S3 Text

Individual-based Simulations

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Here, we describe individual-based simulations to investigate whether the difference in population size between Neanderthals and modern humans can account for the selection coefficient (s) and the exonic density of deleterious sites (μ) that we estimated (main text, S2 Text).

Simulation details

Model

To test the plausibility of our estimates of μ and s, we performed individual-based simulations of a likely demographic scenario prior to admixture between Neanderthals and modern humans. Specifically, we assumed that two diploid populations of constant size N_n (Neanderthals) and N_h (modern humans) split from their common ancestral population of size N_a at time 0. These two populations were then simulated forward in time in complete isolation over T_D non-overlapping generations. In each population we simulated a single biallelic locus with alleles A and a such that the fitness of genotypes AA, Aa, and aa is 1, $1-s$, and $(1-s)^2$. Each generation, we draw two parents of each offspring individual at random and with probability proportional to their fitness. Selection in our model is soft, therefore population size is constant each generation. Mutations between a and A and *vice versa* were assumed to occur at rate u per site and generation. We implemented this by introducing a mutation at frequency $1/(2N)$ with probability $2Nu$ per generation, where N is the absolute number of individuals in the respective population (N_n for Neanderthals and N_h for modern humans).

We assumed that allele frequencies in the ancestral population had reached drift–mutation–selection equilibrium prior to the split. Both the Neanderthal and modern human population were therefore initialized by drawing the frequency of allele a from the diffusion approximation to the respective stationary allele-frequency distribution. Specifically, for each run, the probability that the locus is polymorphic in the ancestral population is equal to the probability that a is

found at any frequency between $1/2N_a$ and $1-1/(2N_a)$, which in the diffusion limit is given by

$$P(\text{site is polymorphic}) = 4N_a u \int_{1/2N_a}^{1-1/2N_a} P(x; N_a, s, u)dx, \quad (1)$$

where $P(x; N_a, s, u)$ is the stationary probability density at frequency x. This density is proportional to equation (9.3.3) in reference [1],

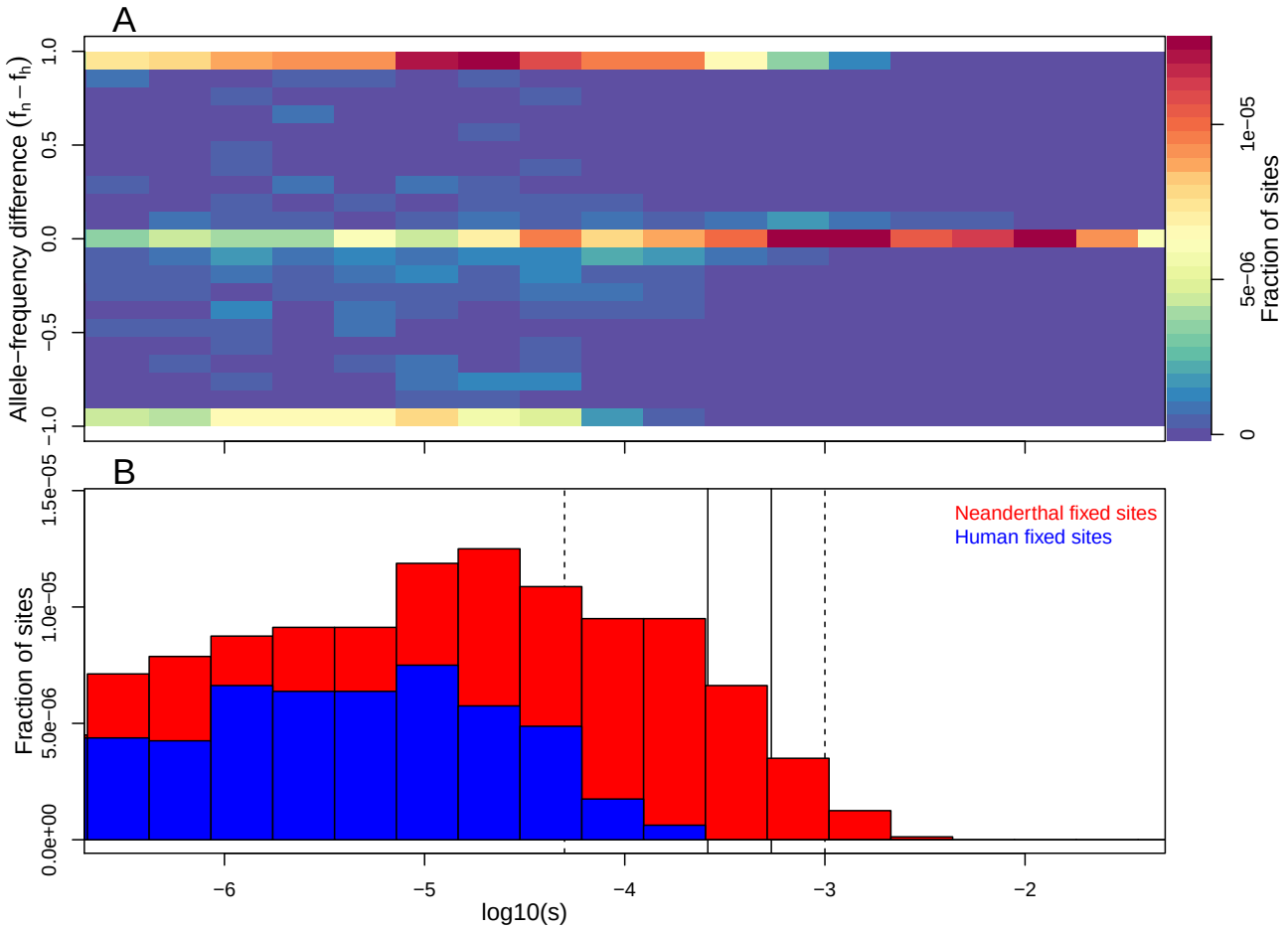
$$P(x; N_a, s, u) \propto e^{-4N_a sx} x^{4N_a u-1}(1-x)^{4N_a u-1}. \quad (2)$$

