# Introduction

Quantitative genetics aims to quantify genetic diversity; this diversity has broad implications for adaptation, it is well described how diversity enhances efficiency of adaptation; adaptation with more Va = faster, more efficient; particularly seen in the case of quantitative genetics, where stabilizing selection is often assumed; different story with the maintenance of variation around a fitness optimum, i.e. after the adaptive walk what happens?; several models have appeared over the last 50 years to explain the maintenance of variation; continuum of alleles vs diallelic; within continuum of alleles, the approximate distribution of allelic effects depends on the relative mutation rate to selection strength; in other words, the strength of new mutations to standing genetic variation; models over the last 50 years have failed to explain natural diversity observed in populations;

The ubiquity of adaptation in evolutionary studies is telling of the impact of Darwin’s seminal work. Over 4600 papers featuring the keyword ‘adaptation’ were published in Nature research journals in 2019. The allure of adaptation comes from the power of Darwin’s theory to explain natural diversity both within and between populations (Brady *et al.* 2019). Yet explanations of diversity via Darwin’s theory have been misinterpreted before – prior to Williams publishing his thesis (1966), the theory of ‘group adaptation’, whereby adaptation is driven by altruistic mutations that benefit populations at the cost of the individual gene, was commonplace and well-regarded. The focus on adaptive traits, and the ability of populations to adapt to new situations is wonderfully intuitive, however, populations are never perfectly adapted: trait values are rarely optimal, populations decline, and extinctions are commonplace (Brady *et al.* 2019). The extent of maladaptation, where populations are stable at some distance from a fitness optimum, seems wide, however the extent of maladaptation is rarely discussed (Nesse 2005). The keyword ‘maladaptation’ was mentioned in just 45 papers in Nature research journals published in 2019, yet it is expected to .

**Evidence for stab sel: in gene regulation, Hodgins-Davis et al – this paper, also m/s/d balance for quant gen models;**

The extent of maladaptation in natural populations has been debated for some time – are populations likely to be restricted in their fit to a phenotypic optimum? Is such an optimum attainable for populations, or is there more likely to be local, stable optima that are difficult to escape?

Much of the variation between and within populations is the result of continuous variability in traits individuals in those populations possess. Differences in such quantitative traits lead to adaptation and speciation. Underpinning adaptation by quantitative traits is additive genetic variance (VA), the heritable component of variation; the amount of which has mystified quantitative geneticists for close to 100 years. Predicting levels VA is reliant on mutation rate and selection strength: both of which are notoriously difficult to estimate in natural populations. Many quantitative traits are subject to stabilizing selection, where intermediate trait values have maximum fitness. Theory suggests that adaptation via stabilizing selection should be more efficient with higher standing VA, and that the selective fixation of this standing variation should decrease VA as adaptation takes place (Fisher 1930; Lande 1975). However, these expectations have not always coincided with observed data.

Depletion of VA with stabilizing selection has been shown both experimentally , and analytically, however increasing amounts of more modern work show no effect of selection strength on VA. Sztepancz and Blows (2017) showed that there was no relationship between genetic variation and the strength of stabilizing selection in *Drosophila serrata­­­.* More modern analysis of Fisher’s (1930) geometric model (upon which stabilizing selection is built) has shown that when the individual effect of selection in alleles is weak, stabilizing selection has a minimal effect on VA, as drift at any individual locus may compete with selection to adjust allele frequencies (Barton 2017). Discrepancies such as these can perhaps be explained by the relative effect of stabilizing selection, depending on where a population is relative to the optimum. When populations are far from the optimum, mutations act under a directional selection model, where larger mutations that bring an individual closer to the optimum are more beneficial (Zhang 2012). However, as populations approach that optimum, large effect mutations become costly as they are more likely to drag populations further away from the optimum.

Barton 2017: selection negligible when individual allles is weak and comparable to drift

Thornton 2019: when phenotypes approach optimum, strength of selection on indivual muts decreases effect on Va under infinitesimal model, selection gets more info when selection on

Zhang 2012: when phenotypes near optimum, selection is stab, while far away, closer to dir sel

Sztep: dir sel more common in nature? Populations more commonly maladapted?

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 additive effect size distribution, the rate of universal pleiotropy, mutational correlation between traits, and the selection strength multiplier, (Table 1). The relative rate of non-QTL, deleterious mutation compared to trait mutations was also varied across models. This parameter led to two alternate outcomes that could influence variation and adaptation: either the reduction in QTL mutation rate due to increasing deleterious mutation rate could cause observed differences, or the effect of the deleterious mutations on fitness could be attributed to the differences. Preliminary analyses indicated that the ratio of QTL mutations to deleterious mutations remained constant across increasing levels of this parameter (Figure S3). This suggests that a similar deleterious load was experienced across populations, and that the effects of increasing this rate were attributable to changes in QTL mutation rate rather than the deleterious effects of non-QTL mutations. The highest QTL mutation rates were experienced by models with low rates of deleterious mutation, and vice versa. Thus, models with high mutation rate and low selection strength (deleterious mutation rate < 0.33; > 660) approximated the Kimura-Fleming-Lande Gaussian approximation of allelic effects (Kimura 1965; Lande 1975; Fleming 1979), while models with low mutation rates and high selection strength approximated Turelli’s (1984) House-of-Cards model. Among all parameter combinations, multiple conditions and assumptions were 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. Populations were assumed to be completely allopatric. Populations first were subject to 50,000 generations of burn-in to build standing variation to mutation-drift balance (figure S1). Individuals were characterized by 8 traits, controlled by 100 loci each. Each trait had an identical effect on fitness, forming a ‘mega-trait’ with varying variance-covariance structures depending on pleiotropy rates. Each locus was assumed to have identical length, and each base pair within it mutationally independent – hence mutations occurred at an arbitrary position within the locus. This assumption is 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), lending credence to the assumption of equal gene length. Mutations were assumed to be completely additive in effect, with no dominance or epistatic interactions, aside from additive epistasis occurring as a result of the fitness function. All loci were assumed to be on the same chromosome, with genetic distance being determined by the recombination rate parameter, r (Table 1). Both models had 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 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:

