

[Close Window](#)[Print Email](#)**Date:** 2018-09-01 01:39**Last Sent:** 2018-09-01 01:39**Triggered By:** Redacted**CC:** Redacted**BCC:** Redacted**Subject:** GENETICS/2018/301449 - Editorial Decision**Message:** August 31, 2018

GENETICS/2018/301449

Genetic draft and valley crossing

Dear Dr. Van Cleve:

Two experts in the field and an additional junior referee have reviewed your manuscript, and I have read it as well. Unfortunately, your manuscript would need to be substantially revised to be acceptable for publication in GENETICS. Both reviewers have comments and concerns that need to be addressed in a revised manuscript. You can read their reviews at the end of this email.

We would reconsider a substantially revised manuscript. Please understand that incremental changes will not be sufficient. Please be aware that, given the extent of the revisions needed, Genetics would consider a resubmitted manuscript as a new submission.

All referees agree that you have identified an important problem (valley crossing with draft) that is worth studying. However, as you can see from the both expert opinions (referee 1+2, both specialists of the field) your simulation results failed to convince the experts. I agree that the results presented here fail to live up to the standards set by previous publications on the same subject. Of course, this is partly because analytical results have not been possible. However, also with a pure simulation study, clearer and more comprehensive results seem possible. In particular, I see the following points:

As mentioned by all referees, the non-standard setup of the simulation scheme makes it very difficult to relate the results to previous work. Although your main conclusion may well be confirmed for a standard infinite-sites model without constraining the background variance, this is by no means guaranteed (see the remarks about the infinitesimal limit by referee 2). To address this point (in the absence of analytical results), there is probably no way around individual-based simulations.

The first point by referee 2 is particularly important: Indeed, it is not clear that serial substitutions and tunneling will dominate in the same parameter regions as for drift (it also may depend on the depth of the fitness valley and on other parameters like the background mutation rate). In your simulations, this point is not addressed at all. However, in the absence of theoretical results, we need an even more comprehensive numerical study.

As mentioned by both referees, also your parameter choices are too limited. Note that additional figures can always be part of an electronic supplement.

Your ms (and in particular the mathematical background part) has clearly been written for specialists. This is ok, but still the comments of referee 3, who is an interested non-specialist, may help you to identify points where points can be made clearer to reach a broader audience.

Since the required changes are substantial and since any revised ms will be treated as a new submission anyway, no deadline for revision is given. Because the manuscript speaks primarily to specialists, any successful revision must meet the high standard of being of "extraordinary interest" to be publishable in GENETICS. It definitely has to fully convince the present referees.

Follow this link to submit the revised manuscript: [Link Not Available](#)

If you have questions about the reviews or this message, please contact me.

Sincerely,

Joachim Hermisson
Associate Editor
GENETICS

Nicholas Barton
Senior Editor
GENETICS

Reviewer #2 (Comments for the Authors (Required)):

see attached pdf

Reviewer #3 (Comments for the Authors (Required)):

The authors study the effect of linked background mutations, termed 'genetic draft', on the time of fixation of a beneficial double mutant composed of singly deleterious mutations. This process known as 'valley crossing' has been studied extensively in the absence of genetic draft. Similarly the dynamics of rapidly adapting populations, for which genetic draft constitutes a major evolutionary force, has been studied extensively in the framework of 'fitness wave' models which usually assume non-epistatic fitness effects. Combining these two themes constitutes an interesting and worthwhile subject of inquiry.

However, in my opinion the manuscript does not satisfy the criteria of quality and scientific substance required for publication in Genetics, for two main reasons. First, the modeling setup seems in several respects arbitrary and poorly motivated. Rather than using a true 'infinite sites' model for the background mutations as is standard in the fitness wave studies mentioned above, the authors choose a genome of 200 loci, two of which are designated as focal; the positioning of the focal loci is specified, though obviously this cannot matter in the absence of recombination. Although the authors do not explicitly say so, I assume that the background fitness is additive or multiplicative across loci. However, rather than simply letting background loci mutate to a new state with a randomly chosen selection coefficients, the authors impose a mutation scheme where a locus mutates whenever it becomes monomorphic. This seems like a highly unrealistic and awkward choice which makes it effectively impossible to externally control parameters such as the background mutation rate and selection coefficients. I find it hard to assess to what extent the results presented here generalize to a more reasonable modeling framework.

Second, compared to the extensive (and well-written) review of the state of the art on pages 1-5, the results section of the paper is remarkably meager. Results are exclusively numerical, subject to large error bars, and largely qualitative. Again, arbitrary parameter choices make it hard to assess the generality of these results. For example, for the comparison between the times required for a valley crossing and the sweep of a single beneficial mutation the authors arbitrarily choose the 'valley' selection coefficient to be ten times that of the sweep. It would seem that choosing the selection coefficients to be same would be more informative.

In addition to these two major issues, I list below some further comments that the authors may wish to address if they choose to resubmit the manuscript elsewhere.

1. page 5, second column: It seems to me that in the discussion below Eq.(1), the background fitness x should be replaced by $x - \bar{x}$ (fitness relative to mean fitness).
2. page 6, second column, second paragraph: Here the authors say that backward mutations at the focal loci are allowed. This contradicts the statement in the first column on page 4.
3. page 7, first paragraph of Results: Why is the null expectation that genetic draft increases the time for valley crossing? At least in their abstract, Neher & Shraiman (2011) appear to claim the opposite trend (last sentence). Or is this only true in the presence of recombination?
4. page 8, second column, line 14: s_{sweep} -> s_{valley}

Reviewer #4 (Comments for the Authors (Required)):

Please refer to the comments in the attachment.

Associate Editor Comments:

Attachment: Reviewer 2 Review Attachment 1 - 2018-08-31 18:09

Attachment: Reviewer 4 Review Attachment 1 - 2018-08-31 18:09

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