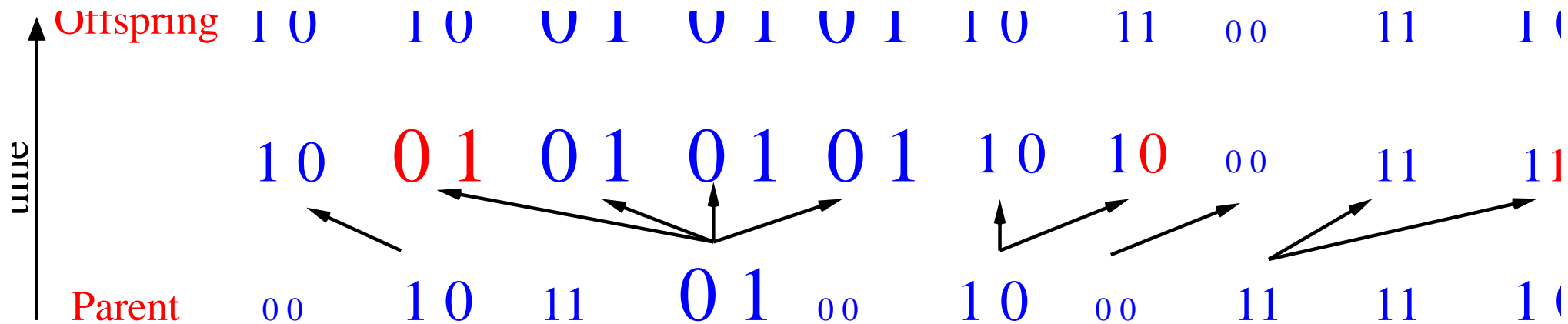


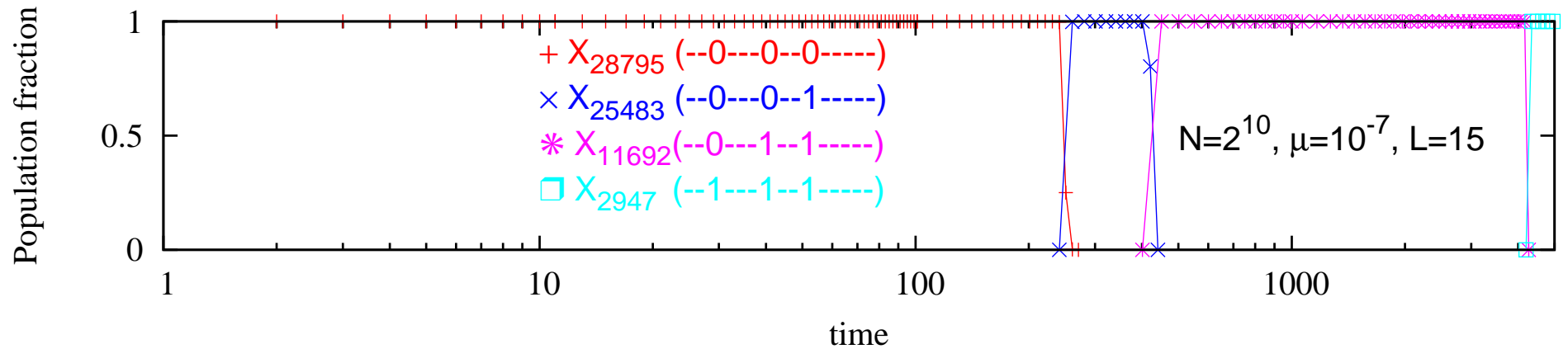
Multiloci Wright-Fisher process

In a population of size N with mutation prob per locus to be μ

avg no. of beneficial mutants produced per locus per generation = $N\mu$



Weak mutation regime, $N\mu \ll 1$ (Jain & Krug, 2007)

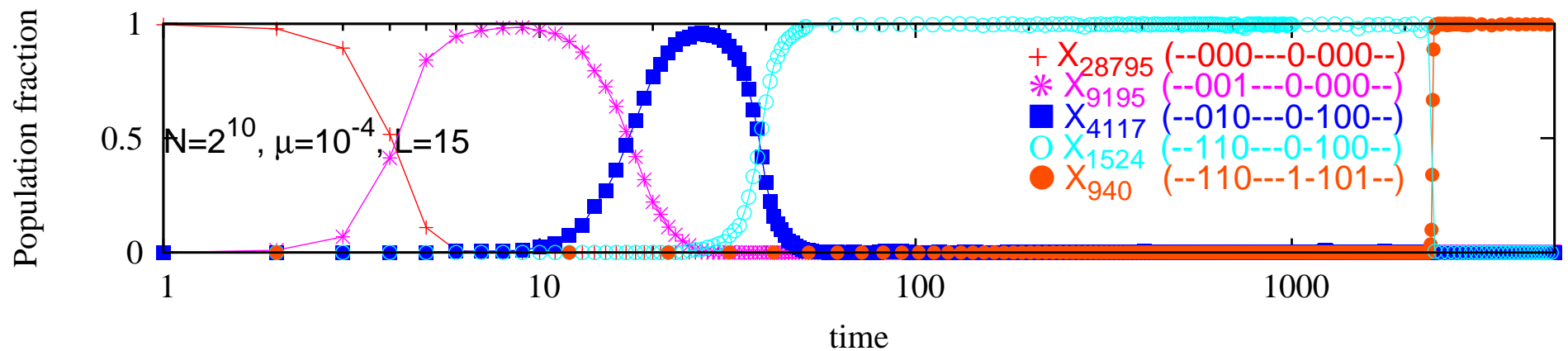


Simulation run of Wright-Fisher process

- Population is localised at one sequence (monomorphic)
- Passes through fitter mutants that are single mutation away
- Stays at a better sequence for a long time

For larger mutation probability,

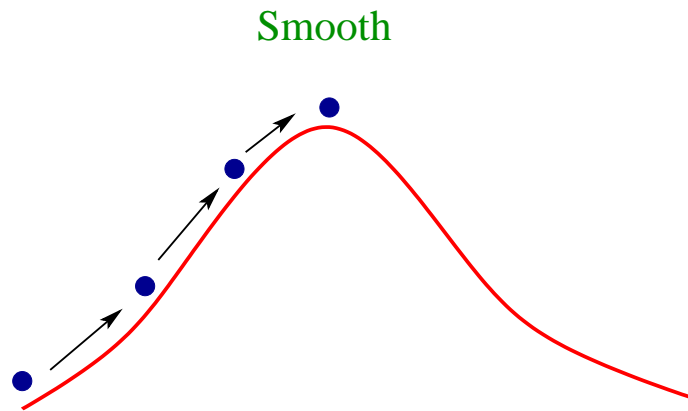
- population is polymorphic at short times



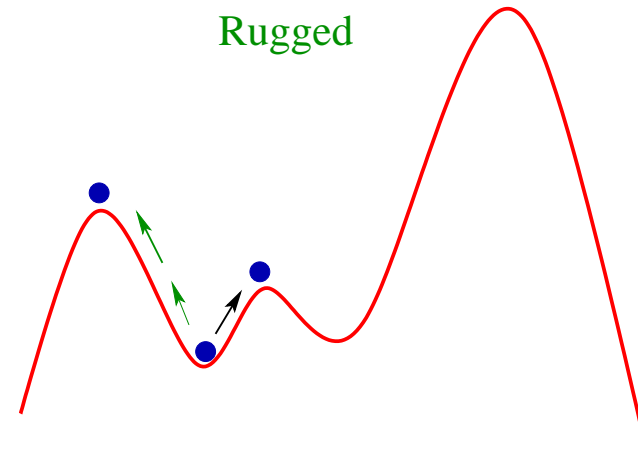
- But, at larger times, population is monomorphic

Evolution of monomorphic population?

