# Introduction

We study evolution to understand natural diversity; adaptation via natural selection is the cause of complex forms; natural selection acts on genetic diversity; the amount and direction of diversity limits a population to a certain range of possible phenotypes; particularly the additive variance in traits is important because it is heritable;

Additive variance is heritable; explains polygenic traits

At the heart of the evolutionary sciences is the need to understand the natural world’s diversity. Darwin’s (1863; SOURCE) introduction of natural selection some 140 years ago led to increasingly accurate glimpses into the units of evolution, genes, and their movement through a population in response to selection (SOURCE). However, these movements, particularly in a multivariate trait space, become a challenging realm to predict (SOURCE; Lande 1979, 80 etc.). To navigate this space, it is necessary to reduce the predictors of trait trajectories to their principles: how they affect additive genetic variance, the heritable component of trait variability.

Additive genetic variability, VA, is regarded as the most important predictor of a population’s adaptability (Lynch and Lande 1998; Aguirre *et al.* 2014; Careau *et al.* 2015), and hence it’s trajectory through time towards a phenotypic optimum. Although a multitude of stochastic and deterministic processes also contribute to the population’s total trait variability, VA is heritable, and therefore predictive of a population’s trajectory over micro-evolutionary time. The VA of a population determines the phenotypic space that population can explore. Hence, it is predicted that populations with large amounts of VA are best suited to adapting to novel environments (Barton and Charlesworth 1998). Such an example is X. However this is not always the case, standing genetic variation is characterized by a variety of architectural and population-level constraints such as rates of pleiotropy, selection strength, additive effect size, linkage, and deleterious mutation/background selection (SOURCE). For example, under infinitesimal models, selection has a trivial impact on standing variation (Barton 2017).

including genetic drift, selective pressures, additive effect sizes, between- and within-gene interactions, and heritability (SOURCES).

* Natural diversity, population movements in trait space
* Heritable variation
* Stabilising selection, effect on variation/need for variation vs drift
  + Expected to remove variation, mutation alone can’t explain why in natural populations we see so much variation: why?
* Additive effect sizes, effects on variation
* Background selection, effect on variation
* Population genetics expectations of variation under bkg sel, additive effects

# Methods

Using the forward-genetics modelling package SLiM 3.4 (Haller and Messer 2019), I constructed two models to explore a portion of the multivariate parameter space that explains genetic variability in natural populations. These parameters included genome wide recombination rate, the amount of deleterious mutation, the additive effect size distribution, and the selection strength multiplier, (Table 1). The rate of universal pleiotropy, and the amount of mutational covariance between traits was also varied across models but was not considered for analysis. Among these models, multiple conditions and assumptions are shared.

## Common model elements

Both of my experimental models consisted of a SLiM 3.4 model simulating a Wright-Fisher population of 8000 diploid individuals evolving over 100,000 generations (with an additional 50,000 generations of burn-in (more information in figure S1 – heterozygosity figure from burn-in test). Each individual is characterized by 8 traits, controlled by 100 loci each. Each trait has an identical effect on fitness, forming a ‘mega-trait’ with varying variance-covariance structures depending on pleiotropy rates. Each locus is assumed to have identical length, and each base pair within it is assumed to be mutationally independent, an assumption supported by a study by Thornton (2019), which found that within-locus differences in linkage had no average effect on either genetic variance or the mean trait value, indicating within-locus independence. In addition, the average number of base pairs per locus is highly conserved within eukaryotes (Xu *et al.* 2006), indicating that the assumption of equal gene length is not too far-fetched. The mutation is modelled as occurring at an arbitrary position within the locus (or its regulatory regions) and is of arbitrary form. The effect of the mutation on chromosomal structure (e.g. effects of deletions, insertions etc.) is not explicitly modelled, but is implied via their effect on fitness and/or the trait. Mutations are assumed to be completely additive in effect, with no dominance or epistatic interactions. All loci are assumed to be on the same chromosome, with genetic distance being determined by the recombination rate parameter, r (Table 1). Both models have a genome-wide germline mutation rate of 8.045x10-6 per locus per generation, based on an average of five groups of eukaryotes (Aston *et al.* 2017).

The chosen effective population size, Ne = 8000, was chosen to compromise between computational performance and the effect of genetic drift on populations under stabilizing selection. This value results in weak genetic drift in comparison with the strength of selection (under strong selection pressures), and appropriate standing genetic variation following burn-in to allow for adaptation (Lynch and Lande 1998).

Mutational effects on trait values were sampled from a normal distribution,

where λ is the additive effect size (Table 1). In the case of pleiotropy, a multivariate normal distribution was used, where n = 8, and

where **Σ** is a covariance matrix with diagonal values equal to λ and non-diagonals pulled from a normal distribution:

where is the parameter value of mutation correlation. **Σ** was ensured to be positive definite by multiplication with its transpose.

Non-trait deleterious mutations had fitness effects sampled from a gamma distribution with

Where and (SLiM Manual). This describes a distribution of fairly weak deleterious mutations on average.

All models were subject to 50,000 generations of burn-in, where mutations accumulate until the population reaches mutation-drift equilibrium. This is tracked as heterozygosity through the simulation, where mutation-drift equilibrium occurs when:

where µ represents the per-locus mutation rate per generation (Kimura and Crow 1964). A population at equilibrium was assumed sufficiently burnt in. Trials indicated that 50,000 generations was sufficient for our population size (FIGURE S1: Plot of heterozygosity). Deleterious mutation (δ) lowered the value of away from expectation in initial burn-in tests, however an alternative equilibrium was reached, satisfying the requirements of burn-in (Figure S1).

## Model specific characteristics

After reaching equilibrium, populations evolved for 100,000 generations of neutral drift or stabilizing selection, depending on the treatment. Neutral drift entailed no change from the properties of the burn-in, whereas stabilizing selection imposed a fitness function on phenotypes, invoking a multivariate optimum a fixed distance from the population mean phenotype post-burn-in. The position of the optimum is defined as:

Where is the vector of phenotype means, is the per-locus, per-generation mutation rate, , is the number of mutational steps to reach the optimum, and is the number of generations of burn-in. For our purposes, and .

The fitness of an individual in the population was defined as:

Where s represents strength of selection, represents the gradient of the selection curve, n is the number of traits, and xn is the phenotype for trait n. For my experiments, s was fixed at s = 0.9, ensuring minimum fitness was 0.1, and maximum fitness was 1. This results in individuals at the optimum being at most ten times as fit as those infinitely far from the optimum. This value differs depending on, which adjusts the realized fitness gradient.

