Gene conversion facilitates adaptive evolution on rugged fitness landscapes

Supplemental Information

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I. MINIMAL 3×3-STATE MODEL

A. Model formulation

The reactions for the minimal 3×3-state model of gene conversion described in the Main text (Fig. 1b), can be rigorously formulated as a set of memoryless reactions

\[
(i, j) \xrightarrow{r_{ij\rightarrow i'j'}} (i, j) + (i', j'), \quad (i'', j'') \rightarrow \emptyset, \quad \text{for } \{i, i', j, j', j''\} = \{0, 1, 2\}, \quad \text{(S1)}
\]

where the first reaction denotes replication of the \((i, j)\) individual that gives rise to one \((i, j)\) individual and one \((i', j')\) individual. If the resulting individual \((i', j')\) is also \((i, j)\), this corresponds to a regular division event, whereas \(i' \neq i\) or \(j' \neq j\) indicates a mutation or gene conversion. The second reaction denotes removal of a random individual \((i'', j'')\) concurrent with the replication of \((i, j)\). The rate of each pair of reactions is equal to the product of the fitness \(F_i\) of the replicating individual \((i, j)\) and the fitness-scaled rate \(r_{ij\rightarrow i'j'}\). The latter are shown for every pair \((i, j), (i', j')\) in the following table

<table>
<thead>
<tr>
<th>((i,j)) ((i',j'))</th>
<th>(0,0)</th>
<th>(0,1)</th>
<th>(0,2)</th>
<th>(1,0)</th>
<th>(1,1)</th>
<th>(1,2)</th>
<th>(2,0)</th>
<th>(2,1)</th>
<th>(2,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0,0)</td>
<td>1−2(\mu)</td>
<td>(\mu)</td>
<td>0</td>
<td>(\mu)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>(0,1)</td>
<td>(\mu + \alpha)</td>
<td>1−3(\mu - 2\alpha)</td>
<td>(\mu)</td>
<td>0</td>
<td>(\mu + \alpha)</td>
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<tr>
<td>(0,2)</td>
<td>(\alpha)</td>
<td>(1−2\mu - 2\alpha)</td>
<td>0</td>
<td>(\mu + \alpha)</td>
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<td>(1,0)</td>
<td>(\mu + \alpha)</td>
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<tr>
<td>(1,1)</td>
<td>0</td>
<td>(\mu)</td>
<td>0</td>
<td>(1−4\mu)</td>
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<td>(\mu + \alpha)</td>
<td>(1−3\mu - 2\alpha)</td>
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<td>(2,0)</td>
<td>(\alpha)</td>
<td>0</td>
<td>0</td>
<td>(\mu)</td>
<td>0</td>
<td>0</td>
<td>(1−2\mu - 2\alpha)</td>
<td>(\mu)</td>
<td>(\alpha)</td>
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<td>0</td>
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<td>0</td>
<td>(\mu)</td>
<td>0</td>
<td>(\mu)</td>
<td>(1−2\mu)</td>
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</table>

where \(\mu\) and \(\alpha\) specify the probability that a division event yields a specific mutant or conversion. The sum of entries in each row is 1, so the total division rate of individuals \((i, j)\) is \(F_i\). Following Ref. [1], we can rescale time by the fitness \(F_0\), then states \((0, j)\) have fitness 1, states \((1, j)\) have fitness \(1−\delta\), and states \((2, j)\) have fitness \(1+s\). We will use \(\delta\) and \(s\) instead of \(F_0, F_1, F_2\) where it simplifies the notation and understanding of our analytical approximations.

As described in the Main text, without gene conversion \((\alpha = 0)\), the index \(j\) of the current state becomes irrelevant, and the problem can be simplified by only tracking the state of the active gene \(i\). The corresponding stochastic model will read

\[
(i) \xrightarrow{r_{i\rightarrow i'}} (i) + (i'), \quad (i'') \rightarrow \emptyset, \quad \text{for } \{i, i', i''\} = \{0, 1, 2\}, \quad \text{(S2)}
\]

The rates of each pair of reactions is equal to the product of the fitness \(F_i\) of the replicating individual \((i)\) and the fitness-normalized rates \(r_{i\rightarrow i'}\) which are shown for every pair \((i), (i')\) in the following table

<table>
<thead>
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<th>(1)</th>
<th>(2)</th>
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<td>(\mu)</td>
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<tr>
<td>(2)</td>
<td>0</td>
<td>(\mu)</td>
<td>1−(\mu)</td>
</tr>
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</table>

This model is very similar (although not identical) to the valley crossing problem considered in Ref. [1] for \(K = 2\) (one deleterious intermediate state with selective disadvantage \(\delta = (F_0−F_1)/F_0\) and the final state with selective advantage \(s = (F_2−F_0)/F_0\).
In a certain range of parameters (more accurately defined below and in the Main text), an approximation known as “stochastic tunneling” \cite{1} can be applied to solving this minimal model. In this regime, the intermediate mutant sub-populations are always much smaller than the population size. Furthermore, it is assumed that the mutation rate is small enough such that different “successful” mutant lineages (defined below) occur sequentially and do not interfere with each other.

**B. Stochastic tunneling regime**

Direct path $0 \leftrightarrow 1 \leftrightarrow 2$. Let us first consider our 3×3-state model without gene conversion ($\alpha = 0$). As mentioned above, this model is similar to the model of Ref. \cite{1} for the case $K = 2$ (two sequential mutations: first neutral or deleterious, second beneficial), but with two important differences. First, we assume that the fitness of an individual characterizes its mutation rate is small enough such that different “successful” mutant lineages (defined below) occur sequentially and do not interfere with each other.

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The time until fixation of the beneficial mutation (state 2) is a sum of the time $t_1$ to produce a successful mutant in state 1 plus time $t_2$ for this mutant to produce the first successful mutant in state 2, plus the time for this mutant to get fixed, $t_f$. It is easy to see that $\langle t_1 \rangle = (N\mu p_1)^{-1}$, and can be shown (see \cite{1}) that for $N\mu \ll 1$ this contribution dominates the other two, so

$$T_1 \approx \langle t_1 \rangle \approx \begin{cases} (N\mu^{3/2}s^{1/2})^{-1}, & \delta \ll \sqrt{(1-\delta)\mu s} \\ \frac{\delta}{N\mu^2s(1-\delta)}, & \delta \gg \sqrt{(1-\delta)\mu s} \end{cases}$$

Gene conversion path $(0,0) \leftrightarrow (0,1) \leftrightarrow (0,2) \rightarrow (2,2)$. Now let us consider the alternative path to beneficial state 2 involving gene conversion from state $(0,2)$ to $(2,2)$. We ignore the direct path assuming that the corresponding
success probabilities are much smaller (to be checked \textit{a posteriori}). In analogy to the direct path calculation above, the probability to succeed in state \((0,1)\) is
\[
 p_{01} = \frac{1 \cdot 0 + (1 - 3\mu - 2\alpha) \cdot [1 - (1 - p_{01})^2] + \mu[1 - (1 - p_{01})(1 - p_{02})] + 2(\mu + \alpha)p_{01}}{1 + 1}
\]
or
\[
 p_{01}(2\alpha + (3 + p_{02})\mu) + p_{01}^2(1 - 2\alpha - 3\mu) - \mu p_{02} = 0. \tag{S8}
\]
The first term in the numerator describes death of the \((0,1)\) individual, the second stands for its symmetric division, and the third corresponds to the division with mutation into state \((0,2)\). The last term describes either conversion or mutation of one descendant of a \((0,1)\) individual to the initial state \((0,0)\) or the deleterious state \((1,1)\), so in both cases the probability of its success is negligible.

