Fixation probability of a beneficial mutant when deleterious effects are weak

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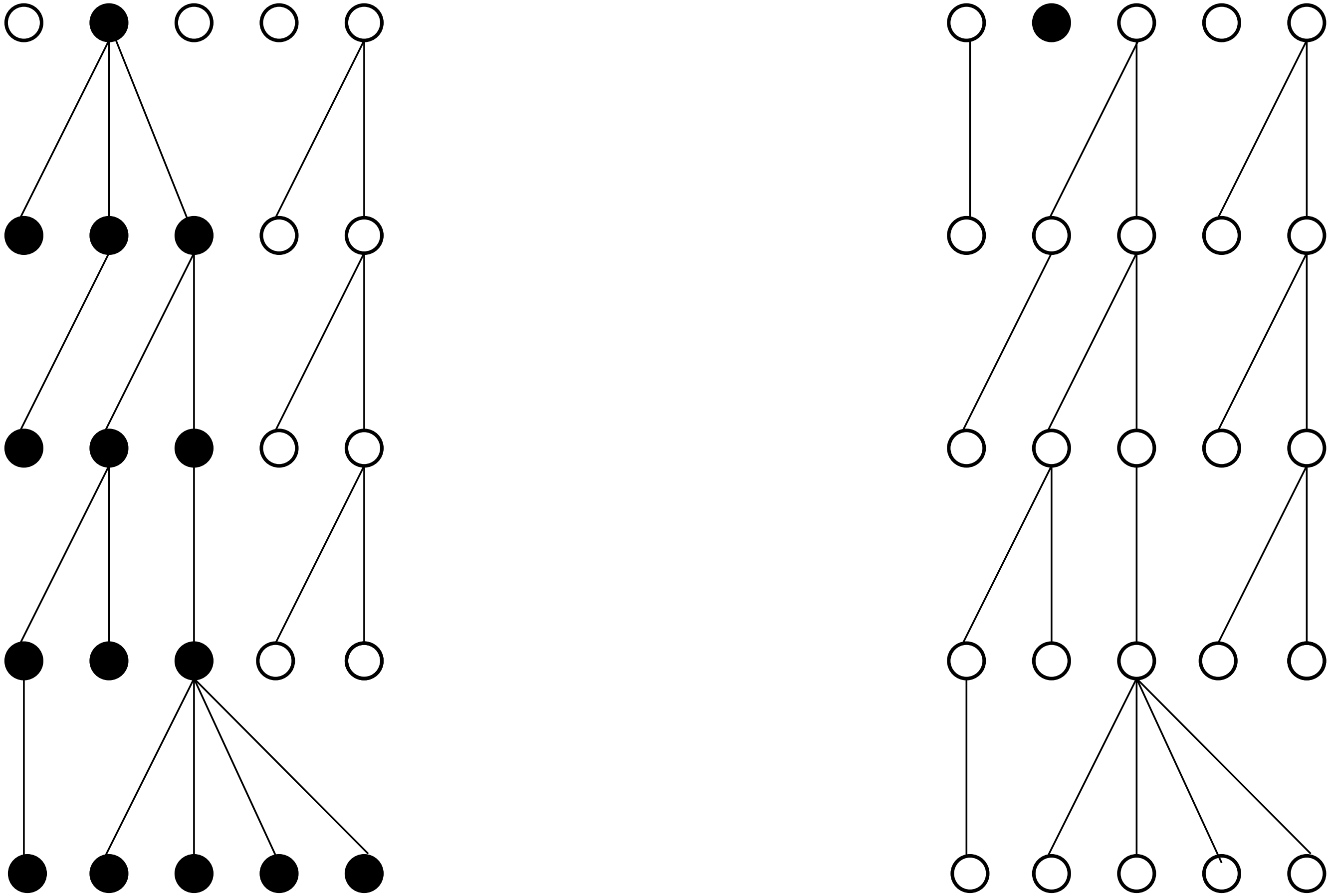
What happens when a new mutant appears in a population?



Fixation probability: Direct selection

- large but finite population
- asexuals
- sequence is infinitely long
- deleterious mutations at rate U_d
- each mutation decreases fitness by a factor $1 - s_d$

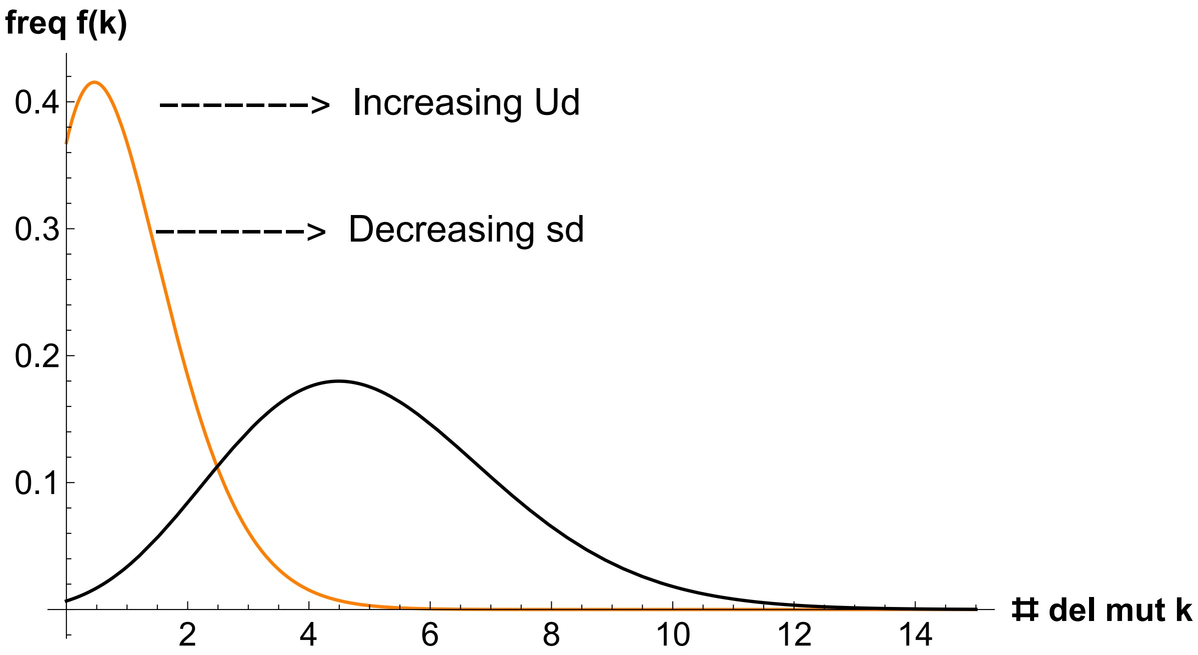
Mutation-selection balance at large times

