

Review - Epistasis, inbreeding depression and the evolution of self-fertilization

The authors present a theoretical analysis of how epistasis can affect the evolution of selfing. By using a general model in which the contribution of different forms of epistasis to an individual's fitness can be analytically decomposed, the authors show not only that epistasis may increase the selective advantage of selfing, but also these forms may select for selfing in distinct ways.

The introduction and conclusion of the paper are easy to follow and set up the background, motivation and take home messages well. While understanding the biological importance of the various epistatic effects here described is somewhat hampered by a lack of empirical data on their sign and magnitude, the theoretical results do give clues about interesting avenues to explore empirically.

It is clear however that this is very theoretically dense paper. My main suggestions for the authors therefore focus on the intervening sections and how I believe the presentation of the results could be clarified. I also have some queries about the calculation, which I detail in the following section.

Organisation of methods and results

The authors present a general expression of the fitness of an individual, Eq. (8), followed by three specific fitness functions, Eqs. (9), (14) and (15) (respectively uniformly deleterious alleles, Gaussian stabilizing selection and non-Gaussian stabilizing selection). In the Results sections, (in particular Effects of epistasis on inbreeding depression, and Effects of epistasis on the evolution of selfing) the authors derive results for the general fitness case and specific fitness functions in turn, however jumping between these treatments can become confusing. I would therefore suggest the following.

- In Supplementary File 1, the analysis is split into four sections (the first untitled); “General fitness expression”, “Uniformly deleterious alleles”, “Gaussian stabilizing selection”, “Non-Gaussian stabilizing selection”. I found this section separation useful, and believe it should be replicated in all the appropriate methods/results sections.
- In line with my previous comment, it would be helpful to stick to a common naming convention for each of the fitness functions. Currently in the appendix, they have the titles above. In the section “General expression for fitness, and special cases” they have no explicit names. In the following text the first fitness function is variously called “unconditionally deleterious alleles with fixed epistasis”, “uniformly deleterious alleles with fixed epistasis” and “the fixed epistasis model”. On first reading it can be confusing as to whether these terms are referring to additional assumptions/conditions on the fitness function or not.
- It would be instructive to see the motivation for considering the different fitness functions stated clearly on their introduction. For instance, while Eq.(8) is general, it contains a large number of free parameters and it is clear that fitness functions that allow us to parametrise the model more simply are useful (although this could also be stated explicitly). However what is the significance of the different functions considered? Is it motivated primarily by the desire to relate these results to previous results, the demonstrate the generality of the insights derived, etc? Could any of these be understood as being more or less reasonable in a biological sense?
- One of the key points throughout the paper is that the form of Eq.(8) is useful for deriving general results that disentangle the various forms of epistasis, but that each of the fitness

functions can be “mapped” to the form of Eq.(8) by assuming that some parameters are small, conducting a Taylor expansion in these parameters and comparing prefactors of $D_{\{U,V\}}$ to infer $a_{\{U,V\}}$. This point is clear in Supplementary File 1, but would also be straightforward (and useful) to explain in the main text.

- Similarly to my third point, when introducing the section “Evolution of selfing in the absence of epistasis”, a little motivation for where we’re headed might be useful (e.g. “In the following section we will consider the effect of epistasis on the evolution of selfing. However first it is useful as a point of comparison to understand how the model dynamics would behave if epistasis were to be ignored”).

Summarizing the above points, I’d say this is a mathematically heavy paper, and guiding the audience at each waypoint with a bit more information of what we’ve seen so far, what we’re about to do and why we’re about to do it would help clarify things.

Queries on analytical results

While the extensive supplementary materials do a great job of thoroughly explaining the calculation, there are a few areas in the main text that I feel could do with more discussion (or perhaps more explicit signposting to relevant sections of the supplementary files).

- I was unclear about what we were assuming about the deleterious mutation rate, U . On line 272, we assume that deleterious alleles stay rare in the population (which I assume holds when U is small) however on line 311 we see this transition where when U gets sufficiently large inbreeding depression moves from being increased to decreased by epistasis. In Figure 1 we have $U \approx 0.25$.
- L272 “Equation 23 assumes ... that the different terms of equation 19 contribute multiplicatively to δ (which often yields better approximations than the additive expression).”

I wasn’t sure what this sentence meant mathematically, and also unclear as to why the additive expression would “often” yield better approximations. What does “often” mean here? Is this a heuristic?

- L388 “The prediction for the case of unlinked loci (obtained by setting $p_{ij} = 0.5$ in equation 36) actually gives a closer match to the simulation results than the result obtained by integrating equation 36 over the genetic map. This may stem from the fact that equation 36 overestimates the effect of tightly linked loci.”

Is it obvious that Eq.(36) would overestimates the effect of tightly linked loci? Is there any way of determining which of the approximations employed would be causing this?

- L416-427 [Equation 39] “..., which increases as Q increases in most cases”.

Is it clear that Eq.(39) typically increases with Q ? How do I see this?

- It’s not immediately clear where Eqs. (10-12) come from – I’m sure an extra line or two could make this more obvious.
- L479-483 “The term in the second line of equation 47 shows that negative additive-by-dominance or dominance-by-dominance epistasis between deleterious alleles increase the

benefit of selfing, by increasing the efficiency of selection against deleterious alleles in homozygous individuals.”

This is difficult for someone not very familiar with the model to read off directly from the equation. As such it probably warrants a longer breakdown of the meaning here (especially given that this is referred back to below Eq.(50)).

- Figures – Somewhere I’d like to know which assumptions used in the analytics are leading to disagreement between the analytic theory and the results of simulations.
- In particular in Figure 1D (which should probably be plotted over a smaller range of δ) it appears that the inbreeding in the simulations responds in the opposite direction to that predicted by the analytics as β is varied. Does this hold for all parameters? In the main text, the authors state that “Remarkably, the increased purging caused by negative epistasis almost exactly compensates the decreased fitness of homozygous offspring, so that inbreeding depression is only weakly affected by epistasis in this particular model, for the parameter values used in Figure 1”. What do other parameter combinations do? Perhaps some additional testing of the robustness of the analytic results to changes in the parameters would be useful in the Supplementary Figures.
- L368 – minus sign missing in front of $\delta V_{\{\sigma\}}$
- L403 The fitness effect of a heterozygous mutation at locus j in an optimal genotype should be added to the parameter/variable list.