S1 General notes on the analysis

Major parts of the analysis are based on branching process approximations. We model the number of double mutants (and occasionally also the number of single mutants) in the standing genetic variation by a subcritical branching process with immigration, where "immigration" happens through mutation or recombination. For the establishment probability of a type AB individual, we apply results from the theory of time-homogeneous or time-inhomogeneous single-type branching processes. In order to determine the probability that a type Ab individual gives rise to a permanent lineage of AB individuals by mutation, we use a two-type branching process. Although the model is formulated in discrete time, we resort to branching processes in continuous time for the mathematical analysis. In the following, we first state some general mathematical results from branching process theory. We thereafter apply them to derive some building blocks that we use repeatedly in the subsequent analysis in Appendix S2 and Appendix S3.

S1.1 Mathematical results from branching process theory

Probability generating function for the number of individuals in a subcritical single type branching process with immigration Following Sewastjanow (1974, p. 163), we can calculate the probability generating function (p.g.f.) for the number of individuals in a subcrititcal branching process with immigration. Individuals reproduce at rate λ and die at rate μ. Immigration happens at rate m. W define the two infinitesimal generating functions

$$f(y) = \mu - (\lambda + \mu)y + \lambda y^2, \tag{S1.1a}$$

$$g(y) = -m + my. \tag{S1.1b}$$

Let P_k be the probability to have k individuals in the limit $t \to \infty$ and

$$F(y) = \sum_{k=0}^{\infty} P_k y^k \tag{S1.2}$$

It then holds

$$\begin{aligned} F(y) &= \exp\left[\int_y^1 \frac{g(x)}{f(x)} \mathrm{d}x\right] \\ &= \left(\frac{\lambda - \mu}{y\lambda - \mu}\right)^{\frac{m}{\lambda}}. \end{aligned} \tag{S1.3}$$

For $\lambda = \frac{1}{2} + \frac{\sigma}{2}$ and $\mu = \frac{1}{2} - \frac{\sigma}{2}$, this gives

$$F(y) = \left(\frac{2\sigma}{y + y\sigma + \sigma - 1}\right)^{\frac{2m}{1+\sigma}}. \tag{S1.4}$$

From the p.g.f., the stationary distribution of the number of individuals can be obtained as

$$P_k = \frac{1}{k!}\frac{\mathrm{d}}{\mathrm{d}y}F(y)|_{y=0} = \frac{1}{k!}\left(\frac{2\sigma}{\sigma - 1}\right)^{\frac{2m}{\sigma+1}+k} \cdot \prod_{i=1}^{k} \frac{2m + (i-1)(1+\sigma)}{(-2\sigma)} \tag{S1.5}$$

for $k > 0$ and $P_0 = F(0)$.

Establishment probability of a reducible two-type branching process Consider a branching process with two types. Type i reproduces at rate λ_i and dies at rate μ_i. Type 2 turns into type 1 at rate u_{eff}.

The survival probability of a process founded by one individual of type 1 is given by (Allen, 2011, p. 253)

$$p_{\text{est}}^{(1)} = \begin{cases} \frac{\lambda_1 - \mu_1}{\lambda_1} & \text{if} \quad \lambda_1 > \mu_1, \\ 0 & \text{else.} \end{cases} \tag{S1.6}$$

The establishment probability of a process founded by a single individual of type 2 can be obtained by solving the equation

$$1 - p_{\text{est}}^{(2)} = \frac{\mu_2}{\lambda_2 + \mu_2 + u_{\text{eff}}} + \frac{u_{\text{eff}}}{\lambda_2 + \mu_2 + u_{\text{eff}}}(1 - p_{\text{est}}^{(1)}) + \frac{\lambda_2}{\lambda_2 + \mu_2 + u_{\text{eff}}}(1 - p_{\text{est}}^{(2)})^2, \tag{S1.7}$$

where the smaller root has to be taken (Uecker *et al.*, 2015):

$$\begin{aligned} p_{\text{est}}^{(2)} &= 1 - \frac{\lambda_2 + \mu_2 + u_{\text{eff}} - \sqrt{(\lambda_2 + \mu_2 + u_{\text{eff}})^2 - 4(u_{\text{eff}}(1 - p_{\text{est}}^{(1)}) + \mu_2)\lambda_2}}{2\lambda_2} \\ &= 1 - \frac{\lambda_2 + \mu_2 + u_{\text{eff}} - \sqrt{(\lambda_2 - \mu_2 - u_{\text{eff}})^2 + 4\lambda_2 u_{\text{eff}} p_{\text{est}}^{(1)}}}{2\lambda_2}. \end{aligned} \tag{S1.8}$$

With $\lambda_2 = \frac{1}{2} + \frac{s}{2}$ and $\mu_2 = \frac{1}{2} - \frac{s}{2}$, this yields:

$$p_{\text{est}}^{(2)} = 1 - \frac{1 + u_{\text{eff}} - \sqrt{(s - u_{\text{eff}})^2 + 2(1+s)u_{\text{eff}} p_{\text{est}}^{(1)}}}{1+s}. \tag{S1.9}$$

Establishment probability of an inhomogeneous single-type branching process The establishment probability of a single allele with time-dependent birth rate $\lambda(t)$, death rate $\mu(t)$, and growth parameter $\lambda(t) - \mu(t) = s_{\text{eff}}(t)$ that arises at time T in a population is given by (Kendall, 1948; Uecker and Hermisson, 2011)

$$p_{\text{est}}(T) = \frac{2}{1 + \int\limits_T^\infty (\lambda(t) + \mu(t)) e^{-\int\limits_T^t s_{\text{eff}}(\tau)\mathrm{d}\tau} \mathrm{d}t}. \tag{S1.10}$$

The extinction time of a single-type branching process Consider a subcritical branching process with an initial number of n_0 individuals. Individuals reproduce at rate λ and die at rate μ. From the probability that the process has gone extinct by time t, $P_0(n_0, t)$, (see Uecker and Hermisson, 2011), we immediately obtain the distribution of the extinction time T_{ext}:

$$P(T_{\text{ext}} \leq t) = P_0(n_0, t) = \left(\frac{\mu(1 - e^{-(\lambda - \mu)t})}{\lambda - \mu + \mu(1 - e^{-(\lambda-\mu)t})} \right)^{n_0}. \tag{S1.11}$$

We denote by

$$p^{(\text{ext})}(t) = \frac{\mathrm{d}}{\mathrm{d}t} P(T_{\text{ext}} \leq t) \tag{S1.12}$$

the corresponding probability density.

S1.2 Essential building blocks

In order to match the results from the continuous-time approximation to the discrete time model, we need to make sure that the growth behavior and the amount of drift are the same (Uecker *et al.*, 2014). First, in order to guarantee that the long-term growth behavior is the same, we replace the growth parameter σ from the discrete-time model by $\ln(1+\sigma)$ in the continuous-time approximation whenever long-term growth is essential. In order to generate the same amount of drift, birth and death rates of individuals must sum up to 1 (at least in the diffusion limit). In a model with selection, this can be achieved in various ways, by distributing the effect of the effective growth parameter σ (or $\ln(1+\sigma)$) on the birth and death rates. If not stated otherwise, we usually do this symmetrically, i.e., $\lambda = \frac{1}{2} + \frac{\sigma}{2}$ and its death rate as $\mu = \frac{1}{2} - \frac{\sigma}{2}$. This is appropriate as long as selection is not too strong. For very large (positive or negative) σ, one of the rates can turn negative. In that case, we switch to a different parameterization (and explicitly state this).

Throughout the analysis, we ignore back mutation. We furthermore assume that the mutation rate is small enough that we can neglect direct generation of the double mutant from the wildtype.

The number of single mutants in the standing genetic variation We assume that mutants are rare in relative frequency in the population, i.e., they only interact with wildtype individuals. This has several implications: (1) birth and death rates are constant (since mean fitness is ≈ 1), (2) a constant influx of new mutations (since $n_{ab} \approx N_0$), (3) recombination has no effect on single mutants (since mutants only recombine with wildtype individuals), (4) interactions with double mutants can be ignored.

Then, from Eq. (S1.4) with $m = uN_0(1 + \sigma_{Ab})$ and $\lambda = \frac{1}{2} + \frac{\sigma_{Ab}}{2}$ and $\mu = \frac{1}{2} - \frac{\sigma_{Ab}}{2}$, we obtain the probability generating function F_{Ab} for the number of Ab mutants in the population; analogous, we obtain F_{aB}:

$$F_{Ab}(y) = \left(\frac{2\sigma_{Ab}}{y + y\sigma_{Ab} + \sigma_{Ab} - 1} \right)^{2uN_0}, \tag{S1.13a}$$

$$F_{aB}(y) = \left(\frac{2\sigma_{aB}}{y + y\sigma_{aB} + \sigma_{aB} - 1} \right)^{2uN_0}. \tag{S1.13b}$$

The mean number of Ab and aB mutants is given by

$$\bar{n}_{Ab} = \langle n_{Ab} \rangle = F'_{Ab}(1) = -\frac{uN_0}{\sigma_{Ab}}(1 + \sigma_{Ab}), \tag{S1.14a}$$

$$\bar{n}_{aB} = \langle n_{aB} \rangle = F'_{aB}(1) = -\frac{uN_0}{\sigma_{aB}}(1 + \sigma_{aB}). \tag{S1.14b}$$

The number of double mutants in the standing genetic variation In a large population, in which single mutants are frequent in absolute but rare in relative numbers, their number can be well approximated by their mean value as given by Eq. (S1.14).