If population is very large, we can ignore genetic drift

del. mutation will lower fitness BUT selection will oppose this

$f(k)$=population frequency with k deleterious mutations

$$\text{Mean, } \bar{k} = U_d/s_d$$



Fixation probability

Now imagine that one of the individual acquires a beneficial mutation

- This happens at a rate U_b
- Increases the fitness by a factor $1 + s_b$

This rare beneficial mutation can get lost due to stochastic fluctuations

What is the probability P_{fix} that it spreads?

When deleterious effects are strong ($s_d \gg s_b$)

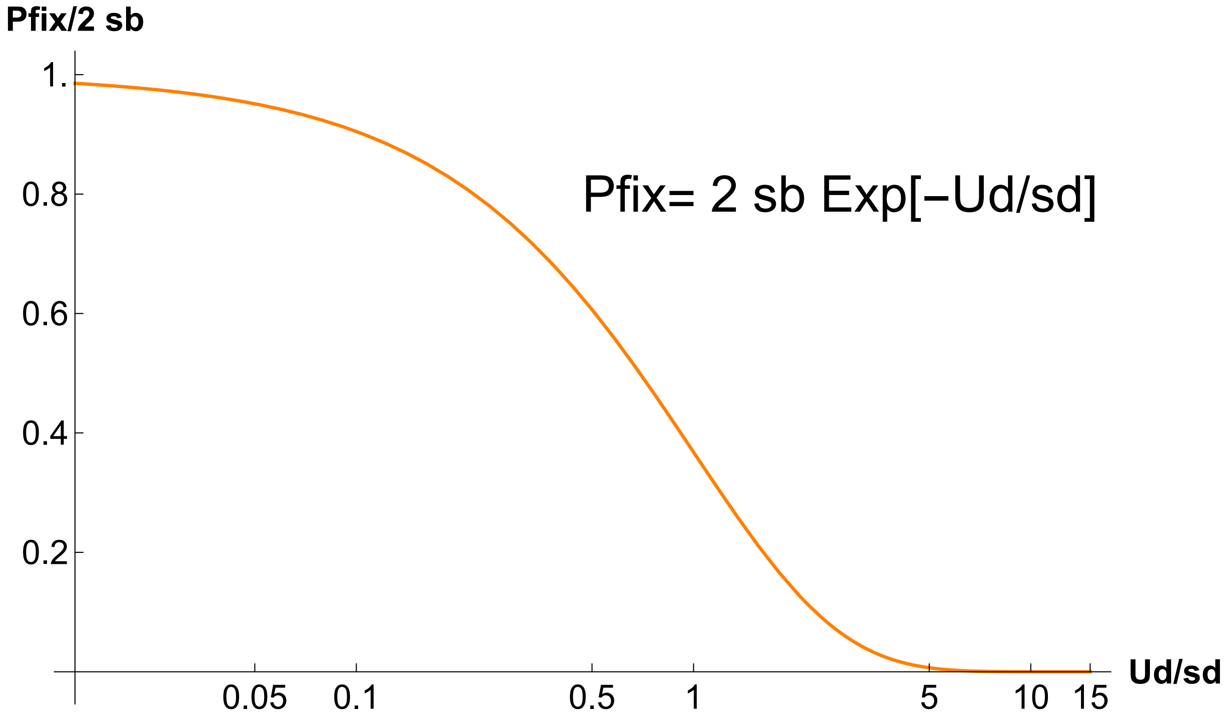
- If no deleterious mutations ($U_d = 0$) (Haldane)