## Model Parameterization

Five parameters were shared between models, with a sixth for testing selection (Table 1). These were sampled using a Latin hypercube sampling design, with 1024 parameter combinations testing the null model, and 256 for the selection model. These samples were generated using the R packages ‘DoE.Wrapper’ and ‘LHS’, using the maximin algorithm (Melo *et al.* 2015; R Developmental Core Team 2019). Each model was repeated 100 times, using 100 seed values fed to SLiM. These seeds were randomly sampled from a uniform distribution of the total range of unsigned 32 bit integers (1 to 232 – 1) using the runif() function in base R (R Developmental Core Team 2019). The array of parameter combinations and replicates was processed across 1152 cores on the University of Queensland’s Tinaroo high performance computing (HPC) system, using embedded Nimrod scripts to feed parameter/seed combinations to individual SLiM processes.

## Analysis

Despite not all data conforming to normality, no data was transformed owing to the large sample sizes. Previous work into the robustness of regression modelling, t-tests, and F-tests have shown that departures from normality can usually still provide reliable estimates, provided the number of observations is large enough that coefficient estimates are approximately normally distributed due to the central limit theorem (Lumley *et al.* 2002). This was verified with diagnostic tools in the R package “jtools” (Long 2020). Heteroscedasticity was accounted for using Eicker-Hubert-White (EHW) robust standard errors, although owing to the large sample size, this adjustment had minimal effect on t-statistics (Eicker 1967; Huber 1967; White 1980).

For analysis, each parameter was grouped into three categories: low, medium, and high, with each bin containing a third of the total data. was the exception to this, with a fourth bin, null, describing the neutral models with no value at all. Across all analyses, means of responses were compared at the final generation of the simulation (100,000) and variances of responses over time (from generations 50,000 to 100,000). Trait variances and covariances were pooled and averaged to form a ‘mega-trait’ average variance and covariance, since traits were functionally identical.

In addition, I computed the population mean Euclidean distance from the optimum for each replicate and model:

Where pi and qi are the population mean and optimum value, respectively, for trait *i*. I compared distances with multiple regression, again with EHW robust standard errors.

Rare alleles were defined as being ≥2 standard deviations away from the mean, 0. This represented two times the additive effect size parameter for a given model, the rarest 5% of mutations.

# Results

## Diagnostics

To determine the dynamics of the model under selection, I plotted variance and distance to the optimum over time across selection strengths. Under low and medium selection, the initial response was a rapid movement towards the optimum. High selection led to no such drop in distance, indicating a lack of ability to adapt given the strong selection regime (Figure 1A). Following the initial decline, all models travelled further away from the optimum before stabilizing to their local ‘best fit’, the closest distance to the optimum where selection strength alone could take them (Figure 1A). Variance similarly decreased initially after introducing the selection regime under low and medium models, before increasing over time due to the prevalence of genetic drift (Figure 1B). By generation 100,000, models have not yet reached mutation-selection-drift equilibrium, as variance continues to increase, however trajectories approach stability. The distance from the optimum remains stable after generation 50,000. Assuming we are approaching equilibrium, we can describe which existing quantitative genetics models best describe our models.

Existing quantitative genetics models predict each locus’s distribution of allelic effects via the strength of selection relative to the mutation rate (Walsh and Lynch 2018). High mutation rates relative to selection strength is an assumption of Gaussian approximation models, and strong selection relative to mutation is an assumption of HOC models. I compared mean trait variance with selection strength to determine the range of CoA models sampled by the parameter space. Selection strength had no effect on mean variance when considered alone (F1, 127998 = 2.475, p = 0.1157, Adjusted R2 < 0.0001). When including the other parameters (deleterious mutation rate, additive effect size, pleiotropy rate, and recombination rate) a weak effect on mean variance, decreasing it with stronger selection by 6.385 ± 1.034 per 10% increase in selection strength (t25588 = 6.174, p < 0.0001). The probability of having zero variance was strongly predicted by selection strength alone (F1, 127998= 73230, p < 0.0001, Adjusted R2 = 0.9686). A 10% increase in selection strength led to a 6.575x10-16 ± 2.429x10-18 increase in probability of zero variance (t127998 = 270.6, p < 0.0001). High levels of unexplained variance within levels of selection indicated that genetic architecture parameters may be more important determining trait variance in populations (Figure 2).

## Patterns of variation with background selection and allelic effect size distributions

To determine the effects of genetic architecture on trait variance, I compared the effects of deleterious mutation rate, and additive effect size on mean trait variance with a linear model (F3, 127996 = 349063.4, p < 0.0001, Adjusted R2 = 0.8911). Recombination rate, pleiotropy rate, and selection strength (along with their pairwise interactions described 0.0051% of variance and were removed from the model. Deleterious mutation rate and allelic effect size contributed strongly to variance (Figure 3). A unit increase in additive effect size resulted in an increase of 110.0 ± 0.1341 units of mean trait variance (t127996 = 820.09, p < 0.0001). A 10% increase in deleterious mutation rate resulted in a decrease of 64.334 ± 0.1327 units (t127996 = -484.7, p < 0.0001). However, these main effects were masked by a strong interaction: the effect of deleterious mutation rate on mean trait variance decreased with increasing additive effect size (β3 = -174.2782 ± 0.4452; t127996 = -391.5, p < 0.0001). Low deleterious mutation rates enabled large increases in mean variance with increasing additive effect size, however this increase was largely constrained under high deleterious mutation rates (Figure 4). These changes to trait variance have strong predictions for adaptation under stabilising selection, specifically in the (Zhang 2012) adherence of trait means to a trait optimum.

## Adherence to a multi-trait optimum with increasing background selection and additive effect size

It is commonly theorised that genetic variability is strongly linked to the adaptability of populations under stabilising selection (Zhang 2012; Walsh and Lynch 2018). To measure this, I calculated Euclidean distances of populations () from the optimum at generation 100,000, and the probability of a given model to reach the optimum, . Deleterious mutation rate and additive effect size, along with their interaction were included in a linear model (F3, 127996 = 122193.3, p < 0.0001, Adjusted R2 = 0.7412; Figure 3). Again, pleiotropy rate, recombination rate, and selection strength (along with their pairwise interactions) explained <1% of variation and were excised from the linear model. Increasing deleterious mutation rate by 10% decreased distance to the optimum by 23.305 ± 0.088 units (t127996= -252.5, p < 0.0001), whilst additive effect size by 1 unit increased the distance to the optimum by 47.874 ± 0.089 units (t127966 = 536.37, p < 0.0001). Again, a significant interaction was observed (Figure 5). Increasing additive effect size under high rates of deleterious mutation resulted in smaller increases in distance to the optimum than under low rates of deleterious mutation (β3 = -36.860 ± 0.296; t127996 = -124.4, p < 0.0001). The probability of reaching the optimum reflected this, with the probability of reaching the optimum increasing with deleterious mutation rate under low effect sizes, but remaining constant at 0 with effect sizes greater than 3 (Figure 6). The probability of reaching the optimum increased linearly under strong selection pressure, however more quadratic trends were visible at lower selection strengths (Figure 6). To understand these patterns, the alleles underpinning trait variation and adaptation needed to be quantified.

