Environmental fluctuations can promote evolutionary rescue in high-extinction risk scenarios

James H. Peniston, Michael Barfield, Andrew Gonzalez and Robert D. Holt

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSPB-2019-2030.R0 (Original submission)

Review form: Reviewer 1

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
The manuscript presents a tidy analysis showing that highly auto-correlated environmental fluctuations can positively affect the chances of evolutionary rescue in very high-extinction-risk populations. The result is nice and makes complete sense, but is not obvious (or at least was not to me) before reading the paper. This is a novel finding with implications for conservation and design of drug treatment regimes as well as theoretical interest.

1. Novelty:
The finding is novel, but the framing of the abstract implies a bit more novelty than is justified in my opinion. The few previous studies of evolutionary rescue in noisy environments [e.g. 11; using ref numbers from the manuscript] focused on the effect of environmental noise in 'low-extinction-risk' (i.e. less harsh) environments -- where increases in the magnitude of environmental fluctuations do increase extinction risk. As Figure 1b of the manuscript shows nicely, when the environment becomes hasher the effect of autocorrelated fluctuations reverses and extinction risk decreases as the magnitude of fluctuations increases. This is an interesting reversal of effects seen in previous studies. However, I don't think the few papers exploring the effect of noise on rescue [8, 9, 11] should be read to imply, as the abstract states, that rescue "is more likely to occur in constant environments". Indeed as this manuscript states and as mentioned in at least one of these references, environmental conditions are essentially never static -- so this previous work should be framed as assuming noise but emphasizing the negative effect of increased magnitude of noise on rescue.

2. Clarifying 'high-extinction-risk'
In this paper, I believe 'high-extinction-risk' means an environment where the mean population trajectory would go below the quasi-extinction threshold N_c*. However, the general statement of this condition is missing and the reason for the quantitative location of the thresholds in Figure 1 and A1 are unclear as a result. I believe the threshold location and definition could be derived as the point (initial population size or size of shift) at which the population trajectory equals N_c at T_r (e.g., using equation 11 from Gomulkiewicz and Holt 1995). This might not be necessary and it could be clearer to just state the condition for the location and which parameters it depends upon.

*: It is less clear to me what the condition is for a generic definition in the monogenetic model but this would be useful to mention, even if one is not derived.

3. Presentation of the figures
In Figures 1, A1, and A4 the symbol-lines really should be replaced with several shades of gray to emphasize that there is a parameter that quantitatively varies parameter among the lines. In Figure 1, the thickness of the line for constant environment should be the same as the others. Some language in the caption (or some notation on the axis if it is introduced) could help clarify the threshold location for Figure 1.

Review form: Reviewer 2 (Helen Alexander)

Recommendation
Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Good

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

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    Is it accessible?
    Yes

    Is it clear?
    Yes

    Is it adequate?
    Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
Please see attachment.

Review form: Reviewer 3 (Yoann Anciaux)

Recommendation
Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Good

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

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> **Is it accessible?**
> Yes

> **Is it clear?**
> Yes

> **Is it adequate?**
> Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
#Summary
The authors study the process of evolutionary rescue after an abrupt environmental change and focus on the effects of temporal fluctuations of conditions in this new environment. To this end, they developed two population-level models (polygenic and monogenic) based on two models complementary which have been commonly used in the theoretical literature of evolutionary rescue. They compared them to individual based simulations with relaxed assumptions (phenotypic variance generated by various processes and demographic stochasticity). They considered both variation of an environmental stressor to which the population can adapt and variations still affecting the fitness but independent of the selective pressure.
Based on these models, they show opposite effects of environmental fluctuations on the probability of extinction depending of the risk of extinction faced by the population after the first abrupt environmental change. One result which stands out from the current literature is that environmental variations, on average, decrease the probability of extinction if the population is already facing a high extinction risk, especially with autocorrelation.

The authors also show that the window over which environmental variations have the most impact is relatively short and start early.

As stated by the authors in the discussion section, these results could give new insights in the debate about the frequency and the strength of treatments against pathogens.

The introduction gives a good overview of the literature, and the methods are quite clear. The authors provide enough material for the reproducibility of their results : the analytical developments of their approximations in appendix and annotated simulation codes. The generality of the main results are difficult to judge as explained below but the authors managed to give intuitive interpretations of their results. The information brought by the figures could be improved as suggested below. Some limits of the result regarding the simulations could be added to the section "Assumptions and caveats". If there is a length issue, the different examples spread over the discussion could be more summarized in the application section.

#Major comments :

I) The first model developed is very similar, among others, to the model from Chevin et al. (2017) at least for variations of the environmental stressor, using the same critical population size as an heuristic for extinction probability.

The authors show in the population-level model that increasing variations (both for the stressor or the fecundity):

(1) increase the probability that the population size will go below the critical heuristic (100) for low initial maladaptation.

(2) decrease the probability that the population size will go below the critical heuristic (100) for high initial maladaptation.

(3) both results (1) and (2) are reinforced by autocorrelation.

Result (1) is in agreement with the individual-based simulation and with previous results of the literature, in particular Chevin et al. (2017).

However result (1) is not observed in the individual-based simulations for the variation in fecundity.

Result (2) is new compared to previous results of the literature, in particular Chevin et al. (2017), but is also not observed in the simulations (neither for the variations of the environmental stressor nor the fecundity).

Result (3) is difficult to compare to the simulations due to the two points above.

As acknowledged by the authors (l236-242), it is difficult to judge if these important discrepancies between the simulations and the analytical models are due to differences in the parameters used (e.g. between figure 1 and A1) or to the assumptions of the model.

These unresolved discrepancies make it difficult to understand to which extent the results of the population-level model can be generalized. Which is directly related to the potential applications mentioned by the authors in discussion. If possible in term of computational power, the authors could add simulations to figure 1 to show if the discrepancies are still visible for similar parameters. And if it is the case, it would be important to discuss (in regard to previous articles such as Chevin et al. 2017) which assumptions might be at the origin of these discrepancies with the simulations and the literature.

II) The second model is based on a model similar to a large part of the evolutionary rescue literature (Gomulkiewicz and Holt 1995, Orr and Unckless 2008, 2014, Martin et al. 2013, Anciaux et al. 2018) based on origin-fixation models (McCandlish and Stoltzfus 2014) but add the environmental fluctuations on top iof it. The authors found analytical approximations for the probability of persistence with variations in the environment which had not been done previously to my knowledge. Thus it would be interesting to compare it (in the case without fluctuations) to previous analytical results.

The results in figure A5 shows a good agreement between the simulations and the analytical approximations. However it would also be interesting to show the same figure as proposed in the previous comment but for the monogenic model (in appendix if it is too repetitive with figure 1).

#Minor comments:
Some of the comments below are suggestions which I think might help the readers but are still only suggestions.

Introduction
- l51-53. Could you give examples from the literature ?
- l58. "(approximated by the magnitude of **the initial abrupt** environmental change". Precising "the initial abrupt" would help the readers to understand the scenario I think.

Method
- The notation for equation 1A is missing.
- l109-114. I think adding few graphs in figure 2 could help the reader to understand the scenario modeled. See the comment on figure 2 below.
- l115-116. "as long as heritability is positive". Heritability in your model, which is defined as in previous models as G/P is always positive no ?
- l116. "the population **size** never ..."
- l168-183. The equations resulting of the analytical approximations (A12-A16) which are derived in the appendix could be shown in the main text either in the method section or the result section because they are shown in figure 3 and seems to give good agreements with the simulations (at least for B and C).

Results
- Figure 2: I think two rows could be added in figure 2 which would help both to understand the scenario modeled and the small window other which variations have an impact. One row with dynamics of mean fitness and mean optimum could be added (as in figure 2A of Chevin et al. 2017) and another row with the probability of extinction (from the heuristic) over time (as in figure 3A of Chevin et al. 2017 but only with one set of parameters that would correspond to the two other rows).
- l203. Is it possible to show in appendix some cases with extreme fluctuations as it seems to be the upper limits for the results you mention in the following lines (l203-206)?
- l208-220. The modifications suggested to figure 2 above could help to visualize these results I think.

Discussion
- l323-329 and l339-340 : The comparison between the polygenic and the monogenic model is less intuitive if we consider different phenotypic variance for the former and different beneficial mutation rate for the latter. If the phenotypic variance is large in the polygenic model but the beneficial mutation rate is small in the monogenic one, I think environmental variation might "be beneficial to evolutionary rescue for a greater range of parameter space" in the polygenic model. This idea could be discussed regarding some works which have been done for evolutionary rescue with the probability of mutations depending on the distance to the optimum and the fitness of the mutants (e.g. see Anciaux et al. 2018 and Anciaux et al. 2019). As I am author on these papers I do not specifically recommend to cite them but I think discussing the affirmation given in these lines regarding a mutation rate or a phenotypic variance depending on the distance to the optimum would be interesting.
- l348. If insects from your example can not adapt to changes of temperature or food availability you should mention it. Otherwise these stressors are not similar to the fecundity in your model.
- l377-379. The effects of the density-dependence implemented in your simulations could be roughly evaluated by comparing it to the form of dependence in Chevin et al. 2017 (see figure. 4)

Decision letter (RSPB-2019-2030.R0)

25-Nov-2019

Dear Mr Peniston:

I am writing to inform you that your manuscript RSPB-2019-2030 entitled "Environmental fluctuations can promote evolutionary rescue in high-extinction-risk populations" has, in its current form, been rejected for publication in Proceedings B.

This action has been taken on the advice of referees, who have recommended that substantial revisions are necessary. Apologies for some delay in obtaining these reviews. With the revisions in mind, we would be happy to consider a resubmission, provided the comments of the referees are fully addressed. However please note that this is not a provisional acceptance. The reviewers and Associate Editor found the paper exciting but need stronger convincing on some points, requiring further analyses.

The resubmission will be treated as a new manuscript. However, we will approach the same reviewers if they are available and it is deemed appropriate to do so by the Editor. Please note that resubmissions must be submitted within six months of the date of this email. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office. Manuscripts submitted after this date will be automatically rejected.

Please find below the comments made by the referees, not including confidential reports to the Editor, which I hope you will find useful. If you do choose to resubmit your manuscript, please upload the following:

1) A 'response to referees' document including details of how you have responded to the comments, and the adjustments you have made.
2) A clean copy of the manuscript and one with 'tracked changes' indicating your 'response to referees' comments document.
3) Line numbers in your main document.

To upload a resubmitted manuscript, log into http://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Resubmission." Please be sure to indicate in your cover letter that it is a resubmission, and supply the previous reference number.

Please note that this decision may (or may not) have taken into account confidential comments.

In your revision process, please take a second look at how open your science is; our policy is that all data involved with the study should be made openly accessible-- see:
https://royalsociety.org/journals/ethics-policies/data-sharing-mining/
Insufficient sharing of data can delay or even cause rejection of a paper.

Sincerely,
Professor John Hutchinson, Editor
mailto: proceedingsb@royalsociety.org

Associate Editor
Board Member: 1
Comments to Author:
Your manuscript has been reviewed by three referees, all of whom feel your study presents very novel results that will be of great interest to our wide readership. However, they also feel you

need to clarify several issues. The comments they provide are very helpful and constructive, you should incorporate them in a new version of your manuscript.

