On the fraught inference of historical generation times

Aaron P. Ragsdale[1,*] and Kevin Thornton[2]

[1]University of Wisconsin–Madison, Wisconsin, USA
[2]University of California, Irvine, California, USA
[*]email@address.edu

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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 for reconstructing genealogical structures of large cohorts (Speidel et al., 2019; Wohns et al., 2022; Hubisz et al., 2020), which are 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 its 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 parental 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 accept 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) dataset (1KGP) have a history of significantly reduced average generation times compared to West African populations. These differences extend to over 10,000 generations, the time period highlighted in this study. In discussing this result the authors state, "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 in part 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. 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 have contributed substantively to different contemporary human populations. While such a scenario of very long-lasting isolation among ancestral popualtions 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 within Africa.

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 $\approx$ 75ka (thousand years ago) (e.g., Pagani et al., 2015; **?**). Even 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 incosistencies in trio-base estimates of mutation profiles, confound inferences of generation times from time series of mutation spectra.

Inconsistencies in inferred mutation spectra over time

Central to the inference of generation intervals from time-stratified mutation spectra is the dating of variant ages. Wang et al. (2023) used published allele ages from Albers and McVean (2020) (using the software `GEVA`). `GEVA` estimates allele ages by considering the number of additional mutations that have accumulated on the ancestral haplotype carrying the focal variant, as well as the effect of recombination in reducing the size of that ancestral haplotype. Singletons are excluded from analysis and are not assigned an age. Partitioning variants by their estimated ages shows that the mutation spectrum (i.e., the distribution of mutations of six mutation types) has changed over time (Figure **??** and see Figure 1C in Wang et al.). Importantly, this assumes that the observed spectrum of segregating variation is not biased with respect to the spectrum of *de novo* mutations occuring during that time. APR: Would require a selection (or genotyping error) argument.

Issues:

1. GEVA-Atlas variant ages result in mutation spectra that change rapidly beyond 10,000 generates (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 unalike 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.