## Distributions of segregating alleles under background selection and growing additive effect size

I compared rare allele frequency (RAF) with increasing additive effect size and deleterious mutation rate. The resulting linear model found significant differences between additive effect size, deleterious mutation rate, pleiotropy rate, stabilizing selection presence/absence and interactions between these four parameters (F15, 63937 = 1174, p < 0.0001, Adjusted R2 = 0.2784).Increasing deleterious mutation rates by 10% decreased RAF by 1.158 ± 0.609, however this difference was marginally insignificant effect (t63937 = -1.903, p = 0.057). Under selection, this decrease became highly significant, decreasing deleterious mutation rate’s effect on RAF by 9.381 ± 0.924 (t63937 = -10.148, p < 0.0001). Increasing additive effect size showed a small increase in the number of rare alleles under no selection (2.288 ± 0.6658 rare alleles per unit increase in additive effect size; t63937 = 3.437, p = 0.0006). Under stabilising selection, this effect was reduced by 5.113 ± 0.894 rare alleles (t63937 = -5.721, p < 0.0001). Under null conditions, the RAF reduction due to increasing deleterious mutation rate decreases by a further 3.020 ± 0.893 for a unit increase in additive effect size (t63937 = -3.388, p = 0.0007). Hence, increasing deleterious mutation rate reduces RAF to a greater extent under higher additive effect sizes. Under selection, this effect was reversed; the RAF reduction due to deleterious mutation is alleviated by 12.437 ± 1.314 units for a unit increase in additive effect size (t63937 = 9.464, p < 0.0001). This implies that deleterious mutation rate reduces RAF to a greater extent under lower additive effect sizes when under stabilising selection. The effects of additive effect size and deleterious mutation rate were highly visible in terms of the distributions of segregating alleles (Figure 7). The total numbers of all mutations decreased with increasing selective pressures (either by the presence of stabilising selection in Figure 7B or increasing deleterious mutation rates).

# Discussion

Surprising result: deleterious mutation reduces distance to optimum under maintenance, particularly under large size effects; still anchored in quant gen theory, even though pop gen predicts the opposite; pop gen – Ne reduced with BS, decreased variation expected, worse selection, more drift etc.

We found that increasing rates of deleterious mutation resulted in populations being more able to maintain their position around the optimum, overcoming some of the difficulties of fending with large-effect alleles that may pull populations away from the optimum (Figures 3, 5). Although it may at first seem counter-intuitive that stronger background selection increases the ability of populations to maintain their position at an optimum (Figure 5, 6), the effect can be explained with existing quantitative genetics expectations. To understand this, we must first explore the population genetics expectations of the effects of background selection on adaptation, and distinguish the difference in expectations between a population approaching the optimum and maintaining its position once it has arrived there.

It is well understood in population genetics that background selection reduces effective population size, reducing the effectiveness of selection and increasing the strength of genetic drift (Charlesworth *et al.* 1997; Houle 1998). As deleterious mutations are removed from the population, close-by linked QTLs are also removed (Charlesworth and Charlesworth 2010). The effect of this is decreased genetic diversity. In population genetics studies this is usually expressed in terms of FST or , whereas in quantitative genetics the analog is additive genetic variance (Falconer 1996; Charlesworth *et al.* 1997). Reductions in VA with increasing background selection were observed in this study, supporting this expectation (Figure 3A, 4). The expected effect of this on adaptation is quite clear when considering the initial approach towards the optimum: in quantitative genetics models, genetic variability is expected to increase the trait space that populations are able to explore, improving their ability to travel towards an optimum (Fisher 1930; Charlesworth and Charlesworth 2010; Aguirre *et al.* 2014). Indeed, these theoretical expectations have been found in natural populations: for example, Pujol and Pannell (2008) showed that populations of annual mercury, *Mercualis annua,* were able to respond to selection for pollen production when standing genetic variation was higher. Similarly, studies into the adaptation of red flour beetle (*Tribolium castaneum*) populations to new niches found high standing variation decreased the likelihood of extinction, and increased rates of niche expansion (Agashe and Bolnick 2010; Agashe *et al.* 2011). However, these expectations do not describe what we found in the current study: the most well-adapted populations consistently have higher rates of deleterious mutation, and hence lower standing genetic variance. The key to this lies in the expectations of the *maintenance* of variation and fitness around an optimum rather than the *approach* towards said optimum. The expectations surrounding this temporal space is considerably less extensive than that of the adaptive walk.

While reduced standing variation is expected to increase the time a population takes to reach an optimum (or perhaps prevent populations from reaching it at all), once a population has reached its optimum or stabilizes around its ‘local optimum’, the closest position it can maintain given the selected traits’ genetic architectures, mutation rates, and the population size – where does the population go?

In theoretical quantitative genetics, much debate is had over which particular models best describe the maintenance of variation in the presence of stabilizing selection over time. Selection is able to retain variation, particularly in large populations where drift is weak, and scenarios where balancing selection creates a non-linear fitness landscape, however the extent of this differs depending on many factors, including selection strength, genetic architectures, epistatic and dominant interactions, and the strength of selection relative to mutation (Walsh and Lynch 2018). Understanding the relative strength of selection to mutation has led to two distinct approximations of expected distributions of allelic effects. When mutation is much stronger than selection, Kimura (**1965a**) and Fleming’s (**1979**) Gaussian approximation holds true, whereas when the opposite occurs, Turelli’s (**1984**) house of cards approximation is more accurate. This distinction between models is arbitrarily granular, mostly for analytical viability. Computational methods allow for a continuous exploration of this space of models.

Figure 3: decrease in var with deleterious mutation is analogous to effects of lower Ne, but on a per locus level rather than genome wide. Hence, gives a proxy of the assumptions of CoA models with N -> Inf

Loss of fitness due to variation around optimum: expected to be 1/4Ne without any background selection (will vary with Ne due to effect on local Ne ) – Lande 1976

# Snippets

Underpinning this model is the continuum of alleles model of allelic effects, suggesting large numbers of alleles at many loci forming a continuous distribution of effect sizes, usually Normal in shape (Lande).

Pleiotropy fundamentally alters the signatures of HCA vs Gaussian approximation in COA so they approach each other - other parameters may as well?