If the locus was polymorphic in the ancestral population in a given run, we drew a frequency x of allele a from the stationary distribution in (2); otherwise we set the initial allele frequency to zero. We assumed that the mutation rate u did not change after the split.

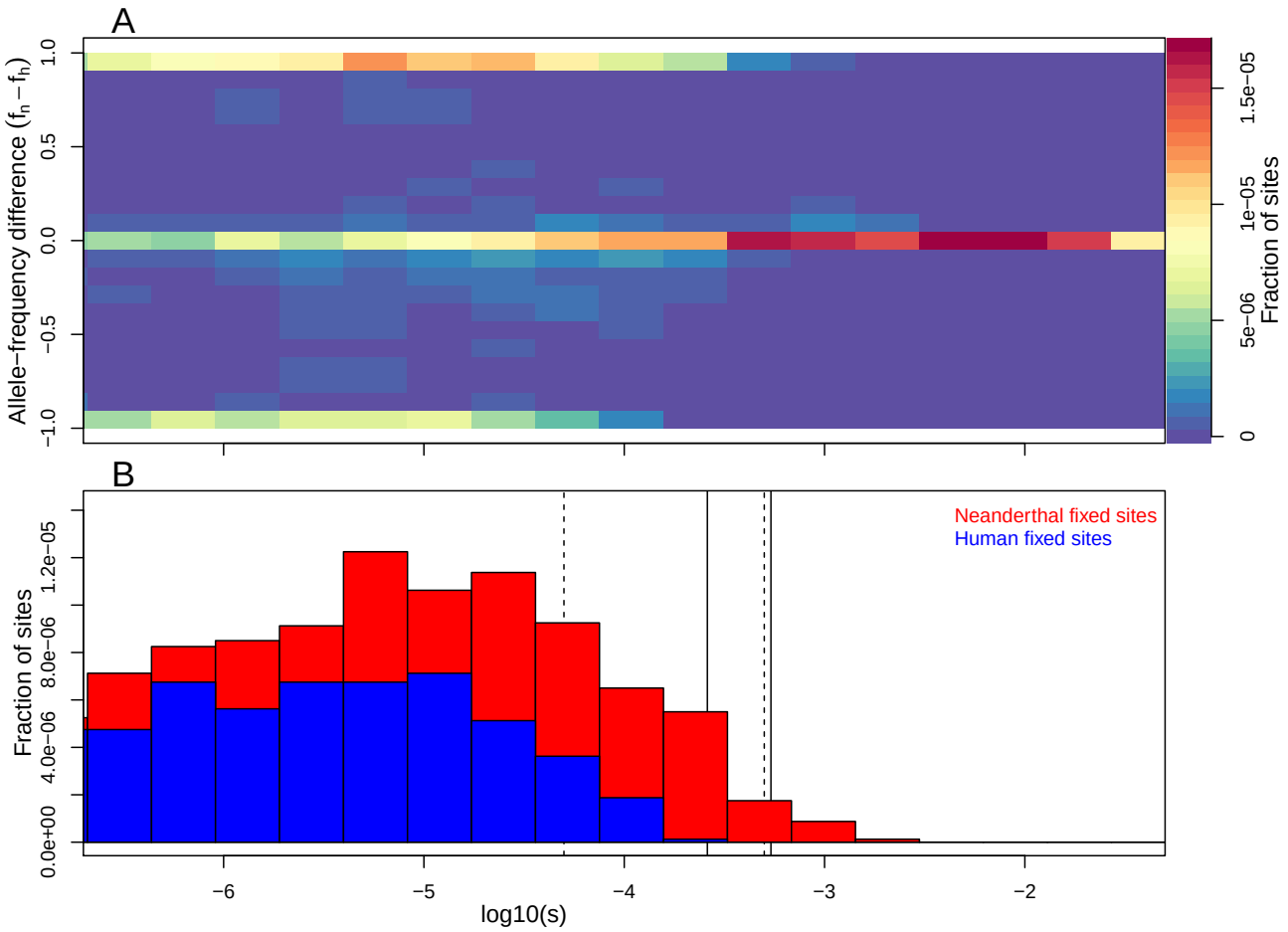
In total, we performed R independent runs. For each run we recorded the frequency of the deleterious allele a in the Neanderthal and human population at the end of the simulation. We then computed the difference d between the frequency of a in Neanderthals and humans, $d = \text{freq}_n(a) - \text{freq}_h(a)$. A difference of $d = 1$ implies that the deleterious allele was fixed in Neanderthals and lost in humans, whereas $d = -1$ implies the converse.

