

On the fraught inference of historical generation times

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Possible titles:

Abstract

Wang et al. (2023) recently proposed an approach to infer the history of human generation times from changes in mutation profiles over time. With the observation that the relative proportions of different mutation types depend on the ages of parents, stratifying variants by the age of mutation allows for the inference of average paternal and maternal generation times at past times. Applying this approach to published allele age estimates, Wang et al. inferred long-lasting sex differences in average generation times and surprisingly found that ancestral generation times of West African populations remained substantially higher than those of Eurasian populations extending tens of thousands of generations into the past. Here we show that these results and interpretations are driven by noise and biases in input data, questionable modeling and statistical choices, and a failure to validate their inferences using independent approaches for estimating allele ages. With the recent development of methods to reconstruct genome-wide gene genealogies, coalescence times, and allele ages, we caution that ...

APR: this seems kind of aggressive...just writing down some thoughts

Recent years have seen the rapid development of methods toward the reconstruction of genealogical structures of large cohorts (Speidel et al., 2019; Wohns et al., 2022; Hubisz et al., 2020), comprised of a series of gene genealogies (or trees) along the genome. Reconstructed genealogies (or informative summaries of them (Albers and McVean, 2020)) have the potential to transform evolutionary and population genetic inference, as biological and evolutionary processes impact the shape and correlation of gene trees and the distribution of variation that arises in the lineages they represent. Relevant to this study, the age of a variant can be estimated by mapping that mutation to the portion of the gene tree in which it is inferred to have occurred.

At the same time, the last few years have seen large sequencing projects that provide ever-increasing resolution of genome biology, including direct measurements of mutation rates and profiles (Jónsson et al., 2017; Halldorsson et al., 2019). Through high-coverage sequencing of multiple generations of families, *de novo* mutations can be determined as maternally or paternally inherited, and with a large enough sample size both the number of mutations and proportions of mutation types (e.g., A→C, A→G, etc.) can be correlated with parental age and sex (Jónsson et al., 2017). Wang et al. (2023) combined these two sets of inferences, the estimated ages of mutations and the paternal age- and sex-dependence of the mutation spectrum, to infer the history of average maternal and paternal generation intervals for human populations of diverse ancestries. In order to avoid overfitting, this approach requires making a number of assumptions about the constancy of the mutational process ?? APR: and others to point out?. For now, let's take these as stated...

Long-lasting differences in human generation intervals

In applying this inference approach to multiple populations of different continental ancestries, Wang et al. (2023) estimated that the ancestors of European, East Asian, and South Asian populations included in the 1000 Genomes Project Consortium et al. (2015) (1KGP) had significantly reduced average generation times compared to West African populations included in the same dataset. These differences extended to at least 10,000 generations, the time period that was highlighted in this study. In discussing this result, the authors state that “the difference among populations beyond 2000 generations ago reflects population structure in humans before their dispersal out of Africa, a structure that is not fully captured by the 1000 Genomes AFR sample. This implies that the simple labels of ‘African’ and ‘non-African’ for these populations conceal differences in generation times that existed on our ancestral continent.” Indeed, a number of recent genetic studies suggest that human population structure within Africa extending hundreds of thousands of years into the past has shaped modern-day genetic variation (Plagnol and Wall, 2006; Hammer et al., 2011; Hsieh et al., 2016; Hey et al., 2018; Ragsdale and Gravel, 2019; Durvasula and Sankararaman, 2020; Lorente-Galdos et al., 2019).

However, in extending their analysis farther into the past, Wang et al. (2023) find that ancestral generation intervals do not converge until many 10s of thousands of generations into the past. With an average generation time of 25–30 years, this corresponds to well over one million years ago. This observation would require some portion of the ancestries of Eurasian and West African populations to have remained isolated for many hundreds of thousands of years, for those structured ancestral populations to have had large differences in average generation times over the course of this history, and for those groups to contributed substantively to different contemporary human populations. While such a scenario of very long-lasting isolation among ancestral populations is not impossible, it is not supported by genetic (Ragsdale et al., 2022; ?) or archaeological (Scerri et al., 2018; ?) evidence, which rather suggest at least periodic connectivity of ancestral human populations.