Similarly, the probability to succeed in state \((0,2)\) is
\[
 p_{02} = \frac{1 \cdot 0 + (1 - 2\mu - 2\alpha) \cdot [1 - (1 - p_{02})^2] + \mu[1 - (1 - p_{01})(1 - p_{02})] + (\mu + \alpha) \cdot p_{02} + \alpha(1 - (1 - p_{02})(1 - p_{22}))}{1 + 1}
\]
or
\[
 p_{02}^2(1 - 2\alpha - 2\mu) + p_{02}(2 + p_{22})\alpha + (2 + p_{01})\mu - \alpha p_{22} - \mu p_{01} = 0, \tag{S9}
\]
where, again, the success probability for back conversions to state \((0,0)\) or mutations to state \((1,2)\) was neglected. The probability of success in state \((2,2)\), \(p_{22} = s\), closes the system of equations \((\text{S8})\) and \((\text{S9})\) for \(p_{01}\) and \(p_{02}\).

Plotting the exact solution for \(p_{01}\) (see Fig. \textbf{S1}), we see that there is an optimal \(\alpha\) for which the success probability is maximized. To approximate the two regimes left and right of this maximum, we examine two approximations: For \(\alpha \gg p_{01}\) and \(\alpha \gg \mu\), Eq. \((\text{S8})\) simplifies to
\[
 2\alpha p_{01} - \mu p_{02} = 0. \tag{S10}
\]
Substituting the solution for \(p_{02}\) into Eq. \((\text{S9})\) and neglecting the appropriate terms for this regime, we have
\[
 4\alpha^2 p_{01}^2 + 2(2 + s)p_{01} \alpha^2 \mu - s\alpha^2 \mu^2 = 0, \tag{S11}
\]
which leads to
\[
 p_{01} = \frac{\mu}{2} \left[ -1 - \frac{s}{2} + \sqrt{1 + \frac{s^2}{4} + \frac{s(1 + \alpha)}{\alpha}} \right], \tag{S12}
\]
that for \(\alpha \ll s\) yields
\[
 p_{01} = \frac{\mu}{2} \sqrt{\frac{s}{\alpha}}, \quad p_{02} = \sqrt{\alpha s}. \tag{S13}
\]
Substituting this \(p_{01}\) into \(\alpha \gg p_{01}\) we get the applicability condition \(\alpha \gg (s\mu^2)^{1/3}\). Note that for \(\alpha \ll s\) the second applicability condition \((\alpha \gg \mu)\) is satisfied automatically.

In the opposite case \(\alpha \ll p_{01}\), Eq. \((\text{S8})\) simplifies to
\[
 3\mu p_{01} + p_{01}^2 - \mu p_{02} = 0. \tag{S14}
\]
Substituting the solution for \(p_{02}\) into Eq. \((\text{S9})\) and neglecting the appropriate terms for this regime, we get
\[
 p_{01}^4 + 6p_{01}^3\mu + 11p_{01}^2\mu^2 + 5p_{01}\mu^3 - s\alpha \mu^2 = 0, \tag{S15}
\]
which has two interesting limits. For \(p_{01} \gg \mu\), the solution of Eqs. \((\text{S14})\) and \((\text{S15})\) is
\[
 p_{01} = \sqrt{\mu \sqrt{\alpha s}}, \quad p_{02} = \sqrt{\alpha s} \tag{S16}
\]
whereas for \(p_{01} \ll \mu\), the solution is
\[
 p_{01} = \frac{\alpha s}{5\mu}, \quad p_{02} = \frac{3\alpha s}{5\mu}. \tag{S17}
\]
As we see, the latter approximation is only valid for \(\alpha \ll \mu^2/s\), which is extremely small for any appreciable selective advantage \(s\), so we ignore the third regime of Eq. \((\text{S17})\) in most of our considerations. \textit{A posteriori} substitution of
the solution $\alpha \ll p_{01}$ and $p_{01} \gg \mu$ shows that it applies for $\mu^2/s \ll \alpha \ll (s\mu^2)^{1/3}$. This range always exists since we generally assume $\mu \ll s$. The three approximations $\alpha \ll (s\mu^2)^{1/3}$, $\alpha \ll (s\mu^2)^{1/3}$, and $\alpha \ll (s\mu^2)^{1/3}$ are illustrated in Fig. $S1$.

The transition from Eq. $S16$ to the larger-$\alpha$ regime $\alpha \ll (s\mu^2)^{1/3}$ happens at $\alpha \sim (s\mu^2)^{1/3}$, which can be obtained by substituting either Eq. $S16$ or Eq. $S13$ into $p_{01} \sim \alpha$. Equating the two estimates $S16$ and $S13$ leads to the formula for the optimum conversion rate

$$\alpha_m \approx 2^{-4/3}(s\mu^2)^{1/3}. \tag{S18}$$

The time to fixation of the beneficial mutation is dominated by the time to produce the first successful individual in state $(0,1)$, i.e. $T_2 \approx (N\mu p_{01})^{-1}$, where $p_{01}$ is calculated from one of the equations $S13$, $S16$, or $S17$ depending on the applicable regime. At the optimal $\alpha_m$, Eq. $S18$, the probability $p_{01}$ of a successful mutant in state $(0,1)$ is $p_{01} \approx (s\mu^2/2)^{1/3}$, from Eq. $S13$ or $S16$. Therefore, the shortest possible fixation time via the conversion path is expected to be

$$T_{2,\text{min}} \approx \frac{2^{1/3}}{Ns^{1/3}\mu^{5/3}}. \tag{S19}$$

**Scaling behavior of fixation times for direct and conversion paths.** Gene conversion can speed up fixation of the beneficial mutation (for the optimal conversion rate $\alpha$) if $T_2$ of Eq. $S19$ is significantly smaller than $T_1$ of Eq. $S7$, which depends on the depth $\delta$ of the fitness valley. However, it is interesting to note that $T_1$ for the strongly deleterious intermediate state (second line of Eq. $S7$) grows more quickly than $T_2$ when $\mu$ or $s$ decrease. This means that the potential for speedup through gene conversion is even larger for biologically relevant mutation rates and selective advantages that are smaller than the relatively large values chosen in the Main text for computational purposes. Also note that for effectively neutral fitness valleys (first line of Eq. $S7$), the scaling behavior is reversed, and smaller mutation rates and selective advantages will always lead to a larger increase in fixation time for the conversion path compared to the direct path. This is intuitive, as the conversion path requires one additional (neutral) mutation before a mutant in the beneficial state can be produced.