$$P_{fix} = 2s_b$$

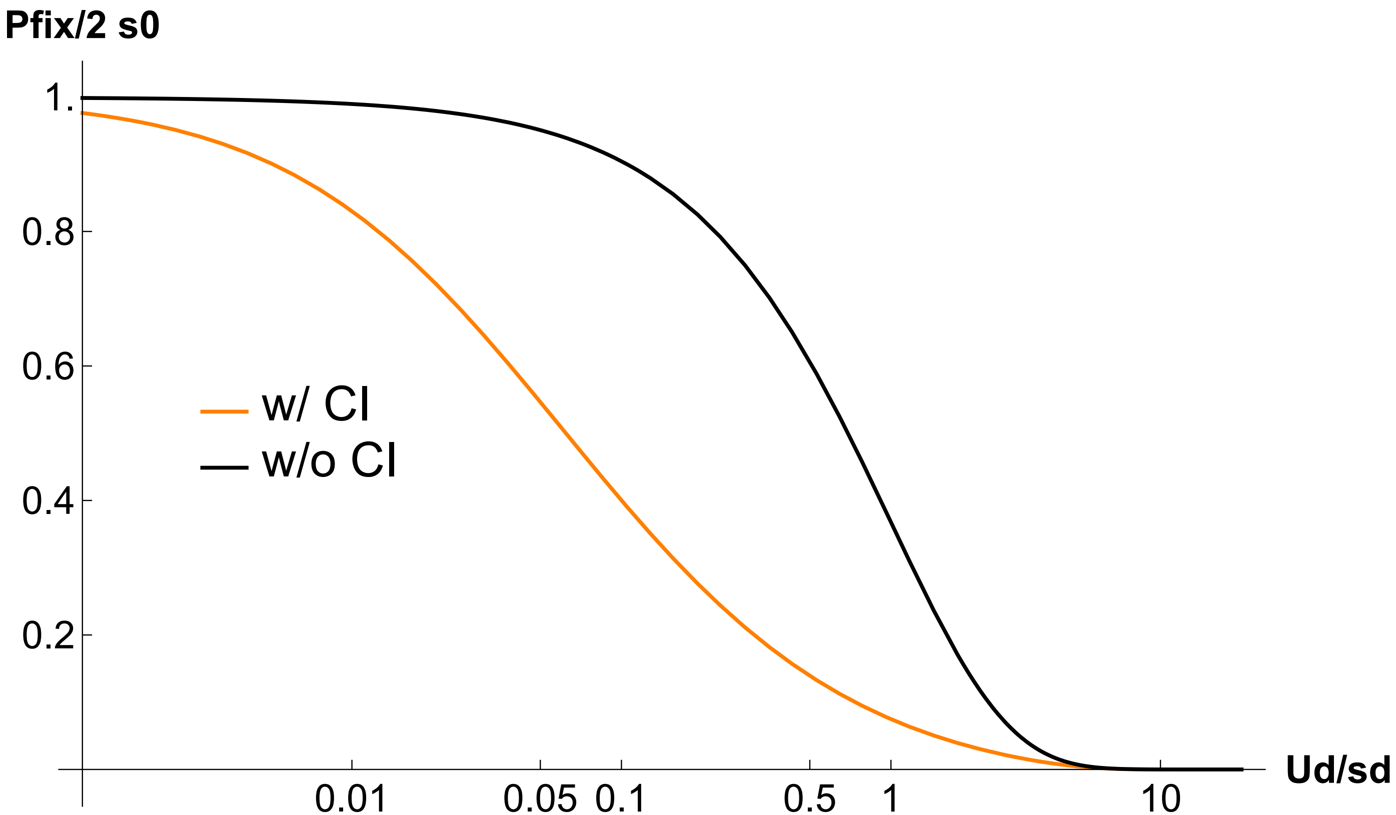
- When deleterious mutations occur and have strong effect, beneficial mutation survives if it arises in individuals with no deleterious mutations (Peck; Orr)

$$P_{fix} = 2s_b f(0) = 2s_b e^{-U_d/s_d}$$

- as expected, deleterious mutations decrease fixation probability



- when many beneficial mutations occur, a better mutant can arise and compete (Gerrish & Lenski; Orr)



Clonal interference decreases fixation probability further

When deleterious effects are weak ($s_d \ll s_b$)

- When deleterious mutations have weak effect, beneficial mutation can survive in many backgrounds. How many? (Johnson & Barton)

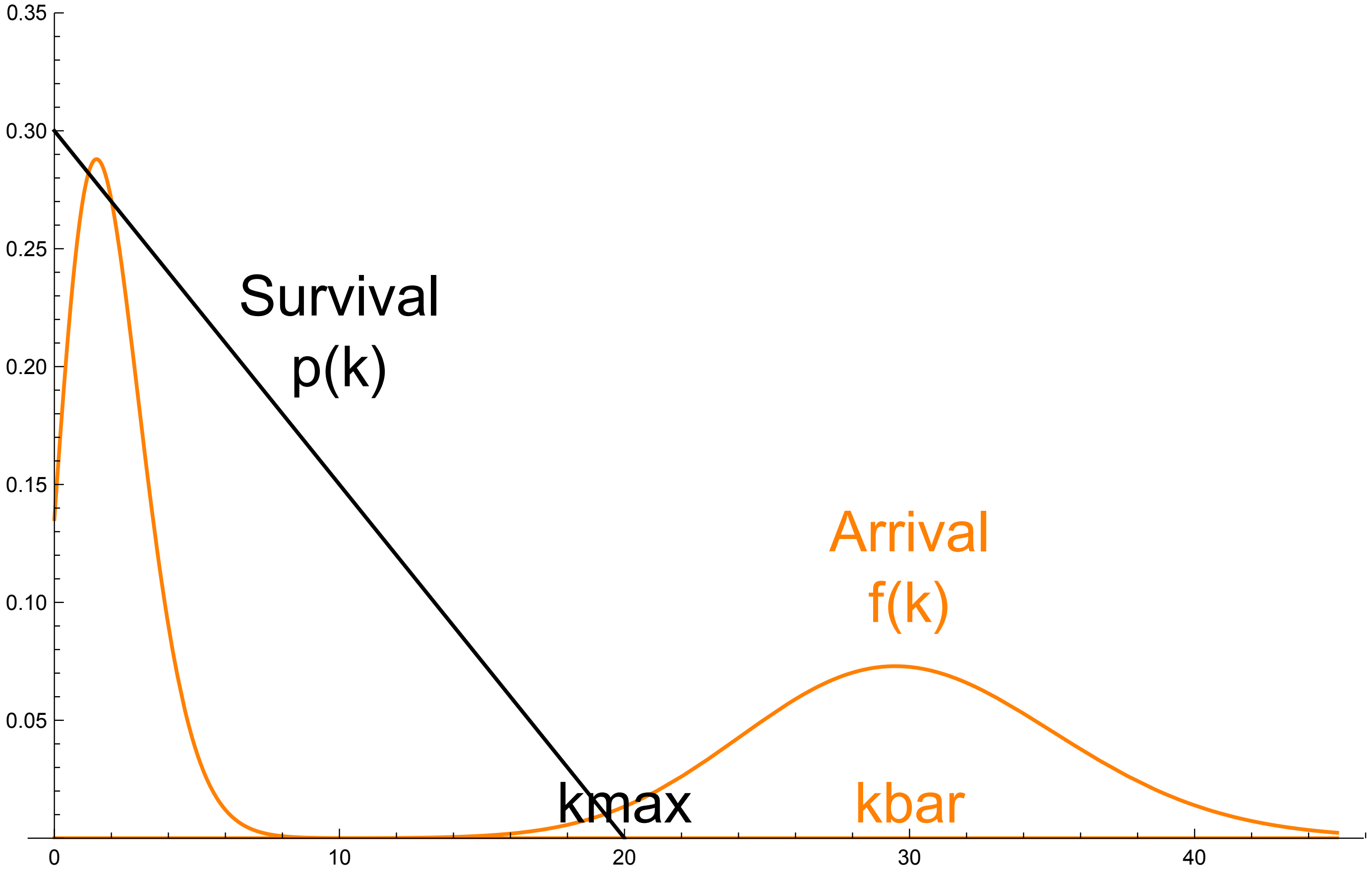
$$k_{\max} = s_b / s_d$$

- But not all of these backgrounds are important

  Since the background frequency is Poisson-distributed, the beneficial mutation is likely to arrive in backgrounds with

