July 18, 2024

Prof. Raquel Assis

Dear Prof. Assis:

Thank you for handling this manuscript, and thanks also to the two reviewers. The reviews were excellent and have led to a major rewrite. Not that the reviewers asked for major changes. One of them suggested that I use arithmetic axes for the archaic PSMC plot. That minor change revealed a pattern that seems not to have been noticed before, and which (I now argue) is probably a consequence of geographic population structure. This seemed far more interesting than the thesis of my previous draft, so I have rewritten the paper around it.

With this new emphasis, the manuscript now contributes to a growing literature on geographic structure within archaic populations. For example, we know that the late Neanderthals from Denisova cave were different from the early ones and were more genetically similar to other Neanderthals from Croatia. This suggests that there were multiple Neanderthal subpopulations and that one of them replaced another in between the early and late occupations of that cave. The Jacobs et al paper (which I cite) shows that there were multiple deeply-diverged Denisovan populations. Mafessoni et al (whom I also cite) use runs of homozygosity to argue for geographic structure within the Neanderthal population.

Because I am now making a positive point (this explains that) rather than a negative one (this cannot explain that), I decided to incorporate local extinctions into the theory. This makes it possible to explain the data without assuming that the effective size of the Neanderthal metapopulation was tiny. My previous draft assumed the Neanderthal metapopulation had an effective size of only 3600. As Prof. Achaz observes, this is not all that much smaller than the figure of 10,000 that is often given for modern humans. Nonetheless, extinctions help explain why both numbers are so small and may be especially important in the case of Neanderthals.

I think the revision makes a useful addition to the theoretical literature. Previous publications on local extinctions have not led to simple formulas that are easy to interpret. The new models are much simpler and more interpretable. I see them as a contribution independent of the empirical

case I try to make.

Comments on review by David Bryant

Prof. Bryant observed that

> In the end, the conclusion is that the demographic estimates are biased, but not sufficiently to explain the apparent decline in ancestral Neanderthal populations. Nevertheless I could imagine this bias could make a significant impact in other contexts, providing further motivation for explicit modelling of potential subdivisions in this class of analysis.

And this is exactly what has happened in the new draft: the bias that introduced by population structure *is* sufficient to explain the more recent decline in estimated N_e that is now the focus of the manuscript.

I also want to thank Prof. Bryant for his kind words about the mathematical exposition in the previous draft.

Comments on review by Guillaume Achaz

Prof. Achaz suggested a more formal approach to fitting parameters:

> I encourage the author to find a simple way to measure the difference/match between the predictions of the model and the observed data (say distance based or likelihood based). Once the function is computable, it can be optimized. The number of parameters are quite reasonable: d, N, m (or d and M in coalescent time scale).

I decided not to do this, because I feared it would imply that I was attributing too much importance to the two models that I discuss. I don't view either model as a plausible description of Neanderthal population history, so I'm not interested in a detailed fit of the data to either one. The current informal approach seems appropriate because the aim is modest: to show that the hypothesis of population structure does not require improbable assumptions about population sizes or rates of mobility among subdivisions.

Prof. Achaz also mentioned that "the fact that figure 1 is log-log and Figure 2 log-linear does not help." I just want to say thanks for this comment, because without it I would not have discovered the empirical pattern that is now the focus of the manuscript.

Another Achaz comment:

> failing to find parameters that will fit the inferred psmc curve with simple symmetrical models such as the ones studied here hardly demonstrate that no structure model can fit the psmc curve.

I agree, and it remains true that the two models I study are unrealistically symmetrical. However, these concerns are less important now that the paper makes a positive point rather than a negative one. In the previous draft, my claim was that population structure cannot explain the observed pattern because two particular models failed to do so. That argument was vulnerable to the objection that some other model might have succeeded. But now I'm arguing that the models do explain the data. If some other model were to fail, that would not alter the conclusion that population structure can explain the observed pattern.

And finally:

> Equilibrium value of $N_e = 3600$ for archaic humans is not so bizarre (isn't 10^4 for modern human?). The bizarreness stems from the fundamental concept of N_e, that can harbor many disguises, many meanings, many metrics and is often misleading.

I agree. I think that one strength of the current manuscript is that it unpacks two of the factors—gene flow and local extinction—that can cause estimates of N_e to depart so dramatically from subjective assessments of population size.

Yours,

Alan R. Rogers