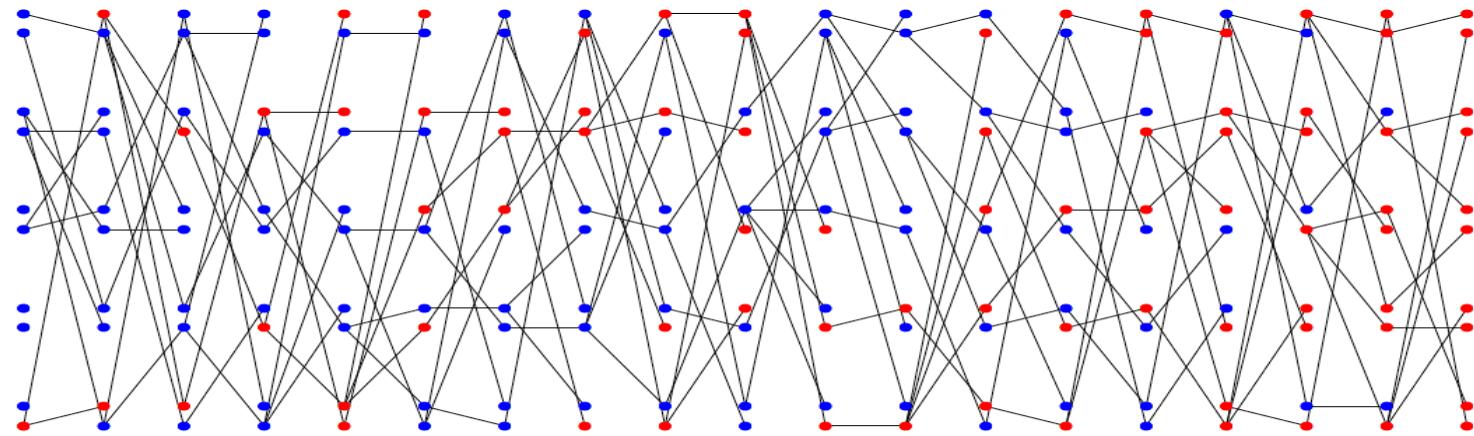
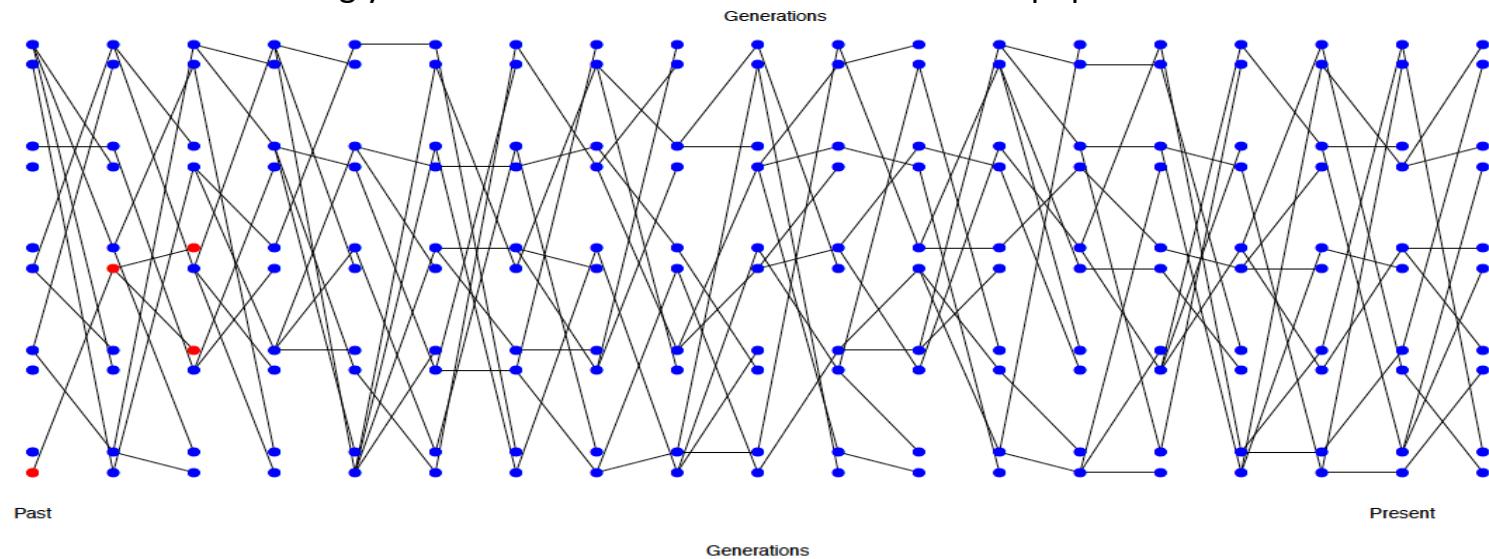


Selected mutation (e.g. from a G->T) spreads through population to become a substitution