I would like to highlight that all reviewers feel that you need to clearly state what the phrase 'high-extinction-risk' means. I do feel that there is a lack of clarity in this regard. In principle and as suggested by referee 2, one should be able to distinguish between a baseline extinction risk, which is intrinsic to the population and determined by vital rates and other population parameters, and a realised extinction risk dependent on both environmental fluctuations and baseline extinction risk. However, to be able to do that you need a model that includes demographic stochasticity, which is not the case in your population-level polygenic model. To overcome this limitation you use a threshold population size that directly determines the realised extinction risk under environmental fluctuations. It is unclear to what extent the results obtained for this model depend on $\backslash N\_c$ since you did not carry out a sensitivity study for this parameter. Under this model, the probability of extinction should be controlled by a composite parameter that includes N_c and the magnitude of the environmental fluctuations. I think that you should present a sensitivity analysis that explores this issue (note that referee 2 highlighted the absence of a sensitivity analysis).

From my point of view, the confusion about what 'high-extinction-risk' means is created by the order in which you present the various models you used. Starting with a population-level polygenic model that does not allow you to define a sensible baseline extinction risk is not a good strategy. I suggest starting with the monogenic models (individual-based and approximation) and then introduce the individual-based and population-level polygenic models. Moreover, you could tune up the population-level polygenic model by using an N_c and environmental fluctuation magnitude that lead to the same extinction probability as the individual-based model under the uncorrelated scenario.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s)
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Referee: 2

Comments to the Author(s)
Please see attachment.

Referee: 3

Comments to the Author(s)
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The authors study the process of evolutionary rescue after an abrupt environmental change and focus on the effects of temporal fluctuations of conditions in this new environment. To this end, they developed two population-level models (polygenic and monogenic) based on two models complementary which have been commonly used in the theoretical literature of evolutionary rescue. They compared them to individual based simulations with relaxed assumptions (phenotypic variance generated by various processes and demographic stochasticity). They considered both variation of an environmental stressor to which the population can adapt and variations still affecting the fitness but independent of the selective pressure.
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The authors also show that the window over which environmental variations have the most impact is relatively short and start early.
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The authors show in the population-level model that increasing variations (both for the stressor or the fecundity):
(1) increase the probability that the population size will go below the critical heuristic (100) for low initial maladaptation.
(2) decrease the probability that the population size will go below the critical heuristic (100) for high initial maladaptation.
(3) both results (1) and (2) are reinforced by autocorrelation.
Result (1) is in agreement with the individual-based simulation and with previous results of the literature, in particular Chevin et al. (2017).
However result (1) is not observed in the individual-based simulations for the variation in fecundity.
Result (2) is new compared to previous results of the literature, in particular Chevin et al. (2017), but is also not observed in the simulations (neither for the variations of the environmental stressor nor the fecundity).
Result (3) is difficult to compare to the simulations due to the two points above.
As acknowledged by the authors (l236-242), it is difficult to judge if these important discrepancies between the simulations and the analytical models are due to differences in the parameters used (e.g. between figure 1 and A1) or to the assumptions of the model.
These unresolved discrepancies make it difficult to understand to which extent the results of the population-level model can be generalized. Which is directly related to the potential applications mentioned by the authors in discussion. If possible in term of computational power, the authors could add simulations to figure 1 to show if the discrepancies are still visible for similar parameters. And if it is the case, it would be important to discuss (in regard to previous articles such as Chevin et al. 2017) which assumptions might be at the origin of these discrepancies with the simulations and the literature.

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The results in figure A5 shows a good agreement between the simulations and the analytical approximations. However it would also be interesting to show the same figure as proposed in the previous comment but for the monogenic model (in appendix if it is too repetitive with figure 1).

#Minor comments:
Some of the comments below are suggestions which I think might help the readers but are still only suggestions.

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Method
- The notation for equation 1A is missing.
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- l116. "the population **size** never ..."
- l168-183. The equations resulting of the analytical approximations (A12-A16) which are derived in the appendix could be shown in the main text either in the method section or the result section because they are shown in figure 3 and seems to give good agreements with the simulations (at least for B and C).

Results
- Figure 2: I think two rows could be added in figure 2 which would help both to understand the scenario modeled and the small window other which variations have an impact. One row with dynamics of mean fitness and mean optimum could be added (as in figure 2A of Chevin et al. 2017) and another row with the probability of extinction (from the heuristic) over time (as in figure 3A of Chevin et al. 2017 but only with one set of parameters that would correspond to the two other rows).
- l203. Is it possible to show in appendix some cases with extreme fluctuations as it seems to be the upper limits for the results you mention in the following lines (l203-206)?
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Discussion
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- l348. If insects from your example can not adapt to changes of temperature or food availability you should mention it. Otherwise these stressors are not similar to the fecundity in your model.
- l377-379. The effects of the density-dependence implemented in your simulations could be roughly evaluated by comparing it to the form of dependence in Chevin et al. 2017 (see figure. 4)

Author's Response to Decision Letter for (RSPB-2019-2030.R0)

See Appendix A.

RSPB-2020-1144.R0

Review form: Reviewer 4

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Acceptable

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

   Is it accessible?
   Yes

   Is it clear?
   Yes

   Is it adequate?
   Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
Peniston et al. describe their theoretical treatment of environmental fluctuation during evolutionary rescue. This is a resubmission and I was not a prior reviewer (and I don't know which reviewer I'm replacing). I've read the reviewer comments and feel that the authors did a nice job in addressing most of those comments. I have a few suggestions, but will try to keep them brief.

I still feel like the discussion of high/low extinction risk is still vague. Would it be possible to include a figure (either based on data or a cartoon) showing how varying parameters moves from one category to the other? A contour plot with population size and mutation rate on the two axes?

It also took me a while to understand that all the environmental variation occurs after the environmental change. I had ideas about environmental variation increasing genetic variation before the change, etc. This could be more clear upfront - an explicit description of the scenario.

On a related note, it took me a while to realize that you were only considering new mutation and never standing genetic variation. That could be made more clear (even in the title).

Line 250 - It would be useful if you described the characteristics (or even showed them graphically) that lead to high or low rates of rescue. It is mentioned later that it is a run of good

years, but what does that look like in your model? Is there a way to represent it? A5 is a good start and could be moved to the main document, but I guess I was thinking something that plotted the optima over those first 20 generations, second 20, etc. and colored based on rescue.

The environmental variance was held constant in the fluctuating environment (97-99). Maybe stress that this is a potential reason for the minor disagreements between the individual and polygenic models.

In equation 3A, it might help to redefine eta(t) since it was only mentioned briefly a couple of pages before.

Decision letter (RSPB-2020-1144.R0)

22-Jun-2020

Dear Mr Peniston:

Your manuscript has now been peer reviewed and the reviews have been assessed by an Associate Editor. The reviewers' comments (not including confidential comments to the Editor) and the comments from the Associate Editor are included at the end of this email for your reference. As you will see, the reviewers and the Editors have raised some concerns with your manuscript and we would like to invite you to revise your manuscript to address them.

We do not allow multiple rounds of revision so we urge you to make every effort to fully address all of the comments at this stage. If deemed necessary by the Associate Editor, your manuscript will be sent back to one or more of the original reviewers for assessment. If the original reviewers are not available we may invite new reviewers. Please note that we cannot guarantee eventual acceptance of your manuscript at this stage.

To submit your revision please log into http://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions", click on "Create a Revision". Your manuscript number has been appended to denote a revision.

When submitting your revision please upload a file under "Response to Referees" in the "File Upload" section. This should document, point by point, how you have responded to the reviewers' and Editors' comments, and the adjustments you have made to the manuscript. We require a copy of the manuscript with revisions made since the previous version marked as 'tracked changes' to be included in the 'response to referees' document.

Your main manuscript should be submitted as a text file (doc, txt, rtf or tex), not a PDF. Your figures should be submitted as separate files and not included within the main manuscript file.

When revising your manuscript you should also ensure that it adheres to our editorial policies (https://royalsociety.org/journals/ethics-policies/). You should pay particular attention to the following:

Research ethics:
If your study contains research on humans please ensure that you detail in the methods section whether you obtained ethical approval from your local research ethics committee and gained informed consent to participate from each of the participants.

Use of animals and field studies:

If your study uses animals please include details in the methods section of any approval and licences given to carry out the study and include full details of how animal welfare standards were ensured. Field studies should be conducted in accordance with local legislation; please include details of the appropriate permission and licences that you obtained to carry out the field work.

Data accessibility and data citation:
It is a condition of publication that you make available the data and research materials supporting the results in the article. Datasets should be deposited in an appropriate publicly available repository and details of the associated accession number, link or DOI to the datasets must be included in the Data Accessibility section of the article (https://royalsociety.org/journals/ethics-policies/data-sharing-mining/). Reference(s) to datasets should also be included in the reference list of the article with DOIs (where available).

In order to ensure effective and robust dissemination and appropriate credit to authors the dataset(s) used should also be fully cited and listed in the references.

If you wish to submit your data to Dryad (http://datadryad.org/) and have not already done so you can submit your data via this link http://datadryad.org/submit?journalID=RSPB&manu=(Document not available), which will take you to your unique entry in the Dryad repository.

If you have already submitted your data to dryad you can make any necessary revisions to your dataset by following the above link.

For more information please see our open data policy http://royalsocietypublishing.org/data-sharing.

Electronic supplementary material:
All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI. Please try to submit all supplementary material as a single file.

Online supplementary material will also carry the title and description provided during submission, so please ensure these are accurate and informative. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details (authors, title, journal name, article DOI). Your article DOI will be 10.1098/rspb.[paper ID in form xxxx.xxxx e.g. 10.1098/rspb.2016.0049].

Please submit a copy of your revised paper within three weeks. If we do not hear from you within this time your manuscript will be rejected. If you are unable to meet this deadline please let us know as soon as possible, as we may be able to grant a short extension.

Thank you for submitting your manuscript to Proceedings B; we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Best wishes,
Dr John Hutchinson, Editor
mailto: proceedingsb@royalsociety.org

Associate Editor Board Member
Comments to Author:
None of the reviewers of your initial submission were available to evaluate this new version. Thus, the resubmitted version has been reviewed by a referee who did not participated in the first

round of evaluations. She/he feels the changes you introduced go a long way towards incorporating the suggestions of the original reviewers. However, there are still some few issues that need to be addressed.

The main remaining issue concerns a lack of clarity on how you define high/low extinction risk. I think the source of the confusion is that you refer to high- and low-risk populations when in fact, you should be talking about low- and high-risk scenarios. In a purely demographic model, the baseline population extinction risk should only be determined by demographic parameters (fecundity and survival). That is, it should be the result of demographic stochasticity. In your case you also have to consider mutation rate because that determines to what extent the population can adapt to the environmental change and is a parameter specific to each population/species. This baseline extinction rate is different from the one you are referring to which also includes a component due to the magnitude of the initial environmental perturbation. For this reason, referring to "scenario" instead of population may help readers to fully understand your model. I think you should incorporate these details in the introduction and then refer only to "scenarios" instead of populations.

The referee also makes other very helpful comments requesting clarifications of other aspects of your study.

Reviewer(s)' Comments to Author:

Referee: 4

Comments to the Author(s).
Peniston et al. describe their theoretical treatment of environmental fluctuation during evolutionary rescue. This is a resubmission and I was not a prior reviewer (and I don't know which reviewer I'm replacing). I've read the reviewer comments and feel that the authors did a nice job in addressing most of those comments. I have a few suggestions, but will try to keep them brief.

I still feel like the discussion of high/low extinction risk is still vague. Would it be possible to include a figure (either based on data or a cartoon) showing how varying parameters moves from one category to the other? A contour plot with population size and mutation rate on the two axes?

It also took me a while to understand that all the environmental variation occurs after the environmental change. I had ideas about environmental variation increasing genetic variation before the change, etc. This could be more clear upfront - an explicit description of the scenario.

On a related note, it took me a while to realize that you were only considering new mutation and never standing genetic variation. That could be made more clear (even in the title).