Where and (SLiM Manual). This describes a distribution of 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 of burn-in was sufficient for our population size (Figure S1). Deleterious mutation/mutation rate lowered the value of away from expectation in initial burn-in tests, however an alternative equilibrium was reached, satisfying the requirements of burn-in regardless of the parameter (Figure S1). During the simulation run, trait variances, covariances, and trait means were collected every 500 generations to track distances from the optimum and trait variability over time. At the end of the simulation, the allelic effects of segregating mutations in all populations were collected.

## 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, 8.045x10-6, 100, and . This distance was close to the original phenotypes, meaning most of the simulation (approximately 98000 generations of the simulation) investigated the maintenance of variation at a fitness optimum.

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

Where s is the selection coefficient, represents the gradient of the selection curve, n is the number of traits, and xn is the phenotype for trait n. To ensure a theoretical minimum and maximum fitness, s was fixed at 0.9, ensuring minimum fitness was , 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. The model-specific maximum fitness difference depends on, which adjusts the realized fitness gradient via the curvature of the fitness function.

## 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 (Figure S1). The hypercube sampling was necessary to explore the entire parameter space, as simple factorial designs would have been impractical to achieve. Each hypercube sample represents a combination of parameters, with the total set of samples designed to maximize the distance between samples (sampling more of the total space), and minimize correlations between them (Helton and Davis 2003). Hypercube 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 sample/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) (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 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). In terms of regression analysis, heteroscedasticity can still remain a problem, even with large sample sizes. To account for this, we used Eicker-Huber-White (EHW) HC2 or HC3 robust standard errors in our linear regression models via the ‘estimatr’ package in R (Eicker 1967; Huber 1967; White 1980; Blair 2020) (HAYES CAI 2007).

For analysis, the interaction between and mutation rate was treated as a ‘model’ parameter, indicating whether the hypercube sample approximated House-of-Cards allelic effects, or Gaussian effects. An additional model type, ‘Null’, summarized the models with no selection and any mutation rate. Remaining models with intermediate selection strengths and deleterious mutation rates were not considered for analysis, although that remains an exciting prospect for the future. Additive effect size, recombination rate, pleiotropy rate, and mutational correlation hypercube values were binned into low, medium, and high categories for simpler analysis.

We compared responses at the final generation of the simulation (100,000) across all analyses. 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*.

To determine the effects of CoA model on adaptation, we explored the distribution of final distances from the optimum, finding a distinct ‘dead zone’ where distances were not represented. We used this dead zone to classify models into two categories: adapted, or maladapted. Adapted models had distances from the optimum less than 16 units, and maladapted with distances greater than 16 units. We used a Chi-square test followed by an odds-ratio post-hoc to determine the differences in representation among CoA models in adapted and maladapted categories. Following this, we discarded maladapted populations, choosing to focus on investigating the genetic architectures underlying adapted populations.

To evaluate the effects of genetic architecture on adaptation under the CoA models, we used EHW-error multiple regression models to determine the effects of CoA model type, additive effect size, recombination rate, pleiotropy rate, and mutational correlations between traits on distance from the optimum, additive variance, and trait covariances.

I also collected the mutational effects of segregating alleles at the end of the simulation. With this, I compared mean distributions of allelic effect sizes in adapted populations according to additive effect size with multivariate multiple regression. Responses included mean allelic effect, variance, and kurtosis of the distribution, as well as the mutation counts contributing to VA within each model. I adjusted for heteroskedasticity with EHW robust standard errors. Multiple regressions were calculated across 50 replicates owing to RAM limitations.

# Results

## Tracking population dynamics over time

To determine the dynamics of the model under selection, we plotted variance and distance to the optimum over time across selection strengths. By generation 100,000, models have not yet reached mutation-selection-drift equilibrium, as variance continues to increase, however trajectories approach stability. Mean variance was consistently greatest over time under a Gaussian model, with House-of-Cards models maintaining variance lower than Null and Gaussian models (Figure 3A). Covariance acted similarly: under Gaussian allelic effects, covariance was greatest, and vice versa for House-of-Cards models (Figure 3B). Mean additive variance remains stable after generation 50,000 across all selection strengths. Covariance reaches an equilibrium with more sizeable fluctuations (Figure 3B). Knowing that by generation 100,000 we are at mutation-selection-drift equilibrium, we can investigate whether specific models have been more successful in allowing populations to reach the optimum.

