In this manuscript, the authors model a very realistic population undergoing domestication. They model an ancestral wild population, a strong bottleneck, and changes in selection pressure that are likely to be experienced by the domesticated population. The authors ask if in such a model, when simulated realistically using forward simulations, it is possible to infer the population history and the full DFE. While population history is not recovered accurately, the authors suggest that the deleterious DFE is estimated accurately. The authors have also extended the method dadi to be able to infer parameters of a change in selective pressure experienced by a population. Overall, it is a good contribution and has the potential to yield interesting results in empirical applications. I have a few concerns listed below that I think should be addressed before it is acceptable for publication:

Major points:

1) If I understand correctly, the authors have extended dadi to infer new parameters of the DFE. For instance, you say in your abstract: “Third, using a novel joint DFE model, we are able to quantify the fraction of mutations that have experienced a change in their selection coefficient (*pc*) during domestication”. But I don’t see a description of the underlying methods. What were the diffusion equations that were solved to estimate p_c? How do you infer the beneficial DFE? These details must be laid out in the main text clearly.
2) It could be nice to add a scenario where there are no beneficial mutations and there is only BGS. This would help understand if mildly beneficial mutations can be causing the misinference of the timing of bottlenecks (lines 440-442).
3) You say that mean s_d values are estimated quite accurately using both polyDFE and dadi (lines 579-582). However, I do not conclude that from Figure 3. I see quite a bit of misinference. Either the scale of misinference is unclear in the Figure or our interpretation is different. But I would not conclude what the authors are concluding here.
4) Lastly, it was a bit difficult to follow the authors’ arguments in some sections (e.g., lines 522-523). It would be great if the authors could proofread the manuscript to improve clarity, sentence structure, etc.

Minor issues:

1) Figure 2 – it’s difficult to see the simulated population history, especially for the wild population. Would be good to change the colors of the simulated line to something that is clearly visible. Also is that relative Ne? Please specify what the y-axis is.

2)Line 137: “Several studies have been focusing on the significant distortions in the DFE shape caused by the effect of linked selection (e.g., Gilbert et al. 2021, Johri et al 2021, Shrider et al. 2016).” -> Neither Johri et al nor Schrider et al evaluated DFE inference. Citations need to be corrected or maybe the way you are phrasing it needs to be modified.

3) “Shrider” should be “Schrider”

4) Although Gilbert et al showed that the population-scaled DFE is misinferred with high rates of inbreeding, Daigle & Johri (2024) show that selection coefficients are misestimated only when HRI effects are very severe. The authors should discuss this.

5) "…, there are more rare synonymous polymorphisms compared to what we would expect if there was free recombination under a constant population size (Nielsen 2005)." -> Needs many more citations (e.g. Charlesworth et al 1995, Nicolaisen and Desai 2013, Ewing and Jensen 2016, Messer and Petrov 2013)

6) I think Figure 1 C and D is quite confusing, although Table 2 helps. It is up to the authors eventually, but it would be great if Figure 1 C and D could be improved for clarity.

References:

Austin Daigle and Parul Johri. 2024. Hill-Robertson interference may bias the inference of fitness effects of new mutations in highly selfing species. bioRxiv 2024.02.06.579142.

Charlesworth, D, B Charlesworth, and M T Morgan, 1995 The pattern of neutral molecular variation under the background selection model. Genetics 141: 1619–1632.

Nicolaisen, L E, and M M Desai, 2013 Distortions in genealogies due to purifying selection and recombination. Genetics 195: 221–230.

Ewing, G B, and J D Jensen, 2016 The consequences of not accounting for background selection in demographic inference. Mol. Ecol. 25: 135–141.

Messer, P W, and D A Petrov, 2013 Frequent adaptation and the McDonald–Kreitman test. Proc. Natl. Acad. Sci. USA 110: 8615–8620.