Quantifying selection against Neanderthal introgression

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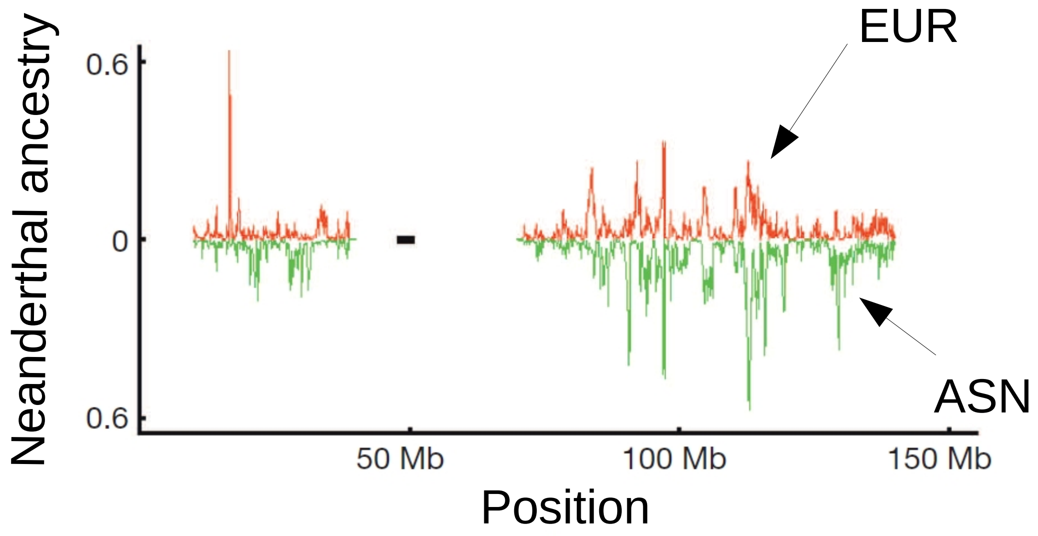
Neanderthal introgression in *H.sapiens*

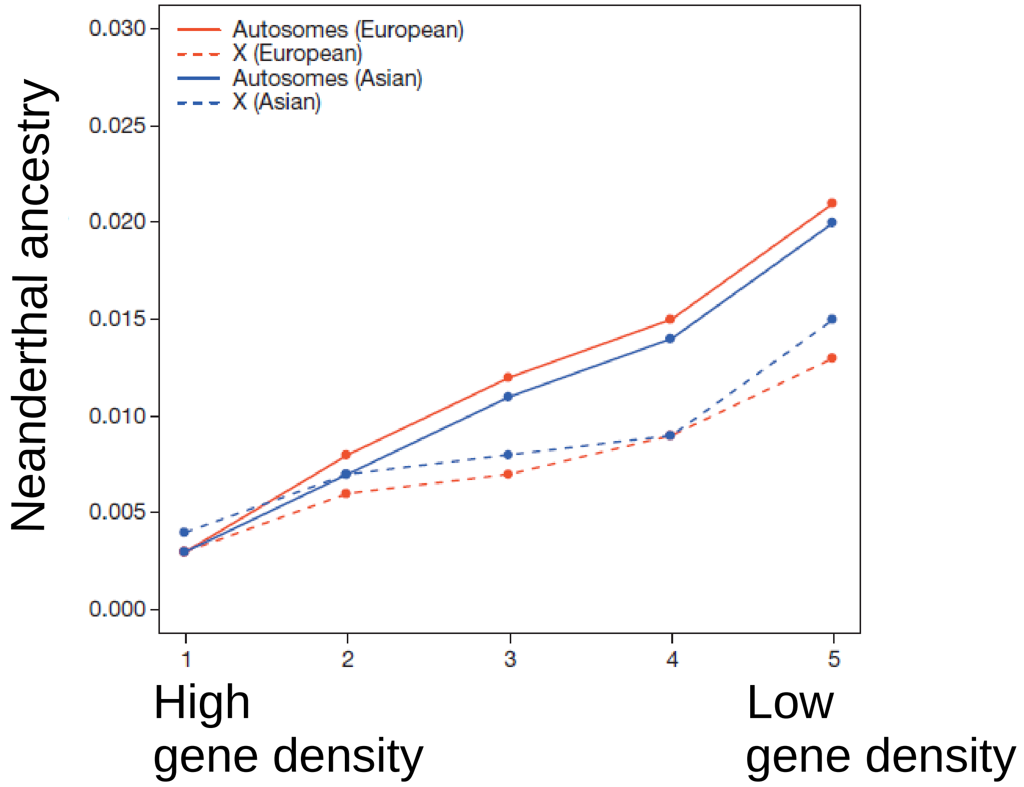
- Humans and Neanderthals hybridized (Green et al. 2010)
  - Neanderthal admixture in modern-day humans is between 1 and 7.9% (Green et al. 2010, Durand et al 2011, Lohse et al 2014)
  - Some introgressed alleles are adaptive, but majority were not
    - Many were deleterious

