The Dynamics of Adaptation on Correlated Fitness Landscapes

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Supporting information

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1 Markov chain formalism and solutions

As described in the main text, we consider an asexual population of fixed size N that evolves according to the Wright-Fisher model in the limit of low mutation rates [1, 2]. The type of an individual is determined solely by its fitness. Since under the weak-mutation limit the population is monomorphic except for negligibly brief periods when a mutation sweeps to fixation, the state of the population as a whole is completely described by the current fitness of its individuals. $\Phi_x(y)dy$ denotes the fitness parametrized landscape, i.e. the probability that the mutation arising in an individual with fitness x has a fitness in $[y, y+dy]$. $s_x(y) = y/x - 1$ is the selection coefficient of such a mutation in a population with fitness x. The probability of fixation of the mutant is then given by [3]

$$\pi_x(y) = \pi(s_x(y)) = \frac{1 - e^{-2s_x(y)}}{1 - e^{-2Ns_x(y)}}, \tag{S1}$$

which, in the infinite population size limit becomes $\pi_x(y) = 1 - e^{-2s_x(y)}$ for $y > x$ and zero otherwise. If the mutation is fixed, the population transitions instantaneously from fitness x to new fitness y. The adaptive walk is then described by a stationary continuous-time Markov chain with state space $[0, +\infty)$. The population waits for the next mutation on average θ^{-1} generations where $\theta = \mu N$ is per locus per generation mutation rate scaled by population size. If time t is measured in the expected number of arrived mutations, the instantaneous transition rate from state x to state y is

$$Q(y|x) = \Phi_x(y)\pi_x(y). \tag{S2}$$

We are interested in the probability $P(y, t|x)$ of finding the population at fitness value y after time t given initial fitness x at time zero and in the probability $P_i(t|x)$ for the population to accumulate i substitutions by time t given initial fitness x. Here we present the general operator-based formulation which is well-suited for the mathematical analysis and for analytic calculations with simple fitness landscapes. We also derive recursion relations appropriate that are convenient for the numerical computation of the distributions $P(y, t|x)$ and $P_i(t|x)$ as well as their moments.

1.1 Formal solutions

Define the forward and backward operators by

$$\begin{aligned}\big(\hat{K}_{\mathrm{f}} f(\cdot)\big)(y) &= \int_0^\infty \big(f(\xi)Q(y|\xi) - f(y)Q(\xi|y)\big)\, d\xi, &\text{(S3)}\\ \big(\hat{K}_{\mathrm{b}} f(\cdot)\big)(x) &= \int_0^\infty Q(\xi|x)\big(f(\xi) - f(x)\big)\, d\xi, &\text{(S4)}\end{aligned}$$

respectively. It follows from the standard Markov chain theory that $P(y,t|x)$ satisfies the forward and backward Kolmogorov equations

$$\begin{aligned}
\frac{\partial P}{\partial t}(y,t|x) &= \big(\hat{K}_{\mathrm{f}} P(\cdot,t|x)\big)(y) && \text{(S5)}\\
\frac{\partial P}{\partial t}(y,t|x) &= \big(\hat{K}_{\mathrm{b}} P(y,t|\cdot)\big)(x), && \text{(S6)}
\end{aligned}$$

with the initial condition

$$P(y,0|x) = \delta(y-x), \tag{S7}$$

where $\delta(z)$ is the Dirac delta-function. The formal solutions to the equations (S5)–(S7) can be written as

$$\begin{aligned}
P(y,t|x) &= \big(\exp\{t\,\hat{K}_{\mathrm{f}}\} P(\cdot,0|x)\big)(y), && \text{(S8)}\\
P(y,t|x) &= \big(\exp\{t\,\hat{K}_{\mathrm{b}}\} P(y,0|\cdot)\big)(x), && \text{(S9)}
\end{aligned}$$

where the operator exponentiation is defined as $\exp\{\hat{F}\} = \sum_{i=0}^{\infty} \hat{F}^i/i!$.

The equations for $P_i(t|x)$ are more cumbersome. In the next section we show that $P_i(t|x)$ satisfy recursive equations

$$\begin{aligned}
\frac{\partial P_0}{\partial t}(t|x) &= -q(x) P_0(t|x), && \text{(S10)}\\
\frac{\partial P_i}{\partial t}(t|x) &= -q(x)\big(P_i(t|x) - P_{i-1}(t|x)\big) + \big(\hat{K}_{\mathrm{b}} P_{i-1}(t|\cdot)\big)(x), \quad i = 1,2,\ldots && \text{(S11)}
\end{aligned}$$

with the initial condition

$$P_i(0|x) = \delta_{i0}, \tag{S12}$$

where δ_{ij} is the Kronecker delta and

$$q(x) = \int_0^\infty Q(y|x)\, dy \tag{S13}$$

is the expected fixation probability of a mutant that occurs in the background x (see also equation (3) in the main text),

The solution to equations (S10)–(S12) is given by

$$\begin{aligned}
P_0(t|x) &= e^{-q(x)t} && \text{(S14)}\\
P_i(t|x) &= \int_0^t d\tau \int_0^\infty e^{-q(x)(t-\tau)} Q(\xi|x) P_{i-1}(\tau|\xi)\, d\xi,\\
&\quad \text{for } i = 1,2,\ldots && \text{(S15)}
\end{aligned}$$

1.2 Derivation of the distribution $P_i(t|x)$

In order to derive the equations (S10), (S11), note that the probability $P(y,t|x)$ of observing the population at fitness y at time t given that it had fitness x at time zero can be expressed as a sum of the probabilities of reaching fitness y from fitness x in time t with any possible number of substitutions,

$$P(y,t|x) = \sum_{i=0}^{\infty} P_i(y,t|x).$$

$P_i(y,t|x)$ is the probability for the population to reach fitness y by time t in exactly i substitution events, given the initial fitness x. Then the probability of having accumulated exactly i substitutions by time t is $P_i(t|x) = \int_0^\infty P_i(y,t|x)dy$. It is easy to derive the recursion relations for $P_i(y,t|x)$ from the following considerations. First note that after zero substitutions the population must have the initial fitness x and, since the first substitution will occur with rate $q(x)$, we have

$$P_0(y,t|x) = \delta(y-x)e^{-q(x)t}. \tag{S16}$$

After integrating this expression over y we obtain (S14). Now, in order for the population to be in fitness y at time t after exactly i substitutions, the first substitution must have occurred at some time $\tau < t$ which moved the population to some fitness ξ after which another $i-1$ substitutions brought it to fitness y in the period of time between τ and t. So, conditioned on ξ and τ, the probability of finding the system in state y at time t is the product of three probabilities: (a) the probability of the first substitution occurring at time τ, $q(x)e^{-q(x)\tau}$, (b) the probability that the first substitution moves the population to fitness ξ, $Q(\xi|x)/q(x)$, and (c) the probability that $i-1$ substitutions move the population from fitness ξ to fitness y in the time period $t-\tau$, $P_{i-1}(y,t-\tau|\xi)$. Therefore, integrating over all τ and ξ,

$$P_i(y,t|x) = \int_0^\infty d\xi \int_0^t e^{-q(x)\tau} Q(\xi|x) P_{i-1}(y,t-\tau|\xi)\, d\tau, \quad \text{for } i = 1,2,\ldots \tag{S17}$$

