Response to reviewers - second round

We are very grateful to the recommender and reviewers for their constructive suggestions, especially because our paper had changed substantially since the first version.

Matthew Hartfield

Many thanks for your substantial revisions of this preprint. Both reviewers and myself find this new version more comprehensive than before, and appreciate the effort made into improving the clarity of these complex analyses. That said, given the large amount of changes that have been made (to me it felt a bit like reading a whole new paper), there are still several suggestions that were made for improving the manuscript and its clarity. I hence feel it is worth further revising the manuscript before it can be recommended by PCI, but I foresee that it would not be sent out for further reviews after the next submission.

I have a few additional comments to add:
- I feel the two functions m, M could be defined earlier, when Figure 1 is introduced. I found it difficult to fully understand Figure 1 on a first read, as it makes references to these functions but they were not yet defined in the text. I think it would be sufficient to simply define the mathematical functions here, and leave the interpretation section in the same location.

We agree this was confusing, and have replaced the inset M and m functions with the actual definitions in terms of the A_i and Δ_i. We've also changed the legend and text referring to the figure accordingly..

- Line 178: missing full stop (or other punctuation mark) at the end of this sentence.
Done.

- Figure 2: It's not clear to me what the big and little arrows represent in the 'Divergence scenarios' box. Furthermore I do not understand why there is a big arrow coming from P1 if only P2 moves in this case?
The arrows represent the directions of the additive effects (all defined from P1 to P2). We should have made this clear in the Figure legend: "In these panels the lighter (darker) arrows show substitutions fixed in the P1 (P2) lineage. The larger arrows show the additive effects (all defined in the direction from P1 to P2), and the smaller arrows the dominance effects. The ancestral phenotype is shown by an empty black circle." We have also removed the dotted line axes from the figure, so as to hopefully cause less confusion about the optima (which are not explicitly plotted).

Luis-Miguel Chevin

This revision is a very different manuscript from the first submission, somewhat unexpectedly as the previous round of reviews were quite positive. The analysis has been extended in a number of ways, mostly by allowing polymorphism in parental populations, such that what used to be expressed in terms of phenotypic effects and frequencies (in hybrids) of alleles fixed in each parental population now appears as components of variance typical of quantitative genetics partitioning (additive, dominance, etc), which accounts for polymorphism. The explored evolutionary scenarios are also partly different, not only regarding directional selection, but also by including a detailed exploration of drift around a constant optimum (described as stabilizing selection). As a consequence, (almost) all the figures have changed, and so has the text. I praise the authors for this effort, which has undoubtedly made the manuscript richer, and even more interesting than it was. On the other hand, this density of results also certainly makes it a difficult read, more so than the previous version. I can't say I've digested all results myself as much as I would have liked, when it comes to contrasting net evolution to total evolution for interactions between additive and dominance terms,

under different scenarios of dominance at the phenotypic level (Figure 4). Still, I can't find any obvious way around this: the authors have pursued a thorough analysis of the model while keeping it rather general (not assuming fixation in parental populations, additivity at phenotypic level, etc), so they just have lots of things to say, some of which are not straightforward. They have done some efforts to synthetize their results in Table 4, and suggest ways to empirically assess some of their predictions. Some presentation choices don't facilitate understanding in my opinion (such as the absence of an explicit ancestral phenotype, instead using directional flow of mutations from P1 to P2), but this has been discussed previously and the authors have their arguments for doing things this way. So I will just list a few minor points below.

Regarding the directions of the arrows, given the focus in the results on the directionality of the chain of effects we do think it would cause confusion of another kind to illustrate the arrows in the ancestral-to-derived direction. However, we now make this clear in the Figure 2 legend.

Minor points:
12: 'making fewer assumptions' than what? Please specify
We have changed this to 'making few assumptions'.

44: perhaps insert 'before hybrids form' after 'that have accumulated"
Done.

144: Perhaps write "sum of phenotypic variances among traits" instead of "sum of the trait variances", as the latter could mean different things, including sum across loci for a given trait.
We have changed it to "the sum of the phenotypic variances over the n traits".

Figure 2: The cartoons on the left are far from being self-evident. For instance, what's the difference between light and dark colors for the thick arrow? I can only guess that this relates to which population evolves, but the precise meaning isn't obvious. And what about the small thin arrows attached to the thick ones? Why are they not described in the caption?
We agree this was unclear, and have added text in the legend of Figure 2 to clarify this: "In these panels the lighter (darker) arrows show substitutions fixed in the P1 (P2) lineage. The larger arrows show the additive effects (all defined in the direction from P1 to P2), and the smaller arrows the dominance effects. The ancestral phenotype is shown by an empty black circle." We have also removed the dotted line axes from the figure, so as to hopefully cause less confusion about the optima (which are not explicitly plotted).

