

Recombination and the undesirable hitchhiker



Sally Otto & Matthew Hartfield

Department of Zoology
&
Biodiversity Research Centre
University of British Columbia

Institute of
Evolutionary Biology
University of Edinburgh

Recombination and the hitchhiker

An important advantage of sex and recombination is that they allow beneficial alleles to escape from surrounding harmful alleles.

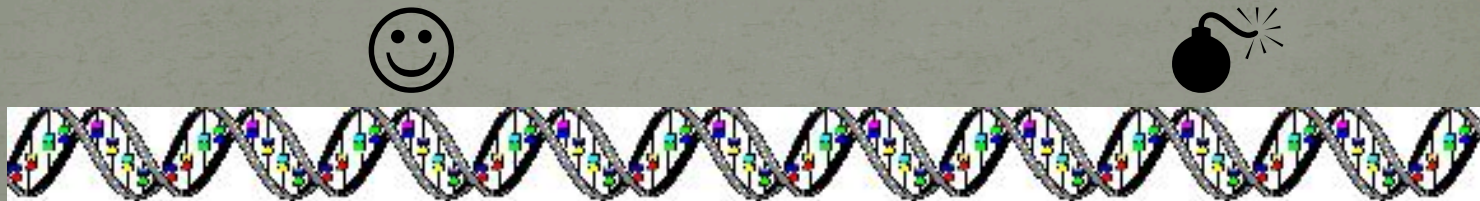
Fisher 1930; Peck 1996; Otto & Barton 1997



Recombination and the hitchhiker

New beneficial mutations are likely to arise with deleterious alleles at some neighboring site.

If the beneficial allele rises to fixation fast enough, and recombination is rare enough, then both alleles will become fixed.

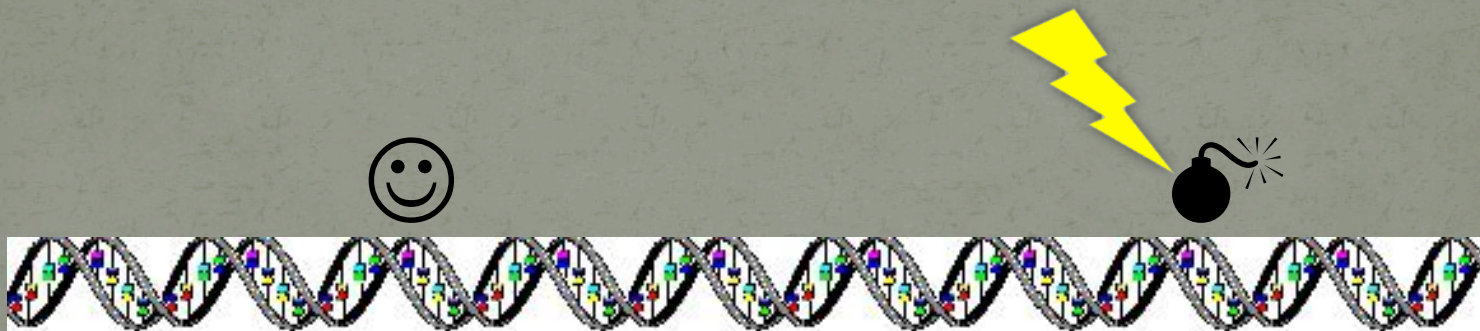


➔ Making it difficult to determine which site was under selection

Recombination and the hitchhiker



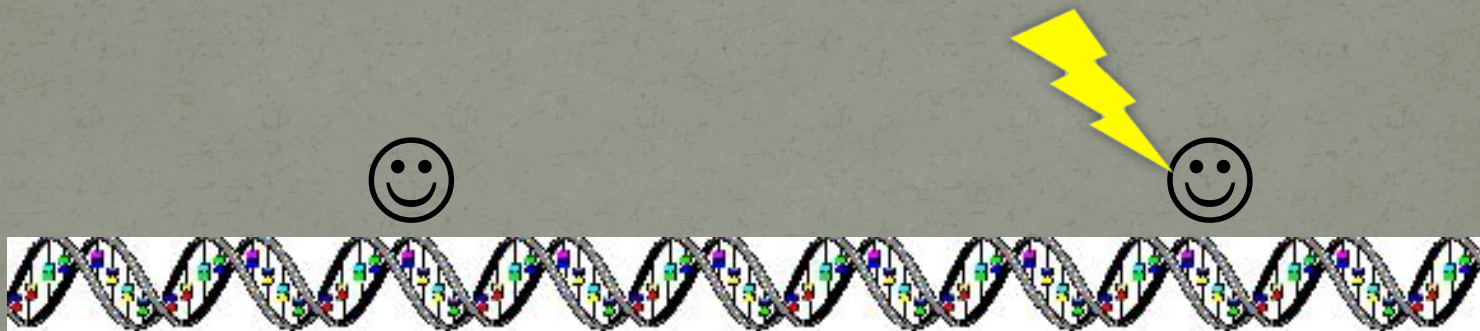
Once fixed, the population will have to wait for a compensatory mutation to occur to eliminate the deleterious hitchhiker.



Recombination and the hitchhiker



Once fixed, the population will have to wait for a compensatory mutation to occur to eliminate the deleterious hitchhiker.