However, the number of double mutants is subject to strong stochasticity. Before the time of environmental change, their distribution can be modeled by a subcritical branching process with immigration. Immigration happens at rate

$$m_{AB} = \left(r \frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0} \right) (1 + \sigma_{AB}) + u(\bar{n}_{Ab} + \bar{n}_{aB})(1 + \sigma_{AB})(1 - r). \tag{S1.15}$$

As the effective selection coefficient of AB individuals, we use

$$\sigma_{AB}^{\text{eff}} = (1 + \sigma_{AB})(1 - r) - 1. \tag{S1.16}$$

Individuals of type AB reproduce at rate $\frac{1}{2} + \frac{1}{2}\sigma_{AB}^{\text{eff}}$ and die at rate $\frac{1}{2} - \frac{1}{2}\sigma_{AB}^{\text{eff}}$.

With Eq. (S1.4), we obtain the probability generating function $F_{AB}(s)$ for the number of double mutants in the standing genetic variation:

$$F_{AB}(y) = \left(\frac{2\sigma_{AB}^{\text{eff}}}{y + y\sigma_{AB}^{\text{eff}} + \sigma_{AB}^{\text{eff}} - 1} \right)^{\frac{2m_{AB}}{1+\sigma_{AB}^{\text{eff}}}}. \tag{S1.17}$$

The mean number of double mutants is given by

$$\begin{aligned}
\langle n_{AB}\rangle = F'_{AB}(1) &= -\frac{m_{AB}}{\sigma_{AB}^{\text{eff}}} \\
&= -\frac{u^2N_0}{\sigma_{Ab}\sigma_{aB}}(1+\sigma_{AB})\frac{r(1+\sigma_{Ab}+\sigma_{aB}+\sigma_{Ab}\sigma_{aB})-(1-r)(\sigma_{Ab}+\sigma_{aB}+2\sigma_{Ab}\sigma_{aB})}{\sigma_{AB}-r(1+\sigma_{AB})} \\
&= -\frac{u^2N_0}{\sigma^2}(1+\sigma_{AB})(1+\sigma)\frac{r(1+\sigma)-2\sigma(1-r)}{\sigma_{AB}-r(1+\sigma_{AB})},
\end{aligned} \tag{S1.18}$$

where the last line holds for $\sigma_{Ab}=\sigma_{aB}=\sigma$.

With $\sigma_{AB}=E_1+(\sigma_{Ab}+\sigma_{aB}+\sigma_{Ab}\sigma_{aB})=E_1+\sigma(2+\sigma)$ and $|\sigma_{Ab}|$, $|\sigma_{aB}|$, and $|\sigma_{AB}|$ small, we can further approximate:

$$\begin{aligned}
\langle n_{AB}\rangle &\approx \frac{u^2N_0}{\sigma_{Ab}\sigma_{aB}}\frac{r-(\sigma_{Ab}+\sigma_{aB})}{r-E_1-(\sigma_{Ab}+\sigma_{aB})} \\
&= \frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-E_1-2\sigma}.
\end{aligned} \tag{S1.19}$$

We see that for $E_1=0$ (no epistasis), $\langle n_{AB}\rangle$ is independent of r; for $E_1<0$ (negative epistasis), $\langle n_{AB}\rangle$ increases with r; for $E_1>0$ (positive epistasis), $\langle n_{AB}\rangle$ decreases with r. For $r=0$, the mean number of double mutants is given by $\frac{u^2N_0}{\sigma^2}\frac{2\sigma}{E_1+2\sigma}$, hence strongly dependent on the degree of epistasis. For $r\gg|\sigma_{Ab}+\sigma_{aB}|$ and $r\gg|\sigma_{AB}|$, it converges to $\frac{u^2N_0}{\sigma_{Ab}\sigma_{aB}}$, independently of epistasis.

Establishment probabilities in the absence of the wildtype In the absence of the wildtype, the double mutant is (effectively) not broken up by recombination. With Eq. (S1.6) and $\lambda_1 = \frac{1}{2} + \frac{1}{2}\ln(1+s_{AB})$ and $\mu_1 = \frac{1}{2} - \frac{1}{2}\ln(1+s_{AB})$ (assuming $\ln(1+s_{AB}) \leq 1$, which is always the case in our examples), we obtain for the survival probability of a process which is founded by a single individual of type AB:

$$p_{\mathrm{est}}^{(AB)} = \frac{2\ln(1+s_{AB})}{1+\ln(1+s_{AB})} \approx 2s_{AB}, \tag{S1.20}$$

where the approximation holds for s_{AB} small.

We also derive an approximation for the survival probability of a process founded by one individual of type Ab (or aB), when type AB can only be generated by mutation (either because $r = 0$ or because the other single mutant type is absent). The problem can then be assessed by means of a two-type branching process. Type Ab has birth rate $\frac{1}{2} + \frac{\hat{s}_{Ab}}{2}$ and death rate $\frac{1}{2} - \frac{\hat{s}_{Ab}}{2}$ with $\hat{s}_{Ab} = \ln(1+s_{Ab})$ (assuming $-1 \leq \ln(1+s_{Ab}) \leq 1$, which is again always fulfilled in our examples). It turns into type AB at rate $u(1+s_{AB})$ (analogously for type aB). With (S1.9) and $Q_1 = 1 - p_{\mathrm{est}}^{(AB)}$, we obtain the establishment probability:

$$\begin{aligned}
p_{\mathrm{est}}^{(Ab)} &= 1 - \frac{1 + u(1+s_{AB}) - \sqrt{(\hat{s}_{Ab} - u(1+s_{AB}))^2 + 2u(1+s_{AB})(1+\hat{s}_{Ab})p_{\mathrm{est}}^{(AB)}}}{1+\hat{s}_{Ab}} \\
&\approx 1 - \frac{1 + u - \sqrt{(s_{Ab}-u)^2 + 4us_{AB}(1+s_{Ab})}}{1+s_{Ab}} \\
&\approx 1 - (1 + u - s_{Ab} - \sqrt{(s_{Ab}-u)^2 + 4us_{AB}}) \\
&= s_{Ab} - u + \sqrt{(s_{Ab}-u)^2 + 4us_{AB}} \\
&\approx \frac{2us_{AB}}{-s_{Ab}}.
\end{aligned} \tag{S1.21}$$

The last approximation holds for $s_{Ab} < 0$ and $s_{Ab}^2 \gg u s_{AB}$. It can be easily interpreted: $\frac{1}{-s_{Ab}}$ is the mean number of descendants of a single Ab individual. Each of these descendants mutates with probability u, leading to a permanently establishing lineage of AB individuals with probability $2s_{AB}$.

Establishment probabilities in the presence of the wildtype If the wildtype dominates over the single mutants at all times, the double mutant virtually always recombines with the wildtype (until it becomes frequent and rescue has occurred). Under these conditions, the effective growth parameter of the rescue type can be approximated as

$$s_{\text{eff}}(t) = \begin{cases} (1+s_{AB})(1-r)-1 & \text{as long as the wildtype exists,} \\ s_{AB} & \text{as soon as the wildype has died out.} \end{cases} \tag{S1.22}$$

If the wildtype decays very slowly and if we can furthermore assume that no double mutants get generated once the wildtype has gone extinct, this yields for the establishment probability of the double mutant:

$$\begin{aligned} p_{\text{est}}^{(AB)} &= \begin{cases} \frac{2\ln[(1+s_{AB})(1-r)]}{1+\ln[(1+s_{AB})(1-r)]} & \text{if} \quad \ln[(1+s_{AB})(1-r)] > 0, \\ 0 & \text{else.} \end{cases} \\ &\approx \max[2(s_{AB}-r), 0]. \end{aligned} \tag{S1.23}$$

Following the same derivation as in Eq. (S1.21), the probability that a single Ab individual will eventually give rise to a successful lineage of AB individuals is

$$
\begin{aligned}
p_{\text{est}}^{(Ab)} &= 1 - \frac{1 + u(1+s_{AB})(1-r) - \sqrt{(\hat{s}_{Ab} - u(1+s_{AB})(1-r))^2 + 2u(1+s_{AB})(1-r)(1+\hat{s}_{Ab})p_{\text{est}}^{(AB)}}}{1+\hat{s}_{Ab}} \\
&\approx s_{Ab} - u(1-r) + \sqrt{(s_{Ab} - u(1-r))^2 + 4u(1-r)\max\left[2(s_{AB}-r), 0\right]} \\
&\approx \frac{2u(1-r)\max\left[2(s_{AB}-r), 0\right]}{-s_{Ab}}.
\end{aligned}
\tag{S1.24}
$$

The simple approximation $p_{\text{est}}^{(AB)}$, Eq. (S1.23), fails when the wildtype population size decays quickly. In case of a fast (but not instantaneous) eradication of the wildtype, we need to apply to a more refined approximation for the establishment probability of type AB. The extinction time of the wildtype is a stochastic variable. If we ignore mutation and recombination, the dynamics of the wildtype is given by a subcritical branching process with initial size $n_{ab}(0) \approx N_0$, and we can calculate the distribution of the extinction time T_{ext} with the help of Eq. (S1.11). Since $\ln(1+s_{ab})$ is considerably smaller than -1 if s_{ab} is strongly negative, we deviate from our default approximation for λ and μ here and choose $\lambda = 1/2$ and $\mu = 1/2 - \ln(1+s_{ab})$ to keep selection at the right level and avoid negative birth rates. With this, we obtain

$$
P(T_{\text{ext}} \leq t) = \left(\frac{1 - e^{-s_{ab}t}}{\frac{2s_{ab}}{1-s_{ab}} + 1 - e^{-s_{ab}t}} \right)^{N_0}
\tag{S1.25}
$$

and from this the probability density $p^{(\text{ext})}(T_{\text{ext}})$.

