Adaptation and Disease

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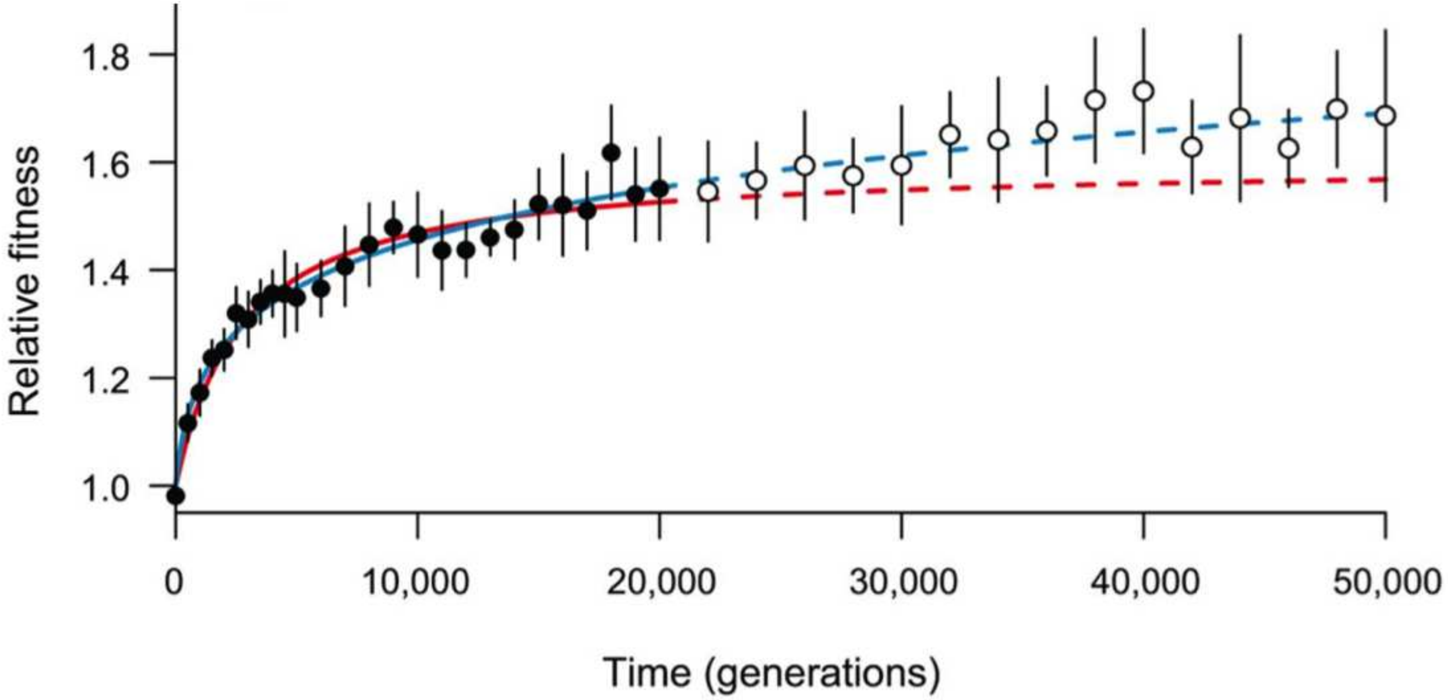
Jain, *Genetics* (2019)

Cost of adaptation (Fay 2013)

Population is said to be adapting if its fitness increases with time



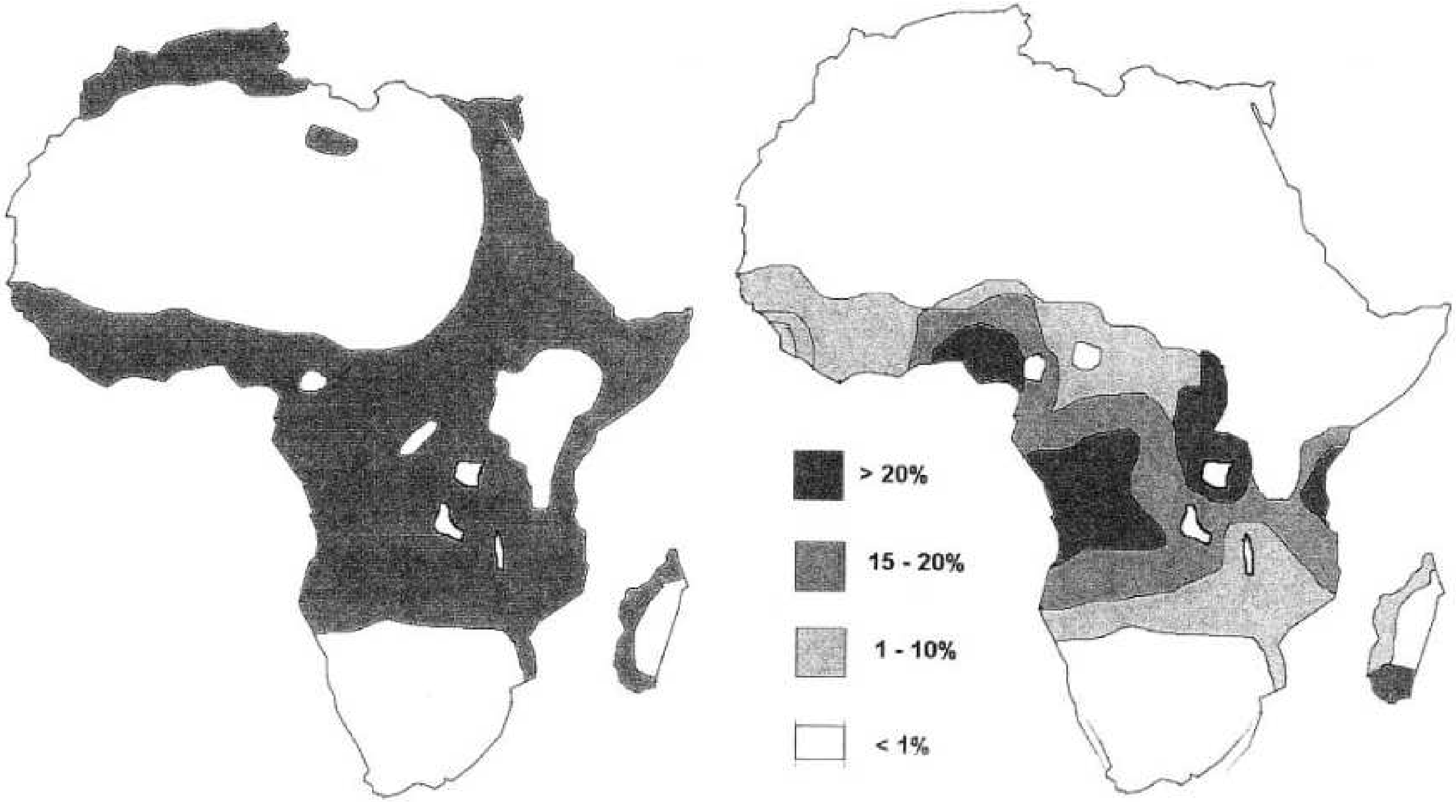
(Wiser et al. 2013)

Because both good and bad mutations occur during evolution

→ Adaptation is <u>net</u> increase in fitness

Balancing selection (Lewontin & Hubby 1966)

Sickle-cell heterozygotes have higher fitness as they are resistant to malaria but suffer from sickle-cell anaemia

