{\text{rescue}}(0) > 0 \) and \( P_{\text{rescue}}(2) < 0 \). However, if I am missing
something, I would like the authors to explain this part with more details, as it concerns the
main result of their work.

*It is true that testing for the existence of a maximum would be a stricter way to
prove that intermediate migration is indeed favored in some cases. However this is
a long derivation and the final result does not bear much power. We decided to opt
for the demonstration that the derivative of \( P_{\text{rescue}}(m) \) is positive at \( m = 0 \) because
it allowed to derive a simple formula, generating intuition about the problem at
hand. We use the word “intermediate” to represent any rate of migration between 0 and 1.

A small remark: I am using $m \in [0, 1]$ since $m/2 = m_{ij}$ and $m_{ij}$ are probabilities, but I have the feeling that the authors require $m_{12} + m_{21} = 1$. If this is the case, please add one line to explain the reason and consider my comment with $m \in [0, 1]$.

No, we meant $m \in [0, 1]$. The reason we use $m/2$ for the symmetric model is to be consistent with the case of the island model (see Uecker et al. 2014), in which case $m_{ij} = m/D$, $D$ being the number of demes in the model. We added a note about this before the definitions (3) and (4), when $m$ is introduced (page 6, lines 156–159).

Also, it is not required by the model that $m_{12} + m_{21} = 1$, but it is an assumption that simplifies calculations and is often used to this goal (see e.g. Barton et al. 2002). This has now also been specified in the text (page 14, line 358).

10. Lines 244-245: “We can see that the chances of survival from standing mutations are maximal in absence of migration (figure 3, also figure S2).” I think the authors refer to figure 2 instead of figure 3. Moreover, in all figures they do not really plot from $m = 0$ but from $m = 1e - 04$. If there a particular reason for this I think it might be worth to state it, otherwise this should be fixed.

The reference to the figure was changed. It is common practice to not show $m = 0$ on a logarithmic axis, unless something noteworthy occurs at that particular point – here there is no consistent difference between $m = 0$ and $m \to 0$.

11. In Supplemental material, appendix B, equation (S6): the parameters $\tilde{\beta}$ and $\tilde{\zeta}$ have not been defined and, even though they can be deduced by equations (16)-(17) of the main text help, I think it might be helpful to add a line for their definition.

Appendix B has been extended without the need to define $\tilde{\beta}$ and $\tilde{\zeta}$ (supplemental material, Appendix B, page 3).

12. lines 303-306: as in previous comments, I think it would be clearer to explain the behaviour of the model using the equations. Following comment 7, for big $\theta$ and big $t < \theta$, during phase 1, the population in deme 1 can be approximated with

$$N_1(t) \approx \frac{m_{21} k_2}{r + m_{12}}.$$ 

This indeed constitutes an approximated initial condition for the population $N_1$ in phase 2. Now, rewriting the above in terms of $\zeta$

$$N_1(t) \approx \frac{(1 - \zeta)m k_2}{r + \zeta m},$$

it is possible to see that this function decreases in $\zeta$ (and its maximum is achieved at $\zeta = 0$). This explains the effect of the migration asymmetry on the rescue probability.

The supplemental material was extended and now gives more details about the mathematical expectations of the model (Appendix A, pages 2–3, lines 35–52).

13. line 346, “the number of individuals of a type i in the non-deteriorated deme”: I think the authors mean “the number of individuals in the non-deteriorated deme i”.

Indeed, there was a mix up of notations from an old version of the manuscript. This has been corrected (page 16, line 407).

14. Equation (18), page 13: (a) the parameter $w_i$ at the numerator has not been defined. Should it be $w_i = w_{i0}$?

This has been corrected (equation 18, page 16, line 410).

(b) As well, it is not clear what $N_{tot}(t)$ and $k$ at the denominator represent. It could be $N_{tot}(t) = N_1(t) + N_2(t)$ and $\kappa = K_{tot}$, but these need to be defined. The same holds for
A definition of $N_{tot}$ has been added, and we modified $\kappa$ in equation (18) (page 16, line 409).

15. line 52 of Supplemental material, “deme 1 is almost depleted after a few generations”: this would be clearer if the authors are able to show it mathematically. As well, I think that a plot of $N_2$, as defined in (S8), would add clarity to the section.

We added a brief mathematical explanation in the supplemental material (Appendix A, page 2, lines 35–40). We also added a plot showing the population dynamics in both demes during the whole process (figure 1).

16. lines 423-424: the main positive effect of gene flow occurs during phase 1, but I feel that the reasons should be discussed more deeply. Indeed, phase 2, except for the initial conditions (see comment 7), is not affected by the gene flow. In a certain sense, one could neglect the separation of the two populations, since
\[\pi_{dn}(t) = 2zu(N_1(t) + N_2(t))\]
and, summing $N'_1$ and $N'_2$, from equation (10) one gets
\[N_1(t) + N_2(t) = (N_1(\theta) + N_2(\theta))e^{-rt}.
\]
Hence, in this phase, the migration rates seem to play a role only on the definition of the initial condition $N_1(\theta) + N_2(\theta)$.

Indeed, during phase 2 we can think of the habitat as one big deme, as every individual experiences the same selective pressures in different demes (according to their allele, of course). We added a note about this in the main text. (page 9, lines 237–238).

Typos
The typos were fixed, the changes can be seen in the main text in red.
When does gene flow facilitate evolutionary rescue?

Matteo Tomasini1, 2, 3, 4, * and Stephan Peischl1, 3, †

1Interfaculty Bioinformatics Unit, University of Bern, 3012 Bern, Switzerland
2Computational and Molecular Population Genetics Laboratory, Institute of Ecology and Evolution, University of Bern, 3012 Bern, Switzerland
3Swiss Institute for Bioinformatics, 1015 Lausanne, Switzerland
4Department of Integrative Biology, Michigan State University, East Lansing, MI 48824, USA

*Current affiliation: Michigan State University
†Corresponding author: stephan.peischl@bioinformatics.unibe.ch

February 28, 2020

Abstract

Experimental and theoretical studies have highlighted the impact of gene flow on the probability of evolutionary rescue in structured habitats. Mathematical modelling and simulations of evolutionary rescue in spatially or otherwise structured populations showed that intermediate migration rates can often maximize the probability of rescue in gradually or abruptly deteriorating habitats. These theoretical results corroborate the positive effect of gene flow on evolutionary rescue that has been identified in experimental yeast populations. The observations that gene flow can facilitate adaptation are in seeming conflict with traditional population genetics results that show that gene flow usually hampers (local) adaptation. Identifying conditions for when gene flow facilitates survival chances of populations rather than reducing them remains a key unresolved theoretical question. We here present a simple analytically tractable model for evolutionary rescue in a two-deme model with gene flow. Our main result is a simple condition for when migration facilitates evolutionary rescue, as opposed as no migration. We further investigate the roles of asymmetries in gene flow and / or carrying capacities, and the effects of density regulation and local growth rates on evolutionary rescue.

Introduction

Evolutionary rescue refers to the process of rapid adaptation to prevent extinction in the face of severe environmental change [Gomulkiewicz and Holt, 1995]. It is of particular interest in light of recent environmental and climatic change, with the potential to lead to new conservation strategies [Ashley et al., 2003]. Evolutionary rescue also plays a major role in other fields of public
importance, such as the evolution of antibiotic or other treatment resistance (e.g., Normark and Normark [2002]), or resistance to pesticides (e.g., Chevillon et al. [1999]). Better understanding of evolutionary rescue is therefore critical in the context of global climatic change as well as in the field of evolutionary medicine. Experimental evolution studies of evolutionary rescue and antibiotic resistance are burgeoning (reviewed in Bell [2017]), empirical evidence for rescue under anthropogenic stress is now abundant [Hughes and Andersson, 2017, Bell, 2017], whereas evidence for rescue under natural conditions is difficult to obtain and more scarce (but see Vander Wal et al. [2013]).

The theoretical foundations for evolutionary rescue in single panmictic populations are laid out [Orr and Unckless, 2014] and several demographic genetic and extrinsic features that affect the chance for rescue have been identified (see table 1 in Carlson et al. [2014] for an overview), including the effects of recombination [Uecker and Hermisson, 2016], mating system [Uecker, 2017], intra-specific competition [Osmond and de Mazancourt, 2013, Bono et al., 2015], inter-specific competition [De Mazancourt et al., 2008], and phenotypic plasticity [Chevin et al., 2013, Carja and Plotkin, 2019]. A major goal of evolutionary rescue theory is to predict a populations chance of survival in the face of severe stress. Key theoretical predictions of evolutionary rescue have been strikingly confirmed in laboratory conditions [Carlson et al., 2014], for instance using yeast populations exposed to high salt concentrations [Bell, 2013]. In particular, it was found that only sufficiently large populations could be expected to persist through adaptation [Lynch, 1993, Bell and Gonzalez, 2009, Samani and Bell, 2010, Bell and Gonzalez, 2011, Ramsayer et al., 2013, Bell, 2013]). A second feature that has been shown to facilitate the chance for evolutionary rescue theoretically as well as experimentally is standing genetic variation [Barrett and Schluter, 2008, Agashe et al., 2011, Lachapelle and Bell, 2012, Vander Wal et al., 2013, Ramsayer et al., 2013]. Despite these advances, however, predicting evolutionary outcomes outside of the lab remains extremely difficult [Gomulkiewicz and Shaw, 2013].