It is easy to show that $\sum_{i=0}^\infty P_i(y,t|x)$ with $P_i(y,t|x)$ defined by equations (S16), (S17) satisfies the backward Kolmogorov equation (S6). To compute the number of substitutions at time t, we rewrite the recursion equation (S17) as

$$P_i(y,t|x) = \int_0^\infty Q(\xi|x)\, d\xi \int_0^t e^{-q(x)(t-\tau)} P_{i-1}(y,\tau|\xi)\, d\tau$$

from which (S15) follows after integration with respect to y. Equations (S10), (S11) follow from (S14), (S15) by differentiating with respect to t.

1.3 Fitness and substitution trajectories

We call the expected value of the distribution $P(y,t|x)$ the fitness trajectory $F(t,x)$ and we call the expected value of the distribution $P_i(t|x)$ the substitution trajectory $S(t,x)$.

1.3.1 General equations for the fitness and substitution trajectories

Multiplying the backward equation (S6) by y and integrating it with respect to y, we obtain

$$\frac{\partial F}{\partial t}(t,x) = \big(\hat{K}_{\mathrm{b}} F(t,\cdot)\big)(x) \tag{S18}$$

with the initial condition

$$F(0,x) = x, \tag{S19}$$

whose formal solution is given by

$$F(t,x) = \big(\exp\{t\hat{K}_{\mathrm{b}}\} I(\cdot)\big)(x), \tag{S20}$$

where $I(x) = x$ is the identity function. Analogously, from equations (S10), (S11) follows that the substitution trajectory satisfies the equation

$$\frac{\partial S}{\partial t}(t,x) = q(x) + \big(\hat{K}_{\mathrm{b}} S(t,\cdot)\big)(x). \tag{S21}$$

with the initial condition

$$S(0,x) = 0, \tag{S22}$$

whose solution is given by

$$S(t,x) = \sum_{i=0}^{\infty} \big(\hat{K}_{\mathrm{b}}^{i} q(\cdot)\big)(x) \frac{(t)^{i+1}}{(i+1)!}. \tag{S23}$$

An obvious result follows immediately from equation (S21): if the rate rate of substitutions is the same for all fitnesses, i.e., if $q(x) = q_0 = \mathrm{const}$, then the substitutions accumulate linearly with time. Indeed, since $\big(\hat{K}_{\mathrm{b}} q_0\big)(x) \equiv 0$, equation (S21) becomes an ordinary differential equation whose solution is $S(t,x) = q_0 t$.

1.3.2 Approximate equations for the fitness and substitution trajectories

In this section we derive equations (1)–(2) in the main text. We assume that the advection approximation holds and the $r(x)$ and $q(x)$ functions are sufficiently smooth. First, we notice that on landscapes for which mutations of large effect become increasingly unlikely as the fitness of the parent increases, most of the contribution to the integral (S4) comes from values $\xi \approx x$ and we can write $f(\xi) - f(x) \approx f'(x)(\xi - x)$. Consequently, $\big(\hat{K}_{\mathrm{b}} f(\cdot)\big)(x) \approx r(x) f'(x)$, where $r(x)$ is given by equation (3) in the main text. Under this so-called advection approximation, equations (S18), (S21) become

$$\begin{aligned} \frac{\partial F}{\partial t}(t,x) &= r(x)\frac{\partial F}{\partial x}, \quad F(0,x) = x & \text{(S24)} \\ \frac{\partial S}{\partial t}(t,x) &= r(x)\frac{\partial S}{\partial x} + q(x), \quad S(0,x) = 0, & \text{(S25)} \end{aligned}$$

where $q(x)$ is defined by equation (4) in the main text (or equation (S13) above).

In fact, equations (S24) and (S25) are equivalent to equations equations (1)–(2) in the main text. To see this, first, let

$$\chi(x_0, x, t) = \int_{x_0}^{x} \frac{d\xi}{r(\xi)} + t.$$

This function is monotonic in x and in x_0 as long as $r(\xi)$ does not change sign. Since we are interested in adaptation, we always have $r(\xi) > 0$, so that we can solve the equation $\chi(x_0, x, t) = 0$ with respect to x_0. Denote the solution as $x_0 = u(x, t)$. Analogously, we obtain the solution of the same equation with respect to x, $x = v(x_0, t)$.

Both equations (S24) and (S25) have the same characteristic which is given by equation

$$\frac{dx}{dt} = -r(x), \quad x(0) = x_0.$$

The solution of equation (S24) does not change along this characteristic, and therefore it is given by $F(t, x) = u(x, t)$. Using the implicit function differentiation rules, it is easy to see that $F(t, x)$ satisfies equation (1) in the main text.

The solution of equation (S25) changes along this characteristic according to equation

$$\frac{dS}{dt} = q(v(x_0, t)), \quad S(x_0, 0) = 0,$$

and therefore it is given by

$$S(t, x) = \int_0^t q(v(u(x, t), \tau))d\tau = \int_x^{F(t,x)} \frac{q(\zeta)}{r(\zeta)} d\zeta.$$

Here we used the fact that $v(x_0, 0) = x_0$ and $v(u(x, t), t) \equiv x$. Now it is easy to see that $S(t, x)$ satifies equation (2) in the main text.

1.4 Numerical algorithm

Only in some special cases can the formulas (S8), (S9), (S14), (S15) be effectively used for evaluating the distributions $P(y, t|x)$ and $P_i(t|x)$. We propose the following recursion equations for the efficient numerical implementation.

