

Supplementary Material: Evolutionary rescue through partly heritable phenotypic variability

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Evolutionary rescue: the density-dependent model

For the density-dependent model, the birth rates of the two genotypes are as presented as below:

Genotype	A	a
Phenotype	Φ_A	Φ_a
Birth rate	$\Phi_A(1 - \frac{N}{K})$	$\Phi_a(1 - \frac{N}{K})$
Death rate	1	1.

The probability of establishment of the new mutant (and therefore the probability of rescue) depends critically on the mutation rate to the a allele, and whether the first a individual is initially introduced with its beneficial or its deleterious phenotype – that is, whether its birth rate is initially larger or smaller than its death rate. We first study the case where the A allele can only mutate to produce an a allele with the beneficial phenotype, denoted by Φ_{a+} . Biologically, this could be due to the presence or absence of an epigenetic marker that makes the deleterious Φ_{a-} phenotype inaccessible directly from the A allele. The population will be rescued, by definition, if the a lineage manages to become established (Uecker and Hermisson, 2011). As shown in **Figure S1A**, similar to the density-independent model presented in the main text, the chance of evolutionary rescue increases monotonically with the strength of phenotypic memory, p . This result makes intuitive sense: high-fitness variants of the a allele are preferentially transmitted to the next generation, and greater phenotypic memory p increases their propensity to maintain the high-fitness phenotype and become established in the population. Moreover, the probability of rescue is uniformly greater when the a allele can express a greater diversity of phenotypes, i.e. for $\text{Var}(\Phi_a)$ large (**Figure S1A**), because the larger variance is associated with a greater fitness for the Φ_{a+} phenotype.

When the a allele is introduced with a deleterious phenotype Φ_{a-} , evolutionary rescue can still occur, because the phenotype of type- a individuals may change between generations. In this case, **Figure S1B** shows that the probability of evolutionary rescue depends non-monotonically on the strength of phenotypic memory p . There is simple intuition for this result as well, which is informed by our mathematical analysis below. Intuitively, the probability of establishment in this case is the product of the probability that some a -type individual produces an offspring with the beneficial phenotype, Φ_{a+} , before the a -lineage is lost, times the probability of establishment associated with such an individual with phenotype Φ_{a+} . Therefore, rescue is facilitated as the strength of phenotypic memory increases above zero (this effect is driven by the increase in the probability of rescue once an individual of phenotype Φ_{a+} arises); but as the phenotypic memory increases further, towards one, the probability of rescue is reduced, because the entire a lineage will likely go extinct before producing any individual with a beneficial phenotype. Or put differently, the a lineage needs sufficient variability to produce the correct phenotype, but not too much to avoid losing it after it has been produced.

To provide a clear analysis of the intuitions described above, we first derive the probability of rescue, $\mathbb{P}_r(a_+)$, when there is recurrent mutation towards the beneficial phenotype Φ_{a+} . We first compute an effective selection coefficient of the entire a lineage, by assuming that the two phenotypes within the a lineage quickly reach epimutation-selection balance (Carja and Plotkin, 2017). Given epimutation rate $u = \frac{1-p}{2}$ between the two phenotypes, the standard mutation-selection balance expression (where x refers to the frequency of the Φ_{a+} phenotype),

$$(\Phi_{a-} - \Phi_{a+})x^2 - (\Phi_{a-} - \Phi_{a+} + u(\Phi_{a-} + \Phi_{a+}))x + \Phi_{a-}u = 0,$$

implies that the equilibrium frequency of phenotype Φ_{a+} within the a -lineage is given by f_{a+} :

$$f_{a+} = \frac{\Phi_{a+} - \Phi_{a-} - u\Phi_{a-} - u\Phi_{a+}}{2(\Phi_{a+} - \Phi_{a-})} + \frac{\sqrt{4\Phi_{a-}u(\Phi_{a+} - \Phi_{a-}) + (\Phi_{a-} - \Phi_{a+} + u\Phi_{a+} + u\Phi_{a-})^2}}{2(\Phi_{a+} - \Phi_{a-})} \quad (1)$$