$$\bar{k} - \sqrt{\bar{k}} < k < \bar{k} + \sqrt{\bar{k}}$$

Arrival and Survival



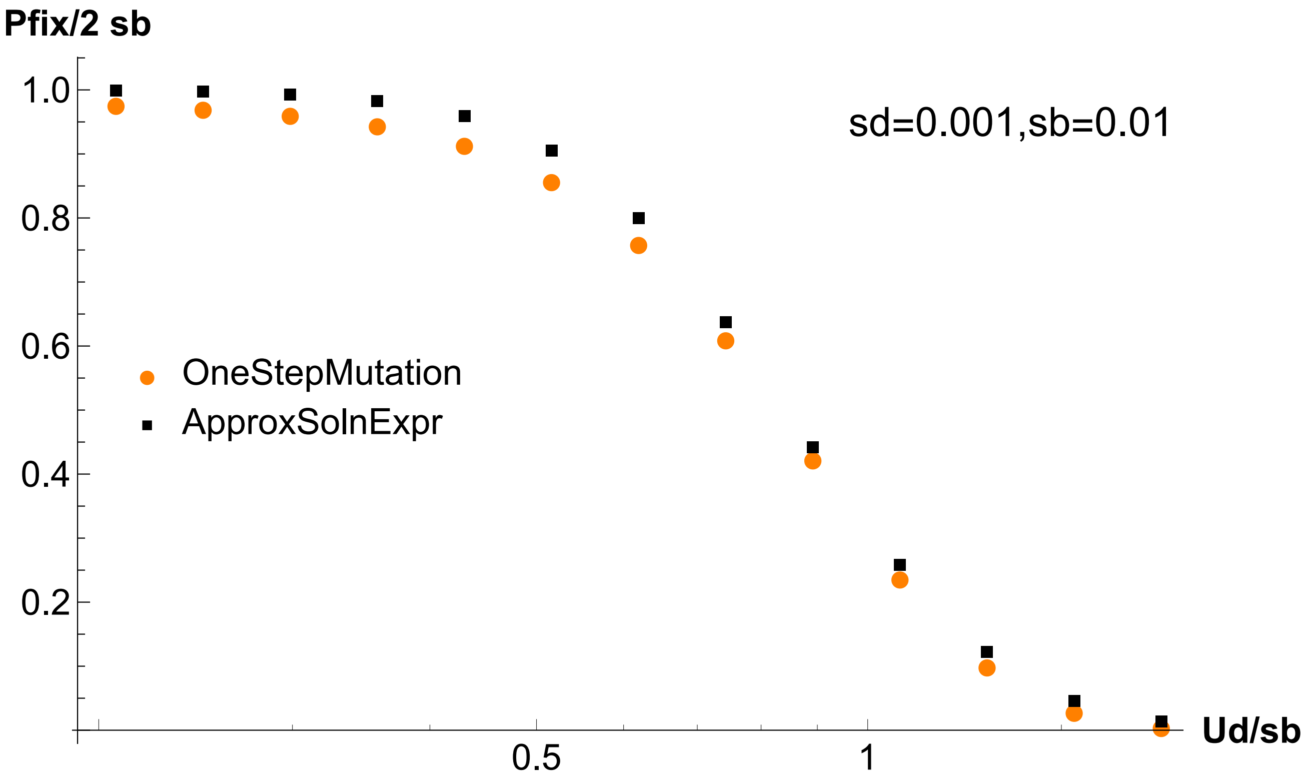
If $k_{\max} \gg \bar{k} + \sqrt{\bar{k}}$