Rather than long-lasting isolation between a large portion of ancestry of West African and Eurasian populations (that represented large differences in generation intervals), Eurasian–West African divergence has been estimated at only $\approx 75\text{ka}$ (thousand years ago) (e.g., Pagani et al., 2015; ?). Even among studies that have inferred deeper divergences of human populations within African would place the Eurasian–West African divergence at around 100–150ka (Schlebusch et al., 2017).

APR: If these estimated divergences represents the majority of ancestry of the two populations, can we do a back of the envelope calculation to see what difference in generation time would be needed between the hypothesized minority of deeply structured ancestry contributing to these pops in order to explain the estimated average differences in generation times? I bet it would be huge.

APR: they do say, “note that age estimates of mutations in the very distant past have decreased accuracy”

Given the implausibility of the stated result, it is natural to ask what may be causing such mis-inferences. Below we show that multiple sources of uncertainty, namely noise and bias in allele age inference and inconsistencies in trio-base estimates of mutation profiles, confound inferences of generation times from time series of mutation spectra.

Inconsistencies in the mutation spectrum over time

Issues:

1. GEVA-Atlas variant ages result in mutation spectra that change rapidly beyond 10,000 generations (which is likely why the weren’t shown?)
2. Allele age estimates between three state-of-the-art methods [GEVA (Albers and McVean, 2020), Relate (Speidel et al., 2019), and tsdate (Wohns et al., 2022)] are only moderately correlated (for example, see Figure S20 in the Supplement of Wohns et al. (2022)).
3. Allele ages provided by each method results in distinct and unlike mutation spectrum histories (Figures 1–2).

4. In turn, these divergent histories provide estimates of generation time profiles that differ completely.

Discrepancies in estimated *de novo* mutation rate profiles

1. *De novo* mutations from the Icelandic trio study have a different mutation profile than the most recent age bins (across all three of the variant dating methods).
2. In the most recent age bins (0 to 50 or 80 generations ago), the three methods estimate very similar spectra of young standing variation. They are closer to each other than any of them are to the spectrum from Jónsson et al. (2017).
3. Wang et al. (2023) acknowledge this:

We found that the mutation spectrum from the large pedigree study (14) consistently differed from the variant spectrum inferred from the 1000 Genomes Project data, possibly because we removed singletons from the polymorphism dataset to reduce errors.”

4. However, they did not test (or at least did not show a test of) this hypothesis that the removal of singletons drives this signal. I don’t think it does, but want to dive into it a bit more thoroughly. Comment: Update: GEVA does not provide ages for singletons. Relate and tsdate do, however, so we can test this hypothesis there.
5. Table 1 shows mutation spectrum from the most recent bin in each dataset.
6. I also don’t think the approach they took is satisfying:

Therefore, to obtain absolute generation times for historical periods, we centered the observed spectra on the most recent bin, subtracting its difference with the average mutation spectrum estimated in (14) from each historical spectrum. This has the effect of assuming that parental ages in the pedigreed mutation dataset reflect generation times in the most recent historical bin.

And I don’t know what biases this introduces. It does have the effect of forcing recent bins to have roughly the same inferred average generation times for mothers and fathers as the iceland trio data (28.2 and 32, resp.). It’s therefore not a *result* that recent time periods match other estimates. It’s a built-in assumption of their model

Circular reasoning in modeling choices..

Conclusions

1. Allele age estimates are noisy, and probably shouldn’t be used for such detailed inferences. You’ll end up fitting the noise and bias of each method.
2. DNM estimates from trios have their own sets of problems. Do we know where the discrepancy between trio-estimated DNM spectrum and observations from pop-gen data come from? Probably needs to be sorted out.