Evolution in weak mutation regime



Reaches the global maximum



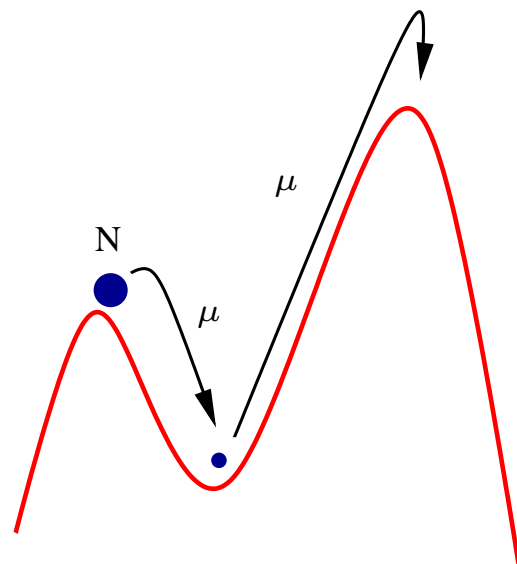
Trapped at a local maximum

Cross fitness valley in

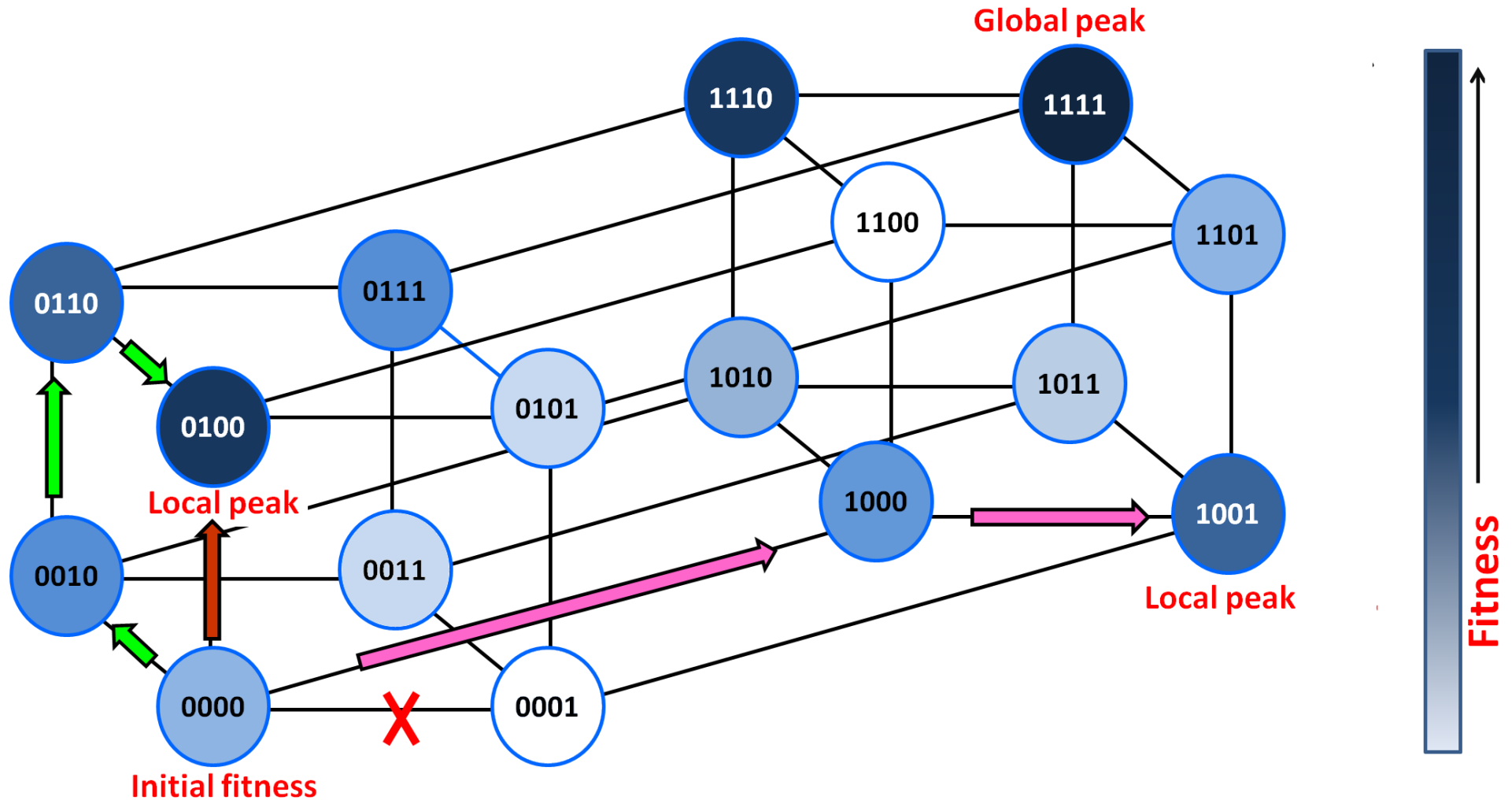
$$\text{time} \sim (N\mu^2)^{-1}$$

Here we work on time

$$\text{scales} \sim (N\mu)^{-1}$$



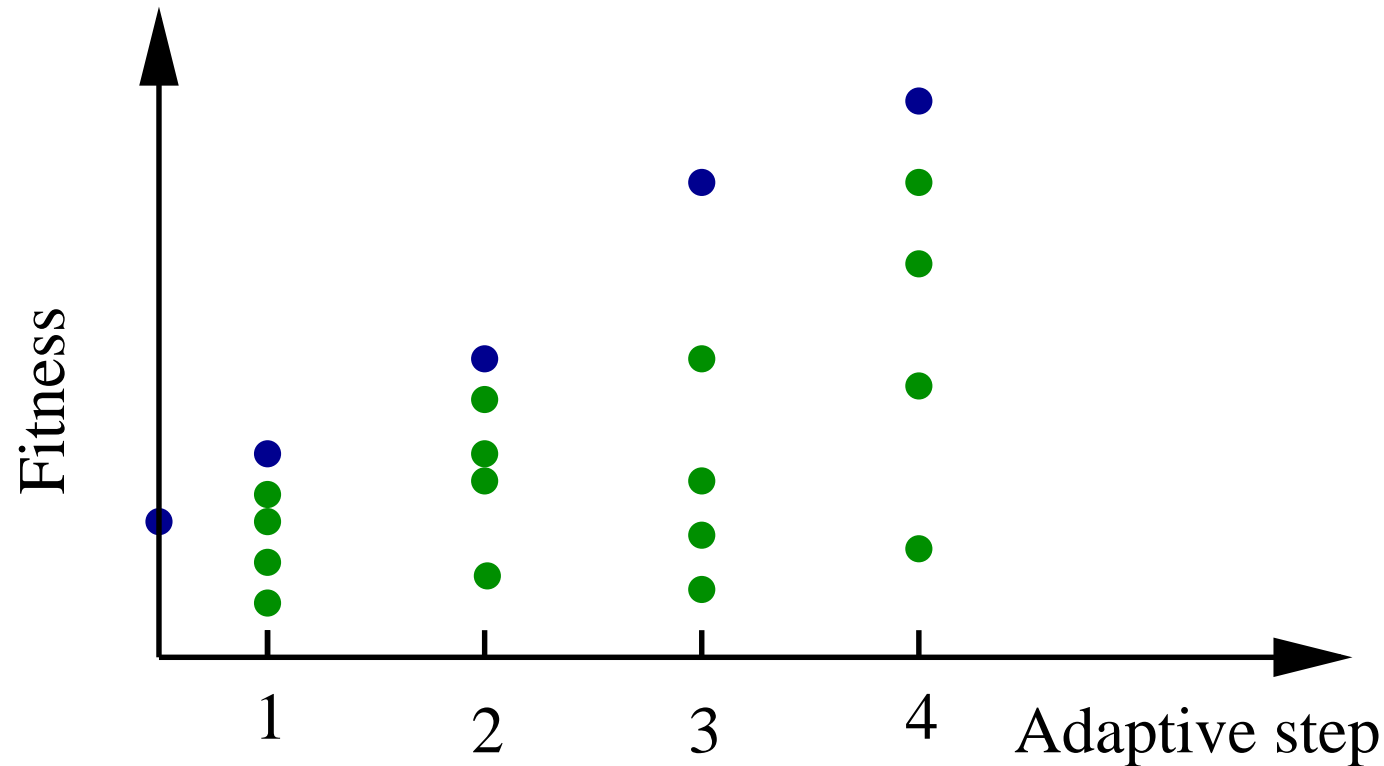
Adaptive walk model (Maynard-Smith, 1970; Gillespie, 1984)