Line 250 - It would be useful if you described the characteristics (or even showed them graphically) that lead to high or low rates of rescue. It is mentioned later that it is a run of good years, but what does that look like in your model? Is there a way to represent it? A5 is a good start and could be moved to the main document, but I guess I was thinking something that plotted the optima over those first 20 generations, second 20, etc. and colored based on rescue.

The environmental variance was held constant in the fluctuating environment (97-99). Maybe stress that this is a potential reason for the minor disagreements between the individual and polygenic models.

In equation 3A, it might help to redefine eta(t) since it was only mentioned briefly a couple of pages before.

Author's Response to Decision Letter for (RSPB-2020-1144.R0)

See Appendix B.

Decision letter (RSPB-2020-1144.R1)

13-Jul-2020

Dear Mr Peniston

I am pleased to inform you that your manuscript RSPB-2020-1144.R1 entitled "Environmental fluctuations can promote evolutionary rescue in high-extinction-risk scenarios" has been accepted for publication in Proceedings B.

The referee(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the referee(s)' comments and revise your manuscript. Because the schedule for publication is very tight, it is a condition of publication that you submit the revised version of your manuscript within 7 days. If you do not think you will be able to meet this date please let us know.

To revise your manuscript, log into https://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, you will be able to respond to the comments made by the referee(s) and upload a file "Response to Referees". You can use this to document any changes you make to the original manuscript. We require a copy of the manuscript with revisions made since the previous version marked as 'tracked changes' to be included in the 'response to referees' document.

Before uploading your revised files please make sure that you have:

1) A text file of the manuscript (doc, txt, rtf or tex), including the references, tables (including captions) and figure captions. Please remove any tracked changes from the text before submission. PDF files are not an accepted format for the "Main Document".

2) A separate electronic file of each figure (tiff, EPS or print-quality PDF preferred). The format should be produced directly from original creation package, or original software format. PowerPoint files are not accepted.

3) Electronic supplementary material: this should be contained in a separate file and where possible, all ESM should be combined into a single file. All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

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4) A media summary: a short non-technical summary (up to 100 words) of the key findings/importance of your manuscript.

5) Data accessibility section and data citation
It is a condition of publication that data supporting your paper are made available either in the electronic supplementary material or through an appropriate repository.

In order to ensure effective and robust dissemination and appropriate credit to authors the dataset(s) used should be fully cited. To ensure archived data are available to readers, authors should include a 'data accessibility' section immediately after the acknowledgements section. This should list the database and accession number for all data from the article that has been made publicly available, for instance:
• DNA sequences: Genbank accessions F234391-F234402
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Once again, thank you for submitting your manuscript to Proceedings B and I look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Sincerely,
Dr John Hutchinson
Editor, Proceedings B
mailto:proceedingsb@royalsociety.org

Associate Editor:
Board Member
Comments to Author:
You have satisfactorily incorporated changes to take into account the comments made by the new referee and I. I feel your manuscript is now very clear and will be of great interest to Proceedings B readership.
There is only a very minor change you need to introduce:
ln. 80: "extinction" ->"extinct"

Author's Response to Decision Letter for (RSPB-2020-1144.R1)

See Appendix C.

Decision letter (RSPB-2020-1144.R2)

15-Jul-2020

Dear Mr Peniston

I am pleased to inform you that your manuscript entitled "Environmental fluctuations can promote evolutionary rescue in high-extinction-risk scenarios" has been accepted for publication in Proceedings B.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it. PLEASE NOTE: you will be given the exact page length of your paper which may be different from the estimation from Editorial and you may be asked to reduce your paper if it goes over the 10 page limit.

If you are likely to be away from e-mail contact please let us know. Due to rapid publication and an extremely tight schedule, if comments are not received, we may publish the paper as it stands.

If you have any queries regarding the production of your final article or the publication date please contact procb_proofs@royalsociety.org

Your article has been estimated as being 10 pages long. Our Production Office will be able to confirm the exact length at proof stage.

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Thank you for your fine contribution. On behalf of the Editors of the Proceedings B, we look forward to your continued contributions to the Journal.

Sincerely,
Editor, Proceedings B
mailto: proceedingsb@royalsociety.org

Appendix A

We appreciate the detailed comments on our manuscript that we have received from the associate editor and reviewers. We believe that all of these comments have greatly improved our manuscript. We have tried to address of the associate editor's and reviewers' concerns in this resubmission. Please find our responses to all comments below. For clarity, we have made all of our response in the color blue and labeled them as "authors' response:". All line numbers refer to line numbers in the "clean" version of the manuscript. We appreciate your consideration of our resubmission.

Associate Editor
Board Member: 1
Comments to Author:
Your manuscript has been reviewed by three referees, all of whom feel your study presents very novel results that will be of great interest to our wide readership. However, they also feel you need to clarify several issues. The comments they provide are very helpful and constructive, you should incorporate them in a new version of your manuscript.

Authors' response: Thank you very much for this overall positive assessment.

I would like to highlight that all reviewers feel that you need to clearly state what the phrase 'high-extinction-risk' means. I do feel that there is a lack of clarity in this regard. In principle and as suggested by referee 2, one should be able to distinguish between a baseline extinction risk, which is intrinsic to the population and determined by vital rates and other population parameters, and a realised extinction risk dependent on both environmental fluctuations and baseline extinction risk. However, to be able to do that you need a model that includes demographic stochasticity, which is not the case in your population-level polygenic model. To overcome this limitation you use a threshold population size that directly determines the realised extinction risk under environmental fluctuations. It is unclear to what extent the results obtained for this model depend on \N_c since you did not carry out a sensitivity study for this parameter. Under this model, the probability of extinction should be controlled by a composite parameter that includes N_c and the magnitude of the environmental fluctuations. I think that you should present a sensitivity analysis that explores this issue (note that referee 2 highlighted the absence of a sensitivity analysis).

From my point of view, the confusion about what 'high-extinction-risk' means is created by the order in which you present the various models you used. Starting with a population-level polygenic model that does not allow you to define a sensible baseline extinction risk is not a good strategy. I suggest starting with the monogenic models (individual-based and approximation) and then introduce the individual-based and population-level polygenic models. Moreover, you could tune up the population-level polygenic model by using an N_c and environmental fluctuation magnitude that lead to the same extinction probability as the individual-based model under the uncorrelated scenario.

Authors' response: Thank you for these comments. We think the concerns brought up by you and the three reviewers on this definitional issue are all valid. We have made an effort to much more clearly define what we mean by "high-extinction-risk" and to distinguish between baseline

extinction risk and realized extinction risk as was suggested by reviewer 2. In the intro, we now explicitly define baseline extinction risk as "the probability of extinction following an initial abrupt environmental change without environmental fluctuations" (Lines 59–60) and at the beginning of the methods we go into more detail and point out that "baseline extinction risk can be an intrinsic property of the population (e.g., initial population size or mutation rate) or a property of the environment (e.g., degree of environmental change)" (Lines 78–83).

In addition, for the population-level polygenic models, we have now provided an analytical solution (equation 4; Line 213) that provides the parameter values at which populations do and do not drop below N_c in an unfluctuating environment. We define any population that would go extinct in the non-fluctuating environment as "high extinction risk" and more generally state that parameters that decrease the time to extinction given by this equation increase the baseline extinction risk. See Lines 212–221.

For our population-level polygenic models, we have now evaluated the sensitivity of our results to differences in key parameter values (critical population size N_c, strength of stabilizing selection ω^2, and additive genetic variance G). These analyses show that our general conclusions do not depend on the values of these parameters (figure A1). We now mention these additional simulations on line 141–143.

We have decided to keep the discussion of the polygenic model first and the monogenic model second. We have made this decision for a few reasons. First, because the polygenic model is more in line with previous theory on evolutionary rescue in fluctuating environments. Second because we believe the example population trajectories (Figure 1) provide a good illustrative example of the core results of our manuscript and as was suggested by Reviewer 2 in comment #24 putting them earlier in the manuscript can make it easier to follow. Finally, now that we have provided a more explicit definition of baseline extinction risk, we do not believe there would be a clear benefit to having the monogenic model first. However, if you still believe the manuscript would be more suitable with the monogenic model first, we are willing to make that edit.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s)
The manuscript presents a tidy analysis showing that highly auto-correlated environmental fluctuations can positively affect the chances of evolutionary rescue in very high-extinction-risk populations. The result is nice and makes complete sense, but is not obvious (or at least was not to me) before reading the paper. This is a novel finding with implications for conservation and design of drug treatment regimes as well as theoretical interest.

Authors' response: We appreciate these kind comments.

1. Novelty:

The finding is novel, but the framing of the abstract implies a bit more novelty than is justified in my opinion. The few previous studies of evolutionary rescue in noisy environments [e.g. 11; using ref numbers from the manuscript] focused on the effect of environmental noise in 'low-extinction-risk' (i.e. less harsh) environments -- where increases in the magnitude of environmental fluctuations do increase extinction risk. As Figure 1b of the manuscript shows nicely, when the environment becomes hasher the effect of autocorrelated fluctuations reverses and extinction risk decreases as the magnitude of fluctuations increases. This is an interesting reversal of effects seen in previous studies. However, I don't think the few papers exploring the effect of noise on rescue [8, 9, 11] should be read to imply, as the abstract states, that rescue "is more likely to occur in constant environments". Indeed as this manuscript states and as mentioned in at least one of these references, environmental conditions are essentially never static -- so this previous work should be framed as assuming noise but emphasizing the negative effect of increased magnitude of noise on rescue.

Authors' response: We appreciate the reviewer pointing this out. We did not intend to frame the abstract in the way they interpreted it. We have now rewritten the sentence beginning on line 4 to fit the reviewer's recommendations. We have now tried to emphasize that previous studies have shown that larger magnitudes of variation increase the probability of extinction. We have also rewritten the sentence in the introduction on lines 40–44 in a similar way, to more accurately summarize previous literature.

2. Clarifying 'high-extinction-risk'
In this paper, I believe 'high-extinction-risk' means an environment where the mean population trajectory would go below the quasi-extinction threshold N_c^*. However, the general statement of this condition is missing and the reason for the quantitative location of the thresholds in Figure 1 and A1 are unclear as a result. I believe the threshold location and definition could be derived as the point (initial population size or size of shift) at which the population trajectory equals N_c at T_r (e.g., using equation 11 from Gomulkiewicz and Holt 1995). This might not be necessary and it could be clearer to just state the condition for the location and which parameters it depends upon.

*: It is less clear to me what the condition is for a generic definition in the monogenetic model but this would be useful to mention, even if one is not derived.

Authors' response: Thank you, this is a very good point. Other reviewers also found the terminology of "high/low-extinction risk" ambiguous. We have tried to make our use of this term more explicit throughout the manuscript. We now use the term baseline extinction risk and differentiate this from realized extinction risk. We define "baseline extinction risk" as the probability of extinction following a step-change without environmental fluctuations (e.g., Gomulkiewicz and Holt 1995).

In the intro, we now explicitly define baseline extinction risk as "the probability of extinction following an initial abrupt environmental change without environmental fluctuations" (Lines 59–60) and at the beginning of the methods we go into more detail and point out that "baseline extinction risk can be an intrinsic property of the population (e.g., initial population size or

mutation rate) or a property of the environment (e.g., degree of environmental change)" (Lines 78–83).

As was suggested in this comment, we have now defined baseline extinction risk in our population-level polygenic model with respect to equation 7 in Gomulkiewicz and Holt (1995). We define any population that would go extinct in the non-fluctuating environment as "high extinction risk" and more generally state that parameters that decrease the time to extinction given by this equation (equation 4; line 213) increase the baseline extinction risk. See Lines 212–221.