Evolutionary dynamics in spatially (or otherwise) structured populations can differ dramatically from those in well-mixed populations [Lion et al., 2011] and unexpected rescue mechanisms may arise in such settings [Peischl and Gilbert, 2018]. Empirical and experimental results have highlighted the importance of dispersal for evolutionary rescue in metapopulations subject to gradual environmental change. Using an experimental metapopulation of yeast exposed to gradually increasing environmental stress, Bell and Gonzalez [2011] showed that gene flow between different habitats can have positive effects on survival in changing environments, depending on dispersal distances and the speed of the environmental change. A detailed theoretical study of evolutionary rescue in structured populations using mathematical analysis and simulations confirmed that intermediate gene flow between populations can maximize the chance of rescue as compared to a population without gene-flow [Uecker et al., 2014] in some cases. Uecker et al. [2014] identified two direct consequences of dispersal: (i) the unperturbed environment acts as a source for wild-type individuals that might mutate, thus increasing the chances of rescue, and (ii) dispersal moves mutant individuals to regions of the environment where the presence of the mutation is costly.
leading to a net reduction of the mutant growth rate, and consequent lower rates of survival. The interplay between these two effects can often lead to situations in which the probability of rescue is maximized for an intermediate migration rate [Uecker et al., 2014]. In a continuous space model where the environment changes gradually across space and/or time, increased dispersal generally decreases the probability of establishment of rescue mutations, but it increases the effective population size of individuals that can contribute to evolutionary rescue [Kirkpatrick and Peischl, 2013].

Individual based simulations of gradually changing conditions and divergent selection between two habitats identified interactions of evolutionary rescue and local adaptation in a two-deme model [Bourne et al., 2014]. These results suggest that gene flow is beneficial for population survival only when divergent selection is relatively weak. These results were largely confirmed in a simulation study of a 2D metapopulation [Schiffers et al., 2013].

Although both theoretical and experimental studies have identified potentially positive effects of gene flow on survival in metapopulation models of evolutionary rescue, the exact conditions when gene flow is detrimental to survival and when not remain unclear. For instance, the observation that gene flow can facilitate rescue in a changing environment is in seeming conflict with more traditional results that show that dispersal does generally not have a positive effect on (local) adaptation [Bulmer, 1972, Holt and Gomulkiewicz, 1997, Lenormand, 2002]. High migration rates can lead to gene swamping in models with divergent selection pressures between different regions [Bulmer, 1972, Lenormand, 2002], thus reducing chances of survival during environmental change.

Identifying conditions under which dispersal facilitates evolutionary rescue in spatially or otherwise structured populations remains a key unresolved question, both theoretically and empirically. In this article, we present an analytically tractable model with two demes that exchange migrants, and with temporal change in environmental conditions. We focus on the case where the two demes deteriorate at different points in time, such that gene flow between the populations influences both the demographic as well as the evolutionary dynamics of evolutionary rescue. In the new environmental conditions, growth rates are negative and the population faces eventual extinction.

We consider rescue mutations at a single locus and assume that they are counter-selected in the original environmental conditions. We derive conditions for when gene flow facilitates evolutionary rescue as compared to two populations without gene flow. We study the role of asymmetric migration rates or asymmetric carrying capacities (both cases can lead to source-sink dynamics, see Holt [1985], Pulliam [1988]), study the contributions of de novo mutations vs. standing genetic variation, and investigate the role of local growth rates and density regulation within demes. Our aim is to understand when gene flow facilitates evolutionary rescue, and to disentangle the interactions between the strength of selection for rescue mutations, the speed and severity of environmental change, and the amount and mode of dispersal.
Model

We consider a haploid population with discrete non-overlapping generations, subdivided into two demes, labeled 1 and 2, with gene flow between them. Individuals migrate from deme $i$ to deme $j$ with probability $m_{ij}$ ($i, j \in \{1, 2\}$). Fitness is determined by a single locus with two alleles: a wild-type allele and a mutant allele. We distinguish two possible environmental states. At the beginning both demes are in what we call the non-deteriorated state (or “old” state) and are at demographic equilibrium, filled with $\kappa_i$ individuals. The total population size is therefore $K_{\text{tot}} = \kappa_1 + \kappa_2$. At time $t = 0$ deme 1 deteriorates (that is, it is now in the “new” state). In the deteriorated environment, wild-type individuals have absolute fitness $w^{(n)}_w = 1 - r < 1$, such that the population size in deme 1 declines at rate $r$. After $\theta$ generations, deme 2 deteriorates too and local population size starts to decline at the same rate as in deme 1. In the absence of adaptation to the novel environmental conditions both demes will eventually go extinct. We assume that rescue mutations that restore positive growth rates in the new environment occur at rate $u$ per individual and generation, and we ignore back mutations. The absolute fitness of a mutant individual is $w^{(n)}_m = 1 + z$ in the new habitat ($z > 0$). We assume that the mutation is detrimental in the old environment and denote its carriers fitness by $w^{(o)}_m = 1 - s$ ($0 < s \leq 1$). We call $r$ the environmental stress due to deterioration, and $s$ and $z$ are the selection coefficients of the mutant allele in the old and new state, respectively.

We will call “phase 1” the phase in which the two demes have different environments ($0 < t < \theta$) and “phase 2” the phase in which both demes are deteriorated.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_i(t)$</td>
<td>Number of wildtype individuals in deme $i$</td>
</tr>
<tr>
<td>$K_{\text{tot}}$</td>
<td>Total carrying capacity of the habitat</td>
</tr>
<tr>
<td>$\kappa_i$</td>
<td>Carrying capacity of deme $i$</td>
</tr>
<tr>
<td>$u = 1/K_{\text{tot}}$</td>
<td>mutation rate</td>
</tr>
<tr>
<td>$m_{ij}$, ($0 \leq m_{ij} \leq 1$)</td>
<td>Rate of migration per population from deme $i$ to deme $j$</td>
</tr>
<tr>
<td>$s$, ($0 &lt; s \leq 1$)</td>
<td>Disadvantage against a mutant copy in the old environment</td>
</tr>
<tr>
<td>$z$, ($0 &lt; z &lt; 1$)</td>
<td>Advantage of a mutant copy in the new environment</td>
</tr>
<tr>
<td>$r$, ($0 &lt; r &lt; 1$)</td>
<td>Stress against the wildtype population in the new environment</td>
</tr>
<tr>
<td>$w^{(o)}_w = 1$</td>
<td>Fitness of a wildtype individual in the old environment</td>
</tr>
<tr>
<td>$w^{(n)}_w = 1 - r$</td>
<td>Fitness of a wildtype individual in the new environment</td>
</tr>
<tr>
<td>$w^{(o)}_m = 1 - s$</td>
<td>Fitness of a mutant individual in the old environment</td>
</tr>
<tr>
<td>$w^{(n)}_m = 1 + z$</td>
<td>Fitness of a mutant individual in the new environment</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Time between deterioration events</td>
</tr>
<tr>
<td>$f_0$</td>
<td>Frequency of rescue mutations at time $t = 0$</td>
</tr>
</tbody>
</table>

### Probability of rescue

Let $P_{\text{rescue}}$ denote the probability that a rescue mutation occurs and escapes genetic drift, such that it will increase in frequency and eventually restore a positive growth rate and rescue the population from extinction. To calculate the probability of rescue, one needs to take into account...
Figure 1: Schematic representation of evolutionary rescue in our model. On the upper panel, we show the population density in deme 1, in the lower panel the population density in deme 2. Deme 1 deteriorates at time $t = 0$, and deme 2 deteriorates at $t = \theta$. The total count of individuals in deme 1 exhibits the typical “U-shape” associated with evolutionary rescue [Gomulkiewicz and Holt, 1995] (the same would be true in deme 2 if we extended the $x$-axis).

two ingredients: (i) the number of mutations entering the population in each generation and (ii) the probability of establishment of each single mutant copy in the population. In a single population, one can write the probability of rescue as

$$
P_{\text{rescue}} = 1 - \prod_{t = -\infty}^{+\infty} (1 - uN(t)p(t)) ,
$$

where $uN(t)$ is the expected number of mutations entering the population in each generation, and $p(t)$ is the probability that the mutation establishes and rescues the population [e.g., Gomulkiewicz and Holt, 1995]. We consider times from $-\infty$ to $+\infty$ here for mathematical convenience. Rescue mutations have a negligible probability of permanent establishment if they occur too early (at negative times $t \ll 0$). Similarly, for large times ($t \gg 0$), the population will be extinct if no rescue mutation was successful before that.