Figures

Many of these to the supplement.

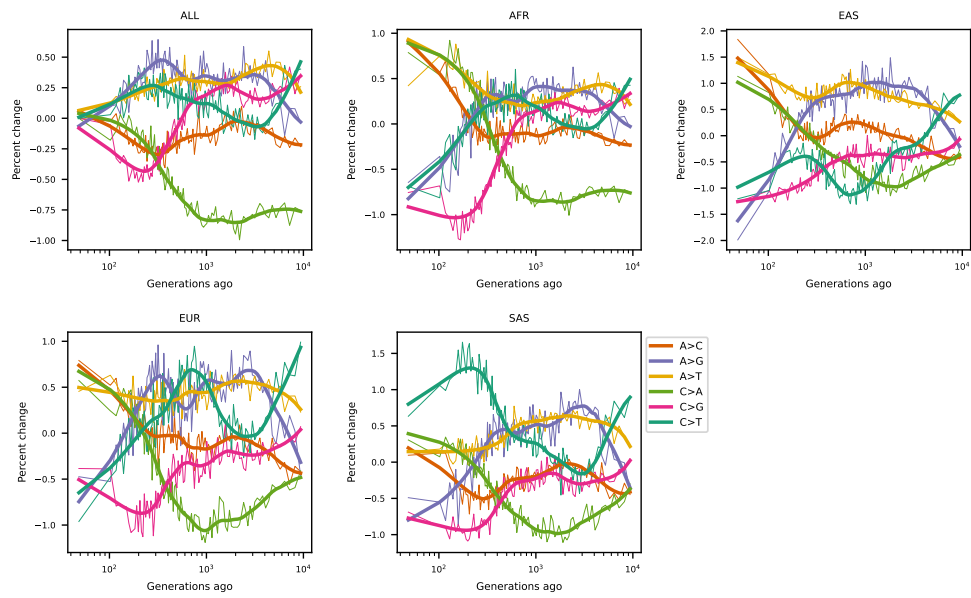


Figure 1: GEVA-inferred mutation spectrum history.

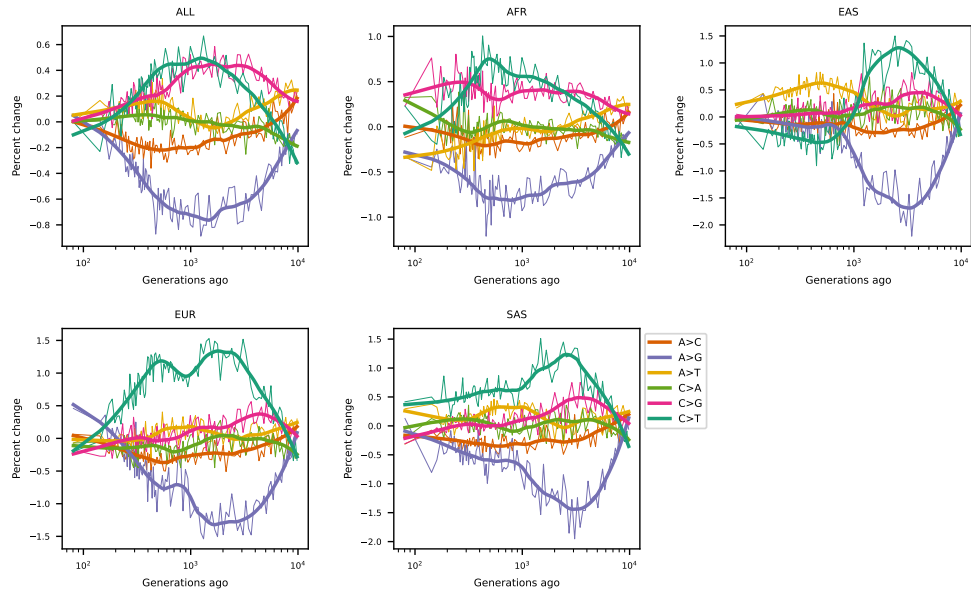


Figure 2: Relate-inferred mutation spectrum history.