For the monogenetic model, we use the same definition of baseline extinction risk as above (extinction risk in the absence of variation). On lines 305–310), we attempt to clearly state that mutation rate is our proxy for extinction risk in our simulations. The equations giving the extinction risk in the absence of variation are given in the appendix. Equation A9 is the expected number of mutants, and the probability that the lineage of each goes extinct is the solution of $q = \exp\{fv(q-1)\}$ (for q), given in the text after equation A16. The product of the expected number of mutants and $1- q$ is the expected number of surviving mutant lineages M, and the probability of extinction is $1 - \exp\{-M\}$ assuming a Poisson distribution of surviving lineages among replicates (this equation is also given in the text in the paragraph after the one for q). For our graphical results, of course, the baseline is the value along the ordinate.

We hope that these changes make our meaning of baseline extinction risk clearer throughout the manuscript. We appreciate these comments.

3. Presentation of the figures
In Figures 1, A1, and A4 the symbol-lines really should be replaced with several shades of gray to emphasize that there is a parameter that quantitatively varies parameter among the lines. In Figure 1, the thickness of the line for constant environment should be the same as the others. Some language in the caption (or some notation on the axis if it is introduced) could help clarify the threshold location for Figure 1.

Authors' response: We have adapted figure 1 (which is now figure 2) and altered to the figure caption as suggested. We have done the same for similar figures in the appendix (figures A1, A2, A4, A7, A9, A10, A11, and A13). We are thankful for this suggestion, we did not think of presenting the results this way and it seems more readable.

Referee: 2

Comments to the Author(s)
Please see attachment.

Authors' response: Our responses to all of reviewer 2's comments are at the bottom of this document.

Referee: 3

Comments to the Author(s)
#Summary
The authors study the process of evolutionary rescue after an abrupt environmental change and focus on the effects of temporal fluctuations of conditions in this new environment. To this end, they developed two population-level models (polygenic and monogenic) based on two models complementary which have been commonly used in the theoretical literature of evolutionary rescue. They compared them to individual based simulations with relaxed assumptions (phenotypic variance generated by various processes and demographic stochasticity). They considered both variation of an environmental stressor to which the population can adapt and variations still affecting the fitness but independent of the selective pressure.
Based on these models, they show opposite effects of environmental fluctuations on the probability of extinction depending of the risk of extinction faced by the population after the first abrupt environmental change. One result which stands out from the current literature is that environmental variations, on average, decrease the probability of extinction if the population is already facing a high extinction risk, especially with autocorrelation.
The authors also show that the window over which environmental variations have the most impact is relatively short and start early.
As stated by the authors in the discussion section, these results could give new insights in the debate about the frequency and the strength of treatments against pathogens.

Authors' response: Thank you for this kind summary of our manuscript.

The introduction gives a good overview of the literature, and the methods are quite clear. The authors provide enough material for the reproducibility of their results: the analytical developments of their approximations in appendix and annotated simulation codes. The generality of the main results are difficult to judge as explained below but the authors managed to give intuitive interpretations of their results. The information brought by the figures could be improved as suggested below. Some limits of the result regarding the simulations could be added to the section "Assumptions and caveats". If there is a length issue, the different examples spread over the discussion could be more summarized in the application section.

#Major comments :
I) The first model developed is very similar, among others, to the model from Chevin et al. (2017) at least for variations of the environmental stressor, using the same critical population size as an heuristic for extinction probability.
The authors show in the population-level model that increasing variations (both for the stressor or the fecundity):
(1) increase the probability that the population size will go below the critical heuristic (100) for low initial maladaptation.
(2) decrease the probability that the population size will go below the critical heuristic (100) for high initial maladaptation.
(3) both results (1) and (2) are reinforced by autocorrelation.
Result (1) is in agreement with the individual-based simulation and with previous results of the literature, in particular Chevin et al. (2017).

However result (1) is not observed in the individual-based simulations for the variation in fecundity.

Authors' response: We do see result (1) for the individual-based simulations for variation in fecundity, however, the effect size of this result is small and thus difficult to see in the white noise simulations (it is more clear in the red noise simulations). This effect is now shown in panels E and F of figure A13.

Result (2) is new compared to previous results of the literature, in particular Chevin et al. (2017), but is also not observed in the simulations (neither for the variations of the environmental stressor nor the fecundity).

Authors' response: For variation in the environmental stressor, result (2) is not observed for uncorrelated fluctuations, but it is observed for positively autocorrelated fluctuations. To emphasize this point, and address another of this reviewers suggestions below, we have remade this figure to more directly compare the population-level simulations with the individual-based simulations (Figure A7). We have also added more discussion directly comparing the population-level simulations to the individual-based ones on lines 263–277.

For variation in fecundity, result (2) is not observed for uncorrelated fluctuations. It is observed for positively autocorrelated fluctuations, but once again the effect size is very small (Figure A13). In response to another reviewer's comments and because of the small effect size in the individual-based simulations for variation in fecundity, we have decided to move our results about variation in fecundity to the appendix. We chose to focus on variation in the environmental stressor because it is more comparable to Chevin et al. (2017) and because the effects are clearer. The comparison between the population-level and individual-based simulations for variation in fecundity is shown in figure A13. This figure also shows that in the population-level simulations, the effect of variation in fecundity is more pronounced with a larger population size. Unfortunately, we were computationally limited from exploring such large population sizes in our individual-based simulations, which may explain why the effect size is so minor in our simulations.

Result (3) is difficult to compare to the simulations due to the two points above.

Authors' response: We have added a new supplementary figure to show result 3 in the population-level simulation (Figure A4). The left panel shows result (3).

Interestingly, reviewer 2 pointed out that there should be a point at which the effect of autocorrelation goes in the opposite direction because at rho = 1, the environment once again becomes constant. We had not realized this. The right panel of figure A4 shows that at very high levels of autocorrelation the pattern switches direction. We discuss this in the manuscript on lines 244–247. However, this is only the case because we assume that the optimal phenotype the first generation after the step changes is mu_theta. If we instead assume that it is a random Gaussian with a mean mu_theta and variance sigma_2, the pattern never switches direction (figure A11C,D). This is now discussed in the section "Generating autocorrelated Gaussian sequences" in the appendix.

We believe that figure A7 shows that the qualitative conclusion that increased autocorrelation is beneficial to high extinction risk populations holds for our individual-based simulations as well. This result can also be seen for variation in fecundity in figure A13, but once again the effect size of that results is very small.

As acknowledged by the authors (l236-242), it is difficult to judge if these important discrepancies between the simulations and the analytical models are due to differences in the parameters used (e.g. between figure 1 and A1) or to the assumptions of the model. These unresolved discrepancies make it difficult to understand to which extent the results of the population-level model can be generalized. Which is directly related to the potential applications mentioned by the authors in discussion. If possible in term of computational power, the authors could add simulations to figure 1 to show if the discrepancies are still visible for similar parameters. And if it is the case, it would be important to discuss (in regard to previous articles such as Chevin et al. 2017) which assumptions might be at the origin of these discrepancies with the simulations and the literature.

Authors' response: We changed the parameter values in the population-level simulations to match the parameter values we used in the individual-based simulations. This was much more computationally feasible than changing the individual-based simulations to match the population-level ones. This comparison is now seen in Figure A7 (for variation in the optimal phenotype). This comparison shows that for autocorrelated fluctuations, the results are qualitatively the same, but the benefits of variation for high-extinction risk populations are dampened. Moreover, we do not see these benefits at all with uncorrelated fluctuations.

As suggested, we have added discussion about which assumptions lead to these discrepancies on 263–277. We have also run some additional simulations to try to understand the differences between our population-level and individual-based simulation. Figure A8 shows the effect of density regulation and Figure A9 shows temporal changes in the additive genetic variation. Neither of these two effects appear great enough to explain the differences between our population-level and individual-based simulations so we conclude that the other sources of stochasticity in our individual-based simulations must explain the remaining differences.

II) The second model is based on a model similar to a large part of the evolutionary rescue literature (Gomulkiewicz and Holt 1995, Orr and Unckless 2008, 2014, Martin et al. 2013, Anciaux et al. 2018) based on origin-fixation models (McCandlish and Stoltzfus 2014) but add the environmental fluctuations on top of it. The authors found analytical approximations for the probability of persistence with variations in the environment which had not been done previously to my knowledge. Thus it would be interesting to compare it (in the case without fluctuations) to previous analytical results.

Authors' response: Gomulkiewicz and Holt 1995 uses a model similar to our first model for their main results, but then compare it with a one-locus model (but diploid). However, the latter model is still is continuous time and still uses a threshold to determine probability of extinction, and we

do not think it is comparable to our one-locus model. Orr and Unckless 2008 use a model similar to ours; their formula gives a somewhat higher probability of persistence than ours for example, 0.054 compared to 0.039 for u = 0.0001), likely due to their assumption that r and s are small, which they are not with our parameters. This affects the probability of persistence of the lineage of a mutant. Their 2014 paper adds standing variation, which we do not have. Martin et al. uses a continuous-time model, but their simplest model is otherwise similar to ours, but again they use an approximation for probability of mutant lineage persistence that would not apply to our parameters. Anciaux et al. use a multivariate character. We have added some text comparing our model to Orr and Unckless 2008 to the appendix. On lines 402–404 of the main text, we also mention that future studies on the effects of environmental variation should consider more complex fitness landscapes as was done Anciaux et al. 2018.

The results in figure A5 shows a good agreement between the simulations and the analytical approximations. However it would also be interesting to show the same figure as proposed in the previous comment but for the monogenic model (in appendix if it is too repetitive with figure 1).

Authors' response: We do not fully understand what the reviewer is asking for here. We hope our verbal comparison above sufficiently addresses this point.

#Minor comments:
Some of the comments below are suggestions which I think might help the readers but are still only suggestions.

Introduction
- l51-53. Could you give examples from the literature ?

Authors' response: We have added a citation of Chevin et al. 2017 as an example (Line 54).

- l58. "(approximated by the magnitude of **the initial abrupt** environmental change". Precising "the initial abrupt" would help the readers to understand the scenario I think.

Authors' response: We have made our definition of baseline extinction risk more explicit in response to other reviewers' comments. As was suggested here, we have included the term "initial abrupt" in this new definition because we agree that it makes the scenario clearer. See line 58–60, for our statement of the definition.

Method
- The notation for equation 1A is missing.

Authors' response: Thank you. We corrected the notation of 1B and 1C to be 1A and 1B. We have decided not to give that first equation a notation.

- l109-114. I think adding few graphs in figure 2 could help the reader to understand the scenario modeled. See the comment on figure 2 below.

Authors' response: Thank you for this suggestion. We have added these additional graphs, but we had to include them in the appendix instead of the main text because of space limitation.

- l115-116. "as long as heritability is positive". Heritability in your model, which is defined as in previous models as G/P is always positive no?

Authors' response: The reason for this clause was that heritability can be zero, and so it does not have to be positive. We have now changed the clause to state "not zero" instead of positive. We hope this makes the meaning clearer (Line 135).

- l116. "the population **size** never ..."

Authors' response: We have added the word "size" (Line 136).

- l168-183. The equations resulting of the analytical approximations (A12-A16) which are derived in the appendix could be shown in the main text either in the method section or the result section because they are shown in figure 3 and seems to give good agreements with the simulations (at least for B and C).

Authors' response: This is a reasonable suggestion, but we have decided not to include the analytical approximations (A12–A16) in the main text because they are a rather complicated series of equations that we feel are not too informative without much of the rest of the context of the full derivation. Because of space limitations, we cannot include the full derivation so we have kept the analytical approximations there as well, but if necessary we are willing to move them to the main text.