**Range of validity of the stochastic tunneling regime for direct and conversion paths.** The validity of the stochastic tunneling regime requires that the first successful single mutant gives rise to the eventual population of the beneficial mutants, i.e. the lineages of successful mutants do not overlap. Thus the average time between successful single mutants should be much larger than the average lifetime of the single-mutant sub-population $\tau_1$. For the direct path, the average time between successful single mutants is $(N\mu p_{01})^{-1}$, which for strongly deleterious intermediate state 1 yields $\delta/[N\mu^2(1-\delta)s]$. The average lifetime of a strongly deleterious single mutant $\tau_1 = \delta^{-1}$, so the condition of validity of the stochastic tunneling regime is

$$N \ll \frac{\delta^2}{(1-\delta)\mu^2s}. \tag{S20}$$

For the gene conversion path, the average time between successful first mutants is $(N\mu p_{01})^{-1}$ and the average time $\tau_{01}$ for which a successful neutral $(0,1)$-mutant lineage will drift before producing the successful $(0,2)$-mutant is $\tau_{01}$, and so the overall validity condition is

$$N \ll \frac{1}{\mu p_{01} \tau_{01}} \tag{S21}$$

For small $\alpha \ll (s\mu^2)^{1/3}$, the state $(0,1)$ is neutral, and $\tau_{01} = 1/\sqrt{\mu p_{02}} = 1/\sqrt{\mu \alpha s}$. In the opposite limit of large $\alpha \gg (s\mu^2)^{1/3}$, the intermediate state $(0,1)$ is effectively deleterious because these single mutants get quickly eliminated by gene conversion to $(0,0)$ or $(1,1)$ states. Therefore, for large $\alpha$, $\tau_{01} \approx (2\alpha)^{-1}$. Substituting these asymptotic expressions and $p_{01}$ from Eqs. $S13$, $S16$ in Eq. $S21$, we obtain Eq. $[8]$ of the Main Text.

On the opposite side of small populations, the validity of stochastic tunneling regime demands that the sub-populations of intermediate mutants remain smaller than the total population size, so the intermediate mutants do not get fixed. For the direct path it translates into the condition that the probability of producing a successful single mutant $p_1$ is much larger than the probability of its fixation $p_1$. Using the expressions for $p_1 = (1-\delta)\mu s/\delta$ and Kimura’s formula for the fixation probability of a mutation with selective disadvantage $\delta$ $[2][3]$, i.e. $p(-\delta)$ from Eq. $[4]$ in the Main text,

$$p_1 = p(-\delta) = \frac{1 - e^{\delta}}{1 - e^{s\delta}}, \tag{S22}$$
we get
\[ N \gg \frac{1}{\delta} \log \left( 1 + \delta \frac{e^\delta - 1}{\mu(1 - \delta)s} \right) \] (S23)

For the gene conversion path, the analogous condition is \( p_{01} \gg \rho_{01} \) where \( \rho_{01} = p(-2\alpha) \), since gene conversion plays the role of additional death rate for state \((0,1)\), which yields the following general validity condition,
\[ N \gg \frac{1}{2\alpha} \log \left( 1 + \frac{2\alpha}{p_{01}} \right) \] (S24)

Using this expression and \( p_{01} \) from Eq. (2), we arrive at Eq. (6) of the Main text, where we simplified the expression for the \( \alpha \ll (s\mu^2)^{1/3} \) regime by approximating \( \log(1 + x) \approx x \) for small \( x \).

C. Deterministic regime

For a very large population size (the corresponding conditions are outlined in the Main text), the dynamics of the minimal model can be described deterministically using rate or mass-action equations for the occupation numbers.
\[ X_{i,j} \] of states \((i, j)\):
\[
\dot{X}_{i,j} = F_i X_{i,j} - d X_{i,j} + \mu F_{i-1} X_{i-1,j} + \mu F_i X_{i,j-1} + \mu F_{i+1} X_{i+1,j} + \mu F_i X_{i,j+1} - (4 - \delta_{i0} - \delta_{j0} - \delta_{i2} - \delta_{j2}) \mu F_i X_{i,j}
\]
\[ -2\alpha F_i X_{i,j} + \alpha \sum_{k=0}^{2} (F_i X_{i,k} + F_k X_{k,i}) \delta_{ij}, \quad \{i, j\} = 0, 1, 2 \]
(S25)

To mimic the Moran process deterministically, we set the death rate \(d\) equal to the current average fitness of the whole population, \(d = \sum_{i,j=0}^{N} F_i X_{i,j} / N\), where \(N = \sum_{i,j=0}^{N} X_{i,j}\) is the (constant) total population size, \(\delta_{ij}\) is the Kronecker delta, and we assume that \(X_{i,j} = 0\) for either \(i\) or \(j < 0\) or \(> 2\). The initial condition for all our simulations is \(X_{0,0} = N\) and all other \(X_{i,j} = 0\).

**Dynamics without gene conversion.** Let us first consider the evolutionary dynamics of the system without gene conversion (\(\alpha = 0\)). Summing the equations (S25) along the \(j\) dimension, we obtain the following equations for the marginal distribution of all individuals with active gene in state \(i\), regardless of the state of the passive gene \(j\), \(Y_i = \sum_j X_{i,j}\):
\[
\dot{Y}_0 = F_0 Y_0 - d Y_0 + \mu F_0 Y_1 - \mu F_0 Y_0,
\]
(S26)
\[
\dot{Y}_1 = F_1 Y_1 - d Y_1 + \mu F_0 Y_0 + \mu F_2 Y_2 - 2\mu F_1 Y_1,
\]
(S27)
\[
\dot{Y}_2 = F_2 Y_2 - d Y_2 + \mu F_1 Y_1 - \mu F_2 Y_2,
\]
(S28)

where \(d = (F_0 Y_0 + F_1 Y_1 + F_2 Y_2) / (Y_0 + Y_1 + Y_2)\), and the initial condition is \(Y_0 = N, Y_1 = Y_2 = 0\). For small mutation rate \(\mu\) the population slowly diffuses into the more fit state 2 via state 1 and eventually localizes there. While the occupation numbers of states 1 and 2, \(Y_1, Y_2 \ll N\), the set of equations (S26) and (S28) can be linearized assuming \(Y_0 = N = \text{const}, d \approx F_0\) and solved using Laplace transform. In the Laplace space, we get
\[
z \tilde{Y}_1 = (F_1 - F_0) \tilde{Y}_1 + \mu F_0 N - \mu F_2 \tilde{Y}_2 - 2\mu F_1 \tilde{Y}_1,
\]
(S29)
\[
z \tilde{Y}_2 = (F_2 - F_0) \tilde{Y}_2 + \mu F_1 \tilde{Y}_1 - \mu F_2 \tilde{Y}_2,
\]
(S30)

where we use \(z\) for the Laplace parameter to distinguish it from the selective advantage \(s\) of state 2.

Solving for \(\tilde{Y}_1, \tilde{Y}_2\) yields
\[
\tilde{Y}_1 = \mu F_0 N \left[ z + F_0 - F_1 + 2\mu F_1 - \frac{\mu^2 F_1 F_2}{z + \mu F_2 - F_2 + F_0} \right]^{-1}
\]
(S31)
\[
\tilde{Y}_2 = \mu^2 F_0 F_1 N s \left[ (z + F_0 - F_1 + 2\mu F_1)(z + \mu F_2 - F_2 + F_0) - \mu^2 F_1 F_2 \right]^{-1}
\]
(S32)

To find the asymptotic behavior of this solution, we need to compute the residue at the largest root \(z_\ast\) of the quadratic equation
\[
(z + F_0 - F_1 + 2\mu F_1)(s + \mu F_2 - F_2 + F_0) - \mu^2 F_1 F_2 = 0
\]
(S33)

It is easy to see that for small \(\mu \ll \delta = (F_2 - F_0) / F_0\), \(z_\ast \approx s = F_2 - F_0\), and the asymptotic solution in the real space is
\[
Y_2 = \frac{\mu^2 F_0 F_1 N}{(F_2 - F_0)(F_2 - F_1)} e^{(F_2 - F_0) t} = \frac{\mu^2 (1 - \delta) N}{s(s + \delta)} e^{st}.
\]
(S34)