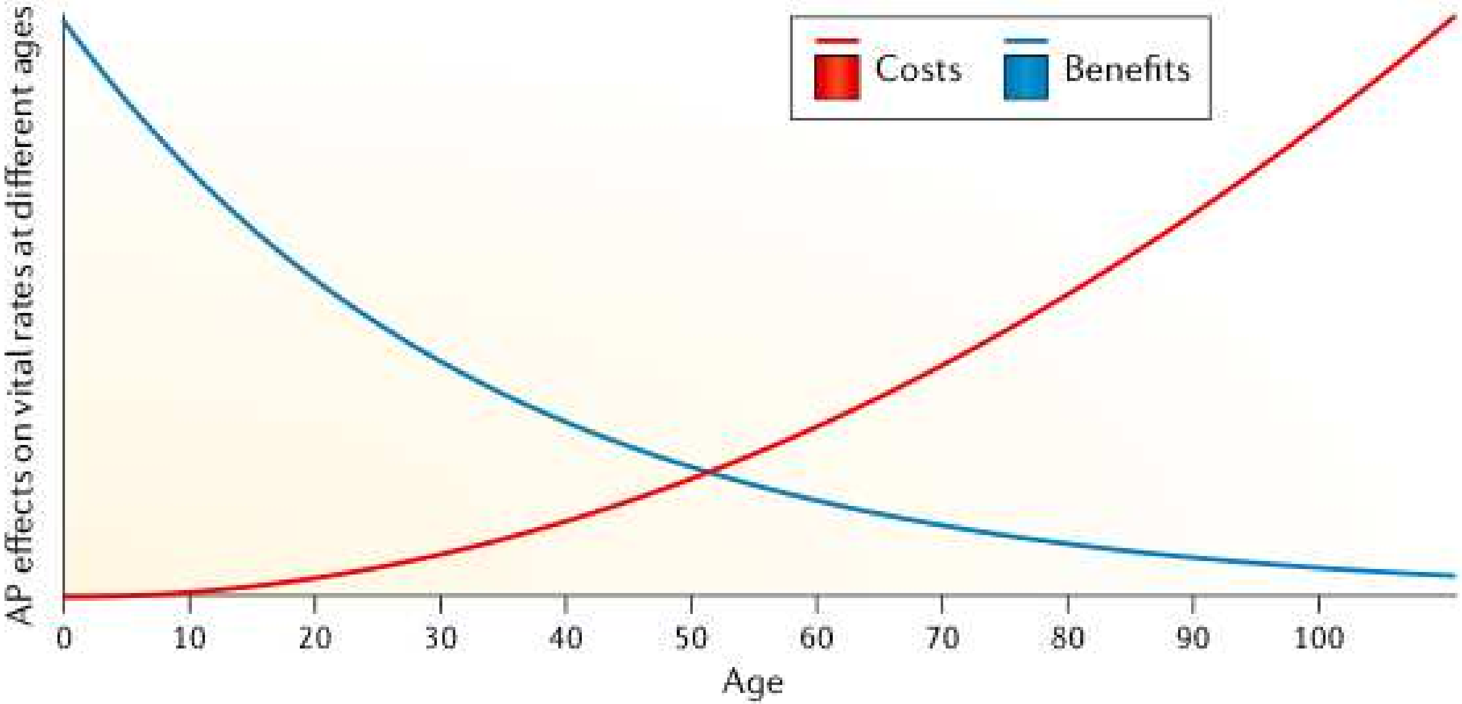


Disease is an agent of natural selection (Allison 1954; 2004)

Antagonistic pleiotropy (Williams 1957)

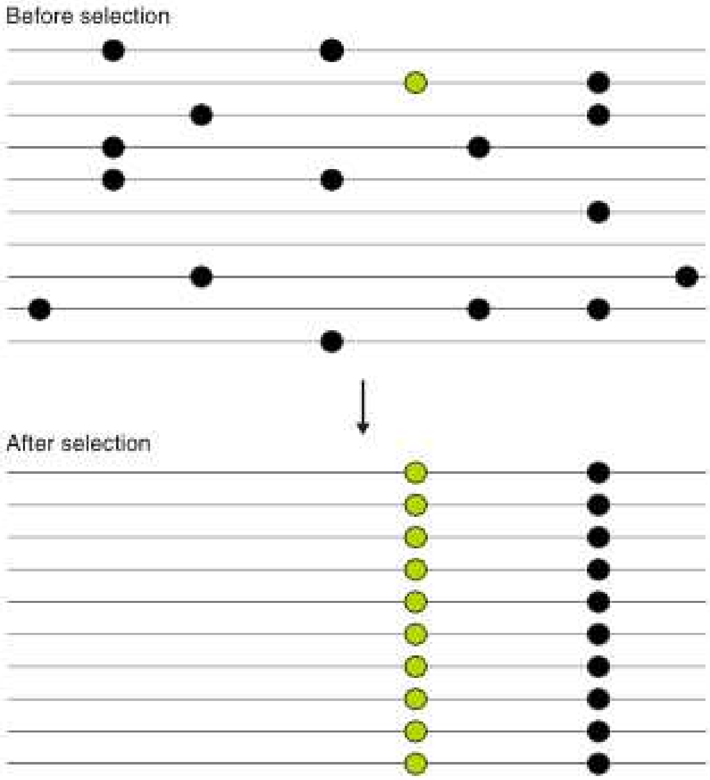
Same gene can control multiple traits, and have both + and - effects on fitness

e.g., mutations in *BRCA* gene increase reproductive success at early age but cause cancer in old age



(Corbett et al. 2018)

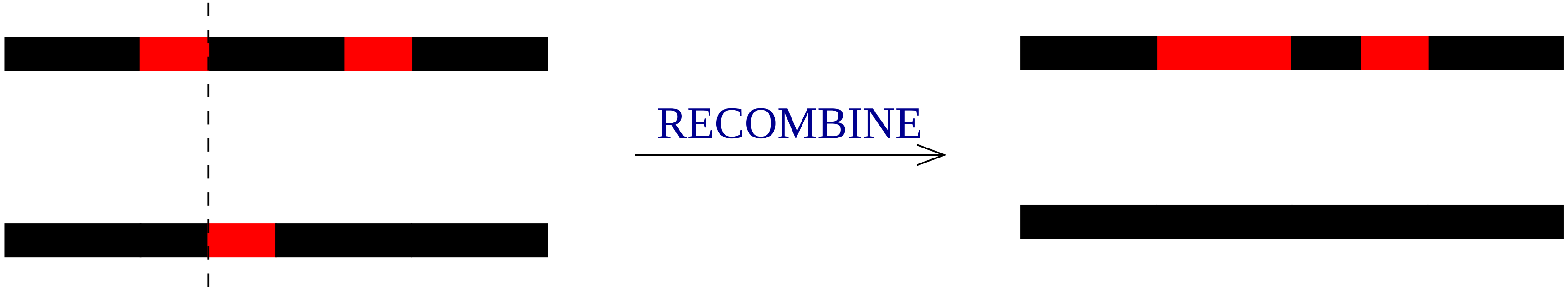
Genetic hitchhiking (Maynard Smith & Haigh 1974)



(McCoy & Akey 2017)

<u>Deleterious</u> SNPs in regions of <u>positive</u> selection for several diseases (Chun & Fay 2011)

Genetic mixing breaks associations



But nonrecombining regions (Y-chromosome) or asexual populations will carry mutational burden

Basic concepts in population genetics

Basic evolutionary processes

- Natural selection
- Mutation
- Stochasticity (random genetic drift)
- Population structure (asexual/sexual; ploidy; migration; ...)