➔ Causing a fixed mutation load until this occurs

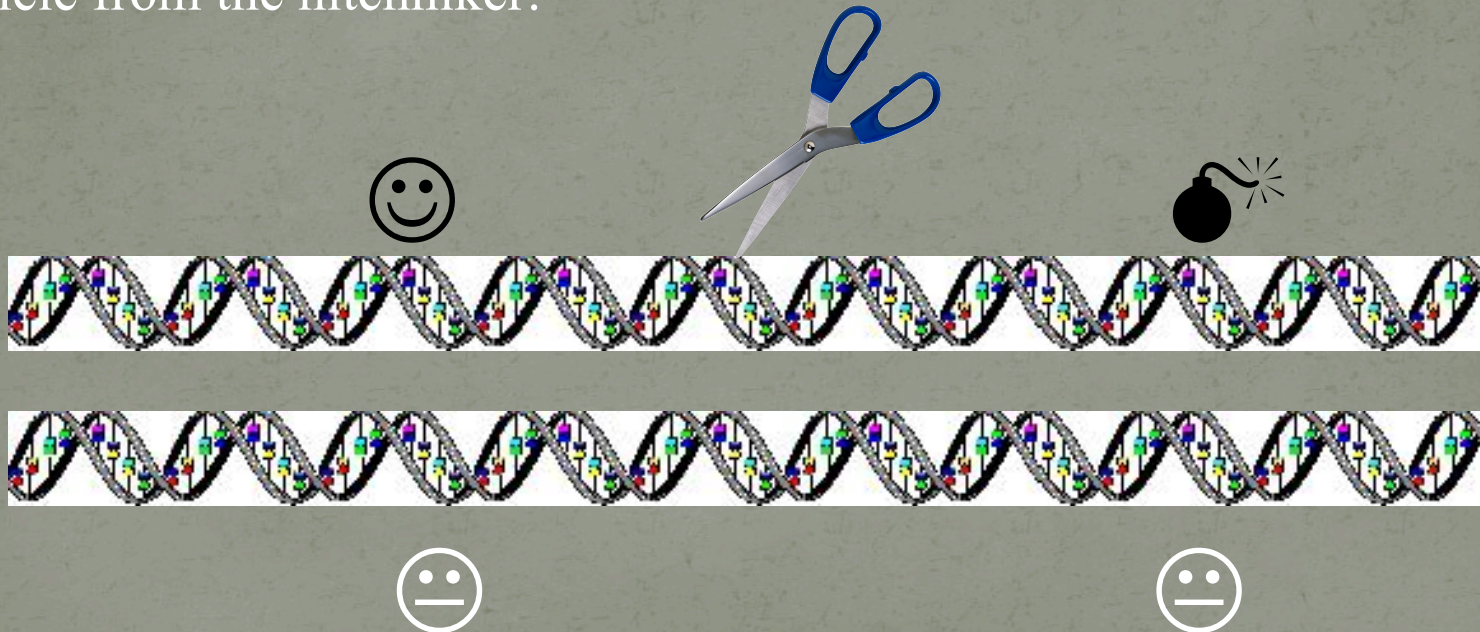
Recombination and the hitchhiker

Recombination can, however, uncouple the beneficial allele from the hitchhiker:



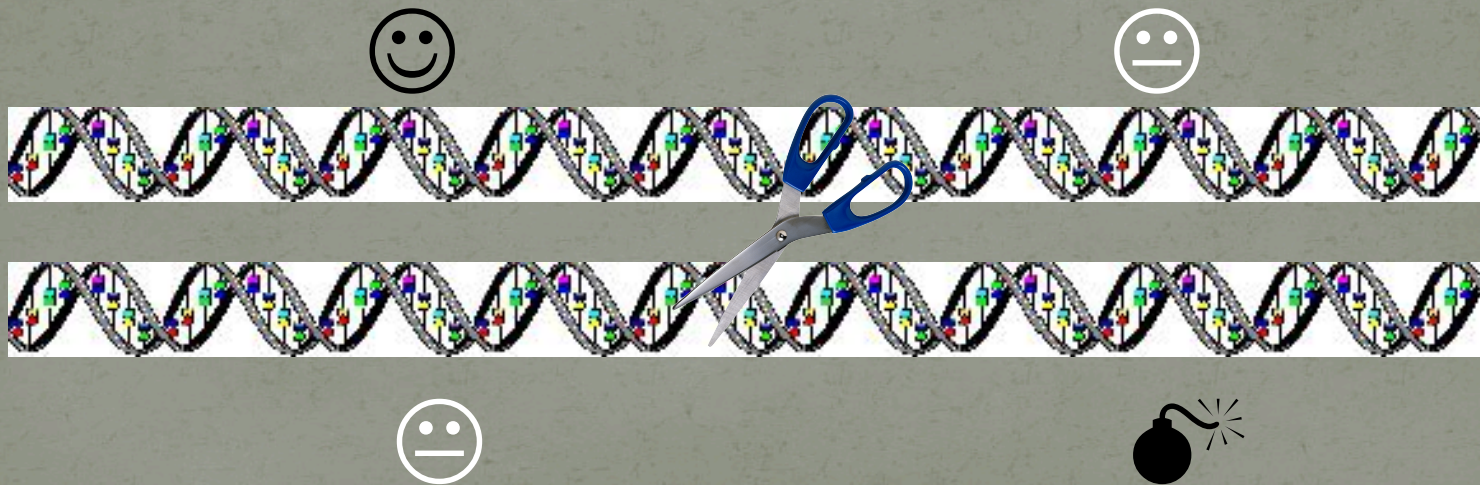
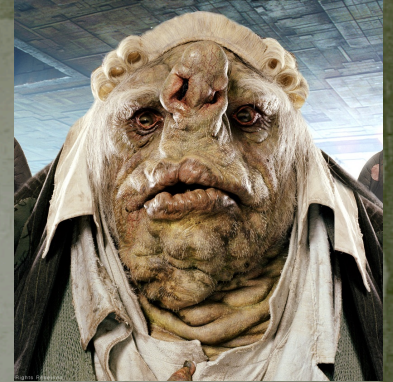
Recombination and the hitchhiker

Recombination can, however, uncouple the beneficial allele from the hitchhiker:



Recombination and the hitchhiker

Recombination can, however, uncouple the beneficial allele from the hitchhiker:



Recombination and the hitchhiker



What is the chance that recombination fails to uncouple a beneficial allele from a deleterious hitchhiker?

- ➔ Making it difficult to determine which site was under selection
- ➔ Causing a fixed mutation load until this occurs

Recombination and the hitchhiker

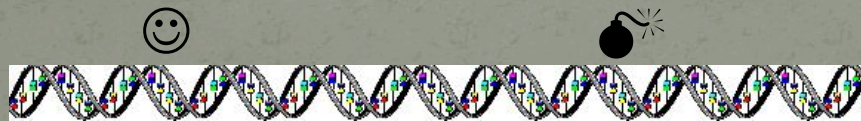
We constructed a haploid model to address this issue.