Of course, this solution is only applicable while \(Y_2 \ll N\), but it can still be used to estimate the characteristic time to switching the population from state 0 to state 2 by equating \(Y_2\) from (S34) to \(N/2\):
\[
T_1 = \left| \frac{1}{F_2 - F_0} \log \frac{(F_2 - F_0)(F_2 - F_1)}{2\mu^2 F_0 F_1} \right| = \frac{1}{s} \log \left[ \frac{s(s + \delta)}{2\mu^2 (1 - \delta)} \right]
\]
(S35)

**Dynamics with gene conversion.** Let us now turn to the case of non-zero \(\alpha\). To simplify the derivation, we will assume \(F_1 = 0\), i.e. the mutants with the active gene in state 1 do not reproduce. In this case the “direct path” from state 0 to state 2 is blocked, and according to Eq. (S35), \(T_1 \rightarrow \infty\). However, gene conversion opens up a bypass route that allows the population to reach high-fitness states \(2^*\) in a finite time via mutations in passive gene to states \((0, 1)\), then \((0, 2)\), and finally by conversion into \((2, 2)\). To describe this process, it suffices to consider the equations for \(X_{0,j}\) and \(X_{2,j}\) only (the contributions of \(X_{1,j}\) are proportional to \(F_1\) and therefore absent), then eqs. (S25) simplify to
\[
\dot{X}_{0,j} = F_0 X_{0,j} - dX_{0,j} + \mu F_0 X_{0,j-1} + \mu F_0 X_{0,j+1} - (3 - \delta_{j0} - \delta_{j2}) \mu F_0 X_{0,j} \\
- 2(1 - \delta_{j0}) \alpha F_0 X_{0,j} + \alpha [F_0 X_{0,1} + F_0 X_{0,2} + F_2 X_{2,0}] \delta_{j0} \\
\dot{X}_{2,j} = F_2 X_{2,j} - dX_{2,j} + \mu F_2 X_{2,j-1} + \mu F_2 X_{2,j+1} - (3 - \delta_{j0} - \delta_{j2}) \mu F_2 X_{2,j} \\
- 2(1 - \delta_{j2}) \alpha F_2 X_{2,j} + \alpha [F_2 X_{2,0} + F_2 X_{2,1} + F_0 X_{0,2}] \delta_{j2}, \quad j = 0, 1, 2.
\]

We again consider small mutation rate, \( \mu \ll (F_2 - F_0)/F_2 \). As in the previous case, \( X_{0,2} \ll X_{0,1} \ll X_{0,0} \), and therefore the reverse mutation flux \((0, 2) \rightarrow (0, 1)\) can be neglected compared with the direct flux \((0, 0) \rightarrow (0, 1)\). Similarly, the reverse mutation flux \((2, 1) \rightarrow (2, 2)\) can be neglected compared with the direct flux from state \((0, 2)\) to \((2, 2)\) due to gene conversion. Therefore the dynamics of \( X_{0,1}, X_{0,2} \) and \( X_{2,2} \) obeys the following closed set of equations

\[
\dot{X}_{0,1} = \mu F_0 N - (3\mu + 2\alpha) F_0 X_{0,1} \\
\dot{X}_{0,2} = \mu F_0 X_{0,1} - 2(\mu + \alpha) F_0 X_{0,2} \\
\dot{X}_{2,2} = (F_2 - F_0) X_{2,2} - 2 \mu F_2 X_{2,2} + \alpha F_0 X_{0,2}
\]

This set of linear equations can again be solved using Laplace transform. In the Laplace space, we get

\[
\tilde{X}_{0,1} = \frac{\mu F_0 N}{[z + F_0(3\mu + 2\alpha)]}, \\
\tilde{X}_{0,2} = \frac{\mu^2 F_0^2 N_p}{[z + F_0(3\mu + 2\alpha)][z + 2F_0(\mu + \alpha)]} \\
\tilde{X}_{2,2} = \frac{\alpha \mu^2 F_0^3 N_p}{[z + F_0(3\mu + 2\alpha)][z + 2F_0(\mu + \alpha)][z + 2\mu F_2 + F_0 - F_2]}
\]

The expression \((S40)\) has a pole at positive \( z_* \approx F_2 - F_0 \), and therefore the corresponding solution in real space is exponentially growing,

\[
X_{2,2} = \frac{\alpha \mu^2 F_0^3 N_p}{(F_2 - F_0 + 2\alpha F_0)^2(F_2 - F_0)} e^{(F_2 - F_0)t}.
\]

Again, we can estimate the time of population switching to the states with fitness \( F_2 \) as the time at which \( X_{2,2} = N/2 \) according to Eq.\((S41)\),

\[
T_2 \approx \frac{1}{F_2 - F_0} \log \left[ \frac{(F_2 - F_0 + 2\alpha F_0)^2(F_2 - F_0)}{2\alpha \mu^2 F_0^3} \right] = \frac{1}{s} \log \left[ \frac{(s + 2\alpha)^2 s}{2\alpha \mu^2} \right]
\]

According to Eq.\((S42)\), the switching time is a non-monotonic function of \( \alpha \) with a minimum at the optimum value

\[
\alpha_m = \frac{F_2 - F_0}{2F_0} = \frac{s}{2}.
\]

It is easy to understand the origin of this optimum: for small \( \alpha \) the gene conversion obviously proceeds very slowly, however for large \( \alpha \) the process is hampered by the strong flux of individuals form states \((0, 1)\) and \((0, 2)\) back to state \((0, 0)\) and to state \((1, 1)\), thus reducing the flux of individuals into state \((2,2)\).

We can also find the value of \( \alpha \) at which \( T_1 = T_2 \), as a root of the quadratic equation

\[
F_1 (F_2 - F_0 + 2\alpha F_0)^2 = \alpha (F_2 - F_1) F_0^2.
\]

For small \( \alpha \ll \delta = (F_2 - F_0)/F_2 \) the solution is

\[
\alpha_c = \frac{F_1(F_2 - F_0)^2}{(F_2 - F_1)F_0^2} = \frac{(1 - \delta)s^2}{s + \delta}.
\]

For \( \alpha \ll \alpha_c \), the effect of gene conversion is negligible, and the fixation time is given by \( T_1 \) that depends on \( F_1 \), but for \( \alpha \gg \alpha_c \), gene conversion dominates the evolution, and the fixation time is given by \( T_2 \) that is independent of \( F_1 \). Interestingly, crossover point \( \alpha_c \) is independent of the mutation rate \( \mu \).
Applicability conditions for the deterministic description. The deterministic description presented in this section is applicable if for every transition between states included in the model $p_{a \rightarrow b} X_a(t_e) \gg 1$, where $p_{a \rightarrow b}$ is the probability of transition from state $a$ to state $b$ and $X_a(t_e)$ is number of individuals of type $a$ at the time $t_e$ at which the population of the beneficial mutants is established, i.e. reaches $O(s^{-1})$. For the direct path, Eq. (S34) yields

$$t_e = s^{-1} \log \left( \frac{s + \delta}{N(1 - \delta)\mu^2} \right).$$

The most stringent limitation is imposed by the transition from state 1 to 2, for which $p_{1 \rightarrow 2} = \mu(1 - \delta)$. For strongly deleterious state 1 ($\delta > s$), $t_e$ is shorter than the time for equilibration of the state 1 subpopulation $\delta^{-1}$, so $X_1(t_e) = \mu N / \delta$, and the applicability condition is

$$N \gg \frac{\delta}{(1 - \delta)\mu^2},$$

(S46)

in agreement with [1].