Due to interplay of these processes, how does gene frequency change?

Selection

- One-locus model with two alleles

Gene	Fitness	Frequency
●	$1+s$	p
○	1	q

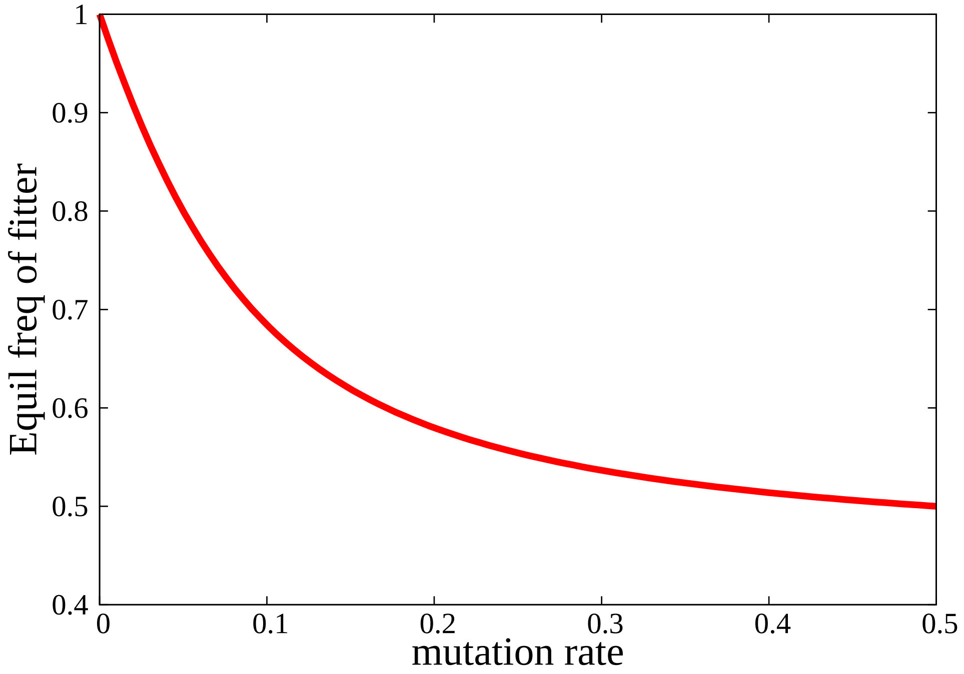
- At large times, <u>fitter</u> variant is selected (Punnett/Norton 1915; Haldane 1924)

$$p_{t+1} \quad \propto \quad \text{Fitness of parent} \times p_t$$

Mutation-Selection balance

- Selection and Mutation act in opposite manner

Gene	Fitness	Mutation
●	$1+s$	● → ○ (deleterious)
○	1	○ → ● (beneficial)

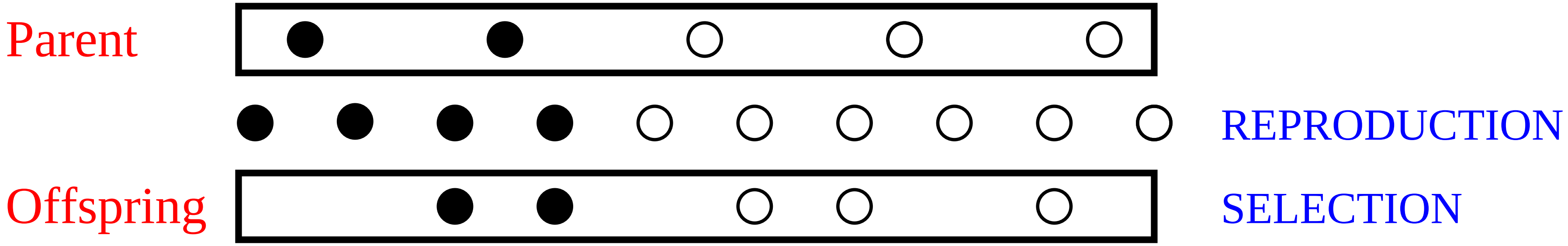


- Phase transitions occur in more complex models

(Eigen 1971; Peliti, Franz,... $\gtrsim$1995; review - Jain & Krug 2007)

Random genetic drift

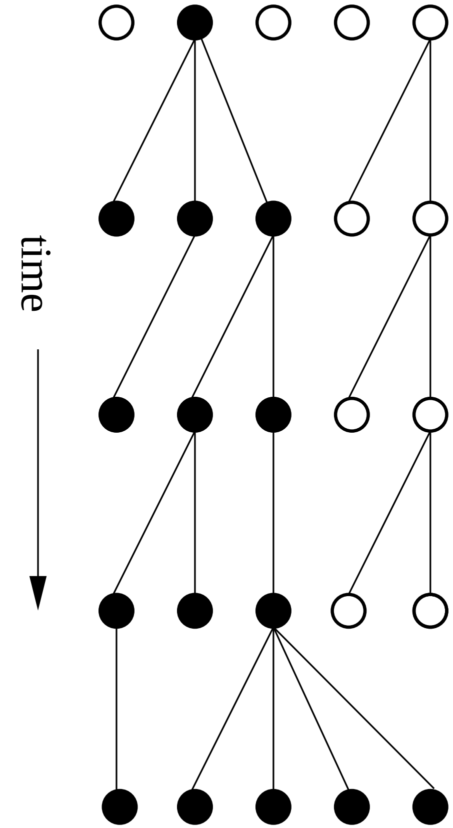
Stochastic evolution because of finite resources (food...)

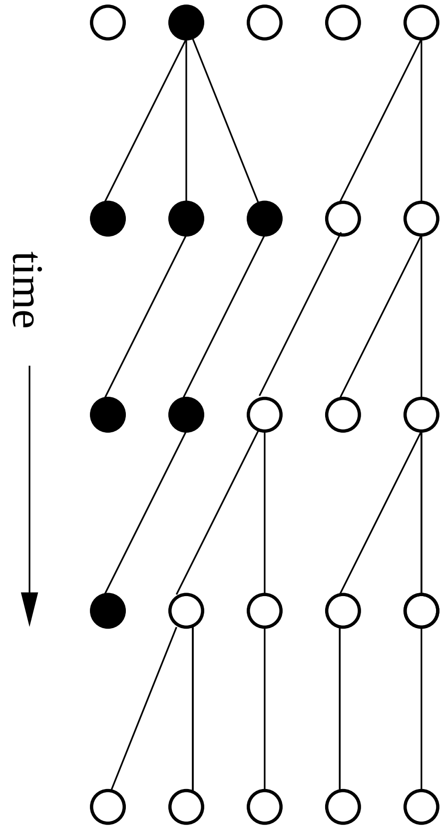


To maintain population size N, $\underline{\text{sample}}$ offspring with

$$\text{Prob} \propto \text{Fitness of parent}$$

What happens when a new mutant appears in a population?