Results
- Figure 2: I think two rows could be added in figure 2 which would help both to understand the scenario modeled and the small window other which variations have an impact. One row with dynamics of mean fitness and mean optimum could be added (as in figure 2A of Chevin et al. 2017) and another row with the probability of extinction (from the heuristic) over time (as in figure 3A of Chevin et al. 2017 but only with one set of parameters that would correspond to the two other rows).

Authors' response: Thank you for these suggestions. We have included the suggested plots in the appendix (figure A3 and A6). We could not include them in the main text because of limitations in the manuscript's length. (Also note that what was figure 2, is now figure 1).

- l203. Is it possible to show in appendix some cases with extreme fluctuations as it seems to be the upper limits for the results you mention in the following lines (l203-206)?

Authors' response: We have now added an additional figure in the appendix (figure A2) showing how at very high levels of variation, increased environmental variation has negative for even high-extinction-risk populations. We apologize, this should have been included in the original manuscript. We reference this figure on line 237.

- l208-220. The modifications suggested to figure 2 above could help to visualize these results I think.

Authors' response: We agree. We have added these figures to the appendix (figure A3 and A6) and have referenced them on line 241, 244, and 259. We appreciate this suggestion.

Discussion
- l323-329 and l339-340 : The comparison between the polygenic and the monogenic model is less intuitive if we consider different phenotypic variance for the former and different beneficial mutation rate for the latter. If the phenotypic variance is large in the polygenic model but the beneficial mutation rate is small in the monogenic one, I think environmental variation might "be beneficial to evolutionary rescue for a greater range of parameter space" in the polygenic model. This idea could be discussed regarding some works which have been done for evolutionary rescue with the probability of mutations depending on the distance to the optimum and the fitness of the mutants (e.g. see Anciaux et al. 2018 and Anciaux et al. 2019). As I am author on these papers I do not specifically recommend to cite them but I think discussing the affirmation given in these lines regarding a mutation rate or a phenotypic variance depending on the distance to the optimum would be interesting.

Authors' response: This is a good point. Based on this comment, and requests from other reviewers to shorten the discussion section, we have decided to significantly shorten our discussion about the effect of genetic system and moved it into the subsection titled "Assumptions and Caveats". We now simply state that the same qualitative patterns hold for the two different genetic systems we considered, but more work is needed to fully understand how the genetic architecture and fitness landscape interact with environmental variation during evolutionary rescue (400–404). We believe that there are some interesting questions to explore regarding the interaction between the fitness landscape and environmental variation, but they remain outside of the scope of this paper and any conclusions made from our models would be too speculative.

- l348. If insects from your example can not adapt to changes of temperature or food availability you should mention it. Otherwise these stressors are not similar to the fecundity in your model.

Authors' response: Thank you for pointing this out. We have now made this explicit on line 371.

- l377-379. The effects of the density-dependence implemented in your simulations could be roughly evaluated by comparing it to the form of dependence in Chevin et al. 2017 (see figure. 4)

Authors' response: This is a valid suggestion, but we believe that evaluating the specifics of density-dependence is outside of the scope of this paper and would make the presentation of our key results less clear. However, in order to see if density regulation explained the differences between our individual-based simulations and the population-level simulation, we reran some individual-based simulations and recorded the proportion of the simulations in which the adult

population ever reached carrying capacity. Only a small proportion of the populations that went extinct ever reached carrying capacity (Figure A8) suggesting that the inclusion of ceiling density dependence does not significantly change our results. However, other forms of density dependence likely will be more important and should be more thoroughly explored in future work.

Reviewer 2

Major Comments

1. I struggle with the author's use of the term "high/low-extinction risk population". Extinction risk is a product of both population parameters (initial population size, mutation rate) and environmental parameters (magnitude/rate of change; any variation). It can therefore be misleading to refer to a <u>population</u> as being of "high/low extinction risk" as this is not only an innate trait of the population. Within the Results, it is reasonably clear that the authors are using initial population size, mutation rate, or magnitude of shift in the mean environment as the variable controlling some sort of baseline extinction risk that would apply in the absence of environmental stochasticity. However, this concept of <u>baseline</u> risk should be made more explicit and distinct from the <u>realized risk</u> (in the presence of environmental stochasticity) throughout the manuscript. Until this point is clarified, this terminology leads to some very confusing sentences: for instance, in the Abstract I was puzzled by "We... assess how extinction risk influences the effects of environmental variation on evolutionary rescue": isn't extinction risk simply the complement of evolutionary rescue, not an independent variable?

To address this, I would ask that the authors try to come up with clearer terminology than "high/low-extinction-risk population" to describe what they mean. If they can't think of a better term, at the very least, they should ensure that their intended meaning of a baseline risk in the absence of environmental stochasticity is absolutely clear and explicit from the start.

Authors' response: This is a very good point. Other reviewers also found the terminology of "high/low-extinction risk" ambiguous. We have tried to make our use of this term more explicit throughout the manuscript. We now use the term baseline extinction risk and differentiate this from realized extinction risk as suggested.

In the intro, we now explicitly define baseline extinction risk as "the probability of extinction following an initial abrupt environmental change without environmental fluctuations" (Lines 59–60) and at the beginning of the methods we go into more detail and point out that "baseline extinction risk can be an intrinsic property of the population (e.g., initial population size or mutation rate) or a property of the environment (e.g., degree of environmental change)" (Lines 78–83).

By stating the definition early in the manuscript, we hope that our meaning of baseline extinction risk is now clear from the start.

In addition, for our population-level polygenic model we have now provided an analytical solution (equation 4; line 213) that provides the parameter values at which populations do and do not drop below the critical population size *Nc* in an unfluctuating environment. We define any population that would go extinct in the non-fluctuating environment as "high extinction risk" and more generally state that parameters that decrease the time to extinction given by this equation increase the baseline extinction risk. This was inspired by comment #22 below and a similar comment by reviewer # 1. See Lines 212–221.

Importantly, baseline and realized risk also seem to be conflated in the Discussion, in a way that I think leads to some over-reaching hypotheses. In particular, the evolution of drug resistance in HIV is now "relatively uncommon" (L422) only because current combination therapies are highly effective, not because HIV is innately unlikely to evolve. Indeed, HIV population sizes and mutation rates are extremely high, and evolution of resistance to early monotherapies was common. I am less familiar with the prostate cancer example, but the authors should likewise think carefully about whether the propensity to evolve resistance to current treatments really reflects an innately low- extinction-risk population.

Authors' response: This is a good point as well. We did not discuss this correctly. What we meant was that under the current treatment regime, the evolution of drug resistance in HIV is "relatively uncommon". Based on our new, more explicit definition of baseline extinction risk, the current treatment regime would determine the baseline extinction risk and not solely intrinsic properties of the population. We have tried to make this clearer. In response to this comment and other ones below, we have reduced the discussion of potential medical treatments and made less specific comments. We have removed all discussion of HIV treatments from the text and only refer to the fact that pulsed treatments have been shown to reduce the probability of resistance evolving in prostate cancer treatments, we no longer say that it is a low-extinction-risk population. Lines 432–439.

2. The choice to model environmental variation in two ways (L94 and beyond) could be better motivated. Although the Introduction does mention that previous studies have only modelled variation as fluctuations in the optimal trait value, and it is a valid question whether this choice matters, it is unclear whether the authors were expecting any differences when they vary fecundity (independent of selection pressure) instead? Also, note that the monogenic model, unlike the polygenic model, only incorporates variation in fecundity, not viability. Why not test both here too?

Furthermore, given that the authors saw very similar results of the polygenic model regardless of how variation was incorporated, I think the exposition could be improved by relegating one of the approaches entirely to the Appendix. My suggestion would be to move variation in optimal trait value to the Appendix, and keep variation in fecundity in the main text for two reasons: (i) it is consistent across polygenic and monogenic models; and (ii) it is arguably more realistic, cf. the authors' explanation on L344-348. (This was a helpful explanation that could usefully be placed much earlier to help motivate the modelling approach!)

Authors' response: We appreciate this suggestion. We should have put more motivation for modeling variation in two ways in the introduction, but as was pointed out in this comment, we also did not want to overemphasize this comparison because the results for each type of variation are quite similar. We have taken this reviewer's suggestion and moved one of these approaches (variation in fecundity) to the appendix.

While, as was pointed out, the variation in fecundity scenario is more comparable to the monogenic model, we chose to focus on variation in the optimal phenotype for two reasons. First, this scenario was the focus of previous papers such as Chevin et al 2017 making our results comparable to the previous literature. Second, the effect of environmental variation on the probability of evolutionary rescue in the individual-based simulations is more pronounced for the variation in the optimal phenotype case (Figure A7) than for the variation in fecundity case (Figure A13).

3. The authors draw general conclusions based on simulations under a very limited number of (apparently arbitrarily chosen) parameter sets. These qualitative conclusions are mostly quite intuitive and I expect they will continue to hold more broadly. However, there should be some parameter sensitivity analysis included in the Appendix. I understand that the extent of the analysis may be limited for the individual-based simulations as these are computationally expensive, but at a minimum, more extensive checks across parameter space should be done with the population-level polygenic model and analytical approximations of the monogenic model.

Authors' response: As suggested, we have included sensitivity analysis for the key parameters in the population-level polygenetic model (Figures A1). These analyses show that general patterns discussed in the manuscript hold for different parameter values (critical population size, strength of stabilizing selection, and additive-genetic variation).

As was pointed out, performing sensitivity analyses for the polygenic individual-based simulations would be computationally expensive. However, in regard to comments from reviewers, we have made a more direct comparison between our population-level model and the individual-based simulations (Figure A7), which suggests that the results of the two should be comparable. We also have added discussion about this comparison in the results section on lines 263–277.

There are very few parameters in the monogenic model and we have presented some information on the effects of varying each of them. The effect on the geometric mean fitness of the wild type after the environmental change depends on the expected number of non-mutant births before their extinction, which is shown in figure 3A for three rates of decline and two autocorrelations as functions of the magnitude of variation. The effect of the geometric mean fitness of the mutant is through the effect on the probability of persistence of a lineage, which is shown in figure 3B. The effect of mutation rate (and magnitude of variation) is shown in the probability of persistence plots (figure 3C). We did not vary the initial population, but for the analytical results it is only the product of N and mu that matters, so varying N should have the same effect as varying mu. It is true that we did not examine high values of rho, but as is shown in the appendix

(and confirmed by simulations), the higher rho is, the higher the inflation in the expected number of births, and the lower the magnitude of sigma for which this value becomes infinite. (The exception to this pattern is when rho becomes very close to 1, a situation that we discuss below in response to comment # 12.

4. The Discussion, at 7 pages, seems disproportionately long compared to the Results (4 pages). I have mixed views on this point, as I appreciate a thorough discussion that makes connections to other studies and sets the results within a bigger picture. However, the Discussion is in danger of losing focus and the authors could consider whether some less-important points could be made more concisely. For example, L386- 393 seem a bit peripheral and it is unclear to me how this study adds to the general understanding of this particular topic. The "Applications" section could also be shortened, given the following comment.

Authors' response: Thank you, these are good suggestions for streamlining the manuscript. We have removed the suggested paragraph that was on L386-393, in retrospect, we agree its points were peripheral to the main focus of our study. In response to this comment, and some other comments by the other reviewers, we have also removed the subsection "Effect of Genetic System" which is now just a single paragraph in the subsection "Assumptions and Caveats" (Lines 400–404). Finally, as suggested, we have rewritten and slightly shortened the medical treatment part of the applications sections as well (Lines 432–439), see response to the next comment for more details. We decided to keep the other sections of the application section because other reviewers seemed to find the suggested hypotheses valuable.