Evolutionary rescue can stem from standing genetic variation, with probability $P_{\text{sgv}}$, or from de novo mutations, with probability $P_{\text{dn}}$. We define de novo mutations as mutations that arose after the first deterioration event occurred (that is, after time $t = 0$). We can thus write:

$$
P_{\text{rescue}} = 1 - \prod_{t = -\infty}^{0} (1 - uN(t)p(t)) \prod_{t = 0}^{+\infty} (1 - uN(t)p(t)) = 1 - (1 - P_{\text{sgv}})(1 - P_{\text{dn}}) .
$$

(2)
Mutations that occur before phase 2 (that is, that occur before all demes are deteriorated) have different probabilities of establishment \( p^{(1)}(t) \) and \( p^{(2)}(t) \) depending on the deme in which they occur and the time at which they occur. However, currently no analytic solution is known for the establishment probabilities in this case. To proceed further we ignore the temporal heterogeneity in fitness values and use the current environmental conditions to calculate establishment probabilities using the results from Tomasini and Peischl [2018] for a time-homogeneous two-deme model (assuming a large population size and small selection coefficient, i.e., \( 1/N < z \ll 1 \)). This should be a good approximation if \( \theta \gg 0 \), since the fate of mutations in temporally changing environments is determined in the first few generations after they occur [Peischl and Kirkpatrick, 2012] and the contribution of mutations occurring just before environments change will be negligible.

In contrast, if \( \theta \approx 0 \), the change in environmental conditions is almost instantaneous across all demes, such that population structure and migration would have virtually no effect on evolutionary rescue [Uecker et al., 2014]. During phase 2, when the two demes are in the same environmental state, the probability of establishment is simply \( 2z \) [Haldane, 1927]. Tomasini and Peischl [2018] use branching processes to obtain the probability of establishment of mutations under divergent selection, as is the case during phase 1. The expression is shown here for a case with symmetric migration \((m_{12} = m_{21} = m/2)\) [Tomasini and Peischl, 2018]. In the symmetric case, we define the rate of migration from one deme to the other as \( m/2 \) for consistency with the island model with \( D \) demes [Uecker et al., 2014], where \( m_{ij} = m/D \), for \( i, j \in \{1, \ldots D\} \).

The probabilities of establishment for the two-deme model with symmetric migration are:

\[
p^{(1)}(t) \approx \begin{cases} \max \left[ z \left( 1 + \frac{z+s}{\sqrt{m^2+(z+s)^2}} \right) - s \frac{m}{\sqrt{m^2+(z+s)^2}}, 0 \right] & \text{if } t \in [0, \theta] , \\ \frac{2z}{2z} & \text{if } t \in [\theta, \infty] . \end{cases}
\]

\[
p^{(2)}(t) \approx \begin{cases} \max \left[ z \left( \frac{m}{\sqrt{m^2+(z+s)^2}} \right) - s \left( 1 - \frac{z+s}{\sqrt{m^2+(z+s)^2}} \right), 0 \right] & \text{if } t \in [0, \theta] , \\ \frac{2z}{2z} & \text{if } t \in [\theta, \infty] . \end{cases}
\]

Because mutations have a negligible probability to establish at \( t \ll 0 \) (see discussion before equation (2)), the probability of rescue due to standing genetic variation, \( P_{\text{sgv}} \), can be calculated as the probability of establishment of the mutations present in the population at time \( t = 0 \) due to mutation-selection balance. We can then write

\[
P_{\text{sgv}} \approx f_0 N_1(0)p^{(1)} + f_0 N_2(0)p^{(2)} ,
\]

where \( f_0 \) is the frequency of rescue mutations in each of the demes at time \( t = 0 \). Similarly, the total probability due to de novo mutations is given by

\[
P_{\text{dn}} = 1 - \prod_{t=0}^{\infty} \left( 1 - \pi_{\text{dn}}(t) \right) .
\]
where we approximate the joint probability that a copy of the rescue mutation will occur in
generation $t$ and then establish permanently by

$$
\pi_{dn}(t) \approx \begin{cases} 
  u \left( N_1(t)p^{(1)} + N_2(t)p^{(2)} \right) & \text{if } t \in [0, \theta[, \\
 2z u \left( N_1(t) + N_2(t) \right) & \text{if } t \in [\theta, \infty[.
\end{cases}
$$

To simplify calculations, we use that

$$
\prod_{t=0}^{\infty} \left( 1 - \pi_{dn}(t) \right) \approx \exp \left[ - \sum_{t=0}^{\infty} \pi_{dn}(t) \right]
$$

if $\pi_{dn}$ is small, and for further simplicity, we do the calculation in continuous time, so that we can switch the sum for an integral. The probability of rescue from de novo mutations is then

$$
P_{dn} \approx 1 - \exp \left[ - \int_{0}^{\infty} \pi_{dn}(t) \, dt \right].
$$

Population dynamics

In order to calculate (6) and (7), we need to explicitly calculate the wild-type population sizes $N_1(t)$ and $N_2(t)$ for $t \geq 0$. We assume that mutants are rare and hence we do not explicitly model their influence on demography. The only case where the number of mutants is large enough to effectively play a role is when a mutation is already on its way to establishment. We model the population dynamics as continuous in time, as we did in (8), and further assume that the mutation rate is low and neglect the number of wildtype individuals lost due to mutation. We assume that population growth and density regulation keep population density in deme 2 at carrying capacity, that is $N_2(t) = \kappa_2$, during phase 1. Population size in deme 1 then follows the differential equation

$$
\frac{dN_1(t)}{dt} = N_1(t) \left( -r - m_{12} \right) + m_{21} \kappa_2,
$$

with initial condition $N_1(0) = \kappa_1$. During phase 2 ($t \geq \theta$), when both demes are deteriorated, $N_1(t)$ and $N_2(t)$ follow

$$
\frac{dN_i(t)}{dt} = N_i(t) \left( -r - m_{ij} \right) + m_{ji} N_j(t),
$$

where $i, j \in \{1, 2\}$ and $i \neq j$. Solutions can be obtained straightforwardly – more details are given in the supplemental material (Appendix A, equation (S4)). Figure 1 shows the typical population dynamic trajectories during an evolutionary rescue event. In the absence of evolutionary rescue, population density would continue decaying until it reaches $N = 0$.

Simulation model

We performed stochastic simulations replicating biological processes to validate and extend our analytical findings. We filled a habitat with 20,000 individuals divided into two demes, labelled $i = 1, 2$, with carrying capacities $\kappa_i$. We fixed the mutation rate at $u = 1/K_{tot} = 5 \times 10^{-5}$, so that in a non-deteriorated habitat at carrying capacity on average one new mutant enters the population per generation. Increasing (decreasing) $K_{tot} \cdot u$ will mainly lead to an increase (decrease) of the total rescue probability, and we hence keep $K_{tot} \cdot u$ fixed throughout the paper. The initial
mutant frequency $f_0$ was assumed at mutation-selection equilibrium, $f_0 = u/s$ [Gillespie, 2004].

At $t = 0$, deme 1 deteriorated, and at $t = \theta$ deme 2 deteriorated. Individuals in each deme reproduced, mutated and migrated, followed by density regulation. Generations are discrete and non-overlapping such that every generation the parental generation is replaced by its offspring. Each individual had Poisson distributed number of offspring with its mean proportional to the individuals fitness $w$ (see table 1 for the definitions of fitnesses $w$). Every generation new mutants entered the population via binomial sampling from the wild-type population with probability $u$. Migration was also modeled as a binomial sampling from the local populations, where migrants from each deme $i$ are sampled with probability $m_{ij}$ ($i, j \in \{1, 2\}, i \neq j$). Density regulation was applied only to deme 2 when $t < \theta$ (non-deteriorated deme), and consisted in bringing the deme back to carrying capacity at the end of the generation. The genetic composition of the regulated deme was composed by binomial sampling, thus maintaining wild-types and mutants in the non-perturbed deme at the same frequency that they reached after reproduction, mutation and migration. We run the simulation for two epochs of $\theta$ generations and add a burn-off period of 500 generations. Rescue was attained if at any moment during the simulation the number of mutants reaches $K_{\text{tot}}/2$. We performed 2000 replicates for each parameter combination, and the probability of rescue is calculated as the proportion of replicates in which rescue occurred.