What is the chance that it “fixes”? → Fixation probability

Essential building block for complex stochastic models of adaptation

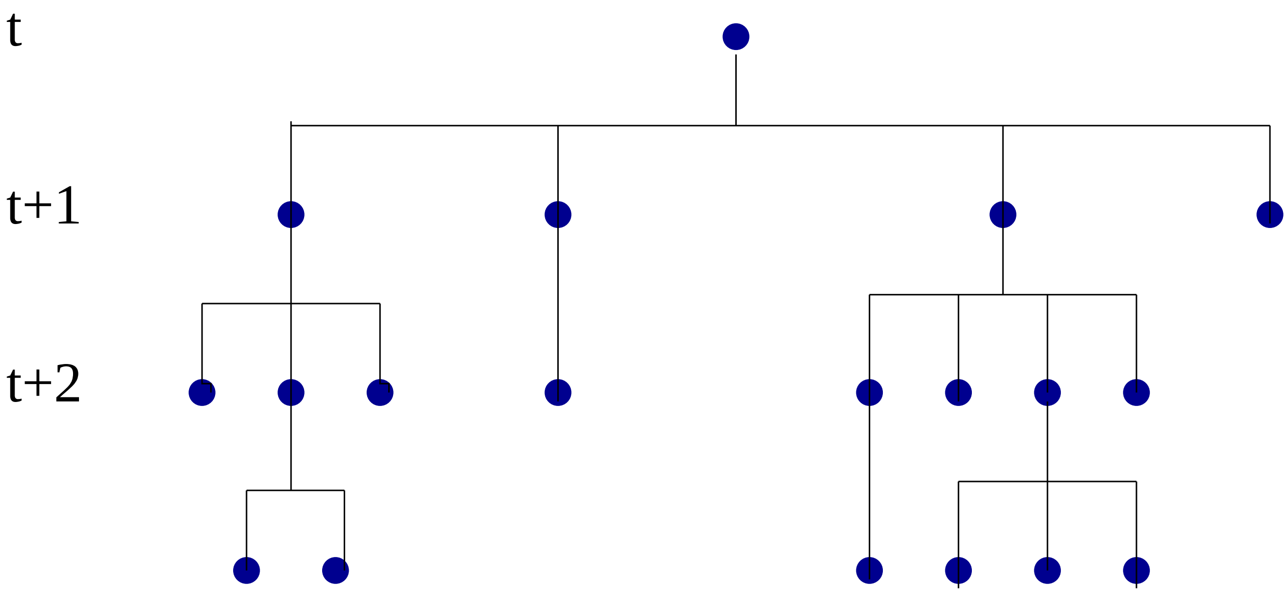
Backward Fokker-Planck equation for absorbing states (van Kampen 1997)

$$-\frac{\partial}{\partial t_0} P(x, t|x_0, t_0) = \left[\underbrace{a(x_0)}_{\text{Deterministic slctn}} \frac{\partial}{\partial x_0} + \underbrace{\frac{x_0(1 - x_0)}{2N}}_{\text{Binomial sampling}} \frac{\partial^2}{\partial x_0^2} \right] P(x, t|x_0, t_0)$$

Progress limited to simple “1d” cases (Fisher 1922; Kimura 1962)

Branching Process (Harris 1963)

$\epsilon(t) =$ Extinction prob of ● that arose at time t in a large pop. of ○



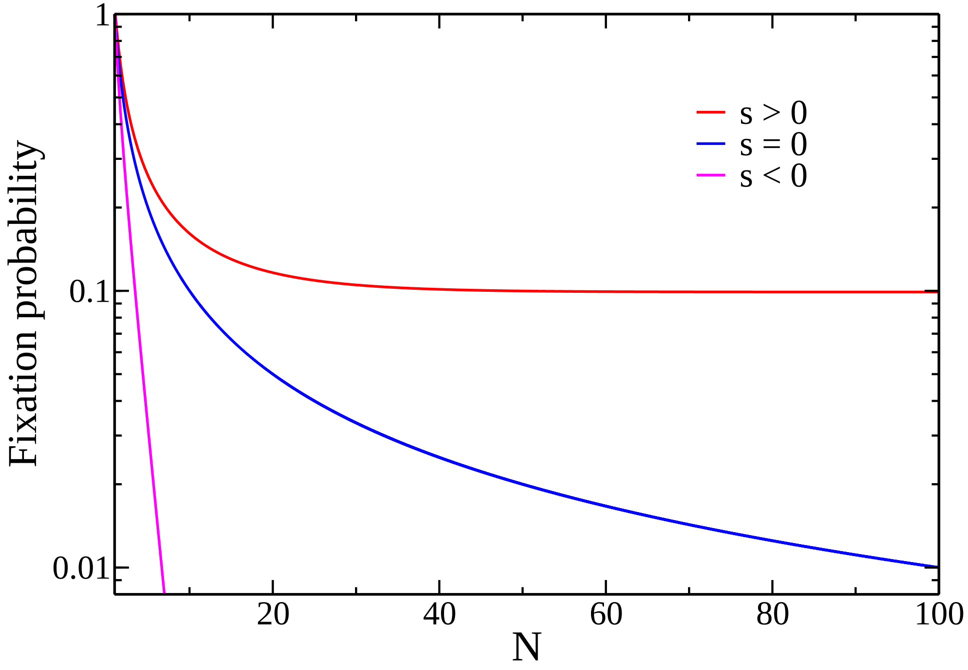
$$\epsilon(t) = \sum_{n=0}^{\infty} \underbrace{\rho(n)}_{\text{offspring distribution}} \underbrace{[\epsilon(t+1)]^n}_{\text{all lineages go extinct}}$$

Fixation probability of a single mutant (Kimura 1962)

wildtype fitness=1

mutant fitness=$1+s$

$$P = \frac{1-e^{-2s}}{1-e^{-2Ns}}$$



- In a small population, beneficial mutation may get lost and deleterious mutation may get fixed !
- In large population, beneficial mutation fixes with probability $2s$

How do linked deleterious mutations affect adaptation?

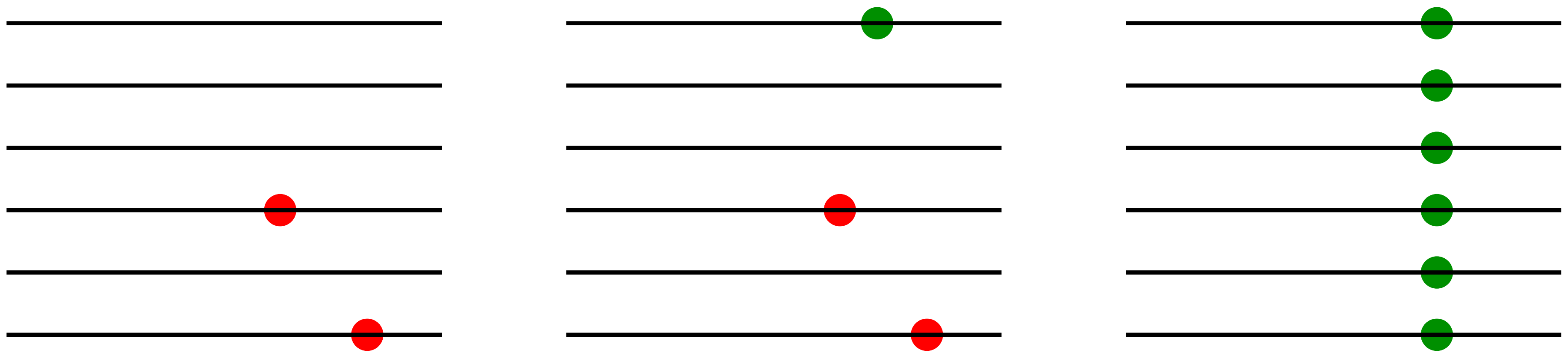
Multilocus stochastic model (Jain 2019)

- Asexual population of size N
- Sequence with large number of loci
- Beneficial mutation occurs at rate u_b, deleterious ones at u_d
- Beneficial mutation increases fitness by s_b, deleterious by s_d

Fixation probability of beneficial mutant(s)?