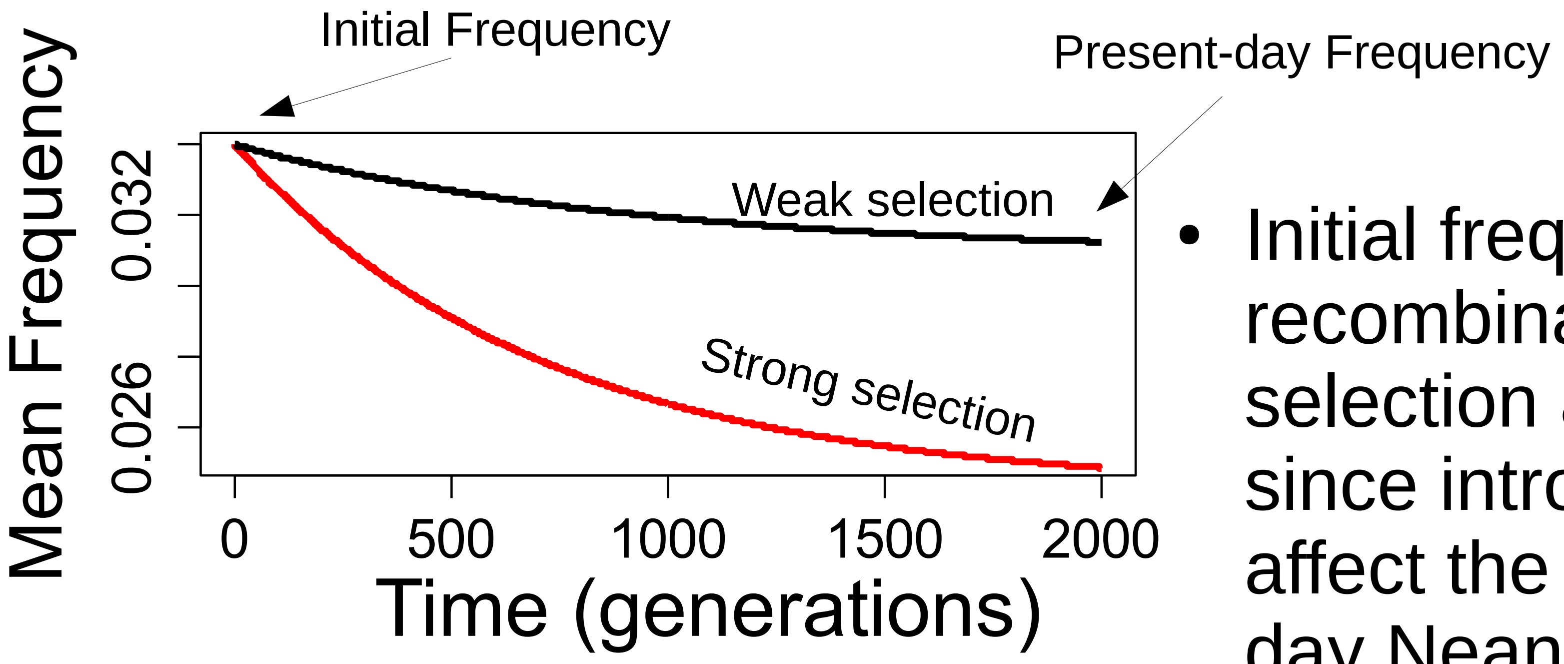
Selection against introgression

- Unequal distribution of Neanderthal ancestry across chromosomes
- Less Neanderthal ancestry in gene dense regions and on X
- No Neanderthal DNA in mitochondria or Y

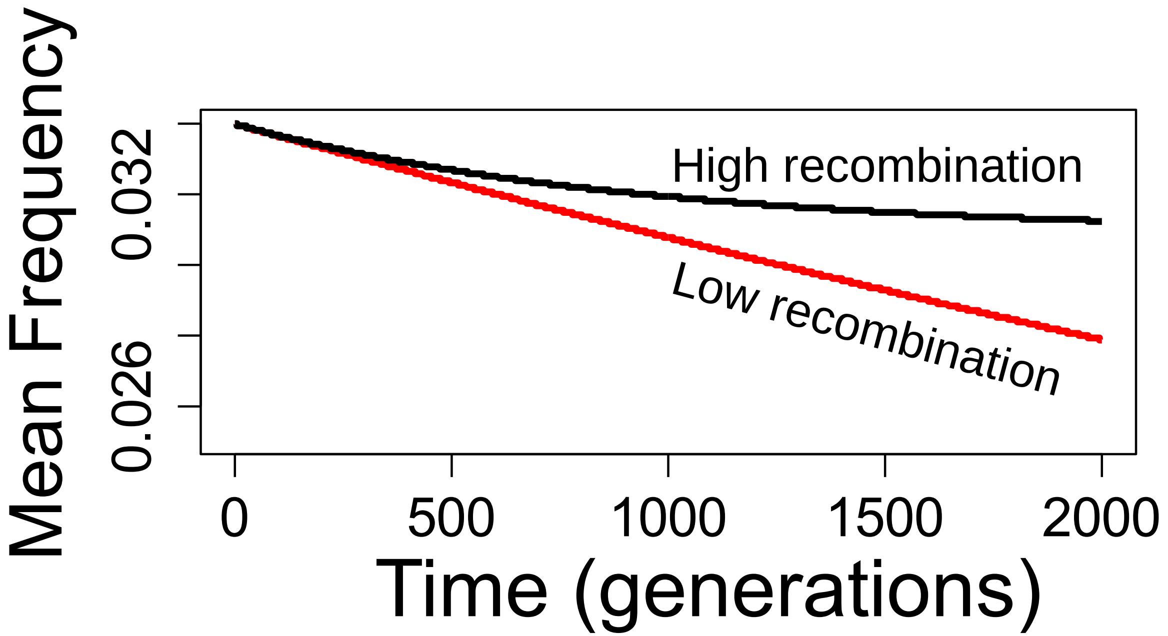
(Sankararaman et al 2014, Vernot and Akey 2014, Prufer et al 2014, Krause et al 2010, Briggs et al 2009,)