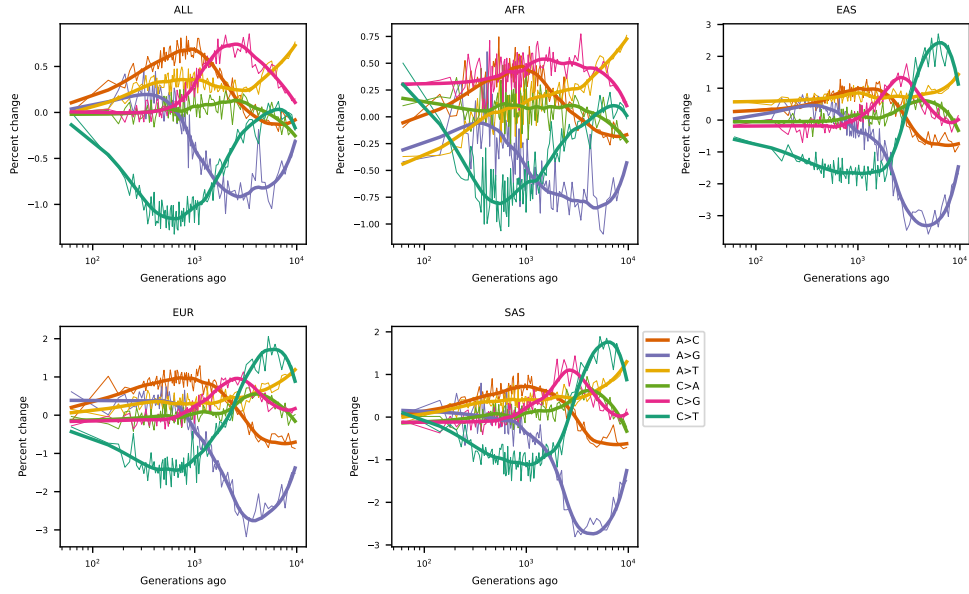


Figure 3: tsdate-inferred mutation spectrum history.

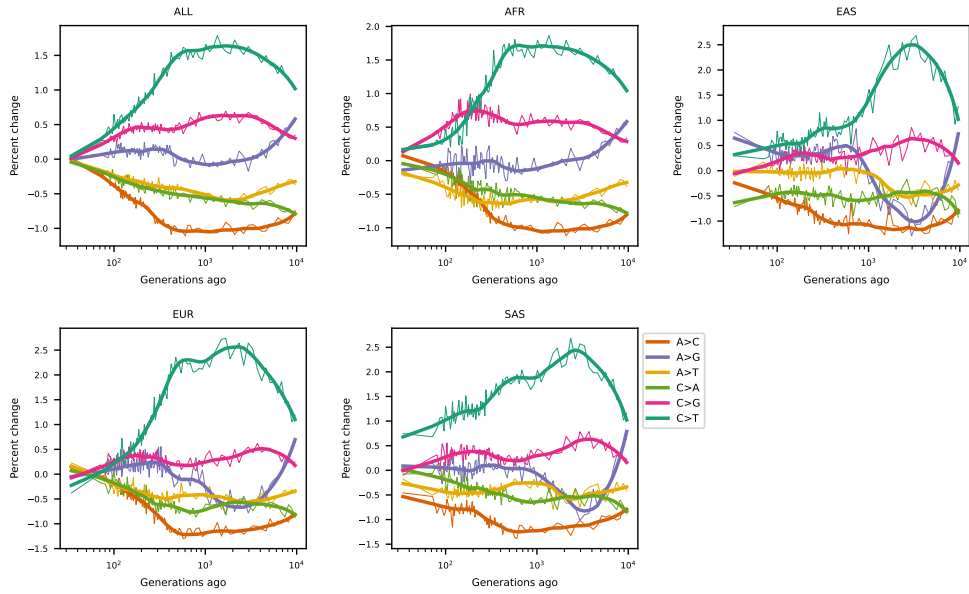


Figure 4: Relate-inferred mutation spectrum history, including singletons.