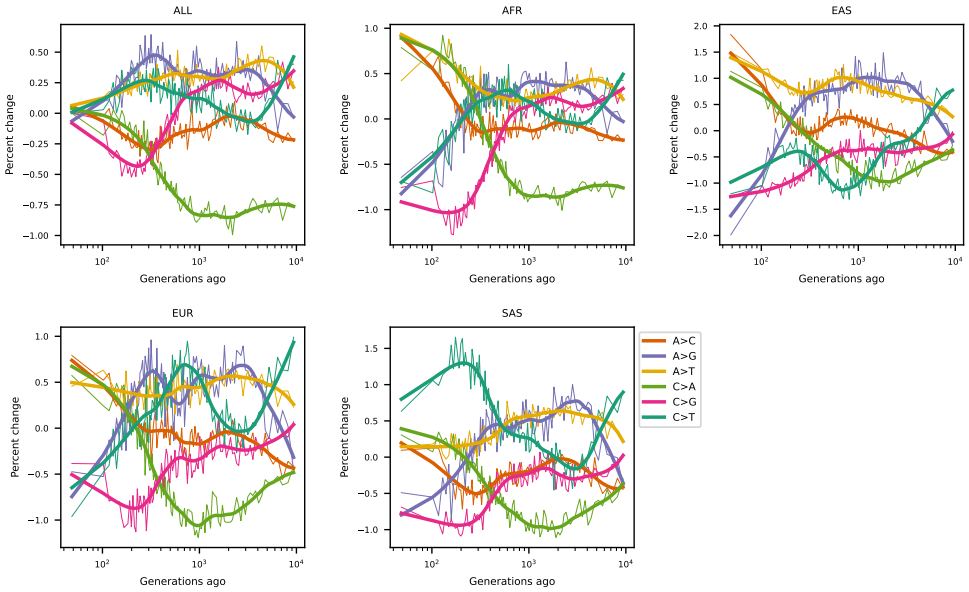

Figure 1: **`GEVA`-inferred mutation spectrum history.**

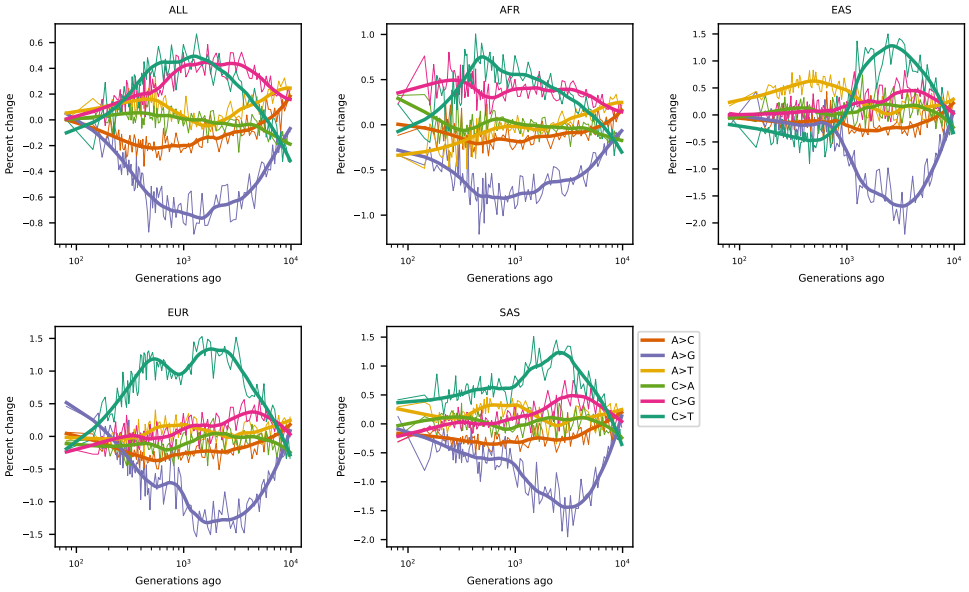

Figure 2: **`Relate`-inferred mutation spectrum history.**

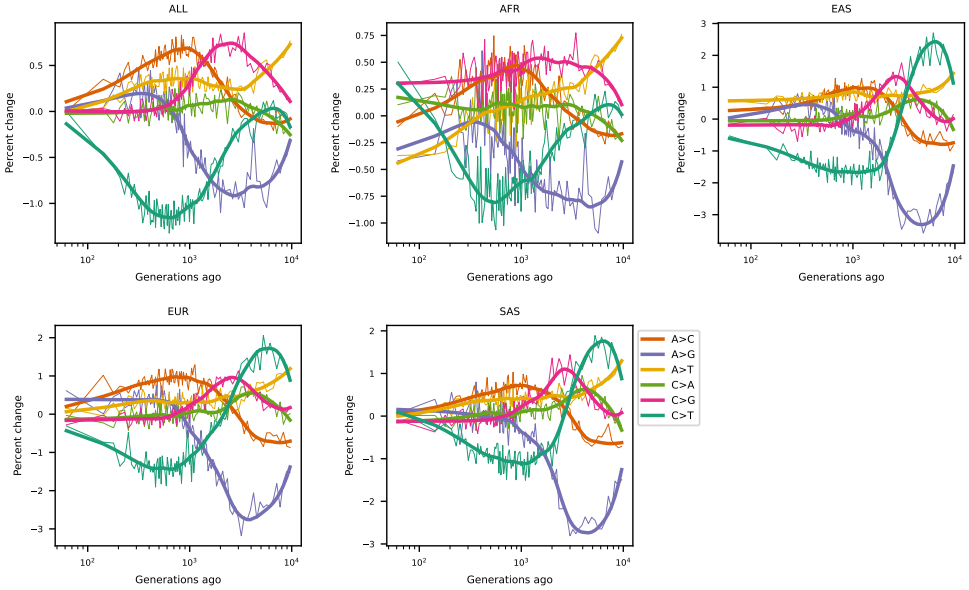

