

Supporting information: The role of recombination in evolutionary rescue

File 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 File S2 and File 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 subcritical branching process with immigration. Individuals reproduce at rate λ and die at rate μ . Immigration happens at rate m . We define the two infinitesimal generating functions

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

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

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

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

It then holds

$$F(y) = \exp \left[\int_y^1 \frac{g(x)}{f(x)} dx \right] \quad (S1.3)$$

$$= \left(\frac{\lambda - \mu}{y\lambda - \mu} \right)^{\frac{m}{\lambda}}.$$

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

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

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

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

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)

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

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

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

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

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

$$= 1 - \frac{\lambda_2 + \mu_2 + u_{\text{eff}} - \sqrt{(\lambda_2 - \mu_2 - u_{\text{eff}})^2 + 4\lambda_2 u_{\text{eff}} p_{\text{est}}^{(1)}}}{2\lambda_2}.$$

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

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

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)

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

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} :

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

We denote by

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

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 parametrization (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} :

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

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

The mean number of Ab and aB mutants is given by

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

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

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

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

As the effective selection coefficient of AB individuals, we use

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

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:

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

The mean number of double mutants is given by

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

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:

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

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 $\frac{u^2 N_0}{\sigma^2} \frac{2\sigma}{E_1 + 2\sigma}$, hence strongly dependent on the degree of epistasis. For $r \gg |\sigma_{Ab} + \sigma_{aB}|$ and $r \gg |\sigma_{AB}|$, it converges to $\frac{u^2 N_0}{\sigma_{Ab}\sigma_{aB}}$, 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 :

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

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 $Q_1 = 1 - p_{\text{est}}^{(AB)}$, we obtain the establishment probability:

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

The last approximation holds for $s_{Ab} < 0$ and $s_{Ab}^2 \gg us_{AB}$. 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

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

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:

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

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

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

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 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

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

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

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

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

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

with

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

where s_1 and s_2 are given by \hat{s}_{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

$$p_{\text{est}}^{(AB)}(t) = \int_t^\infty p(T_{\text{ext}}) \frac{2}{1 + I(t, T_{\text{ext}})} dT_{\text{ext}} + \int_0^t p(T_{\text{ext}}) \frac{2 \ln(1 + s_{AB})}{1 + \ln(1 + s_{AB})} dT_{\text{ext}}. \quad (\text{S1.29})$$

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