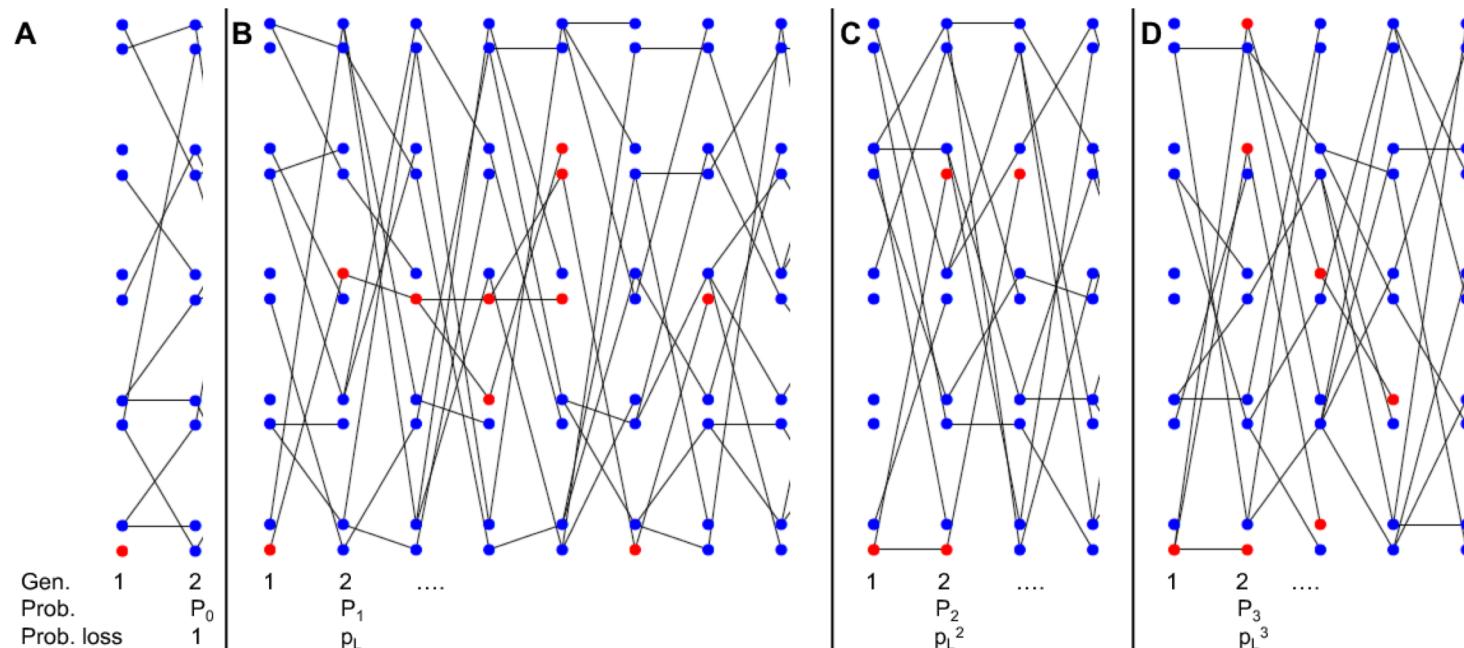


But even strongly beneficial mutations can be lost from the population when rare



A selected allele which increases its bearer's relative fitness by s has just been introduced by mutation

Strongly advantageous alleles $s \gg 1/(2N_e)$ have a probability s of fixing in population



Chance (genetic drift) plays a role in the fate of all alleles.

Assuming $s \ll 1$. The probability a haploid allele fixes is

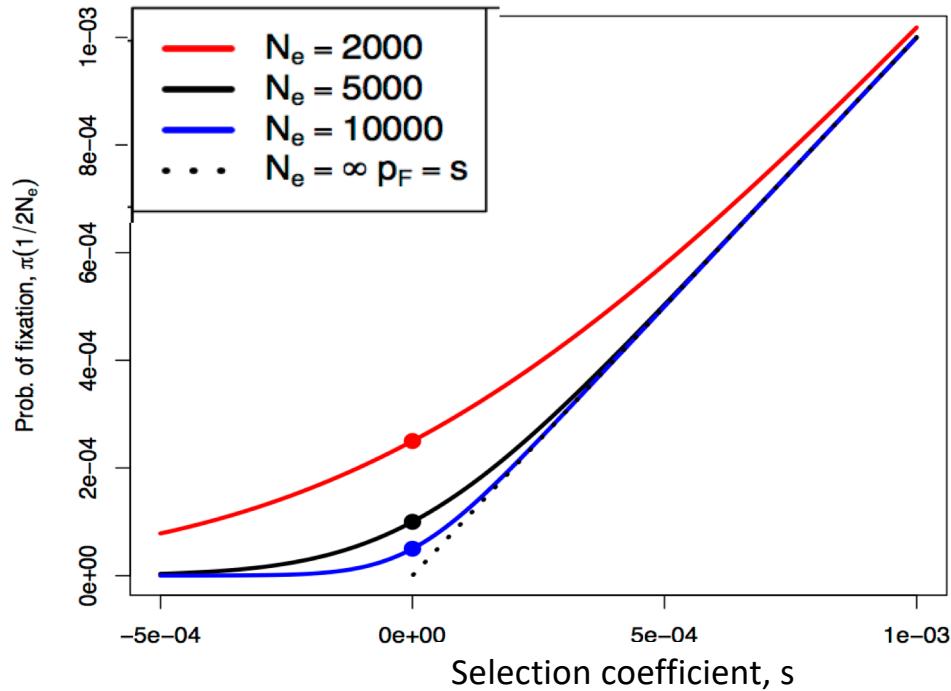
$$p_F = 2s.$$

Generalizing to diploid model an allele which gives heterozygotes a relative fitness advantage of $1+hs$, has a probability of $p_F = 2hs$ of fixing in population (assuming $h>0$ & $s \ll 1$)

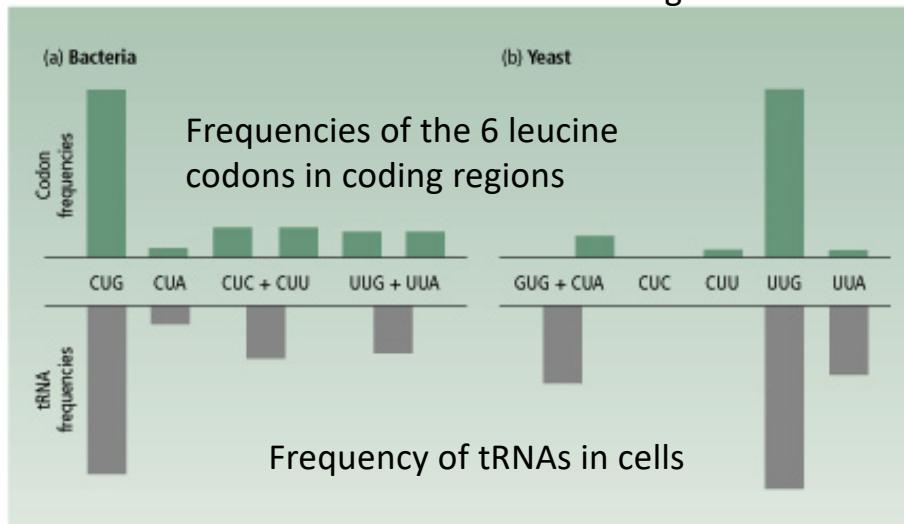
Chance (genetic drift) plays a role in the fate of all alleles.

For strongly selected alleles mostly when they're rare in the population.

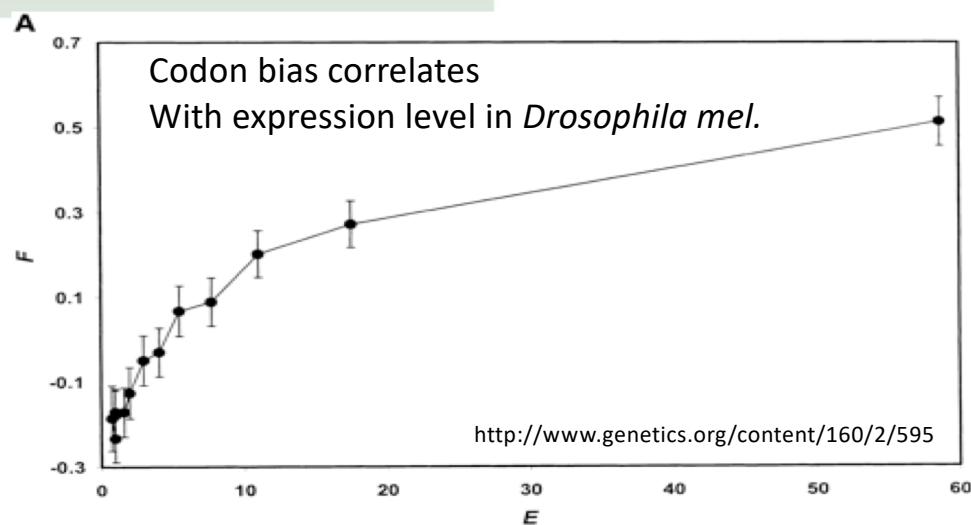
- A selected allele which increases its bearer's relative fitness by s has just been introduced by mutation
- Strongly advantageous alleles $s \gg 1/(2N_e)$ have a probability s of fixing in population
- Very deleterious alleles $|s| \gg 1/(2N_e)$ can never fix
- Alleles with $|s| < 1/(2N_e)$ are effectively neutral & have $1/(2N_e)$ fixing in population.