Results

Probability of rescue if mutations are lethal in the old environment

We start by evaluating (2) for the symmetric case where $\kappa_1 = \kappa_2 = \kappa$ and $m_{12} = m_{21} = m/2$. Furthermore, we assume that the mutation is lethal in the old environment ($s = 1$), hence each rescue event will result from a de novo mutation. This allows us to outline our main results in a simple model and to provide some intuition about the involved mechanisms at play. We relax these assumptions later. Figure 2A shows the total probability of rescue (equation (2)) as a function of the migration rate, as well as the decomposition into mutations occurring during and after the deterioration of the environment. We observe that the probability of rescue with respect to migration is maximized for an intermediate migration rate for the parameter values used in Figure 1. This is consistent with previous results [Uecker et al., 2014]. The existence of an optimal intermediate migration rate reflects two effects that are at play here. On one hand the non-deteriorated deme acts as a source of wildtype individuals, preventing extinction in deme 1, thus increasing the chance for rescue to occur. On the other hand, too much migration between demes prevents rescue mutations from establishing despite being positively selected in one of the two demes, a process called gene swamping [Bulmer, 1972, Lenormand, 2002, Tomasini and Peischl, 2018] (Fig. 2). The limit beyond which gene flow causes swamping is $m > zs/(s - z)$ (see red line in Fig. 2A) [Bulmer, 1972, Lenormand, 2002, Tomasini and Peischl, 2018]. Hence, for large migration rates, rescue can only occur during phase 2. In addition to these two processes, increasing the migration rate should also lead to an increased flux of individuals moving from deme 2 to deme 1, which
Figure 2: (A) The total probability of rescue and its decomposition in terms of de novo mutations during phases 1 and 2. The red vertical line represents the theoretical limit beyond which gene swamp disrupts rescue in phase 1. Parameters are $z = 0.02$, $s = 1.0$, $r = 0.5$ and $\theta = 500$. (B) Comparison between simulations and prediction (equation 2), parameters are $z = 0.02$, $s = 1.0$ and $\theta = 500$, in black $r = 0.3$ and in gray $r = 0.9$.

would increase the total wildtype population size at the beginning of phase 2 (see supplemental material, Appendix A). Thus, we expect a mild positive effect on evolutionary rescue during phase 2 when increasing $m$ (Fig. 2, also supplementary material, fig. S1). The mild positive effect of large migration during phase 2 stems from the fact that at time $t = \theta$ the number of individuals in deme 1, maintained exclusively by the influx of individuals from deme 2, increases with increasing migration rate (see supplemental material, Appendix A), the two demes behaving like one population. Because a larger population size increases the chance for rescue, our model predicts a slight increase of rescue for very large migration rates. This can be seen directly from equation (7). Figure 2B shows comparison with simulations and reveals a very good fit of our analytical approximation for low to intermediate migration rates. For large migration rates, however, we underestimate the true probability of rescue. This is because we ignore the temporal change of the fitness of rescue mutations. In particular, we underestimate the establishment probabilities of mutations that occur at the end of phase 1, just before the environment in deme 2 deteriorates. Our approximation ignores this change in environmental conditions in deme 2 and hence assumes that individuals carrying mutations that occurred during phase 1 will be counter-selected in deme 2, even during phase 2 when they are actually positively selected in that deme. This effect is negligible for small migration rates but can have considerable effect for large migration rates. Because our model underestimates the rescue chance for migration rates slightly larger than the swamping limit, this might also explain why we do not see an increase in the chance for evolutionary rescue for very large migration rates in simulations.

Importantly, the probability of survival for $m \to 0$, as well as the optimal intermediate migration rate that maximizes the chance of rescue are correctly estimated by equation (2), at least for mutants with a large initial disadvantage $s$ (Fig. S7). For small $s$ and small $\theta$, the temporal inhomogeneity in selection coefficients becomes more important, as mutations may take a long time to escape drift and eventually establish. This effect is weak for small migration rates, but with
high migration rates, a relatively large number of mutants in deme 2 will be displaced to deme 1 where their establishment probability will increase (Fig. S7).

Another effect that we have ignored in our model is the increase in probability of rescue for high migration rates due to what Uecker et al. [2014] called “relaxed competition”. Density regulation in the non-deteriorated deme fills the habitat to carrying capacity at the end of each generation. For high migration rates, the non-deteriorated deme is strongly depleted and density regulation can increase the total number of mutants in a single generation (e.g. see figure S3 in the supplemental material to see the relaxed competition in a case without de novo mutations).

When does intermediate migration favors rescue?

A key unresolved question for evolutionary rescue in structured populations is: when does gene flow facilitate evolutionary rescue as compared to two populations in isolation? Our model allows us to derive a condition for when intermediate migration helps chances of survival by calculating when the derivative of \( P_{dn}^1 \) (that is, the probability of rescue due to de novo mutations during phase 1) with respect to \( m \) at \( m = 0 \) is positive. This is the case if (see supplemental material, Appendix B)

\[
\frac{1}{z} \lesssim r \theta .
\]  

(11)

Thus, our model predicts that gene flow has a positive effect on evolutionary rescue if rescue mutations are strongly beneficial in the deteriorated environment (\( z > 0 \)), respectively, if environmental change occurs slowly across demes (large \( \theta \)), and/or if the new environment is very harsh (large \( r \)). The left hand side (11) simply quantifies the strength of positive selection. A larger selection coefficient of a rescue mutation increases the fitness gain of a mutant migrant that moves into the deteriorated deme. The right-hand side of condition (11) relates the strength of selection to the impact of demographic dynamics. Both \( \theta \) and \( r \) influence the imbalance in population density between the two demes: the strength of stress, \( r \), determines both the rapidity of decay of the population size in deme 1 as well as the equilibrium density of the population (see equation (9) and Fig. 1, as well as equation (S5) in Appendix A of the supplemental material). The length of an epoch \( \theta \) determines the length of the period where deme 1 has a small population size relative to deme 2 such that gene flow is more likely to bring mutants into the deme where they are adapted to, rather than removing them from the deme where they can establish. Hence a long deterioration time or high stress extends the period where population size is low in deme 1 and large in deme 2, which is when gene flow has positive effects on rescue.

Figure 3 shows the comparison between analytical model and simulation for different combinations of parameters. In the first row \( 1/z \geq r \theta \), and as predicted by theory we observe that simulations show a roughly constant probability of rescue over the range of the migration rate \( m \). A small increase in the probability of rescue can be observed as \( \theta \) increases (from left to right), in particular in the top-right plot (\( 1/z = r \theta \)). This increase is clearly observed in all subsequent rows (for higher \( z \), top to bottom), confirming that condition (11) predicts when gene flow will facilitate
evolutionary rescue.

Figure 3: Evolutionary rescue for different combinations of parameters: first row \( z = 0.005 \), second row \( z = 0.01 \), third row \( z = 0.02 \), fourth row \( z = 0.05 \); left column \( \theta = 500 \), center column \( \theta = 1000 \), right column \( \theta = 2000 \). In all figures, \( r = 0.1 \), \( s = 1.0 \). The vertical black line in each figure is the limit for swamping, \( sz/(s-z) \). In the top two rows, we can see that passing from a situation where \( s/z > r\theta \) to one where \( s/z < r\theta \) makes the optimal migration rate more and more important. More extreme differences (e.g. third row, right column) yield a higher probability of evolutionary rescue at the optimal migration rate.

Non-lethal rescue mutations

If we consider only de novo mutations, eq. (11) can be readily generalized to non-lethal mutations and becomes

\[
\frac{s}{z} \lesssim r\theta,
\]

as is shown in the supplemental material (Appendix B). Note that this includes the condition (11) for lethal mutations as a special case if \( s = 1 \). If rescue mutations are sub-lethal or only slightly deleterious (\( s < 1 \)), the range of parameters for which gene flow facilities evolutionary rescue increases. Migration is less detrimental because a mutant experiences a milder change in fitness when migrating from one deme to another. This is sensible as gene swamping is less likely if mutations are less deleterious in the environment to which they are not adapted [Bulmer, 1972, Lenormand, 2002, Tomasini and Peischl, 2018].

Unless the selective disadvantage \( s \) of rescue mutations is very large, rescue mutations will generally be present at low frequencies in the population before the deterioration of the environment. We
Figure 4: We show the total probability of rescue and its decomposition in terms of de novo mutations during phases 1 and 2, and standing genetic variation. Parameters are $z = 0.02$, $s = 0.5$, $r = 0.5$, $\theta = 500$ and $f_0 = u/s$ (i.e. at mutation-selection equilibrium).