Parameter values and settings

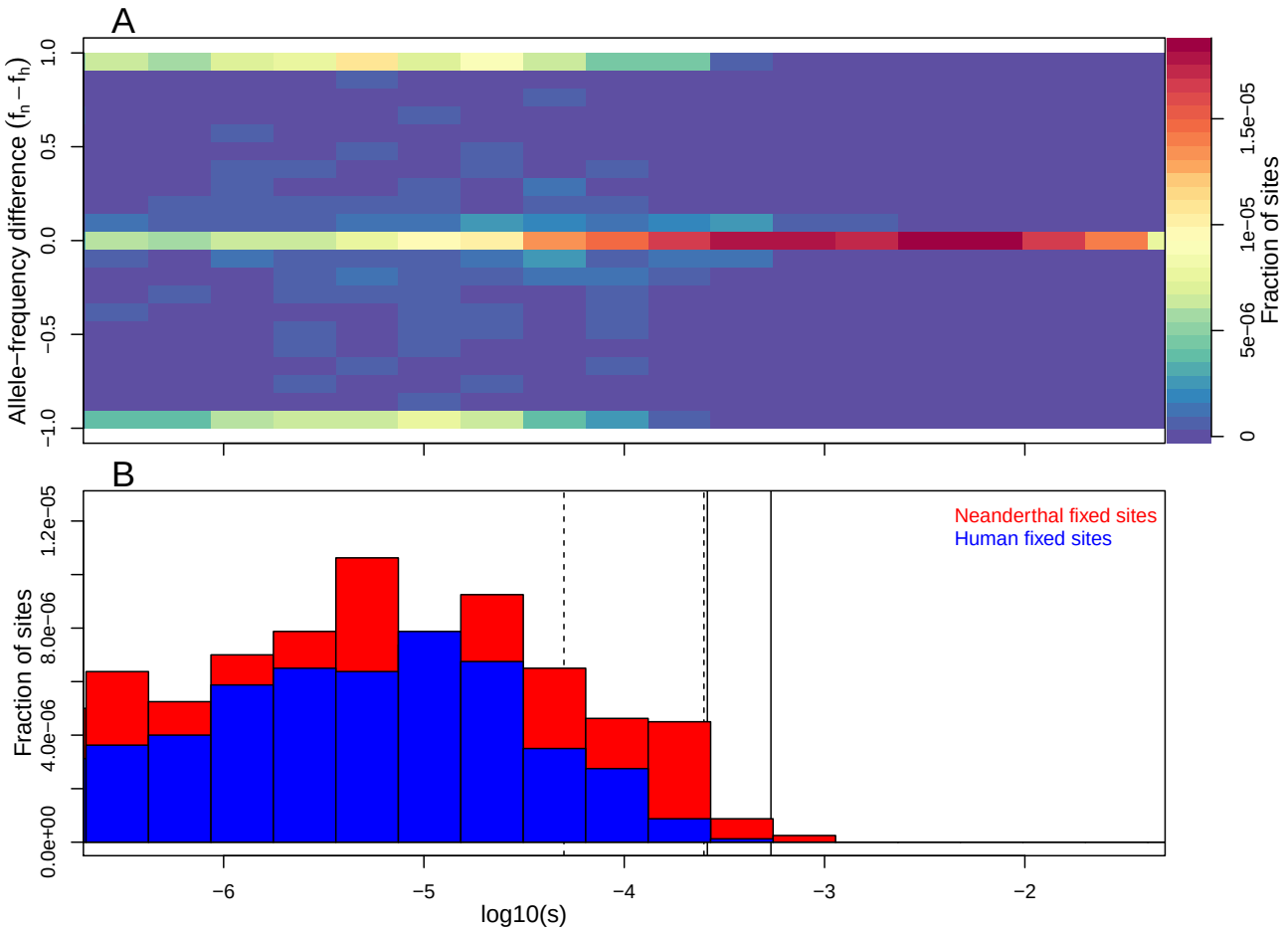
We chose the size of the human population to be the same as the one of the ancestral one, and kept them at $N_h = N_a = 10000$. We ran simulations for three different Neanderthal population sizes: $N_n = 500$, 1000, and 2000. These values span a range of Neanderthal effective population sizes proposed and used by others (e.g. [2, 3]). We also used three different mutation rates, $u = 10^{-8}$, 2×10^{-8}, and 3×10^{-8}, to reflect a range of plausible per-nucleotide mutations rates in humans [4]. Note that in our context, the mutation rate should be thought of as a rate of non-synonymous mutation in genic regions to make it an appropriate match for the parameters used in reference [5]. For the runs shown in the paper we kept $u = 1 \times 10^{-8}$, because pilot runs with other values of u did not strongly change our qualitative conclusions. For each parameter set, we simulated 8 million runs. In each simulation run, we drew s from a distribution of scaled selection coefficients proposed by reference [5]. We used their estimated gamma distribution for $2Ns$ (with parameters $\alpha = 0.184$ and $\beta = 8200$), where $N = 25,636$ is the effective population size in their model [5].



S18 Fig. Simulations showing that the Neanderthal population is predicted to harbor an excess of weakly deleterious fixed alleles compared to humans. (A) A two-dimensional histogram of the difference in allele frequency between Neanderthal and human population, and the deleterious selection coefficient over all simulated sites. (B) The fraction of sites in the simulations where there is a human- or Neanderthal-specific fixed difference, binned by selection coefficient. Dotted lines indicate the nearly-neutral selection coefficient (i.e. the inverse of the effective population size) for Neanderthal (right) and Human (left) populations. Solid lines show the 95% CI of s for ASN (the larger of the two CI) that we inferred. Note that monomorphic sites are not shown, but are included in the denominator of the fraction of sites. In these simulations, $N_n = 500$ and $u = 10^{-8}$.



S19 Fig. As in S18 Fig, but with $N_n = 1000$.



S20 Fig. As in S18 Fig, but with $N_n = 2000$.

References

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