## Patterns of adaptation with Continuum of Alleles models

Knowing that by generation 100,000 populations had reached mutation-selection-drift equilibrium, we explored the distribution of distances around the optimum given CoA model type (Fig. 4A). We found a bimodality within selection models that was not present in null models: both Gaussian and House-of-Cards models showed a small proportion of populations that came within 16 units from the optimum, with a visible division between adapted and maladapted populations (Fig. 4). Adapted populations encompassed 0 to 16 units from the optimum, before a ‘dead space’ from this point separated these populations from more maladapted models. To further explore this, we used a Chi-square test to analyze the differences between models in the ability to reach this ‘adapted’ versus ‘maladapted’ space. Populations were more likely to belong to the adapted zone if they belonged to either selection model over the null model (χ2 = 9602.1, df = 2, p < 0.0001). 15.23% of Gaussian populations reached the adapted space, while House-of-Cards populations reached this 16.1% of the time. By contrast, 0.53% of null populations reached the adapted space. A post-hoc odds ratio test found significant differences between null and Gaussian (OR = 33.566, 95% C.I. = 29.5, 38.2, p < 0.0001) and null and House-of-Cards (OR = 35.872, 95% C.I. = 31.5, 40.85, p < 0.0001), but not between Gaussian and House-of-Cards (OR = 1.069, 95% C.I. = 0.93, 1.23, p = 0.35). To understand the underlying genetic architectures of these populations that were able to come so close to the optimum, we compared the effects of genetic architecture and the CoA model on distance to the optimum (Fig. 5), mean trait variance (Fig. 6), and mean trait covariance (Fig. 7).

We compared the effects of increasing additive effect sizes, recombination rates, pleiotropy rates, and mutational correlations on Euclidean distances of ‘adapted’ populations under Gaussian or House-of-Cards mutational models. All parameters had significant effects on distance, however many effects were small (F17, 921 = 745.2, p < 0.0001, Adjusted R2 = 0.233). For brevity, only the most important predictors for distance from the optimum (as well as variance and covariance) will be discussed in detail. The mean distance from the optimum for Gaussian and House-of-Cards models was not significantly different, with both around 1.75 units away (t921 = 0.118, p = 0.906). Mean distance from the optimum was lowest when effect sizes were low (0.841 ± 0.181; Fig. 4A); this did not change between CoA models (t921 = -0.422, p = 0.998). However, House-of-Cards models were more robust to changes in additive effect size than Gaussian models (t921 = -2.583, p = 0.01). When increasing effect size from low to high under a Gaussian mutation model, adapted populations’ mean distance from the optimum increased by 2.203 ± 0.232 units (t921 = -9.504, p < 0.0001). The same change in effect size under a House-of-Cards model resulted in no significant change to mean distance (t921 = -0.587, p = 0.827). Recombination had a weak effect on distance under the Gaussian model, increasing distance with increasing recombination (t921 = -3.185, p = 0.0043; Fig. 4B). This effect was insignificantly stronger under House-of-Cards (t921 = 1.955, p = 0.051), increasing distance from the optimum by 1.115 ± 0.262 units (t921 = -4.248, p = 0.0001). Pleiotropy rate also had an effect on distance, however there was no interaction between pleiotropy and model type (t921 = 0.843, p = 0.399; Fig. 4C). Increasing pleiotropy rate from low to high led to an average 1.261 ± 0.178 unit decrease in distance from the optimum (t921 = 7.099, p < 0.0001). Mutational correlations between traits also had weak effects under a Gaussian model, on average increasing distance from the optimum (t921 = -2.973, p = 0.0085; Fig. 4D). This effect was weaker under House-of-Cards (t921 = -2.336, p = 0.02), with a marginally insignificant increase in distance with mutational correlation (t921 = -2.268, p = 0.061). These effects on distance were not necessarily mirrored with the effects of genetic architecture on trait variance.

On average, House-of-Cards models near the optimum had considerably more additive variance than Gaussian models (40.4 ± 18.72 units vs 2.6 ± 0.07 units; t921 = -2.019, p = 0.044). Under a Gaussian model, increasing the additive effect size of populations in the adapted zone marginally increased trait variance (t921 = -14.386, p < 0.0001; Fig. 5A), however this was not the case under a House-of-Cards model (t921 = -1.958, p = 0.123). Similar increases in trait variance under Gaussian models were seen for increasing recombination from low to high (t921 = -10.895, p < 0.0001; Fig. 5B), with no effect under a House-of-Cards model (t921 = 0.073, p = 0.997). Pleiotropy rate marginally decreased trait variance under a Gaussian model (t921 = 8.095, p < 0.0001; Fig. 5C), with no change under House-of-Cards (t921 = 0.706, p = 0.76). Mutational correlations had no effect on additive variance under House-of-Cards models (t921 = -0.456, p = 0.892; Fig. 5D). Under Gaussian models, increasing mutational correlation from medium to high contributed a small decrease in variance (t921 = 3.153, p = 0.005). Trait covariance was similarly stagnant across models.