The effective birth rate of the a lineage is

$$s_a = \Phi_{a-}(1 - f_{a+}) + \Phi_{a+}f_{a+}. \quad (2)$$

Taking into account that $\Phi_{a-} = \Phi_A - \sigma_{\Phi_a}$ and $\Phi_{a+} = \Phi_A + \sigma_{\Phi_a}$, this birth rate can be rewritten as a function

of the mean $\mathbb{E}(\Phi_a)$ and the standard deviation σ_{Φ_a} of the two alleles:

$$f_{a+} = \frac{2\sigma_{\Phi_a} - 2\mathbb{E}(\Phi_a)u + \sqrt{(2\mathbb{E}(\Phi_a)u - 2\sigma_{\Phi_a})^2 - 8\sigma_{\Phi_a}(\sigma_{\Phi_a}u - \mathbb{E}(\Phi_a)u)}}{4\sigma_{\Phi_a}} \quad (3)$$

and

$$s_a = (\mathbb{E}(\Phi_a) - \sigma_{\Phi_a})(1 - f_{a+}) + (\mathbb{E}(\Phi_a) + \sigma_{\Phi_a})f_{a+}, \quad (4)$$

as in Carja and Plotkin (2017).

The effective birth rate s_a determines the equilibrium population size for the adapted population, should adaptation and rescue occur: $N_{eq} = K(1 - \frac{1}{s_a})$, assuming $s_a > 1$. When the effective birth rate s_a of the a lineage exceeds its death rate (unity), the probability of establishment of this new mutation arising at time τ in the population is given by

$$\mathbb{P}_{est,a+}(\tau) = \frac{2}{1 + \int_0^\infty (s_a(1 - \frac{N(t+\tau)}{K}) + 1) \exp(-\int_0^t (s_a(1 - \frac{N(t'+\tau)}{K}) - 1) dt') dt} \quad (5)$$

following Uecker and Hermisson (2011) and Wilson et al. (2017). Assuming that the mutant lineages have independent probabilities of establishment, and thus neglecting the mutant population size, $N(t)$ can be approximated by the A allele population size, which, due to the density-dependence in birth rate for the wild-type A , has the form

$$N(t) = \frac{(1 - (1 - \mu)\Phi_A)KN_0}{e^{(1-(1-\mu)\Phi_A)t}(K - (1 - \mu)\Phi_A(K - N_0)) - (1 - \mu)\Phi_A N_0}, \quad (6)$$

where $N_0 = N(t = 0)$. This expression takes into account mutations away from A at rate μ .

We can now derive the probability of evolutionary rescue from at least one adaptive mutant by modeling mutant establishments using a time-inhomogeneous Poisson process with intensity function $\mu N(t)\Phi_A(1 - \frac{N(t)}{K})P_{est,a+}$. The probability of evolutionary rescue then becomes one minus the probability that no mutants establish:

$$\mathbb{P}_{rescue,a+} = 1 - \exp\left(-\int_0^\infty \mu N(t)\Phi_A(1 - \frac{N(t)}{K})P_{est,a+}(t)dt\right). \quad (7)$$

This analytic approximation is shown in **Figure S1A** alongside the results of Monte Carlo simulations. For comparison to simulation, we defined rescue as the population reaching 99% of the equilibrium population size of the adapted population N_{eq} , and we count any cases in which N_{eq} was smaller than 100 as extinction (because population sizes so small can easily fluctuate to extinction).

Conversely, when the a mutation is introduced with its deleterious phenotypic state, Φ_{a-} , we first derive an approximation for the probability of establishment $\mathbb{P}_{est,a-}(t)$ as the probability of at least one epimutation to Φ_{a+} before the loss of the a allele, followed by the establishment of this a_+ mutation:

$$\mathbb{P}_{est,a-} = 1 - e^{-\int_0^\infty u\Phi_{a-}(1 - \frac{N(t)}{K})N_{a-}(t)\mathbb{P}_{est,a+}(t)dt}, \quad (8)$$

according to epimutation viewed as a time-inhomogeneous Poisson process, where

$$N_{a-}(t) = \frac{(1 - (1 - u)\Phi_{a-})K}{e^{(1-(1-u)\Phi_{a-})t}(K - (1 - u)\Phi_{a-}(K - 1)) - (1 - u)\Phi_{a-}} \quad (9)$$

represents the decline in the a population from a single individual with negative expected growth rate and mutation away from a_- at rate u . Then the analytic expression for the probability of rescue becomes

$$\mathbb{P}_{rescue,a-} = 1 - \exp\left(-\int_0^\infty \mu N(t)\Phi_A(1 - \frac{N(t)}{K})\mathbb{P}_{est,a-}(t)dt\right). \quad (10)$$

This analytical approximation is shown in **Figure S1B**, alongside the results of an ensemble of Monte Carlo simulations. In **Supplementary Figure S2** we show the analytic approximation along with evolutionary simulations for a range of rates of mutation.