In large populations selection can act on very small fitness benefits
Codon-usage bias



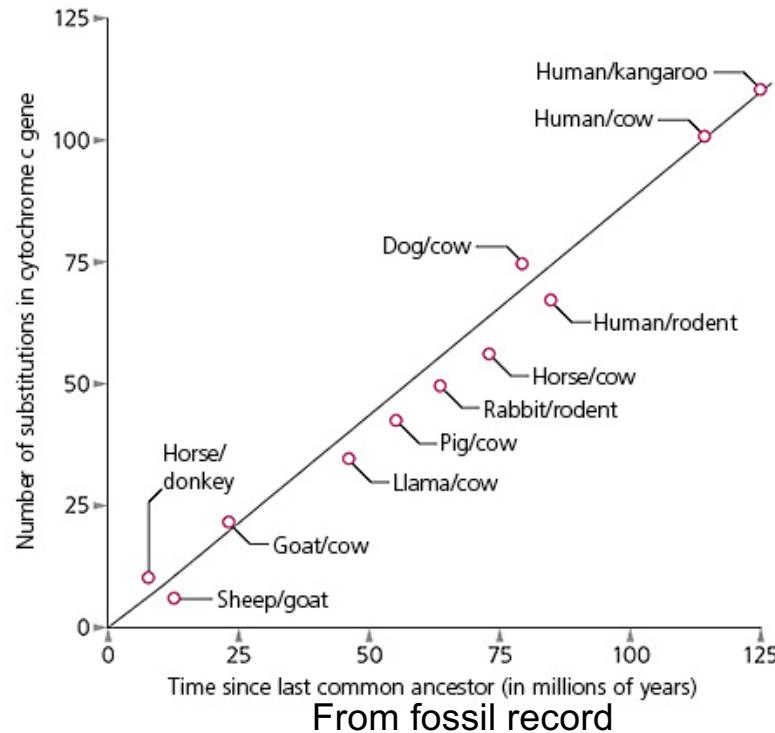
This effect is not strongly seen
in vertebrates



The Molecular Clock

Observation: Rate of **amino acid** substitution in many, but not all, proteins surprisingly constant over time, i.e. evolve in a clock-like manner.

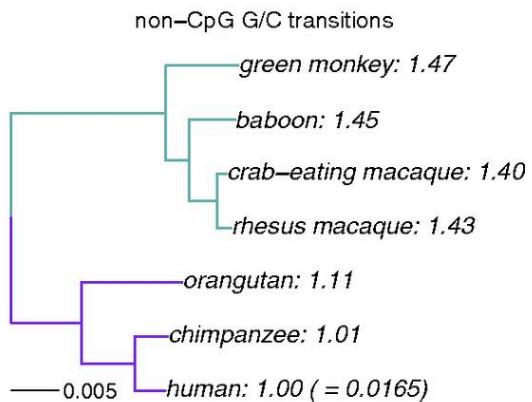
- Neutral theory Claim:** Due to most amino acid replacement substitutions between species being neutral



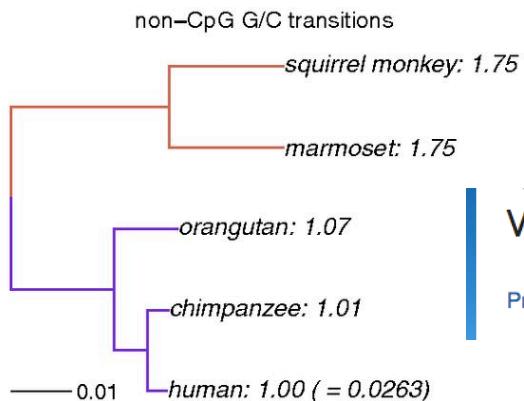
From fossil record

Zimmer book

Generation time effect



Strong generation time effect seen for least constrained sites.
i.e. the changes most likely to be neutral, do not show a molecular clock in years
Non-syn. substitutions show much less of a generation time effect.



Variation in the molecular clock of primates

Priya Moorjani^{a,b,1,2}, Carlos Eduardo G. Amorim^{a,1}, Peter F. Arndt^c, and Molly Przeworski^{a,d,2}

Phylogenograms using mostly non-coding sequence data

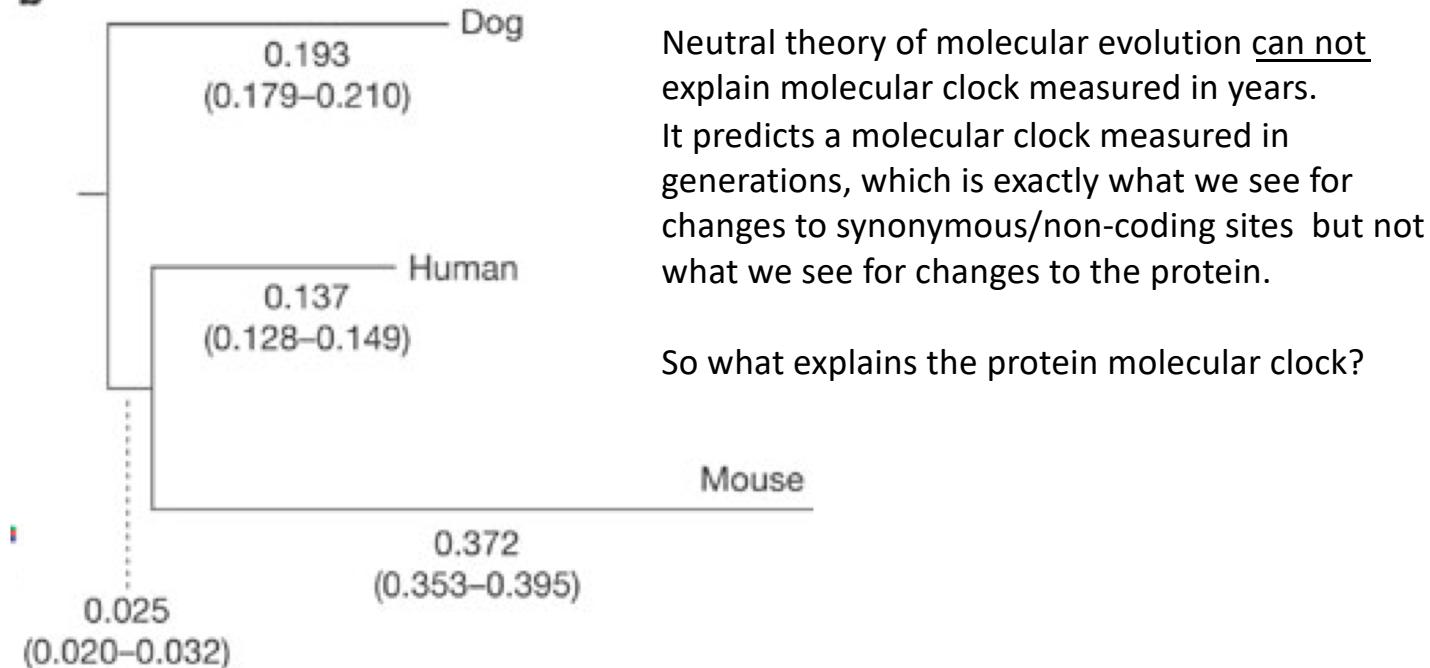
Generation time effect

Strong generation time effect seen for least constrained sites.