1.4.1 Computing distribution $P(y, t|x)$

The basic idea behind the recursion is to write the probability $P(y, t|x)$ as the sum over all possible paths connecting the initial fitness x with fitness y at time t, each with a particular number $m = 0, 1, \ldots$ of mutations.

$$P(y, t|x) = \sum_{m=0}^{\infty} U_m(t)\ V_m(y|x). \tag{S26}$$

Here, $U_m(t)$ is the probability of observing m mutations during time interval $[0, t]$, and $V_m(y|x)$ is the probability for a change in fitness from initial value x to final value y that takes exactly m mutational attempts. Because the mutations arise independently, $U_m(t)$ is the Poisson distribution with parameter t,

$$U_m(t) = \frac{(t)^m}{m!} e^{-t}. \tag{S27}$$

Note that the sum in equation (S26) runs over all possible numbers of mutations, some of which will fix and some of which will not; if we conditioned on the mutations having been fixed, the distribution U would no longer be Poisson.

The sequence $V_m(y|x)$ can be written as follows:

$$\begin{aligned} V_0(y|x) &= \delta(y - x), && \text{(S28)} \\ V_m(y|x) &= \int_0^\infty Q(y|\xi) V_{m-1}(\xi|x)\, d\xi + V_{m-1}(y|x) \int_0^\infty (1 - \pi_y(\xi)) \Phi_y(\xi)\, d\xi && \\ \text{for} \quad & m = 1, 2, \ldots. && \text{(S29)} \end{aligned}$$

The relations (S29) have a simple intuitive interpretation. For each m but $m = 0$, the distribution of fitnesses after exactly m mutations is a sum of two terms. The first term accounts for the situation when $m - 1$ mutations preceding the current one have brought the population into state ξ. This term equals the probability that a mutation with fitness y arises and is successfully fixed in the population with the intermediate fitness ξ. The second term accounts for the situation when fitness y has already been reached with the preceding $m - 1$ mutations. In order for the final fitness to still be y, the m-th mutation whose fitness is ξ must fail to fix.

In practice, one computes the distribution of the number of mutations from equation (S27) to find the range of m over which U is non-negligible, evaluates by recursion the terms in equation (S29) in the relevant range, and finally sums them up according to equation (S26). A Matlab implementation of this algorithm is available upon request.

Now we show that the solution to the recursion relations (S26)–(S29) in fact coincides with the solution (S8) of the forward equation (S5). First, note that equations (S29) can be written in the form

$$V_m(y|x) = V_{m-1}(y|x) + \big(\hat{K}_\mathrm{f} V_{m-1}(\cdot|x)\big)(y)$$

for $m = 1, 2, \ldots$ Now it is easy to see that, in fact,

$$V_m(y|x) = \left(\sum_{i=0}^{m} \binom{m}{i} \hat{K}_\mathrm{f}^i V_0(\cdot|x) \right)(y). \tag{S30}$$

Substituting (S27) and (S30) into (S26) and changing the order of summation, we obtain

$$P(y, t|x) = \left(\sum_{i=0}^{\infty} \frac{(t\hat{K}_\mathrm{f})^i}{i!} V_0(\cdot|x) \right)(y),$$

which coincides with (S8).

1.4.2 Computing distribution $P_i(t|x)$

To compute the distribution $P_i(t|x)$, let us first write it as

$$P_i(t|x) = \sum_{m=i}^{\infty} U_m(t) W_m(i|x), \tag{S31}$$

where $W_m(i|x)$ is the probability that out of m mutations exactly i have fixed, given the initial fitness x; clearly $W_m(i|x) \equiv 0$ if $i > m$. First, note that the probability w_j that the j-th mutation has fixed, is given by the first term of equation (S29) integrated over all final fitnesses y,

$$w_j(x) = \int_0^{\infty} dy \int_0^{\infty} Q(y|\xi) V_{j-1}(\xi|x)\, d\xi, \quad j = 1, 2 \ldots$$

Let us describe the fate of m mutations by a vector $\boldsymbol{\sigma}_m = (\sigma_1, \sigma_2, \ldots, \sigma_m)$ where $\sigma_j = 1$ if the j-th mutation has fixed, and $\sigma_j = 0$ if it was lost. The event that out of m mutations exactly i have fixed encompasses all events that are described by vectors $\boldsymbol{\sigma}_m$ such that $\sum_{j=1}^{m} \sigma_j = i$. Denote the set of all such elementary events by $\Sigma_{m,i} = \{\boldsymbol{\sigma}_m : \sum_{j=1}^{m} \sigma_j = i\}$. For example, the event that, out of 2 mutations, exactly one has fixed can be realized by $\boldsymbol{\sigma}_2 = (1, 0)$ where the first mutation has fixed and the second has not and by $\boldsymbol{\sigma}_2 = (0, 1)$ where the second mutation has fixed and the first has not; therefore $\Sigma_{2,1} = \{(1, 0), (0, 1)\}$. Then, since all members of the set $\Sigma_{m,i}$ are mutually exclusive,

$$W_m(i|x) = \sum_{\Sigma_{m,i}} \prod_{j=1}^{m} w_j^{\sigma_j}(x)(1 - w_j(x))^{1-\sigma_j}. \tag{S32}$$

Of course, if $w_j(x)$ were equal for all j, this expression would reduce to the binomial probability with parameters m and $w_j(x)$. In general, $w_j(x)$ are not equal, and equation (S32) is difficult to evaluate. We conjecture, however, that the sum in (S32) is usually dominated by a small number of terms, which one could try to find knowing each $w_j(x)$ from the recursion relations.

Fortunately, calculating some lower order statistics, like the mean of the distribution $P_i(t|x)$, or its variance, is much easier. The expected number of fixations of the j-th mutation is $1 \cdot w_j(x) + 0 \cdot (1 - w_j(x)) = w_j(x)$. Thus, the expected number of substitutions that occurred after m mutations took place is

$$\sum_{i=0}^{\infty} i W_m(i|x) = \sum_{j=1}^{m} w_j(x). \tag{S33}$$

The substitution trajectory can then be finally written as

$$S(t, x) = \sum_{m=0}^{\infty} U_m(t) \sum_{i=0}^{\infty} i W_m(i|x) = \sum_{m=1}^{\infty} U_m(t) \sum_{j=1}^{m} w_j(x). \tag{S34}$$

The variance in the number of substitutions can be similarly calculated, taking into account that the variance in the expected number of fixations of the j-th mutation equals $w_j(x)(1 - w_j(x))$, and the total variance is the sum over individual mutational steps.