Finally, we can approximate the probability of rescue when novel mutations to the a allele are introduced with random phenotype (Φ_{a+} or Φ_{a-}) with equal probability (**Figure S1C**). Although there are several ways to make an analytic approximation, the simplest is simply to note that the probability of rescue from mutation to Φ_{a+} is larger by an order of magnitude than the probability of rescue from mutation to Φ_{a-} . Therefore we can approximate the overall probability of rescue with random initial phenotype as the probability of rescue from mutation to Φ_{a+} using mutation rate $\frac{\mu}{2}$. It follows that

$$\mathbb{P}_{rescue} = 1 - \exp\left(-\int_0^\infty \frac{\mu}{2}N(t)\Phi_A(1 - \frac{N(t)}{K})\mathbb{P}_{est,a+}(t)dt\right). \quad (11)$$

As expected, the density-independent approximation for the rescue probability is similar to the full

67 density-dependent treatment for systems starting far from carrying capacity (**Supplementary Figure S3**).

68 **References**

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List of Figures

Figure S1. Probability of evolutionary rescue from a new mutation, with density-dependent births. The lines represent the analytical approximations. The dots represent the ensemble average across 10,000 replicate Monte Carlo simulations. Here, $K = 5000$, $N_0 = 1000$, $N_0\mu = 0.01$ and $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$. **Panel A:** Probability of rescue when A can only initially access the a_+ phenotype. **Panel B:** Probability of rescue when A can only initially access the a_- phenotype. **Panel C:** Probability of rescue when A can initially access both a phenotypes.

Figure S2. Probability of evolutionary rescue as a function of $N\mu$, density-dependent birth. The lines are analytic approximations, while the dots represent the ensemble average across 10,000 replicate Monte Carlo simulations. Here, the A allele can only mutate to the a_+ phenotype, $K = 5000$, $N_0 = 1000$, $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$ and $\text{Var}(\Phi_a) = 0.25$.

Figure S3. Comparison of density-independent and density-dependent analytic approximations, as $\frac{N}{K}$ becomes small. Probability of evolutionary rescue from a new mutation. Here, $N_0 = 100$, $K = 1000000$, $N_0\mu = 0.01$ and $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$.

Figure S4. Probability of evolutionary rescue with resistance locus, one abrupt change in environment scenario, for different mutation rates to a . Here $K = 20000$, $N_0 = 10000$, $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$, $\text{Var}(\Phi_a) = 0.0025$, birth rate of R is 10 and mutation rate to R is 10^{-6} . **Panel A:** Mutation rate to a is 0.01. **Panel B:** Mutation rate to a is 0.05. **Panel C:** Mutation rate to a is 0.1.

Figure S5. Probability of evolutionary rescue with resistance locus, one abrupt change in environment scenario, for different birth rates of R . Here $K = 20000$, $N_0 = 10000$, $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$, $\text{Var}(\Phi_a) = 0.0025$, and mutation rate to R is 10^{-5} . **Panel A:** Mutation rate to a is 0.05 and birth rate of R is 2. **Panel B:** Mutation rate to a is 0.1 and birth rate of R is 2. **Panel C:** Mutation rate to a is 0.05 and birth rate of R is 10. **Panel D:** Mutation rate to a is 0.1 and birth rate of R is 10.

Figure S6. Mean time to population extinction for populations fixed on the wild-type A . Here $f^1(\Phi_A) = 0.5$, $f^2(\Phi_A) = 1.5$ and the carrying capacity is $K = 1,000$.