5. The "Applications" section of the Discussion is rather tenuously linked to the present Results. I am skeptical that stochastic fluctuations in the environment, as modelled here, can be representative of any temporal pattern of environmental variation, such as those patterns imposed by interventions discussed in this section. To their credit, the authors do point out this distinction (L397-398), yet they devote quite a long discussion (cf. above comment) to what strike me as over-reaching hypotheses. I particularly disagree with the authors' interpretation of skipped doses and pulsing treatments in the context of medical treatment. I don't think that a "reconciliation between these opposing viewpoints" is needed: skipping doses will generally reduce the total amount of drug

Authors' response: We agree with the point about our misinterpretation about skipping doses. We were envisioning a scenario in which the patient forgets to take a dose one day and then takes double the dose the next day to "make up for it". However, that is not the scenario we described.

In response to this comment, we have removed the discussion about skipping doses and a "reconciliation between opposing viewpoints". We now simply say that previous studies have shown that pulsed treatments might reduce the probability of resistance evolving and that our results suggest that the benefit of pulsed treatments might be context-dependent (Lines 434–439).

Minor comments

6. Abstract: The term "fluctuating environment" is not sufficiently clear here: the authors should specify that they mean random variation (and not, e.g., periodic changes). Likewise, in L7 "previous studies" should be more specific about (presumably) referring only to studies dealing with environmental stochasticity.

   Authors' response: We apologize, the term "fluctuating environment" was too vague. We have now restructured that sentence to state, "This process, known as evolutionary rescue, is believed to be less likely to occur with increased magnitudes of random environmental fluctuations because environmental variation decreases the expected population size, increases variance in population size, and increases evolutionary lag." (Lines 4–7).

   We have also made the line about "previous studies" more specific to read "previous studies of evolutionary rescue in fluctuating environments". (Line 7).

7. Intro, L56: I believe ref. [26] (Lindsey et al) deals with rate, not magnitude, of environmental change.

   Authors' response: Thank you for catching this error. We have now moved the Lindsey et al citation to the part of the sentence about rate of change. We have also added the citation of Ramsayer et al. 2013 to the statement about different magnitudes, a citation which we forgot to include in the original submission. (Line 57–58).

8. It would be helpful to clearly summarize somewhere (perhaps last paragraph of Intro or first paragraph of Results?) the differences between the various models being used: not only the genetic basis, but also e.g. the consideration of demographic stochasticity (absent in the "population-level" polygenic model, but included in the individual-based simulations). This would make the results easier to follow.

   Authors' response: As suggested, we have now summarized the differences between the various models in the last paragraph of the introduction (Lines 62–73). We appreciate this suggestion. We believe this makes the manuscript easier to follow especially if a reader does not read the methods closely.

9. There are some issues with equation numbering (missing #1A; labelled #2F-H instead of 2A-C).

   Authors' response: Thank you for catching these mistakes. We have now corrected them.

10. The description of the polygenic model (p. 5) needs some more details, specifically about the life history being assumed. Is the trait z determined at birth and fixed through the organism's lifetime? If so, should t in the expression for viability (L72) be taken as t at birth? Is viability V then the probability of surviving from birth to adulthood, as opposed to from any given

present time to adulthood? (I only realize as writing this that maturation to adulthood is probably assumed to happen within less than one generation, and thereafter trait value has no impact?) In turn, I wasn't sure how to interpret mean viability of the population in generation t (L84): is this mean viability of all newborns in this generation? Finally, Equations 1A-C need either a citation or a bit more explanation/derivation.

Authors' response: We apologize for this being unclear. On lines 86–89, we have now added more detail about the life history assumed in the model. At the start of each generation, the population consists entirely of juveniles. These juveniles than undergo viability selection following the equation given in the text, in which the trait z was determined at birth. All individuals that survive viability selection than mature into adults and reproduce. After mating, all adults die and the next generation begins with the offspring that were just born (i.e., the generations are discrete).

Yes, mean viability of the population is the mean viability of all newborns in that generation because at the time of viability selection, all individuals in the population are newborns. We hope this is now clearer in the main text with our more detailed description of the life history.

We have added citations of Bürger and Lynch (1995, ref 8 in the manuscript) and Gomulkiewicz & Holt (1995, ref 1 in the manuscript) for equations 1A–B. Equation 1A is equivalent to equation 4 of Bürger and Lynch (1995) and equation 5 in Gomulkiewicz & Holt (1995). Note that Gomulkiewicz and Holt's equation is in terms of distance of the mean phenotype from the optimum, but this can be converted to our recursions. Neither of these citations provide a full derivation of the equation, which is provided in part A1 in the appendix of Peniston et al 2019 (American Naturalist, 194.3, 2019).

11. The equations for a Gaussian random sequence (L100-102) should be cited.

Authors' response: We do not know who should be credited with this method, which we have used for decades, so rather than providing a citation, we show in the appendix that the method produces the desired statistical properties of the sequence.

12. Note that Equations 2F-2G, along with the initial condition, collapse to a constant environment when sq=0 or r=1, although I assume the authors mean the former when they refer to a "non-fluctuating environment" (e.g. in figure captions). However, one of the authors' findings is that the impact of environmental variation gets stronger as r increases. How is this finding reconciled with the mathematical equivalency of the model as either sq->0 or r->1 ? Is there a non-monotonic effect hidden for sufficiently large r (which would be revealed by a parameter sensitivity analysis, cf. major comment #3), or am I missing something?

Authors' response: Thank you for pointing this out. We should have explored this parameter space in the original submission. As was predicted in this comment, when rho because very high (> 0.98 for parameters used in figure 2), the effects of increasing autocorrelation actually switch directions. This is now shown in figure A4. This occurs because at these high levels of autocorrelation the fluctuations become so slow that the model behaves similarly to

when there are no fluctuations. We have added text to the results section mentioning this result on lines 244–246.

We note that this new result is dependent on our assumption about how the random process is started. We assumed that the initial degree of environmental variation was always μ_θ. With this assumption, if rho = 1, the result is the same as when the environment variation is 0 and thus the optimum phenotype is always the mean degree of environmental change. An alternative assumption, is to have the initial value be a random Gaussian with mean μ_θ and standard deviation σ_θ. With this assumption, the effect of increasing autocorrelation no longer switches directions at very high levels of variation (Figure A11) because with rho = 1, the optimal phenotype is simply constant at whatever the random value was, which in essence is evaluating the effect of having a randomly drawn degree of environmental change. We made the choice to keep the initial degree of environmental change constant because the effects of the initial degree of environmental change are well known and we were focused on the effects of variation afterwards. Beside the effect at very high levels of autocorrelation, changing this assumption does not alter our qualitative results (Figure A11). We now explain the justification of this assumption on lines 127–131 in the main text. We also go into more detail about the statistical properties of the assumption in the "Generating autocorrelated Gaussian sequences" section of the electronic supplementary material.

13. Paragraph starting L109: How is the population initialized in these simulations?

Authors' response: Thank you, this should have been stated. We have added that the simulations were initiated with an initial population size of N^* and an initial phenotype of zero (Line 125–126).

14. L116 confusing wording: the population never reaches, and also never asymptotically approaches, zero; or rather, never reaches, but does asymptotically approach?

Authors' response: We intended the first suggestion above. The population never reaches zero and it also never asymptotically approaches it. In other words, the final population size will always approach infinity as time approaches infinity because the population always eventually adapts. To make this clearer, we have changed the word "or" to "nor" (Line 136).

15. L117: I'm aware that the critical population size heuristic has been used in previous work and is a somewhat accepted convention. However, given that the authors also have individual-based simulations to hand, they could consider defining Nc in a less arbitrary way based on the population size below which populations go extinct in these simulations with some threshold (high) probability. On the other hand, I don't expect the qualitative results will change if a somewhat higher/lower Nc is used, and the authors could make this argument.

Authors' response: In response to this comment, we have run simulations with different values of the heuristic population size N_c and confirmed that the same qualitative patterns hold (figure A1A).

The suggestion of choosing the value of N_c based on the individual-based simulations is a good idea, which we might do in future studies. However, because the same qualitative results hold for different values of N_c, in this study we decided to continue using the our arbitrarily chosen value of 100 because this does not require us adding additional text to explain the methods of selecting N_c and as was mentioned, this is conventional in the field.

16. L134: is the zero-mean, unit-variance normal random component to be interpreted as equivalent to E (environmental variance) in the population model?

Authors' response: Yes, we have changed the wording to state "which was the sum of allelic values at 10 freely recombining, additive loci plus a zero-mean plus a random environmental component drawn from a normal distribution with mean zero and unit-variance" to make this clearer (Lines 156–157).

17. L159: the authors suggest that the "appropriate" random variable for total number of offspring is Poisson. However, it's worth noting that this a model assumption, which may or may not be realistic. For example, many organisms that reproduce clonally (as the monogenic model also assumes) reproduce by binary fission.

Authors' response: We apologize, that was not our meaning here. The assumption that the number of offspring was Poisson was given prior to this point, as were the facts that each offspring has a fixed probability of dying (dependent on its genotype) and that each non-mutant offspring had a fixed probability of a mutation. Given these assumptions, the random number generators indicated should give a number of offspring, new mutations, and surviving adults that have the correct statistics. We have added '(given our assumptions above)' to emphasize that these random number generators depend on our assumptions.

18. Around L168: would be useful to mention at the outset that these derivations can be found in the Appendix.

Authors' response: We have taken this suggestion and mentioned earlier the mathematical details can be found in the electronic supplementary material (Lines 197–198).

19. Start of the Results section: This is a bit of an abrupt start, especially as some readers may not go through the Methods first. Consider adding a paragraph briefly outlining the different models and what is to be done with them.

Authors' response: We followed the above suggestion (comment #8) of summarizing the differences in the various models in the last paragraph of the introduction. We think this addresses the concerns of this comment because it should make the results easier to follow even for a reader that has not read the methods. Thank you for this suggestion.

20. L186/L188: clarify that Fig 1 shows the population-level model and Fig. A1 shows the individual-based model.

Authors' response: Thank you for this suggestion, this should have been clarified in the original submission. In response to other suggestions from reviewers, we have reorganized what is being shown in each figure. But we have kept this comment in mind and tried to ensure that we are always clear when we are referring to the population-level model and when we are referring the individual-based simulations.

21. L190: population-level simulations never went extinct: i.e. never reached exactly zero, or never dropped below Nc? It would be helpful around here to re-iterate that the population-level simulations do not account for demographic stochasticity, whereas the individual-level simulations do.

Authors' response: To make this clearer, we have added a sentence at the beginning of this section stating "Recall, this model ignores demographic stochasticity and assumes that the population goes extinct when it drops below a critical population size N_c" (210–212). We appreciate this suggestion, we believe it makes our results and assumptions clearer to the reader.

22. In Fig. 1, a critical value of change in mean optimal phenotype is evident, at which probability of persistence drops from 1 to 0 in the absence of environmental variation. If I remember correctly, this critical value was derived analytically by Bürger & Lynch 1995; perhaps this expression could be included somewhere?

Authors' response: We appreciate this suggestion. We should have included the analytical solution for this critical value in the original manuscript. We have re-read Bürger & Lynch (1995) and we do not believe that they provided such a solution for the step-change scenario we investigated. However, Gomulkiewicz & Holt (1995, ref 1 in the manuscript) did derive an implicit solution. We have now included this as equation 4 in the manuscript (Line 213). The critical value at which probability of persistence drops from 1 to 0 can be numerically derived as the point at which there are roots t to equation 4. As mentioned above, including this equation has also allowed us to more formally define baseline extinction risk.