Strongly deleterious mutations (Charlesworth 1994)

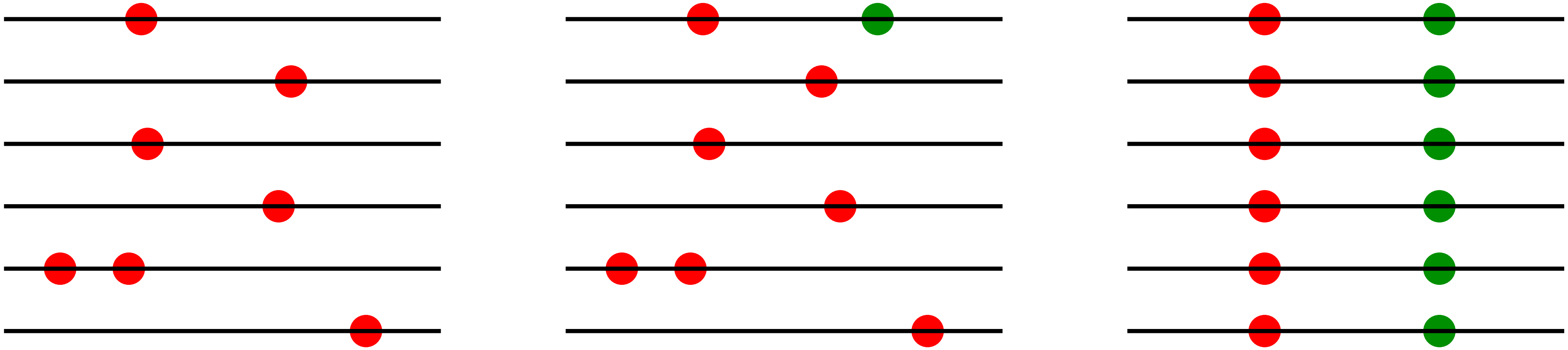
If deleterious mutation is lethal, beneficial can survive in sequence without it



$$P \approx 2s_b \; , \; s_d > s_b$$

Weakly deleterious mutations + Low mutation rates

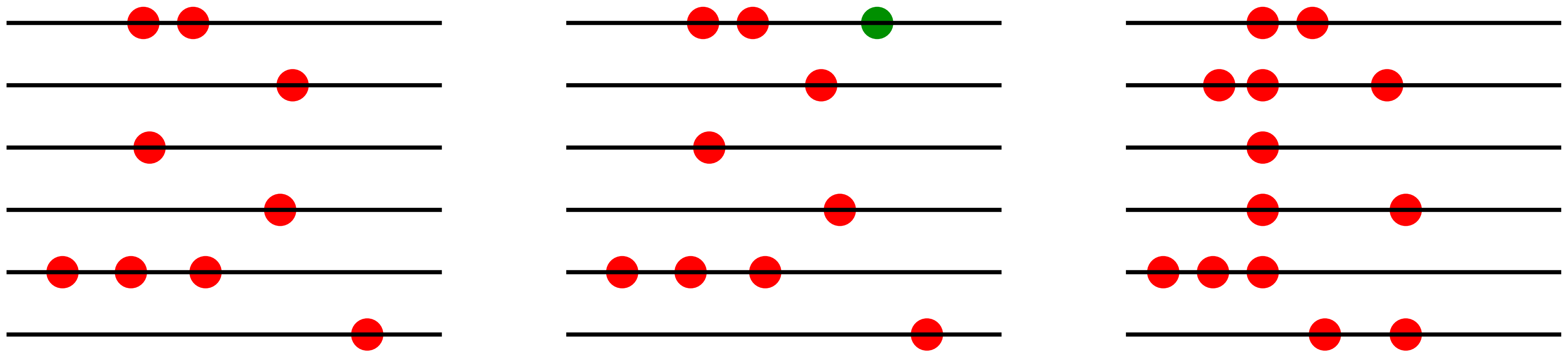
If deleterious mutations decrease fitness mildly and do not accumulate



$$P \approx 2s_b \ , \ u_d, s_d < s_b$$

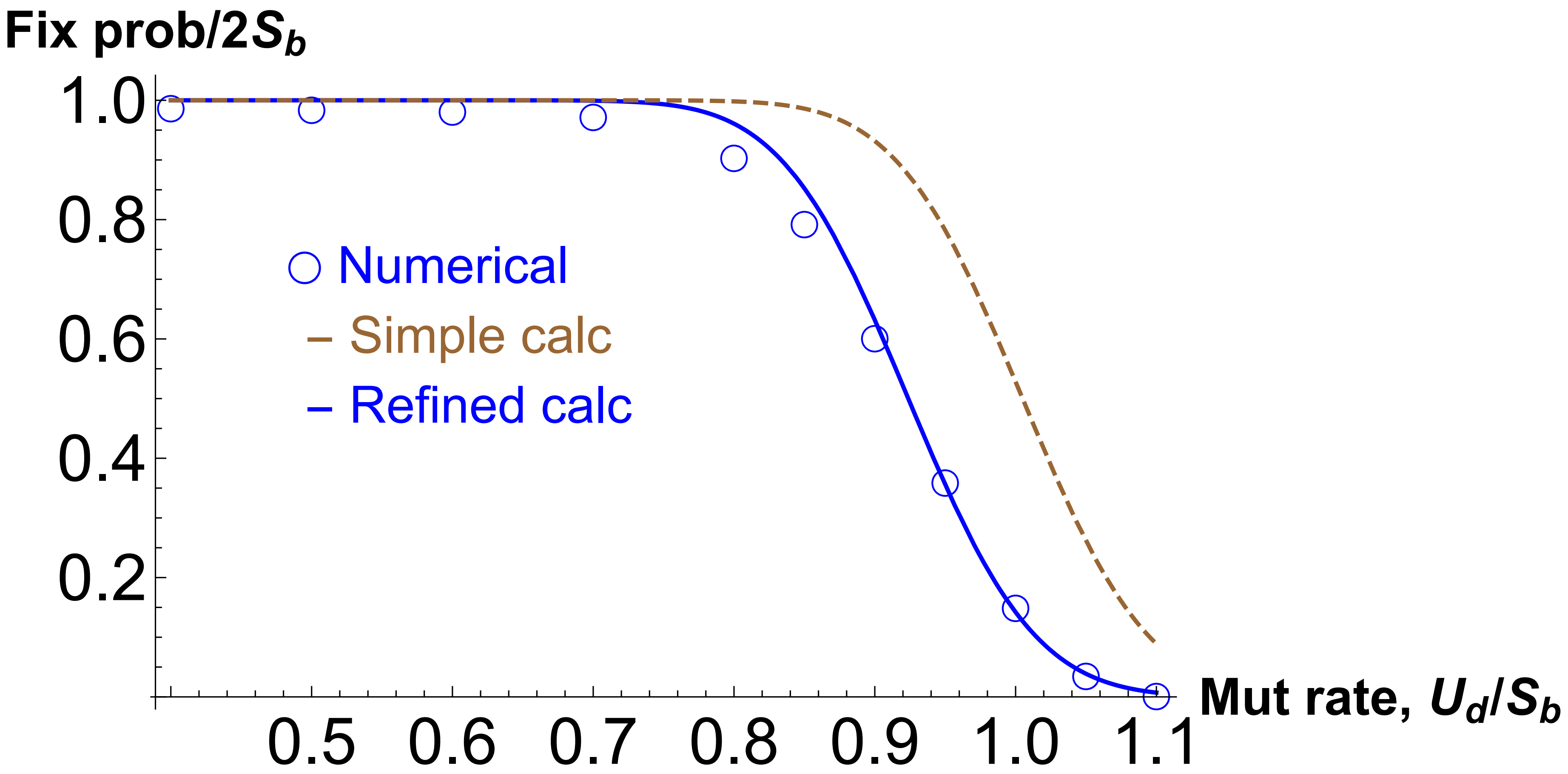
Weakly deleterious mutations + High mutation rates