Figure S7. Probability of evolutionary rescue from a resistance mutation in periodically changing environments. The dots represent the probability of evolutionary rescue for a phenotypically-variable population, while the lines represent this probability for a phenotypically-fixed population, across 10,000 replicate simulations. All populations are initiated at $N = 500$, with a

carrying capacity $K = 5000$, with a single mutant genotype a drawn with a random phenotype introduced into a random one of the two different environments. The two environments then cycle deterministically with each environmental epoch lasting n time units (with n as in the legend), where time is measured in units of the expected lifespan of an individual. Here $f^1(\Phi_A) = 0.5$, $f^2(\Phi_A) = 1.5$ and $\text{Var}(\Phi_a) = 0.16$ and mutation rate to R is 10^{-6} . **Panel A:** Birth rate of R is 1.5 (across both environments). **Panel B:** Birth rate of R is 1.9 (across both environments). **Panel C:** Birth rate of R is 2 (across both environments).

Figure S8. Probability of evolutionary rescue (for the scenario with one abrupt change in environment) and time to extinction (for the scenario when the environments change periodically) when the a allele has access to more than two phenotypes. **Panel A:** Here, $N_0 = 1000$, $N_0\mu = 0.01$ and $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$, with $\text{Var}(\Phi_a)=0.156$. **Panel B:** Parameters are the same as in **Panel A**, with $\text{Var}(\Phi_a)=0.11$. **Panel C:** Parameters are the same as in **Figure 6B** with $\text{Var}(\Phi_a)=0.076$.

Figure S9. Probability of evolutionary rescue when the a allele has access to more than two phenotypes, same phenotypic range. Here, $N_0 = 1000$, $N_0\mu = 0.01$ and $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$, with the a allele with access to two or six phenotypes, such that its phenotypic range is constant (the maximum growth rate available to a is 1.45). The different numbers of phenotypes accessible to a determine the two different variances of the a allele phenotypes. The lines represent the analytic approximations computed using the right values of phenotypic variance. This also shows that it is not the maximum growth rate available to a that drives evolutionary dynamics, and instead it is its variance.

Figure S10. Probability of evolutionary rescue from a new mutation, density-independent birth. The lines represent the analytical approximations. The dots represent the ensemble average across 10,000 replicate Monte Carlo simulations. Mutation at the A/a locus can access both versions of the a allele. Here, $K = 5000$, $N_0 = 1000$, $N_0\mu = 0.01$ and $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.8$.

Figure S11. Probability of evolutionary rescue with resistance locus, one abrupt change in environment scenario, for different phenotypic range for a . Here $K = 20000$, $N_0 = 10000$, $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.9$, $\Phi_{a-} = 0.91$, $\Phi_{a+} = 0.99$, birth rate of R is 10 and mutation rate to R is 10^{-6} . **Panel A:** Mutation rate to a is 0.01. **Panel B:** Mutation rate to a is 0.05. **Panel C:** Mutation rate to a is 0.1.