2 The role of neutral and deleterious mutations in adaptation

In this section we investigate how the distributions $P(y,t|x)$ and $P_i(t|x)$ change if a constant fraction of neutral or deleterious mutations is added to the NFD.

2.1 Neutral mutations

Suppose that on the fitness landscape Φ_x the distribution of fitnesses at time t is $P(y,t|x)$ and the distribution of the number of accumulated substitution is $P_i(t|x)$. Let

$$\tilde{\Phi}_x = \nu\delta_x + (1-\nu)\Phi_x \tag{S35}$$

where δ_x is a point mass centered at x, be a new fitness landscape with a fraction ν of neutral mutations. Let the distribution of fitnesses at time t on this landscape be $\tilde{P}(y,t|x)$ and let the distribution of substitutions be $\tilde{P}_i(t|x)$. We claim that

$$\begin{aligned} \tilde{P}(y,t|x) &= P(y,(1-\nu)t|x) && \text{(S36)} \\ \tilde{P}_i(t|x) &= \sum_{j=0}^{i} U_j(N^{-1}\nu t) P_{i-j}\big((1-\nu)t|x\big), && \text{(S37)} \end{aligned}$$

where $U_j(N^{-1}\nu t)$ is, as before, the Poisson distribution with parameter $N^{-1}\nu t$. Expression (S36) shows that the evolution of the distribution $P(y,t|x)$ proceeds on the landscape $\tilde{\Phi}_x$ with mutation rate θ exactly as on the landscape Φ_x with a smaller mutation rate $(1-\nu)\theta$. Expression (S37) shows that, if the random variables Q_t and $\tilde{Q}_t$ describe the number of substitutions that occurred by time t on the fitness landscapes Φ_x and $\tilde{\Phi}_x$, respectively, then $\tilde{Q}_t = Q_{(1-\nu)t} + R_{\nu t}$, where R_t is a Poisson process with rate N^{-1}. In other words, neutral mutations simply add an independent Poisson counting process to the original substitution process.

To show that (S36) and (S37) hold, we substitute (S35) into (S4) and (S13) and obtain

$$\begin{aligned} \big(\tilde{K}_\mathrm{b} f(\cdot)\big)(x) &\overset{\mathrm{def}}{=} \int_0^\infty \tilde{\Phi}_x(\xi)\pi_x(\xi)\big(f(\xi)-f(x)\big)\,d\xi = (1-\nu)\big(\hat{K}_\mathrm{b} f(\cdot)\big)(x), && \text{(S38)} \\ \tilde{q}(x) &\overset{\mathrm{def}}{=} \int_0^\infty \tilde{\Phi}_x(\xi)\pi_x(\xi)\,d\xi = \nu N^{-1} + (1-\nu)q(x). && \text{(S39)} \end{aligned}$$

From (S38) follows that the backward equation for $\tilde{P}(y,t|x)$ differs from the backward equation for $P(y,t|x)$ only by the scaling factor $1-\nu$. Now,

$$\begin{aligned} \frac{\partial \tilde{P}_0}{\partial t}(t|x) &= -N^{-1}\nu U_0(N^{-1}\nu t)P_0\big((1-\nu)t|x\big) - (1-\nu)q(x)U_0(N^{-1}\nu t)P_0\big((1-\nu)t|x\big) \\ &= -\tilde{q}(x)\tilde{P}_0(t|x), \end{aligned}$$

and

$$\begin{aligned}
\frac{\partial \tilde{P}_i}{\partial t}(t|x) &= \sum_{j=0}^{i} \Big[- N^{-1}\nu U_j(N^{-1}\nu t) P_{i-j}\big((1-\nu)t|x\big) - (1-\nu) U_j(N^{-1}\nu t) q(x) P_{i-j}\big((1-\nu)t|x\big) \Big] \\
&+ N^{-1}\nu \sum_{j=1}^{i} U_{j-1}(N^{-1}\nu t) P_{i-j}\big((1-\nu)t|x\big) + (1-\nu) q(x) \sum_{j=0}^{i-1} U_j(N^{-1}\nu t) P_{i-j-1}\big((1-\nu)t|x\big) \\
&+ (1-\nu) \sum_{j=0}^{i-1} U_j(N^{-1}\nu t) \big(\hat{K}_{\mathrm{b}} P_{i-j-1}\big((1-\nu)t|\,\cdot\,\big)\big)(x) \\
&= -\big(\tilde{P}_i(t|x) - \tilde{P}_{i-1}(t|x)\big) + \big(\tilde{K}_{\mathrm{b}} \tilde{P}_i(t|\cdot)\big)(x)
\end{aligned}$$

which implies that $\tilde{P}_i$ given by equation (S37) satisfy equations (S10), (S11) for the landscape $\tilde{\Phi}_x$. As a consequence, the fitness trajectory $\tilde{S}(t,x)$ on the landscape $\tilde{\Phi}_x$ is given by

$$\tilde{S}(t,x) = S\big((1-\nu)t, x\big) + \nu N^{-1} t,$$

which can also be obtained directly by substituting expression (S39) into solution (S23).

2.2 Deleterious mutations

In general, it is hard to predict how deleterious mutations would influence the dynamics of adaptation. However, their effect becomes negligible as the population size goes to infinity, at least in the weak-mutation limit. Indeed, the fixation probability (S1) of deleterious mutations quickly tends to zero as the population size increases. For example, the probability of fixation of a moderately deleterious mutation with the selective disadvantage of 0.1% is less than 10^{-3} for a population of size of 10^3 and is less than 10^{-11} for a population of size of 10^4. Thus, even in moderately large populations, the vast majority of deleterious mutations will not go to fixation. Therefore, on the long time scale, all deleterious mutations are equivalent to being lethal. Intuitively, this means that if we add a fraction d of deleterious mutations to the NFD of all genotypes, this fraction of mutations will simply be wasted and only the remaining fraction $1-d$ will be potentially utilized in the process of adaptation. To illustrate that this indeed is happening, we add a fraction d of deleterious mutations to the non-epistatic and stairway to heaven landscapes. We call the resulting landscapes NEPI+d and STH+d, respectively. The fitness and substitution trajectories for these landscapes are shown in Figure S1. As expected, the analytical approximations calculated under the assumption that deleterious mutations are wasted gives an excellent fit to simulations.

An important consequence of this observation is that the weak mutation theory holds when $\theta_b \ll (4\log N)^{-1}$ instead of the more stringent $\theta \ll (4\log N)^{-1}$, where $\theta_b \equiv (1-d)\theta$. If the genomic rate of beneficial mutations μ_b is 10^{-5} [4], then this condition is satisfied for population sizes smaller than 1000.