For the conversion path with $\delta \gg \alpha$, from Eq. (S41) we obtain

$$t_e = s^{-1} \log \left( \frac{s^2}{N\alpha\mu^2} \right).$$

The most stringent limitation here is imposed by the transition from state (0,2) to (2,2), for which $p_{02 \rightarrow 22} = \alpha$ and $X_{02}(t_e) = N\mu^2 \alpha^2$. From $p_{02 \rightarrow 22} X_{02}(t_e) \gg 1$ we obtain the following condition of applicability of the fully deterministic description of the gene conversion path

$$N \gg \frac{s^2}{\alpha\mu^2},$$

(S47)

which for small $\mu$ and $\alpha$ is very stringent.

D. Monoclonal regime

As discussed in the Main text, if the probability of fixation of an intermediate mutant state is much greater than the probability of producing a beneficial mutant, mutant sub-populations will get fixed before giving rise to the "next" mutant. The condition of such monoclonal approximation for the direct path is the opposite limit of Eq. (S23)

$$N \ll \frac{\delta}{(1 - \delta)\mu^2},$$

(S48)

For the gene conversion path, the condition of validity of the fully monoclonal approximation is different from simply the opposite limit of Eq. (S24). As discussed above and in the Main text, the stochastic tunneling regime approximation is valid when $p_{01} \gg \rho_{01}$. In the opposite limit $p_{01} \ll \rho_{01}$, i.e. the reverse of Eq. (6),

$$N \ll \left\{ \begin{array}{ll}
\frac{1}{\sqrt{\nu^2 s}} & \alpha \ll (s\mu^2)^{1/3} \\
\frac{1}{25} \log \left( 1 + \frac{\alpha}{\mu \sqrt{s}} \right) & \alpha \gg (s\mu^2)^{1/3},
\end{array} \right.$$

(S49)

the state (0,1) gets fixed before the successful mutant (0,2) is born. For the fully monoclonal approximation to be valid, we also require that $p_{02} \ll \rho_{02}$, so the population will get fixed in state (0,2) before a successful (2,2) mutant is born. For both state (0,1) and state (0,2), the effective fitness is $(1 - 2\alpha)$, therefore the fixation probability $\rho_{02} = 1/N$ is that of a neutral mutation. From Eqs. (S13) and (S16) we see that $p_{02} = \sqrt{\alpha s}$ for both regimes, therefore the condition is

$$N \ll \frac{1}{\sqrt{\alpha s}}.$$

(S50)

Comparing conditions (S49) and (S50), we observe that the latter is more stringent if $\mu \ll \sqrt{\alpha s}$. For relevant parameters, this is usually the case, which is why we ignored the opposite case of $\alpha \ll \mu^2 / s$ (i.e. extremely small $\alpha$) in the tunneling regime.
Since $N \ll 1/\sqrt{\alpha s}$ is always required for the validity of the monoclonal approximation, and we generally assume $\alpha \ll s$, this also implies that $N\alpha \ll 1$. Therefore, even though $\alpha$ theoretically plays the role of a selective disadvantage for state (0,1), the conditions for the monoclonal approximation ensure that the fixation probability $p(-\alpha)$ is always $\approx 1/N$, i.e. we can assume that states (0,1) and (0,2) are effectively neutral.

**Direct path.** In the monoclonal approximation, the dynamics of the direct path $0 \leftrightarrow 1 \leftrightarrow 2$ can be represented as a finite 3-state machine with a single “absorbing state” 2. We are interested in the mean time for the population to reach the “absorbing state” (2,2). Again treating the system of population dynamics as a finite 4-state machine as shown in Fig. 5 of the Main Text with $\alpha$ represented in the form $\mu N p(-\alpha)$, this also implies that $N\alpha \ll 1/\sqrt{\alpha s}$, i.e. we can assume that states (0,1) and (0,2) are effectively neutral.

Applying the same logic to the gene conversion path, we represent the monoclonal dynamics of the direct path 0 $\leftrightarrow$ 1 $\leftrightarrow$ 2 can be computed by the first element of the 3-dimensional row vector $g = N1$, where $1 = (1 \ 1)^T$, and $N$ is the $2 \times 2$ fundamental matrix

$$N = (1 - Q)^{-1} = \frac{1}{\mu N p(-\delta) + s} \begin{pmatrix} \frac{1}{p(-\delta)} & \frac{1}{1 - \delta} \\ \frac{1}{p(-\delta)} & \frac{1}{1 - \delta} \end{pmatrix},$$
which yields

$$T_1 = \frac{p(-\delta) + (1 - \delta)[p(\delta) + p(\delta + s)]}{N(1 - \delta)\mu p(-\delta)p(\delta + s)}.$$

**Gene conversion path.** Applying the same logic to the gene conversion path, we represent the monoclonal population dynamics as a finite 4-state machine as shown in Fig. 5 of the Main Text with $\alpha' = \alpha N p(s)$. We are interested in the mean time for the population to reach the “absorbing state” (2,2). Again treating the system of Fig. 5 as a discrete-time Markov chain with corresponding transition probabilities per time step (that is a cell division time), it can be completely characterized by the transition matrix that can be represented in the form

$$P = \begin{pmatrix} Q & V \\ 0 & 1 \end{pmatrix},$$

with

$$Q = \begin{pmatrix} 1 - \mu N p(-\delta) & \mu N p(-\delta) \\ (1 - \delta)\mu N p(\delta) & 1 - (1 - \delta)\mu N \cdot [p(\delta) + p(\delta + s)] \end{pmatrix},$$

$$V = (0 \ (1 - \delta)\mu N p(\delta + s))^T,$$ and $0 = (0 \ 0)$. The mean number of transitions from the state 0 to the absorbing state 2 can be computed by the first element of the 2-dimensional row vector $g = N1$, where $1 = (1 \ 1)^T$, and $N$ is the $2 \times 2$ fundamental matrix

$$N = (1 - Q)^{-1} = \frac{1}{\mu N p(\delta + s)} \begin{pmatrix} \frac{p(\delta) + p(\delta + s)}{\mu N} & \frac{1}{1 - \delta} \\ \frac{1}{\mu N} & \frac{1}{1 - \delta} \end{pmatrix},$$
which yields

$$T_1 = \frac{p(-\delta) + (1 - \delta)[p(\delta) + p(\delta + s)]}{N(1 - \delta)\mu p(-\delta)p(\delta + s)}.$$

For completeness, in the neglected regime of extremely small $\alpha \ll \mu^2/s$, $p_{01} = \alpha s/(5\mu)$ (Eq. (S17)), shown by yellow lines in Fig. S1 and $p_{02} = 3\alpha s/(5\mu)$. Substituting $p_{01} = \alpha s/(5\mu)$ into the reverse of Eq. (S24) leads to the condition $N \ll 5\mu/(\alpha s)$ for the monoclonal transition (0,0) $\rightarrow$ (0,1). The condition for the monoclonal transition (0,1) $\rightarrow$ (0,2) is $N \ll 1/p_{02}$, which yields the same condition up to a numerical factor, namely $N \ll 5\mu/(3\alpha s)$. This condition is more permissive than $N \ll 1/\sqrt{\alpha s}$ for these extremely small conversion rates, allowing for larger populations to still exhibit monoclonal dynamics. Note that because of our general assumption that $\mu \ll s$, this condition still implies $N \ll 1/\alpha$, rendering the intermediate states effectively neutral with $p(-\alpha) \approx 1/N$, as for the other two regimes.
FIG. S2. Stochastic simulations of evolution in the minimal 3×3-state model. Fixation times (symbols) are averages from 5000 stochastic simulations with δ = 1, i.e. isolating the gene conversion path. (a) Fixation time for \( s = 0.01 \) as a function of the population size \( N \) for different values of \( \alpha \) and \( \mu \). The solid line indicates the analytical prediction from the monoclonal approximation, Eq. (16), with \( \alpha' \) according to the diffusion approximation Eq. (4). (b) Same as in (a), but for a larger selective advantage \( s = 0.1 \). Vertical dashed lines indicate the border of the regime of applicability of the monoclonal approximation, i.e. \( N = 1/\sqrt{\alpha s} \). (c) Same as in (b), but for \( s = 0.5 \).

