Dear Aurélien Tellier,

We have now made the final modifications to our manuscript that address the remaining issues. We provide some additional discussion for them below. Thank you for your work managing our submission.

Sincerely,

Miguel de Navascués, on behalf of all authors

Review by anonymous reviewer (1)

[…] Please add a link to the VCF files used in this study […]

VCF files are available now in the Zenodo repository (doi:10.5281/zenodo.4599735).

Review by Lawrence Uricchio

[…]

1. The spirit of my comment about including some additional discussion of Poisson Random Field and MK-based work is because many readers will naturally compare this approach to PRF, which is still very widely used for inferring similar models. I agree that PRF is less likely to be useful for such short time periods (~10 generations), and that it doesn't account for linked selection. But it can infer genome-wide selection and demographic parameters. Many readers looking at your Figure 1 will wonder specifcally how/when your method improves on PRF since it solves a model that is (conceptually) identical to models that were solved with PRF (e.g. Boyko et al 2008). Under which scenarios should we prefer an approch like yours to PRF? Highliting the deficiencies of SFS-based analyses for short timescale changes in population size and stating when specifically PRF-based approaches will fail due to linkage would be helpful. How many generations is too few to infer an expansion (as in your model) with PRF? How much linked selection is needed before the problem is severe with PRF? Even a couple of sentences would be helpful.

We have now included the methods based on PRF and McDonal-Kreitman in the introduction of methods that infer demography and selection. However, it is impossible for us to answer the questions put forward by L. Uricchio. These questions are undoubtedly pertinent. Unfortunately, our results do not inform us about the performance of an inference approach based on PRF. To the best of our knowledge, there are no implementations of methods based on PRF to analyse the type of temporal data that we are treating in this work, which make impossible to compare our approach to such potential method. Under the circumstances, we are not better placed than any reader for answering these questions.

2. The authors write in their reply "Therefore, we are more interested in the short term effects of negative selection on allele frequency changes than in long term effects on the site frequency spectrum." I think the issue here is that the allele frequency dynamics themselves are not independent of the population history in burn-in. With low recombination and a high rate of beneficial alleles, the dynamics may look more like clonal interference. If there is a lower rate of positive selection but high backgriound selection, the trajectories of the beneficial alleles may be subject to less perturbation by interference than an equivalent reduction in Ne due to positive selection, but the effect depends on the selection coefficients. I appreciate the section on limitations that discusses background selection, but it is not very clear in the manuscript how this will affect inference under this model. Some discussion of the ways that negative seleciton might affect the parameter inference would be helpful.

Our precedent version of the manuscript intended to reflect that the presence of background selection can have the potential to affect our inferences, but maybe it was not explicit enough. We have modified the text in a way that we hope it is more clear.

Review by anonymous reviewer (2)

[...] However, I was taken aback by the reluctance to estimate the robustness to deleterious mutations given how easy it is to simulate nowadays. It would have been straightforward to do. In their defense, the authors have added discussion about this potential limitation, in particular suggesting that heterogenous background selection and deleterious mutations could be problematic. The approach has potential, so I do hope that the authors explore these questions in the future to validate the goals behind their approach.

We understand the frustration of anonymous reviewer 2 regarding the (lack of) inclusion of background selection in our approach. However, we would like to insist that the ease to simulate deleterious mutations must not be confused with a proper treatment of background selection in the data analysis and evaluation of the method, which will require redefining the model, priors and summary statistics, and running a significant amount of new simulations.