For a given T_{ext}, we can calculate the establishment probability of a single double mutant based on a time-inhomogeneous branching process with death rate $\frac{1}{2} - \frac{\hat{s}_{\text{eff}}(t)}{2}$ and birth rate $\frac{1}{2} + \frac{\hat{s}_{\text{eff}}(t)}{2}$ with $\hat{s}_{\text{eff}}(t)$ defined by

$$\hat{s}_{\text{eff}}(t) = \begin{cases} \ln\left((1+s_{AB})(1-r)\right) & t \leq T_{\text{ext}}, \\ \ln\left(1+s_{AB}\right) & t > T_{\text{ext}} \end{cases} \tag{S1.26}$$

(see Eq. (S1.10)). This gives for $t < T_{\text{ext}}$:

$$p_{\text{est}}^{(AB)}(t|T_{\text{ext}}) = \frac{2}{1 + I(t, T_{\text{ext}})} \tag{S1.27}$$

with

$$\begin{aligned} I(t, T_{\text{ext}}) &= \int\limits_{t}^{\infty} e^{-\int\limits_{t}^{T} \hat{s}_{\text{eff}}(\tau)\mathrm{d}\tau} \mathrm{d}T \\ &= \frac{1}{s_1} - \left(\frac{1}{s_1} - \frac{1}{s_2}\right) e^{-s_1(T_{\text{ext}}-t)}, \end{aligned} \tag{S1.28}$$

where s_1 and s_2 are given by $\hat{s}_{\text{eff}}$ before and after extinction of the wildtype respectively. For $t \geq T_{\text{ext}}$, the establishment probability is given by Eq. (S1.20).

Over all possible extinction times, we get

$$p_{\text{est}}^{(AB)}(t) = \int\limits_{t}^{\infty} p(T_{\text{ext}}) \frac{2}{1 + I(t, T_{\text{ext}})} \mathrm{d}T_{\text{ext}} + \int\limits_{0}^{t} p(T_{\text{ext}}) \frac{2\ln\left(1+s_{AB}\right)}{1 + \ln\left(1+s_{AB}\right)} \mathrm{d}T_{\text{ext}}. \tag{S1.29}$$

The numerical evaluation of integrals is done in Mathematica (Wolfram Research, Champaign, USA).

S2 No recombination

For complete linkage, approximations have been derived in Iwasa *et al.* (2003, 2004). These approximations model all allele frequencies in the standing genetic variation deterministically. We extend these results by a stochastic treatment of the number of double mutants standing genetic variation.

The distribution of standing genetic variation In principle, the number of single and double mutants in the population can be modeled as a two-type branching process with immigration. However, analytical solutions for the p.g.f. are not easily derived. We therefore propose two simpler approximations to estimate the contribution of the standing genetic variation for rescue. (1) If the population size is small, double mutants in the standing genetic variation can often be neglected; the number of single mutants is subject to stochasticity. The probability generating functions F_{Ab} and F_{aB} are given by Eq. (S1.13). (2) If the population size is large, the number of single mutant types is well approximated by their expected value (Eq. (S1.14)). The probability generating function for the number of double mutants F_{AB} is then given by Eq. (S1.17).

Establishment probability of the rescue mutant After the change in the environment, a lineage initiated by one individual of type AB survives with probability $p_{\text{est}}^{(AB)}$ as given by Eq. (S1.20) A lineage that is founded by a single individual of type Ab (or aB) survives with probability $p_{\text{est}}^{(Ab)}$ as given by Eq. (S1.21). These results do not depend on the dynamics of the wildtype when $r = 0$ because of our assumption of a hard carrying capacity (no density dependence until $N \geq N_0$).

The probability of evolutionary rescue We first consider the case that the number of double mutants before the change in the environment can be ignored. Rescue can now either pass via single mutants from the standing genetic variation or via newly generated single mutants. The number of successful offspring of a single type Ab individual is Poisson distributed with parameter $(1 + s_{Ab})p_{\text{est}}^{(Ab)}$. If n_{Ab} individuals of type Ab are present at the time of environmental change, they hence do not establish a permanent lineage with probability $\exp\left[-n_{Ab}(1 + s_{Ab})p_{\text{est}}^{(Ab)}\right]$. It remains to average over the distribution of n_{Ab}, for which one can conveniently use the p.g.f. F_{Ab}, Eq. (S1.13) (analogous for type aB). In order to determine the number of single mutants that get generated after the environmental change, we assume that the decay of the wildtype population size can be well described deterministically by $n_{ab}(t) \approx N_0(1 + s_{ab})^t$ (cf. Orr and Unckless, 2008; Uecker *et al.*, 2014). The number of de-novo generated single mutants is then given by $\sum_{t=0}^{\infty} un_{ab}(t)(1 + s_{Ab}) \approx \frac{uN_0}{-s_{ab}}(1 + s_{Ab})$. With this, we obtain:

$$P_{\text{rescue}} = 1 - F_{Ab}(e^{-(1+s_{Ab})p_{\text{est}}^{(Ab)}})F_{aB}(e^{-(1+s_{aB})p_{\text{est}}^{(aB)}})e^{-\frac{uN_0}{-s_{ab}}(1+s_{Ab})p_{\text{est}}^{(Ab)} - \frac{uN_0}{-s_{ab}}(1+s_{aB})p_{\text{est}}^{(aB)}}. \tag{S2.1}$$

If single mutants are frequent and we describe double mutants stochastically, using the expected values $\bar{n}_{Ab}$ and $\bar{n}_{aB}$, we have:

$$\begin{aligned} P_{\text{rescue}} = 1 - F_{AB}(e^{-(1+s_{AB})p_{\text{est}}^{(AB)}})e^{-u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})p_{\text{est}}^{(AB)}} e^{-\bar{n}_{Ab}(1+s_{Ab})p_{\text{est}}^{(Ab)} - \bar{n}_{aB}(1+s_{aB})p_{\text{est}}^{(aB)}} \\ \times e^{-\frac{uN_0}{-s_{ab}}(1+s_{Ab})p_{\text{est}}^{(Ab)} - \frac{uN_0}{-s_{ab}}(1+s_{aB})p_{\text{est}}^{(aB)}}. \end{aligned} \tag{S2.2}$$

If we can treat the number of double mutants deterministically, we obtain:

$$\begin{aligned} P_{\text{rescue}} = 1 - e^{-(1+s_{AB})\bar{n}_{AB}p_{\text{est}}^{(AB)}} e^{-u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})p_{\text{est}}^{(AB)}} e^{-\bar{n}_{Ab}(1+s_{Ab})p_{\text{est}}^{(Ab)} - \bar{n}_{aB}(1+s_{aB})p_{\text{est}}^{(aB)}} \\ \times e^{-\frac{uN_0}{-s_{ab}}(1+s_{Ab})p_{\text{est}}^{(Ab)} - \frac{uN_0}{-s_{ab}}(1+s_{aB})p_{\text{est}}^{(aB)}} \end{aligned} \tag{S2.3}$$

with

$$\bar{n}_{AB} = \frac{u(\bar{n}_{Ab} + \bar{n}_{aB})}{-\sigma_{AB}}(1 + \sigma_{AB}). \tag{S2.4}$$

Comparison to Iwasa *et al.* (2003, 2004) We can compare our approximations to the approximation derived in Iwasa *et al.* (2003, p. 2574) and Iwasa *et al.* (2004, Eq. (9)), who describe all allele frequencies prior to the environmental change deterministically (derived as the stationary solution of a system of differential equations). Consequently, as can be seen from Fig. S2.1, the approximation is in good agreement with Eq. (S2.3) (up to minor deviations due

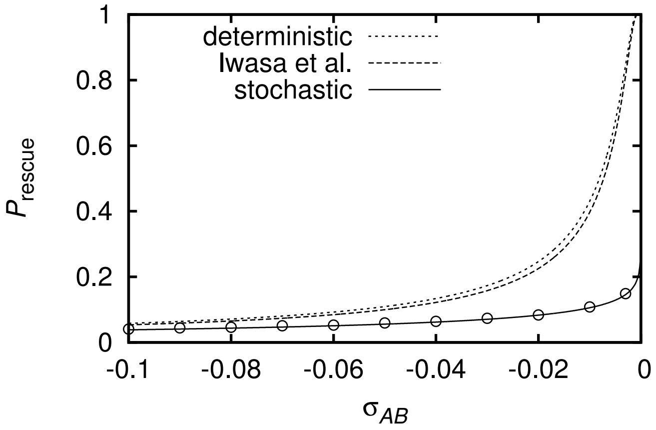

Fig. S2.1: **Probability of evolutionary rescue as a function of $\boldsymbol{\sigma_{AB}}$.** The theoretical predictions are based on Eq. (S2.2) (solid line), Iwasa *et al.* (2003, 2004) (long-dashed line), and Eq. (S2.3) (short-dashed line). Parameter values: $\sigma_{Ab} = \sigma_{aB} = -0.01$, $s_{Ab} = s_{aB} = s_{ab} = -0.5$, $s_{AB} = 0.15$, $u = 10^{-5}$, $N_0 = 10^6$. Symbols denote simulation results. Each simulation point is the average of 10^5 replicates.

to details in the model and the analysis). Both strongly overestimate the real rescue probability in Fig. S2.1. The reason is that the number of double mutants in the standing genetic variation – from which rescue mainly occurs in the parameter regime shown in the figure – is subject to strong fluctuations. This matters mainly for weakly deleterious double mutants: Then, the average number of double mutants is high enough to provide a population with a decent chance to survive, and the deterministic approximation assumes that each replicate population contains this average number of double mutants. Stochastically, however, some replicate populations have a very high chance to survive (but a single population can only get rescued once; the very high number of double mutants is hence redundant), while most of them contain no double mutants at all and go extinct.