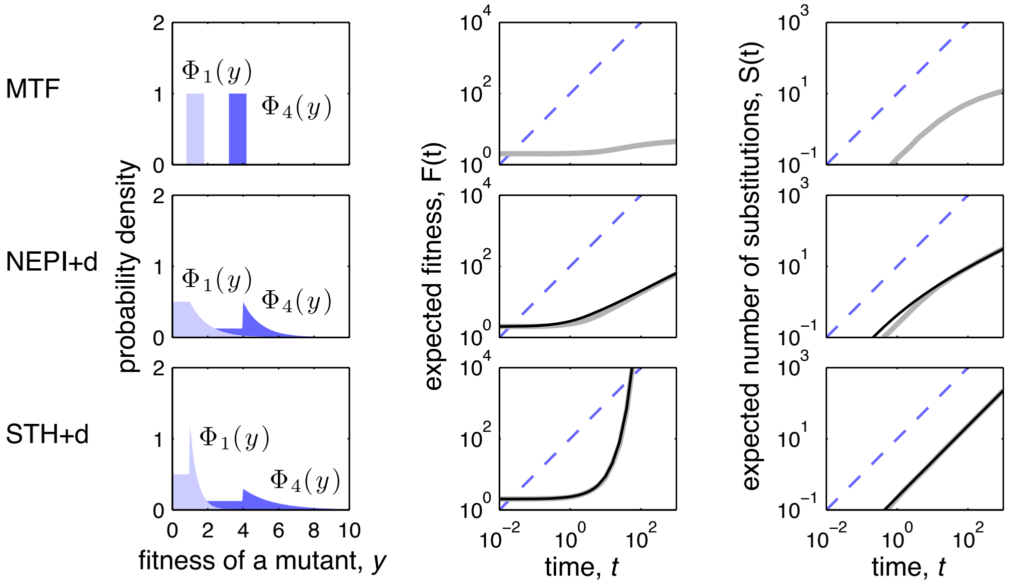

Figure S1: Dynamics of adaptation on the continuous additive Mount Fuji landscape (MTF), the non-epistatic landscape with deleterious mutations (NEPI+d) and the stairway to heaven landscape with deleterious mutations (STH+d). Notations are as in Figure 1 in the main text. Parameter values used: $N = 1000$, $\mu = 10^{-5}$ ($\theta = 0.01$), $L = 1000$, number of replicate simulations $= 10^3$. MTF landscape: $x_{\max} = 5$, $a = 1$; NEPI+d landscape: $d = 0.5$ and $a = 1$. STH+d landscape: $d = 0.5$ and $a = 0.42$. The same analytical approximations were used here for the NEPI+d and STH+d landscapes as in the main text, but time was rescaled by $\theta(1 - d)$ instead of θ.

3 Classical landscapes

Recall that we employ the following definitions (see main text).

1. The house of cards or the uncorrelated landscapes are the landscapes on which the NFD is the same for all genotypes (and fitnesses),
$$\Phi_x(y)\ dy = \Psi(y)\ dy.$$
2. The non-epistatic landscapes are landscapes on which the distribution of fitness effects $\Psi(v)$ remains the same for all genotypes, so that the NFD is given by
$$\Phi_x(y)\ dy = \Psi(y-x)\ dy.$$
3. The stairway to heaven landscapes are the landscapes on which the distribution of selection coefficients of mutations, $\Psi(s)$, is the same for all genotypes, so that the NFD is given by
$$\Phi_x(y)\ dy = \frac{1}{x}\Psi\left(\frac{y-x}{x}\right)\ dy.$$

In the main text we considered special cases of these landscapes when the distribution Ψ was of exponential form (see Table 1 in the main text),

$$\begin{aligned} &\text{House of cards} && \Phi_x(y) = \frac{1}{a}\exp\left\{-\frac{y}{a}\right\}, \quad y \geq 0 && \text{(S40)} \\ &\text{Non-epistatic} && \Phi_x(y) = \frac{1}{a}\exp\left\{-\frac{y-x}{a}\right\}, \quad y \geq x && \text{(S41)} \\ &\text{Stairway to heaven} && \Phi_x(y) = \frac{1}{ax}\exp\left\{-\frac{y-x}{ax}\right\}, \quad y \geq x && \text{(S42)} \end{aligned}$$

3.1 Correlation structure

The house of cards, non-epistatic, and stairway to heaven landscapes differ by the correlation structure between parent and offspring fitnesses. By definition, there is no such correlation on the house of cards landscape. By contrast, the offspring fitness is positively correlated with the parent fitness on both non-epistatic and stairway to heaven landscapes. Let X be the fitness of the parent that is drawn randomly from some distribution, and Y be the fitness of the offspring.

On non-epistatic landscapes, $Y = X + V$, where V is the fitness increment which is drawn from distribution $\Psi(v)$ independently of X. Then

$$\begin{aligned} \mathrm{Cov}(X,Y) &= \mathbb{E}\left[(X-\bar{X})(X-\bar{X}+V-\bar{V})\right] \\ &= \mathrm{Var}(X) > 0, \end{aligned}$$

where, $\bar{X}$ and $\mathrm{Var}(X)$ are the mean and the variance of the distribution from which the parent is drawn, and $\bar{V} > 0$ is the mean of the distribution of fitness increments.

On the stairway to heaven landscapes, $Y = X(1+S)$, where S is the selection coefficient which is drawn from distribution $\Psi(s)$ independently of X. Then

$$\begin{aligned} \mathrm{Cov}(X,Y) &= \mathbb{E}\left[(X-\bar{X})(X-\bar{X}+XS-\bar{X}\bar{S})\right] \\ &= \mathrm{Var}(X)\ (1+\bar{S}) > 0, \end{aligned}$$

where $\bar{S} > -1$ is the mean of the distribution of selection coefficients.