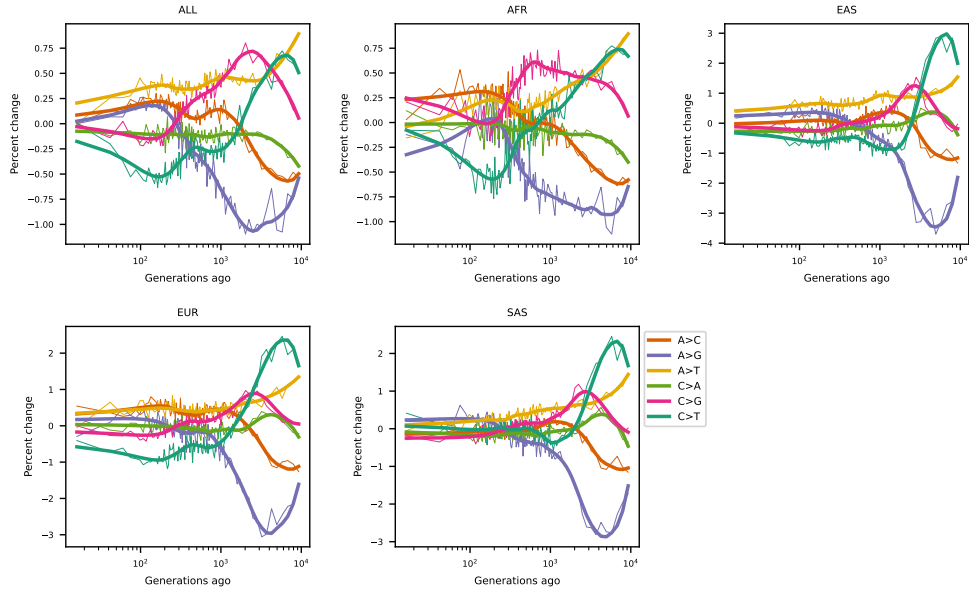


Figure 5: tsdate-inferred mutation spectrum history, including singletons.

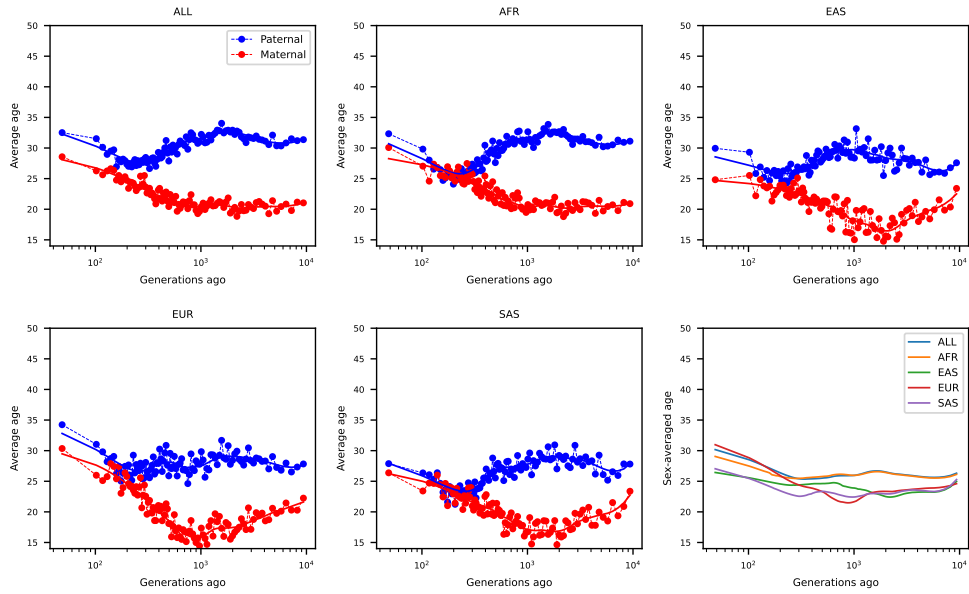


Figure 6: GEVA-inferred generation time histories.