314: I think you mean VI and not IV here.
Agreed, changed.

Eq 42, second line for P_BB,i: one of the terms in the difference in parentheses should harbour P_1 instead of P_2, otherwise this term vanishes
Changed, thanks.

652: typo 'phenoptypic'
Fixed. Thanks.

656: 'positive epistasis in an optimal background'. Note that epistasis does not depend on genetic background, but only on mutation phenotypic effects, in this classic quadratic/Gaussian version of FGM
We have removed 'in an optimal background'.

Juan Li

The authors have greatly improved their clarity. Thank the authors for clarifying the epistasis in Appendix 1. In this version, my remaining comments are limited to clarifications.

We are grateful for this constructive and thorough review

I appreciate the authors' effort in including the segregating sites mathematically. However, some significant results come from simulations, and the author used divergence between populations to demonstrate. This makes me wonder about the reason for using shared polymorphism. How should we understand the contribution of shared polymorphism and fixed differences to hybrids or to postzygotic RI? Are they the same in two species? And how much of the shared polymorphism do we expect from two species? Since the authors and reviewer Chevin have discussed this, I hope the authors could explain a bit, like explicitly writing a paragraph in the introduction or method.

We appreciate that this is confusing. We have attempted to clarify that the simulations are a special case of the analytical model, by adding to the end of this sentence in the introduction: 'We will assume that individuals in these populations vary at D biallelic loci, and that the allele frequencies might vary between populations, which includes the case when an allele is fixed in one population and absent in the other.' We have also added the sentence 'Note that fixed differences and shared polymorphisms contribute in identical ways, as long as the $\mathbf{A}_i$ and $\mathbf{\Delta}_i$ are correctly defined (eqs.(3) and (6))' after eq. (13).

Abstract – In general, "The key quantities" include two properties of the evolution changes and their interactions, right? This term is not obvious to me.

We changed this to 'these estimable quantities' and hope this is clearer.

Table 6 and page 21 – I am confused with the inbreeding coefficient in the F1 population. If the two parental populations perform random mating to form the F1 hybrid population, the inbreeding coefficient is 0 in the F1 population (HWE). If the F1 population contains only hybrids of two populations, the F1 population is a result of complete assortative mating ("an excess of heterozygotes").

The F1 represents matings between randomly-chosen P1 individuals with randomly-chosen P2 individuals. This leads to an excess of heterozygotes, and so a negative coefficient of inbreeding.

Table 6, eq. 6, eq. 32, eq. 33. – I am confused with d_ij and delta_ij. Are they describing the same thing, the dominance in Table 5? Or is delta_ij about dominance at the population level? Is the dominance defined at a single locus (Table 5) equal to the mean dominance (eq. 33)?

the d_ij are defined as the effects of individual alleles, and the $\delta_i j$ defined at the population-level. The two quantities turn out to be identical in practice in the situation we are considering, but we use different variables to be consistent with previous literature.

Eq. 49 – Please notice that the equation is too large to show on one line.

Fixed. Thanks.

Figure 2 – The black circle is the ancestry population, shown in the panel illustrating scenario I. I guess that the center of each panel is not the optimum (the cross in figure 1), but the two dots are two optima. I guess that the large arrow indicates the direction of additive effects, and the small arrow indicates the dominance. It might be helpful to clarify this in the figure legend.

We agree this was unclear, and have added text in the legend of Figure 2 to clarify this: "In these panels the lighter (darker) arrows show substitutions fixed in the P1 (P2) lineage. The larger arrows show the additive effects (all defined in the direction from P1 to P2), and the smaller arrows the dominance effects. The ancestral phenotype is shown by an empty black circle." We have also removed the dotted line axes from the figure, so as to hopefully cause less confusion about the optima (which are not explicitly plotted).

Figure 4 – I suggest the authors keep the panels to describe two scenarios of stabilizing selection (in old

Figure 2, like the left panels in new Figure 2). It makes it easier to understand a theoretical paper.
We removed the old cartoons, as they no longer apply to the simulations that we ran in the new version. The distinction between both populations evolving and one only evolving is, moreover, difficult to represent visually. However, we have added explanatory text to the two column titles in Figure 4 which we hope makes things clearer.

Line 321 – "Unlike terms involving additive or dominance effects alone, the interaction terms capture differences in the evolutionary changes between two populations." The word, "differences", is not clear to me. Throughout the whole section, the author explains how dominance affects the fixation of mutations, Haldane's Sieve. Maybe, rephrase this sentence?
We have rephrased as suggested. We now say "the interaction terms tell us whether the two populations have evolved in different ways."