Most effort in understanding stabilizing selection has focused on assuming either a Gaussian (as in this paper) or quadratic fitness function

Pleiotropy also had strong effects, due to contributing more than one trait value per mutation. Increasing pleiotropy rate by 10% increased RAF by 59.366 ± 2.531 alleles under no selection (t63937 = 23.458, p < 0.0001). Increasing deleterious mutation with pleiotropy rate significantly reduced this effect, with a 10% increase in pleiotropy rate and deleterious mutation rate simultaneously leading to a total loss of 22.555 ± 5.994 alleles (t63937 = -17.795, p < 0.0001). Under stabilising selection, a simultaneous 10% increase in pleiotropy rate and deleterious mutation rate led to an increase of 23.553 ± 8.567 alleles (t63937 = 19.193, p < 0.0001).

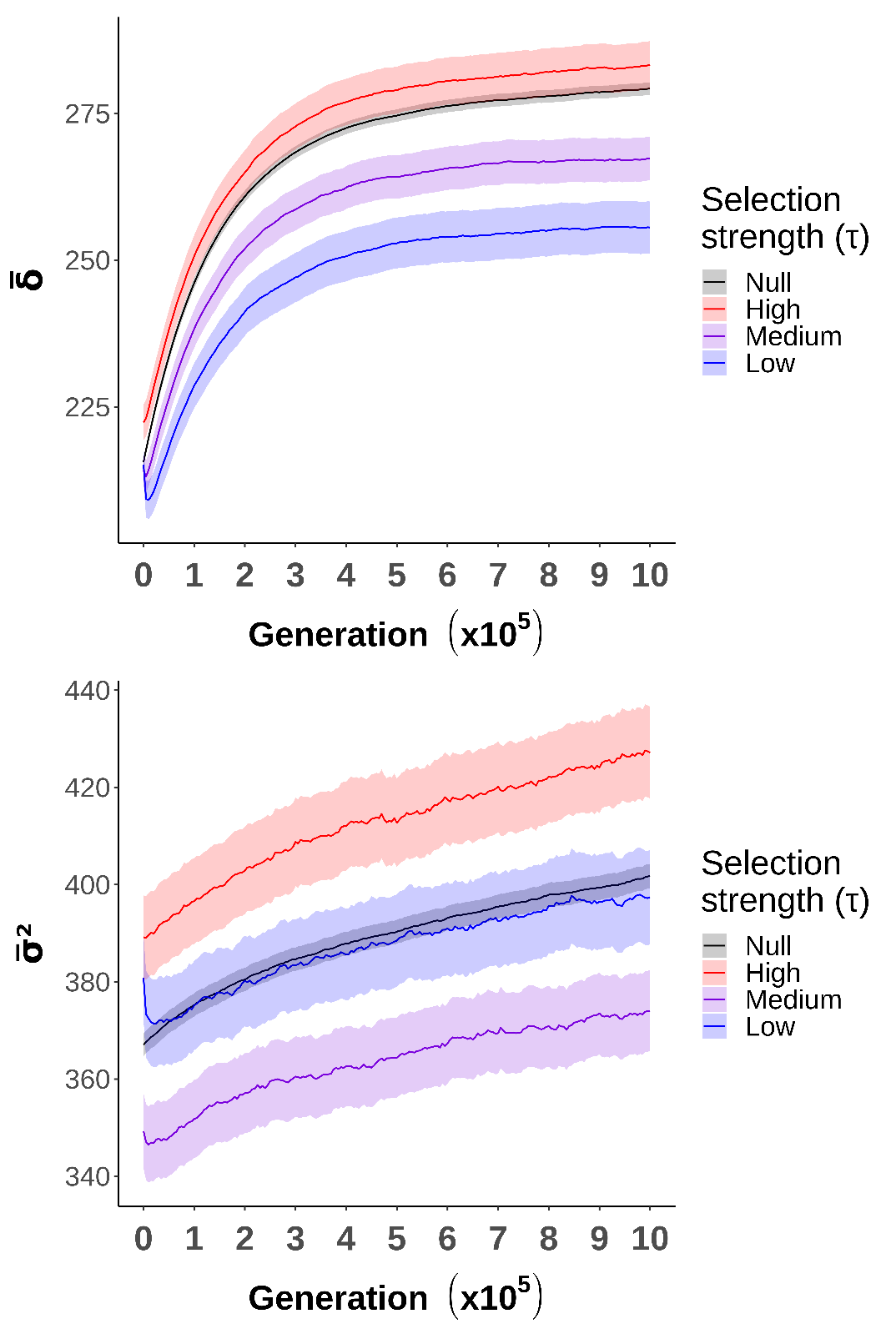


Figure 1 – Mean Euclidean distance from the optimum (A) and mean trait variance (B) over 100,000 generations of stabilizing selection of different strengths (). 256 total models were sampled across the spectrum of selection strengths () with an additional 1024 models sampling the null space of parameters ().