3.2 Approximate solution for the exponential house of cards landscape

On the house of cards landscape (S40) we have, for large population sizes and for large x,

$$\begin{aligned} q(x) &= \frac{1}{a}e^{-\frac{x}{a}}\int_x^\infty e^{-\frac{y-x}{a}}\left(1-e^{-2\frac{y-x}{x}}\right)\,dy = \frac{2a}{x+2a}e^{-\frac{x}{a}} \approx 2ae^{-\frac{x}{a}} \\ r(x) &= \frac{1}{a}e^{-\frac{x}{a}}\int_x^\infty (y-x)e^{-\frac{y-x}{a}}\left(1-e^{-2\frac{y-x}{x}}\right)\,dy = \frac{4a^2(x+a)}{(x+2a)^2}e^{-\frac{x}{a}} \approx 4a^2e^{-\frac{x}{a}}. \end{aligned}$$

The last approximate inequality for $q(x)$ and $r(x)$ is not very accurate since it neglects the term of order x^{-1},but it captures the fact the exponential decay in both $q(x)$ and $r(x)$ will dominate the power-law decay as x gets large. After substituting these functions into equations (1), (2) in the main text, we solve them using the method of characteristics to obtain expressions for the fitness and substitution trajectories presented in Figure 1 (main text).

3.3 Approximate solution for the exponential non-epistatic landscape

On the non-epistatic landscape (S41) we have, for large population sizes, and for large x,

$$\begin{aligned} q(x) &= \frac{1}{a}\int_x^\infty e^{-\frac{y-x}{a}}\left(1-e^{-2\frac{y-x}{x}}\right)\,dy = \frac{2a}{x+2a} \approx \frac{2a}{x} \\ r(x) &= \frac{1}{a}\int_x^\infty (y-x)e^{-\frac{y-x}{a}}\left(1-e^{-2\frac{y-x}{x}}\right)\,dy = \frac{4a^2(x+a)}{(x+2a)^2} \approx \frac{4a^2}{x}. \end{aligned}$$

After substituting these functions into equations (1), (2) in the main text, we solve them using the method of characteristics to obtain expressions for the fitness and substitution trajectories presented in Figure 1 (main text).

3.4 Exact solution for an arbitrary stairway to heaven landscape

It is possible to solve equations (S18)–(S22) for an arbitrary stairway to heaven landscape, $\Phi_x(y) = x^{-1}\Psi(y/x - 1)$. First note that the expected fixation probability of a mutation, $q(x) = \int_{-1}^{\infty} \Psi(s)\pi(s)\, ds = \langle \pi(s) \rangle$, is independent of the fitness x of the parental genotype. In addition, $r(x) = x \int_{-1}^{\infty} s\Psi(s)\pi(s)\, ds = x\langle \pi(s)s \rangle$, which suggests, after exploring the advection approximation, the ansatz $F(t, x) = f(t)x$ and $S(t, x) = g(t)$ for the equations (S18)–(S22). With this ansatz we obtain

$$\begin{aligned}
\big(\hat{K}_{\mathrm{b}} F(t,\cdot)\big)(x) &= \int_0^{\infty} \frac{1}{x}\Psi\left(\frac{\xi - x}{x}\right) \pi_x(\xi) f(t)(\xi - x)\, d\xi = \langle \pi(s)s \rangle\ F(t, x), \\
\big(\hat{K}_{\mathrm{b}} S(t,\cdot)\big)(x) &= 0,
\end{aligned}$$

where $\langle \pi(s)s \rangle$ is the expected selection coefficient of a random mutation to any genotype, weighted by its fixation probability. Equations (S18)–(S22) become simple ODE's whose solutions are given by

$$F(t, x) = x e^{\langle \pi(s)s \rangle t} \tag{S43}$$

$$S(t, x) = \langle \pi(s) \rangle t, \tag{S44}$$

Expressions for the fitness and substitution trajectories presented in Figure 1 (main text) follow from expressions (S43), (S44) by noting that, for large population sizes,

$$\begin{aligned}
\langle \pi(s) \rangle &= \frac{1}{a}\int_0^{\infty} e^{-\frac{s}{a}}\left(1 - e^{-2s}\right)\, ds = \frac{2a}{1 + 2a}, \\
\langle \pi(s)s \rangle &= \frac{1}{a}\int_0^{\infty} s\, e^{-\frac{s}{a}}\left(1 - e^{-2s}\right)\, ds = \frac{4a^2(1 + a)}{(1 + 2a)^2}.
\end{aligned}$$

It can be shown analogously that the k-th moment of the distribution of fitnesses, $M_k(t, x)$, evolves according to

$$M_k(t, x) = x^n e^{\kappa_n t},$$

where $\kappa_n = \sum_{j=1}^{n} \binom{n}{j} \langle \pi(s)s^j \rangle$. In particular, the relative width of the distribution of fitnesses increases with time, $M_2(t, x)/F^2(t, x) = e^{\langle \pi(s)s^2 \rangle t} - 1$.

3.5 Mount Fuji landscape

In addition to the classical fitness landscape considered above, the class of fitness parametrized landscapes encompasses many other landscapes. To demonstrate this, we present here a version of the "Mount Fuji" landscape. On this landscape, the fitness decreases monotonically with the Hamming distance from the single optimal genotype, so that the fitness of the genotype that differs by h mutations from the optimal one is $(1 - s)^h$, where $0 < s < 1$. If formulated in terms of neighbor fitness distributions, such *multiplicative* mount Fuji landscape would be defined for a discrete set of fitnesses $x \in \{1, 1-s, \cdots, (1-s)^L\}$, where L is the genome size,

$$\Phi_x(y) = b_h \delta_{x(1-s)^{-1}}(y) + (1-b_h)\delta_{x(1-s)}(y).$$

Here, δ_z is, as before, a point measure centered at z, and b_h is the probability of a beneficial mutation to a genotype with h mutations. These probabilities can be easily calculated knowing the genome length L and the alphabet size $|\mathcal{A}|$. For instance, $b_0 = 1$, $b_1 = (|\mathcal{A}|L)^{-1}$and $b_L = 1$.

A continuous version of the *additive* Mount Fuji landscape can also be defined, for example, as follows.

$$\Phi_x(y) = \begin{cases} \frac{1}{a}, & \text{if } y \in \left[x(1-\frac{a}{x_{\max}}), x(1-\frac{a}{x_{\max}})+a\right] \\ 0, & \text{otherwise} \end{cases}$$

On this landscape, the fraction of beneficial mutations decreases linearly from 1 to 0 as the fitness changes from 0 to the maximum value $x_{\max}$. Parameter a defines the width of the NFD. The dynamics of adaptation on this landscape is shown in Figure S1.

4 Relaxation of the weak-mutation limit

In this section we investigate, by means of simulations, the validity of our theory outside of the weak-mutation limit. We perform full stochastic simulations of the infinite alleles Wright-Fisher model with $N = 1000$ individuals. We vary the mutation rate from $\mu = 10^{-5}$ to $\mu = 10^{-2}$ per individual per generation, which corresponds to θ ranging from $\theta = 0.01$, where our theory should well describe the Wright-Fisher model, up to $\theta = 10$, where clonal interference and piggybacking effects cannot be ignored.

