

$$k(s) = 2N\mu \frac{1 - e^{-s}}{1 - e^{-2Ns}}$$

substitution

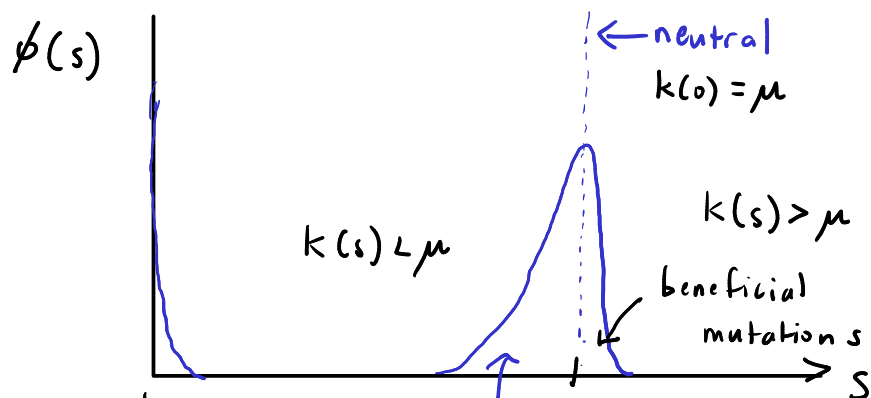
rate of a mutation

w/ selection coeff. s

$$k(0) = \mu$$

$\phi(s)$ = distribution of fitness effects (DFE)

= prob. that a random mutation at locus of interest has sel. coeff. s



things that kill you

mutations that slightly mess you up

$$s = \frac{f_{mut}}{f_{wt}} - 1$$

$$f_{mut} = 0 \Rightarrow s = -1$$

strategy: take two indep. lineages (humans vs. orangutans)

compare: mean substitution rate for synonymous sites

$$\bar{k}_{syn} = \mu$$

mean substitution for non-synonymous sites

$$\bar{k}_{non-syn} = \int ds \phi(s) k(s)$$

estimated
ratio

$$\omega = \frac{dN}{ds} = \frac{\overline{k}_{\text{non-syn}}}{\overline{k}_{\text{syn}}} \approx 0.25$$

for
humans

$\Rightarrow$ direct evidence that $\phi(s)$
is skewed toward deleterious
mutations

$\Rightarrow$ most selection is "purifying":
essentially removing freq.
deleterious mutations from popul.

$\Rightarrow$ however some of these
(slightly) deleterious mutations
will fix