

Recommendation on the second version of the manuscript entitled “The role of pseudo-overdominance in maintaining inbreeding depression” by D. Abu-Awad and D. Waller.

First of all, I would like to deeply apologize for the very long delay in answering to this review, which was due to the difficulty of obtaining reviews for this second version and lack of availability from my own side.

We finally obtained two reviews for this revised version. Both are positive and stress the improvement compared to the previous version and the great interest of the results. They only suggested a few minor corrections that can easily be handled. Reviewer 2 noted that the title doesn't fully reflect the main findings of the manuscript. I think it's a matter of taste that can be left to the authors. As the title focus on the maintenance of inbreeding depression, I think it is quite directly related to how long it takes to erode POD regions.

The authors made a great effort to respond to the comments, in particular to clarify the objectives of the study and to extend the analysis of the model to a much broader range of parameters. Overall, it strongly reinforced the initial findings and it should stimulate more empirical work to assess the qualitative and quantitative importance of such POD genomic regions.

I thus consider that this manuscript can be recommended by PCI, but I also recommend the authors to address before the few minor comments raised by the two reviewers (and see the few additional ones below).

We would like to thank you and the reviewers for the constructive comments that have contributed to strengthening and clarifying this work.

Sylvain Glémin

Additional minor comments

L 106: “We assume complete linkage among matched sets of mildly...” I think it should be “ We assume initial complete linkage...” as it can then be broken by recombination as loci are spread every 1 cM.

We have reworded this part accordingly

L 127 “Inbreeding depression δ is a local variable”. What do you exactly mean by “local variable”? Do you mean “within population”?

Exactly. This has been changed to “population specific variable”

L 144. The full expression of $I = s_1 s_2 / (s_1 + s_2)$ could be given in the main text and when $s_1 = s_2 = s_H$ it could be noted that $I = s_H / 2$ instead of $s_H^2 / 2 s_H$.

Indeed it can. This was left over from a more detailed general calculation (with $s_1 \neq s_2$), and has been corrected. Thank you!

L 144: a space is missing after “EQ. A2”.

Done

L 211 : “At higher mutation rates, singletons will be frequent.” This is not clear to me. The number of singletons should indeed increase but as all kinds of mutations. At stationary state, the proportion of singleton should be the same. Is it correct?

Yes, this is the case. This and the following sentence should have been removed from this version, as we have since changed our measure of H_e , leading to different results and interpretations.

L 365: Note that small genome does not necessarily imply tight linkage because the number of crossovers per chromosome varies little such that recombination rate is higher in small chromosomes. So genes are physically closer on a small chromosome but not necessary more genetically linked.

This is true, but as we are under the infinite loci assumption, our definition of a small genome is one with a small map length, which in hindsight may have been too abrupt of a shortcut. We have replaced “small genome” by “small map length” to avoid confusion.

L 393: “we face the question of what force perpetuates these even within small and inbred populations”

→ add a comma between “these” and “even”

Done

L504: space missing after “viability”

Added

Reviews

Reviewed by anonymous reviewer, 26 Oct 2022 09:23

The paper has been modified and improved compared with the last version. The authors applied both theoretical and numerical methods to discuss the maintenance and the break-down of the POD (pseudo-overdominant) region. The factors such as spatial distribution of individual mutants, individual selection strength, recombination, dominance, and differentiated fitness between homozygotes, have been taken into consideration. The authors also learned the interactions between the POD and the background mutations occurring elsewhere. I think the manuscript is of great interest and could trigger further studies on the relevant topics.

Thank you for having contributed to bettering this work.

Some mistakes and concerns are as follows:

1. Line 99, “ $s_x = \text{mins}_{1,s_2}$ ” should be changed to “ $s_x = \min\{s_1,s_2\}$ ”;

A slight compilation error, thank you!

2. Line 144, “see Eq. A2from Supp. File 1” should be modified as “see Eq. A2 from Supp. File 1”.

Fixed.

3. Line 162, I think what the authors really meant was the “Ordinary Difference Equations” rather than the “Ordinary Differential Equations”, as the equations (10) do not contain the derivatives.

It is indeed what we meant, thank you for pointing it out.

4. Line 192, “The probability that a recombination event occurs between two trans-mutations is then l.” should be modified as “The expected number of recombination events occurring between two trans-mutations is then l.”

Modified as suggested.

5. Figure 3 a and b, I think this might be something wrong, Since the proportion of fixation and loss at some positions are negative (especially for the blue and green solid lines), I cannot see a reason for this.

There was a slight recalibration issue after applying a smoothing function to the data. Figures that may have been affected have been replotted.

Reviewed by anonymous reviewer, 02 Nov 2022 18:07

Dear editor,

I have reviewed the manuscript entitled "The role of pseudo-overdominance in maintaining inbreeding depression" by Abu Awad and Waller for PCI Evol Biol. I was not involved in the first round of review, and have read the updated version of the MS as well as the comments and replies from the first round.

I really enjoyed reading the MS. Pseudo-overdominance is an important issue in evolutionary biology, and such theoretical models on how pseudo-overdominance zones erode over generations is, I think, a timely contribution. The MS reads well and the findings are interesting. It seems to me that the authors have well addressed the previous comments, such as a better justification for the origin of the POD zone and a better clarity of the results section and figures. I have thus only a few very minor comments.

Thank you for having accepted to review the manuscript and for the encouraging remarks.

MINOR COMMENTS

Title: To me, the main message of the MS is about how POD zones erode over time, which is not captured by the title.

It's true that since our initial version, the focus of the paper has become more broad. We have therefore changed the title to:

“Conditions for maintaining and eroding pseudo-overdominance and its contribution to inbreeding depression”

line 70: The authors may want to indicate the estimated divergence time between *Capsella* and *Arabidopsis*.

Added

lines 126-156: Having never worked on inbreeding depression, it is unclear to me what 'delta s' and 'delta od' capture. It may need to be explained.

These two expressions for delta are derived under different hypotheses. δ_s is the expected level of inbreeding depression for recessive and slightly deleterious mutations, each with a given coefficient of selection s and dominance h . δ_{od} is the expression derived for the level of inbreeding depression due to overdominant mutations, accounting for partial self-fertilisation. We have re-organised the section on inbreeding depression so as to clarify this.

line 222: The verb is missing in "The general map length $R = 1$ and 10 Morgans ...".

Remedied.

lines 258-261: This result may be briefly explained. It is not intuitive to me why, when no mutations have been cleaved off, the recombinant haplotype is selected against. It has the same number of deleterious mutations than the two other haplotype.

In this case the fitness of heterozygotes made up of a recombinant H_c and an initial haplotype (H_1 or H_2) is inferior to that of a heterozygote made up of the two initial haplotypes ($H_1 H_2$). The fitness of an $H_c H_1$ haplotype would be $(1 - s)^{n_c} (1 - hs)^{n_d}$, with here n_c the number of mutations they will now have in common, and n_d those that they do not share (because it is the portion of the POD zone initially found in H_2 haplotypes). The fitness of $H_1 H_2$ haplotypes is $(1 - hs)^{(n_1 + n_2)}$, with n_1 and n_2 the number of mutations carried by H_1 and H_2 respectively. For $h < 0.5$, a homozygote mutation will have a stronger effect than two heterozygote mutations. So it is not a question of number of mutations per haplotype, but a question of their state in a given genotype. We have added a short explanation on lines 267-272.

Figure 2: In the legend, is sH equal to 0.455, or to 0.45?

0.45 – this has been corrected

Figure S2: The fifth line of the legend seems to be encapsulated in the formula.

Fixed.