How does the population choose a better mutant?

Model 1: Greedy walk (Orr, 2003)

Choose the best mutant at each step: every chosen fitness is a record !



$$\text{Prob(at least } j \text{ steps)} = 1 \frac{L}{L} \frac{L}{2L} \frac{L}{3L} \dots \frac{L}{jL} = \frac{1}{j!}$$

Model 2: Random adaptive walk (Flyvbjerg & Lautrup, 1992)

Choose any of the better mutants with equal probability

Heuristic argument: for uniformly distributed fitnesses,

$$f_0 = 0, \quad f_1 = \frac{\int_0^1 dx x}{\int_0^1 dx} = \frac{1}{2}, \quad f_2 = \frac{\int_{1/2}^1 dx x}{\int_{1/2}^1 dx} = \frac{3}{4}, \dots$$

Walk terminates when average fitness = local peak fitness

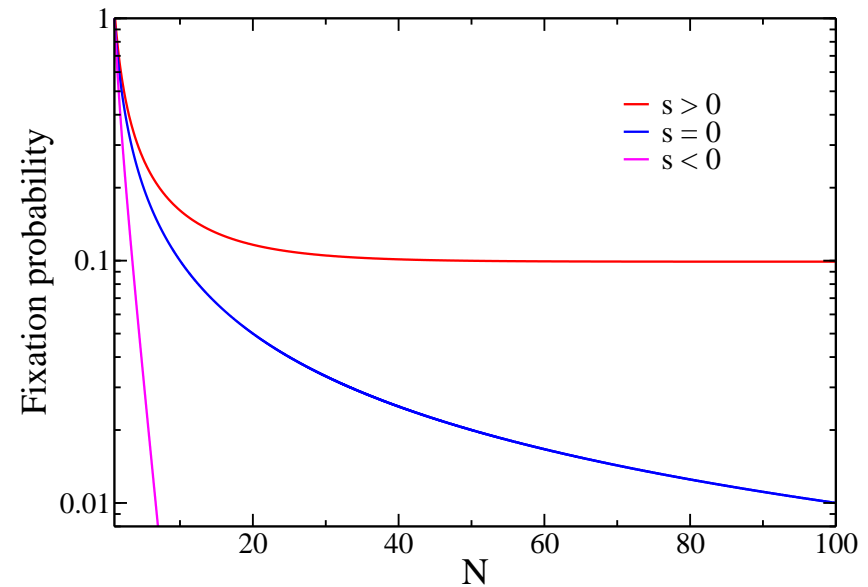
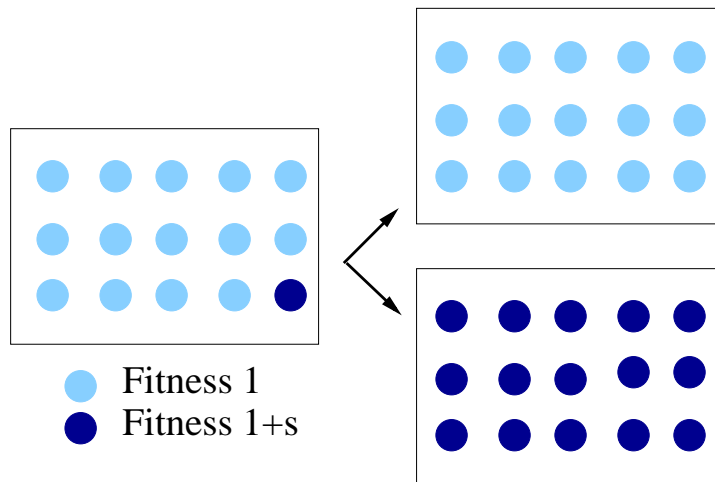
$$1 - 2^{-J} \sim 1 - L^{-1}$$

Yields the logarithmic dependence of walk length !

Model 3: Natural selection walk

Better the mutant, higher is its chance to be chosen

At any time, only two types present → one locus problem



$$\text{Probability (all } \bullet) = \frac{1 - e^{-2s}}{1 - e^{-2Ns}} \quad (\text{Kimura, 1962})$$

$$\text{Probability (all } \bullet \text{)} = \frac{1 - e^{-2s}}{1 - e^{-2Ns}} \quad (\text{Kimura, 1962})$$

Strong selection regime, $N|s| \gg 1$:

- Neglect deleterious and neutral mutations
- Fixation probability of beneficial mutations $\approx 1 - e^{-2s}$

Basic recursion equation (Flyvbjerg & Lautrup, 1992; Jain & Seetharaman, 2011)

$P_J(f|f_0)$ = Prob(fitness fixed is f at the J th step, starting from f_0)

$$P_{J+1}(f|f_0) = \int_{f_0}^f dh \underbrace{T(f \leftarrow h)}_{\text{Transition prob}} \underbrace{(1 - q^L(h))}_{\text{Availability prob}} P_J(h|f_0)$$

where

$$q^L(h) = \text{Prob(none are better than } h) = \left(\int_0^h dg p(g) \right)^L$$