$$P_{fix} \to 2s_b$$

If $k_{\max} \ll \bar{k} - \sqrt{\bar{k}}$

$$P_{fix} \to 0$$

- As before, deleterious mutations decrease fixation probability

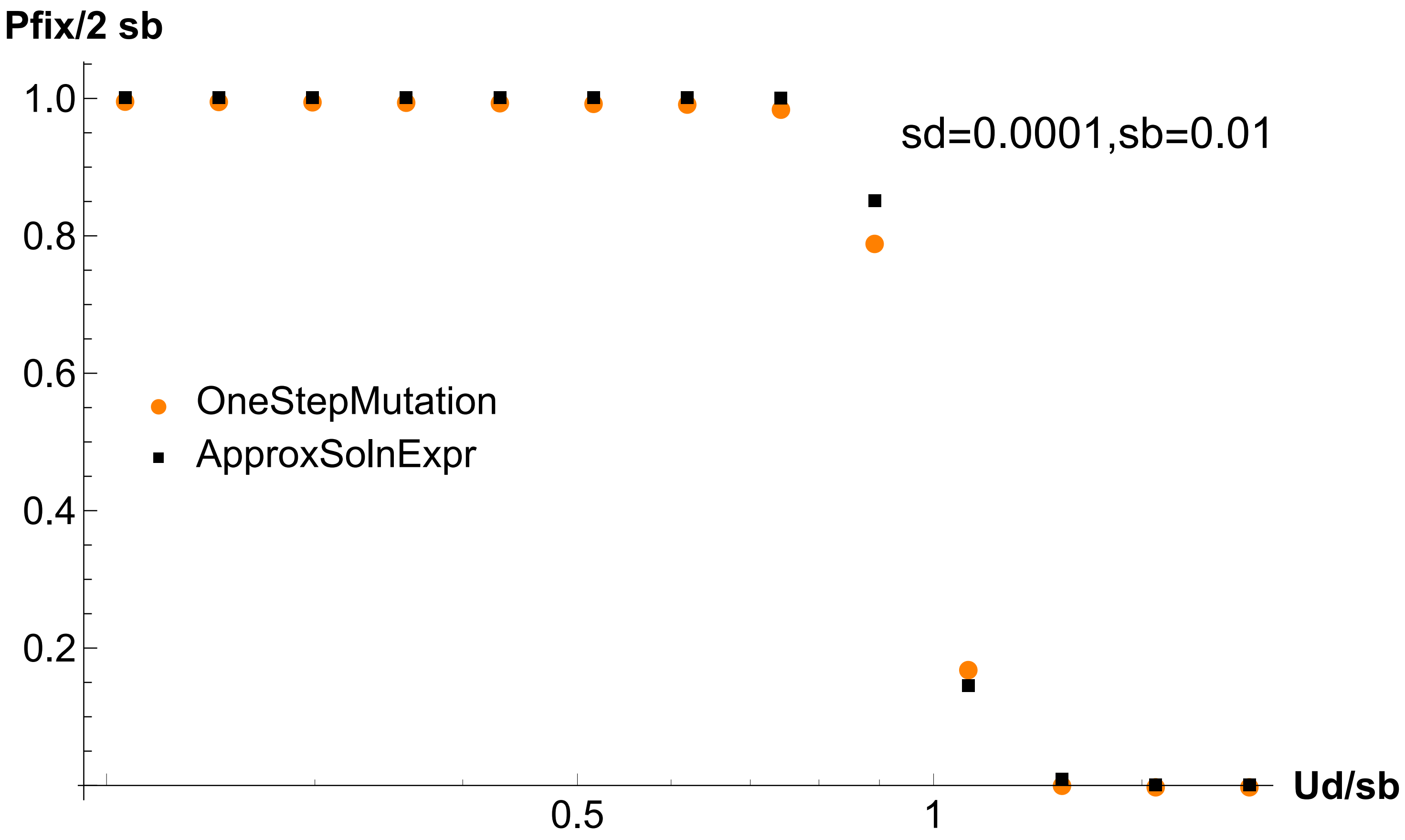


- Width decreases with decreasing s_d

$$\text{If } k_{\max} \gg \bar{k} + \sqrt{\bar{k}}$$
$$\text{or, } s_b \gg U_d + \sqrt{U_d s_d}$$
$$P_{fix} \to 2s_b$$

$$\text{If } k_{\max} \ll \bar{k} - \sqrt{\bar{k}}$$
$$\text{or, } s_b \ll U_d - \sqrt{U_d s_d}$$
$$P_{fix} \to 0$$

Sharp transition at $U_d = s_b$ when $s_d \to 0$ (Penisson et al.)



When deleterious effects are very weak, high mutation rate inhibits fixation

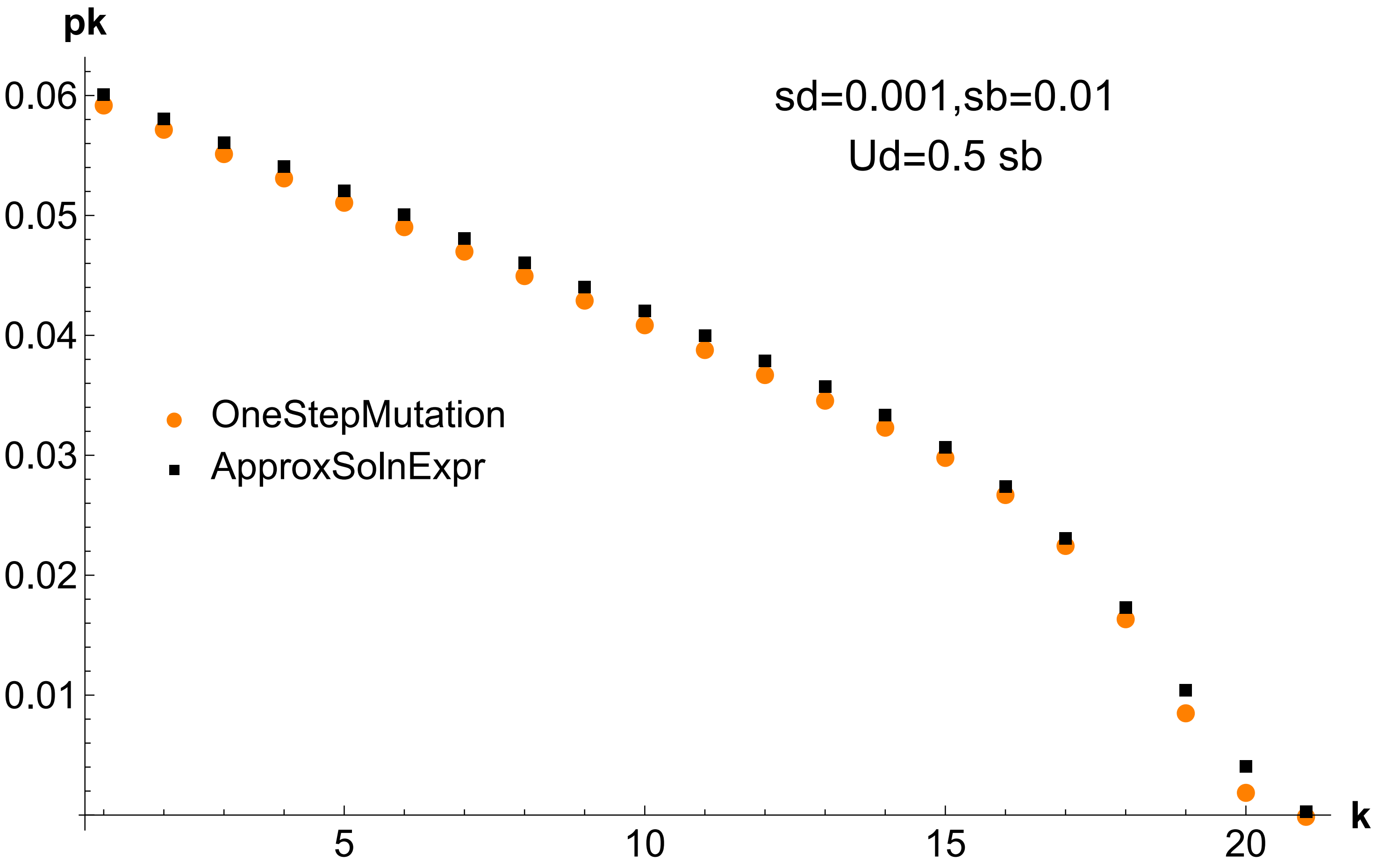
Branching process: quadratic approximation (Haldane)