Average trait covariance differed between models (t921 = 2.147, p = 0.032; Fig. 6), with Gaussian models covarying very little (0.014 ± 0.005), and House-of-Cards models covarying slightly more (-3.616 ± 1.691). Similar robustness against covariance changes was seen in House-of-Cards models, with Gaussian models being more susceptible to slight changes in covariance. Increasing additive effect size from low to high in Gaussian models led to slight declines in covariance (a decrease of 0.039 ± 0.005; t921 = 7.526, p < 0.0001; Fig. 6A). No significant effect of increasing additive effect size on covariance was seen in House-of-Cards models (t921 = 1.937, p = 0.129). The difference in response to additive effect size between models was marginally insignificant (t921 = -1.929, p = 0.054). Recombination had no effect on covariance across both types of models (t921 = -0.942, p = 0.614; Fig. 6B). Both pleiotropy rate (Fig. 6C) and mutational correlation (Fig. 6D) showed similar patterns to additive effect size on covariance: slight increases in covariance under a Gaussian model (pleiotropy rate: t921 = -2.893, p = 0.011; mutational correlation: t921 = -3.453, p = 0.002), and no change under House-of-Cards (pleiotropy rate: t921 = -0.7, p = 0.763; mutational correlation: t921 = 0.919, p = 0.628).

From these analyses, it became obvious that additive variance and covariance were rather robust under House-of-Cards models, and less so under Gaussian models. Additive effect size in particular seemed important to understanding the interplay between adaptation and VA. To analyze the underlying cause of these variances, covariances, and by extension, distances, the underlying allelic effect size distributions are needed. We compared the means, variances, kurtosis, and count of mutations contributing to these distributions across models to understand the mutational limitations imposed by genetic architectures under the two CoA models.

To assess the mutational bias of models, we first compared the means of distributions across models and genetic architectures. The resulting regression was insignificant (F17, 411 = 1.127, p = 0.325, Adjusted R2 = 0.189), indicating a lack of directional mutational bias. We then turned our attention to the variance of distributions to understand the constraints that genetic architectures may apply to mutational models (F17, 411 = 55.04, p < 0.0001, Adjusted R2 = 0.851). Average variances across models were 9.77 ± 5.28 units for Gaussian and 12.64 ± 5.47 units for House-of-Cards models. The difference between these was not significant (t411 = -0.377, p = 0.706). Under a Gaussian model, increasing additive effect size from low to medium significantly increased allelic effect variance by 6.02 ± 0.372 units (t411 = -16.188, p < 0.0001; Fig. 8), however no significant difference occurred for increasing variance from low to high or from medium to high. No significant changes to variance with increasing effect size were seen under House-of-Cards models. Recombination had no effect on allelic effect variance, regardless of model type (t411 = 2.195, p = 0.073). Under a Gaussian mutation model, increasing pleiotropy rate from low to medium increased allelic variance by 2.517 ± 0.744 units (t411 = -3.383, p = 0.0023). Increasing pleiotropy rate further from medium to high resulted in a decrease in variance of 1.781 ± 0.353 units (t411 = -5.039, p < 0.0001). Under a House-of-Cards model, any change in pleiotropy rate decreased variance: an increase in pleiotropy rate from low to high resulted in 3.005 ± 0.740 units less variance (t411 = -4.061, p = 0.0002). These model-specific responses to increasing pleiotropy rate were statistically significant (t411 = -5.262, p < 0.0001). Increasing mutational correlations from high to low decreased variance under a Gaussian model by 3.554 ± 0.526 units (t411 = -6.758, p < 0.0001). There were no significant effects of mutational correlation on allelic variance under a House-of-Cards model.

A third aspect of allelic effect distributions is their kurtosis – the area of a density function encompassed by its tails. We compared kurtosis across models and genetic architectures with another multiple regression to investigate the rarity of rare alleles relative to common alleles (F17, 411 = 12.36, p < 0.0001, Adjusted R2 = 0.6). Averaging across genetic architectures, both models had similar mean kurtosis – 5.44 ± 2.29 for Gaussian models and 5.47 ± 1.59 for House-of-Cards models. These were not significantly different (t411 = -0.011, p = 0.991). Under the Gaussian model, increasing additive effect size from low to medium increased kurtosis by 0.985 ± 0.159 (t411 = -6.206, p < 0.0001). No analogous effect was seen under the House-of-Cards model (t411 = -0.944, p = 0.6130). Recombination had no significant effect on kurtosis across either model. Increasing pleiotropy rate from low to medium increased kurtosis by 0.854 ± 0.342 (t411 = -2.497, p = 0.035). Again, House-of-Cards models were robust to changes in pleiotropy rate, showing no change in kurtosis. Increasing mutation correlation from low to high decreased kurtosis by a small amount under House-of-Cards models (t411 = -3.262, p = 0.003), however no such effect was seen under Gaussian models.

The number of segregating mutations at any one time gives an indicator of the genetic diversity of populations. To assess the effects of genetic architecture and models on promoting many or few alleles, we compared mutation counts between models (F17, 411 = 580.2, p < 0.0001, Adjusted R2 = 0.94). The mean number of mutations in Gaussian models was considerably higher than that of House-of-Cards models, but this came with a large standard error that made differences non-significant: 1516 ± 6608 mutations for Gaussian models versus 374 ± 114 for House-of-Cards (t411 = 0.173, p = 0.863). Increasing additive effect size from low to medium decreased the number of mutations seen in Gaussian populations by 959.8 ± 192 (t411 = 5.001, p < 0.0001). No such change was seen in House-of-Cards populations (t411 = 0.458, p = 0.891). Under both Gaussian and House-of-Cards models, recombination increased the number of segregating mutations (Gaussian: 355.2 ± 144.4, t411 = 2.459, p = 0.038; House-of-Cards: 109.1 ± 25.8, t411 = 4.231, p = 0.0001). There was no significant difference between models in their response to recombination (t411 = -1.677, p = 0.094). In Gaussian populations, increasing pleiotropy rate from medium to high increased the number of segregating mutations by 964.4 ± 256.1 (t411 = 3.766, p = 0.0006). Under House-of-Cards models, we observed a similar response: the number of mutations increased by 322.4 ± 21.6 (t411 = 14.926, p < 0.0001). Finally, when mutational correlations were increased from low to high, Gaussian models responded with increased numbers of mutations (an increase of 1646.1 ± 367.1; t411 = 4.484, p < 0.0001), whereas House-of-Cards models were insensitive to the same change in mutational correlation.

