

# Simulating the fitness impacts of Neandertal-introgressed mutations

**Sara A. Carioscia**, Rajiv C. McCoy | Department of Biology, Johns Hopkins University

## Introduction

- Purifying selection is less efficient in small populations.
- Genomic data suggests that Neandertals experienced prolonged population bottlenecks prior to admixing with modern humans.
- How does introgression from archaic hominins contribute to the fitness effects of contemporary human variation?

## Methods

- Forward genetic simulations of neutral and deleterious mutations using SLiM. Mutations were drawn from a gamma distribution of fitness effects (shape = -0.015, mean = 0.9)
- Human demographic model, adapted from Gravel et al. (2011), includes:
  - Neandertals ( $N_e = 1,000$ ) diverging from modern humans 500 kya
  - Out-of-Africa migration 60 kya
  - Admixture with Neandertals 55 kya
  - Recent Eurasian population expansion

## Results

- We compare the selection coefficients of mutations present in the modern Eurasian population, which could have arisen in the ancient human population and persisted, the small Neandertal population and introgressed, or the modern Eurasian population.
- Neandertal-introgressed mutations are modestly enriched for deleterious effects (beta = 0.5215, standard error = 0.171,  $p < 0.01$ ) compared to age-matched non-introgressed alleles.
- Recent mutations arising within the recently expanded Eurasian population make the largest contribution to harmful variation (beta = 2.287, standard error = 0.071,  $p < 0.001$ ).

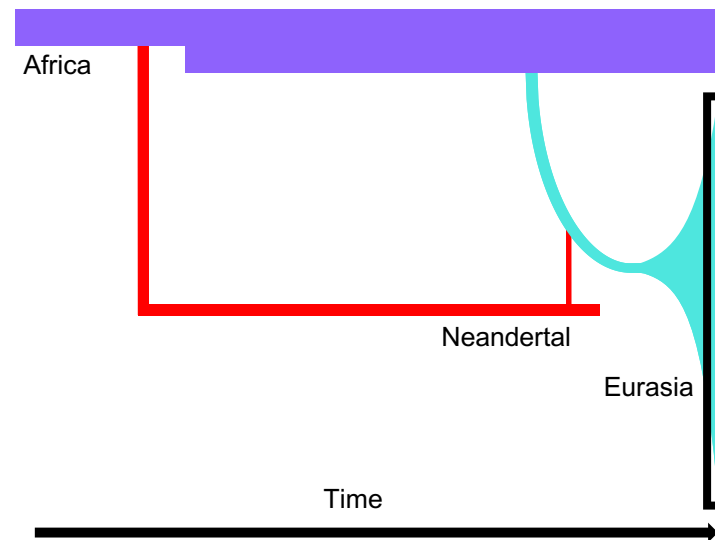
## References

Gravel et al. 2011. Demographic history and rare allele sharing among human populations. *Proceedings of the National Academy of Sciences*, 108(29), 11983-11988.  
Haller & Messer. 2019. SLiM 3: Forward Genetic Simulations Beyond the Wright-Fisher Model. *Molecular Biology and Evolution*, 36(3), 632-637.

## Conclusions

- Rare, recent mutations make an outsize contribution to segregating deleterious genetic variation, outweighing the effects of this long divergence time and the strong drift in the Neandertal population.
- This raises the possibility that complex disease associations attributed to archaic admixture may be driven by rare modern mutations that segregate in linkage disequilibrium with archaic haplotypes.
- Our findings provide a theoretical foundation for studies of the functional and fitness impacts of archaic introgression and comparisons with mutations of modern human origin.

## Human Demographic History



## Acknowledgements

McCoy Lab, MARCC Computing Cluster, NIH NIGMS