S3 The role of recombination

From now on, we assume that the population is large enough that we can approximate the number of Ab and aB mutants in the standing genetic variation by their expected number, Eq. (S1.14). For the number of double mutants prior to the environmental change, we use F_{AB}, Eq. (S1.17). In order to keep the equations simple, we usually assume $\sigma_{Ab} = \sigma_{aB} = \sigma$. Generalization to unequal selection coefficients for single mutants before the environmental change is straightforward.

S3.1 Single mutants are lethal in the new environment

The wildtype is lethal too In the absence of any other types, a single rescue type individual establishes a permanent lineage with probability $p_{\text{est}}^{(AB)}$, Eq. (S1.20). In the first generation after the switch, with our choice of the life cycle (mutation and recombination before selection), the wildtype and the single mutants are, however, still present in the population (leading to the generation and deletion of AB mutants). A single rescue type individual present at the time of environmental change will hence not establish a permanent lineage with probability $\exp\left[-p_{\text{est}}^{(AB)}(1+s_{AB})(1-r)\right]$, and the probability that no new successful lineage is generated by recombination or mutation in this first generation is given by $\exp\left[-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N}(1+s_{AB}) + u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}\right]$. With this, the probability of evolutionary rescue is given by

$$P_{\text{rescue}} = 1 - F_{AB}(e^{-(1+s_{AB})(1-r)p_{\text{est}}^{(AB)}}) \times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}(1+s_{AB})+u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}}. \tag{S3.1}$$

With $p_{\text{est}}^{(AB)} \approx 2s_{AB}$ and $\sigma_{Ab} = \sigma_{aB} = \sigma$, we can approximate

$$\begin{aligned}
&F(e^{-(1+s_{AB})(1-r)p_{\text{est}}^{(AB)}}) \approx F(1-2s_{AB}(1-r)) \\
&= \left(1 + \frac{2s_{AB}(1+\sigma_{AB})(1-r)^2}{2(1-r)(1+\sigma_{AB}) - 2s_{AB}(1-r)^2(1+\sigma_{AB}) - 2}\right)^{\frac{2(1+\sigma_{AB})\left[r\frac{u^2N_0}{\sigma^2}(1+\sigma)^2+\frac{u^2N_0}{-\sigma}(1+\sigma)(1-r)\right]}{(1+\sigma_{AB})(1-r)}} \\
&= \left(1 + \frac{s_{AB}(1-r)^2}{-s_{AB}(1-r)^2 + (1-r)\sigma_{AB} - 1}\right)^{-\frac{2u^2N_0}{\sigma^2}\left[2\sigma - \frac{r}{1-r}\right]} \\
&\approx \left(\frac{r-(2\sigma+E_1)(1-r)}{s_{AB}(1-r)^2 + r - (2\sigma+E_1)(1-r)}\right)^{-\frac{2u^2N_0}{\sigma^2}\left[2\sigma - \frac{r}{1-r}\right]} \\
&\approx \left(\frac{r-2\sigma-E_1}{s_{AB}(1-r)^2 + r - 2\sigma - E_1}\right)^{-\frac{2u^2N_0}{\sigma^2}\left[2\sigma - \frac{r}{1-r}\right]},
\end{aligned} \tag{S3.2}$$

where the first approximation is a series expansion of the exponential function up to first order in the exponent and the second approximation is based on dropping higher order terms in σ_{AB} and σ in the enumerator, the denominator, and the exponent. The approximation in the last line consists in approximating $r - (1-r)(2\sigma + E_1) \approx r - 2\sigma - E_1$ since the second term only matters when r is small, i.e. when $1 - r \approx 1$. If we furthermore ignore new mutations after the switch in the environment, we obtain:

$$P_{\text{rescue}} \approx 1 - \left(\frac{r - 2\sigma - E_1}{s_{AB}(1-r)^2 + r - 2\sigma - E_1}\right)^{-\frac{2u^2N_0}{\sigma^2}\left[2\sigma - \frac{r}{1-r}\right]} e^{-2s_{AB}r\frac{u^2N_0}{\sigma^2}}. \tag{S3.3}$$

If we do not take stochasticity in the number of double mutants in the standing genetic variation into account, we get

$$\begin{aligned} P_{\text{rescue}}^{\text{det}} &= 1 - e^{-\langle n_{AB}\rangle(1+s_{AB})(1-r)p_{\text{est}}^{(AB)}} \times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N}(1+s_{AB})+u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}} \\ &\approx 1 - e^{-2\frac{u^2N_0}{\sigma^2}s_{AB}\left[1-\frac{(1-r)(2-2\sigma-E_1)}{r-2\sigma-E_1}\right]} \\ &\approx 1 - e^{-2s_{AB}\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1}}, \end{aligned} \tag{S3.4}$$

where the first approximation makes use of the approximation for $\langle n_{AB}\rangle$ (Eq. S1.19) and furthermore uses $p_{\text{est}}^{(AB)} \approx 2s_{AB}$ and $1 + s_{AB} \approx 1$ and ignores new mutations from generation 0 to 1.

With this, we can compare the probability of evolutionary rescue (1) without epistasis and without drift (Eq. S3.4 with $E_1 = 0$), (2) without epistasis but with drift (Eq. S3.1 with $E_1 = 0$), (3) with epistasis but without drift (Eq. S3.4 with $E_1 \neq 0$), and (4) with epistasis and with drift (Eq. S3.1 with $E_1 \neq 0$). Fig. S3.1 shows all four cases. Note that the establishment of the rescue type after the environmental change is in any case subject to strong stochasticity.

Last, we want to estimate the influence of drift on the rescue probability

$$d = \frac{P_{\text{rescue}} - P_{\text{rescue}}^{\text{det}}}{P_{\text{rescue}}^{\text{det}}}. \tag{S3.5}$$

For this, we approximate by a Taylor expansion up to leading order in s_{AB} (and similar approximations as in Eq. S3.4):

$$\begin{aligned} P_{\text{rescue}} - P_{\text{rescue}}^{\text{det}} &\approx \left(e^{-2s_{AB}\langle n_{AB}\rangle(1-r)} - \langle e^{-2s_{AB}n_{AB}(1-r)}\rangle\right) e^{-2s_{AB}r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}} \\ &\approx -2s_{AB}^2(1-r)^2\mathrm{Var}[n_{AB}] + \mathcal{O}\left(s_{AB}^3\right). \end{aligned} \tag{S3.6}$$

This leaves us with

$$\begin{aligned} d &\approx -\frac{s_{AB}(1-r)^2\mathrm{Var}[n_{AB}]}{(1-r)\langle n_{AB}\rangle + r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}} + \mathcal{O}\left(s_{AB}^2\right) \\ &= -\frac{-s_{AB}(1-r)^2\frac{\mathrm{Var}[n_{AB}]}{\langle n_{AB}\rangle}}{(1-r) + r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0\langle n_{AB}\rangle}} + \mathcal{O}\left(s_{AB}^2\right) \\ &\approx \frac{\mathrm{Var}[n_{AB}]}{\langle n_{AB}\rangle}\cdot\frac{-s_{AB}(1-r)^2}{1+r\frac{E_1}{r-2\sigma}} + \mathcal{O}\left(s_{AB}^2\right). \end{aligned} \tag{S3.7}$$

For the last line, we used Eq. (S1.19) and $n_{Ab} = n_{aB} \approx -\frac{uN_0}{\sigma}$. For the ratio of variance to mean, we obtain:

$$\begin{aligned} \frac{\mathrm{Var}[n_{AB}]}{\langle n_{AB}\rangle} &= \frac{F_{AB}''(1) + F_{AB}'(1) - F_{AB}'(1)^2}{F_{AB}'(1)} \\ &= \frac{1}{2}\left(1 + \frac{1}{r(1+\sigma_{AB}) - \sigma_{AB}}\right), \end{aligned} \tag{S3.8}$$

which is a decreasing function of r, i.e., the relative importance of drift decreases with r. Note that the variance itself depends on epistasis and is not decreasing over the entire parameter range (it can be increasing, decreasing, or be non-monotonic).

For $|\sigma|$ and $|\sigma_{AB}|$ small, we can further approximate

$$d \approx -\frac{\mathrm{Var}[n_{AB}]}{\langle n_{AB}\rangle} s_{AB}(1-r)^2 \approx -\frac{1}{2}(1-r)^2(1+r)\frac{s_{AB}}{r-\sigma_{AB}}. \tag{S3.9}$$

Although the approximation deviates from the exact result for small r, we can read off the qualitative behavior: d is negative and monotonically increasing with r, i.e., the larger r, the less drift reduces P_{rescue}. We can distinguish two regimes: (1) If $|\sigma_{AB}| \gg s_{AB}$, drift does not play a significant role, irrespective of r. (2) If $|\sigma_{AB}| \ll s_{AB}$, drift has a significant influence unless $r \gg s_{AB}$.