Figure 3: `tsdate`**-inferred mutation spectrum history.**

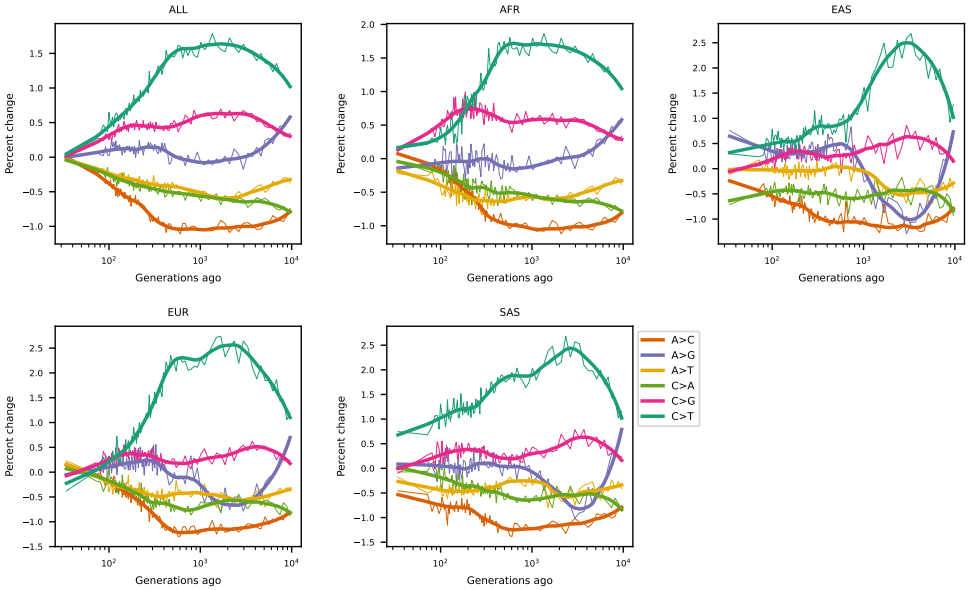

Figure 4: `Relate`**-inferred mutation spectrum history, including singletons.**

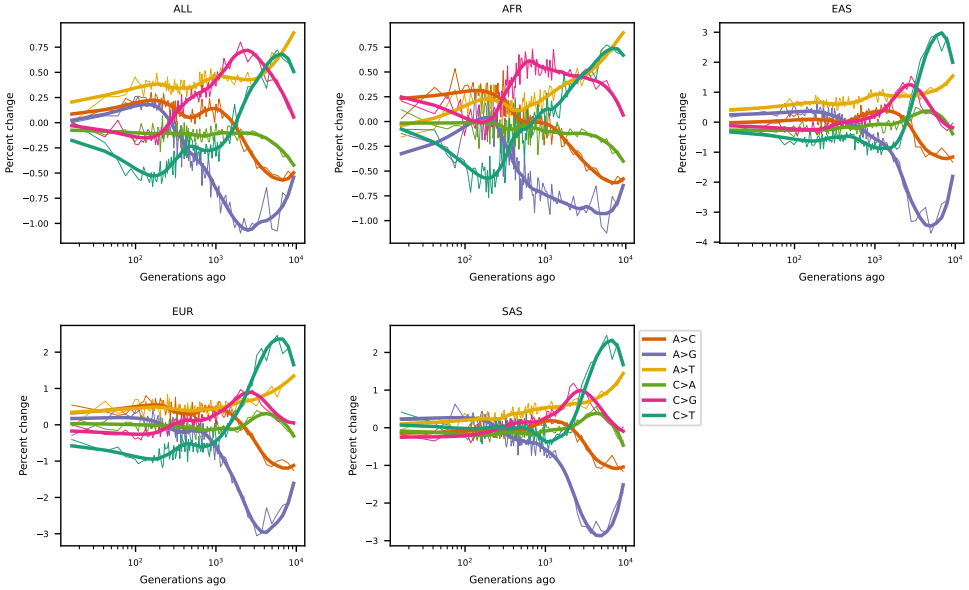