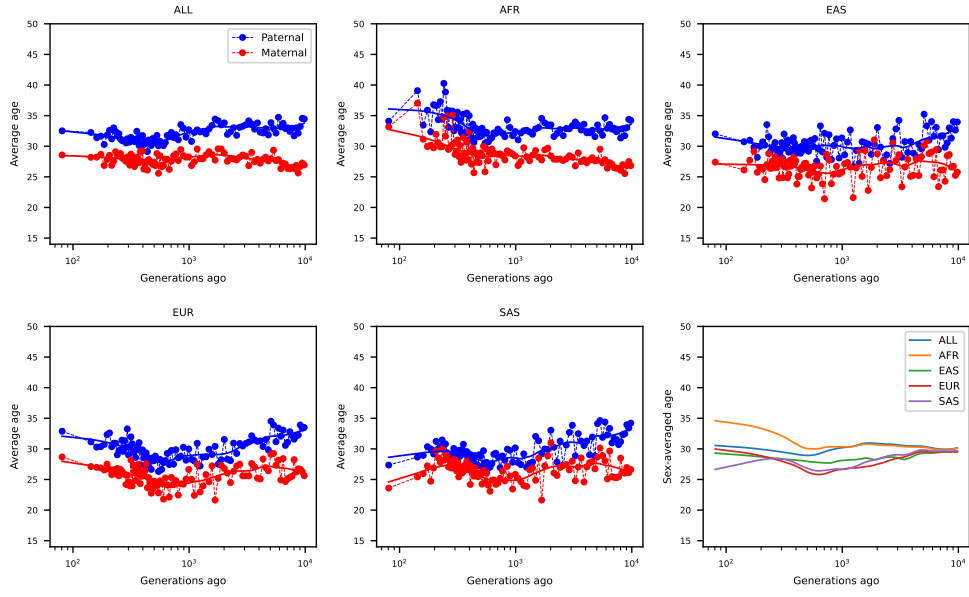


Figure 7: Relate-inferred generation time histories.

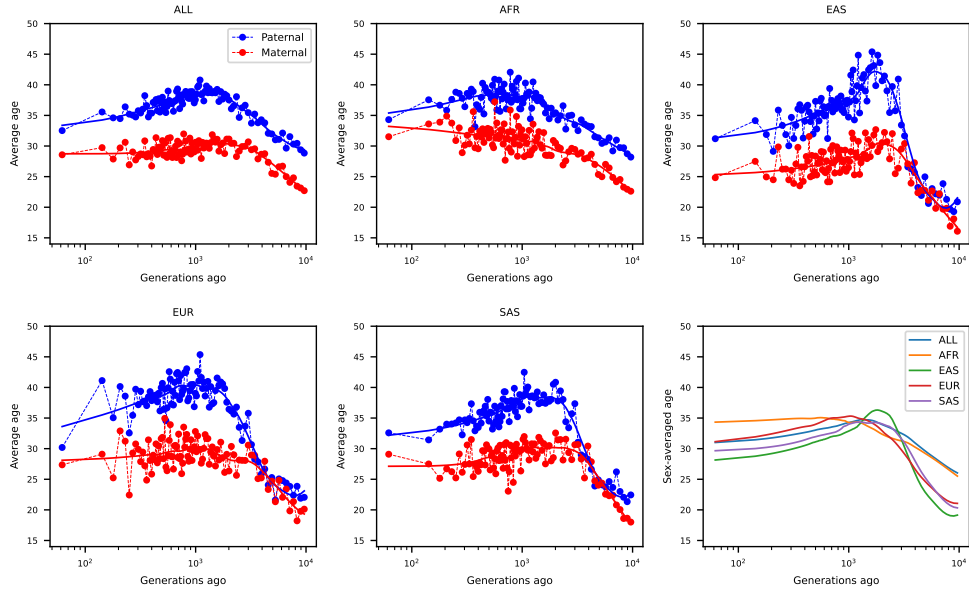


Figure 8: tsdate-inferred generation time histories.