It should be noted that, for almost all practical purposes, the transition rates \( \mu \) and \( \alpha \) of the 4-state Markov chain correspond to the rates \( \mu' \) and \( \alpha' \) of the full model. In the full model, mutations occur with rate \( \mu N \), survive the initial removal step of the Moran process with probability \( N/(N+1) \) and get fixed with probability \( 1/N \), leading to a total rate of fixed mutations of \( \frac{\mu}{N+1} \approx \mu \). However, for very small population sizes, \( \frac{N}{N+1} \) may appreciably differ from 1, and so \( \alpha, \alpha' \) and \( \mu \) have to be corrected by this factor in the 4-state Markov model in order to obtain exact predictions. This allows for accurate results down to population sizes as low as \( N = 10 \), (see Fig. S2).

The optimal \( \alpha_m \) for which Eq. (S57) is minimized is given by

\[
\alpha_m = \mu \sqrt{3 + \frac{Np(s)}{1 + Np(s)}}. \quad (S58)
\]

With this, the minimum \( T_2 \) achievable in the monoclonal regime evaluates to

\[
T_{2,\text{min}} = \frac{4 + 3Np(s) + 2\sqrt{3 + 3Np(s)}}{\mu Np(s)}, \quad (S59)
\]

which scales as \( \mu^{-1} \), same as \( T_1 \) for the direct path. Therefore, the speedup factor of fixation through gene conversion in the monoclonal approximation is independent of the mutation rate, in contrast to the tunneling regime above. In both cases, the advantage of gene conversion is at least preserved towards smaller \( \mu \).

E. Comparison across regimes

In the Main text, we use the applicability conditions for the approximations developed in sections A, C and D to visualize the arrangement of the different regimes of the gene conversion path in terms of population size \( N \) and gene conversion rate \( \alpha \) (Fig. 7a). Here we use these approximations to plot the fixation times for the direct path \( T_1 \) and for the gene conversion path \( T_2 \) in the regions of their applicability (Fig. S3). Their ratio is plotted in Fig. 7b of the Main text. The gaps between different regions correspond to mixed (semi-deterministic or semi-monoclonal) regimes where our approximations do not hold.

II. RUGGED FITNESS LANDSCAPES

A. Generalized NK model

We extend the widely-known NK model of epistatic interactions [5]: In the standard NK model, a specific genotype is defined as a sequence of \( N \) bits that we denote by \( b_i \), \( 1 \leq i \leq N \). Each bit \( b_i \) has epistatic interactions with \( K \)
FIG. S3. Fixation times for (a) the direct path ($T_1$) and (b) the gene conversion path ($T_2$) across regimes for fixed $\mu = 10^{-6}$ and $s = 0.1$. The ratio is of these two times plotted in Fig. 2 of the Main text. As in the Main text, calculations are shown for a fixed gene conversion rate $\alpha_0 = (16 \cdot 10^{13})^{-1/3}$ (the optimum in the tunneling regime; blue lines) and the optimal $\alpha$ for each regime and population size (red lines). The results of the direct path (panel (a), black line) do not depend on $\alpha$.

other bits $b_{e,i}$. Each of the $2^X+1$ unique combinations of the bits $b_1, b_{e,1}, \ldots, b_{e,X}$ is assigned a random fitness contribution $f_i(b_1, b_{e,1}, \ldots, b_{e,X})$ from a continuous uniform distribution on the interval $[0,1]$. The total fitness associated with a full string of $N$ bits is then defined as the arithmetic average of all $f_i$:

$$f(b_1, \ldots, b_N) = \frac{1}{N} \sum_{i=1}^{N} f_i(b_1, b_{e,1}, \ldots, b_{e,X}),$$

We associate the string $b_1, b_2, \ldots, b_N$ with the genetic code for a (possibly part of a) particular gene, whose product has to fulfill a particular function. In addition, we define the fitness $f$ of a particular genotype as zero if any of the $N_0(<N)$ bits differ from predefined values. Without loss of generality, we choose the first $N_0$ bits as essential and set their predefined values to 1. The fitness of all possible genotypes then defines the fitness landscape. To include gene conversion, we augment the active region of $N$ bits described above by an additional “passive region” of equal length that corresponds to the duplicate sequence which does not contribute to the fitness in Eq. (S60).

**B. Stochastic simulations**

To simulate the evolution of a population in this fitness landscape, we use the well-known concept of a greedy adaptive walk [6] based on the results for the monoclonal approximation in the minimal model. We assume that single-bit mutations represent a memoryless Markov process with nominal rate $\mu$ per bit per individual, so in a population of size $N$, a single mutation occurs with the probability $2N\mu$. However, because of the different selective pressures, we distinguish between mutations in the active and passive regions. The mutation in the active region that occurs with the total probability $N\nu_0$ can be either deleterious or beneficial. If the mutation is deleterious, it is purified, and the genotype does not change. If it is beneficial, we assume that the fixation probability is 1, and the fixation time is negligible compared to the time between mutations. The mutations in the passive region are neutral, and so they get fixed with probability $1/N$ [2]. As in the monoclonal approximation for the minimal model, we assume that fixation time in the passive region is also negligible compared to the time between mutations, and thus generating successful (fixed) mutations is a simple Markov process with the rate $N\nu$. The gene conversion (copying all $N$ bits) from the active to the passive region occurs with the nominal rate $\alpha$ per individual, i.e. $N\alpha$ overall. Since it is a neutral mutation, it gets fixed in the population with probability $1/N$. The total rate with which a copy from active to passive gets fixed in the population is therefore $\alpha$. The gene conversion from the passive to the active region also occurs with nominal rate $\alpha N$ per individual, i.e. $N\alpha$ overall, but becomes either fixed or discarded depending on whether it improves fitness. Thus, the stochastic greedy adaptive walk is performed as follows. We simulate the evolutionary process as a superposition of four Markovian “reactions” : (1) single bit-flip in the active region (rate
transitions to higher-fitness genotypes. (2) single bit-flip in the passive region (rate \( N\mu \), always accepted), (3) whole N-bit string conversion from active to passive region (rate \( \alpha \), always accepted), (4) whole N-bit string conversion from passive to active region (rate \( N\alpha \), accepted if it improves fitness). The overall Markov process is simulated using the direct Gillespie algorithm \(^7\), so the time to the next event is selected from an exponential time distribution with the time constant \((N\mu + N\mu + \alpha + N\alpha)^{-1}\) and then a particular event is selected based on their relative rates. Note that, in this framework, the population is always monoclonal, as we ignore the short periods of time when a mutation either gets fixed or is eliminated from the population and the corresponding fixation probabilities are included in the above rates.