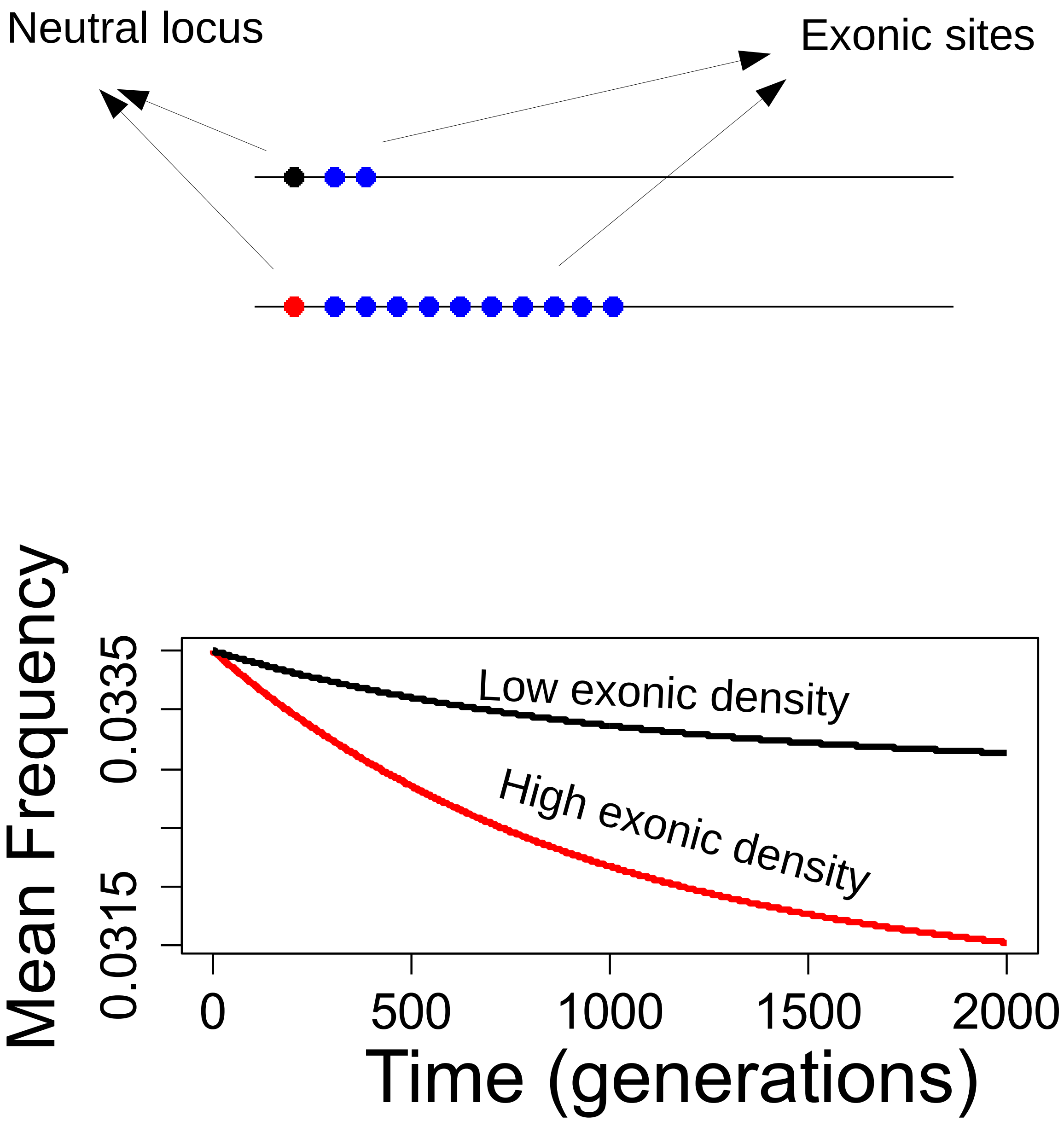






- Initial frequency, recombination, selection and time since introgression affect the present-day Neanderthal allele frequency.