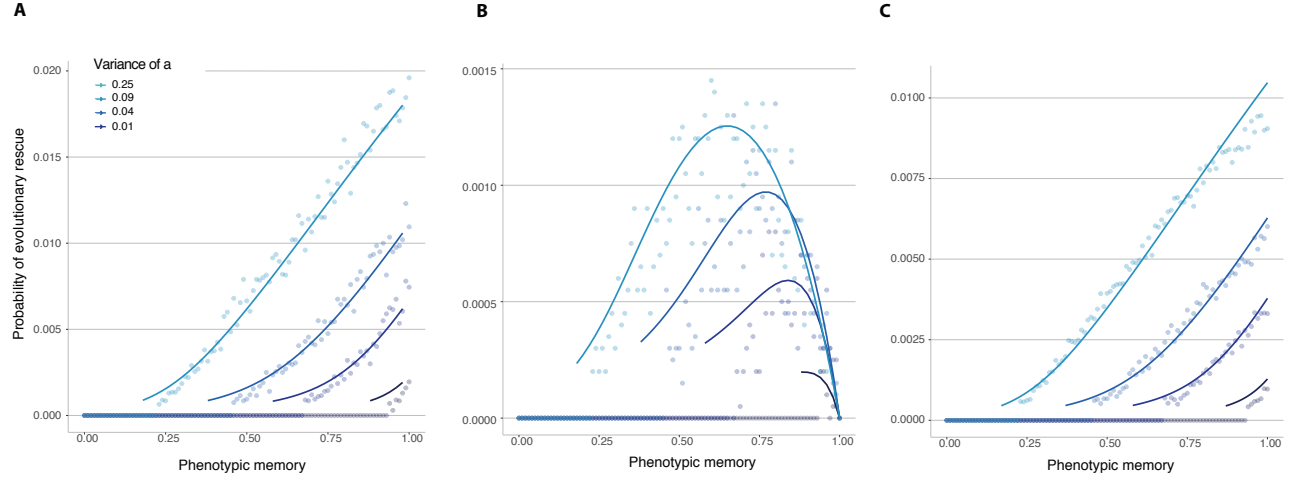


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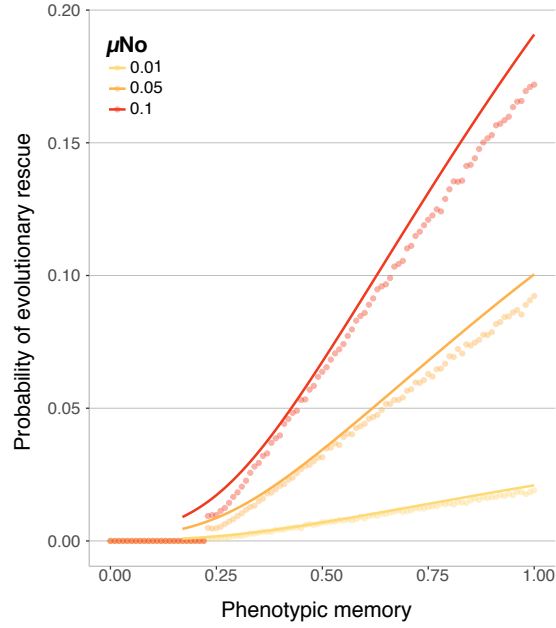


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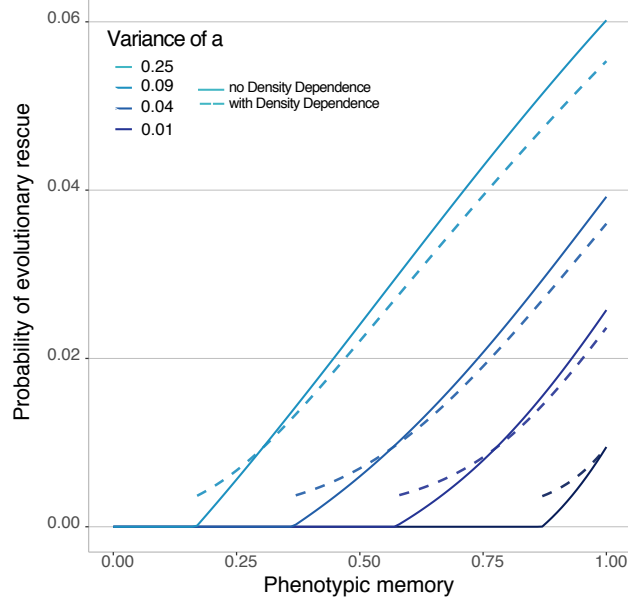


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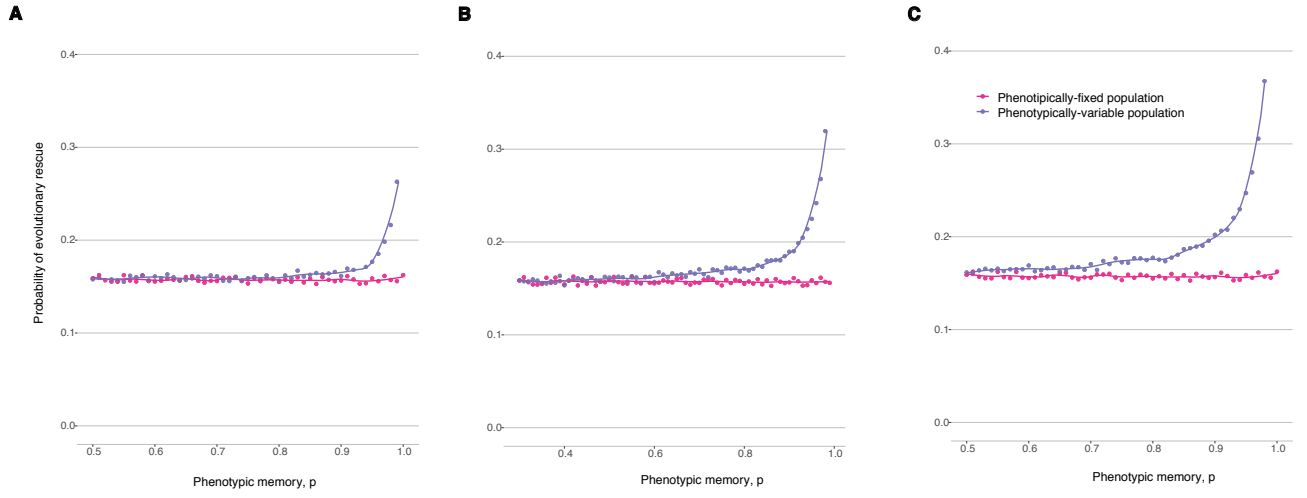