If deleterious mutations decrease fitness mildly but accumulate



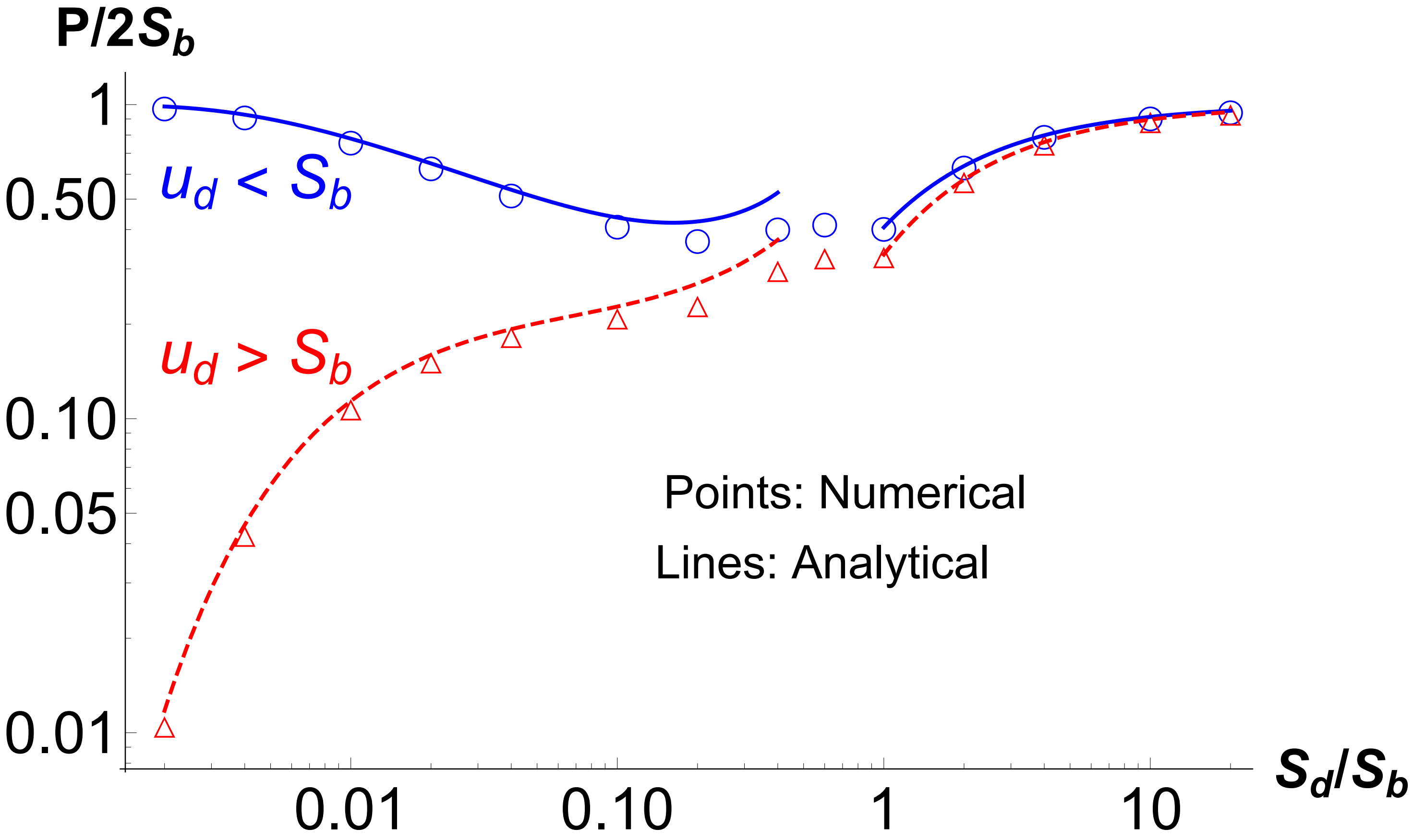
$$P \approx 0\ ,\ s_d < s_b < u_d$$

Fixation probability vanishes (Jain 2019)



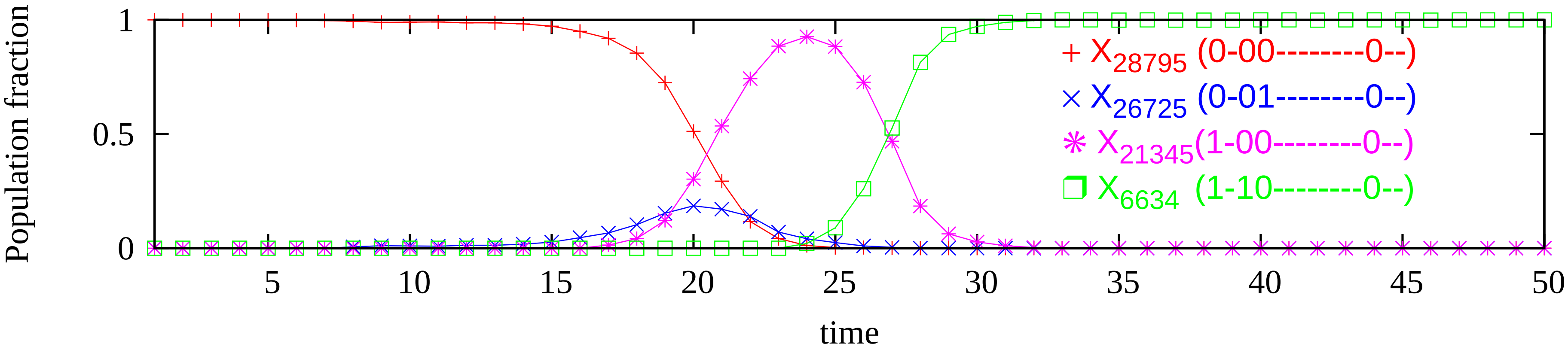
Weak deleterious mutations strongly affect adaptation

Transition in the fixation probability (Jain 2019)

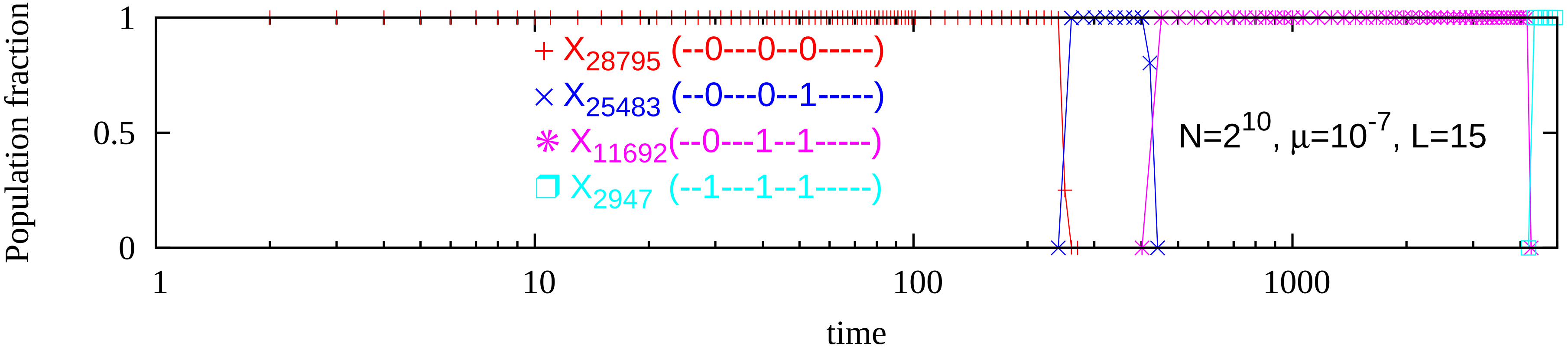


Clonal interference (Gerrish & Lenski 1998)

