Review on The role of pseudo-overdominance in maintaining inbreeding

Following several first-order approximations (mainly inspired by Kimura M, Ohta T 1971), this manuscript theoretically discussed the potential role POD blocks (Pseudo Overdominance blocks) could play in maintaining population diversity and inbreeding depression. I am excited about the manuscript and find its results valuable.

The Brief Idea of the Manuscript:
This manuscript uses model studies and simulations to investigate:

1. The mechanisms of maintenance and erosion of the POD block.
2. The interactions between POD and the "background selection" elsewhere.
    - Recurrent deleterious mutations to POD block
    - POD block to recurrent deleterious mutations
3. POD's influences on inbreeding depression
   The overdominance generated by a POD increases the amount of inbreeding coefficient, and it will reduce the decline in inbreeding depression (***delta**) caused by the increase of ***sigma***.

The model the authors adopted a specific model where mild mutations evenly distributed along the incipient POD in repulsion to alternating mutations on the opposite chromosome. The authors argued this model maximize the effects of POD, and they also tested more general model settings with randomly distributed mutations within the POD.

Comments:
The followings are some thoughts I want to share with the authors and readers:

- In the original literature, Equation 1 is based on the assumption "without loss of generality, s_2<=s_1 and s_2 < 0.5". And I suggest to write Equation 1 as

  $$\sigma < \frac{2s(1-s)}{s_1+s_2-2s_1s_2}$$ where $s = min\{s_1, s_2\} < 0.5$

  In the line above equation 1, the authors mentioned with both alleles at a frequency of 0.5, which is not right, as this is only true when s_1=s_2.
- I do not like the terminology "background selection" across the manuscript.
    1. Since the literature has carefully discussed the impacts of recurrent recessive deleterious mutations: When the (effective) population size/selection is sufficiently large, such mutations will reduce the neutral diversity, we refer to such effects as background selection; while when the population size is small, the strongly recessive deleterious mutations will help to maintain neutral diversity, such effects are called associative overdominance.
    2. In several parts of this manuscript, the author observed the opposite effects of background selection, e.g., in lines 345-348, the author wrote "When fewer loci (n) contribute to a POD and linkage is loose, recurrent deleterious mutations speed the decay of heterozygosity." "In fact, when selfing and mutation rates are high (U = 0.5), POD heterozygosity actually increases"; in figure S9a, the author observed an unexpected increase of inbreeding depression as ***sigma*** grows. since a larger proportion of selfing is assumed

in both cases, the effective population size Ne will be relatively small, given the authors chose s_d = 0.01 and h_d = 0.2 for recurrent deleterious mutations, I highly suspect it is the AOD effects of the recessive mutations that dominate both cases (See Zhao and Charlesworth 2016 for details). Since Zhao and Charlesworth 2016 was based on a higher-order moment iteration, it should be able to give a better explanation than Eqn 6 did for figure S9a. If the authors want to reduce the unexpected increase of POD heterozygosity, I suggest to try h_d=0.5, as it always in the regime of background selection.

3. I believe the suprising results the authors mentioned in the paragraph starting at line 310 can also be phrased and explained using the similar idea as Zhao and Charlesworth 2016.
4. So briefly speaking, in my point of view, the interactions between POD and the recurrent deleterious mutations elsewhere can be summarised as AOD (associative overdominance) and POD collaborate to maintain the diversity, while BGS (background selection) reduces the POD heterzygosity.

- As the authors indicated, the current hypothesis of the origin of POD is less convincing. AOD might also be the source to build up POD blocks from smaller ones, but this might need to be tested.