# Discussion

Truly adapted ones – at distance = 0

Really rare to be close under null

At the optimum (Po = 1), the Gaus and HoC are not like Null

This is the power of pop gen models – get to see these allele frequencies, the whole spectrum

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).

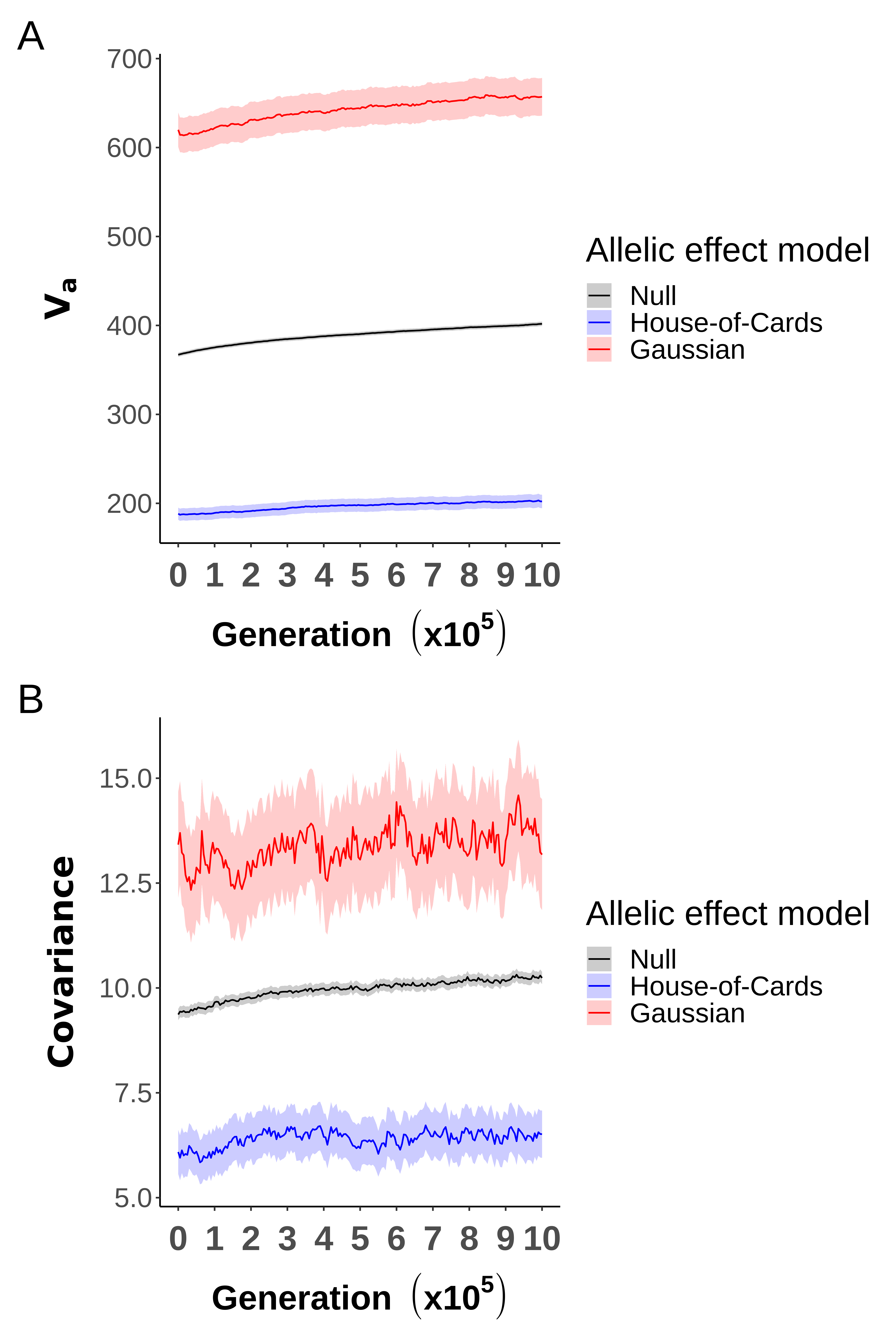


Figure 3 – Mean additive variance (VA; panel A) and mean between-trait covariance (B) over 100,000 generations of stabilizing selection of different strengths (). 256 total models were sampled across the spectrum of selection strengths () with an additional 1024 models sampling the null space of parameters ().