$p(k)$=fixation probability when background has k del mutations

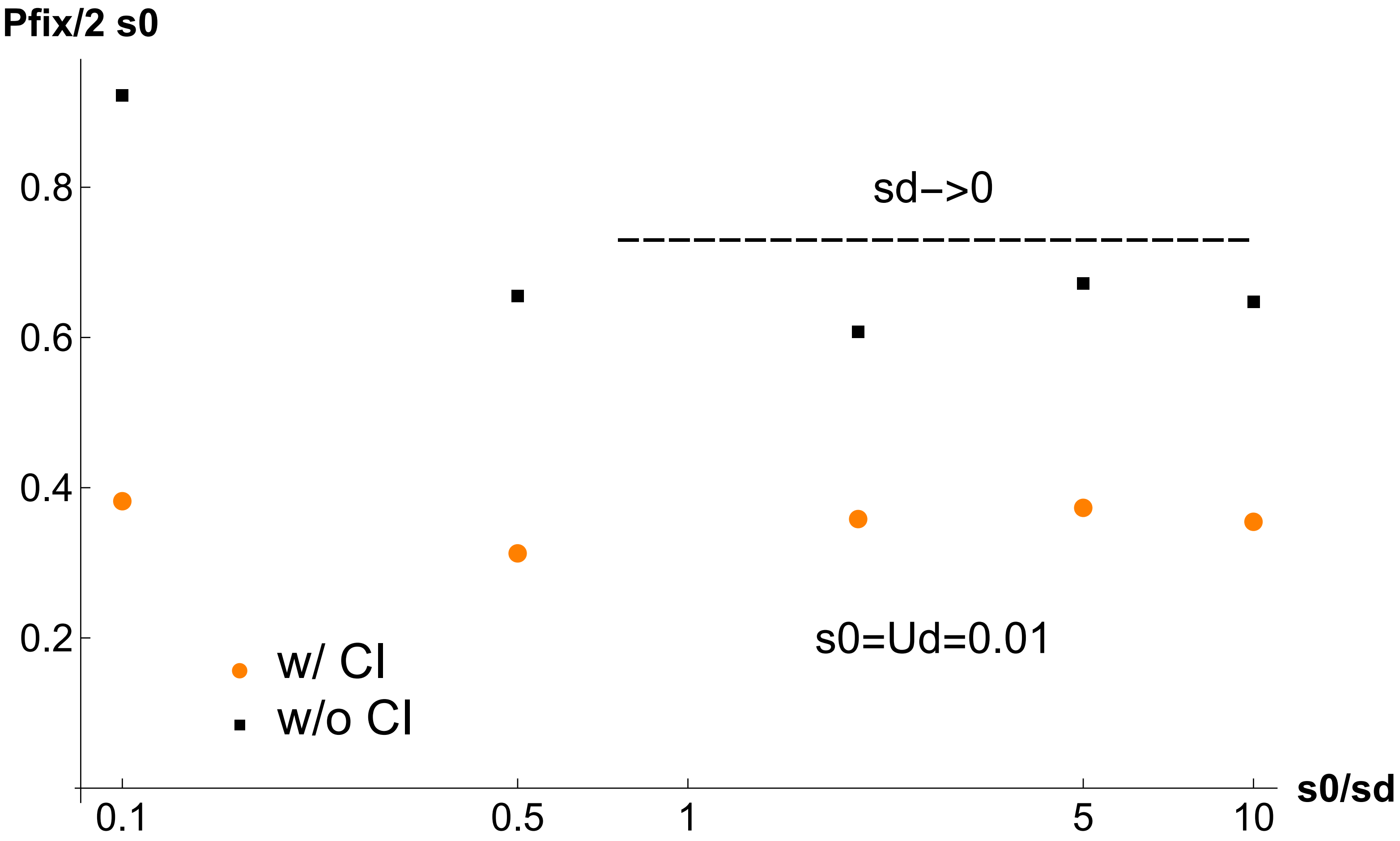
$$q^2(k) = \frac{U_d}{s_b} q(k+1) + \left(1 - \frac{k}{k_{\max}}\right) q(k)$$

Approximate solution when $s_d < U_d$

$$\frac{p(k)}{2s_b} \approx 1 - \underbrace{\frac{k}{k_{\max}}}_{\text{linear}} + \frac{U_d}{s_b} \underbrace{\left(\frac{1}{k_{\max}}\right)^{2^{k-k_{\max}+1}}}_{\text{double-exponential}}$$


pk
0.06
0.05
0.04
0.03
0.02
0.01
k
5
10
15
20
sd=0.001,sb=0.01
Ud=0.5 sb
● OneStepMutation
■ ApproxSolnExpr

When is clonal interference more important?



Almost constant drop when many relevant backgrounds

Fixation probability : Indirect selection

As before,

- Large asexual population at mutation-selection equilibrium
- Deleterious mutations occur at a rate U_d
- Each mutation decreases fitness by a factor $1 - s_d$

But now the invader is a nonmutator

- Deleterious mutations occur at a rate $u_d < U_d$
- Each mutation decreases fitness by a factor $1 - s_d$

When deleterious effects are strong ($s_d \gg U_d$) (Lynch et al.)