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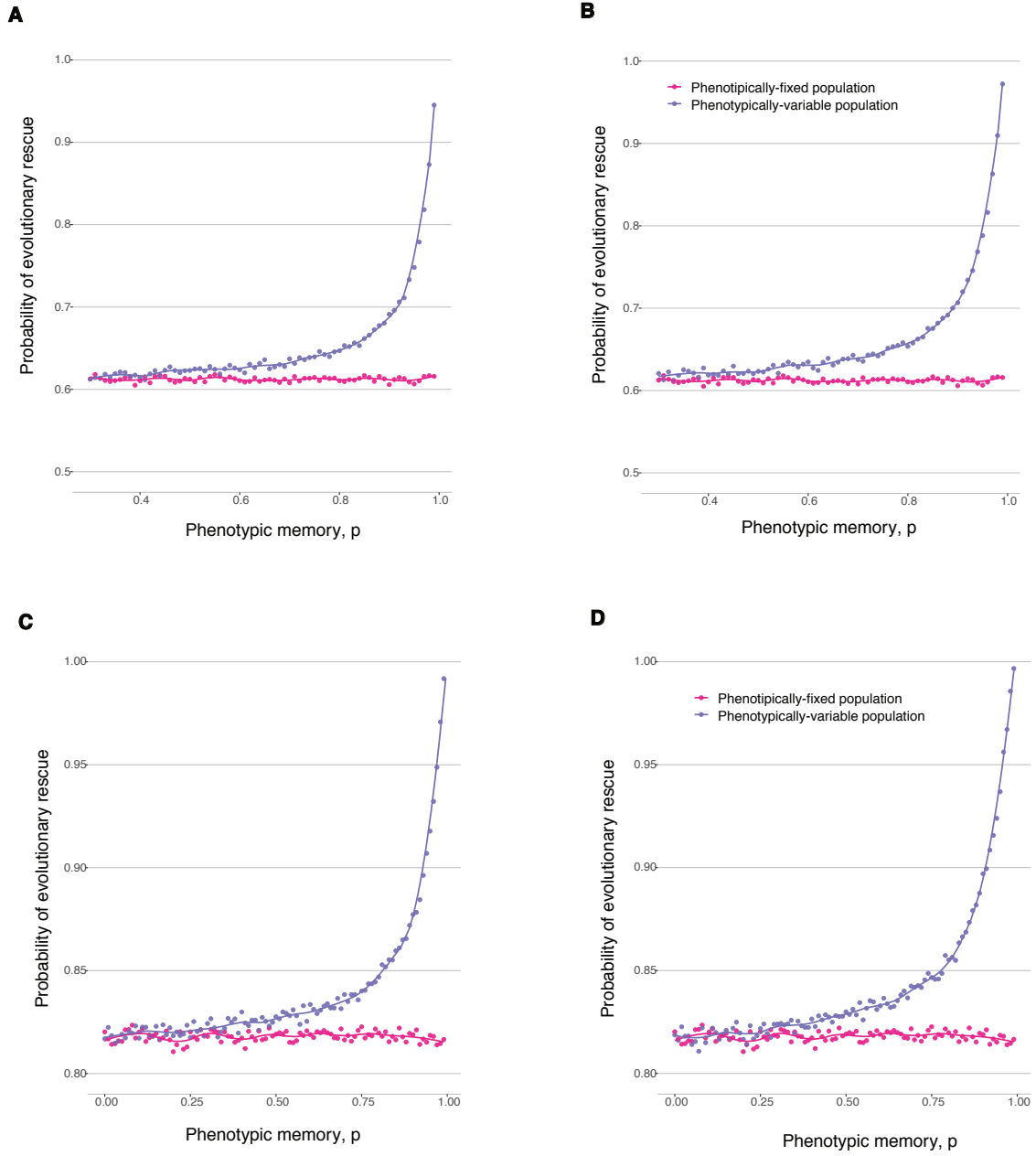