- Initial frequency, recombination, selection and time since introgression affect the present-day Neanderthal allele frequency, **as well as the density of selected sites.**

Quantifying selection against Neanderthal ancestry

Initial frequency

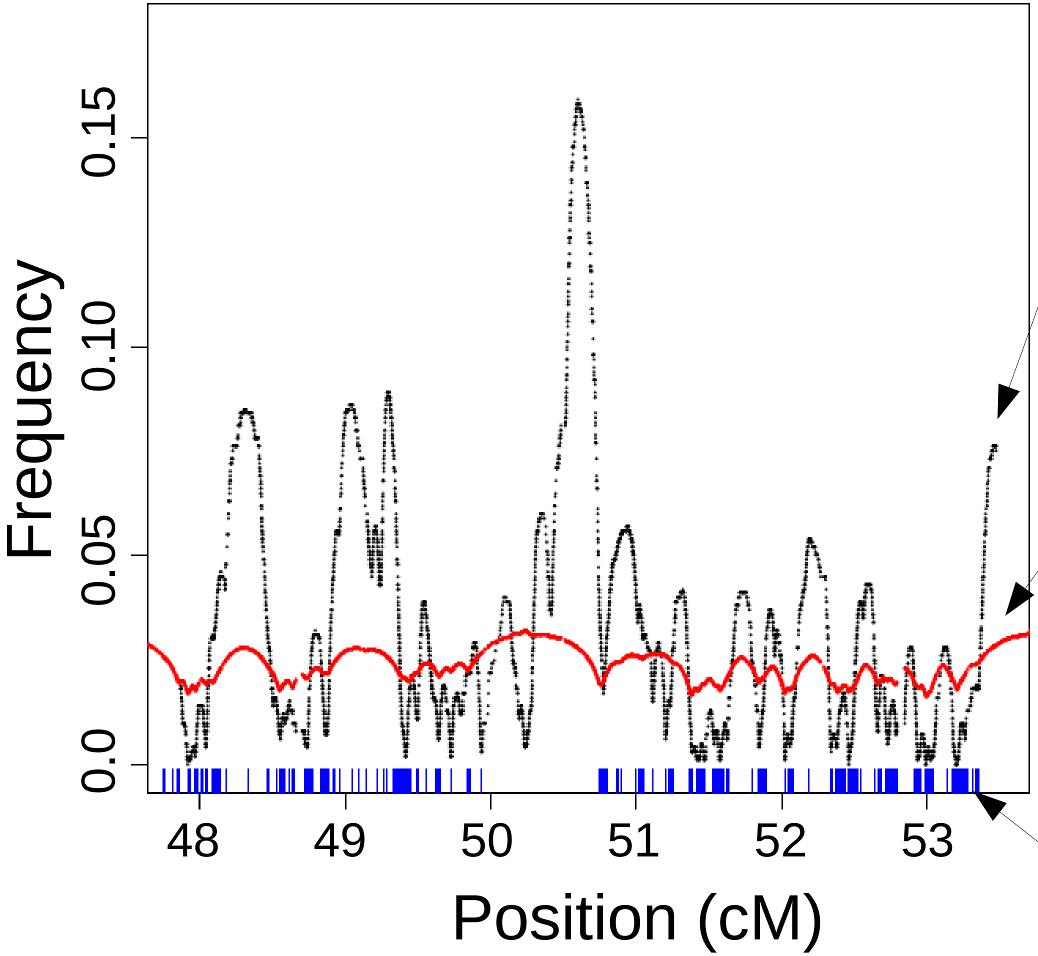
$$E[p_{k,t}] = p_0\left(\mu \sum_{j=1}^{i} (1-\mu)^{j-1} f(s, r_j, t) + (1-\mu)^{i}\right)$$

Expected present-day frequency of Neanderthal allele at locus k

Probability that exonic bp is deleterious

Effects of selection, recombination and the time since introgression

Combining Data and Theory



Observed frequency (black)
(Sankararaman et al 2014)

Expected frequency (red)

Exons (blue)

Inference

- Find s, μ and p_0 that minimize the sum of squared differences between the expected and the observed Neanderthal allele frequencies.