- In analogy to Haldane's result, here

$$P_{fix} = 2(e^{-U_d} - e^{-u_d}) \approx 2(U_d - u_d)$$

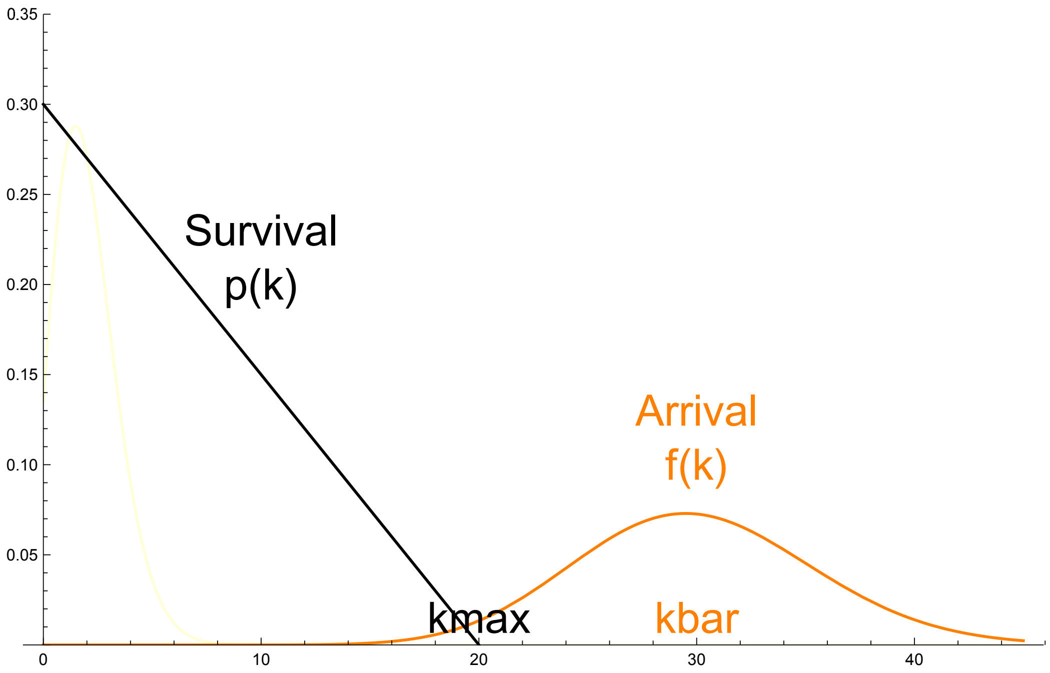
- In a population of (effective) size N, mutation rates keep evolving until selection is rendered neutral

$$U \sim N^{-1}$$

Larger populations have smaller mutation rates

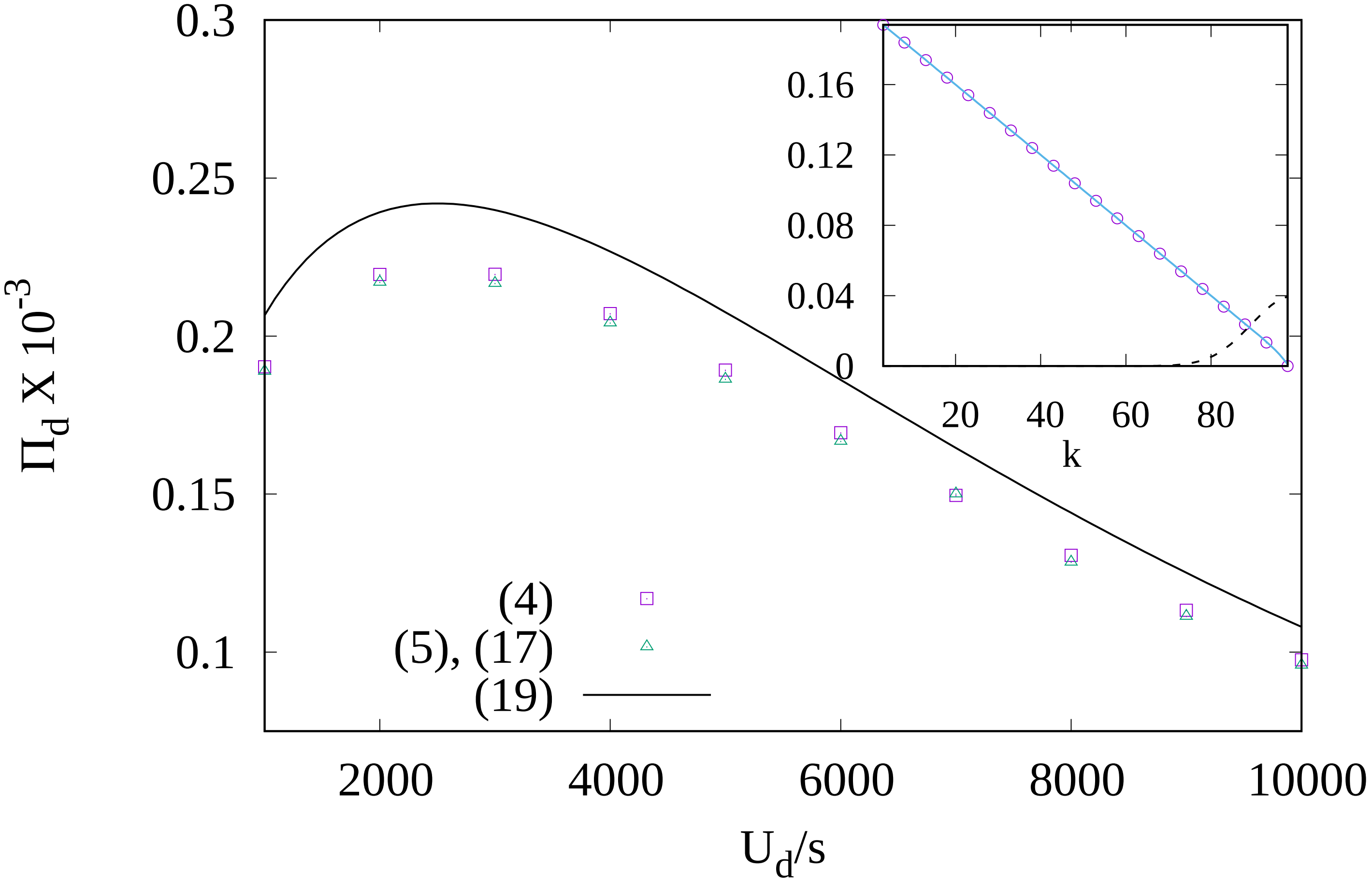
When deleterious effects are weak ($s_d \gg U_d$) (James & KJ; KJ & James)