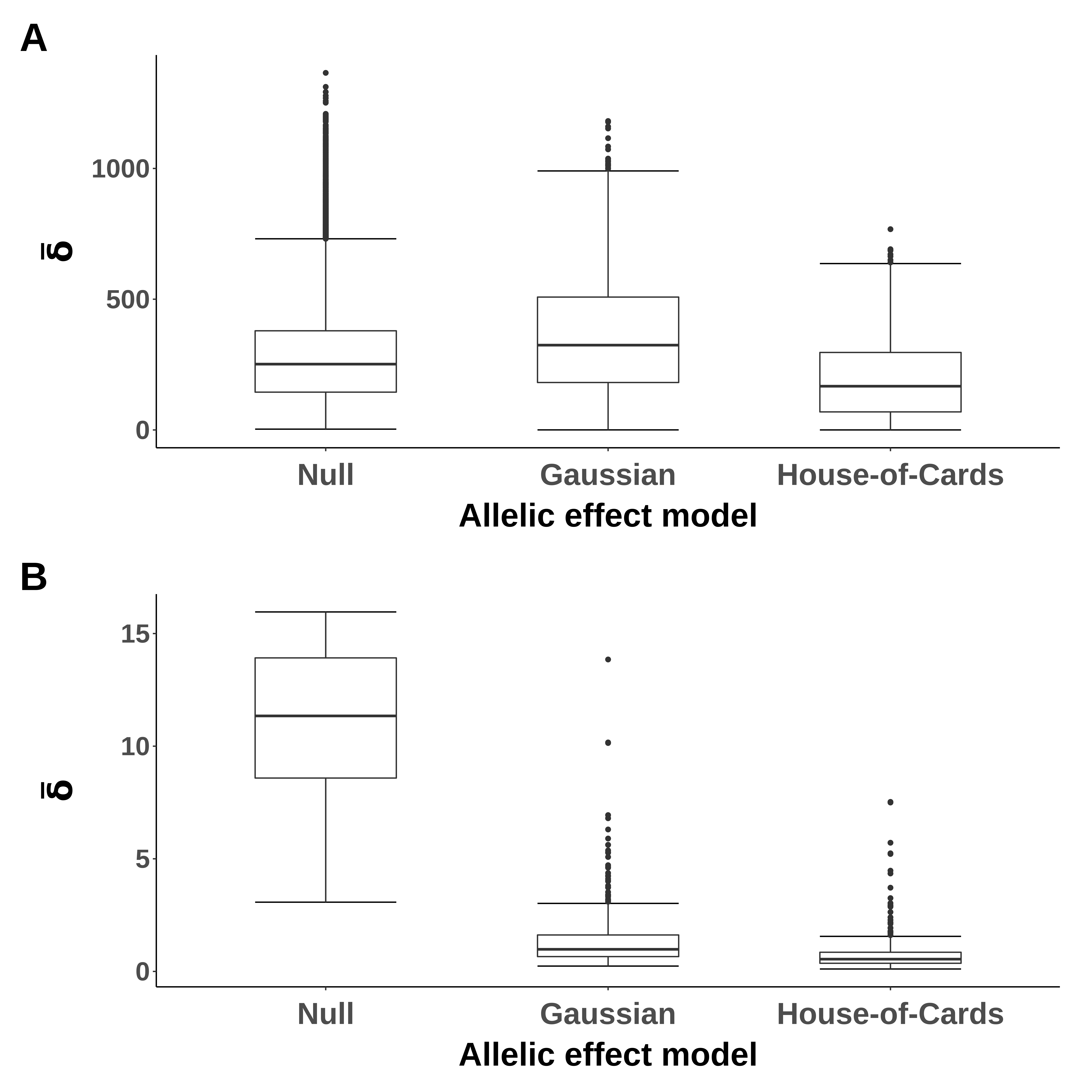


Figure 4: Euclidean distances from the optimum over models. (A): total distributions of all models. (B): distributions of ‘adapted’ models with small distance to the optimum.