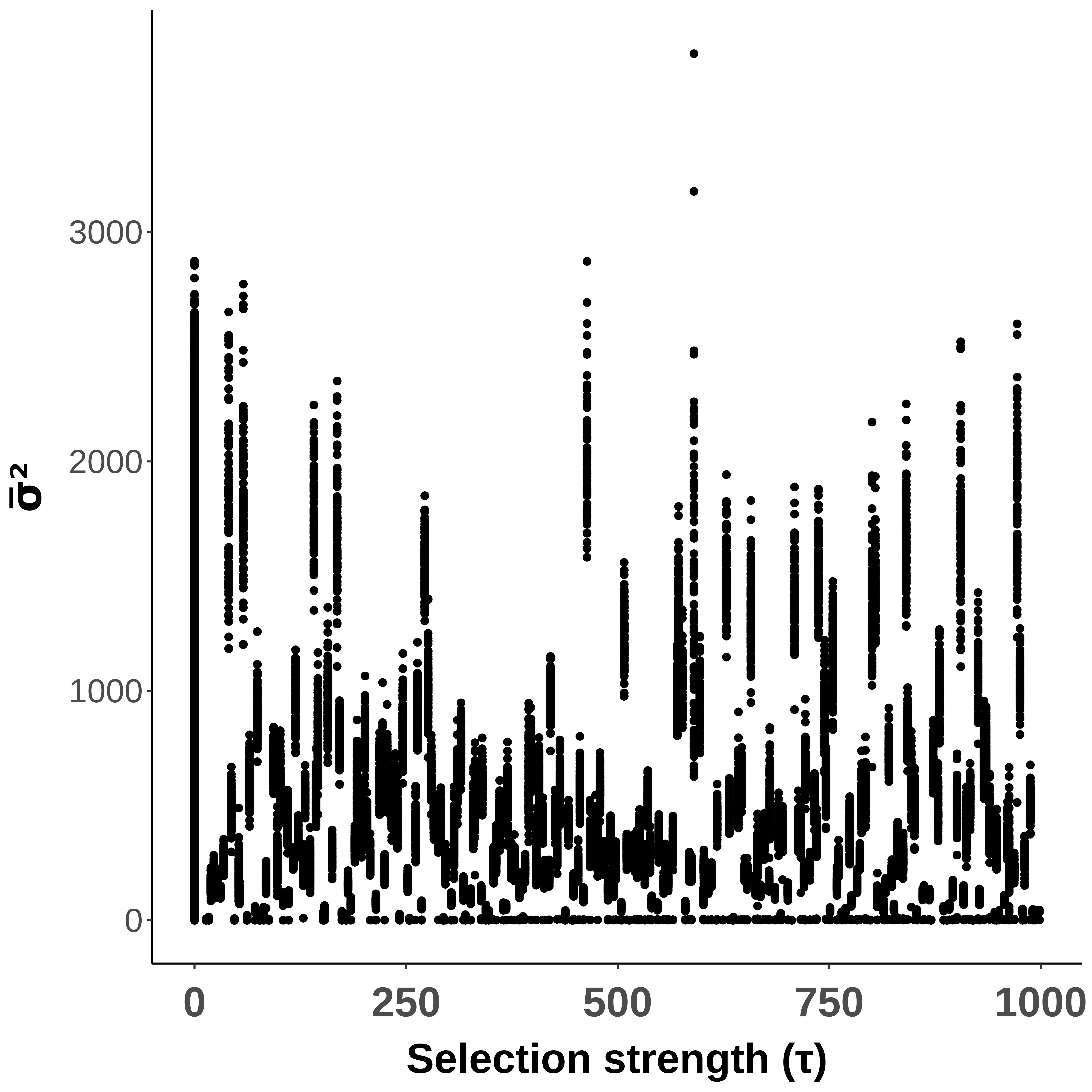


Figure 2: Mean trait variance with increasing selection strength explains very little shift in variance patterns across models. Note that () represents null models with no selection pressure, but values represent the range of selection models. Means of 1024 null models and 256 selection strengths are represented here.

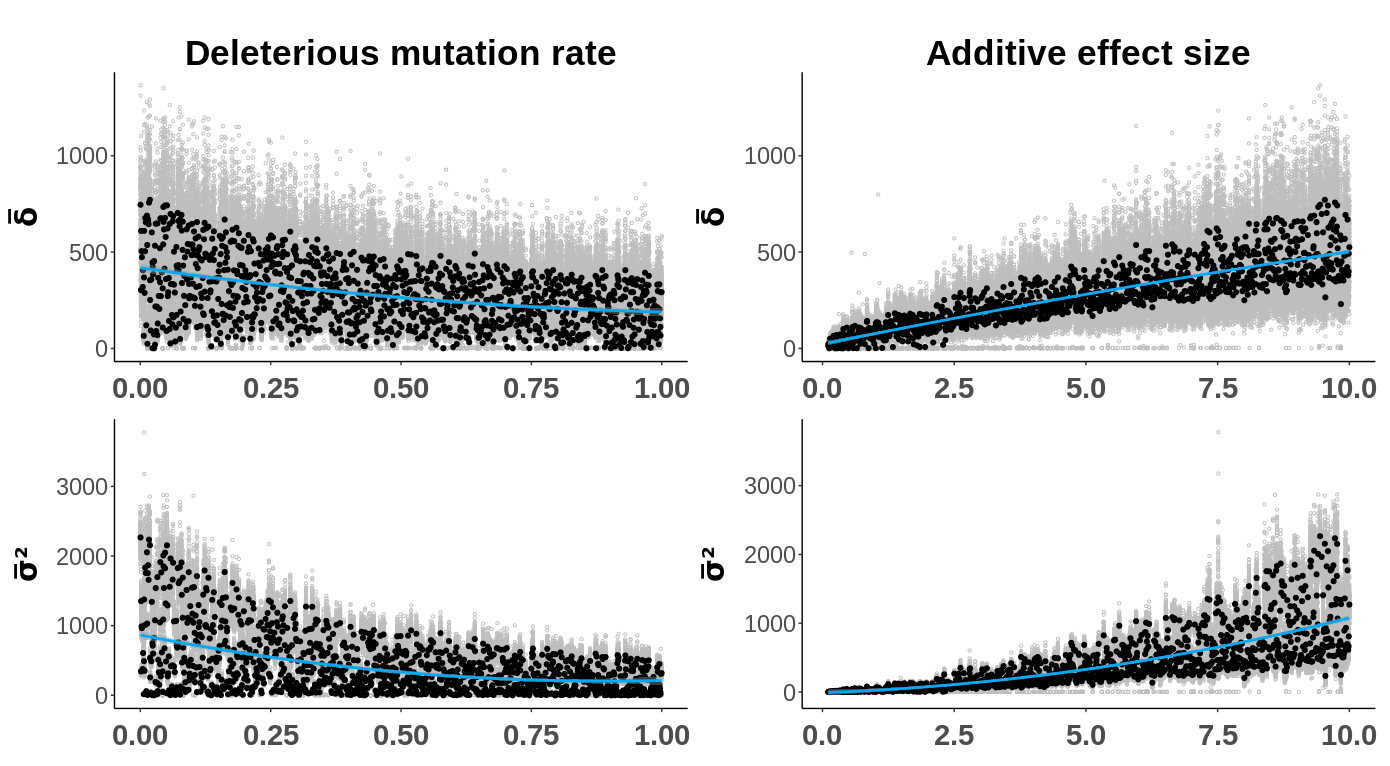


Figure 3: Euclidean distances from the optimum () and mean trait variances () with increasing deleterious mutation rate (A) and additive effect sizes (B). Black dots indicate mean distances/trait variances of 100 replicates, grey dots indicate raw data.