Thus need to account for the contribution of standing genetic variation to the probability of rescue (figure 4). We can see that the chances of survival from standing mutations are maximal in absence of migration (figure 4, also figure S3). The reason is the following: a mutation in deme 1 at $t = 0$ will have higher chances of surviving compared to a mutation in deme 2, where it is counter-selected, that is, $p^{(1)} > p^{(2)}$ for any combination of parameters. Further, because $p^{(1)}$ is monotonically decreasing [Tomasini and Peischl, 2018], $P_{sgv}$ tends to decrease with increasing migration rates (except if $s$ is small and $m$ is large, see Figure S3). By adding the contribution of standing genetic variation (as calculated with (5)) the equivalent of condition (12) yields

$$\frac{s}{z} \leq \frac{e^{\theta r}(f_0 + u \theta)}{e^{\theta r}(f_0 r + u) - u}. \quad (13)$$

For $f_0 = 0$, we recover equation (S11) in the supplemental material (Appendix B), which is in turn approximated to (12). When $f_0$ increases, the right-hand part of (13) decreases, and gene flow loses importance. In fact, since $P_{sgv}$ is monotonically decreasing with increasing migration rate $m$, standing genetic variation only matters for small to intermediate migration rates. Standing mutations will establish during phase 1 and are hence subject to gene swamping. Thus, if standing genetic variation is the predominant source of rescue mutations, gene flow is unlikely to have positive effects on rescue.

Figure S7 shows comparison between simulations and theoretical expectations for different values of $s$ (with standing genetic variation). Our approximation is again very accurate for small value of $m$, whereas simulations and analytical approximations disagree for larger values of $m$. This disagreement is more pronounced for small values of $s$. This is due to new mutants that will spread so slowly that they will reach high frequencies only during phase 2, when both environments are
Figure 5: Total probability of rescue as a function of different parameters. When not otherwise stated in the legend, parameters are $z = 0.02$, $s = 1.0$, $r = 0.25$, and $\theta = 200$. (A) Variation with $r$, (B) variation with $\theta$, (C) variation with $z$, (D) variation with $s$ (and no standing genetic variation).

deteriorated. The contribution of these mutants to the probability of rescue, however, is calculated through their probability of establishment in phase 1, which does not account for the temporal change in fitness of rescue mutations at time $\theta$. The discontinuity between $p(i(t < \theta)$ and $p(i(t > \theta)$ causes our approximation to underestimate the probability of rescue, especially for large migration rates. Along these lines we also find that (13) is not accurate for small values of $s$ (e.g., $s = 0.1$ in Figure S7). The analytical theory for standing genetic variation becomes accurate for sub-lethal mutations with a large selective disadvantage (e.g. Figure S8, $z = 0.02$, $s = 0.5$, $r = 0.5$, $\theta = 500$, and $s/z = 25 < 250 = r\theta$).

Effects of the parameters of the model

Figure 5 illustrates the influence of various parameters on the probability of rescue. Increasing $z$ has the main effect of increasing the probability of rescue, because a more beneficial mutation clearly has a larger chances of surviving (Figure 5A). At the same time, the optimal migration rate (when it exists) increases with increasing $z$. The reason is that the critical migration rate beyond which gene swamping occurs increases with increasing $z$: the condition for gene swamping is $m > sz/(s-z)$ [Bulmer, 1972, Lenormand, 2002, Tomasini and Peischl, 2018]. For $z \ll 1$, this reduces to $m \gtrsim z$, which thus allows establishment to occur for larger $m$. Decreasing the strength
of environmental stress, \( r \), leads to a higher overall probability of rescue because population sizes decline more slowly, leaving more time for rescue to occur (Figure 5B). The critical threshold at which swamping occurs remains unaffected, as it depends on the ratio between \( z \) and \( m \) only [Tomasini and Peischl, 2018]. Increasing \( \theta \) extends the length of phase 1, which can increase the probability of rescue dramatically for intermediate migration rates but not for low or high migration rates (Figure 5C). For low migration rates, the length of phase 1 has very little impact since the two demes evolve almost independently. For strong migration, the length of phase 1 does not matter, because swamping prevents the establishment of rescue mutations during phase 1. Figure 5D shows that decreasing the deleterious effect of rescue mutations \( s \) has a similar effect on the probability of evolutionary rescue from \textit{de novo} mutations as increasing \( \theta \). Decreasing \( s \) also affects the critical migration rate beyond which gene swamping occurs [Bulmer, 1972, Tomasini and Peischl, 2018], but this effect is rather weak. This can be seen if we rewrite the condition for gene swamping as \( m > z/(1-z/s) \). In particular, if \( z < s \), the effect of \( s \) becomes negligible.

**Asymmetric carrying capacities and migration rates**

We next consider the effect of asymmetric migration rates or asymmetric carrying capacities. For better comparison across models (see e.g. Barton et al. [2002]) and without loss of generality, we introduce two new parameters \( \zeta \) and \( \beta \) that measure the degree of asymmetry:

\[
\begin{align*}
m_{12} &= \zeta m, \\
m_{21} &= (1 - \zeta) m, \\
\kappa_1 &= \beta K_{\text{tot}}, \\
\kappa_2 &= (1 - \beta) K_{\text{tot}}.
\end{align*}
\]

With these definitions, the model is symmetric with respect to migration rates if \( \zeta = 0.5 \) and carrying capacities if \( \beta = 0.5 \). For \( \zeta < 0.5 \), migration from deme 1 to deme 2 is smaller, while the opposite is true when \( \zeta > 0.5 \). Figure 6A shows the probability of rescue as a function of \( m \).
for different values of $\zeta$. For $\zeta = 0.9$, deme 2 receives many more migrants than it sends out, as compared to the symmetric model. The main effect of this asymmetry in migration is to decrease the total probability of rescue because rescue mutations are more likely to be removed from the deme to which they are adapted to as compare to the symmetric case. Further, gene swamping happens for lower values of $m$ [Bulmer, 1972], thus reducing any beneficial effects of gene flow. The opposite is true for $\zeta = 0.1$: wildtype individuals are removed at a smaller rate from the deme where they are adapted to, which increases the chances of survival. At the same time, gene swamping occurs for larger values of $m$ with respect to the symmetric case. The reduced effect of gene swamping with decreasing $\zeta$ also becomes apparent from the increase of the migration rate that maximizes the chance for evolutionary rescue. Figure S6A and S7A show comparison with simulations for de novo mutations and standing genetic variation with asymmetric migration rates.

We next keep migration rates symmetric, such that $m_{12} = m_{21} = m/2$, and investigate the effect of asymmetries in carrying capacities. Figure 6B shows the probability of rescue as a function of $m$ for different $\beta$. We are going to call deme 2 “the reservoir”, as during phase 1 it is left untouched and it never goes extinct. We observe that a larger reservoir yields higher probability of rescue, and vice versa, when a reservoir is smaller the probability of rescue decreases. This is mainly due to de novo mutations during the second phase. Hence, chances of new mutants to establish increase because there are more wildtype individuals to start with at $t = \theta$. When it exists, the optimal migration rate remains the same as in the symmetric model, even though it yields higher chances of survival for a larger reservoir. Figures S6B and S7B show comparison with simulations for de novo mutations and standing genetic variation with asymmetric carrying capacities. The condition for when gene flow facilitates evolutionary rescue from de novo mutations as compared to no migration becomes (see supplemental material, Appendix B)

$$\frac{s}{z} \lesssim Fr\theta,$$

(16)

where

$$F = \frac{m_{21} \kappa_2}{m_{12} \kappa_1}.$$

(17)

Condition (16) generalizes conditions (11) and (12) (it is also easy to generalize condition (13), as shown in the supplementary information, Appendix B, (S10)). This reflects the dynamics of a source-sink scenario. When deme 2 is large – the source is large – it sends many wild-types to the sink, where new mutants could arise and prosper. The same happens if immigration in deme 1, $m_{21}$, is large. In extreme cases, when $\kappa_1 < m_{21}\kappa_2$, immigration in deme 1 causes overflow. This corresponds to a situation in which the population in a sink (in this case in deme 1) does not decline until the reservoir (deme 2) becomes deteriorated. On the other hand, since what matters most for ultimate rescue is the number of mutants, this high rate of migration also causes purifying selection in deme 1, not allowing any mutant to survive for long.

Figure S8 in the supplemental material (Appendix D) shows a comparison between theoretical expectations and simulations for asymmetric scenarios, revealing a good fit for small to intermediate
migration rates.