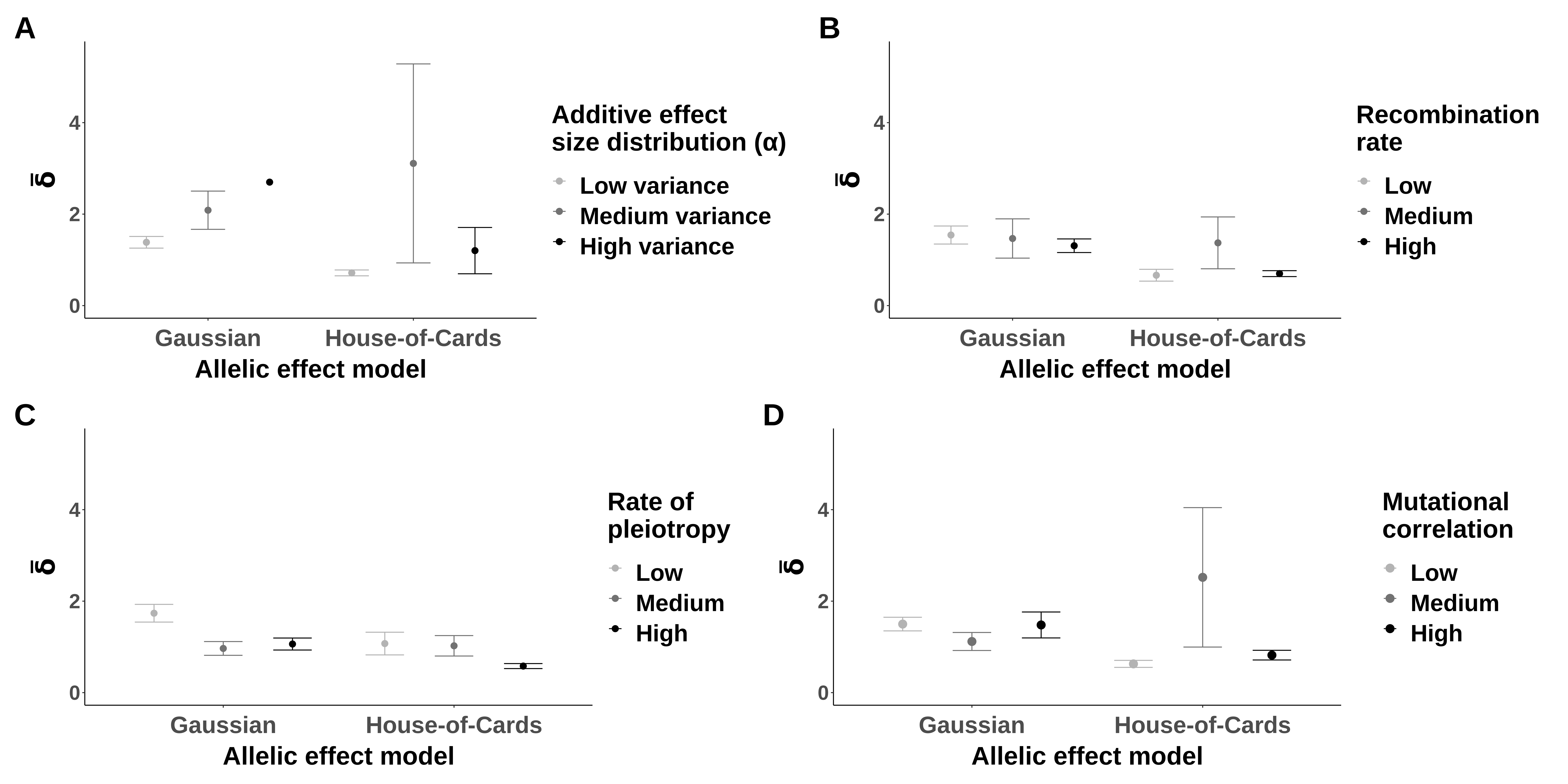


Figure 5: Euclidean distances from the optimum () among adapted populations with increasing additive effect size (A), per-locus recombination rate (B), pleiotropy (C), and mutational correlations (D). Note that there was only one adapted Gaussian population with high additive effect size as shown in (A).