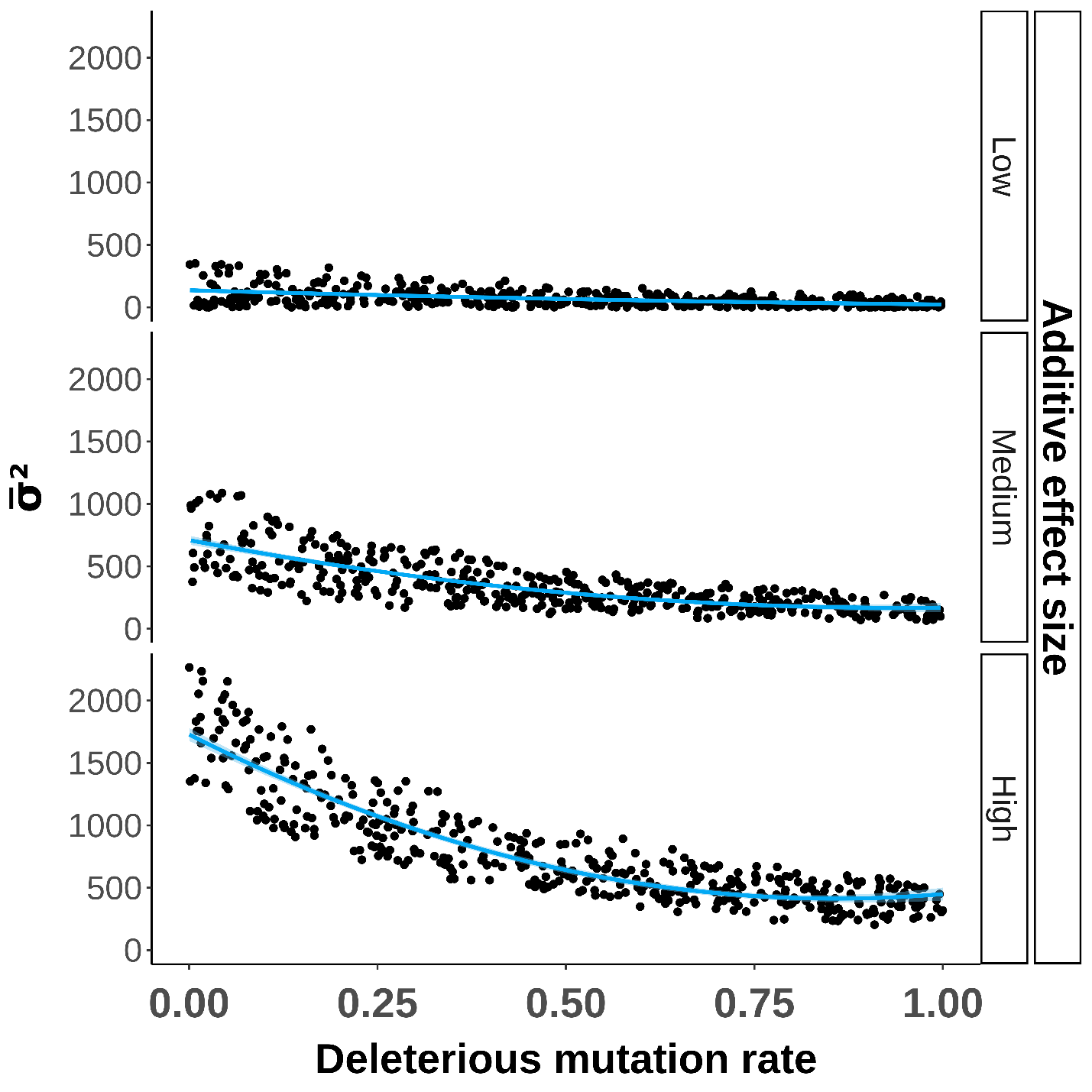


Figure 4: Mean trait variance with increasing deleterious mutation rate and additive effect size. Taken across null and selection models, for a total of 1280 means of n = 100 replicates.

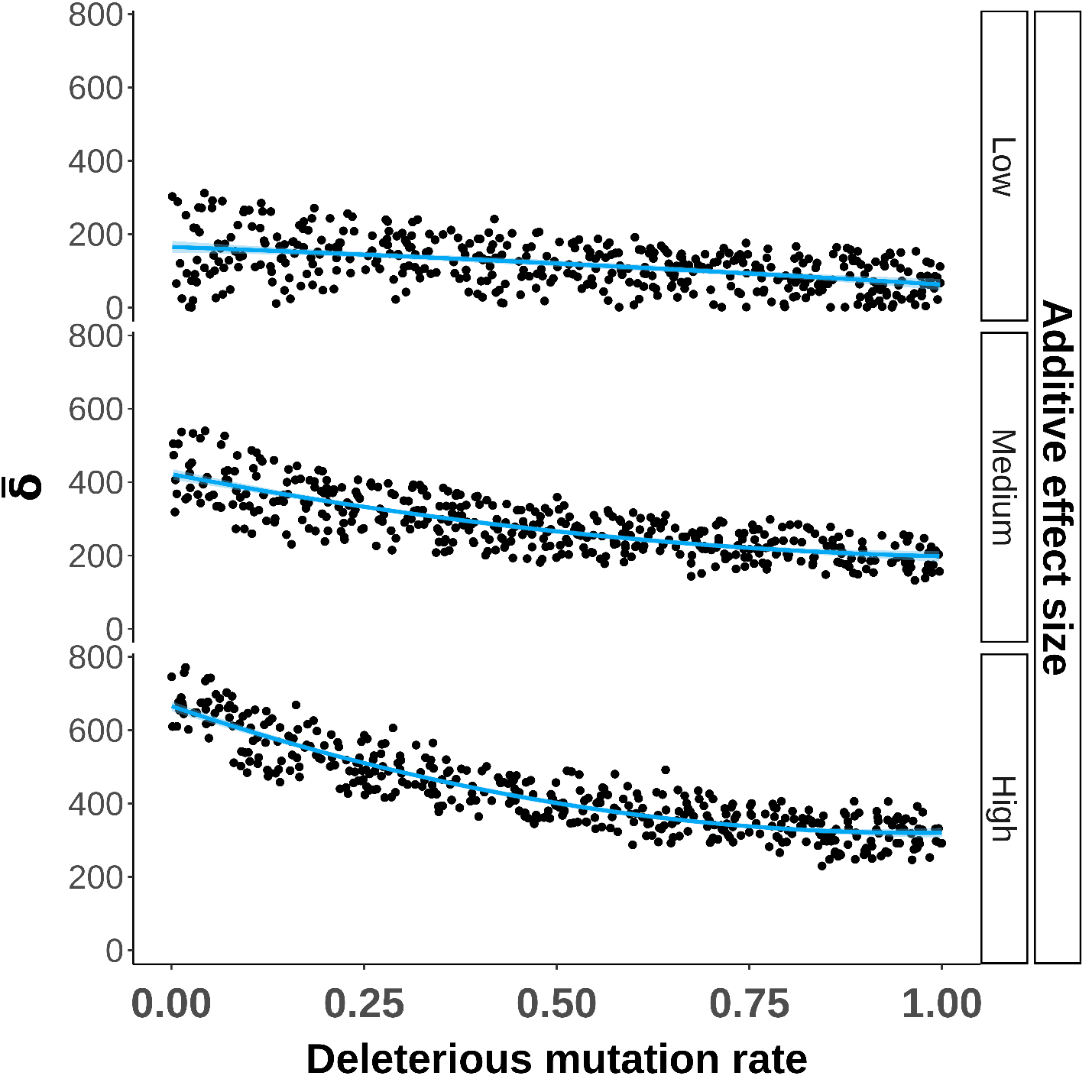


Figure 5: Mean Euclidean distance from the optimum with increasing deleterious mutation rate and additive effect size. Lower values indicate better ability of the population to maintain position at the optimum. Taken across null and selection models, for a total of 1280 means of n = 100 replicates.