Figure 5: **`tsdate`-inferred mutation spectrum history, including singletons.**

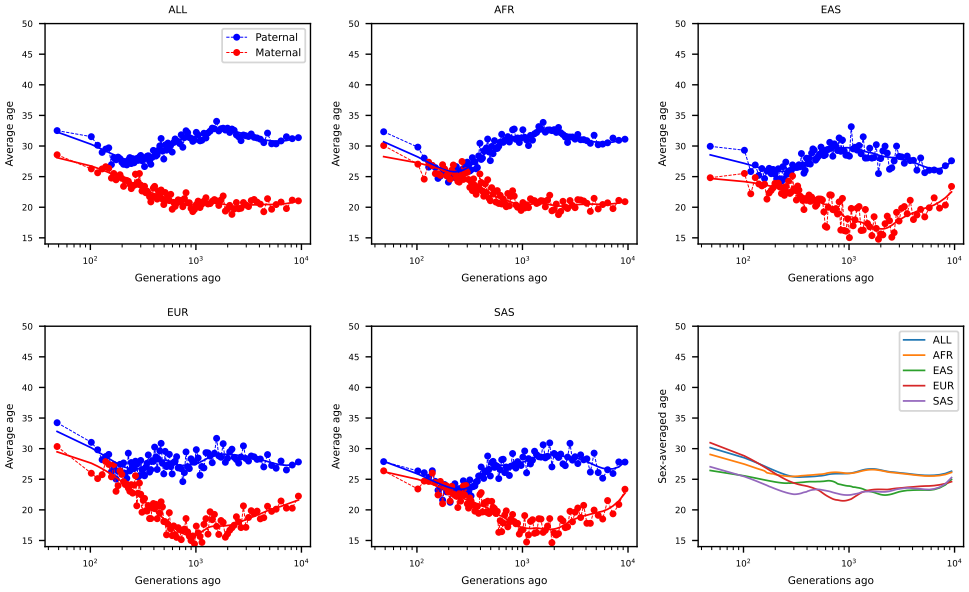

Figure 6: **`GEVA`-inferred generation time histories.**

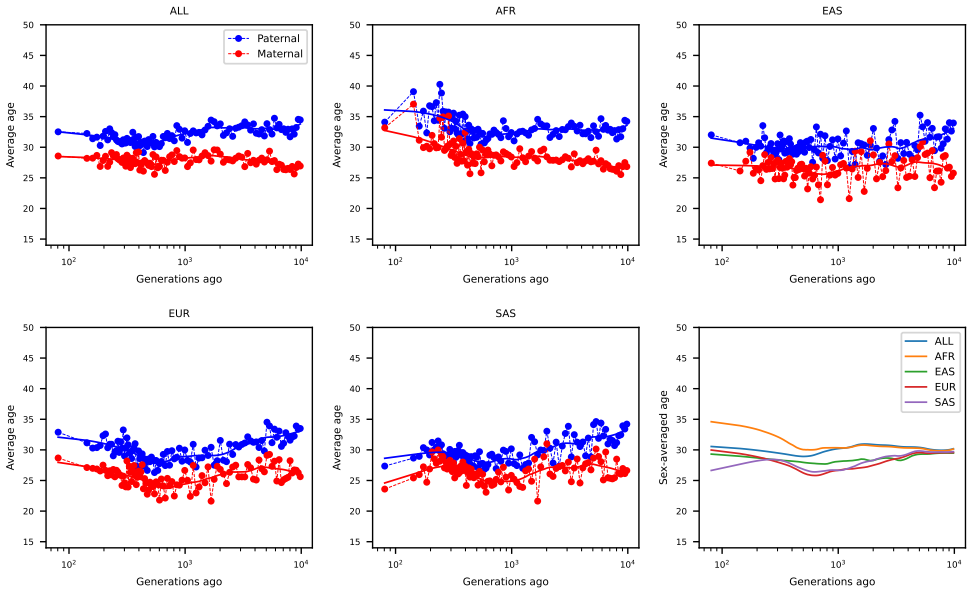

Figure 7: `Relate`**-inferred generation time histories.**