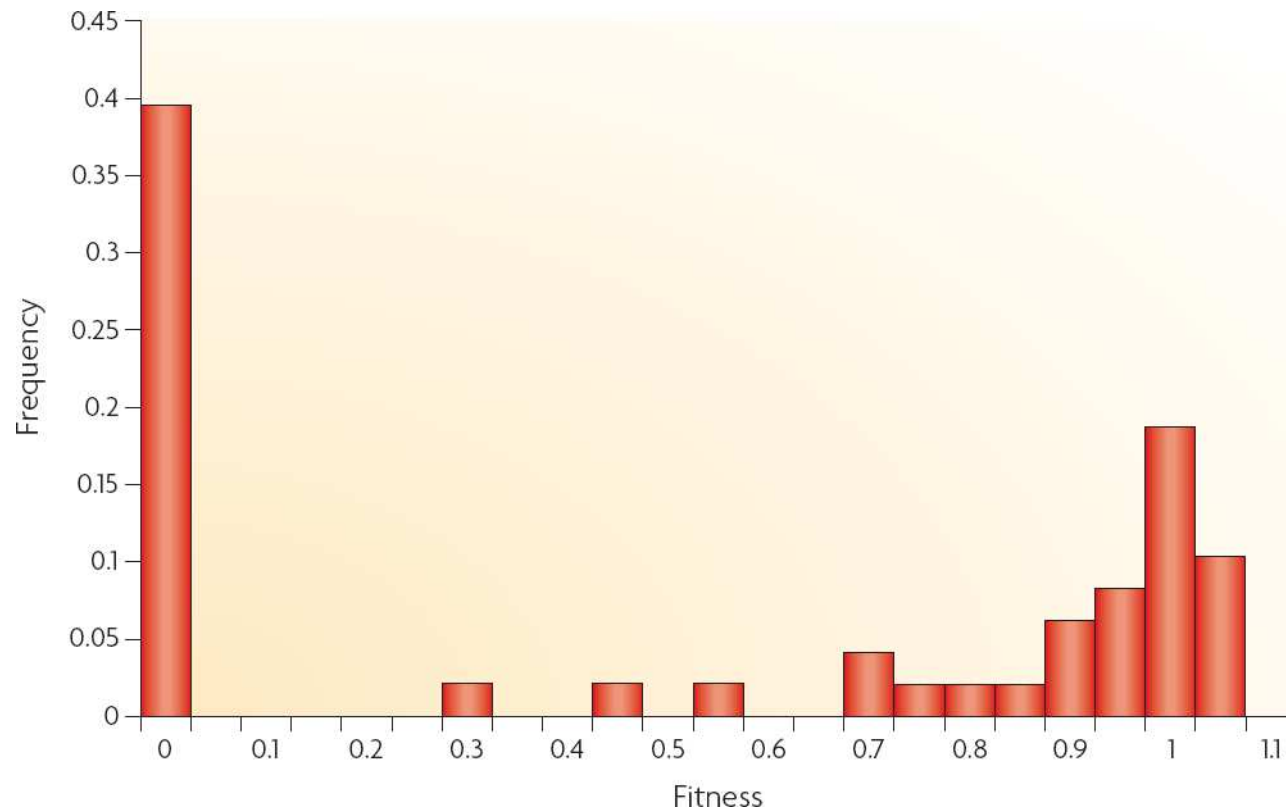
$$T(f \leftarrow h) = \text{Transition probability} \propto 1 - e^{-2\left(\frac{f-h}{h}\right)}$$

No longer universal: biologically relevant fitness distribution(s)?

Fitness distribution: experiments (Eyre-Walker & Keightley, 2007)

Introduced random single-mutations in wild type virus with fitness 1

Fitness: relative growth rate of the mutant (Sanjuan et al. 2004)

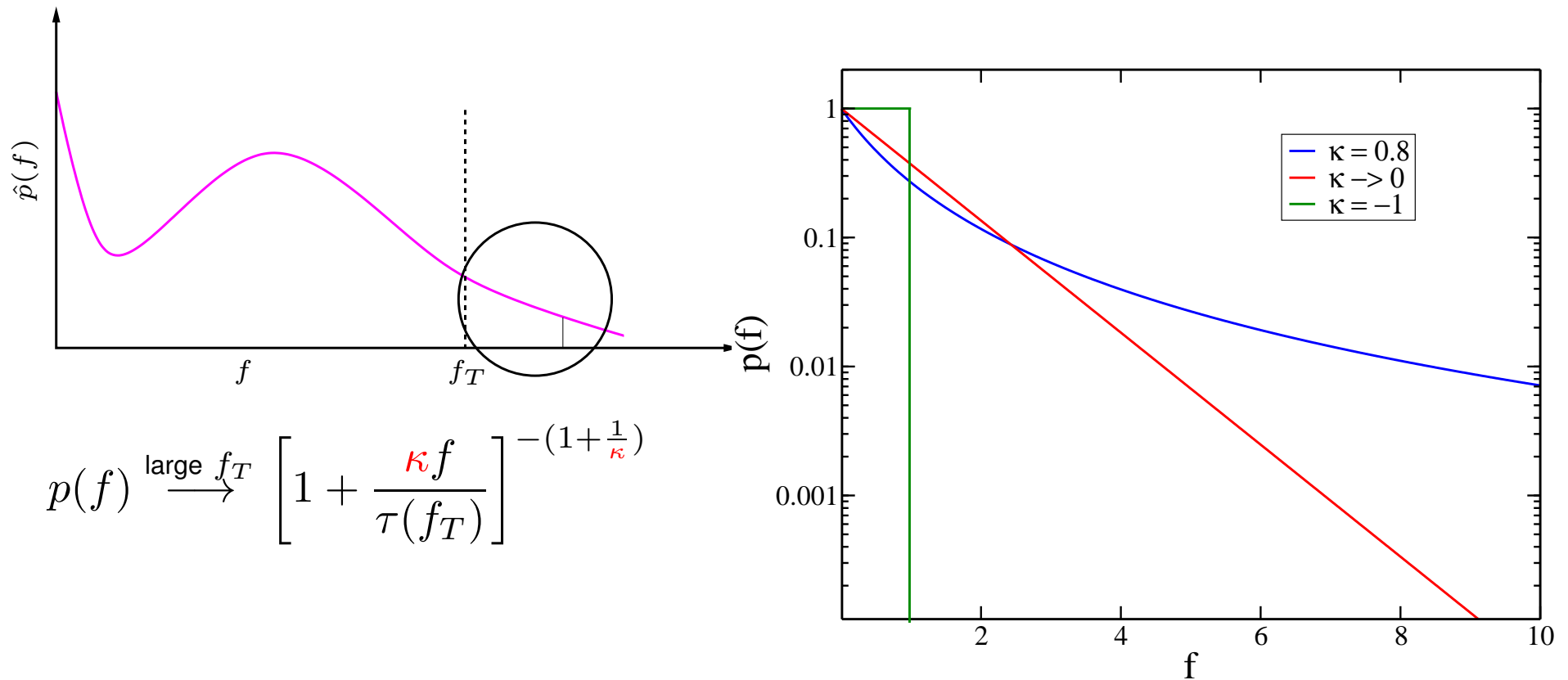


Beneficial mutations are much rarer than the deleterious ones

Distribution of beneficial fitnesses: theory (Gillespie 1983; Orr 2003)

Rare events can be described by an extreme value theory

Conditional distribution above a large threshold can be of only three types !



many effects of small size OR few effects of very large size?

Distribution of beneficial fitnesses: experiments

Direct measurement of DBFE:

- measure the fitness of one-step mutants above a large threshold
- fit it to the extreme value distribution

$$p(f) \xrightarrow{\text{large } f_T} \left[1 + \frac{\kappa f}{\tau(f_T)} \right]^{-\left(1 + \frac{1}{\kappa}\right)}$$

All the three domains have been observed in experiments !