The role of density regulation

So far we have assumed that density regulation keeps the unperturbed deme at carrying capacity at all times. This requires sufficiently high local growth rates so that any reduction of the populations size due to emigration is immediately compensated by rapid growth within the unperturbed deme. This has the advantage that we do not need to model density regulation explicitly and is the same kind of density regulation as described in [Uecker et al., 2014]. We relax this assumption by assuming Beverton-Holt dynamics [Beverton and Holt, 1957] in the unperturbed deme: this means that the number of individuals $N_i$ of each type $i$ (wild-types or mutants, $i \in \{\text{wt, m}\}$) in the non-deteriorated deme in the next generation will follow

$$N_i(t+1) = N_i(t) \frac{w_i^{(o)} \rho}{(1 + (\rho - 1)N_{\text{tot}}(t)/\kappa)},$$

where $\rho$ denotes the growth rate of the population, $N_{\text{tot}}(t)$ the total number of individuals in the deme, and $w_i^{(o)}$ the fitness of individuals of type $i$. Differences between the two modes of density regulation are summarized in supplemental material (Appendix C). We performed simulations of this model and compare the outcomes to the model with instantaneous growth (Figure 7). In all considered cases, the two modes of density regulation do not show any difference for low to intermediate migration rate. This is not surprising, as emigration affects the total number of individuals in the unperturbed deme only mildly, and even small values of $\rho$ ensure that carrying capacity is maintained. For intermediate to large migration rates, however, the behavior can change dramatically (Figure 7). In particular, our simulations show that for large migration rates, the probability of rescue can be much lower if the growth rate $\rho$ is small. To understand this behavior, let us first consider the case where population growth is instantaneous. The source population (unperturbed deme) is constantly losing individuals due to emigration into the sink population (perturbed deme). As a consequence, population growth will increase the absolute fitness of the remaining individuals in the source population [Tomasini and Peischl, 2018]. Thus selection in the unperturbed deme is less efficient as compared to the case without gene flow. The increase of the probability of rescue as $m$ increases is due to relaxed competition and has been demonstrated formally in a two-deme model with source-sink dynamics [Tomasini and Peischl, 2018]. But if density regulation is logistic and growth rates are small, the advantage of relaxed competition disappears as emigration removes individuals more quickly than they can be reproduced. In this case we would expect that the probability of rescue starts to decline once the migration rate exceeds the critical value beyond which population growth can no longer maintain the population at carrying capacity. To calculate this critical migration rate, we approximate the net loss of individuals due to migration in deme 2 by solving

$$N_2(t+1) \approx N_2(t) \left(1 - \frac{m}{2}\right) \frac{\rho}{1 + (\rho - 1)N_2(t)/\kappa_2}.$$
Note that in this calculation we neglect the number of individuals coming from deme 1 and all the mutant individuals. The evolution of the individuals in deme 2 is calculated explicitly in the supplemental material (see Appendix C, equation (S14)). Now, extinction occurs when \( N_2(t) = 0 \) for some \( t > 0 \). This happens when
\[
\rho \left( 1 - \frac{m}{2} \right) \leq 1,
\]
or when the product of the rate of growth and the rate of migration (loss) is smaller than 1. We should note that relation (20) is a conservative limit. As we do not take into account the presence of mutants, but only the net loss of wildtype individuals, this result does not account for the possibility of having a mutant establishing in the first generations after the deterioration event, as it is often the case [Peischl and Kirkpatrick, 2012]. The vertical lines in Figure 7 indicate this critical migration rates and confirm our intuitive explanation above.

Figure 7: Comparison between different types of density selection for harsh changes over short periods. Here, \( z = 0.02 \), \( s = 0.1 \), \( r = 0.9 \) and \( \theta = 100 \). The vertical lines show the critical migration rate for which equation (20) holds. Points and lines in blue refer to \( \rho = 1.01 \), in green \( \rho = 1.25 \), in orange to \( \rho = 1.5 \) and we show hard density regulation in purple.

Hence, density regulation can reduce the beneficial effects of gene flow if the growth rate \( \rho \) is not large enough such that the unperturbed deme does not remain at carrying capacity, and there is no relaxed competition. Even when there is the potential for relaxed competition in terms of \( s \), \( r \) and \( \theta \) (see [Uecker et al., 2014]), a slower growth rate lowers the chances of rescue for intermediate migration rates and higher (see figure 7). Ultimately, small growth rate \( \rho \) disrupts all effects due to migration and allows gene swamping to occur more readily. This is sensible, as low growth rate means that there will be fewer individuals in deme 2 and migration is mainly detrimental to the establishment of rescue mutations and also reduces the population size that can contribute to evolutionary rescue.
Discussion

We studied a model for evolutionary rescue in a structured population using recent analytical results for establishment probabilities in structured populations [Tomasini and Peischl, 2018]. Our main result is an analytical prediction for the conditions under which gene flow facilitates evolutionary rescue in structured populations as compared to a population without gene flow. The potentially positive effect of gene flow on evolutionary rescue has been described previously both experimentally and theoretically; experimentally during adaptation to a gradient of salinity in a yeast meta-population [Gonzalez and Bell, 2013], mathematically in a model for evolutionary rescue in structured populations [Uecker et al., 2014], and via simulations of the evolution of treatment resistance in solid tumours [Waclaw et al., 2015]. These findings are in contrast to the fact that dispersal does generally not have a positive effect on (local) adaptation [Bulmer, 1972, Holt and Gomulkiewicz, 1997, Lenormand, 2002] in populations with more stable demographic scenarios, and the conditions for when gene flow facilitates survival in the face of drastic environmental change were previously not known. Our study fills this gap and provides surprisingly simple and intuitive conditions for when we expect positive effects of gene flow on survival via adaptation. Furthermore, our model allowed us to describe the interactions between density regulation, demographic dynamics and gene flow during adaptation to severe environmental stress.

We showed that the probability of evolutionary rescue from de novo mutations will be maximized for a migration rate \( m > 0 \) if \( s/z < r\theta \), where \( r \) describes the harshness of the new environment, \( \theta \) the speed of environmental change, \( s > 0 \) is the cost of carrying a rescue mutation in the original environment (e.g., the cost of having a antibiotic mutation in the absence of antibiotics), and \( z > 0 \) is the selective advantage of a rescue mutation in harsh environments (e.g., the advantage of carrying an antibiotic resistance mutation in the presence of antibiotics). Thus, our model predicts that gene flow has a positive effect on evolutionary rescue if (i) rescue mutations are strongly beneficial/weakly deleterious in the deteriorated/original environment, respectively, if (ii) environmental change occurs slowly across demes (large \( \theta \)), and/or if (iii) the new environment is very harsh (large \( r \)). We then extended this result to account for the effects of standing genetic variation, asymmetry in carrying capacities and the direction of gene flow between demes. Finally, we investigate the details of density regulation and find that they strongly affect whether gene flow will facilitate survival or not. In particular, if local growth rates in unperturbed demes are so low that carrying capacities cannot be maintained due to emigration of individuals, positive effects of gene flow diminish. The predictions that we derive from the model are corroborated by stochastic simulations.

Our results show that the main positive effect of gene flow is during phase 1, i.e. during the epoch in which only one deme is deteriorated. Gene flow from the unperturbed deme into the perturbed deme provides the raw material which can increase the chance of evolutionary rescue as compared
to two populations without gene flow. This phenomenon has recently been formally studied in a
two-deme model with divergent selection, where gene flow can be beneficial to the rate of establish-
ment of locally adapted mutations [Tomasini and Peischl, 2018]. This is reflected in the equation
\( s/z < r \theta \); the stronger the source-sink dynamics of the unperturbed and perturbed habitat (large
\( r \)) and the longer these source-sink dynamics last (large \( \theta \)), the more likely it is that gene flow is
beneficial for evolutionary rescue. This effect is further amplified if carrying capacities or gene flow
is asymmetric such that more individuals migrate from the unperturbed to the perturbed habitat
\( (F > 1 \text{ in eq. (16))} \). Our model matches the results found by Uecker et al. [2014], in particular in
the range where gene swamping does not occur (see Fig. S2 for a direct comparison).

We found that interactions between gene flow and density regulation play an important role. Ultimately,
when the growth rate \( \rho \) of the wild-type in deme 2 is large enough to compensate emigration
to deme 1, the system remains in a source-sink scenario (see e.g. Gomulkiewicz et al. [1999]) and
gene flow can be beneficial for evolutionary rescue. Furthermore, if the growth rate is very large,
we observe relaxed competition (see also Uecker et al. [2014]) which can counter the negative effects
of rescue mutations in the unperturbed habitat. If, however, gene flow depletes individuals too
quickly in the unperturbed deme such that density regulation cannot replace these individuals, the
positive effects of gene flow disappear (Figure 7).

It has been argued that standing genetic variation, along with initial population density, is the
main factor determining the chances of evolutionary rescue [Gomulkiewicz and Holt, 1995, Barrett
and Schluter, 2008, Agashe et al., 2011, Lachapelle and Bell, 2012, Ramsayer et al., 2013, Van-
der Wal et al., 2013]. While we find that this is the case in the absence of gene flow or if gene flow
is very high, we also find that the contribution of de novo mutations can dwarf the contribution
of standing variation for intermediate migration rates (see e.g., Figure 2). Also, we find that not
only the initial size of the total population plays a major role, but also the variation in population
densities across habitats (Figure 6).