In the simulations, each individual is characterized by its allelic type z (a float number between 0 and 1); x_z is the fitness of allele z, k_z is the number of mutations that have occurred on the line of descent of an individual of type z. A mutant offspring of individual of type z has type z' which is drawn randomly from $[0, 1]$; fitness $x_{z'}$ is then drawn from the distribution Φ_{x_z}, and $k_{z'} = k_z + 1$.

At each time point t the population is characterized by a collection of $K(t)$ types $z_1, z_2, \ldots, z_{K(t)}$ and their frequencies $f_1, f_2, \ldots, f_{K(t)}$. We use the shorthand notations $x_i \equiv x_{z_i}$ and $k_i \equiv k_{z_i}$. In the simulations we track four summary statistics:

1. The mean fitness of the population $\sum_{i=1}^{K(t)} x_i f_i$
2. The mean number of mutations since the initial time point $\sum_{i=1}^{K(t)} k_i f_i$
3. The population heterozygosity $1 - \sum_{i=1}^{K(t)} f_i^2$
4. The number of alleles present in the population, $K(t)$

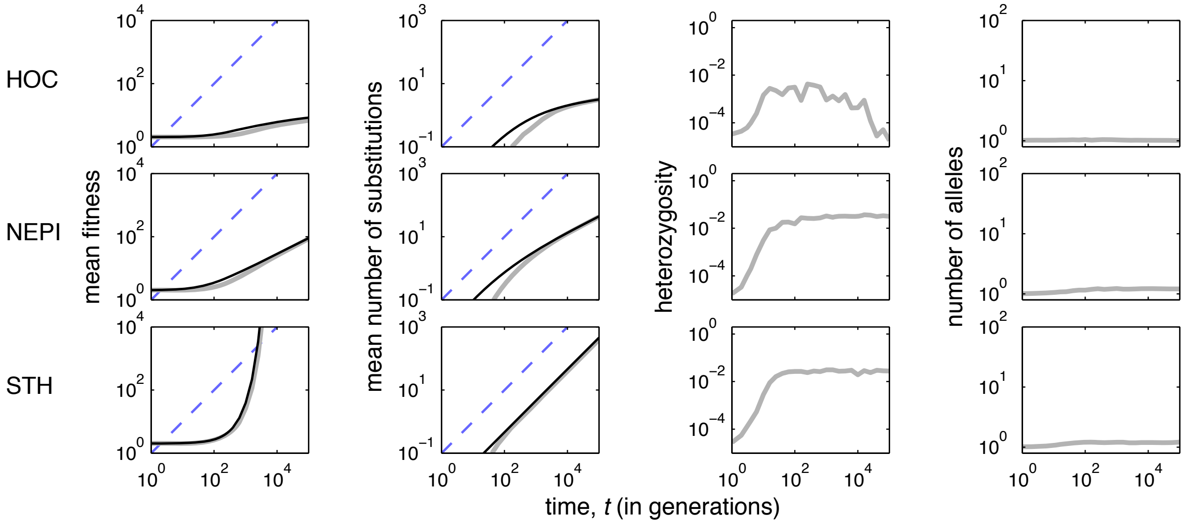

Figure S2: Dynamics of adaptation in the full Wright-Fisher model with $\mu = 10^{-5}$, $N = 10^3$ on three classical landscapes. The first and second columns show the fitness and substitution trajectories (see text for details). Black lines correspond to the predictions of our theory; gray lines show the results of the Wright-Fisher simulations; dashed lines show a linear function, for reference. The third column shows the evolution of heterozygosity, and the fourth column shows how the number of alleles in the population changes over time (see text for details). Note that time is measured in generations. Parameter values are the same as in Figure 1 in the main text, except number of replicate simulations is 10^3; at time zero the population is monomorphic with a type with fitness 2. Simulations are terminated prematurely if the fitness of an indiviual exceeds 10^{100}.

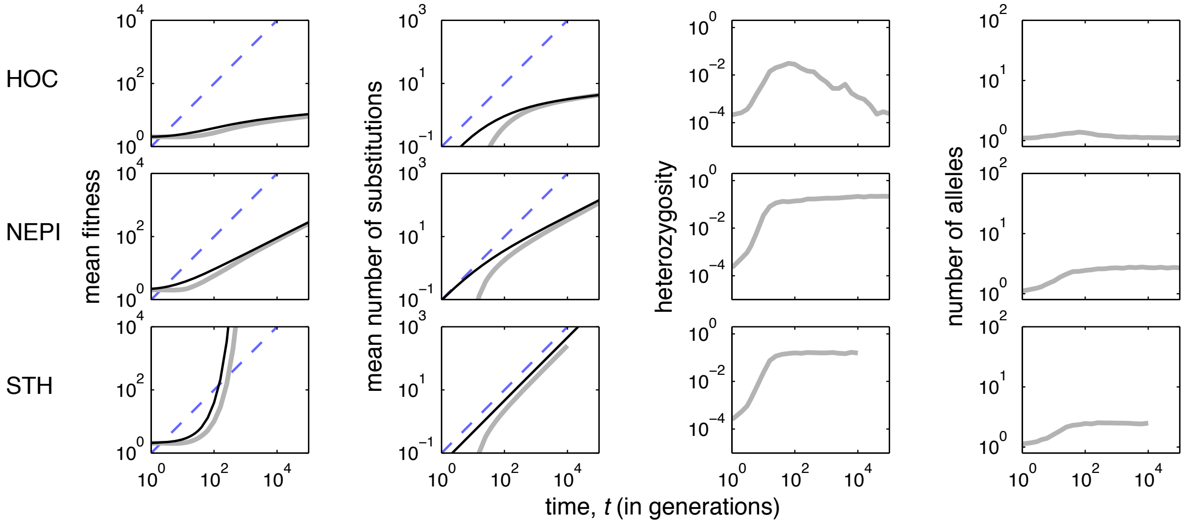

Figure S3: Dynamics of adaptation in the full Wright-Fisher model with $\mu = 10^{-4}$, $N = 10^3$. Notations as in Figure S2.