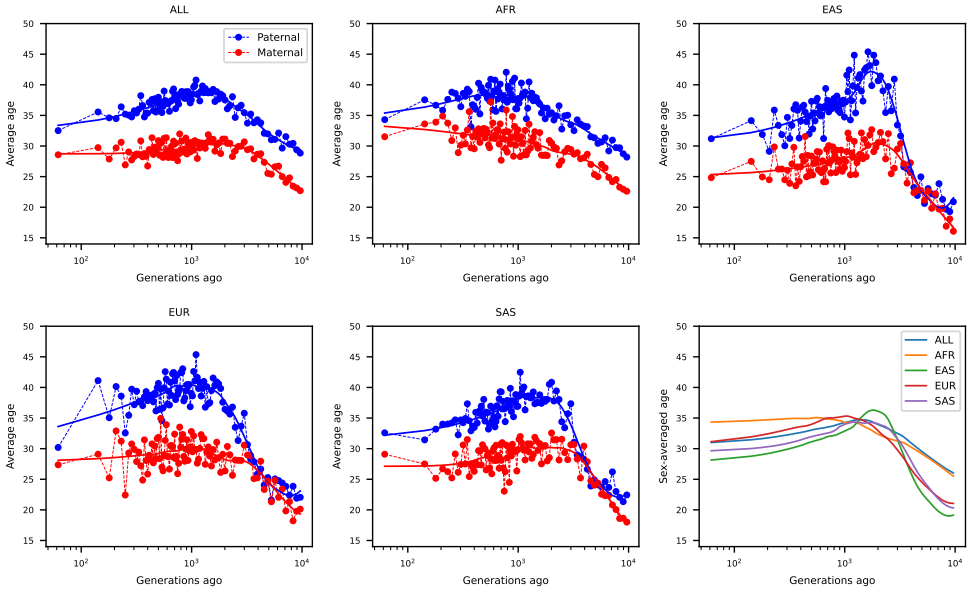

Figure 8: `tsdate`**-inferred generation time histories.**

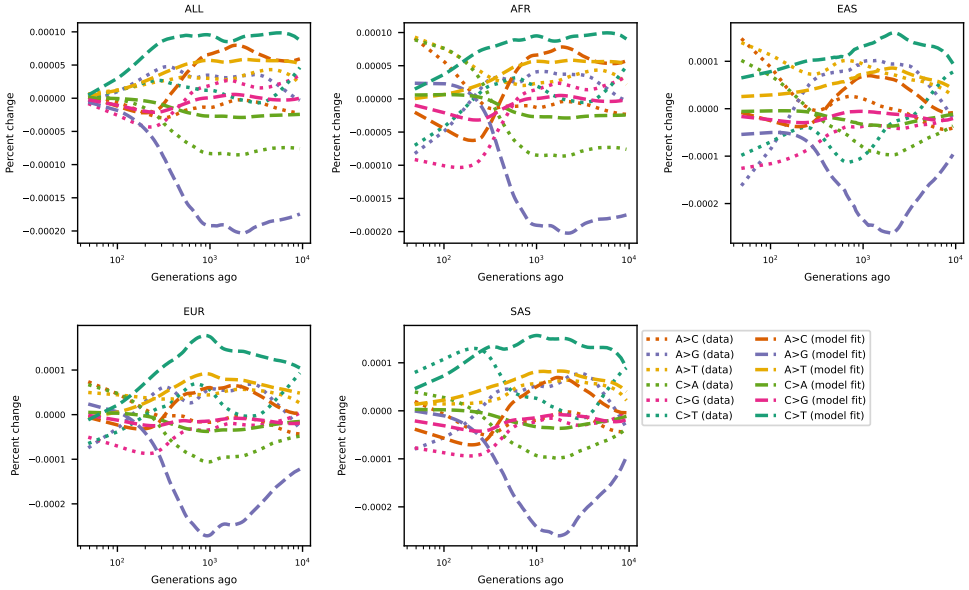

Figure 9: **Prediction of mutation spectrum history from `GEVA`-inferred generation times.**