Large population: More beneficial mutations but more competition



Small population: No interference

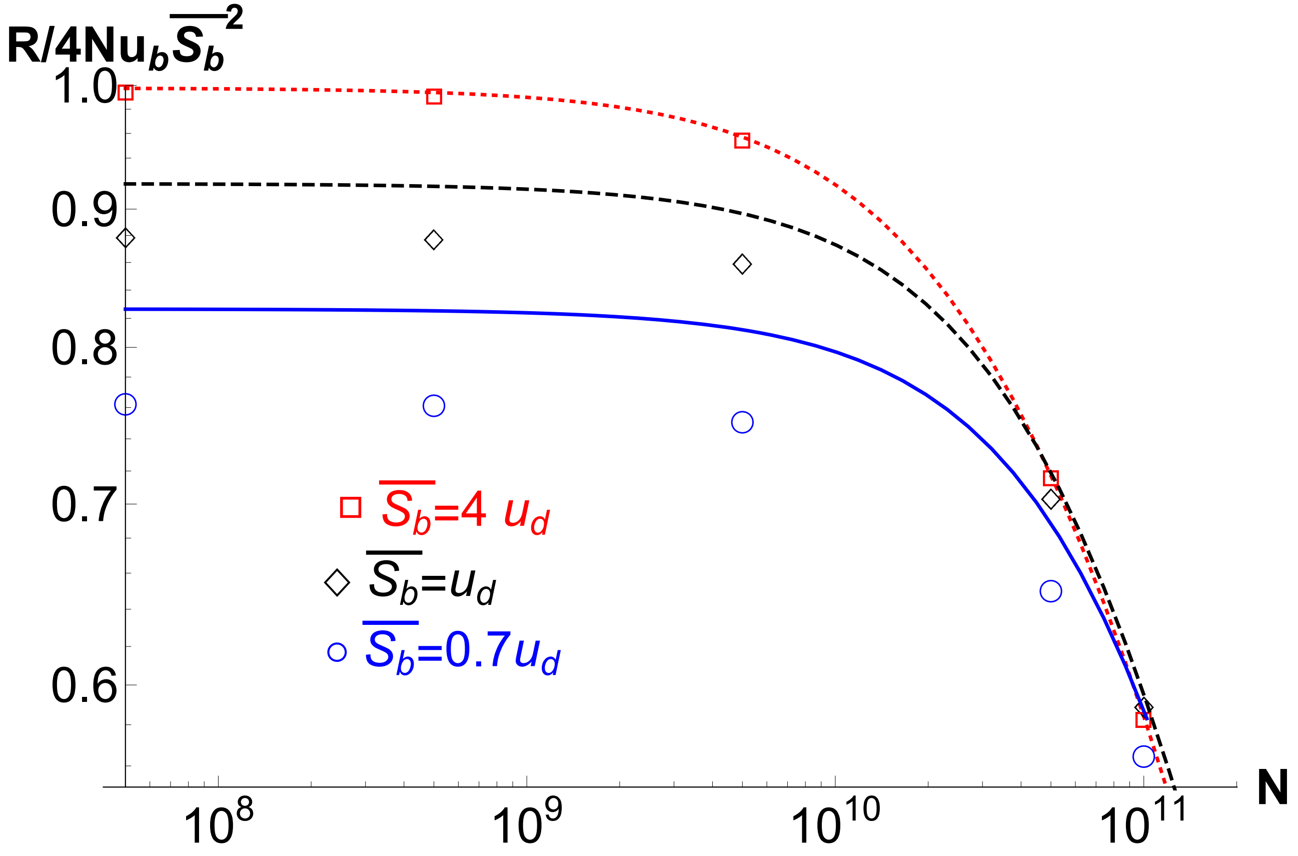


Competition with superior beneficial mutations (Wilke 2004)

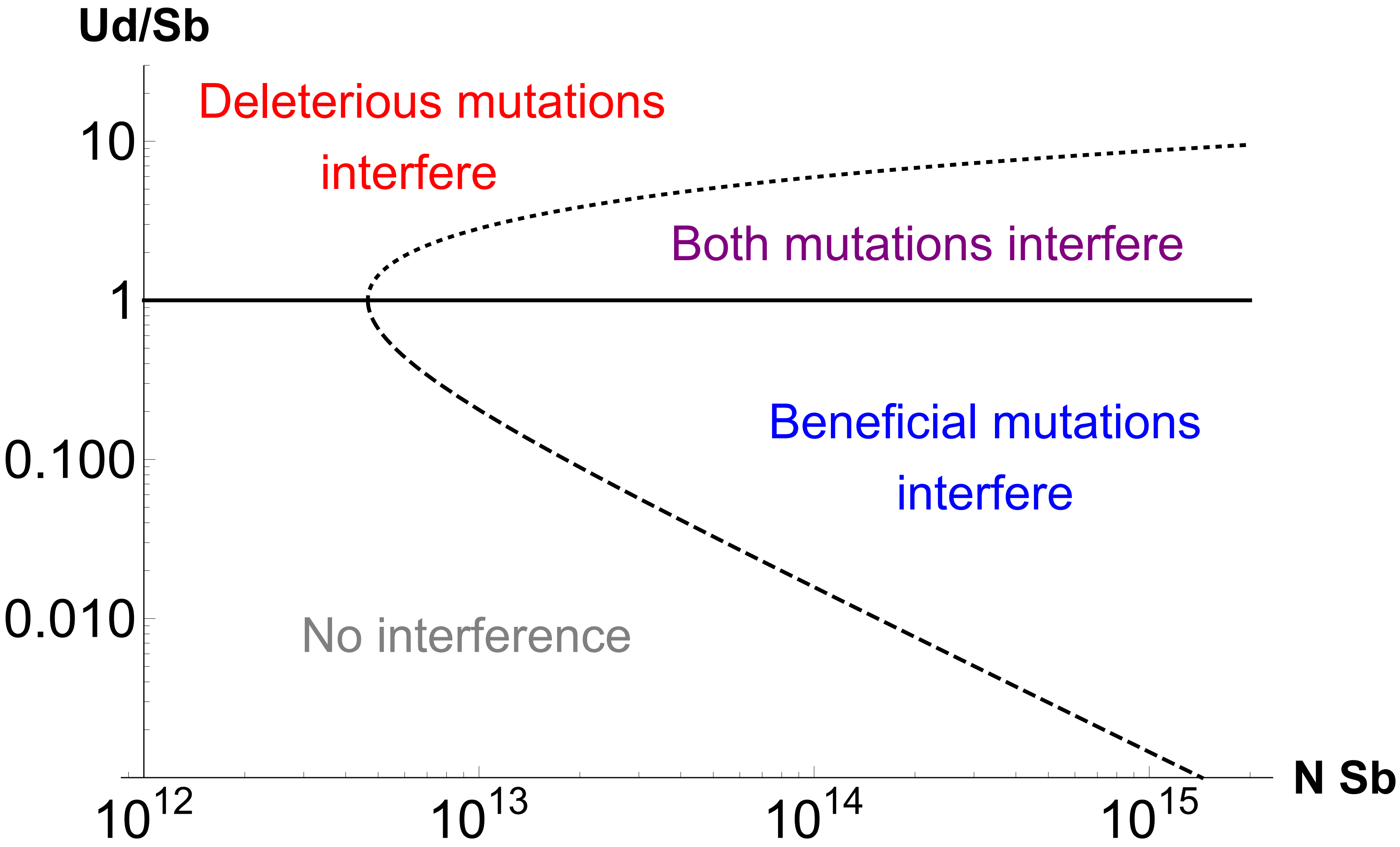
$$R \propto \begin{cases} Nu_b \ , & \text{for small populations} \\ \ln(Nu_b) \ , & \text{for large populations} \end{cases}$$