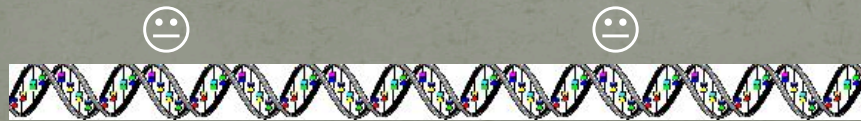
Fitnesses:



$$1 + s_a$$



$$1 + s_a - s_d$$



$$1$$



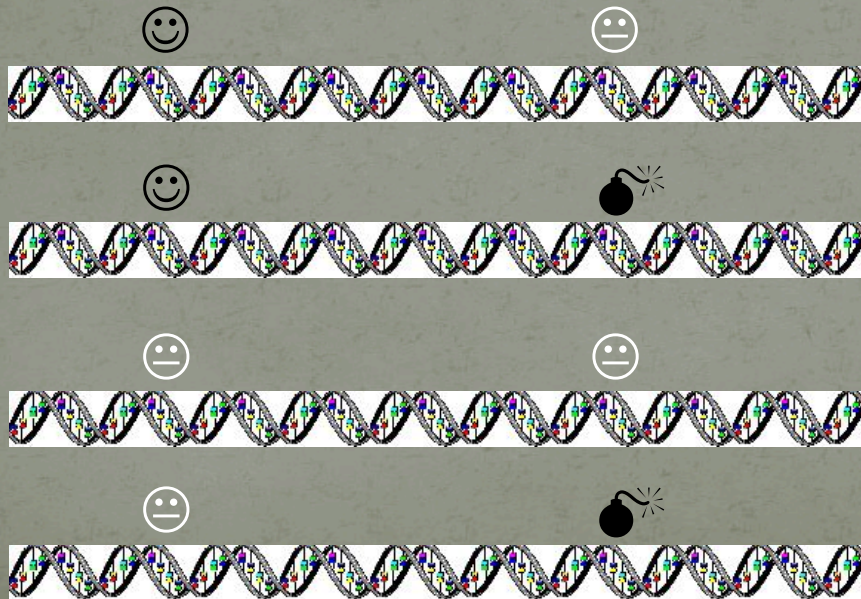
$$1 - s_d$$

Recombination and the hitchhiker

We constructed a haploid model to address this issue.



Initial population:



0

$$p_0 = 1/N$$

$$\sim 1 - p_0$$

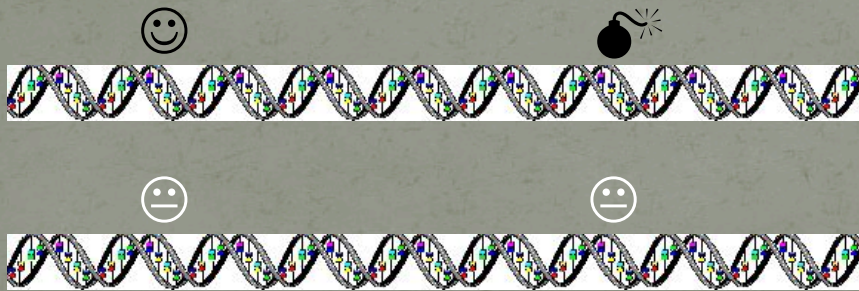
rare

Recombination and the hitchhiker

We constructed a haploid model to address this issue.



Initial population:



$$p_0 = 1/N$$

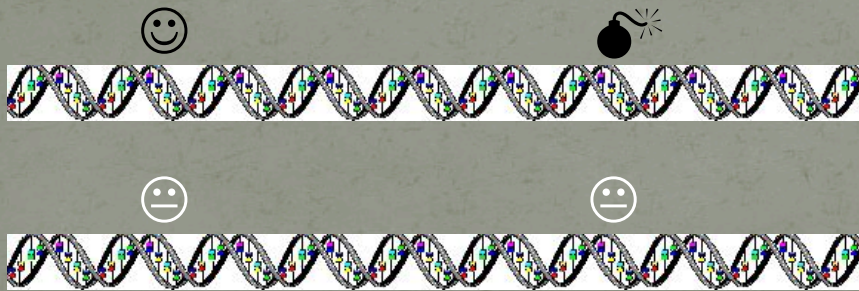
$$\sim 1 - p_0$$

Recombination and the hitchhiker

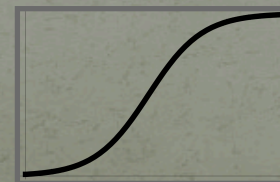
We constructed a haploid model to address this issue.



Over time:



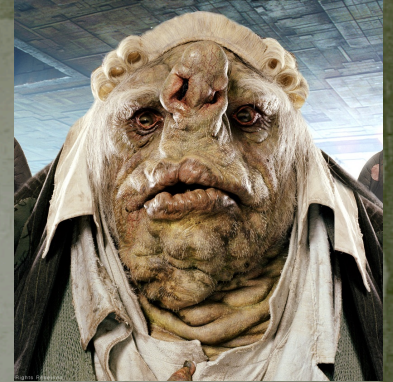
$$\frac{dp_t}{dt} = (s_a - s_d) p_t (1 - p_t)$$



$$p_t = \frac{p_0 e^{(s_a - s_d)t}}{p_0 e^{(s_a - s_d)t} + (1 - p_0)}$$

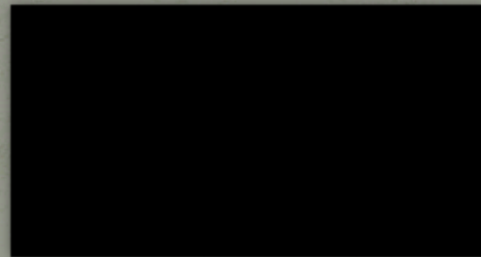
Recombination and the hitchhiker

For the deleterious allele to hitch all the way to fixation there must be no “successful” recombination events.



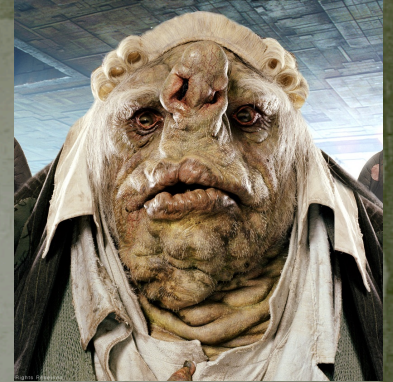
- Chance of a recombinant $= 2 p_t (1-p_t) r$
- Chance of the fitter recombinant $= 2 p_t (1-p_t) r/2$
- Chance that a recombinant establishes $= \Pi_t$

$$\Pi_t =$$



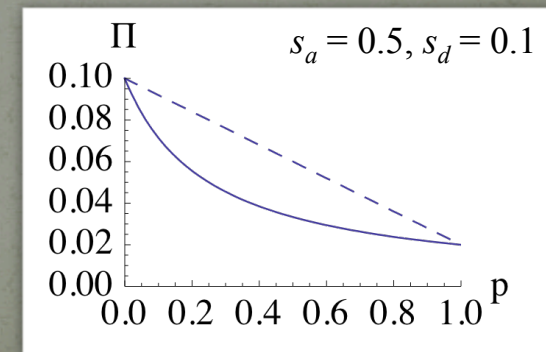
Recombination and the hitchhiker

For the deleterious allele to hitch all the way to fixation there must be no “successful” recombination events.