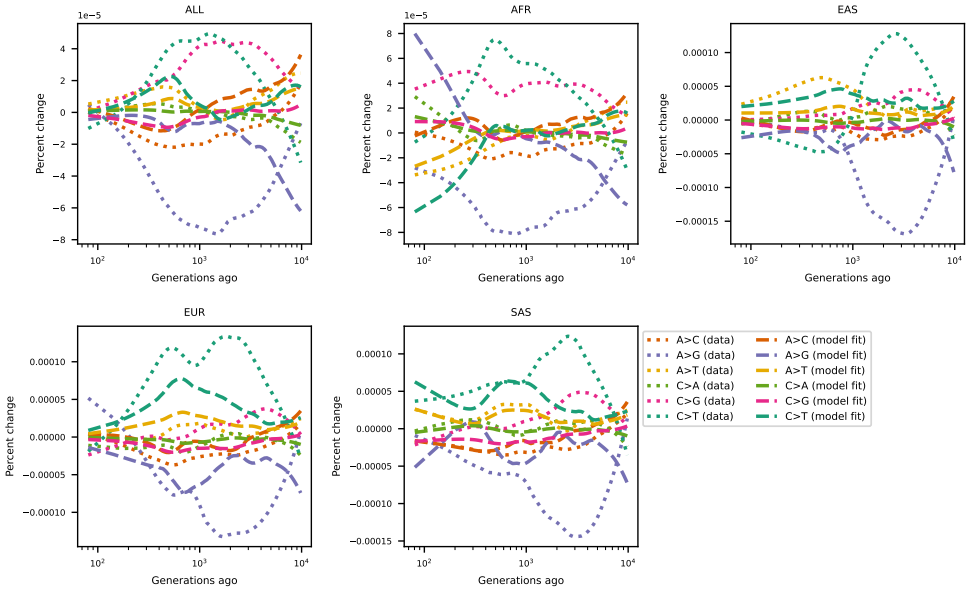

Figure 10: **Prediction of mutation spectrum history from `Relate`-inferred generation times.**

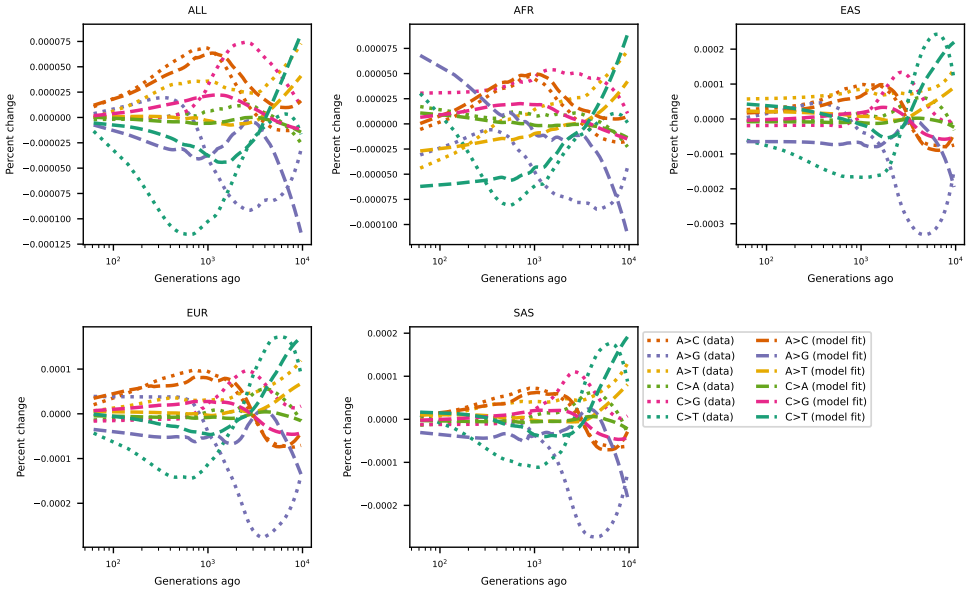

Figure 11: **Prediction of mutation spectrum history from `tsdate`-inferred generation times.**

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

References

1000 Genomes Project Consortium, Adam Auton, Lisa D Brooks, Richard M Durbin, Erik P Garrison, Hyun Min Kang, Jan O Korbel, Jonathan L Marchini, Shane McCarthy, Gil A McVean, and Gonçalo R Abecasis. A global reference for human genetic variation. *Nature*, 526(7571):68–74, October 2015.

Patrick K Albers and Gil McVean. Dating genomic variants and shared ancestry in population-scale sequencing data. *PLoS biology*, 18(1):e3000586, 2020.

Arun Durvasula and Sriram Sankararaman. Recovering signals of ghost archaic introgression in african populations. *Science Advances*, 6(7):eaax5097, 2020.

Bjarni V Halldorsson, Gunnar Palsson, Olafur A Stefansson, Hakon Jonsson, Marteinn T Hardarson, Hannes P Eggertsson, Bjarni Gunnarsson, Asmundur Oddsson, Gisli H Halldorsson, Florian Zink, et al. Characterizing mutagenic effects of recombination through a sequence-level genetic map. *Science*, 363 (6425):eaau1043, 2019.

Michael F Hammer, August E Woerner, Fernando L Mendez, Joseph C Watkins, and Jeffrey D Wall. Genetic evidence for archaic admixture in africa. *Proceedings of the National Academy of Sciences*, 108(37):15123–15128, 2011.