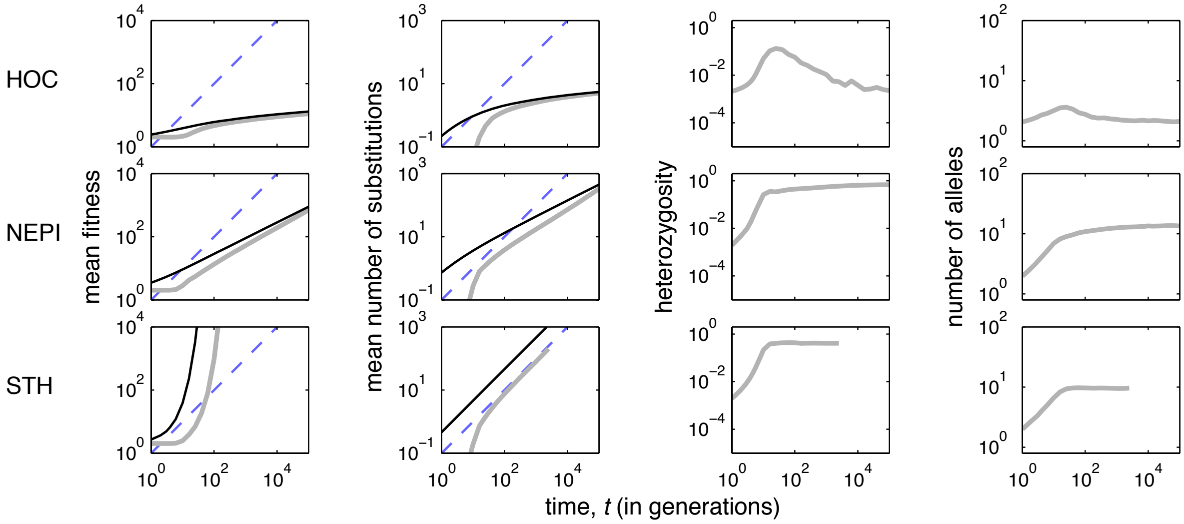

Figure S4: Dynamics of adaptation in the full Wright-Fisher model with $\mu = 10^{-3}$, $N = 10^3$. Notations as in Figure S2.

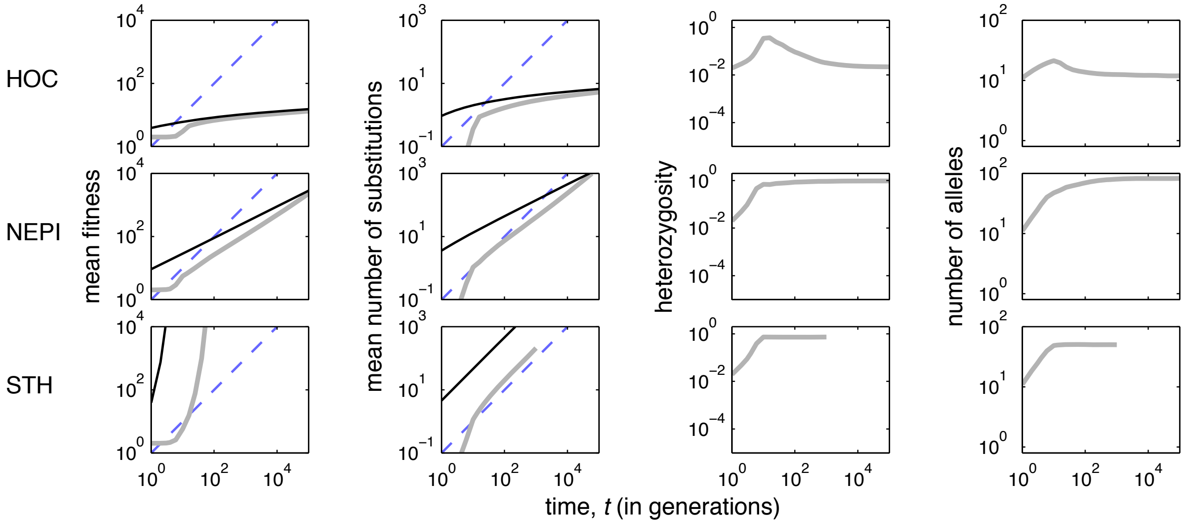

Figure S5: Dynamics of adaptation in the full Wright-Fisher model with $\mu = 10^{-2}$, $N = 10^3$. Notations as in Figure S2.

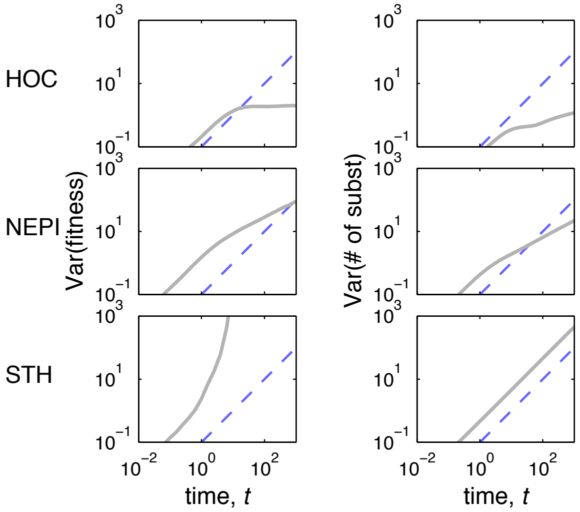

Figure S6: Variance of the ensemble distribution of fitnesses (top row) and substitutions (bottom row) for classical landscapes. Notations and parameter values are as in Figure 1 in the main text.

Figures S2–S5 show the average values of these statistics across 1000 independent replicas. For $\theta = 0.01$ (Figure S2) and even for $\theta = 0.1$ (Figure S3), our theory accurately describes the dynamics of adaptation, as expected. For $\theta = 1$ (Figure S4) and $\theta = 10$ (Figure S5), the quantitative predictions of our theory are poor. Indeed, when $\theta > 1$, the population is polymorphic most of the time—this can be seen in the graphs showing the population heterozygosity and the number of coexisting alleles. Thus, in simulations with $\theta > 1$ clonal interference and piggybacking certainly occur. Surprizingly, even in this regime the qualitative predictions of our theory still hold. In particular, we observe that, even though the curvature of the fitness and substitution trajectories depends on the mutation rate, its sign does not. In other words, landscapes that give rise to concave (convex) fitness (substitution) trajectories in the weak-mutation limit continue to give rise to concave (convex) fitness (substitution) trajectories even in the presence of clonal interference and piggybacking. This implies that we can use the weak mutation theory to obtain qualitative conclusions about the fitness landscape, even if the observed trajectories were generated under high mutation rates.

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