- Chance of a recombinant $= 2 p_t (1-p_t) r$
- Chance of the fitter recombinant $= 2 p_t (1-p_t) r/2$
- Chance that a recombinant establishes $= \Pi_t$

$$\Pi_t = 2 \frac{s_a s_d}{s_a p_t + s_d (1 - p_t)}$$



Recombination and the hitchhiker

For the deleterious allele to hitch all the way to fixation there must be no “successful” recombination events.

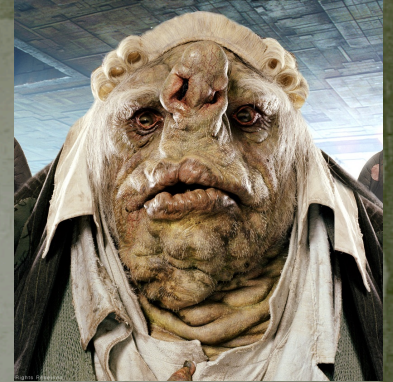


- Chance of a recombinant $= 2 p_t (1-p_t) r$
- Chance of the fitter recombinant $= 2 p_t (1-p_t) r/2$
- Chance that a recombinant establishes $= \Pi_t$
- Chance that no fitter recombinant establishes in generation t :
 $= (1 - p_t (1-p_t) r \Pi_t)^N$
- Chance that no fitter recombinant establishes in any generation:

$$\Pr(Hitch) = \prod_{t=0}^{fixation} \left(1 - p_t (1 - p_t) r \Pi_t\right)^N$$

Recombination and the hitchhiker

For the deleterious allele to hitch all the way to fixation there must be no “successful” recombination events.



- Chance of a recombinant $= 2 p_t (1-p_t) r$
- Chance of the fitter recombinant $= 2 p_t (1-p_t) r/2$
- Chance that a recombinant establishes $= \Pi_t$
- Chance that no fitter recombinant establishes in generation t :
 $= (1 - p_t (1-p_t) r \Pi_t)^N$
- Chance that no fitter recombinant establishes in any generation:

$$\Pr(Hitch) = \left(\frac{s_a}{s_d} \right)^{-\omega}$$

$$\omega = \frac{2 N r s_a s_d}{(s_a - s_d)^2}$$

Recombination and the hitchhiker



This simple result ignores:

- drift
- stochastic acceleration of the ☺💣 chromosome, given it is not lost while rare

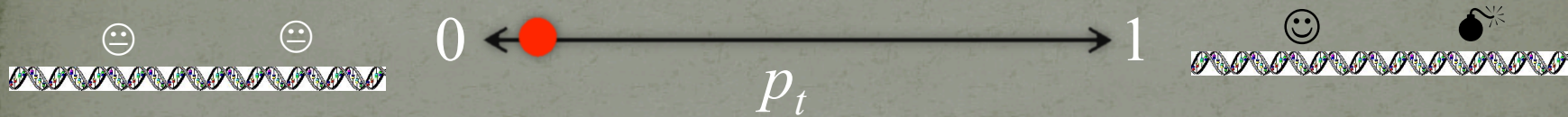
$$\Pr(Hitch) = \left(\frac{s_a}{s_d} \right)^{-\omega}$$