i.e. the changes most likely to be neutral, do not show a molecular clock in years

Non-syn. substitutions show much less of a generation time effect.

b



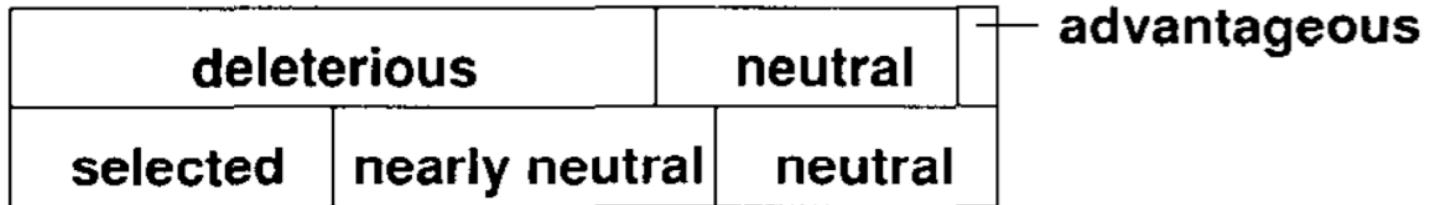
Phylogram from Dog genome paper (Nature 2005)

Using mostly non-coding sequence data



Nearly Neutral theory proposed by Ohta
Perhaps much of molecular evolution
due to substitutions with selection coefficients $|s| \sim 1/(2N_e)$

Simple neutral theory

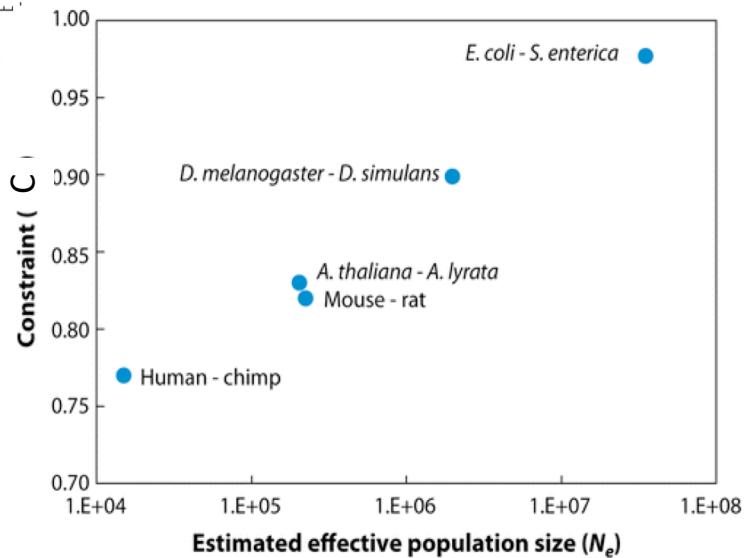
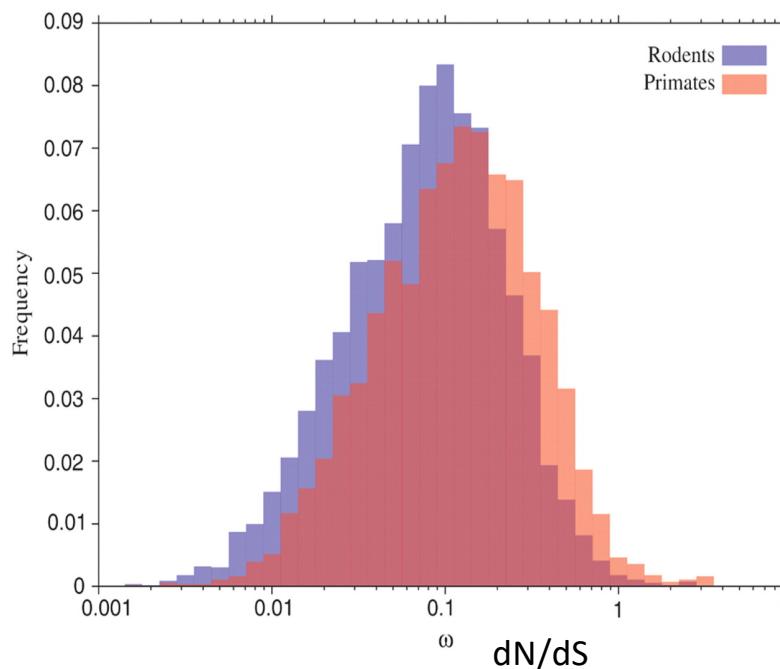


Nearly neutral theory



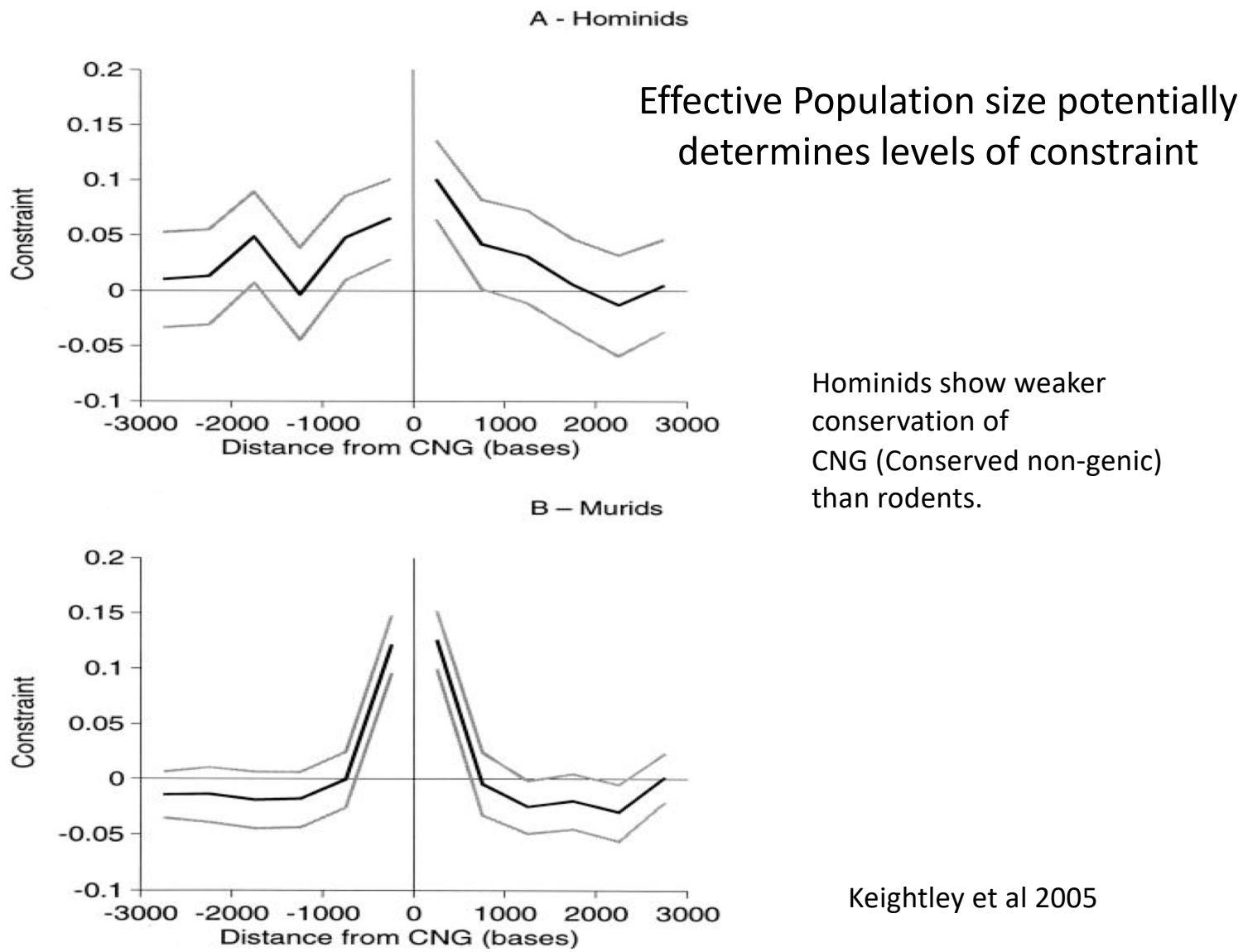
Nearly Neutral theory proposed by Ohta
Perhaps much of molecular evolution
due to substitutions with selection coefficients $|s| \sim 1/(2N_e)$