- Here $k_{\max} = \delta U_d / s_d, \bar{k} = U_d / s_d$ so that $k_{\max} < \bar{k}$



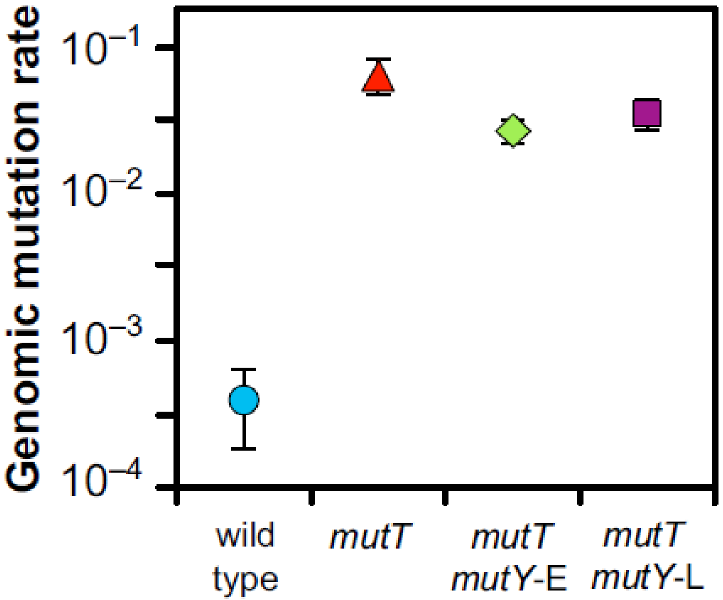
- $P_{fix} \to 0$ when $k_{\max} \ll \bar{k} - \sqrt{\bar{k}}$
- Also in the opposite limit since $k_{\max} < \bar{k}$ (“no room”)

$$\frac{P_{fix}}{2s_d} \sim \sqrt{\frac{U_d}{s_d}}\, e^{-\frac{U_d}{2\lambda^2 s_d}} \ , \ \lambda = U_d/u_d$$



Fall of mutation rates in adapted population

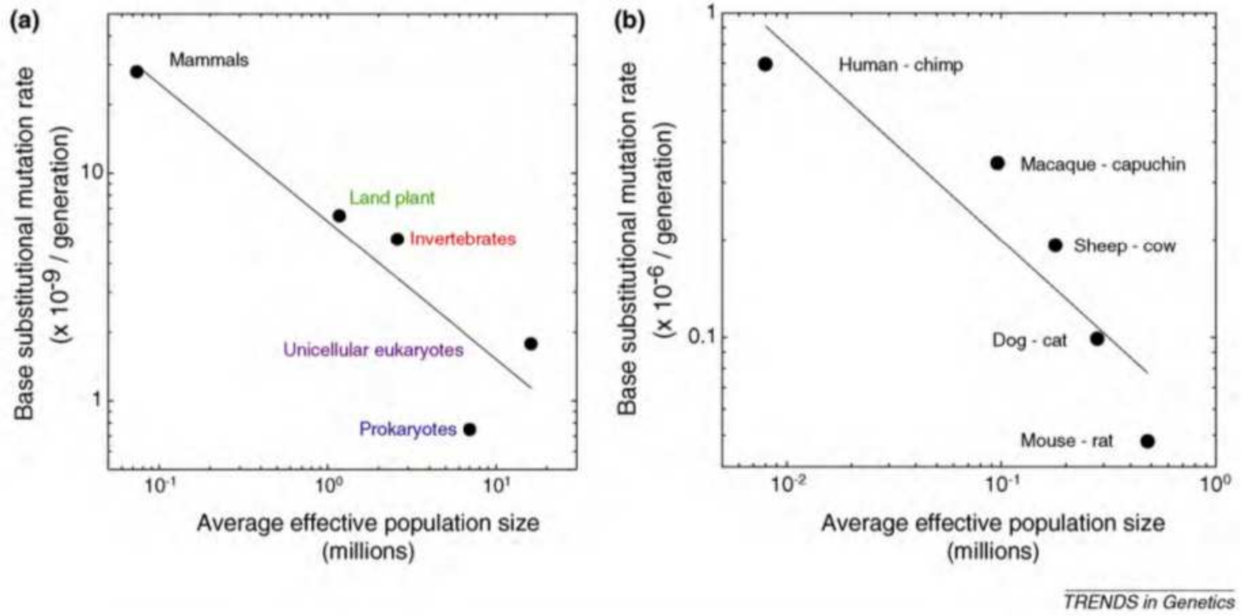
Nonmutator of strength $\lambda \sim \sqrt{U_d/s_d}$ most likely to fix



- Lenski data: $U_d = 0.03, \lambda = 2 \implies s_d \sim 10^{-2}$ (Wielgoss et al. 2013)
- For weak selection $(10^{-4} - 10^{-2})$ and high mutation rates $\sim 10^{-2}$, small reduction in mutation rate is expected

Lower bound on mutation rates

$$U_d \propto \begin{cases} N^{-1} & , \ s_d \gg U_d \quad \text{(strong del effect)} \\ s_d^{-1} N^{-2} & , \ s_d \ll U_d \quad \text{(weak del effect)} \end{cases}$$



Assuming a single law, $U_d \sim N^{-\beta}$, $\beta = 0.7 - 0.9$ (Sung et al., 2012)

Take home message

Some results beyond the canonical “2 s”

Work in progress

Build upon these results to answer questions about

- rate of adaptation
- effect of clonal interference etc...