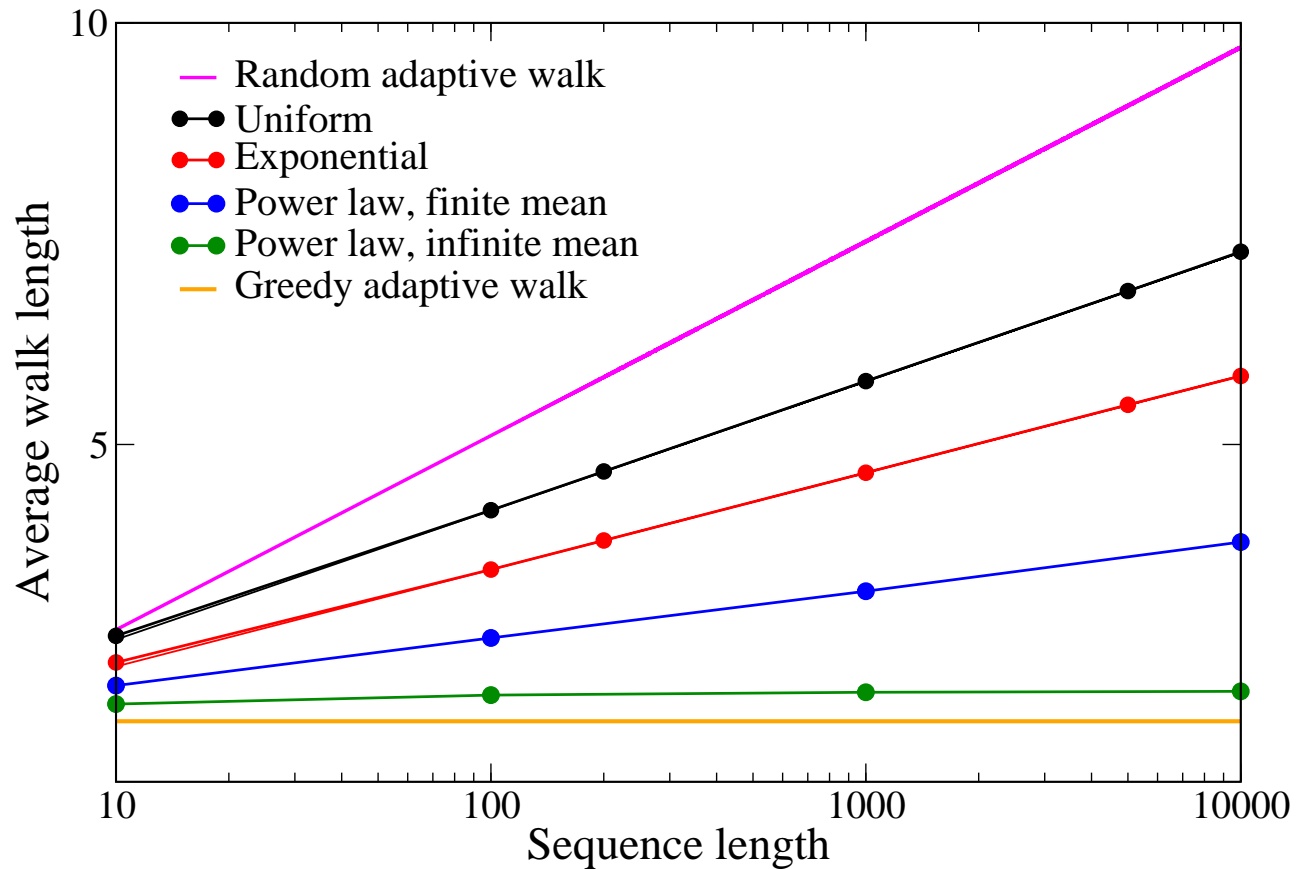
$\kappa \rightarrow 0$ (Exponential): Sanjuan et al. 2004, several others

$\kappa < 0$ (Bounded): Rokyta et al. 2008; Bataillon et al. 2011

$\kappa > 0$ (Fat-tailed): Schenk et al. 2012

What can we learn about DBFE from adaptation dynamics?

Transition in the walk length (Jain & Seetharaman, 2011; Jain, 2011)



For $L \rightarrow \infty$: walk length is infinite (finite), if mean of $p(f)$ is finite (infinite)

Transition in the walk length: an argument

$$T(f \leftarrow h) = \frac{(f - h)p(f)}{\int_h^\infty dg(g - h)p(g)}$$

If the mean of the fitness distribution is finite:

transition probability is finite for finite fitness differences

\implies for infinitely long sequence, walk goes on forever

If the mean of the fitness distribution is infinite:

denominator is dominated by an extreme value fitness

transition probability is finite when fitness differences are large

\implies for infinitely long sequence, walk terminates

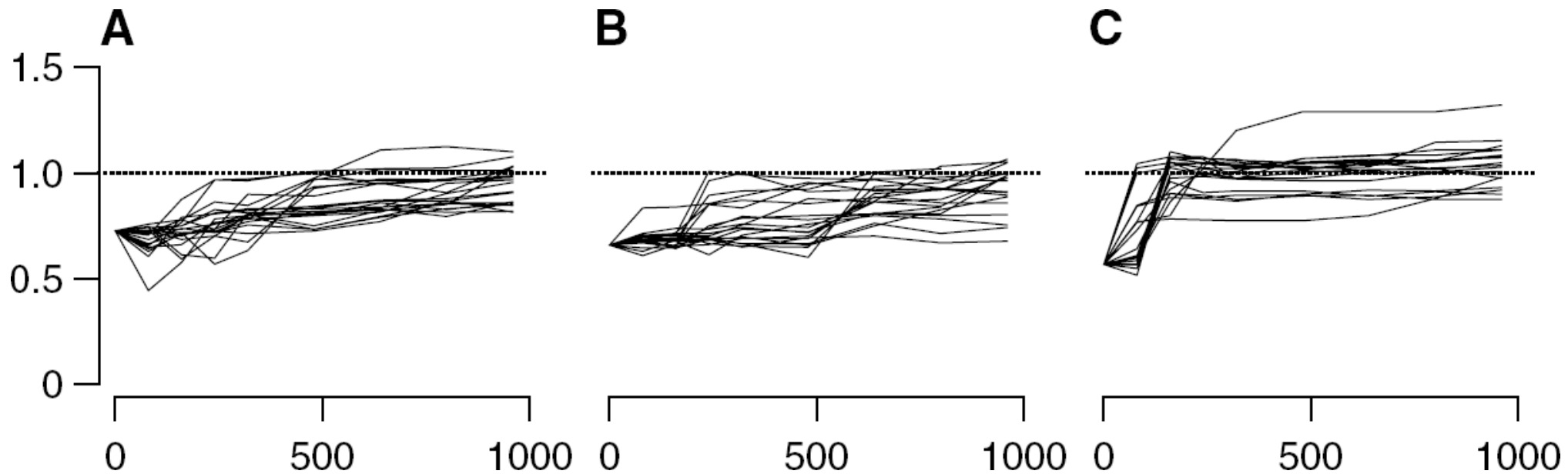
(Generating function of distribution $P_J(f)$ can be found)

Walk length in experiments (Gifford et al., 2011)

20 replicate populations of *A. nidulans* evolved for 800 generations

Fitness (growth rate) of the colony measured

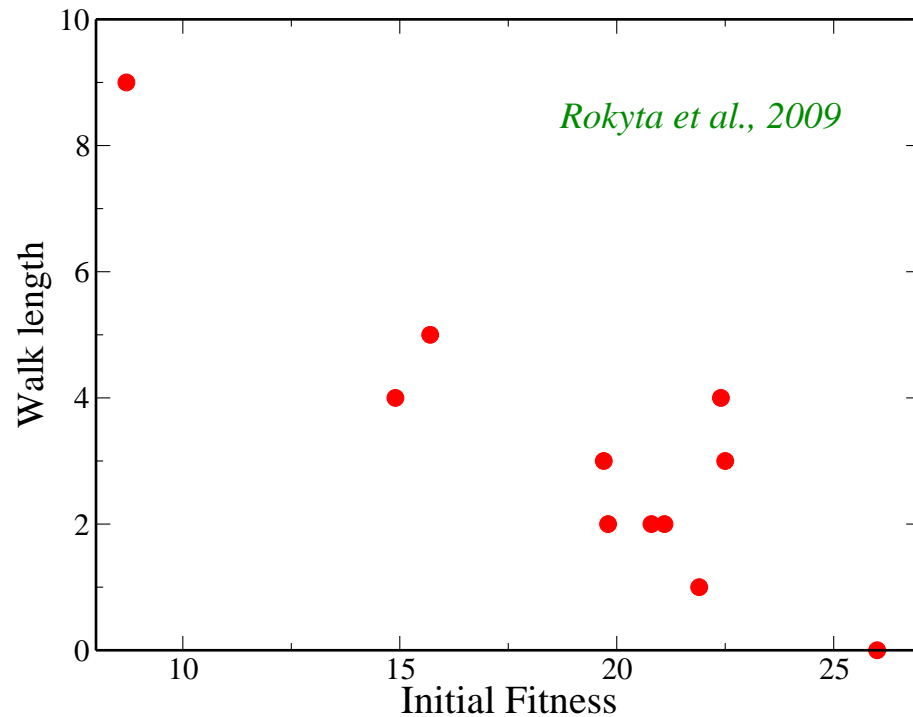
For different initial conditions, counted substitutions until fitness saturated