Jody Hey, Yujin Chung, Arun Sethuraman, Joseph Lachance, Sarah Tishkoff, Vitor C Sousa, and Yong Wang. Phylogeny estimation by integration over isolation with migration models. *Molecular biology and evolution*, 35(11):2805–2818, 2018.

PingHsun Hsieh, August E Woerner, Jeffrey D Wall, Joseph Lachance, Sarah A Tishkoff, Ryan N Gutenkunst, and Michael F Hammer. Model-based analyses of whole-genome data reveal a complex evolutionary history involving archaic introgression in central african pygmies. *Genome research*, 26(3): 291–300, 2016.

Melissa J Hubisz, Amy L Williams, and Adam Siepel. Mapping gene flow between ancient hominins through demography-aware inference of the ancestral recombination graph. *PLoS genetics*, 16(8):e1008895, 2020.

Hákon Jónsson, Patrick Sulem, Birte Kehr, Snaedis Kristmundsdottir, Florian Zink, Eirikur Hjartarson, Marteinn T Hardarson, Kristjan E Hjorleifsson, Hannes P Eggertsson, Sigurjon Axel Gudjonsson, et al. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. *Nature*, 549(7673): 519–522, 2017.

Belen Lorente-Galdos, Oscar Lao, Gerard Serra-Vidal, Gabriel Santpere, Lukas FK Kuderna, Lara R Arauna, Karima Fadhlaoui-Zid, Ville N Pimenoff, Himla Soodyall, Pierre Zalloua, et al. Whole-genome sequence analysis of a pan african set of samples reveals archaic gene flow from an extinct basal population of modern humans into sub-saharan populations. *Genome biology*, 20(1):1–15, 2019.

Luca Pagani, Stephan Schiffels, Deepti Gurdasani, Petr Danecek, Aylwyn Scally, Yuan Chen, Yali Xue, Marc Haber, Rosemary Ekong, Tamiru Oljira, et al. Tracing the route of modern humans out of Africa by using 225 human genome sequences from Ethiopians and Egyptians. *The American Journal of Human Genetics*, 96(6):986–991, 2015.

Vincent Plagnol and Jeffrey D Wall. Possible ancestral structure in human populations. *PLoS genetics*, 2 (7):e105, 2006.

Aaron P Ragsdale and Simon Gravel. Models of archaic admixture and recent history from two-locus statistics. *PLoS genetics*, 15(6):e1008204, 2019.

Aaron P Ragsdale, Timothy D Weaver, Elizabeth G Atkinson, Eileen Hoal, Marlo Möller, Brenna M Henn, and Simon Gravel. A weakly structured stem for human origins in africa. *bioRxiv*, pages 2022–03, 2022.

Eleanor ML Scerri, Mark G Thomas, Andrea Manica, Philipp Gunz, Jay T Stock, Chris Stringer, Matt Grove, Huw S Groucutt, Axel Timmermann, G Philip Rightmire, et al. Did our species evolve in subdivided populations across africa, and why does it matter? *Trends in ecology & evolution*, 33(8):582–594, 2018.

Carina M Schlebusch, Helena Malmström, Torsten Günther, Per Sjödin, Alexandra Coutinho, Hanna Edlund, Arielle R Munters, Mário Vicente, Maryna Steyn, Himla Soodyall, et al. Southern African ancient genomes estimate modern human divergence to 350,000 to 260,000 years ago. *Science*, 358(6363):652–655, 2017.

Leo Speidel, Marie Forest, Sinan Shi, and Simon R Myers. A method for genome-wide genealogy estimation for thousands of samples. *Nature genetics*, 51(9):1321–1329, 2019.

Richard J Wang, Samer I Al-Saffar, Jeffrey Rogers, and Matthew W Hahn. Human generation times across the past 250,000 years. *Science Advances*, 9(1):eabm7047, 2023.

Anthony Wilder Wohns, Yan Wong, Ben Jeffery, Ali Akbari, Swapan Mallick, Ron Pinhasi, Nick Patterson, David Reich, Jerome Kelleher, and Gil McVean. A unified genealogy of modern and ancient genomes. *Science*, 375(6583):eabi8264, 2022.