To compute the average rate of fitness increase \( r \) for given parameters \( N, K, N_0, N, \mu, \) and \( \alpha \), we generated 20 different fitness landscapes and performed 1000 stochastic runs starting from a population initialized at different local fitness peaks. Averaging over stepwise stochastic trajectories of fitness vs. time, we obtained smooth curves as in Fig. Fig. S5a,b,c and computed their slopes at small times.

**Analytical approximations**

When the population is located at a fitness peak, we can ignore mutations in the active region, as they will always be deleterious and therefore will not get fixed. As explained in the main text, the behavior of the model can then be understood in terms of the remaining three rates: The rate of fixation of neutral mutations in the passive regions \( N\mu \), the rate of fixation of neutral conversions from the active to the passive region \( \alpha \), and the rate of fixation of conversions from the passive to the active region \( N\alpha P_b \). Here, \( P_b \) is the probability that the current genotype in the passive region confers a fitness advantage and hence will get fixed when copied to the active region with rate \( N\alpha \). Depending on the regime (see below), \( P_b \) can be expressed in terms of global properties of the fitness landscape or local properties around fitness peaks.

With these processes in mind, three different regimes (1, 2 and 3) can be identified, which are related to each other in a hierarchical manner: For regimes 1 and 2, we assume that \( N\alpha \gg \mu N \), and regime 3 represents the opposite case \( N\alpha \ll \mu N \). The condition \( N\alpha \gg \mu N \) means that conversions from passive to active occur more frequently than mutations in the passive region and therefore any potentially beneficial genotype in the passive region will get the chance to get “activated”, whereas in the opposite limit, many mutations may occur between gene conversions from passive to active, and gene conversions from active to passive that reset the pseudogene occur with even lower rate \( \alpha \). For \( N\alpha \gg \mu N \), we can differentiate between the case \( \alpha \gg \mu N \) (regime 1) and \( \alpha \ll \mu N \) (regime 2). In the first case, conversions from active to passive (i.e. resets) happen more frequently than mutations in the passive region, whereas in the second case, usually multiple mutations happen before the passive region is reset to the state of the active gene. Note that regime 2 only exists for large enough population size \( N \), since \( N\alpha \gg \mu N \) from above is still required (every beneficial mutation is activated) and the overall condition reads \( \alpha \ll \mu N \ll N\alpha \).

Within regime 2, two further cases 2a and 2b can be identified, depending on how often the passive region is reset to the state of the active gene, i.e. how much smaller \( \alpha \) is than \( \mu N \). The reason for the qualitative difference between cases 2a and 2b is a little subtler: Depending on the number \( N_0 \) of essential bits, the passive region can only sustain a certain number of random mutations until one of the essential bits has been altered almost surely. Discovering a beneficial genotype with correct essential bits later is not impossible but highly unlikely, and so the contribution of these late discoveries only becomes dominant for very small \( \alpha \) (when the exploration phase between resetting events is long enough for them to happen, case 2b). For larger \( \alpha \) (case 2a), the beneficial mutations discovered during the initial phase after a gene conversion from active to passive are the only relevant ones, and so these two contributions have to be considered separately. We will derive the exact condition for differentiating between these two cases below.

**Regime 1, \( \alpha \gg \mu N \).** In the case of \( \alpha \gg \mu N \), the freedom for the passive region to mutate to a potentially fitter genotype is limited by frequent conversions that reset it back to the original active genotype. To estimate the average rate of fitness increase \( r \), we calculate the typical time it takes the passive region to escape from the original genotype to a better genotype. The probability that \( k \) consecutive mutations occur before the next resetting event is \( [\mu N/(\alpha + \mu N)]^k \approx (\mu N/\alpha)^k \). Since \( \alpha \gg \mu N \), many of resetting events (with an average between them \( \approx 1/\alpha \)) will occur before the first successful \( k \)-bit mutant is found that will replace the original genotype. The rate for this successful escape is therefore approximately \( \alpha (\mu N/\alpha)^k \). Since the original genotype is by construction at a local fitness maximum, we know that \( k = 1 \) can never lead to a fitness increase. The rate of successful escapes to \( k > 2 \) is smaller than the rate of escapes to \( k = 2 \) by at least a factor \( \mu N/\alpha \), so we assume that \( r \) is dominated by \( k = 2 \) transitions to higher-fitness genotypes.\(^2\) Once a better genotype has been found, it will almost certainly be copied

\(^2\) Of course this assumes that better genotypes at Hamming distance 2 from the peak are actually available, which is the case for at least 50% of the fitness peaks in our NK landscapes as shown in Fig. S4b. Also see the discussion section of the Main text.
to the active region, because $N\alpha \gg \mu N$. This reactivated copy in the active region will then quickly converge to a different (better) local fitness maximum. We make a simplifying assumption that this next local fitness maximum is a random maximum with fitness greater than the fitness of the previous one. This assumption ignores possible correlations between the heights of the neighboring local peaks on the fitness landscape, but as our numerical results show, this approximation seems to hold well even for relatively low ruggedness of $\mathcal{K} = 2$. This approximation allows us to decouple the statistics of the landscape from the statistics of the evolutionary random walk. Let $P_2$ be the fraction of beneficial genotypes at Hamming distance 2 from the maximum and $\Delta \bar{f}$ the expected fitness increase when switching from one peak to another random peak with higher fitness. These parameters can be easily computed by analyzing statistics of NK-landscapes with given $N$ and $\mathcal{K}$ (Fig. S4a and d). Then, the initial rate of fitness increase is

$$r_1 \approx \frac{\Delta \bar{f}^2 \mu N^2}{\alpha} P_2,$$

(S61)

which is shown as a blue dashed line in Fig. S8 and is in excellent agreement with our numerical simulations. Note that $P_2$ implicitly contains the deleterious effect of altering any of the essential bits, which is consistent with the fact that we considered all possible mutations two bit flips away from the current maximum and did not treat the essential bits in any special way (genotypes with altered essential bits are simply never counted as beneficial for $P_2$). Figure S5a in addition shows $r$ as a function of the gene conversion rate for different values of the ruggedness parameter $\mathcal{K}$ along with the same approximations as in Fig. S8a. As can be seen, the approximation holds remarkably well even for low ruggedness.

Regime 2, $\alpha \ll \mu N \ll N\alpha$. If $N$ is large, there may be an intermediate range of $\alpha$ for which this condition holds. In this regime, as in regime 1 above, gene conversion happens for almost every beneficial genotype that is discovered in the passive region, while potentially many mutations occur in between copying events from the active to the passive region that happen with rate $\alpha$. Note that the probability to discover a better fitness in the passive region decays exponentially with time from the last direct conversion event since the essential bits will accrue more and more probability to evolve away from their correct initial values. This leads to two different sub-cases: (2a) for not too small $\alpha$, the beneficial mutation at the time of the next conversion event from passive to active is more likely to be found in the wake of a reset (gene conversion from active to passive) while the essential bits have not yet mutated away from their original values, and (2b) for very small $\alpha$, the time between copying events becomes so large that multiple mutations in essential bits become very likely, and the probability to find a beneficial genotype is dominated by the random discovery of such a genotype (with correct essential bits) after all memory of the last-reset genotype is lost. The contribution of regime 2b is exponentially small for large $N_0$, we will determine an explicit condition for the transition between cases 2a and 2b below.