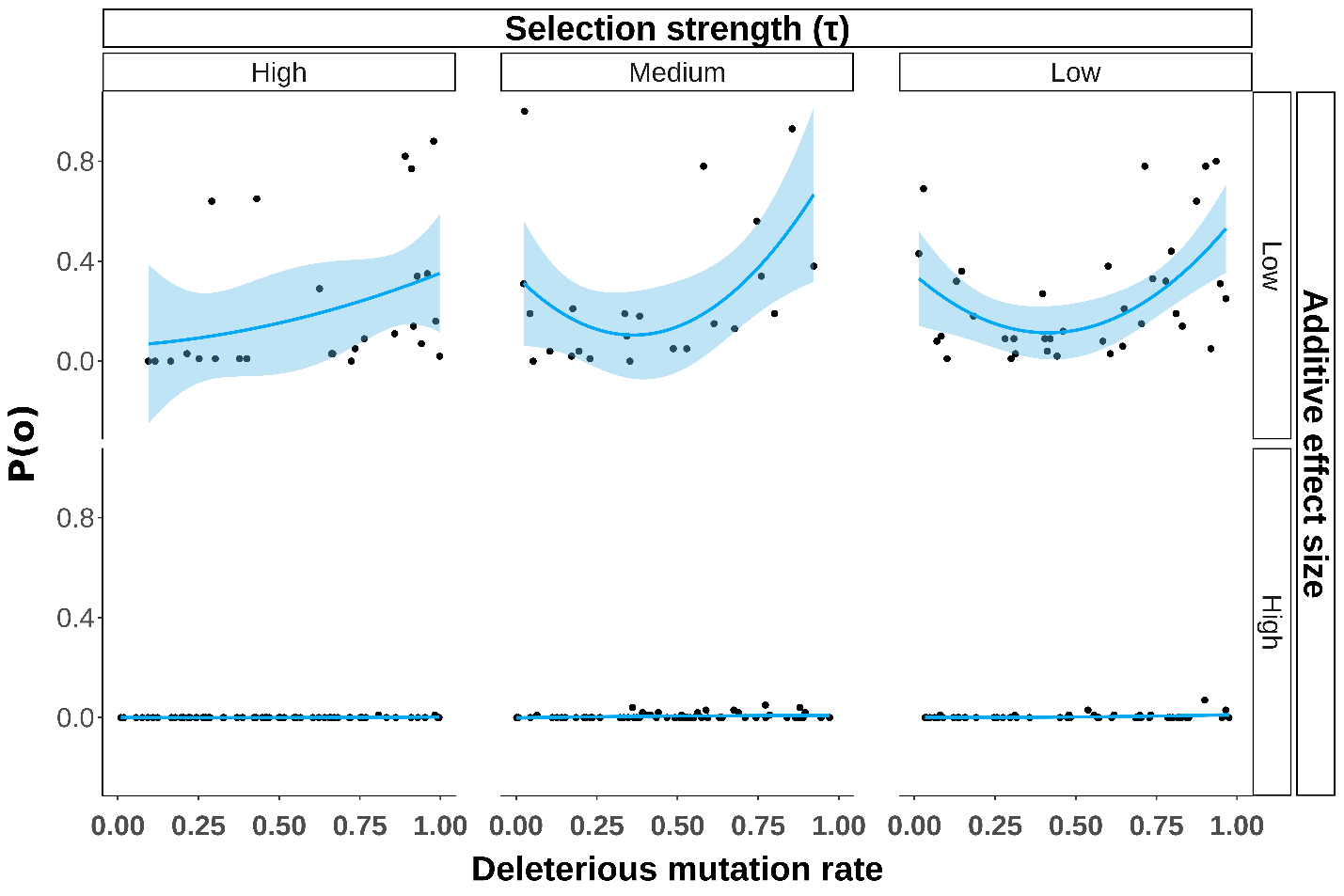
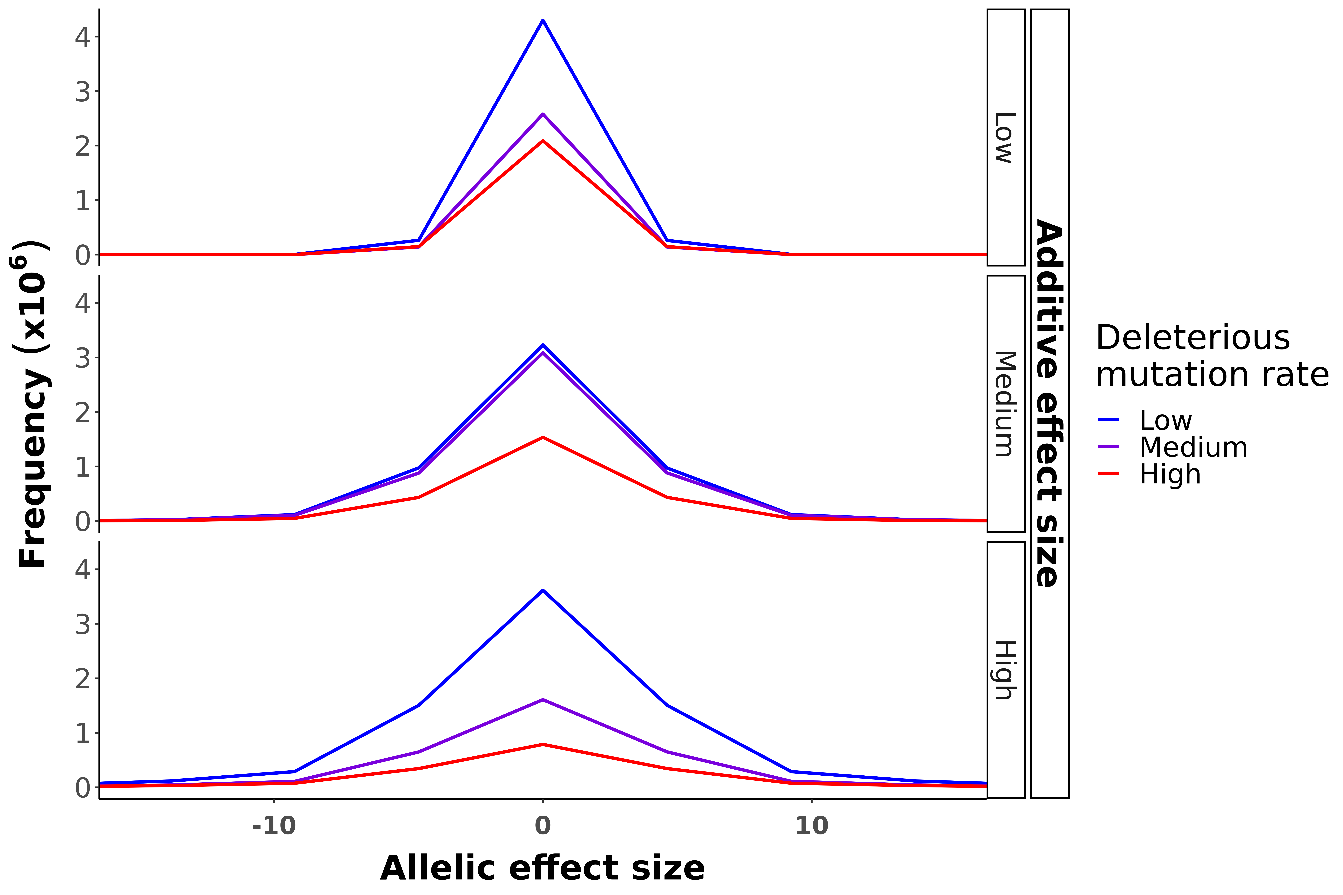