Walk length in experiments

Adaptive walks in bacteriophage

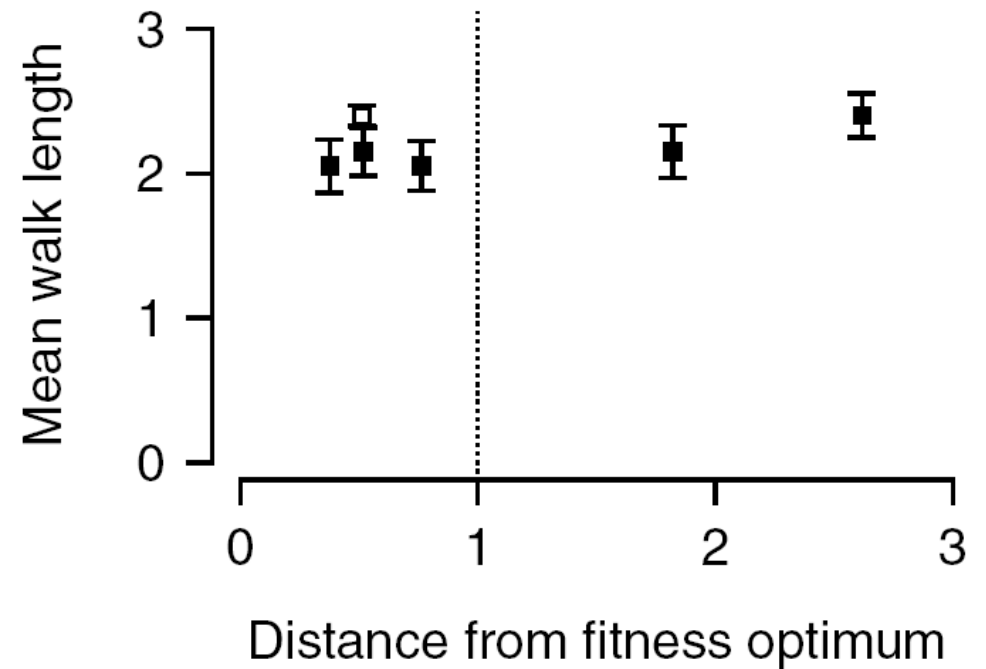
(Rokyta et al. 2009)



consistent with theory

Adaptive walks in fungus *A. nidulans*

(Gifford et al. 2011)



inconsistent with theory

Average fitness fixed during the walk

$$\bar{f}_J(f_0) = \int_{f_0}^u df f P_J(f|f_0)$$

For large initial fitnesses, we find the fitness fixed to be of the form

$$\bar{f}_{J+1} = a \bar{f}_J + b, \quad \kappa < 1$$

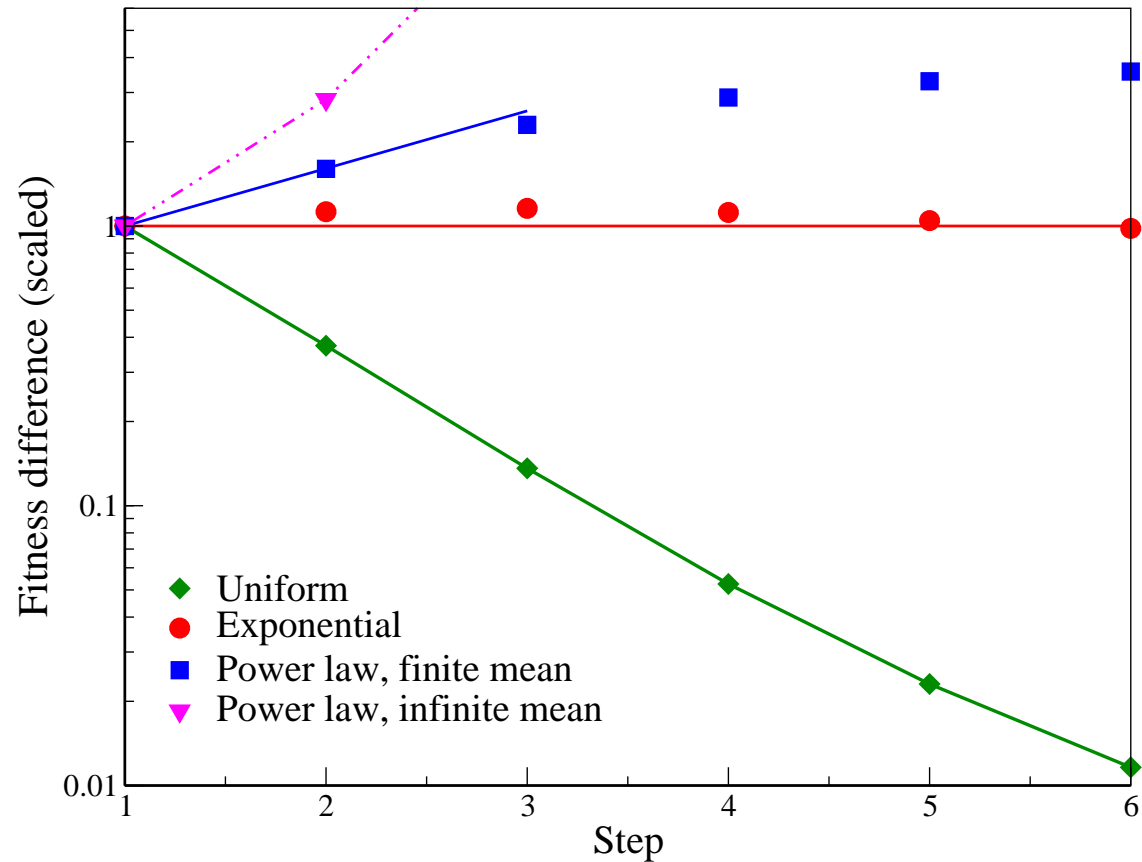
where

$$a = \begin{cases} (1 - 2\kappa)^{-1} & < 1 & \text{(bounded)} \\ 1 & & \text{(exponential)} \\ \frac{\kappa - e^2(1-\kappa)E_{1/\kappa}(2)}{2e^2\kappa(1-\kappa)E_{1/\kappa}(2)} & > 1 & \text{(unbounded)} \end{cases}$$