23. Fig. 1: note that probability of persistence is an estimate, based on a finite number of stochastic simulations of the environment. Please mention in the caption how many simulations were performed, and give error bars on the plotted estimates. (This comment also applies to all other figures showing simulations.) It would also be helpful to define persistence (i.e. N_t > Nc at all t) in the caption, and mention the initial population size in the list of parameter values.

Authors' response: Thank you for point this out. We should have included the number of simulations and our definition of persistence in the legends. We have now rewritten the legend of the figure (now figure 2) to state "Each point represents the proportion of 1,000 runs of the simulation in which the population persisted until the end of the simulation (N_t > N_c for all t)" and we have made similar changes to other figure legends were appropriate. We have also added the initial population size to the list of parameters (we have now defined initial population size as N^*).

It would be possible to put error bars on the simulation plots, but we do not think they are useful. With simulation, it is usually possible to do a sufficiently large number of 'replicates' that virtually any differences are statistically significant. However, that doesn't mean that they are large enough to be biologically meaningful, and we think that is the important question, which can be addresses by looking at the means. With 1000 replicates, the maximum standard deviation of a proportion (which should have a binomial distribution) is 1.6%. In other simulations, we use 1,000,000 replicates, which gives a much lower error standard deviation (maximum of 0.05%). So, we think errors bars will complicate the figures without providing useful information.

24. I strongly suggest to swap the order of Figures 1 and 2: I think the exposition would be much clearer if the sample trajectories were shown first, and perhaps annotated to illustrate how probability of persistence is calculated from these simulations. (E.g. colour-code the trajectories according to those that did or did not drop below Nc, and annotate with the number of such trajectories.) I also suggest including a few more panels in Fig. 2 (sample trajectories), illustrating the effects of varying r and sq.

Authors' response: As suggested, we have swapped the order of figure 1 and 2 and agree this makes the exposition much clearer. We have also made the suggested change of adding a colour-code to figure 1 (sample trajectories) showing which trajectories dropped below N_c. We appreciate this suggestion because we had not thought of presenting the results this way.

Because of space limitations, we did not add additional panels to the figure of sample population trajectories (figure 1). We have added some additional supplementary figures to help illustrate the effects of varying rho and sigma (figures A2, A3, A4). We did not add additional figures with population trajectories, but we can add these figures as well if necessary.

25. L201-203: as magnitude of variation (sq) increases further, probability of persistence drops again. Please do show these results (in the Appendix)! Similarly on L225-227. What these results suggest is that there is not simply an increase in the probability of rescue with the extent of environmental variability (in this parameter space), as the Abstract/Conclusions more prominently state; but rather, there is an intermediate optimal level of variability. I think this message should be clearer. Can the authors say anything about how this optimum depends on parameter values?

Authors' response: We apologize, we should have included these results in the original manuscript. We have now added an additional supplementary figure which shows this result (Figure A2). As suggested, we have also emphasized this point more in the results section of the main text on lines 235–237.

It is unclear to us at what specific value variability begins to become detrimental because it likely depends on many of the parameter values. Two particularly important parameters might be the degree of environmental change (theta) and the width of the fitness function (omega). When the fluctuations in the optimal phenotype become nearly as large as the initial step change, populations that could not withstand the step change without fluctuations, likely

will also not be able to be able to withstand fluctuations equally as large. Similarly, once the standard deviation of environmental variation becomes close to the width of the fitness function, any population is at risk of suddenly become extinct (Bürger and Lynch 1995). Beyond these broad patterns, we are unsure how to pinpoint an exact value.

26. The method of "prediction" (L209 onwards / Fig. A2) was entirely unclear to me; please add method details. I'm also not familiar with McFadden's R^2: does it account for the idea in L213-214 that models can already attain a certain accuracy simply by always predicting extinction? This seems worth mentioning as well. Similarly, the caption to Fig. A2 was too brief to understand what was going on: Is each dot one simulation? What does probability of persistence then represent?

Authors' response: We apologize, we should have included our methods for prediction. These are now included in the electronic supplementary material. To summarize, we ran 1,000 runs of the simulations and fit the data to a generalized linear model with a binomial distribution and logit link function. The independent variable was the mean optimal phenotype from years t_i to t_j and the response variable was whether or not the population dropped below the critical population size N_c ("extinct" or "persisted"). We then ran an additional 1,000 runs of the simulation and evaluated how well the generalized linear model that was fit to the first 1,000 runs could predict the results of the second 1,000 runs.

We agree, the caption of Fig A2 (now Figure A5) was too brief thank you for pointing this out. We have updated the description to be more detailed. Yes, each dot represented one run of the simulation, but the reviewer is correct, the vertical axis should not have been labeled "probability of persistence". We have changed the vertical axis label to be "Extinct" or "Persisted". Also, instead of showing individual points, we have made violin plots which shows the probability density of different mean phenotype values in each group. We believe this shows the results more clearly.

27. L218-220: this point does not seem to be clearly shown by Fig. A2.

Authors' response: We believe the point was not clearly shown because of the lack of detail in the figure legend. We believe the updated figure (now A5) and legend shows this point more clearly now.

28. L236-242: This (lack of) explanation is not very satisfying. Can the authors dig a bit deeper into the reason behind these differences between population-level and individual-level models? If parameter values were chosen to make computation efficient in the individual-based simulations, why not use the same parameter values in the population-level model to exclude one source of differences? Likewise, can the density regulation in the simulations be removed, with a stopping condition when the population reaches a given size? (Also relates to comment #38.)

Authors' response: In response to this comment, we have run some additional simulations to try to better explain this pattern. First, as suggested, we ran population-level simulations with the same parameter values as the individual-based simulations. These results are now shown

in A7 and we discuss the differences between the population-level and individual-based simulations in the paragraph that starts on line 263.

As suggested, we have also ran additional simulations in an effort to better understand the differences between the population-level and individual-based simulations. Figure A8 shows the effect of density regulation (as suggested in comment #38) and Figure A9 shows temporal changes in the additive genetic variation. Neither of these two effects appear great enough to fully explain the differences between our population-level and individual-based simulations so we conclude that the other sources of stochasticity in our individual-based simulations must explain the remain differences.

29. Consider moving Fig. 3A-3B to the Appendix, where the components of population persistence in this model are explained in more details. If the authors decide to leave these panels in the main figure, then the caption needs some rewriting to make it clear what is being plotted without having to look up equations in the appendix. The caption of Fig. 3 should also make it clear when an analytical approximation vs. a simulation result is being plotted.

Authors' response: We think there is merit to the suggestion of moving figure 3A and 3B to the appendix, but we decided to leave them in the main text because they provide insight into why we see the result in 3C. As suggested, we have rewritten to legend to clarify which results are analytical (A,B) and which are from simulation (C).

We have removed the reference to the equations from the figure legend, so that it now just indicates what the figures show and refers the reader to the appendix for details, which we do not think are necessary to understand A and B.

30. L250 "This is likely": poor choice of words; it sounds like this is a statement to do with probabilities. Rather "We hypothesize/interpret this as...". I also don't follow how this explains why variation has little effect.

Authors' response: We have changed the wording to 'We believe this is', and have added some explanation, which explains that autocorrelation has less of an effect because runs of good or bad years (unless very short) do not have time to act (Lines 290–294).

31. L251-254 "the positive effect of inflation... is generally larger than the negative effect" and L257-258 "for most mutation rates...": These statements are entirely dependent on the choice of parameter values, and there is no basis to say that the set of parameter values chosen here is most realistic. Please rephrase in more neutral terms, e.g. "for sufficiently low mutation rate...". Similarly, later on L324-325, "for a greater range of parameter space": this entirely depends on what range of parameter space one chooses to look at.

Authors' response: We have now qualified the statement on lines 294–298, which refers to figure 3A and B. We think those figures show a reasonable range of the parameters. As suggested, we have rephrased "for most mutation rates" to read "for sufficiently low

mutation rates" on line 310. The reviewer is correct about our statement of "most" being arbitrary.

In regard to the "greater range of parameter spaces" comment we had made in the discussion, we have removed the direct comparison between these two models all together. As was correctly pointed out, these conclusions entirely depended on the range of parameter space and the comparisons we made were not well grounded. Thank you for making us aware of this issue.

32. Discussion, L292-296: This is an interesting connection. It also reminds me of the effect of increasing mutation rate when both beneficial and deleterious mutations are modelled: increasing mutation rate increases the probability of survival if and only if a population is likely to go extinct without acquiring a critical beneficial mutation (Alexander & Day, *J R Soc Interface* 7:1455-1474, 2010). I will leave it to the authors' judgement whether to actually include this point in the already-long Discussion.

Authors' response: This is interesting connection that we had not made. We decided not to include it in the discussion in an effort to keep the discussion from becoming too long and unfocused. However, we appreciate the reviewer making us aware of this interesting idea.

33. L298-299 "The existence of such a critical period may be necessary...": This sounds tautological; surely such a period is called "critical" precisely because it has an impact on rescue. The intended meaning became clearer on L357-360 but needs some rewording at the earlier point.

Authors' response: Thank you for pointing this out. We have removed the statement from L298-299 because it was stated more clearly on later as was pointed out.

34. L320 "changes in correlation structure": what does this mean, other than simply varying the correlation coefficient r as already studied here?

Authors' response: Sorry, we should have been more specific. What we intended was "temporal changes in correlation structure" meaning that an environment would be become more or less autocorrelated throughout the simulation. In this study, we simply compared correlated vs uncorrelated fluctuations and did not allow the degree of correlation to change throughout an individual run of the simulation. We have added the word "temporal" to line 362 to make this clearer.

35. L349 "changes in extinction probabilities" – changes with respect to what? Extent of environmental variation?

Authors' response: Yes, we intended "changes in extinction probabilities with respect to the extent of environmental variation". We have rewritten the sentence on line 373 to state this. Sorry for the confusion.

36. L355 pollution and habitat loss don't seem like great examples of abrupt environmental change; I'd imagine these are also usually gradual.

Authors' response: We agree that both of these (and the other examples) could be interpreted as either abrupt or gradual changes. It would depend on the specifics of the situation. However, we behave there are many situations where pollution and habitat loss could be treated as abrupt changes.

For pollution, it may often be the case that a new pollutant can become abundant in a natural system very quickly (in less than one generation of the focal species) representing an abrupt change. For instance, when land managers decide to start using a new pesticide, this might rapidly become a new selection pressure for the local community. We agree that there are certainly many other cases were pollutants slowly accumulate in the environment over long period of time. Generally speaking, it seems like point source pollution will more typically be abrupt changes while nonpoint source pollution would be more gradual.

In regards to habitat loss, a forest might be suddenly clear cut. This would abruptly expose many organisms, such as understory plants, to completely new selective regimes such as increased sunlight. We think is type of situation would be best modelled as an abrupt change.

37. L367-368: This statement overlooks density-dependent effects arising specifically at low density, e.g. Allee effects.

Authors' response: This is correct. We should have said "negative density dependence". However, in an effort to shorten the discussion, we have removed this sentence all together. Allee effects would be part one of the forms of density dependence that acts even at small population sizes considered in the next sentence on 392–393.

38. L377-379: Could this possible explanation be checked by recording whether the population ever reached carrying capacity in the individual-based simulations?

Authors' response: Thank you for pointing this. Although obvious in retrospect, we did not think to do this. We have now run these simulations and included the results in the results section on lines 271–274 and in figure A8. We have removed this sentence from the discussion because it is now addressed in the results.

39. L412: "optimal" is imprecise; rather say "maximizing extinction probability"

Authors' response: We have changed optimal to "minimize the probability of resistance evolving" on line 430.