The main short-coming of our approach is the inability to account correctly for the time-inhomogeneity
of selective coefficients of wildtype and mutant individuals. This becomes critical for mutants aris-
ing just before the second deterioration event, as their probability of establishment will be closer
to \( 2z \) than the approximation we used. This discrepancy increases with increasing migration rate
(see eqs. (3) and (4)) and decreasing \( s \) (as slightly deleterious mutations are less likely to be
purged before time \( \theta \)). Hence, for slightly deleterious mutations our model underestimates the
probability of rescue (see figure S4). It would be interesting to generalize our approach in such
a way to account correctly for time-inhomogeneous selective coefficients, which could be achieved
by fusing the approaches of Peischl and Kirkpatrick [2012] and Tomasini and Peischl [2018]. This
is, however, a mathematically challenging endeavour and beyond the scope of this paper. Another
interesting extension of our model would be to account for more than two demes. This would allow
us to study different modes of dispersal, e.g., island models vs. stepping stone model, and could
help to explain experimental findings that show that the mode of dispersal can strongly influence
a populations chance of survival [Bell and Gonzalez, 2011].
In our analysis, we assumed mutations that establish in isolation from other genetic events that may interfere with the process (e.g. clonal interference, [Gerrish and Lenski, 1998]). Therefore, we expect our results to hold in species reproducing sexually with strong recombination. In diploid individuals, the degree of dominance of rescue mutations may impact the evolutionary dynamics or rescue mutations. If mutations are co-dominant or partially recessive, our results can be carried over to diploid models by redefining our parameters $s$ and $z$ as the fitness effects of mutations in heterozygotes in the two environments. By excluding competition with concurrent mutations from our analysis, we expect this model to be less predictive for organisms reproducing with low recombination rates - or for mutations occurring in regions with low recombination rate. However, some of our results could still be valuable, as many of the effects that we described depend strongly on ecological aspects (such as carrying capacities, growth rate, migration rate) and evolutionary rescue focuses on relatively short periods such that co-segregation of multiple mutations seems unlikely.

Our approach could help improve understanding some of the results found in experimental setups (e.g. Bell and Gonzalez [2011]) and in theoretical investigations (e.g. Uecker et al. [2014]) about the effects of dispersal on the probability of evolutionary rescue. The simple and intuitive analytical predictions are imperative for our understanding of evolutionary rescue in structured populations and help us sharpen our intuition about the interactions of ecological and evolutionary process on short time-scales. A setup similar to the one proposed by Bell and Gonzalez [2011], with sub-populations of yeast exposed to a gradient of salt changing in time would be ideal to test our predictions.

Acknowledgements

We thank Mark Kirkpatrick, Sally Otto and Katie Peichel for stimulating discussions on this subject. We also thank Joachim Hermisson and Laurent Excoffier for helpful comments on the first manuscript. We gratefully acknowledge helpful comments from Claudia Bank, as well as three anonymous reviewers.

Conflict of interest disclosure

The authors of this pre-print declare that they have no financial conflict of interest with the content of this article.

References


Appendix A: probability of rescue

We calculate the probability of rescue from beneficial mutations in a two-deme model in which habitats deteriorate over time. A mutation has selective coefficient \( z > 0 \) in a deteriorated region and coefficient \( s > 0 \) in a non-deteriorated region. We distinguish three different temporal phases: (phase 0) at \( t < t_0 \), both demes are not deteriorated; (phase 1) at \( t_0 \) we deteriorate deme 1; (phase 2) at time \( t = t_0 + \theta \) we deteriorated deme 2.

To evaluate equations (5)–(8) (at end of phase 0 and during phase 1) we use the probabilities of establishment of mutations experiencing different selection pressure in each patch of a two-deme model [Tomasini and Peischl, 2018]. A mutation can arise in deme 1 or in deme 2, and it establishes with probabilities \( p^{(1)} \) and \( p^{(2)} \) respectively:

\[
p^{(1)} = z(1 + \sigma - \Delta) - s\mu_{12},
\]

\[
p^{(2)} = z\mu_{21} - s(1 - \sigma + \Delta),
\]

where

\[
\sigma = \frac{z + s}{\lambda}, \quad \mu_{ij} = \frac{2m_{ij}}{\lambda}, \quad \Delta = \frac{\mu_{12} - \mu_{21}}{2}
\]
and \( \lambda = \sqrt{(m_{12} + m_{21})^2 + (z + s)^2 - 2(m_{12} - m_{21})(z + s)} \). The derivation is based on slightly super-critical branching processes and is valid for large populations with weak selection \((1/N < z \ll 1)\). The method is valid for slightly super-critical branching processes (see Tomasini and Peischl [2018] for a full discussion of the validity of the model). Note that these equations do not account for the temporal in-homogeneity in selection coefficients at time \( t = \theta \), and hence should be a good approximation if \( \theta \gg 0 \) and if \( s \gg 0 \).

**Probability of rescue for de novo mutations**

In order to calculate formula (7) we need to solve equations (9) and (10). During phase 1 \((t < t_0 + \theta)\), \( N_2(t) = \kappa \). Solving (9) yields

\[
N_1(t) = e^{-(m_{12} + r)t} \left[ \kappa_1 - \frac{m_{21} \kappa_2}{m_{12} + r} \right] + \frac{m_{21} \kappa_2}{m_{12} + r} \tag{S4}
\]

**Equilibrium population in deme 1 increases with \( m \)**

In the following we assume that \( \theta \) is large. For large \( t < \theta \), the exponential term of equation (S4) goes to zero. For the symmetric case \((m_{12} = m_{21} = m/2)\) then, population in deme 1 reaches an equilibrium described by

\[
N_1(t) \approx \frac{m \kappa_2}{m + 2r} \tag{S5}
\]

Then, this is also the population of deme 1 at time \( t = \theta \). This shows that the population in deme 1 increases when \( m \) increases (see main text, discussion of figure 2). Note that this approximation is only valid for \( \theta \gg 0 \).

During phase 2, when both demes are deteriorated, \( N_1(t) \) and \( N_2(t) \) follow equation (10) with initial conditions \( N_1(\theta) \) given by (S5) and \( N_2(\theta) = \kappa_2 \).

Equation (S5) does not only represent the population in deme 1 at time \( t = \theta \), but also during most of phase 1, as the left-hand term of equation (S5) decreases exponentially.

We can show that the same is true for the case with asymmetric migration or asymmetric carrying capacities. With asymmetric migration \((m_{12} = \zeta m \text{ and } m_{21} = (1 - \zeta)m, \text{ see main text, equations (14) and (15)})\), for large \( t < \theta \), equation (S5) yields

\[
N_1(t) \approx \frac{(1 - \zeta)m \kappa_2}{\zeta m + r} \tag{S6}
\]

This increases with \( \zeta \), and hence we deduce that the larger migration is from deme 2 to deme 1 \((\zeta \text{ increases})\) the larger \( N_1(t) \) is over time, and the larger the probability of rescue.

For \( m_{12} = m_{21} = m/2 \) and asymmetric carrying capacities (from the main text, \( \kappa_2 = (1 - \beta)\kappa \)), the equilibrium population in deme 1 is

\[
N_1(t) \approx \frac{m(1 - \beta)\kappa}{m + 2r} \tag{S7}
\]
which increases when $\beta$ decreases (hence when $\kappa_1$ becomes smaller than $\kappa_2$).

The solutions $N_1(t)$ and $N_2(t)$ can be obtained straightforwardly for $t > t_0 + \theta$ but are very long and it does not bear any use to write them explicitly here. Plugging everything into (7) and (8), we obtain a straightforward analytical formula for the probability of rescue from de novo mutations during phase 1. All calculations can be easily carried out with software such as Mathematica.

**Gene swamping does not allow for rescue in phase 1 for high $m$**

In the main text we discuss how for high migration rates $m_{ij}$, establishment during phase 1 cannot occur because of a phenomenon called gene swamping. Gene swamping arises generally in two-deme models with divergent selection. Establishment probabilities during phase 1 (equations (S1)–(S3)) are 0 if $m > \frac{m_{21}}{m_{12}}$ (in the case of symmetric migration, but the same can be calculated for asymmetric migration, see Tomasini and Peischl [2018]). This condition is equivalent to the gene swamping limit in deterministic models derived in Bulmer [1972] and Lenormand [2002]. Thus, rescue mutations cannot occur during phase 1 if the migration rate exceeds this limit.