$$RSS = \sum_{\text{all SNPs}} (p_{obs} - E[p])^2$$

Observed present-day frequency

Expected present-day frequency

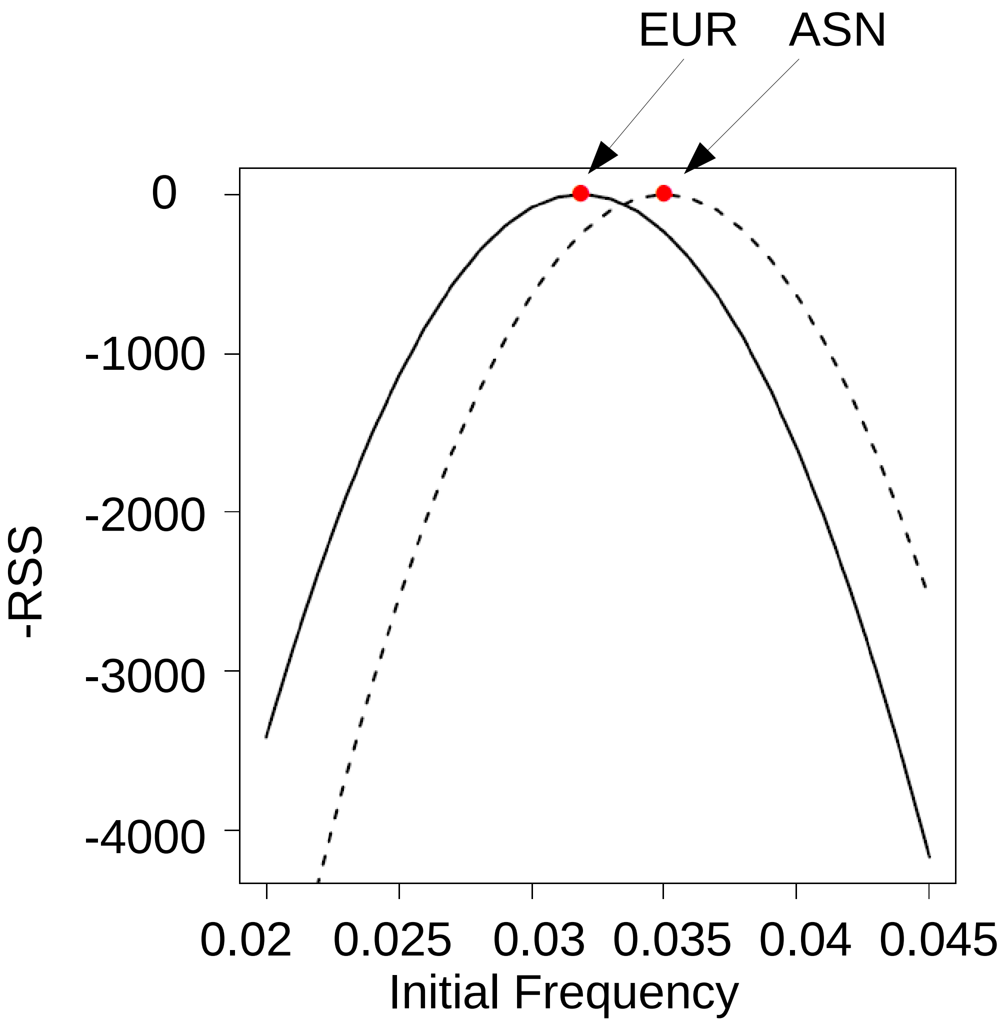
Estimates of initial admixture proportion

- Larger initial average frequency of Neanderthal allele in Asian population.

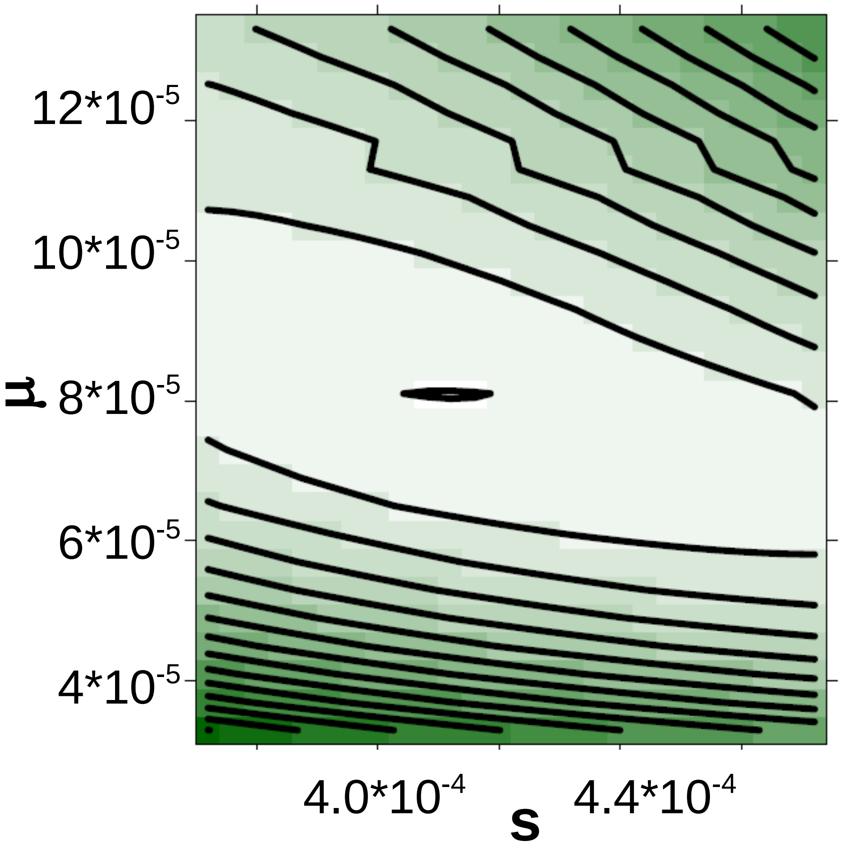
(Prufer et al 2014, Sankararaman et al 2014, Vernot and Akey 2014)