40. Appendix, for both polygenic and monogenic simulations: any evidence that the number of generations simulated was sufficient to attain a reasonably high accuracy?

Authors' response: For the population-level polygenic simulations we have added a Figure A6, which shows that for almost all the simulations that have population sizes below N_c,

these sizes occur before generation 100. So, for those simulations 1,000 generations should be much longer than is actually necessary.

For the individual-based polygenic simulations, given our parameter values, 1,000 generations should also be much longer than is actually necessary. Our simulations and parameter values are very similar to those used in Barfield & Holt (2016; Evolutionary Ecology Research, 17(6), pp.771-786). Figure 8 of that paper shows that no populations went extinct after 120 generations.

We are likewise confident that 1,000 generations was enough for the monogenic simulations. Based on the parameters used, the non-mutant populations would be expected to go extinct by 25 generations (without variation), so the original mutant lineages must have been generated early, and it is highly unlikely that a lineage could survive until generation 1,000 and then gone extinct. (In fact, probably no populations reached generation 1,000, since the simulations were stopped if the number of mutants reached 1,000 or the population went extinct, and both were likely to occur in the first 100 generations).

41. Appendix, throughout the monogenic model description: for consistency across models, I suggest using the term "fecundity" rather than "birth rate" unless there is meant to be a difference.

Authors' response: This is a good suggestion. We have replaced birth rate with fecundity where appropriate.

42. Appendix, monogenic simulation methods: would seem more natural to refer to "total births", rather than "non-mutant births", from which a number of mutants are then drawn

Authors' response: Before we referred to 'non-mutant births', we described reproduction of non-mutants and mutants, each giving rise to their own type. Then, we describe the simulation of new mutants, which are produced by mutations only on non-mutant offspring in the current generation.

43. Appendix, 1st line of p. 5: "The geometric mean of F_tV is m": should this be exp(m)?

Authors' response: Yes, it should be exp(m). Thank you for catching this mistake.

44. Appendix, 8th line of p. 5: Please define μf within the Appendix. It's also not obvious to me why sigma and rho are the same?

Authors' response: We have now defined $μ_f$ as the mean fecundity. We did not mean that sigma = rho, but that both sigma and rho are the same for F_t and F_t V. We have changed the wording to make this clear.

45. Appendix, definition of maladaptation: Non-mutants are said to be maladapted if m<0. Yet a stronger condition is needed for the series giving total number of non-mutant births to converge. Doesn't this suggest that the definition of maladaptation should be revised?

46. Just below Eq. A8: define $F = \exp(m)/V$.

47. Appendix, 2nd-last line of p. 6: "the remaining part of the summation above": this is hard to follow; I'm not sure which summation is meant.

48. Appendix, p. 8 just below the equations: would be helpful to add "F_t is a Gaussian random sequence". Also, I think G_t in the following line should be G_t.

49. Appendix, 3rd line on p. 9: the distribution of the number of mutants

50. The assumption of a Poisson-distributed number of mutants with persisting lineages, and the conditions under which this will be a good approximation, can be justified with reference to G. Martin et al, *Phil Trans R Soc B* 368:20120088. Below, when the assumption of a Poisson distribution becomes "less justified", the authors could be more specific that the actual distribution becomes overdispersed. I think the effect the authors see, that the analytical approximation is an overestimate in this case, can be explained in the same way as Uecker & Hermission, *Genetics* 202:721-732 (2016): the probability of rescue is a concave function of the number of mutants, thus when the number of mutants is overdispersed, deviations below the mean outweigh deviations above the mean.

observed in Uecker & Hermission (2016). We have now included this explanation in the appendix on.

51. Figure A1: Please specify in the caption that this is the polygenic model. Why aren't the ranges on the x-axis the same as in the main Fig. 1? Also note that the carrying capacity used here (250) is much smaller than the initial population size used in the main figures (10,000): why not make this consistent (also cf. comment #28)?

Authors' response: This exact figure is no longer in the manuscript as we have changed it in response to other comments. As mentioned above, we have now ran simulations of the individual-based and the populations-level polygenic models with the same parameter values in order to allow better comparison. Figure A7 now compares the population-level and individual-based simulations.

52. Figures A2 & A3: The captions need more detail (cf. comment #26). I think there is also a typo in the caption, should generations 10-20 rather be 1-20 as in the figure panel? Please also highlight what differs between figures A2 and A3, and consider combining these into one multi-panel figure for easier comparison.

Authors' response: As we mentioned in our response to comment #26, we have remade these figures. Our original figures were poorly made, and the figure legends were not detailed enough. We believe we have addressed these issues with the new figures, now figures A5 and A14. For more information, see our response to comment #26.

The difference between what was figure A2 (now A5) and figure A3 (now A14) is that in figure A2 the x-axis is the mean optimal phenotype and figure A3 the x-axis is the mean fecundity.

53. Fig. A5: presumably the simulation results (shown with solid lines) are only actually simulated at discrete parameter values? Please indicate.

Authors' response: The simulation results were calculated at intervals of 0.01. This has been added to the figure legend. Thank you.

Appendix B

<div align="center">**Response to Referees**</div>

We appreciate the comments on our manuscript that we have received from the associate editor and reviewer. We believe that all of these comments have improved our manuscript. We have tried to address of the associate editor's and reviewer's concerns in this revision. Please find our responses to all comments below. For clarity, we have made all of our response in the color blue and labeled them as "authors' response:". All line numbers refer to line numbers in the "clean" version of the manuscript. We appreciate your consideration of our revision.

Associate Editor Board Member
Comments to Author:
None of the reviewers of your initial submission were available to evaluate this new version. Thus, the resubmitted version has been reviewed by a referee who did not participated in the first round of evaluations. She/he feels the changes you introduced go a long way towards incorporating the suggestions of the original reviewers. However, there are still some few issues that need to be addressed.

Authors' response: We are grateful that you were able to find a fourth reviewer and appreciate them taking the time to review our manuscript.

The main remaining issue concerns a lack of clarity on how you define high/low extinction risk. I think the source of the confusion is that you refer to high- and low-risk populations when in fact, you should be talking about low- and high-risk scenarios. In a purely demographic model, the baseline population extinction risk should only be determined by demographic parameters (fecundity and survival). That is, it should be the result of demographic stochasticity. In your case you also have to consider mutation rate because that determines to what extent the population can adapt to the environmental change and is a parameter specific to each population/species. This baseline extinction rate is different from the one you are referring to which also includes a component due to the magnitude of the initial environmental perturbation. For this reason, referring to "scenario" instead of population may help readers to fully understand your model. I think you should incorporate these details in the introduction and then refer only to "scenarios" instead of populations.

Authors' response: Thank you. This is a very useful suggestion that we had not thought of. We have rewritten the manuscript to refer to extinction risk scenarios instead of populations. We have also changed the title accordingly to refer to high-extinction-risk scenarios instead of populations.

The referee also makes other very helpful comments requesting clarifications of other aspects of your study.

Authors' response: We appreciate these comments, as well as your own, and believe we have addressed them all. Thank you for this careful reading of our manuscript.

Reviewer(s)' Comments to Author:

Referee: 4

Comments to the Author(s).
Peniston et al. describe their theoretical treatment of environmental fluctuation during evolutionary rescue. This is a resubmission and I was not a prior reviewer (and I don't know which reviewer I'm replacing). I've read the reviewer comments and feel that the authors did a nice job in addressing most of those comments. I have a few suggestions, but will try to keep them brief.

Authors' response: We appreciate this reviewer's useful comments that have improved our manuscript.

I still feel like the discussion of high/low extinction risk is still vague. Would it be possible to include a figure (either based on data or a cartoon) showing how varying parameters moves from one category to the other? A contour plot with population size and mutation rate on the two axes?

Authors' response: As was suggested by the associated editor, we have changed our wording to refer to high/low extinction risk scenarios instead of populations. We believe this makes the discussion of these scenarios clearer. As suggested by this comment, we have also added another figure to the appendix showing how the degree of environmental change and initial population size affect extinction risk (Figure A2). We refer to this new figure on lines 224–228 of the main text. We appreciate this suggestion. We think that it has made the explanation of these scenarios clearer.

It also took me a while to understand that all the environmental variation occurs after the environmental change. I had ideas about environmental variation increasing genetic variation before the change, etc. This could be more clear upfront - an explicit description of the scenario.

Authors' response: We apologize for this confusion. We should have written this more clearly. We have now added a sentence explicitly stating that the environment was constant before the change on lines 128–129. It is also stated in regard to our polygenic individual-based simulations on line 163.

On a related note, it took me a while to realize that you were only considering new mutation and never standing genetic variation. That could be made more clear (even in the title).

Authors' response: In both our polygenic models, we do include initial (meaning at the time of the environmental change) standing variation, which is very important to evolutionary rescue. We apologize for not explaining our assumptions more clearly. We do not explicitly model mutation at all in the polygenic population-level model. Instead, that model assumes that genetic and phenotypic variance are temporally fixed (and thus there is initial variation that is implicitly replenished by mutation, and recombination, so it is not depleted by selection or drift). This is stated in the methods on line 100–102. In the individual-based simulations, there is once again standing genetic variance, which is initiated using the stochastic-house-of-cards approximation of Bürger and Lynch (1995; reference in the main text). After initiation, the simulations were run

for 1,000 generations in an unfluctuating environment (but with mutation) to allow the population to reach selection-mutation-drift balance. This is explained in the *Polygenic individual-based simulations methods* section of the appendix. In regard to the previous comment, all of our individual-based simulations assume that there are no environmental fluctuations before the environment change to control for the effects of environmental fluctuations on standing genetic variation.

It is true, however, that in our monogenic model, adaptation can only occur via the arrival and fixation of new mutations. We have added a sentence on lines 166–168 clarifying this difference between the two models. We did not change the title as suggested because our manuscript does include standing genetic variation.

Line 250 - It would be useful if you described the characteristics (or even showed them graphically) that lead to high or low rates of rescue. It is mentioned later that it is a run of good years, but what does that look like in your model? Is there a way to represent it? A5 is a good start and could be moved to the main document, but I guess I was thinking something that plotted the optima over those first 20 generations, second 20, etc. and colored based on rescue.

Authors' response: We have added a figure that shows the optimal phenotype over the first 100 generations for 100 randomly selected runs of the simulation (Figure A8). As suggested, the plot is color coded based on whether or not rescue occurred in the simulation. We believe this addresses the reviewer's comment and shows how when rescue occurs, the mean optimal phenotype is typically lower in the first 20 generations. While we agree with the reviewer that it would be nice to include this as another figure in the main text, we are limited by space restrictions, so we left it in the appendix. We now refer to this figure on line 268 of the main text.

The environmental variance was held constant in the fluctuating environment (97-99). Maybe stress that this is a potential reason for the minor disagreements between the individual and polygenic models.

Authors' response: We appreciate this suggestion. We had not thought about how the stochasticity in the environmental effects could have led to the disagreements between our individual-based and polygenic models. As suggested, we have now mentioned this in the text on lines 282–284.

In equation 3A, it might help to redefine eta(t) since it was only mentioned briefly a couple of pages before.

Authors' response: We have now redefined eta(t) on line 177.

Appendix C

Comments from Associate Editor:
You have satisfactorily incorporated changes to take into account the comments made by the new referee and I. I feel your manuscript is now very clear and will be of great interest to Proceedings B readership.
There is only a very minor change you need to introduce:
ln. 80: "extinction" -> "extinct"

Authors' response: We appreciate this kind feedback on our revision. We have made the edit suggested. We are grateful that you caught this mistake.