Adaptation slows down due to

- Burden of linked deleterious mutations
- Competition with superior beneficial mutations



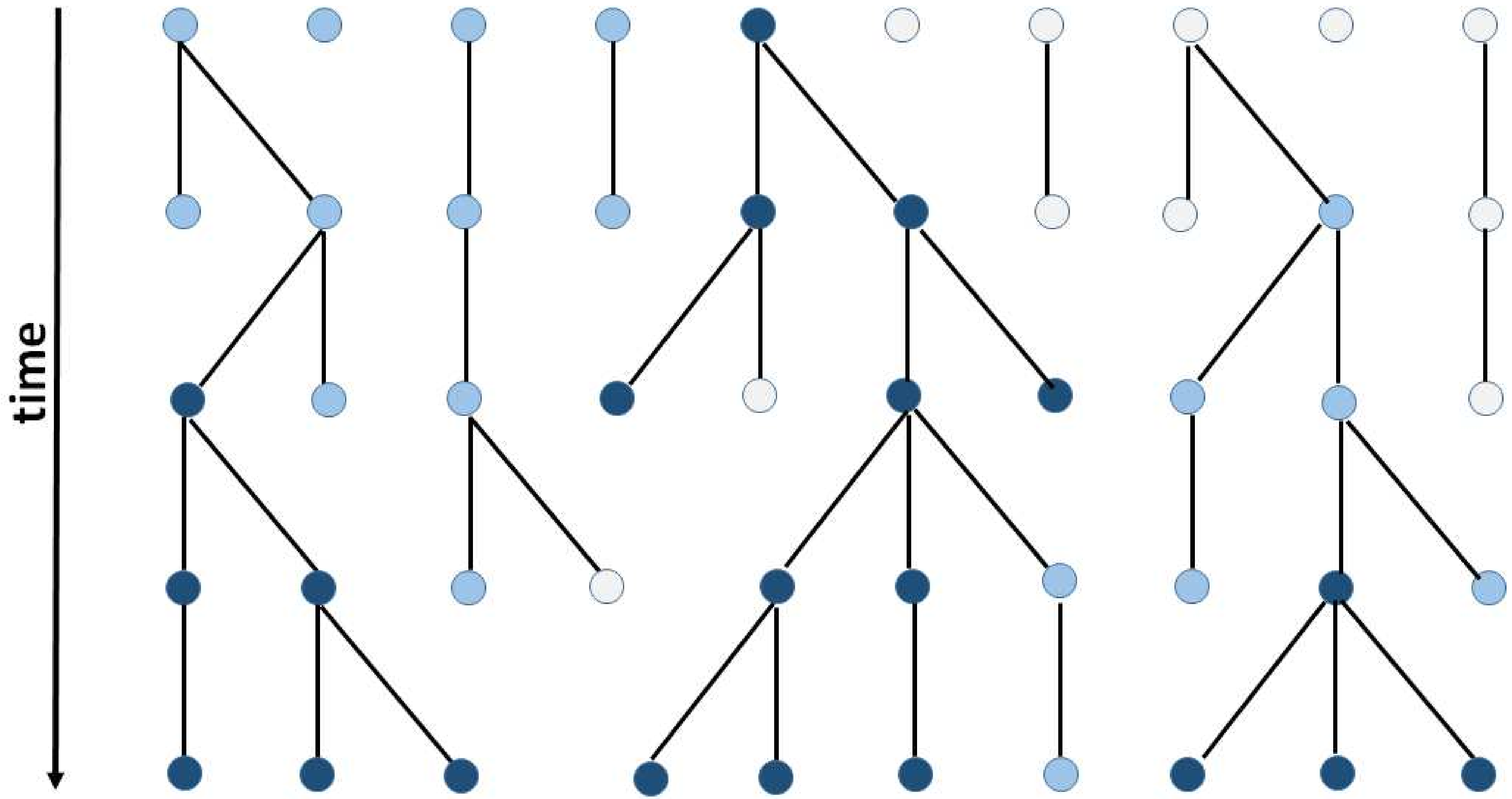
Impediments to asexual adaptation (Jain 2019)



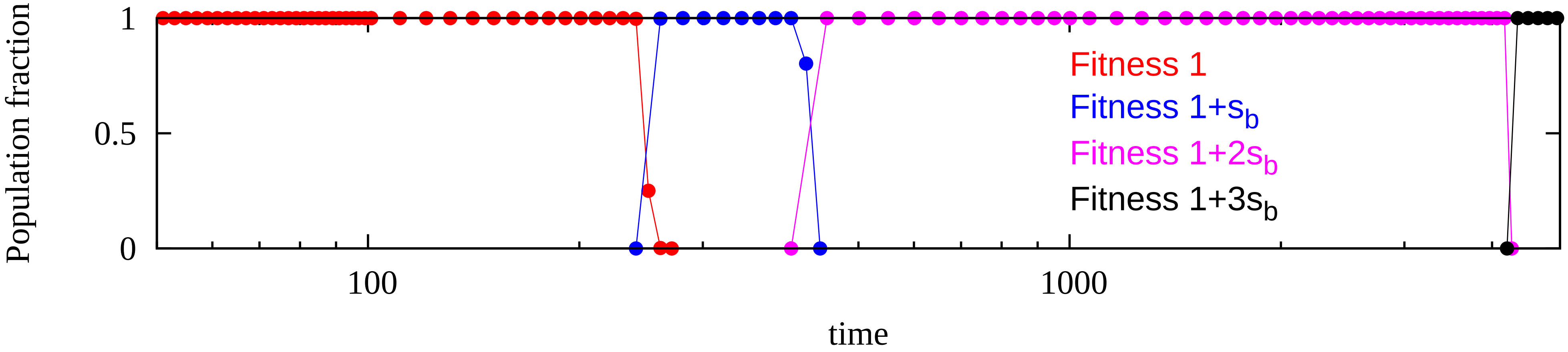
Summary

- Deleterious mutations (disease) can hitchhike with beneficial ones (adaptation) in absence of genetic mixing
- Weak deleterious mutations and high mutation rates have adverse effect on adaptation rate
- Recombination can alleviate these. But to what extent is not understood

Wright-Fisher dynamics (Fisher, Wright ∼1920s)



Rate of adaptation: simplest scenario



Simulation run of Wright-Fisher process (Jain & Krug 2007)

$$
\begin{aligned}
R &= \text{Rate at which population fitness increases} \\
&= \underbrace{N u_b}_{\text{beneficial mutation production rate}} \times \underbrace{2 s_b}_{\text{fixation prob}} \times \underbrace{s_b}_{\text{fitness gain per fixation}}
\end{aligned}
$$

Rapid adaptation if beneficial mutations are <u>common</u> and mutant is <u>very fit</u>