$p_{0,ASN} = 3.60\%$

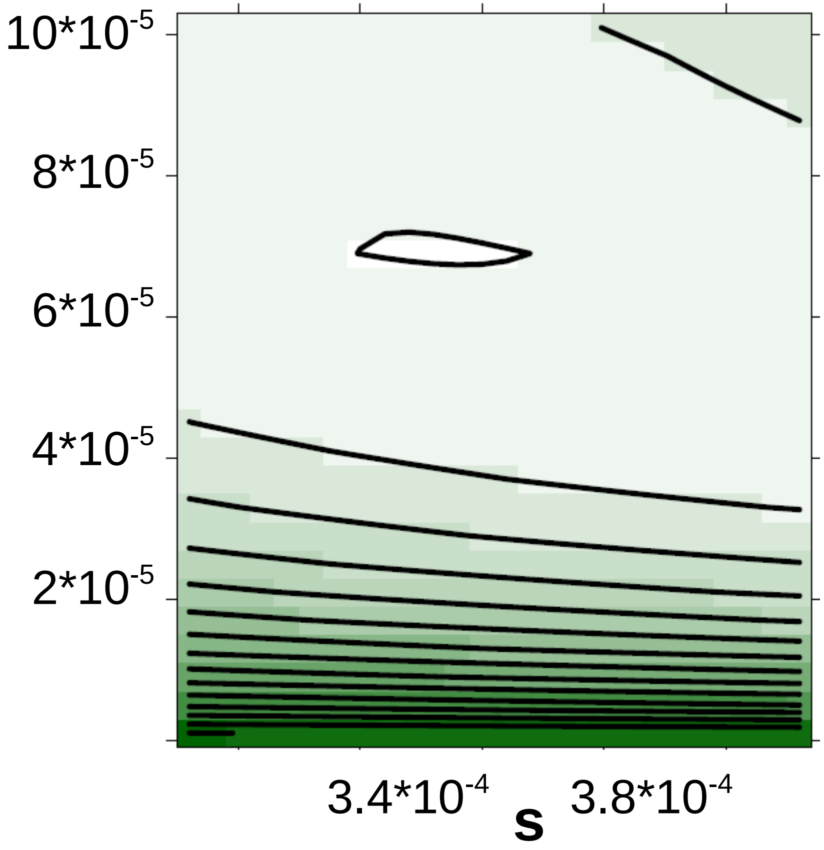
$p_{0,EUR} = 3.38\%$



Estimates of μ and *s* for autosomal chromosomes



EUR



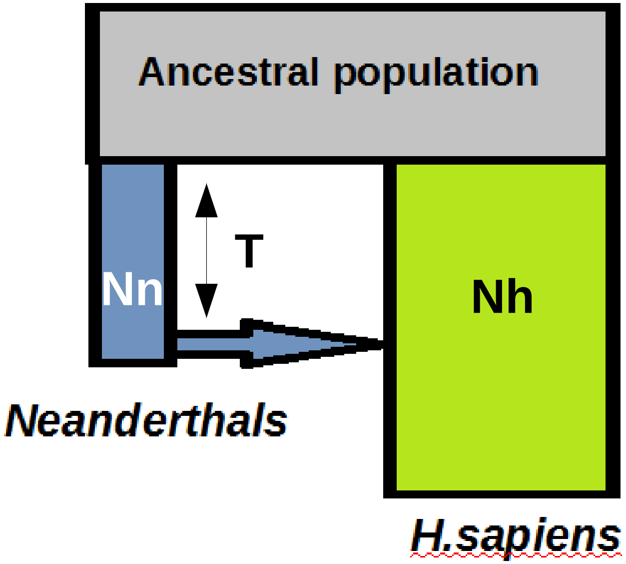
ASN

$s = 4.12 * 10^{-4}$
$\mu = 8.1 * 10^{-5}$ (per exonic site)