This has the consequence that

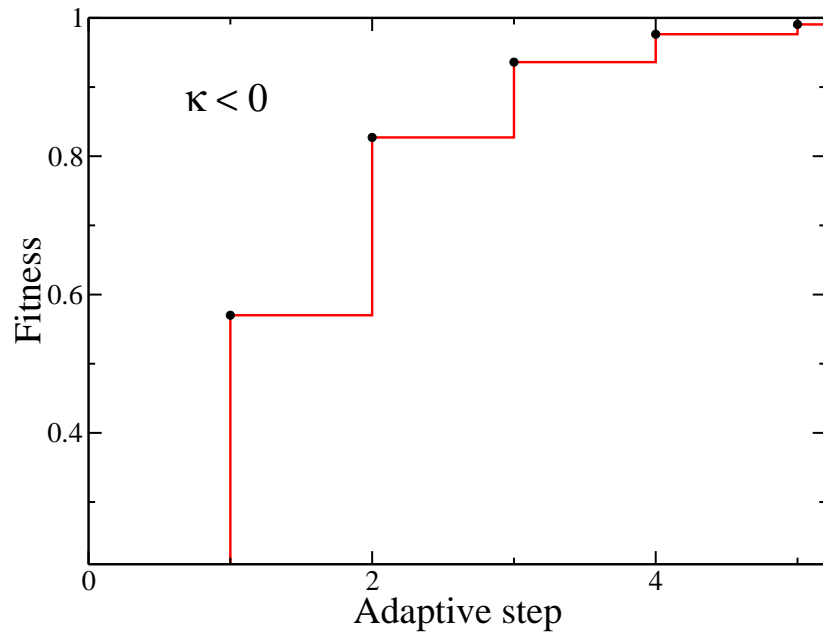
$$\bar{f}_{J+1} - \bar{f}_J = a^J ((a - 1)f_0 + b)$$

Fitness difference is qualitatively different in three domains

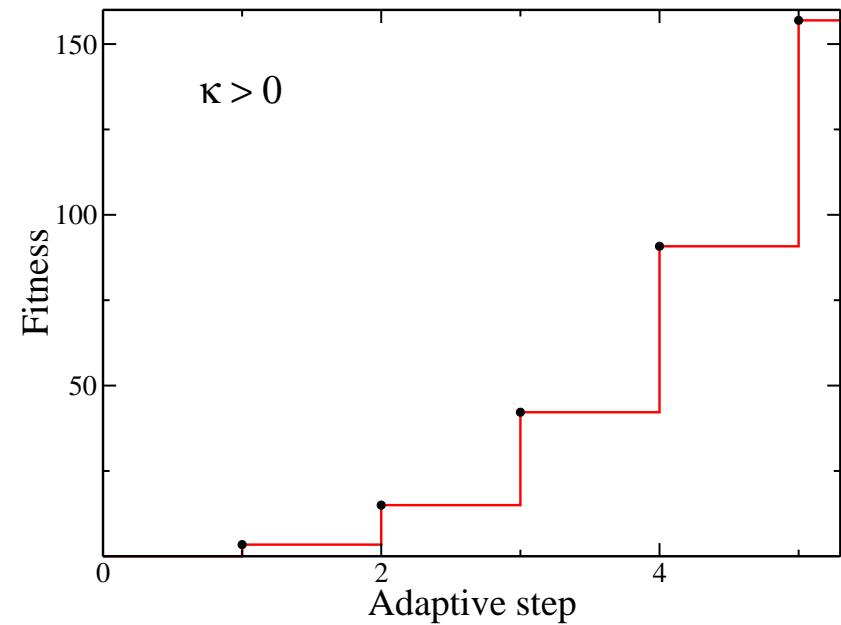


$$\bar{f}_{J+1} - \bar{f}_J \sim a^J$$

Fitness difference is qualitatively different in three domains



Diminishing returns

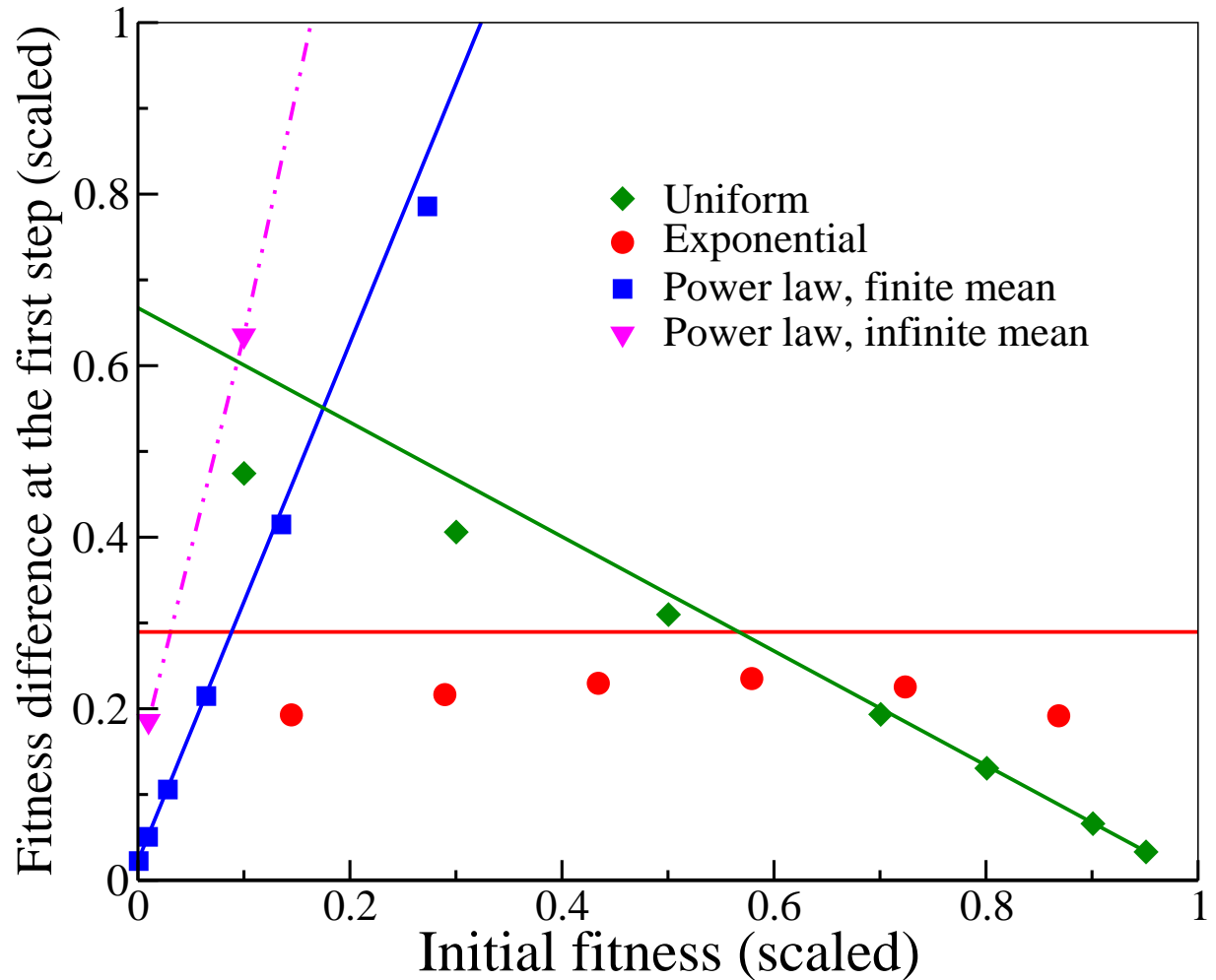


Accelerating returns

Fitness difference is qualitatively different in three domains

Since adaptive walks are short, measure fitness fixed at first step by changing initial fitness