The wildtype remains If the wildtype population size decays slowly after the environmental change, the establishment probability of a single rescue mutant is well approximated by Eq. (S1.23). Analogous to before, we then obtain

$$P_{\text{rescue}} = 1 - F_{AB}\left(e^{-(1+s_{AB})(1-r)p_{\text{est}}^{(AB)}}\right) \times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}(1+s_{AB})+u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}}. \tag{S3.10}$$

Actually, $e^{-(1+s_{AB})(1-r)(1-q_{AB})} = q_{AB}$ (where q_{AB} is the exact extinction probability of a branching process with Poisson distributed offspring numbers with mean $(1+s_{AB})(1-r)$), and so we

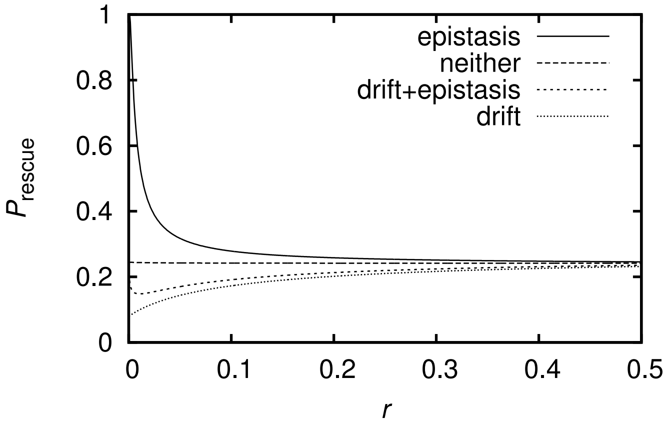

Fig. S3.1: **Probability of evolutionary rescue as a function of recombination (cf. Fig. 1).** The curves are based on Eq. (S3.1) (drift) and Eq. (S3.1) (no drift). Paramater values are: $\sigma_{AB} = -0.0199$ (no epistasis) and $\sigma_{AB} = -0.0001$ (epistasis), $\sigma_{Ab} = \sigma_{aB} = -0.01$, $u = 10^{-5}$, $N_0 = 10^6$, $s_{AB} = 0.15$, $s_{Ab} = s_{aB} = s_{ab} = -1$.

could simply use $F_{AB}(1 - p_{\text{est}}^{(AB)})$. Since we use an approximation for q_{AB} (which is our approximation $1 - p_{\text{est}}^{(AB)}$), we prefer the above form for consistency with the previous paragraph.

As before, we can derive an approximation, ignoring stochasticity in the number of double mutants

$$\begin{aligned}
P_{\text{rescue}}^{\text{det}} &= 1 - e^{-\langle n_{AB}\rangle(1+s_{AB})(1-r)p_{\text{est}}^{(AB)}} \times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N}(1+s_{AB}) + u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}} \\
&\approx \begin{cases} 1 - e^{-2\frac{u^2 N_0}{\sigma^2}(s_{AB}-r)\left[1-\frac{(2-2\sigma-E_1)(1-r)}{r-2\sigma-E_1}\right]} \approx 1 - e^{-2(s_{AB}-r)\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1}} & \text{if} \quad s_{AB}-r > 0, \\ 0 & \text{else,} \end{cases}
\end{aligned} \tag{S3.11}$$

where we approximate $p_{\text{est}}^{(AB)} \approx \max\left(2(s_{AB}-r), 0\right)$.

The wildtype is quite unfit If the wildtype is not very fit, we need to resort to the more accurate approximation Eq. (S1.29) for the establishment probability of the double mutant. For the probability of rescue, we obtain as before:

$$P_{\text{rescue}} = 1 - F_{AB}\left(e^{-(1+s_{AB})(1-r)p_{\text{est}}^{(AB)}(1)}\right) \times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}(1+s_{AB})+u(n_{Ab}+n_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}(1)}. \tag{S3.12}$$

Sensitivity of the approximation How sensitive are the approximations to the assumption of lethality of the single mutants? Fig. S3.2 compares the approximations (assuming $s_{Ab} = s_{aB} = -1$) to simulations with $s_{Ab} = s_{aB} = -0.99$ (Panel A) and $s_{Ab} = s_{aB} = -0.9$ (Panel B). The fitter the wildtype the less sensitive is the approximation to deviations from strict lethality of the single mutants. For a lethal wildtype, even a slight increase in the fitness of mutants above lethality drastically increases P_{rescue}.

S3.2 One single mutant is viable, the other lethal

Let us now consider the situation $s_{Ab} > -1$ and $s_{aB} = -1$ after the environmental change.

The wildtype is lethal The presence of one of the single mutant types after the environmental change opens up a new rescue pathway: new double mutants can be generated by mutation after generation 0. Analogous to before, the probability that the population is rescued via this

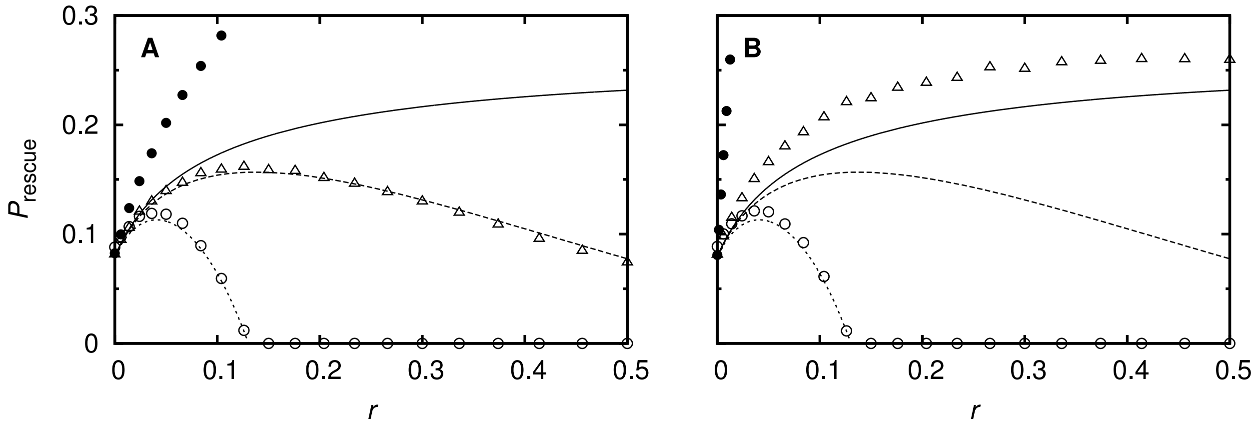

Fig. S3.2: **Probability of evolutionary rescue as a function of recombination.** The figure is identical to Fig. 1 except for that we set $s_{Ab} = s_{aB} = -0.99$ (Panel A) and $s_{Ab} = s_{aB} = -0.9$ (Panel B) in the simulations. The growth parameter of the wildtype is $s_{ab} = -1$ (solid lines, filled circle), $s_{ab} = -0.99$ (dashed line, triangles), $s_{ab} = -0.005$ (dotted line, empty circles). Circles and triangles denote simulation results. Each simulation point is the average of 10^5 replicates.

pathway is given by

$$1 - e^{-(\bar{n}_{Ab}+uN_0)(1+s_{Ab})p_{\mathrm{est}}^{(Ab)}} \tag{S3.13}$$

with $p_{\mathrm{est}}^{(Ab)}$ given by Eq. (S1.21). Combination with Eq. (S3.1) yields the total probability of evolutionary rescue:

$$P_{\mathrm{rescue}} = 1 - F_{AB}\left(e^{-(1+s_{AB})(1-r))p_{\mathrm{est}}^{(AB)}}\right) \times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}(1+s_{AB})+u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\mathrm{est}}^{(AB)}} \\ \times e^{-(\bar{n}_{Ab}+uN_0)(1+s_{Ab})p_{\mathrm{est}}^{(Ab)}}. \tag{S3.14}$$

We can estimate the respective significance of the contributions by a comparison of Eq. (S3.13) with Eq. (S3.4), assuming $\sigma_{Ab} = \sigma_{aB}$. Approximating $\bar{n}_{Ab} \approx \frac{uN_0}{-\sigma_{Ab}}$ and $1+s_{Ab} \approx 1$ and ignoring the term that accounts for new mutations ($\sim uN_0$) in Eq. (S3.13) and setting $E_1 = 0$ in

Eq. (S3.4), we arrive at the condition

$$p_{\text{est}}^{(Ab)} > 2\frac{us_{AB}}{-\sigma_{Ab}} \tag{S3.15}$$

for the contribution of new rescue mutations after the environmental change being larger than the contribution by double mutants from the standing genetic variation. With the last approximation for $p_{\text{est}}^{(Ab)}$ in Eq. (S1.21), this condition simplifies to

$$\frac{2us_{Ab}}{-s_{Ab}} > \frac{2us_{Ab}}{-\sigma_{Ab}} \quad \Leftrightarrow -\sigma_{Ab} > -s_{Ab}. \tag{S3.16}$$