$s = 3.52 * 10^{-4}$
$\mu = 6.9 * 10^{-5}$

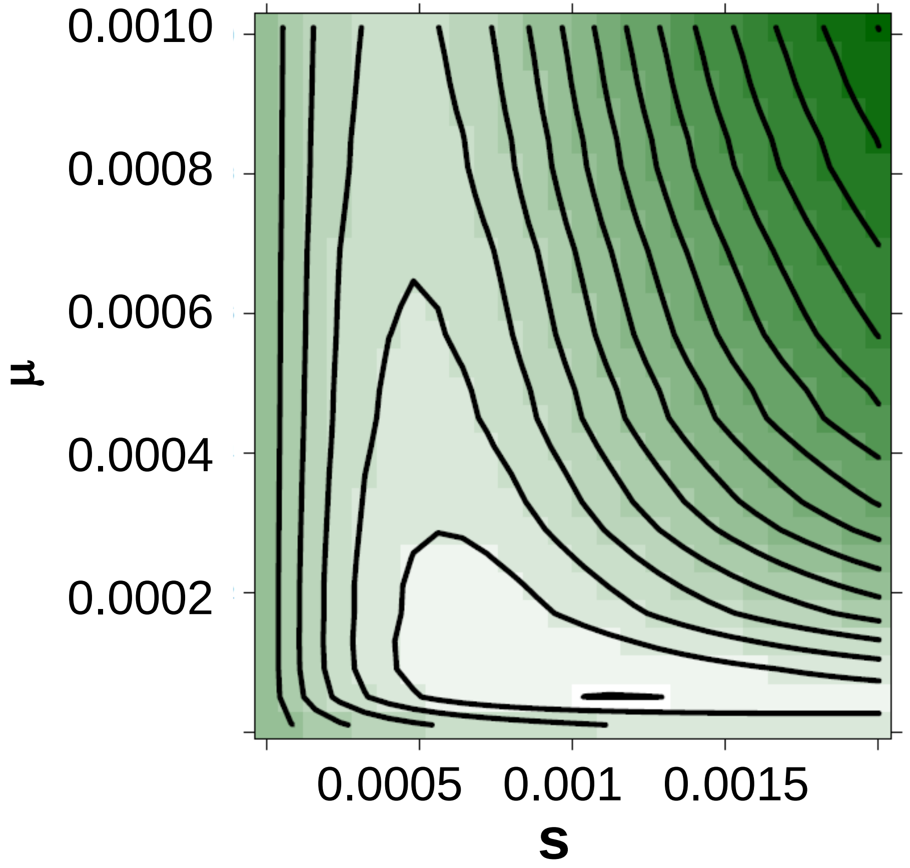
Purge due to differences in population sizes

- Neanderthals had more deleterious mutations. Those alleles were purged from humans due to increased efficiency of selection.
- Supported by individual-based simulations.

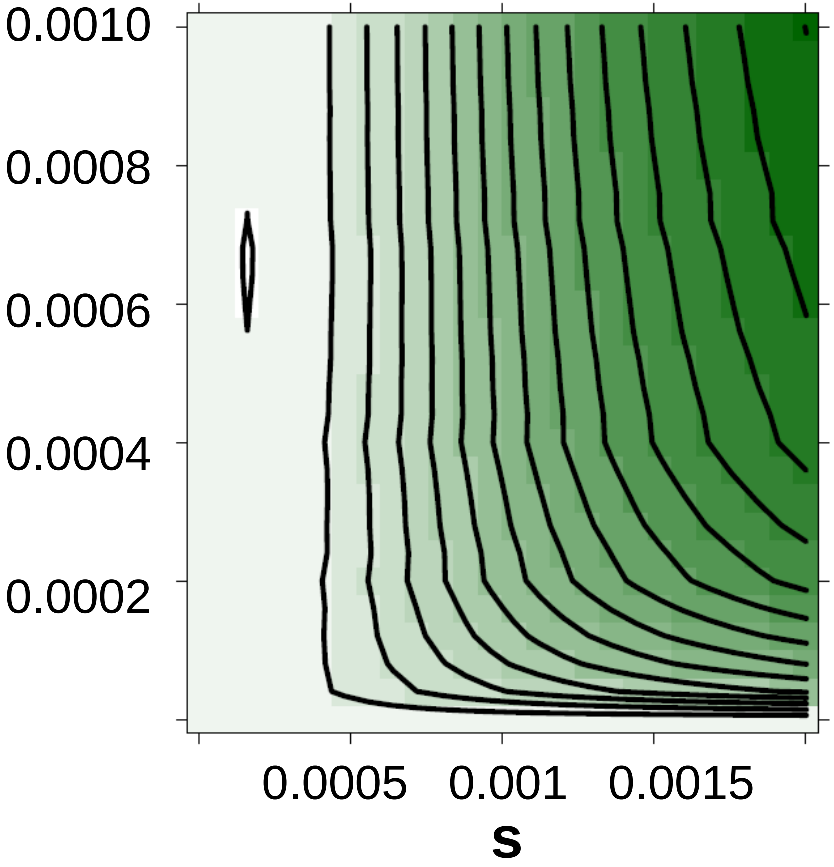


Name	s	μ
EUR	$4.12 * 10^{-4}$	$8.1 * 10^{-5}$
ASN	$3.52 * 10^{-4}$	$6.9 * 10^{-5}$
Model Nh = 10 000 Nn = 3 000 T = 20 000	$1.07 * 10^{-4}$	$1.3 * 10^{-5}$