Effective Population size potentially determines levels of constraint



Wright SI, Andolfatto P. 2008.

Annu. Rev. Ecol. Evol. Syst. 39:193–213



Current status of views on molecular evolution

Most* of the substitutions/polymorphism in non-coding DNA & synonymous changes in organisms with large genomes are likely neutral, as are a reasonable fraction of non-synonymous changes.

Weakly deleterious alleles likely make a significant contribution to substitution rates in species (such as our own) with small effective population sizes.

There is increasing evidence that a reasonable fraction (>10%) of non-synonymous changes are driven by selection in species with large effective population sizes. But the selection coefficients may be very small $\sim 1/(2N_e)$. We have no clue what most of these do!

* --but not all

The Strength of Selection against Neanderthal Introgression

Ivan Juric , Simon Aeschbacher , Graham Coop 

Published: November 8, 2016 • <http://dx.doi.org/10.1371/journal.pgen.1006340>

<http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1006340>



    The New York Times

SCIENCE

Why You Don't Have Much Neanderthal DNA in Your Genome

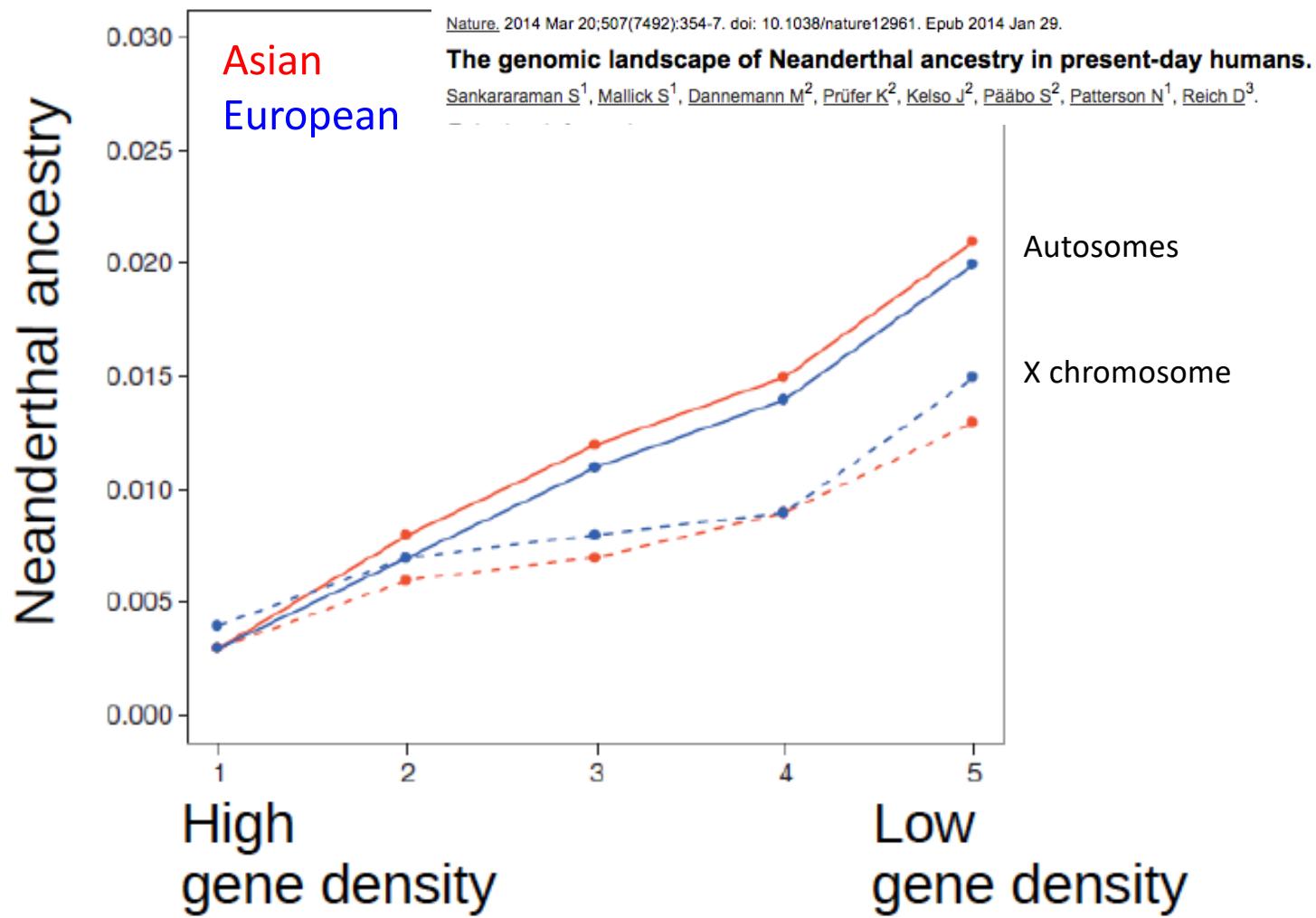
Trilobites

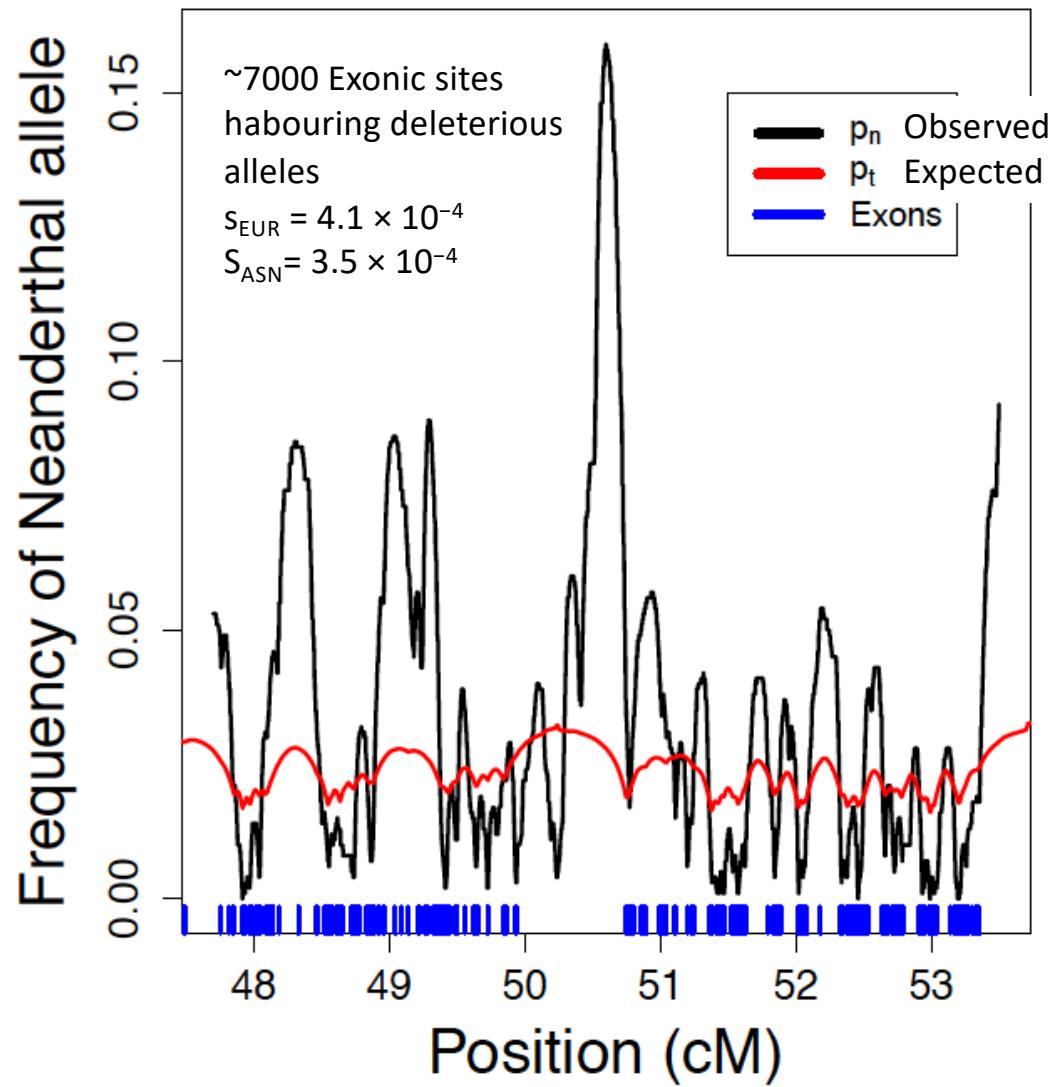


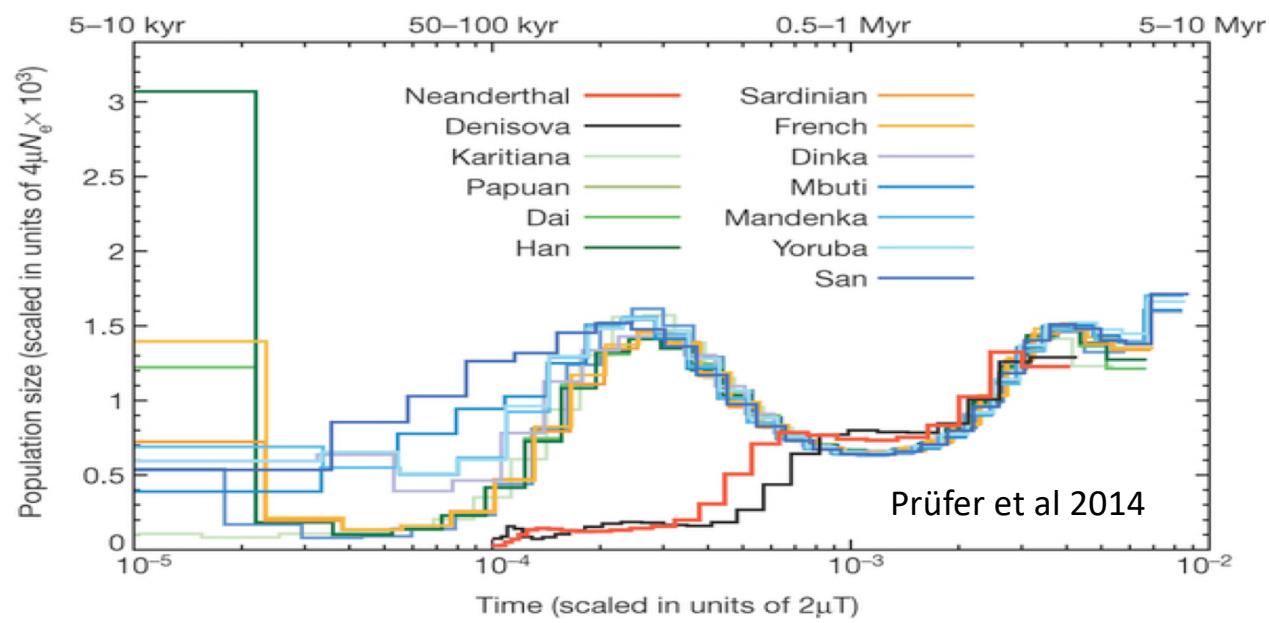
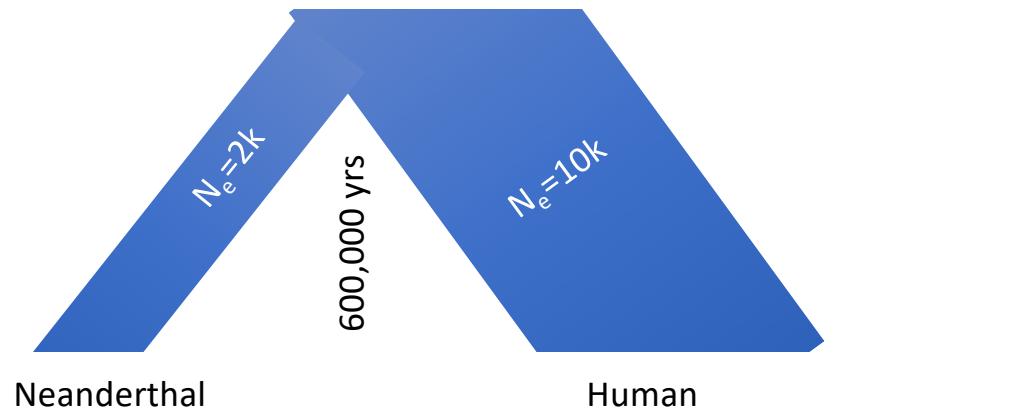
<http://www.nytimes.com/2016/11/09/science/neanderthal-dna-natural-selection.html>