$$\omega = \frac{2Nr s_a s_d}{(s_a - s_d)^2}$$

Recombination and the hitchhiker



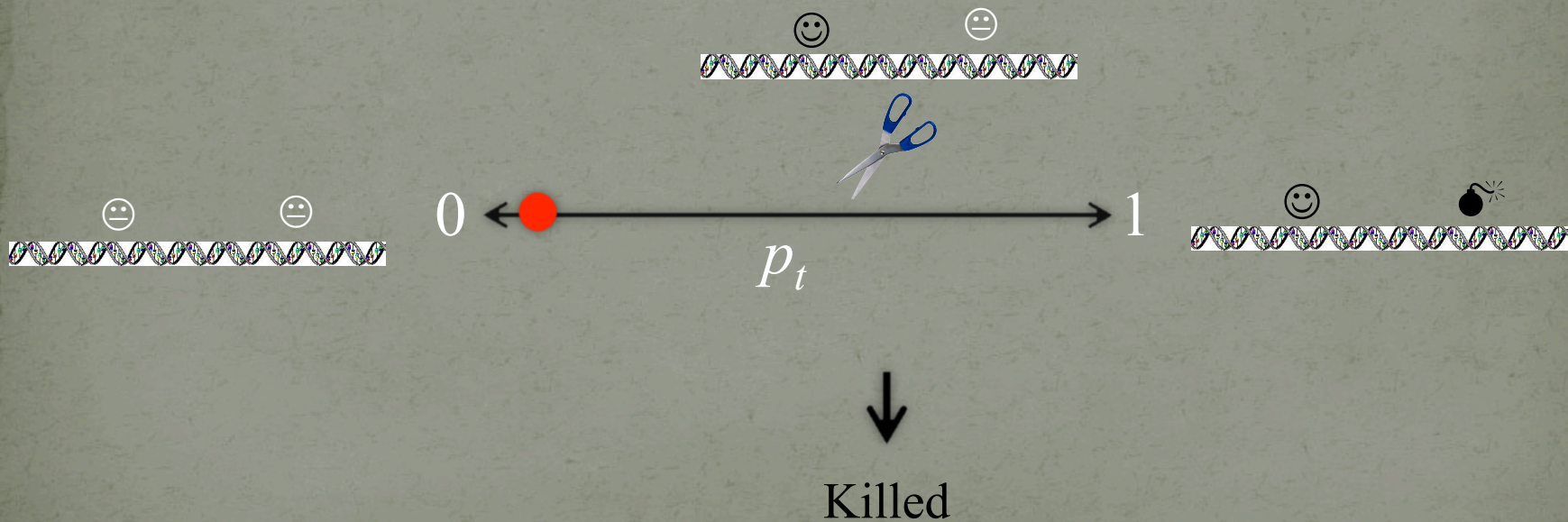
- Diffusion



Recombination and the hitchhiker



- Diffusion with killing



Recombination and the hitchhiker



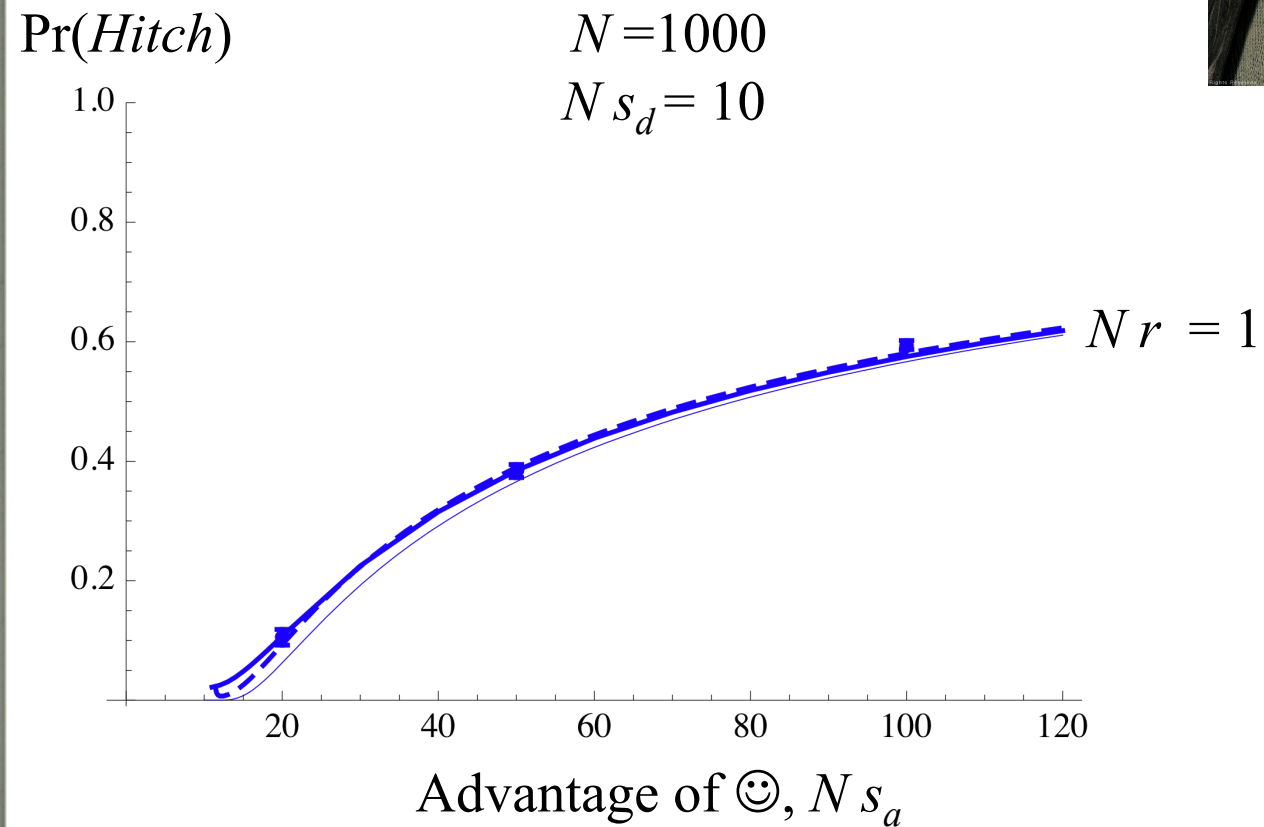
$$\Pr(Hitch) = \left(\frac{1 - e^{-2S_{net}}}{1 - e^{-2pS_{net}}} \right) \times \frac{U_{-\omega}^0[-2(pS_{net} + S_d)]L_{\omega}^{-1}[-2S_d] - U_{-\omega}^0[-2S_d]L_{\omega}^{-1}[-2(pS_{net} + S_d)]}{U_{-\omega}^0[-2(S_{net} + S_d)]L_{\omega}^{-1}[-2S_d] - U_{-\omega}^0[-2S_d]L_{\omega}^{-1}[-2(S_{net} + S_d)]}$$

$$\Pr(Hitch) \approx \left(e^{-1/(Ns_d)} \frac{S_a}{S_d} \right)^{-\omega}$$

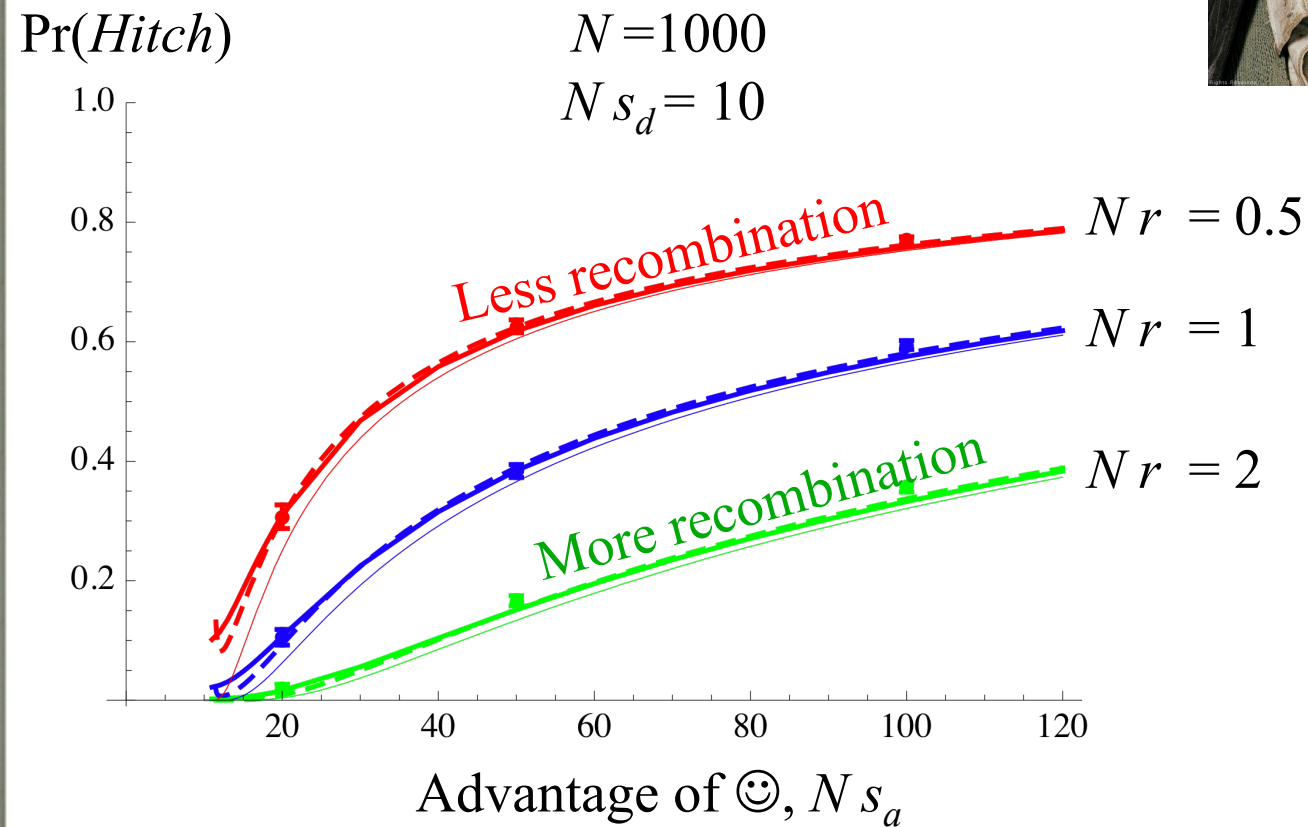
➔ *Slightly* higher probability of hitching