Estimates of μ and *s* for X chromosome



EUR



ASN

$s = 9.8 * 10^{-4}$
$\mu = 6.6 * 10^{-5}$

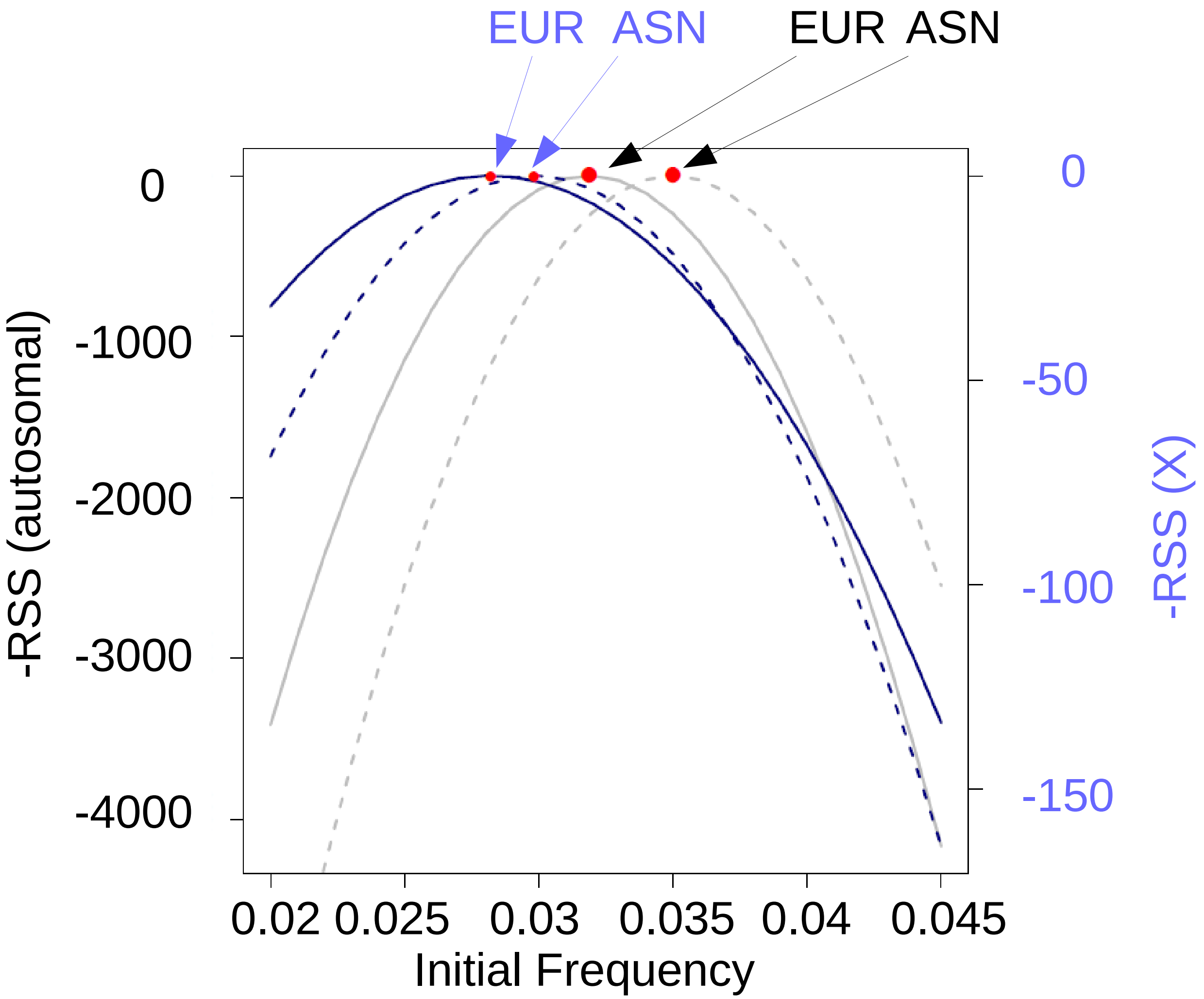
$s = 1.65 * 10^{-4}$
$\mu = 6.8 * 10^{-4}$

Estimates of initial admixture proportion for X chromosome

$p_{0x,ASN} = 3.00\%$

$p_{0x,EUR} = 2.82\%$

- Lower than autosomes
- Implies around 3 Neanderthal male x *H.sapiens* female matings for each Neanderthal female x *H.sapiens* male mating



Conclusions

- Autosomal chromosomes:
  - Lack of Neanderthal ancestry in Humans can be explained, in part, by increased efficiency of selection once Neanderthal genes were introduced into the human population.
    - deleterious alleles are purged faster from larger populations
- X chromosomes:
  - Potentially stronger selection against Neanderthal ancestry on X

Thank you!

#ThisIsACoop