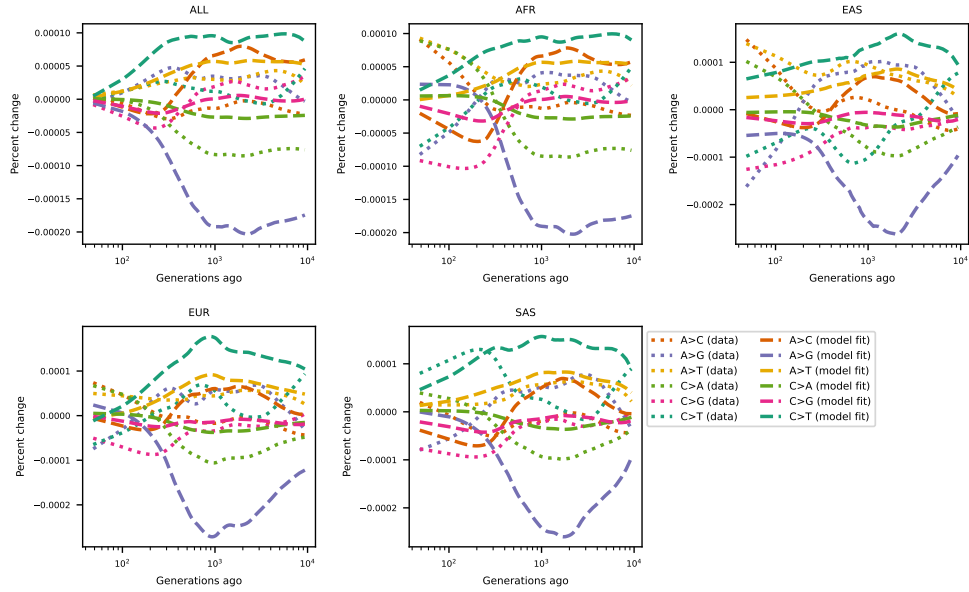


Figure 9: **Prediction of mutation spectrum history from GEVA-inferred generation times.**