If $s_{Ab} > 0$, rescue is not contingent on the generation of the double mutant. Depending on the mutation rate and the fitness effects of mutations, generation of the double mutant might still help rescue or be negligible. In the latter case, results from single step rescue apply (Orr and Unckless, 2008; Bell and Collins, 2008; Uecker *et al.*, 2014). Formation of the double mutant after the environmental change cannot be ignored in Eq. (S3.13) if

$$\begin{aligned}
& 2s_{Ab} \ll p_{\text{est}}^{(Ab)} \\
\Leftrightarrow \quad & 2s_{Ab} \ll s_{Ab} - u + \sqrt{(s_{Ab}-u)^2 + 4s_{AB}u} \\
\Leftrightarrow \quad & s_{Ab} + u \ll \sqrt{(s_{Ab}-u)^2 + 4s_{AB}u} \\
\overset{s_{Ab} \gg u}{\Leftrightarrow} \quad & s_{Ab} \ll \sqrt{s_{Ab}^2 + 4s_{AB}u} = s_{Ab} \cdot \sqrt{1 + \frac{4s_{AB}u}{s_{Ab}^2}} \\
\Leftrightarrow \quad & 4s_{AB}u \gg s_{Ab}^2.
\end{aligned} \tag{S3.17}$$

Altogether, generation of the double mutant cannot be ignored if

$$\begin{aligned}
& 2s_{Ab}\frac{uN_0}{-\sigma} \ll p_{\text{est}}^{(Ab)}\frac{uN_0}{-\sigma} + 2s_{AB}\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\Leftrightarrow\quad & 2s_{Ab} \ll s_{Ab} - u + \sqrt{(s_{Ab}-u)^2 + 4s_{AB}u} + 2s_{AB}\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\Leftrightarrow\quad & s_{Ab} + u \ll \sqrt{(s_{Ab}-u)^2 + 4s_{AB}u} + 2s_{AB}\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\overset{s_{Ab}\gg u}{\Leftrightarrow}\quad & s_{Ab} \ll s_{Ab}\cdot\sqrt{1+\frac{4s_{AB}u}{s_{Ab}^2}} + 2s_{AB}\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\Leftrightarrow\quad & 4s_{AB}u \gg s_{Ab}^2 \quad \text{or} \quad 2s_{AB}\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \gg s_{Ab}.
\end{aligned} \tag{S3.18}$$

The wildtype is at least as fit as the viable single mutant Viability of the wildtype has two consequences: (1) The double mutant can be broken up by recombination. (2) The wildtype can generate new *Ab* mutants on its course to extinction. Modeling the wildtype deterministically, we obtain for the probability of rescue by de-novo generated double mutants

$$1 - e^{-\bar{n}_{Ab}(1+s_{Ab})p_{\text{est}}^{(Ab)}} \times e^{-\frac{uN_0}{-s_{ab}}(1+s_{Ab})p_{\text{est}}^{(Ab)}}. \tag{S3.19}$$

Combination with Eq. (S3.10) yields again the total probability of evolutionary rescue:

$$\begin{aligned}
P_{\text{rescue}} = 1 - F_{AB}(e^{-(1+s_{AB})(1-r))p_{\text{est}}^{(AB)}}) &\times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}(1+s_{AB}) + u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}} \\
&\times e^{-(\bar{n}_{Ab}+\frac{uN_0}{-s_{ab}})(1+s_{Ab})p_{\text{est}}^{(Ab)}}.
\end{aligned} \tag{S3.20}$$

As before, we can compare the different pathways to rescue, (a) from double mutants from the standing genetic variation, (b) mutation of single mutants from the standing genetic variation after the change in the environment, (c) complete de-novo generation via the wildtype after the environmental switch. Pathway (c) is more important than pathway (b) if

$$-s_{ab} < -\sigma_{Ab}. \tag{S3.21}$$

Pathway (b) is more important than pathway (a) if

$$-s_{Ab} < -\sigma_{Ab}. \tag{S3.22}$$

If $s_{Ab} > 0$, analogous to the previous paragraph, formation of the double mutant after the environmental change cannot be ignored if

$$\begin{aligned} & 2s_{Ab} \ll p_{\text{est}}^{(Ab)} \\ \Leftrightarrow \quad & 2s_{Ab} \ll s_{Ab} - u + \sqrt{(s_{Ab}-u)^2 + 4\max\left((s_{AB}-r),0\right)u} \\ \Leftrightarrow \quad & s_{Ab} + u \ll \sqrt{(s_{Ab}-u)^2 + 4\max\left((s_{AB}-r),0\right)u} \\ \overset{s_{Ab} \gg u}{\Leftrightarrow} \quad & s_{Ab} \ll \sqrt{s_{Ab}^2 + 4s_{AB}u} = s_{Ab} \cdot \sqrt{1 + \frac{4\max\left((s_{AB}-r),0\right)u}{s_{Ab}^2}} \\ \Leftrightarrow \quad & 4\max\left((s_{AB}-r),0\right)u \gg s_{Ab}^2. \end{aligned} \tag{S3.23}$$

Altogether, it cannot be ignored if

$$\begin{aligned}
& 2s_{Ab}\frac{uN_0}{-\sigma} \ll p_{\text{est}}^{(Ab)}\frac{uN_0}{-\sigma} + \max\left[2(s_{AB}-r),0\right]\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\Leftrightarrow\quad & 2s_{Ab} \ll s_{Ab} - u + \sqrt{(s_{Ab}-u)^2 + 4\max\left[(s_{AB}-r),0\right]u} + \max\left[2(s_{AB}-r),0\right]\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\Leftrightarrow\quad & s_{Ab} + u \ll \sqrt{(s_{Ab}-u)^2 + 4\max\left[(s_{AB}-r),0\right]u} + \max\left[2(s_{AB}-r),0\right]\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\overset{s_{Ab}\gg u}{\Leftrightarrow}\quad & s_{Ab} \ll s_{Ab}\cdot\sqrt{1+\frac{4\max\left[(s_{AB}-r),0\right]u}{s_{Ab}^2}} + \max\left[2(s_{AB}-r),0\right]\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \\
\Leftrightarrow\quad & 4\max\left[(s_{AB}-r),0\right]u \gg s_{Ab}^2 \quad \text{or} \quad \max\left[2(s_{AB}-r),0\right]\frac{u^2N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} \gg s_{Ab}.
\end{aligned} \tag{S3.24}$$

S3.3 Both single mutants are viable

Finally, we consider the case $s_{Ab} = s_{aB} = s > -1$. With $\sigma_{Ab} = \sigma_{aB} = \sigma$, deterministically, the number of Ab mutants and aB mutants is hence equal at any point of time. In the following, we formulate equations in terms of type Ab.

The wildtype is lethal Ignoring recombination, from generation 0 to generation 1, the number of Ab individuals changes to

$$n_{Ab}(1) = \left(\bar{n}_{Ab}(1-2u) + uN_0\right)(1+s). \tag{S3.25}$$

From then on, it evolves according to the recursive equation

$$\begin{aligned} n_{Ab}(t+1) &= (1+s)(1-2u)\left(n_{Ab}(t) - r\frac{n_{Ab}(t)n_{aB}(t)}{n_{Ab}(t)+n_{aB}(t)}\right) \\ &= (1+s)(1-2u)\left(n_{Ab}(t) - \frac{r}{2}n_{Ab}(t)\right), \end{aligned} \tag{S3.26}$$

where the second line holds since $n_{Ab}(t) = n_{aB}(t)$. With this, we have

$$n_{Ab}(t+1) = n_{Ab}(1)\left((1+s)(1-2u)\left(1-\frac{r}{2}\right)\right)^t. \tag{S3.27}$$

From generation 1 on, the number of newly generated AB individuals follows a Poisson distribution with parameter

$$\left(u(n_{Ab}(t)+n_{aB}(t)) + \frac{r}{2}n_{Ab}(t)\right)(1+s_{AB}). \tag{S3.28}$$

Putting all together and using again $n_{Ab}(t) = n_{aB}(t)$, we obtain for rescue from generation 1 on:

$$1 - e^{-\sum_{t=0}^{\infty}\left(2u+\frac{r}{2}\right)n_{Ab}(t+1)(1+s_{AB})p_{\text{est}}^{(AB)}}. \tag{S3.29}$$

With

$$\sum_{t=0}^{\infty} n_{Ab}(t+1) = \sum_{t=0}^{\infty} n_{Ab}(1)\left((1+s)(1-2u)\left(1-\frac{r}{2}\right)\right)^t = n_{Ab}(1)\frac{1}{1-(1+s)(1-2u)\left(1-\frac{r}{2}\right)}, \tag{S3.30}$$

this yields

$$1 - e^{-\left(\frac{(1+s_{AB})\left(2u+\frac{r}{2}\right)n_{Ab}(1)}{1-(1+s)(1-2u)\left(1-\frac{r}{2}\right)}\right)p_{\mathrm{est}}^{(AB)}} \approx 1 - e^{-2s_{AB}\frac{\frac{r}{2}\frac{uN_0(1+s)}{-\sigma}}{\frac{r}{2}+2u-s}}. \tag{S3.31}$$

Combining with Eq. (S3.1), we obtain for the total probability of evolutionary rescue

$$\begin{aligned} P_{\mathrm{rescue}} = 1 - F_{AB}(e^{-(1+s_{AB})(1-r)p_{\mathrm{est}}^{(AB)}}) \times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}(1+s_{AB})+u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\mathrm{est}}^{(AB)}} \\ \times e^{-\left(\frac{(1+s_{AB})\left(2u+\frac{r}{2}\right)n_{Ab}(1)}{1-(1+s)(1-2u)\left(1-\frac{r}{2}\right)}\right)p_{\mathrm{est}}^{(AB)}}. \end{aligned} \tag{S3.32}$$