Regime 2a. To determine the rate of beneficial mutations in this regime, we calculate the first beneficial mutation is discovered and transferred to the active region in a small time interval $\Delta t$ at some time $t$ after the reset (conversion event from active to passive). Because of the ruggedness of the landscape, we assume that altering any bit (other than the essential bits) has the same fixed probability $P_g$ of yielding a fitter genotype which is equal to the fraction of all genotypes with correct essential bits that have a higher fitness than the current maximum. This fraction can be computed by analyzing statistics of our NK landscapes for given $N$, $\mathcal{K}$, and $N_0$ (Fig. S4a). To discover the first beneficial mutation at time $t$, it must not have been discovered in any of the preceding $\Delta t$ (probability $[1 - (N - N_0)\mu P_g \Delta t]^t/\Delta t$) and the essential bits must not have been altered (probability $[1 - N_0\mu \Delta t]^{\alpha t}$). Taking the limit $\Delta t \to 0$, we obtain the probability distribution for the discovery of a beneficial mutation at time $t$ after the previous reset:

$$P_d(t) = (N - N_0)\mu P_g \exp[-(N_0 + (N - N_0) P_g)\mu t]$$

(S62)

Note that this distribution is not normalized since the discovery of a beneficial mutation is not guaranteed, and the total probability of success is $\int_0^\infty P_d(t) \, dt = (N - N_0)P_g/[N_0 + (N - N_0) P_g]$. If we assume that $\alpha$ is small enough such that the probability distribution $P_d(t)$ is close to zero when the next reset occurs with rate $\alpha$, then the rate of discovery of beneficial mutations in this limit is simply $\alpha \int_0^\infty P_d(t) \, dt$, leading to

$$r_{2a} = \frac{\Delta \bar{f} (N - N_0) P_g}{N_0 + (N - N_0) P_g} \alpha.$$

(S63)

Note that this can only be an approximation, as we know that the first bit flip can never yield a fitness increase (because the population is located at a local fitness maximum). In regime 1, we had to explicitly consider this fact since the ability of the population to evolve even only two bit flips away from the maximum is severely limited in that regime, and so the genotypes only one bit flip away from the maximum represent a large fraction of the explored genotype space. In contrast, here, potentially many mutations are possible, and so the fact that the first one can never yield a fitter genotype is a smaller correction than in regime 1.

In contrast to regime 1, it is necessary to treat bit flips of essential and non-essential bits separately in this case: In regime 2a, altering only one essential bit irreversibly terminates the search for a better genotype (randomly discovering a genotype with correct essential bits later would correspond to regime 2b). In contrast, non-essential bits can be flipped repeatedly to discover a better phenotype with probability $P_g$. Consequently, the fraction $P_g$ is defined here using the set of only the genotypes with correct essential bits, as the possibility of a deleterious mutation due to the flipping of an essential bit is considered separately.
FIG. S4. **Landscape statistics.** For all panels, statistics were generated by analyzing at least 1000 maxima from sufficiently many NK landscapes with $N = 20$ and $N_0 = 10$. (a) Average $P_g$ and $P_2$ as a function of the ruggedness parameter $K$. (b) Probability of finding a genotype with higher fitness at a Hamming distance $k = 2$ from a local maximum in the landscape—i.e. the fraction of all fitness peaks which have a better genotype with $\Delta f > 0$ available two bit flips away—as a function of the landscape roughness parameter $X$. (c) Average fitness increase when switching from any local maximum to a different local maximum with higher fitness. (d) Average fitness increase when switching from a local maximum with given fitness $f$ to a different local maximum with higher fitness. Data was binned with respect to $f$.

This dependence is shown by the yellow dashed line in Fig. S and by the solid black line in Fig. S5b. For small $P_g$, it simplifies to $r_{2b} \approx \Delta f \frac{N_{\text{active}}}{N_0} P_g \alpha$.

**Regime 2b.** For very small $\alpha$ (to be specified below) the passive genotype drifts far away from the genotype of the active region, and the memory about it is essentially lost. In this regime, the fitness improvement may only occur through random discovery of a fitter genotype anywhere in the fitness space. In this regime, the rate of improvement is easily calculated as

$$r_{2b} = \overline{\Delta f \mu N P_g^*},$$

where $P_g^*$ is the average fraction of all genotypes with fitness higher than a random local peak for given landscape parameters. The fraction $P_g$ was defined above in the same way, but only among the subset of genotypes with correct essential bits instead of all genotypes. Therefore, $P_g^*$ and $P_g$ are related by $P_g^* = 2^{-N_0} P_g$, since there is exactly one in $2^{N_0}$ sequences with correct essential bits. This $\alpha$-independent rate of fitness increase $r_{2b}$ is depicted by horizontal lines in Fig. S3 and Fig. S5a for small $\alpha$, but it only manifests itself in the numerical data if $N \alpha$ is still much larger than $\mu N$, i.e. for large enough $N$ (see black dashed line in Fig. S5b).

Which regime (2a or 2b) is the dominating source of beneficial mutations when $\alpha \ll \mu N \ll N \alpha$ depends on the relative magnitude of $r_{2a}$ and $r_{2b}$: When $r_{2a}$ becomes smaller than $r_{2b}$, the random discovery dominates. Thus, the condition for regime 2b ($r_{2b} \gg r_{2a}$) can be written as

$$\alpha \ll 2^{-N_0} \frac{\mu N N_0}{N - N_0}.$$

(S65)
FIG. S5. **Fitness improvement rate in NK landscapes with different $K$ and $N$.** In both panels, circles are the results of numerical simulations, lines represent theoretical predictions. Numbers $i = 1$, $2a$, $2b$, $3$ indicate approximations $r_i$ for the different regimes. (a) $r$ for $N = 20$, $N_0 = 10$, $N = 10^5$ and different ruggedness parameters $K$. Lines correspond to the same three regimes ($1$, $2a$, $2b$) as shown in Fig. 8d. The color for all three regimes indicates the value of $K$. (b) $r$ in the small-$\alpha$ regime for $N = 20$, $K = 19$, $N_0 = 10$ and varying $N$. Black lines indicate the approximations $r_{2a}$ (solid, regime 2a) and $r_{2b}$ (dashed, regime 2b), corresponding to Eqs. (19) and (20) in the main text, respectively. Solid colored lines represent the approximation $r_3$ (regime 3) for the corresponding population size $N$.

and the opposite inequality gives the condition for regime 2a (provided, of course, that $\alpha \ll \mu N \ll N\alpha$). This formula confirms the intuitive expectation that discovering a fitter genotype by pure chance anywhere in the fitness space is highly unlikely for large numbers of essential bits $N_0$.

**Regime 3, $N\alpha \ll \mu N$.** For very small $\alpha$ such that even $N\alpha \ll \mu N$, the attempts to reactivate the genotype in the passive region (i.e., to copy it into the active region) will occur very rarely (with rate $N\alpha$). Between these reactivation attempts, the genotype in the passive region will have mutated with the much larger rate $\mu N$ far away from the original sequence. Therefore, reactivating the copy is equivalent to picking random genotypes from the landscape, and fitness improvements will occur with rate $N\alpha P_*^g$. The initial rate of fitness increase in this limit is again $\alpha$-dependent,

$$r_3 \approx \Delta f N\alpha P_*^g \quad (S66)$$

Since this rate is very small for large $N_0$ and therefore difficult to measure numerically, we carried out additional simulations specifically of the low $\alpha$ regime, which are shown in Fig. S5b, where the approximation of Eq. (S66) is shown as solid lines in the corresponding color.