$$\begin{aligned} S_d &= Ns_d \\ S_{net} &= N(s_a - s_d) \\ \omega &= \frac{2Nr s_a s_d}{(s_a - s_d)^2} \end{aligned}$$

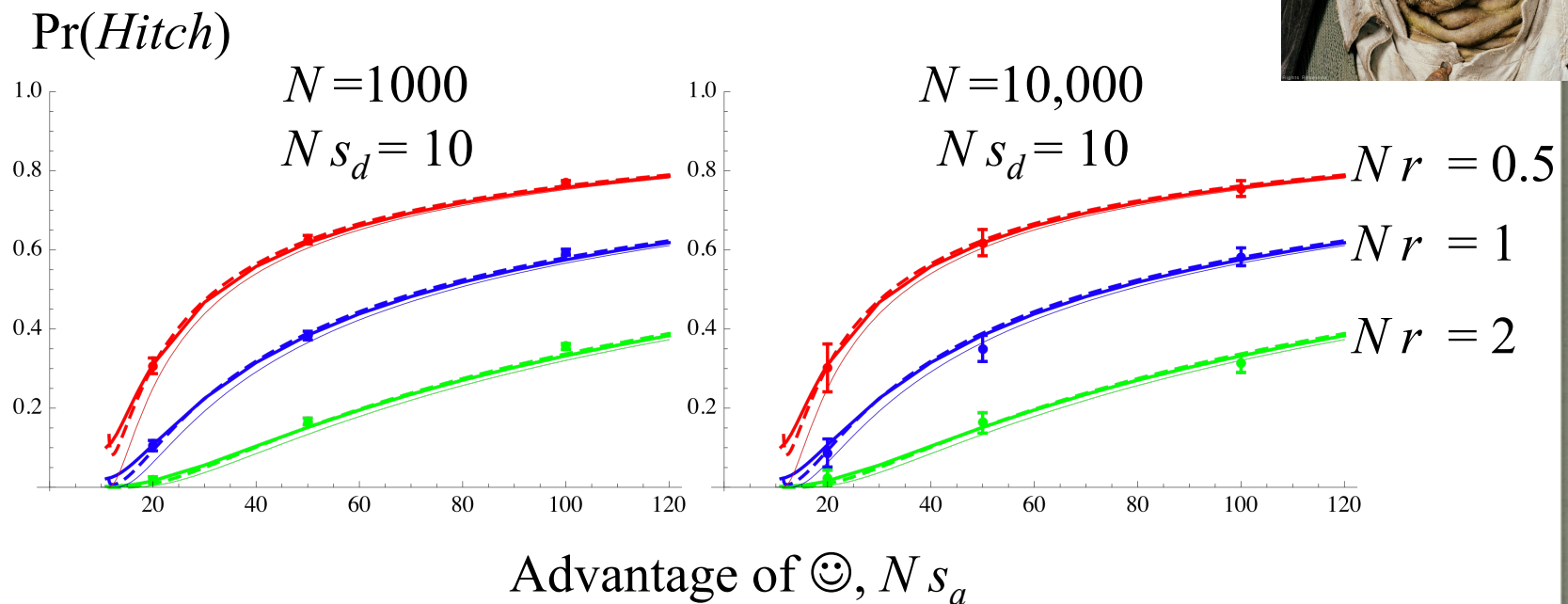
Recombination and the hitchhiker



Recombination and the hitchhiker



Recombination and the hitchhiker



➔ Net selection and recombination rates matter,
not population size on its own.