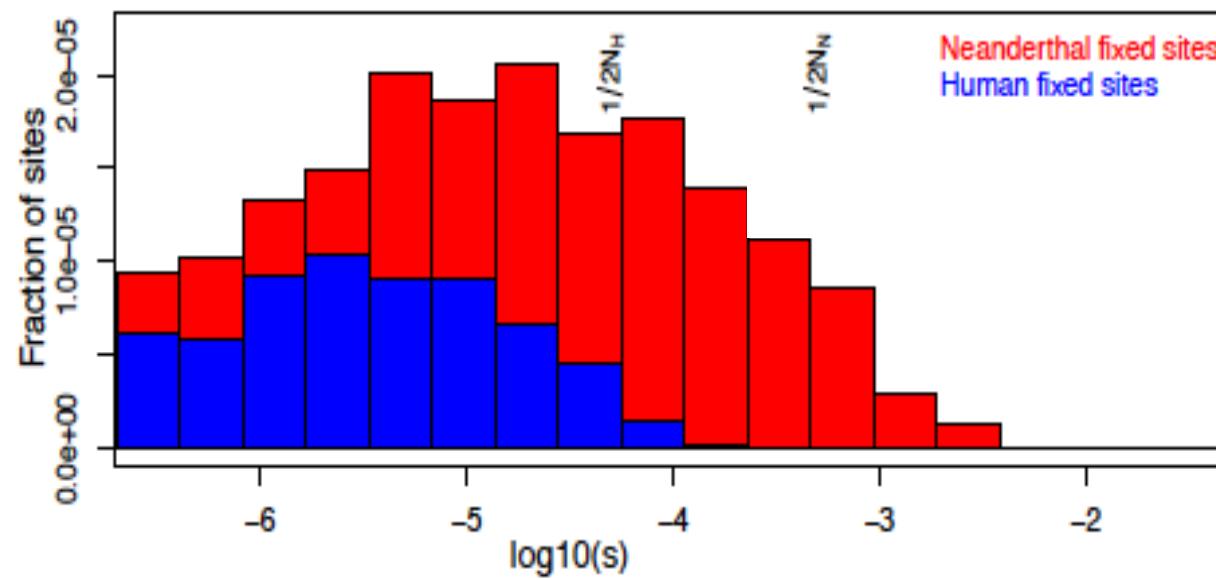
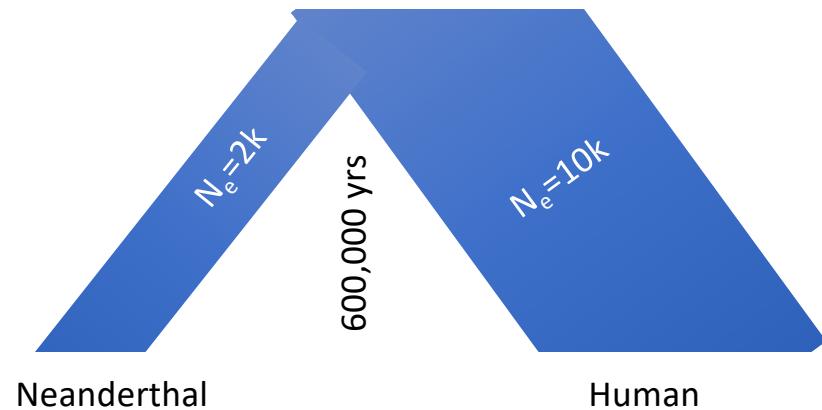
See also Harris & Nielsen 2016

<https://www.flickr.com/photos/hmnh/3033749380/>









Implications

- Levels of Neanderthal introgression are shaped by weakly deleterious alleles.
 - Likely due to nearly neutral alleles drifting up in N.
- Despite being weakly deleterious in aggregate fitness drop many be profound.
- Differences in population size common across closely related species, so these dynamics may be generally important