The wildtype is as fit as the single mutants As a second scenario, we consider the special case $s_{ab} = s_{Ab} = s_{aB} = s$. If we ignore mating between single mutants (note that unlike in the previous scenario, they are now relatively rare), we obtain for the deterministic dynamics

$$n_{ab}(t+1) = (1+s)(n_{ab}(t) - 2un_{ab}(t)), \tag{S3.33a}$$

$$n_{Ab}(t+1) = (1+s)(n_{Ab}(t) + un_{ab}(t)), \tag{S3.33b}$$

$$n_{aB}(t+1) = (1+s)(n_{aB}(t) + un_{ab}(t)) \tag{S3.33c}$$

with the solutions

$$n_{ab}(t) = \bar{n}_{ab}((1+s)(1-2u))^t, \tag{S3.34a}$$

$$n_{Ab}(t) = n_{aB}(t) = \frac{1}{2}\left(N_0(1+s)^t - \bar{n}_{ab}((1+s)(1-2u))^t\right). \tag{S3.34b}$$

Type AB is generated at rate

$$r\frac{n_{Ab}(t)n_{aB}(t)}{N(t)}(1+s_{AB})+u(n_{Ab}(t)+n_{aB}(t))(1+s_{AB})\,(1-r) \tag{S3.35}$$

and establishes with probability $p_{\text{est}}^{(AB)}$ as given by Eq. (S1.23). This yields for the probability of evolutionary rescue via this pathway

$$1-e^{-\sum\limits_{t=1}^{\infty}\left(r\frac{n_{Ab}(t)n_{aB}(t)}{N(t)}(1+s_{AB})+u(n_{Ab}(t)+n_{aB}(t))(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}}. \tag{S3.36}$$

Evaluating the sums yields

$$\begin{aligned}&\sum_{t=1}^{\infty}\frac{n_{Ab}(t)n_{aB}(t)}{N(t)}\\&=-\frac{N_0}{4s}-\frac{N_0-\bar{n}_{Ab}-\bar{n}_{aB}}{2(1-(1+s)(1-2u))}+\frac{(N_0-\bar{n}_{Ab}-\bar{n}_{aB})^2}{4N_0}\frac{1}{1-(1+s)(1-2u)^2}-\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}.\end{aligned} \tag{S3.37a}$$

$$\sum_{t=1}^{\infty}(n_{Ab}(t)+n_{aB}(t))=-\frac{N_0}{s}-\frac{N_0-\bar{n}_{Ab}-\bar{n}_{aB}}{1-(1+s)(1-2u)}-\bar{n}_{Ab}-\bar{n}_{aB}. \tag{S3.37b}$$

Putting it all together, we obtain:

$$\begin{aligned}P_{\text{rescue}}=1-F(e^{-(1+s_{AB})(1-r)p_{\text{est}}^{(AB)}})\times e^{-\left(r\frac{\bar{n}_{Ab}\bar{n}_{aB}}{N_0}(1+s_{AB})+u(\bar{n}_{Ab}+\bar{n}_{aB})(1+s_{AB})(1-r)\right)p_{\text{est}}^{(AB)}}\\ \times e^{-\left(r(1+s_{AB})\sum\limits_{t=1}^{\infty}\frac{n_{Ab}(t)n_{aB}(t)}{N(t)}+u(1-r)(1+s_{AB})\sum\limits_{t=1}^{\infty}(n_{Ab}(t)+n_{aB}(t))\right)p_{\text{est}}^{(AB)}}.\end{aligned} \tag{S3.38}$$

The wildtype is fitter than the single mutants If $s_{Ab} = s_{aB} = s$ and $s_{ab} > s$, we can proceed as in the previous section. The dynamics of the wildtype population are again given by

$$n_{ab}(t) = \bar{n}_{ab}(1 + s_{ab})^t(1 - 2u)^t. \tag{S3.39}$$

The dynamics of the single mutants follow

$$n_{Ab}(t+1) = n_{aB}(t+1) = (1 + s)(n_{Ab}(t) + un_{ab}(t)), \tag{S3.40}$$

yielding

$$n_{Ab}(t) = \frac{(uN_0(1+s) + \bar{n}_{Ab}(s - s_{ab})(1 - 2u))(1+s)^t - u\bar{n}_{ab}(1+s)(1+s_{ab})^t(1-2u)^t}{s - s_{ab} + 2u(1 + s_{ab})}. \tag{S3.41}$$

With the approximations

$$\begin{aligned} C &:= s - s_{ab} + 2u(1 + s_{ab}), \\ \alpha &:= u\bar{n}_{ab}(1 + s), \\ \beta &:= uN_0(1+s) + \bar{n}_{Ab}(s - s_{ab})(1 - 2u), \end{aligned} \tag{S3.42}$$

and $N(t) \approx n_{ab}(t)$ we obtain

$$\begin{aligned}\sum_{t=1}^{\infty}(n_{ab}(t)+n_{aB}(t)) &= \frac{\beta\sum_{t=1}^{\infty}(1+s)^t - \alpha\sum_{t=1}^{\infty}(1+s_{ab})^t(1-2u)^t}{C} \\ &= \frac{\beta\frac{1+s}{-s} - \alpha\frac{(1+s_{ab})(1-2u)}{1-(1+s_{ab})(1-2u)}}{C}\end{aligned} \tag{S3.43a}$$

$$\begin{aligned}\sum_{t=1}^{\infty}\frac{n_{Ab}(t)n_{aB}(t)}{N(t)} &= \frac{\alpha^2(1+s_{ab})^{2t}(1-2u)^{2t} - 2\alpha\beta(1+s_{ab})^t(1-2u)^t(1+s)^t + \beta^2(1+s)^{2t}}{C^2\bar{n}_{ab}(1+s_{ab})^t(1-2u)^t} \\ &= \frac{1}{C^2\bar{n}_{ab}}\left(\alpha^2\frac{(1+s_{ab})(1-2u)}{1-(1+s_{ab})(1-2u)} - 2\alpha\beta\frac{1+s}{-s} + \beta^2\frac{(1+s)^2}{(1+s_{ab})(1-2u)-(1+s)^2}\right).\end{aligned} \tag{S3.43b}$$

Since the wildtype dominates at all times (unless rescue has occurred), we can again approximate $p_{\text{est}}^{(AB)} = 2\max[(s_{AB}-r),0]$.

Fig. S3.3 shows P_{rescue} for various values of s_{ab} with all other parameter values as in Fig. 3C.

S3.4 Both single mutants have fitness greater than one

We here formalize the special case $s_{ab} = -1$, $s_{Ab} = s_{aB} = s > 0$. For this, we consider pairs consisting out of one Ab and one aB mutant. Such a pair reproduces at rate $\frac{1}{2}+\hat{s}$ and dies at rate $\frac{1}{2}-\hat{s}$ with $\hat{s} = \ln(1+s)$. At rate $\frac{r}{2}(1+s_{AB})$, it turns into an individual of type AB (this ignores mutation). The growth rate of a pair is $2\hat{s}$, since in reality, we are not interested in pairs but establishment of any type (Ab, aB, AB) is fine, and each single mutant has growth rate s. However, it is pairs that convert into double mutants, and with this approximation,

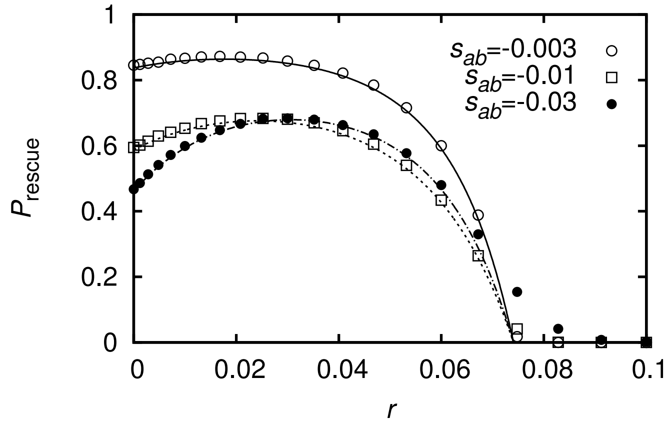

Fig. S3.3: **Probability of evolutionary rescue as a function of recombination for various values of s_{ab}.** All other parameter values are chosen as in Fig. 3C. Theoretical predictions are based on Eq. (S3.38) with Eq. (S3.43a). Symbols denote simulation results. Each simulation point is the average of $5 \cdot 10^4$ replicates. For the simulations with $s_{ab} = -0.003$, we considered a population as rescued when the number of double mutants reached $0.2N_0$ (changing the criterion to $0.3N_0$ did not alter the results).

we assume that for every single mutant of type Ab, there is a single mutant of type aB to recombine with and vice versa. A single individual of type AB establishes a permanent lineage with probability $p_{\text{est}}^{(AB)} \approx 2s_{AB}$. Using Eq. (S1.8), we can calculate the survival probability of a process founded by exactly one pair:

$$\begin{aligned} p_{\text{est}}^{(Ab,aB)} &= 1 - \frac{1 + \hat{s} + \frac{r}{2}(1+s_{AB}) - \sqrt{(\hat{s} - \frac{r}{2}(1+s_{AB})^2 + (1+2\hat{s})r(1+s_{AB})p_{\text{est}}^{(AB)}}}{1+2\hat{s}} \\ &\approx 2s - \frac{r}{2} + \sqrt{\left(2s - \frac{r}{2}\right)^2 + 2s_{AB}r}. \end{aligned} \tag{S3.44}$$