Recombination and the hitchhiker



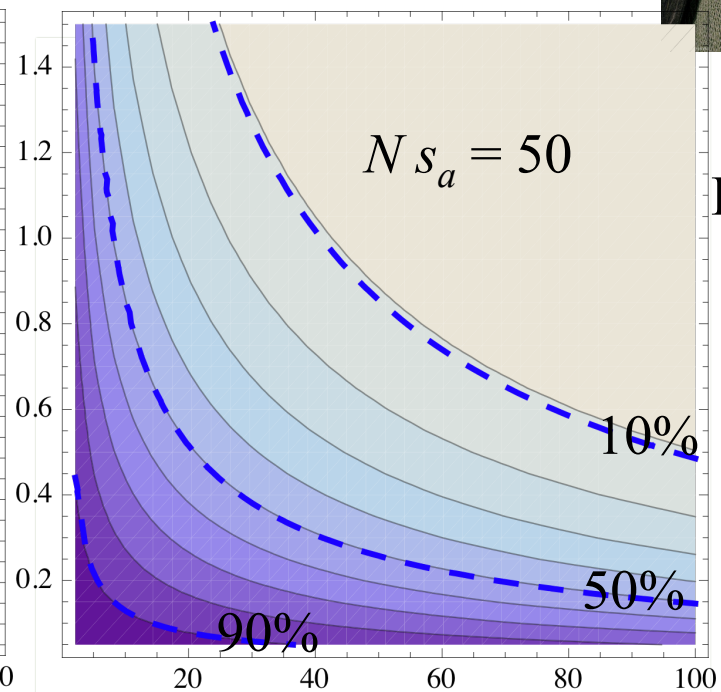
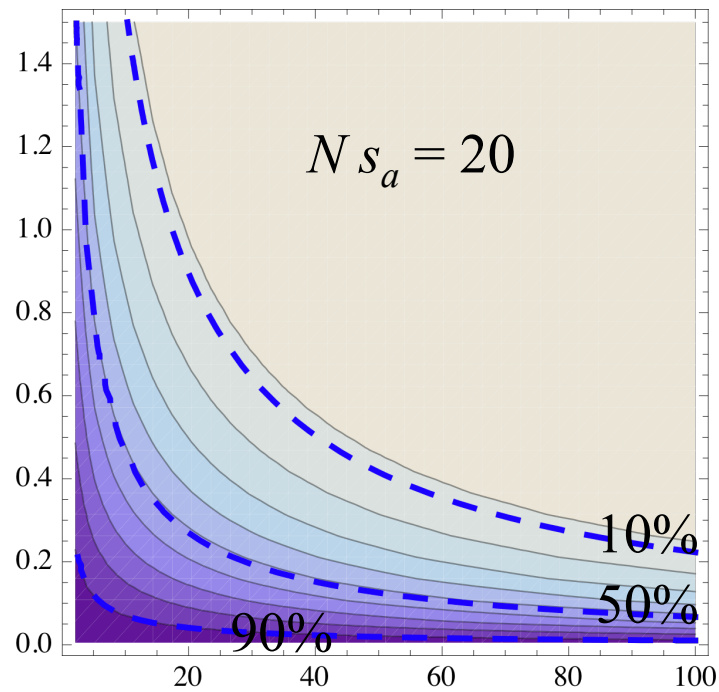
For hitchhiking to occur more than a fraction, c , of the time:

$$r < r_{crit} \approx \frac{s_a - s_d}{Ns_d} \left[\frac{\ln(1/c)}{2(1 + s_d/(s_a - s_d))(\ln((s_a - s_d)/s_d) - 1/(Ns_d))} \right]$$

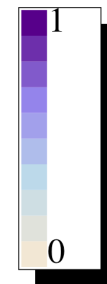
Recombination and the hitchhiker



Nr



$\text{Pr}(\text{Hitch})$



Disadvantage of \bullet^* , Ns_d

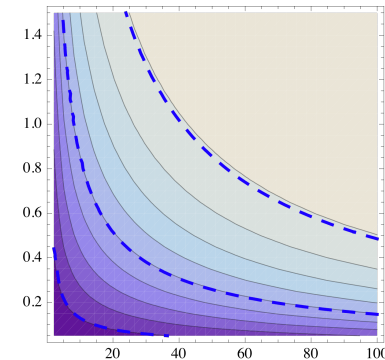
Recombination and the hitchhiker



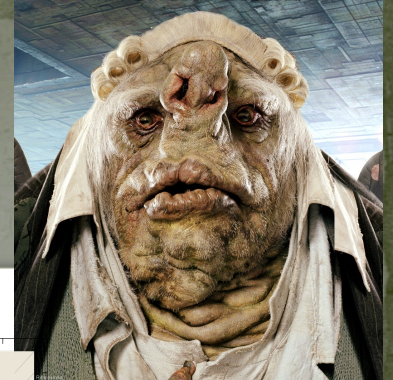
- ➔ Net selection and recombination rates matter, not population size on its own.
- ➔ The probability of a hitch declines exponentially with recombination.
- ➔ The faster the sweep (higher s_a), the more likely a hitch.
- ➔ The worse the load (higher s_d), the less likely a hitch.

Rough rule of thumb: A linked deleterious allele hitchhikes to fixation more than 50% of the time if

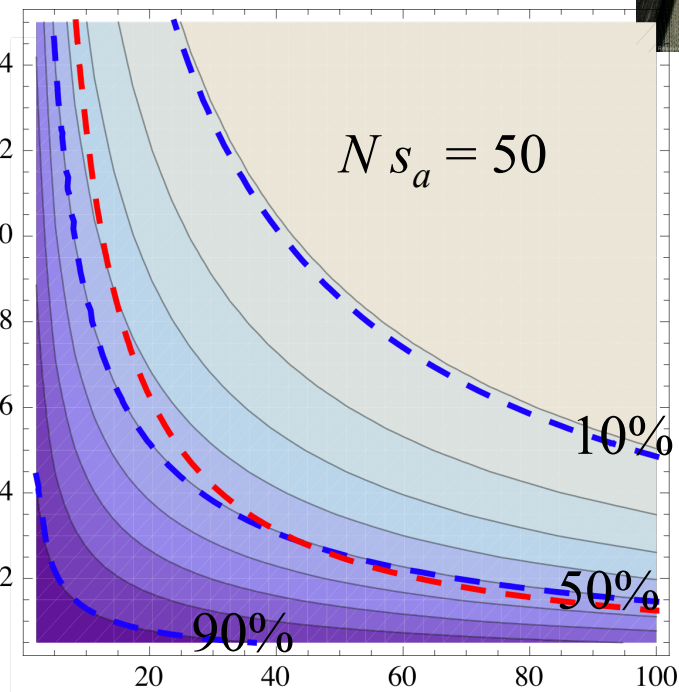
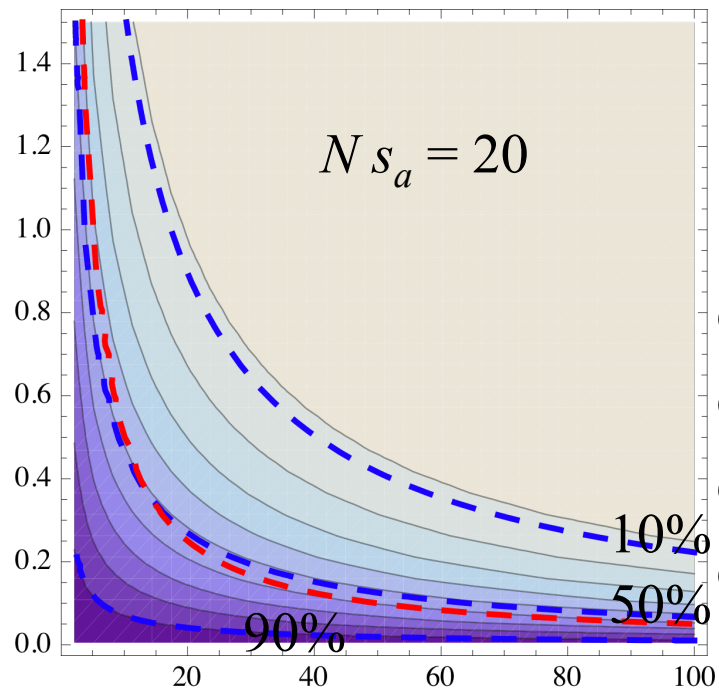
$$r < \frac{(s_a - s_d)}{4Ns_d}$$