**Appendix B: when does gene flow facilitate rescue?**

We want to know for which set of parameters intermediate migration increases the chance for evolutionary rescue, as compared to no migration. This is equivalent to the set of parameters for which

$$\frac{\partial P_{res}}{\partial m} \bigg|_{m=0} > 0.$$  \hspace{1cm} \text{(S9)}

To do this, we use an approach similar to the one used in Tomasini and Peischl [2018] to find an approximated form of the probabilities of establishment (also see Appendix A). We first re-scale all parameters with respect to $z$ ($s = z\xi$, $m_{ij} = z\chi_{ij}$) and then linearize (2) with respect to $z$.

Then, we take the derivative of the linearized form of $P_{res}$ and find its root. Switching back to the original variables, we find that condition (S9) is satisfied when

$$\frac{s}{z} < \frac{m_{21} \kappa_2}{m_{12} \kappa_1} \cdot \frac{e^{r\theta}(f_0 + u\theta)}{e^{r\theta}(f_0 + u) - u}.$$  \hspace{1cm} \text{(S10)}

If we set $f_0 = 0$ (hence no standing genetic variation), we find that the condition reads

$$\frac{s}{z} < \frac{m_{21} \kappa_2}{m_{12} \kappa_1} \cdot \frac{e^{r\theta} \theta}{e^{r\theta} - 1}.$$  \hspace{1cm} \text{(S11)}

Because the function $xe^x/(e^x - 1) \approx x$ if $x$ is large enough (approximately for $x \gtrsim 4$), we obtain equation (16). Note that conditions (11), (12) and (13) in the main text refer to the symmetric model ($m_{21}/m_{12} = \kappa_2/\kappa_1 = 1$, and with $s = 1$ in condition (11)), while here we derive the general result. In the main text we further define $F = m_{21}\kappa_2/m_{12}\kappa_1$. 

3
Appendix C: the role of density regulation and local growth rates

Figure 7 shows examples for the probability of evolutionary rescue when the density of the non-deteriorated deme is regulated following a Beverton-Holt model of logistic growth [Beverton and Holt, 1957]:

$$N_2(t + 1) = N_2(t) \frac{\rho}{1 + (\rho - 1)N_{\text{tot}}(t)/\kappa}.$$  \hfill (S12)

We find that the probability of rescue in this case can deviate strongly from the regime of instantaneous growth, where the population in the non-deteriorated deme always remains at carrying capacity. The latter should be a good approximation to the former if the growth rate $\rho$ is large enough relatively to the migration rate.

Here, we explore this intuition quantitatively. We calculate the loss of individuals from deme 2 during one generation, neglecting individuals coming in from deme 1. This works in particular for $t$ large, since deme 1 is almost depleted after a few generations and we can ignore the influx of immigrants from deme 1 into deme 2. Hence, we solve

$$N_2(t + 1) = N_2(t) \left(1 - \frac{m}{2}\right) \frac{\rho}{1 + (\rho - 1)N_2(t)/\kappa}.$$  \hfill (S13)

with initial condition $N_2(t = 0) = \kappa$. We find

$$N_2(t) = \frac{\kappa(2 - 2\rho + mp)}{2 - 2\rho + 2\rho^2 m \rho \left(\frac{1}{2\rho - mp}\right)^t}.$$  \hfill (S14)

Now, gene flow should be detrimental to evolutionary rescue if the interplay of $m$ (causing loss of individuals from deme 2) and $\rho$ (causing gain of individuals in deme 2) causes deme 2 to eventually go extinct. We find that $N_2(t) \to 0$, when $t \to \infty$, if

$$\rho \left(1 - \frac{m}{2}\right) \leq 1.$$  \hfill (S15)

In particular, condition (S15) is very accurate for large $m$, as rescue for that range of migration is ensured exclusively by mutations arising during phase 2 (see figure 2). Figure 7 shows that this rule of thumb remains accurate over the whole range of $m$ when other kinds of density regulation are at play.
Figure S1: **Symmetric model:** contribution of mutations arising during phase 2 to evolutionary rescue for different $r$, $z = 0.02$, $s = 1$, $\theta = 200$. All curves increase with $m$. 
Figure S2: **Comparison:** (A and B) we plot approximation (2) in the main text VS. the approximation for two demes without standing genetic variation proposed by Uecker et al. [2014], with respect to the migration rate $m$, with $r = 0.1$ and (A) $\theta = 250$, (B) $\theta = 500$; (C and D) we plot the same comparison with respect to the stress $r$, with $\theta = 500$ and (C) $m = 0.02$ (corresponding to the ideal migration rate) and (D) $m = 0.1$. The two approximations are most similar for low $r$. Other parameters are $z = 0.02$, $s = 1.0$. Uecker et al. [2014] used a time-dependent process but did not model demes explicitly. Furthermore their solution is only for lethal mutations in the new environment ($s = 1$). We model both demes explicitly but do not take into account time-inhomogeneities, and our result is valid for $s < 1$. Our approach allows the derivation of general closed-form equations for the probability of rescue (while in Uecker et al. [2014] equations for every scenario need to be calculated separately). The two models yield very similar results for $m$ up to intermediate values.
Figure S3: **Standing genetic variation**: contribution to evolutionary rescue by standing genetic variation in the symmetric model, simulations with analytical expectations (see equation (5)). Parameters are $z = 0.02$, $\theta = 500$, $r = 0.3$. Black points show $s = 0.1$, gray points $s = 0.9$. (A) After density up-regulation, mutants are not replaced according to mutant frequencies preceding the regulation. (B) Mutants are replaced according to mutant frequencies. We can notice the effect of relaxed competition for mildly deleterious mutations (see main text).

Figure S4: **Symmetric model**: evolutionary rescue as a function of $m$ for different selective coefficients $s$ (cost in the unperturbed deme). Comparison between theoretical calculations and simulations, for $z = 0.02$, $\theta = 500$ and $r = 0.3$, $s = 0.1$ (orange), $s = 0.5$ (purple), $s = 1.0$ (green). We observe that our model is unable to correctly account for mildly deleterious mutations (see orange line).
Figure S5: Comparison between model and simulations for different combinations of parameters: first row $s = 0.1$ and $\theta = 100$, second row $s = 0.5$ and $\theta = 200$, third row $s = 1.0$ and $\theta = 400$; left column $r = 0.1$, center left column $r = 0.25$, center right column $r = 0.5$, right column $r = 0.9$. In all figures, $z = 0.02$. The vertical black line in each figure is the limit for gene swamping, $sz/(s - z)$. In general, our approximation requires a very large $\theta$ to be precise. The values selected for $\theta$ in the first and second row are very low and we can observe that condition (12) in the main text is not clearly shown in simulations, in this case. Furthermore, the first row shows comparison between simulation and theory for very low $s$: we know that our model isn’t able to correctly account for the time-inhomogeneity for such low values of $s$ (see also figure S4). Finally, choosing a very high value for $r$ (right column) yields very low probability of rescue, and simulations cannot clearly discern if gene flow facilitates rescue or not.
Figure S6: **Asymmetric models for lethal mutations**: comparison between theoretical calculations and simulations, for $z = 0.02$, $\theta = 500$, $r = 0.3$, $s = 1.0$. (A) Asymmetric migration rates. In orange, $\zeta = 0.1$, in purple $\zeta = 0.5$, in green $\zeta = 0.9$. (B) Asymmetric carrying capacities. In orange, $\beta = 0.1$, in purple $\beta = 0.5$, in green $\beta = 0.9$.

Figure S7: **Asymmetric models with standing genetic variation**: comparison between theoretical calculations and simulations, for $z = 0.02$, $\theta = 500$, $r = 0.3$, $s = 0.5$. (A) Asymmetric migration rates. In orange, $\zeta = 0.1$, in purple $\zeta = 0.5$, in green $\zeta = 0.9$. (B) Asymmetric carrying capacities. In orange, $\beta = 0.1$, in purple $\beta = 0.5$, in green $\beta = 0.9$. We can see that at $m \to 0$ expectations are different than simulations (see Appendix A).
Figure S8: **Comparison between model and simulations for different combinations of parameters**: upper row is for asymmetric migration, lower row for asymmetric carrying capacities; left top panel has $\zeta = 0.25$, center top $\zeta = 0.5$ and right top $\zeta = 0.75$; left bottom has $\beta = 0.25$, center bottom $\beta = 0.5$ and right bottom $\beta = 0.75$. In all figures, $z = 0.01$, $s = 0.5$, $r = 0.1$, $\theta = 800$. The vertical black line in each figure is the limit for gene swamping, $sz/(s - z)$. This condition is calculated for a case with symmetric migration, thus it fails when $\zeta \neq 0.5$. Even in these scenarios, our model is able to predict reasonably well when migration facilitates evolutionary rescue. We also note that in simulations, while for the symmetric case (center top and bottom panels) $P_{\text{Rescue}}$ is the same for $m \to 0$ and $m \to 1$, this is not the case for both cases where there is an asymmetry in the system.

**References**


102 Ministry of Agriculture, Fisheries and Food, 1957.