Figure 6: Probability of reaching the optimum with increasing deleterious mutation rate, additive effect size, and selection strength (. Dots represent means of 100 replicates, with 256 dots representing the total sample space.



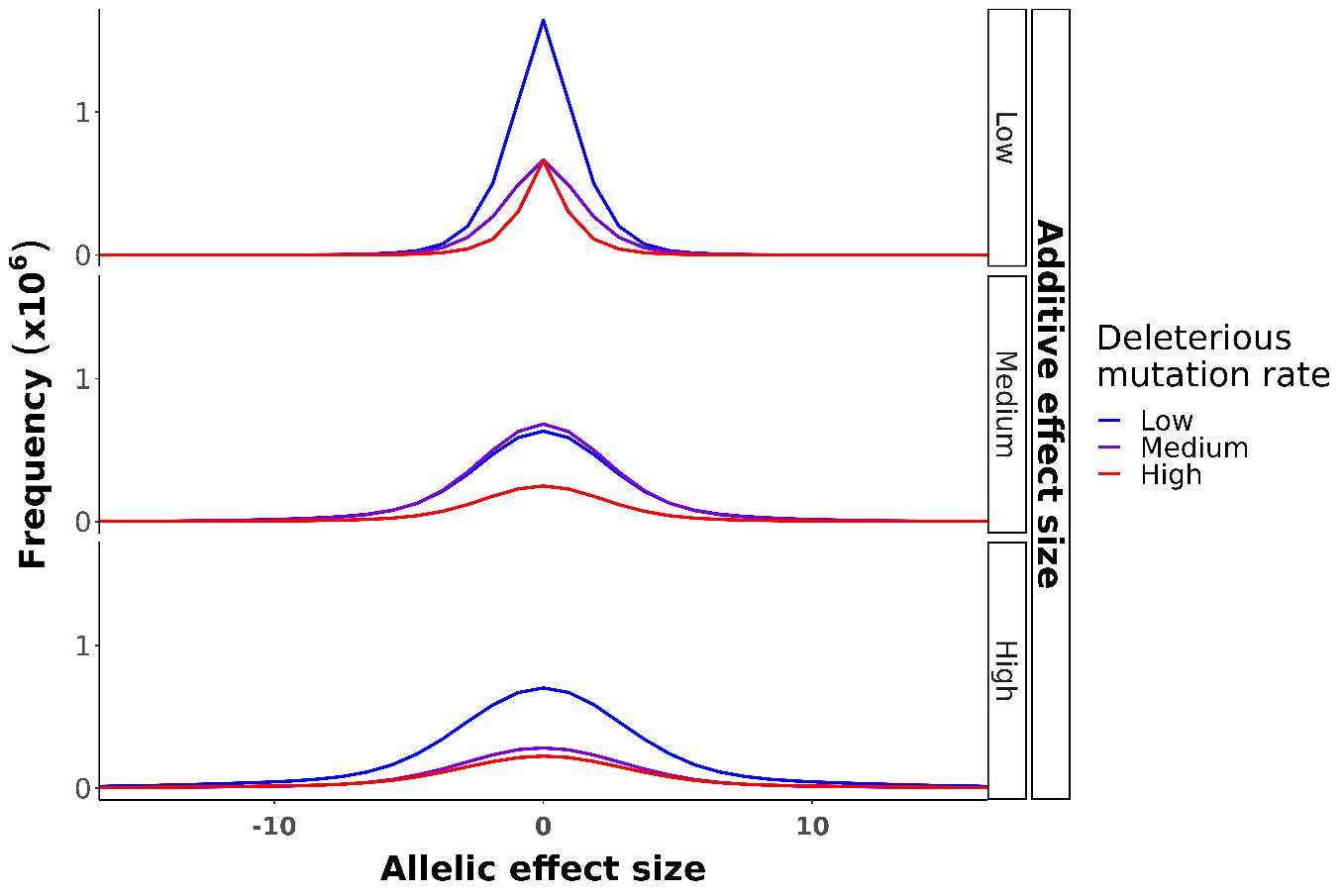
Figure 7: Frequency distribution of mutational effect sizes at generation 100,000 under no selection (A) and stabilizing selection (B), with deleterious mutation rate and additive effect size. Both figures represent mean distributions of 100 replicates of 256 models. 256 of the 1024 null models were randomly sampled to calculate these means.

Table 1: Model parameters for both null and stabilizing selection models. The range of values is based on literature, but values are adjusted to be practical for the time of the experiment.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Symbol | Range | Description | Source(s) |
| Genome wide recombination rate | r | 0 to 1.241x10-4 per locus | The singular recombination rate used across the entire simulated genome. | Stapley et al. 2017 |
| Background selection rate | δ | 0 to 1 | The number of non-trait, deleterious mutations that occur relative to trait mutations. |  |
| Rate of universal pleiotropy | ϖ | 0 to 0.5 | The proportion of trait mutations that affect all traits rather than a single trait. While 100 loci control a trait independently by default, this may be changed by this parameter. However ratios of loci affecting each trait will remain constant, especially across multiple replicates. | Chesmore et al. 2017; |
| Mutational pleiotropic correlation | m | 0 to 0.5 | The mutational correlation between additive effects of pleiotropic mutations determines the similarity of trait effects between traits for the same pleiotropic mutation. |  |
| Additive effect size | λ | 0.1 to 10 | Additive effect size controls the variance of trait effect size around mean 0, so that N(0, λ). | Albert et al. 2008; |
| Selection strength (selection model only) |  | 10 to 10000 | The parameter that controls the curve of the fitness function (eq. 3), with higher values resulting in a smaller difference in fitness between trait-differing individuals. |  |

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