The probability of evolutionary rescue from generation 1 on is given by

$$1 - e^{-\bar{n}_{Ab}(1+s_{Ab})p_{\text{est}}^{(Ab,aB)}}. \tag{S3.45}$$

Neglecting the contribution of double mutants from the standing genetic variation to rescue, the possibility to generate the double mutant has a significant effect if either

$$p_{\text{est}}^{(Ab,aB)} \gg 4s \quad \text{or} \quad p_{\text{est}}^{(Ab,aB)} \ll 4s. \tag{S3.46}$$

These conditions simplify in few steps to

$$s_{AB} \gg 2s \quad \text{or} \quad s_{AB} \ll 2s. \tag{S3.47}$$

S3.5 Two-step rescue vs single-step rescue

We briefly discuss some instances where two-step rescue (as analyzed in this paper) is more likely to happen than single-step rescue (where there are only two types – the wildtype and the rescue type – and a single mutational step between them). For easier comparison, we denote the wildtype by ab and the rescue genotype by AB for single-step rescue as well. Mutation from wildtype to rescue mutants may happen with probability u_s. With Eq. (S1.4), the p.g.f. for the number of rescue mutations in the standing genetic variation is derived to be

$$F_{AB}^{\text{ssr}}(y) = \left(\frac{2\sigma_{AB}}{y + \sigma_{AB} y + \sigma_{AB} - 1} \right)^{2u_s N_0}. \tag{S3.48}$$

The probability of evolutionary rescue for single-step rescue is given by

$$\begin{aligned} P_{\text{rescue}}^{\text{ssr}} &= 1 - F_{AB}^{\text{ssr}}\left(e^{-(1+s_{AB})p_{\text{est}}^{(\text{AB})}}\right)e^{-\frac{u_s N_0}{-s_{ab}}(1+s_{AB})p_{\text{est}}^{(AB)}} \\ &= 1 - e^{-p_{\text{est}}^{(AB)}(1+s_{AB})\left[\frac{u_s N_0}{-\sigma_{AB}}(1+\sigma_{AB}) - \frac{u_s N_0}{-s_{ab}}\right]} \approx 1 - e^{-2s_{AB}\left[\frac{u_s N_0}{-\sigma_{AB}} - \frac{u_s N_0}{-s_{ab}}\right]}. \end{aligned} \tag{S3.49}$$

where the first summand in the brackets accounts for the contribution of standing genetic variation and the second one for new mutations after the environmental change (cf. also Orr and Unckless (2008, 2014); Bell and Collins (2008); Uecker *et al.* (2014)).

In the following, we focus on scenarios where the wildtype is lethal in the new environment and approximate single-step rescue by

$$P_{\text{rescue}}^{\text{sgv}} \approx 1 - e^{-2s_{AB}\frac{u_s N_0}{-\sigma_{AB}}}. \tag{S3.50}$$

Lethal single mutants For two-step rescue, we use approximation Eq. (8):

$$P_{\text{rescue}} \approx 1 - e^{-2s_{AB}\frac{u^2 N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1}} \overset{r \text{ large}/E_1 = 0}{\approx} 1 - e^{-2s_{AB}\frac{u^2 N_0}{\sigma^2}}. \tag{S3.51}$$

Comparing with Eq. (S3.50) shows that two-step rescue is more likely if

$$\frac{u^2}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} > \frac{u_s}{-\sigma_{AB}}. \tag{S3.52}$$

For large recombination, this reduces to

$$\frac{u^2}{\sigma^2} > \frac{u_s}{-\sigma_{AB}}. \tag{S3.53}$$

For $E_1 = 0$ (which implies $\sigma_{AB} \approx 2\sigma$):

$$\frac{u^2}{-\sigma} > \frac{u_s}{2}. \tag{S3.54}$$

One viable single mutant Following section S3.2, two-step rescue can be approximated by

$$1 - e^{-2s_{AB}\frac{u^2 N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1}} \times e^{-\frac{uN_0}{-\sigma}\frac{2s_{AB}u}{-s_{Ab}}}. \tag{S3.55}$$

Under these conditions, two-step rescue is more likely than single-step rescue if

$$\frac{u^2}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} + \frac{u^2}{\sigma s_{Ab}} > \frac{u_s}{-\sigma_{AB}}. \tag{S3.56}$$

Again, for strong recombination:

$$\frac{u^2}{\sigma^2} + \frac{u^2}{\sigma s_{Ab}} > \frac{u_s}{-\sigma_{AB}}. \tag{S3.57}$$

And for $E_1 = 0$:

$$\frac{u^2}{-\sigma} + \frac{u^2}{-s_{Ab}} > \frac{u_s}{2}. \tag{S3.58}$$

Viable single mutants Last, we consider a scenario with both single mutants viable. With Eq. (10), the probability of evolutionary rescue is given by

$$1 - e^{-2s_{AB}\frac{u^2 N_0}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1}} \times e^{-2s_{AB}\frac{uN_0}{-\sigma}(1+s_{Ab})\frac{r}{r-2s_{Ab}}}. \tag{S3.59}$$

This yields for the condition that two-step rescue is more likely than single-step rescue

$$\frac{u^2}{\sigma^2}\frac{r-2\sigma}{r-2\sigma-E_1} + (1+s_{Ab})\frac{u}{-\sigma}\frac{r}{r-2s_{Ab}} > \frac{u_s}{-\sigma_{AB}}, \tag{S3.60}$$

which for strong recombination simplifies to

$$\frac{u}{-\sigma}\left(\frac{u}{-\sigma} + (1+s_{Ab})\frac{r}{r-2s_{Ab}}\right) > \frac{u_s}{-\sigma_{AB}}. \tag{S3.61}$$

For $E_1 = 0$:

$$\frac{u^2}{-\sigma} + (1+s_{Ab})\frac{ur}{r-2s_{Ab}} > \frac{u_s}{2}. \tag{S3.62}$$

S4 Limits of the approximations

Our approximations assume that wildtype individuals and single mutants are sufficiently frequent to describe their dynamics deterministically. This requires a sufficiently large population size and a sufficiently high fitness of single mutants prior to the change in the environment. Fig. S4.4 takes Fig. 3A as a starting point and varies several parameters in order to probe

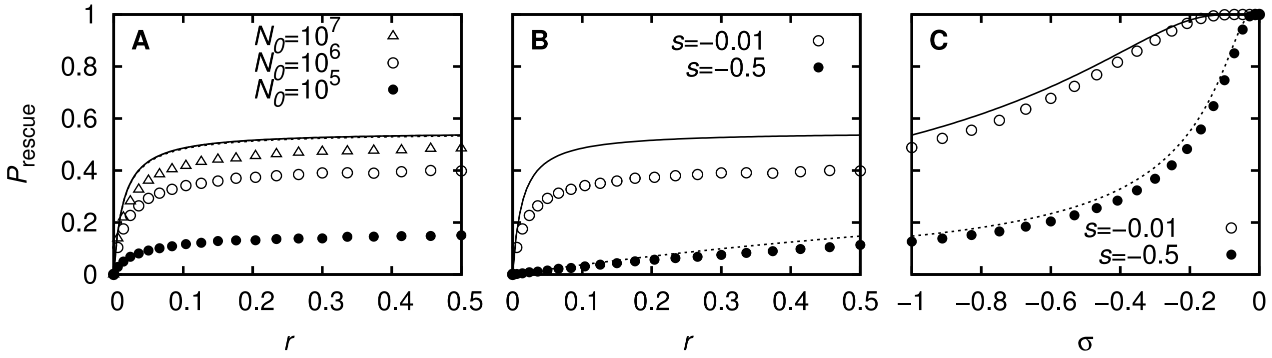

Fig. S4.4: **Probability of evolutionary rescue as a function of recombination for various population sizes N_0 with $N_0 s_{AB} = 2000$ kept constant (Panel A), recombination r for various values of s (Panel B), and the strength of selection against single mutants in the old environment σ (Panel C).** The figure varies parameters from Fig. 3A. For all Panels: $u = 2 \cdot 10^{-6}$, $\sigma_{AB} = -0.1$, $s_{ab} = -1$. Panel A: $N_0 s_{AB} = 2000$, $\sigma = -0.01$, $s = -0.01$; Panel B: $s_{AB} = 0.002$, $\sigma = -0.01$, $N_0 = 10^6$; Panel C: $s_{AB} = 0.002$, $r = 0.5$, $N_0 = 10^8$. Symbols denote simulation results. Each simulation point is the average of $5 \cdot 10^4$ replicates.

the limits of the approximations. Panel A shows P_{rescue} for various initial population sizes N_0 with the product $N_0 s_{AB}$ kept constant such that the theoretical predictions virtually coincide. However, as the population size gets smaller, simulation results greatly deviate from this prediction. Note that the number of single mutants for $N_0 = 10^5$ is as low as $\bar{n}_{Ab} = \bar{n}_{aB} = 20$. While in Panel A the number of single mutants in the standing genetic variation differs for different population sizes, it is – on average – the same at the right edge of Panel B ($N_0 = 10^6$, $\sigma = -0.01$) and the left edge of Panel C ($N_0 = 10^8$, $\sigma = -1$) but stochasticity is higher in Panel B, leading to larger deviations between the analytical prediction and simulation results.

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