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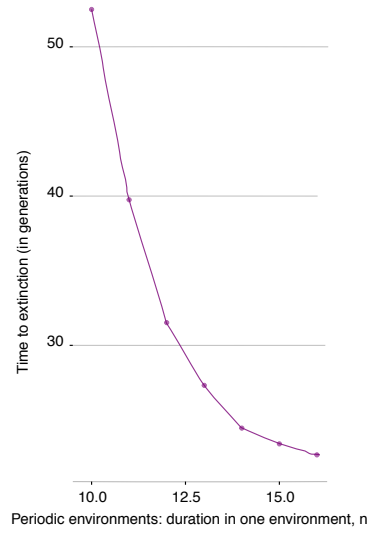


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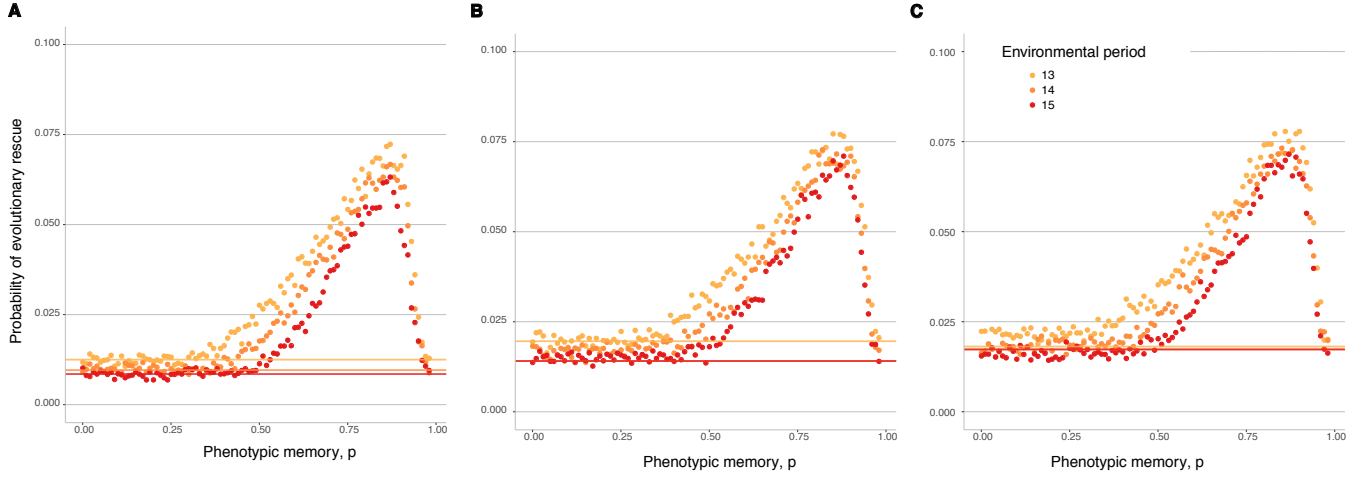


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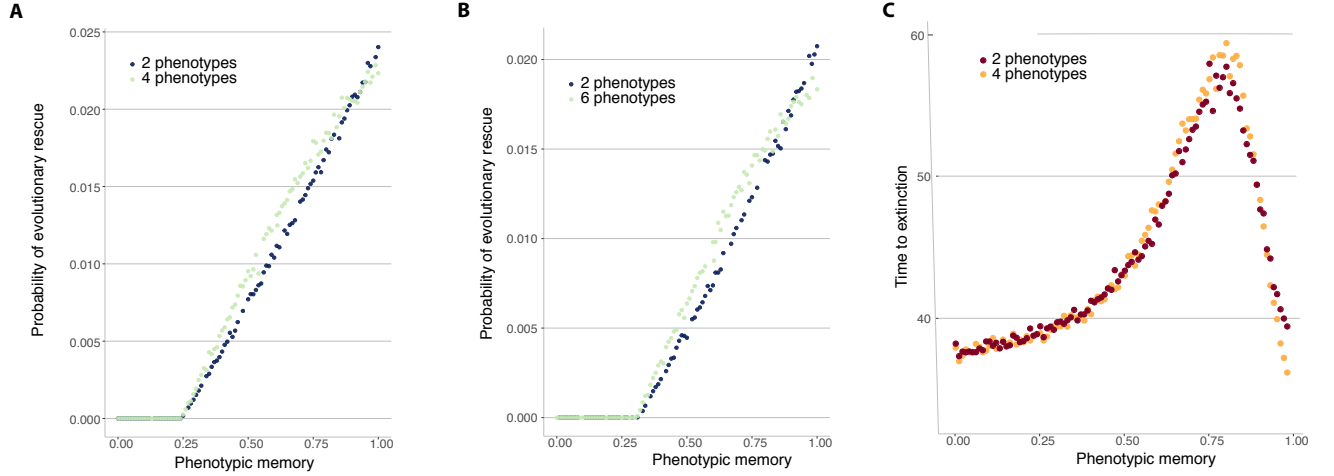