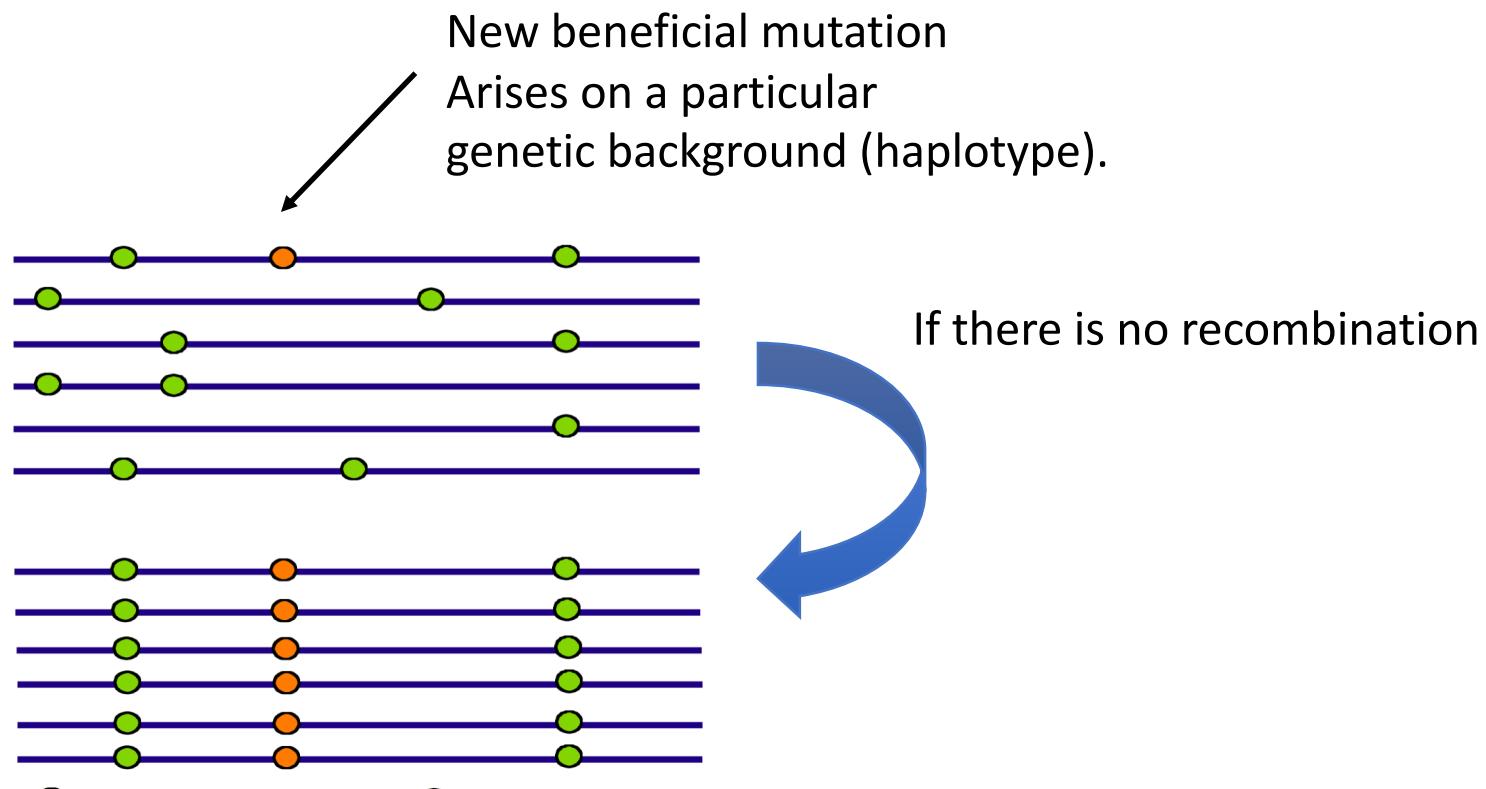
Diversity-reducing selection

Best studied models:

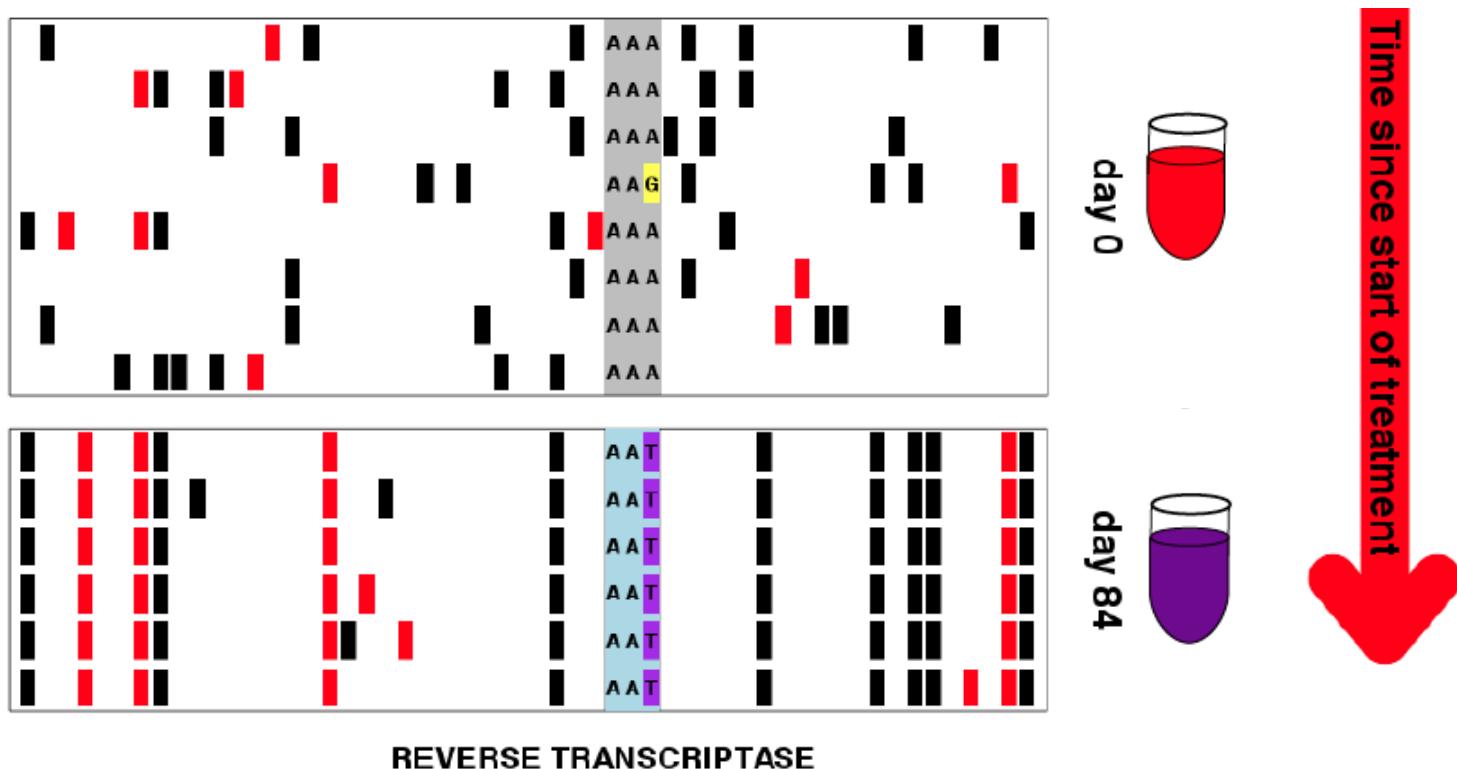
- hitch-hiking models (Maynard-Smith and Haigh 1974; Kaplan et al. 1989)
- background selection models (Charlesworth et al. 1993; Hudson and Kaplan 1994).

The hitchhiking effect:

Indirect impact of selection on patterns of linked diversity



The effect of hitchhiking at the reverse transcriptase gene in HIV in response to drug treatment.

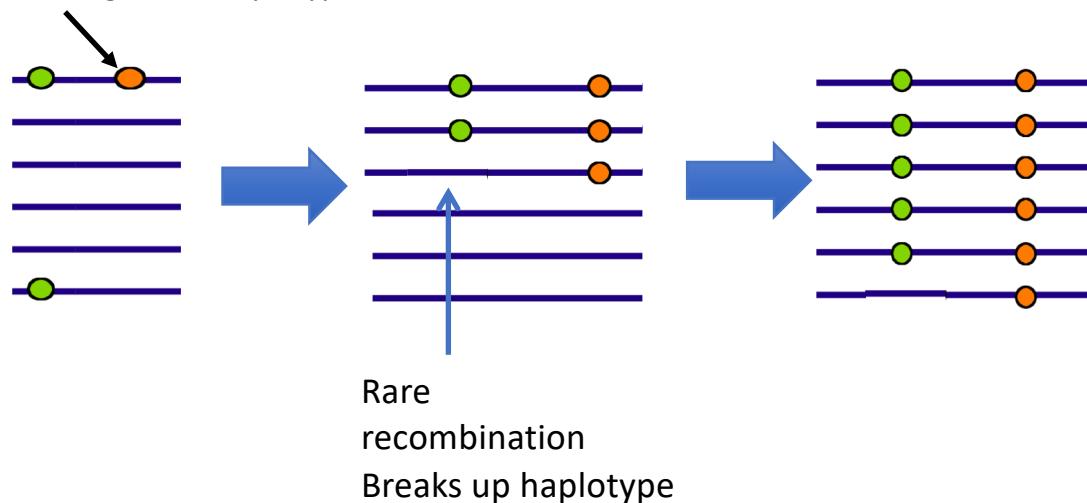


Indirect impact of selection on patterns of diversity

The hitchhiking effect

When recombination occurs

New beneficial mutation
Arises on a particular
genetic background (haplotype).



A haplotype a set of alleles physically linked on a chromosome