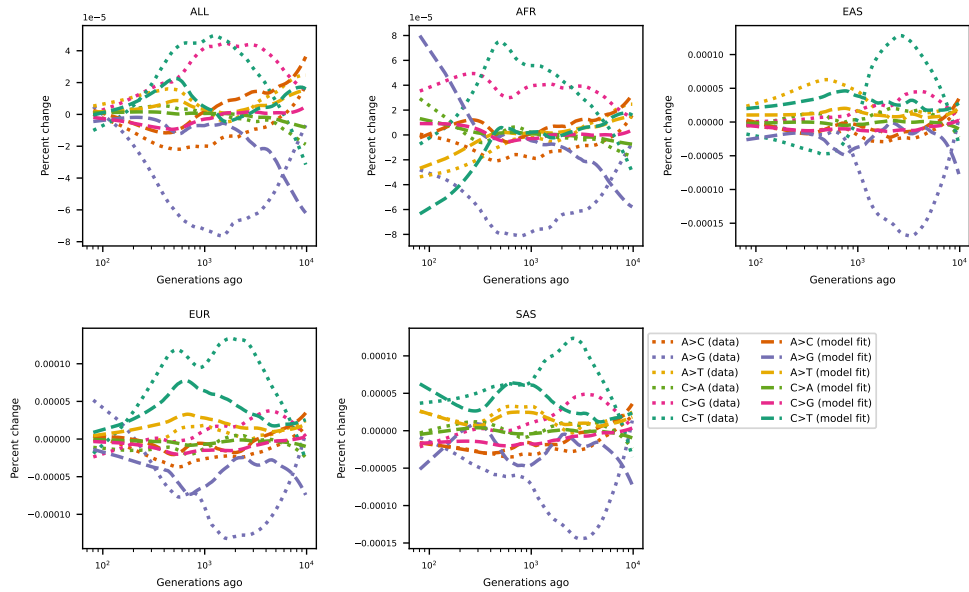


Figure 10: **Prediction of mutation spectrum history from Relate-inferred generation times.**

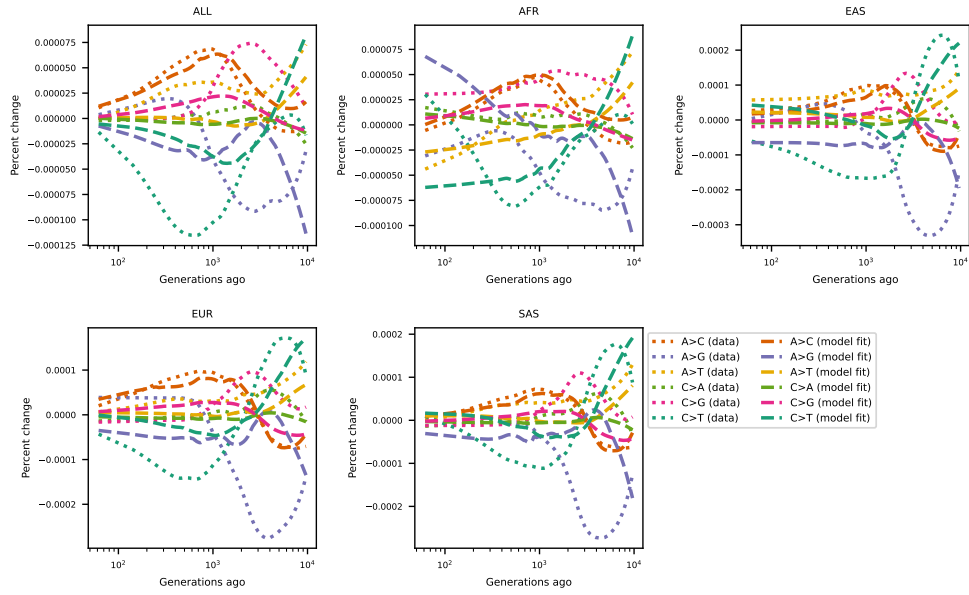


Figure 11: Prediction of mutation spectrum history from tsdate-inferred generation times.

Tables

Table 1: **Mutation profiles from the past 100 generations, compared to Iceland trios.** The most recent time bin for each method included the past ≈ 150 generations. When singletons were included (when using data from **tsdate** and **Relate**), the spectra of estimated recent standing variation were largely similar. Note that **GEVA** does not report ages for singletons. While the three methods provide similar spectra from recent mutations, the spectrum from the Iceland trios differs substantially. The similarity in the spectrum between mutations that were phased in Jónsson et al. (2017) and all mutations (phased and unphased) are very similar to each other.

Dataset	A→C	A→G	A→T	C→A	C→G	C→T
GEVA	0.0946	0.3600	0.0886	0.1201	0.1057	0.2310
tsdate	0.0931	0.3579	0.0899	0.1146	0.1061	0.2384
tsdate (w/singletons)	0.0989	0.3598	0.0908	0.1168	0.1062	0.2275
Relate	0.0991	0.3610	0.0863	0.1124	0.1038	0.2374
Relate (w/singletons)	0.1002	0.3590	0.0921	0.1164	0.1060	0.2263
Trios (phased)	0.1071	0.4100	0.0881	0.0481	0.0847	0.2620
Trios (all mutations)	0.1080	0.4086	0.0903	0.0483	0.0839	0.2610

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