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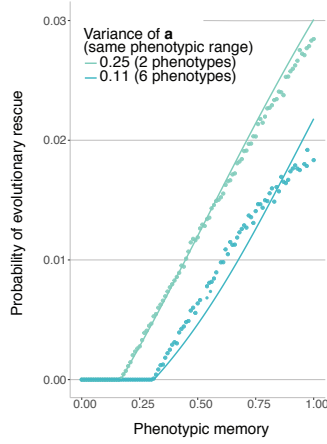


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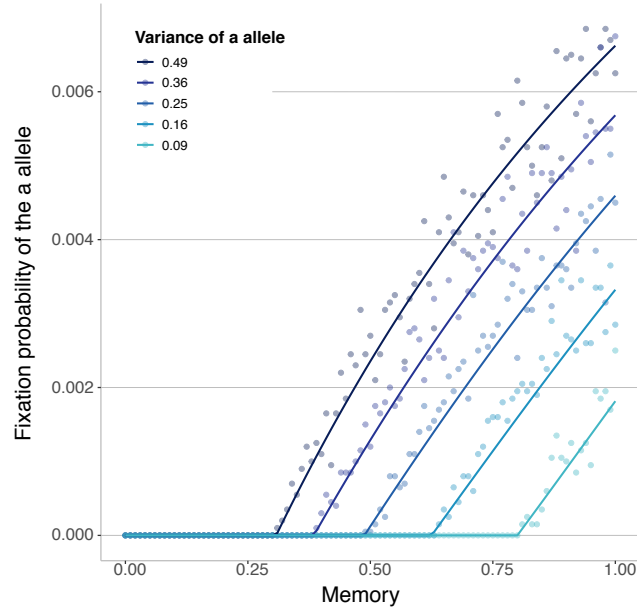


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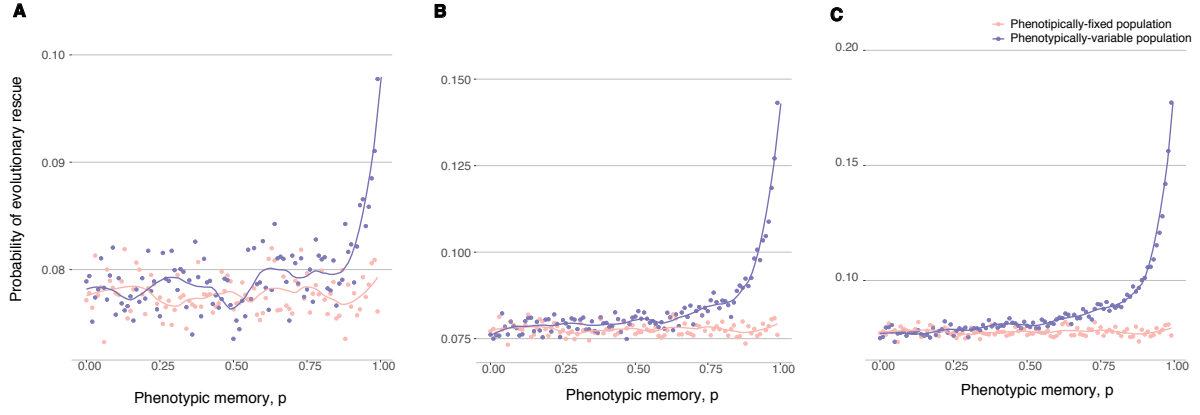


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