Simple, experimentally accessible way to deduce DBFE from adaptation dynamics

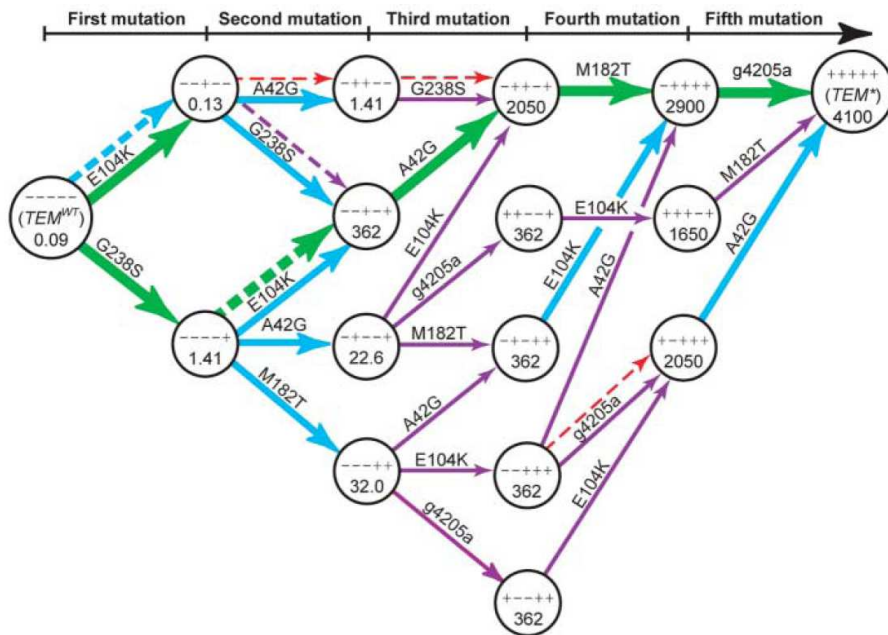


$$\bar{f}_1 - f_0 = (a - 1)f_0 + b$$

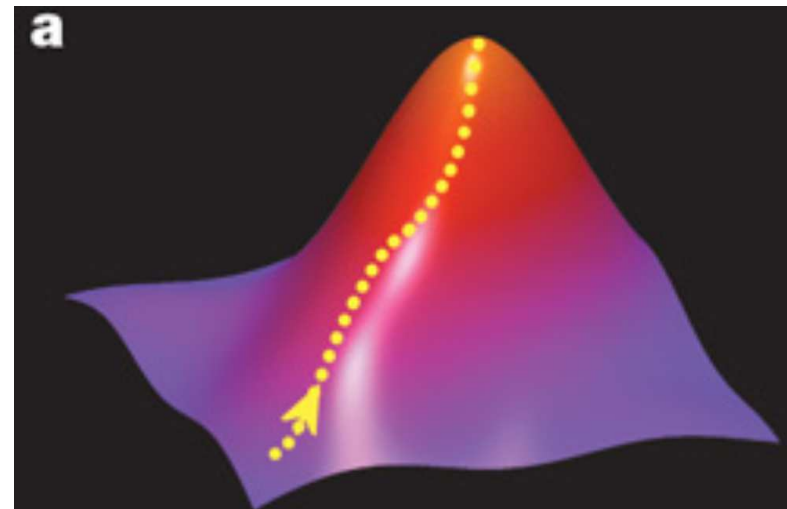
Fitness landscape: experiments (Weinreich et al. 2006)

Worked with five loci and generated all 32 mutants of WT

Fitness: minimum antibiotic concentration that blocked bacterial growth



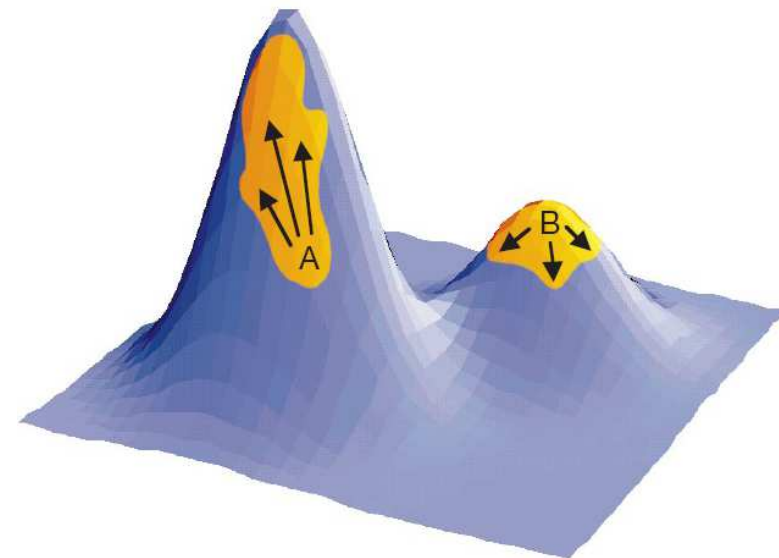
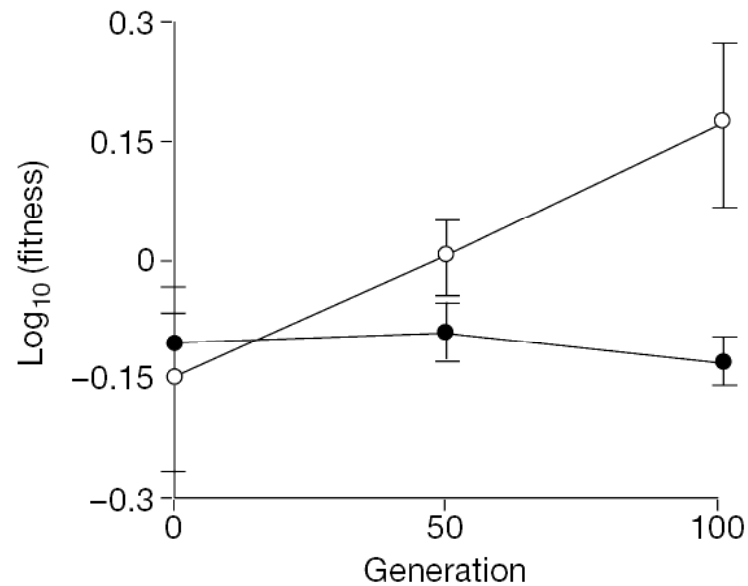
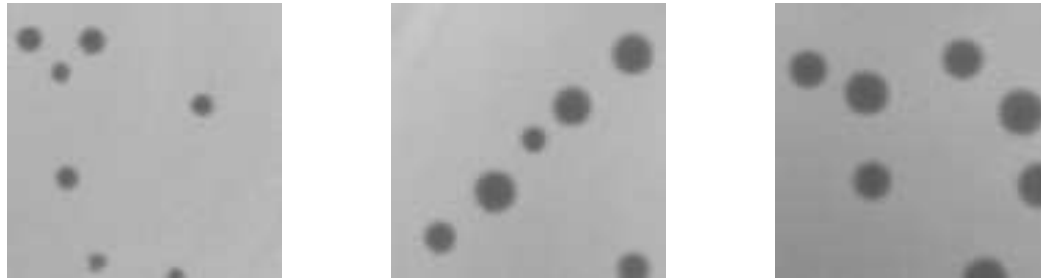
At every step, at least one fitter mutant was found



Smooth fitness landscape

Fitness landscape: experiments (Burch & Chao, 2000)

Fitness: size of the viral plaques on bacterial lawn



Rugged fitness landscape