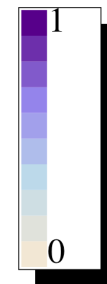
Recombination and the hitchhiker



Nr



$\text{Pr}(\text{Hitch})$



Disadvantage of hitchhiker, Ns_d

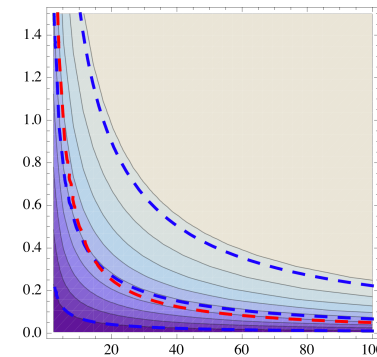
Recombination and the hitchhiker



- ➔ Net selection and recombination rates matter, not population size on its own.
- ➔ The probability of a hitch declines exponentially with recombination.
- ➔ The faster the sweep (higher s_a), the more likely a hitch.
- ➔ The worse the load (higher s_d), the less likely a hitch.

Rough rule of thumb: A linked deleterious allele hitchhikes to fixation more than 50% of the time if

$$r < \frac{(s_a - s_d)}{4Ns_d}$$



Recombination and the hitchhiker



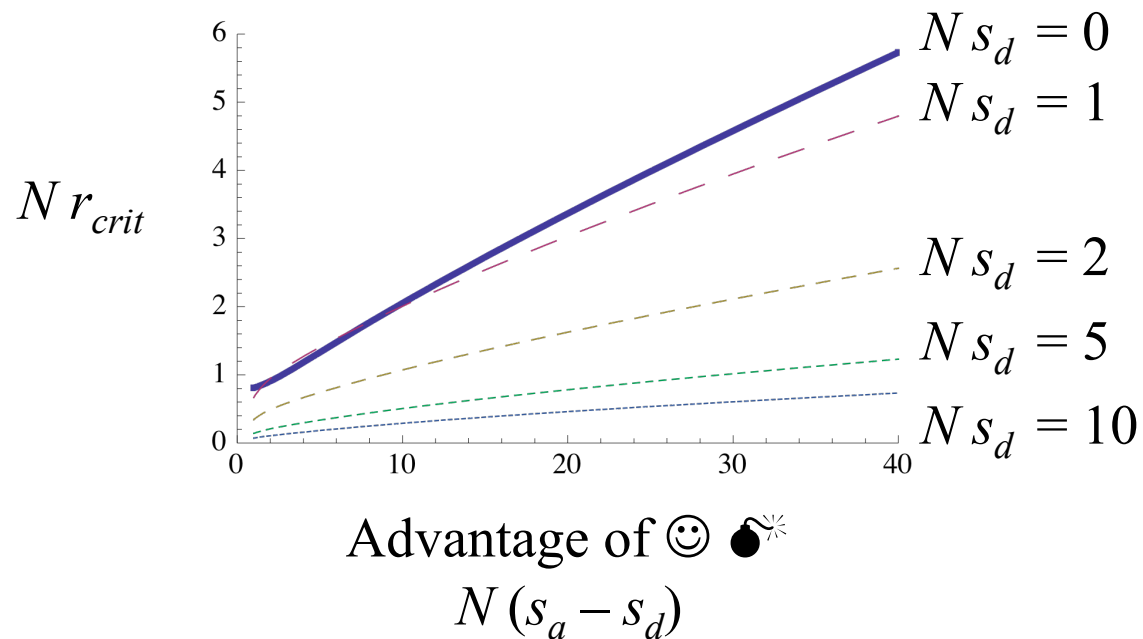
A similar calculation can be performed for a neutral allele:

$$\Pr(Hitch) \approx \left(2 e^{\gamma} N s_a\right)^{-r/s_a}$$

Rough rule of thumb: A linked neutral allele hitchhikes to fixation more than 50% of the time if

$$r < \frac{s_a}{4}$$

Recombination and the hitchhiker

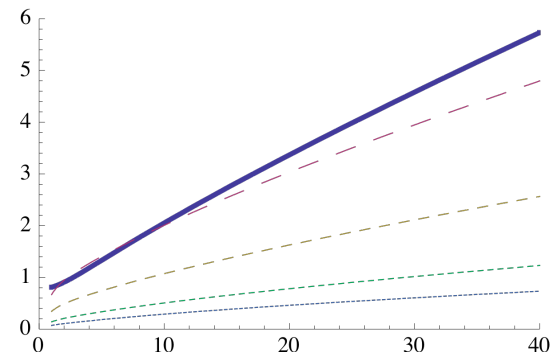


➔ Neutral and weakly deleterious alleles are much more likely to hitch

Recombination and the hitchhiker



- ➔ Neutral and weakly deleterious alleles are much more likely to hitch
- ➔ “Missing hitchhikers”: The fact that deleterious alleles fail to hitchhike as often as neutral alleles implies that recombination events are enriched in the region of selective sweeps, obscuring signs of selection.



Recombination and the hitchhiker

Within the human genome:

- Recombination rate within gene: $N_e r \sim 1$ ($N_e = 10,000$)
- Expected proportion of genes with deleterious alleles

0.53 for $N_e s_d < 1$

0.031 for $1 < N_e s_d < 10$

0.007 for $10 < N_e s_d$

- ➔ Reasonable chance of a within-gene weakly deleterious allele hitching
- ➔ Recombination between genes typically too high in humans
- ➔ Hitching more likely in facultative sexuals



Selection from Boyko et al 2008
Recombination from McVean et al (2004)
U from Eyre-Walker & Keightley (1999)

Recombination and the hitchhiker



- For organisms like humans, deleterious hitchhikers are likely confined to within the gene
- More problematic for facultative sexuals or selfers
- Unlinking deleterious hitchhikers is likely to preserve genetic variation in genomic regions surrounding a selected site, obscuring signs of selection