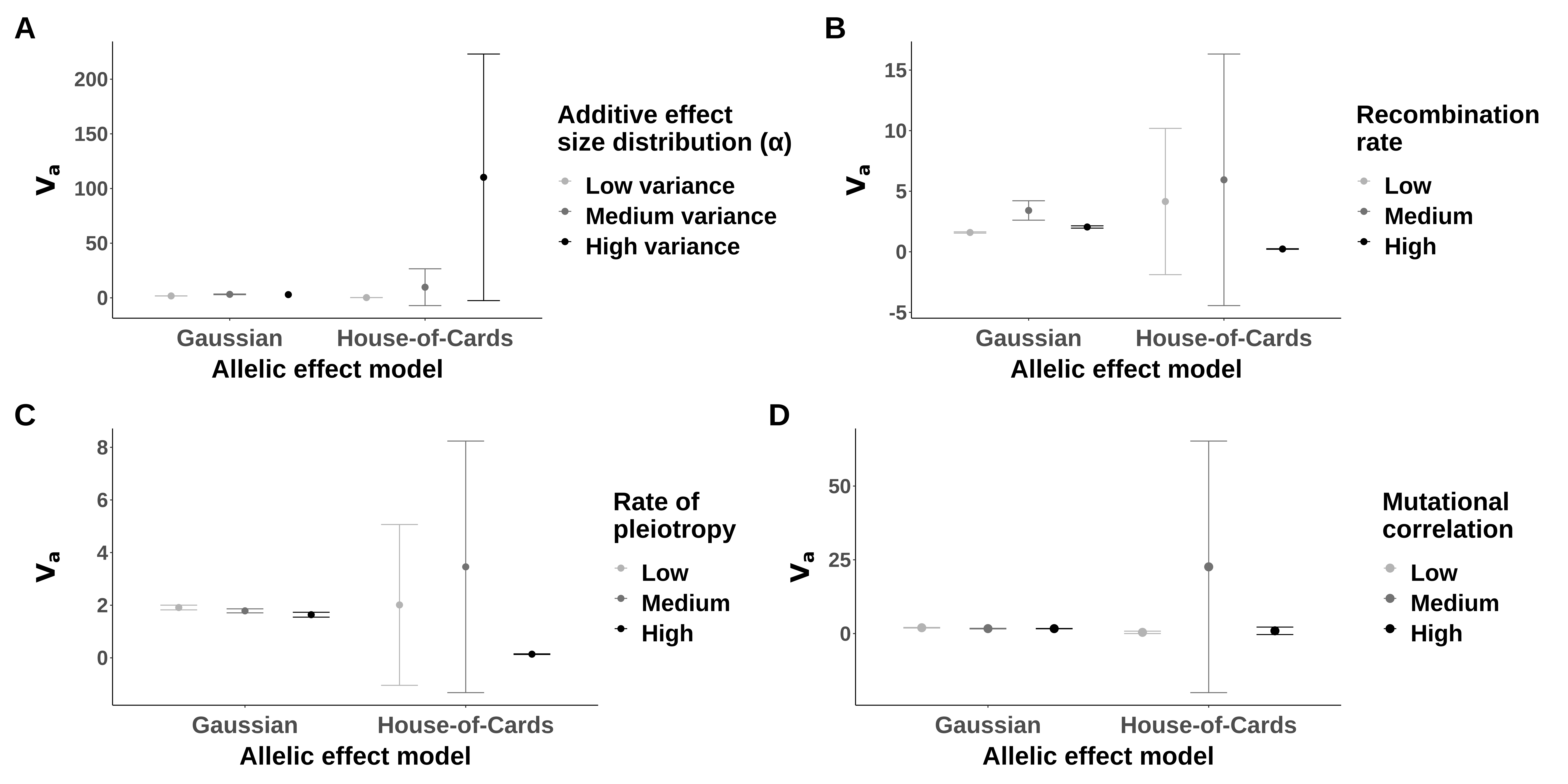


Figure 6: Mean additive variance (VA) among adapted populations with increasing additive effect size (A), per-locus recombination rate (B), pleiotropy (C), and mutational correlations (D). Note that there was only one adapted Gaussian population with high additive effect size as shown in (A).

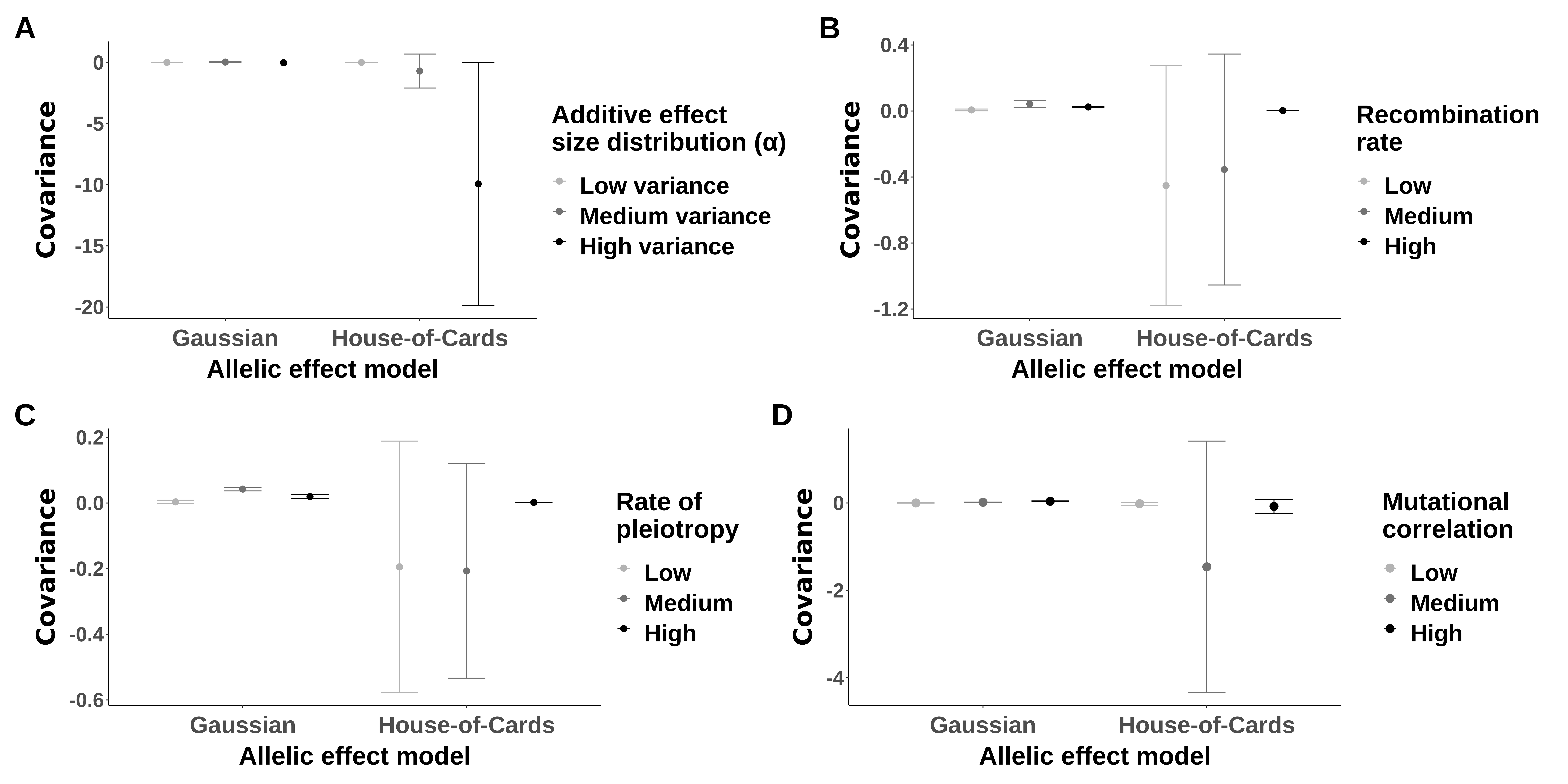


Figure 7: Mean trait covariance among adapted populations with increasing additive effect size (A), per-locus recombination rate (B), pleiotropy (C), and mutational correlations (D). Note that there was only one adapted Gaussian population with high additive effect size as shown in (A).

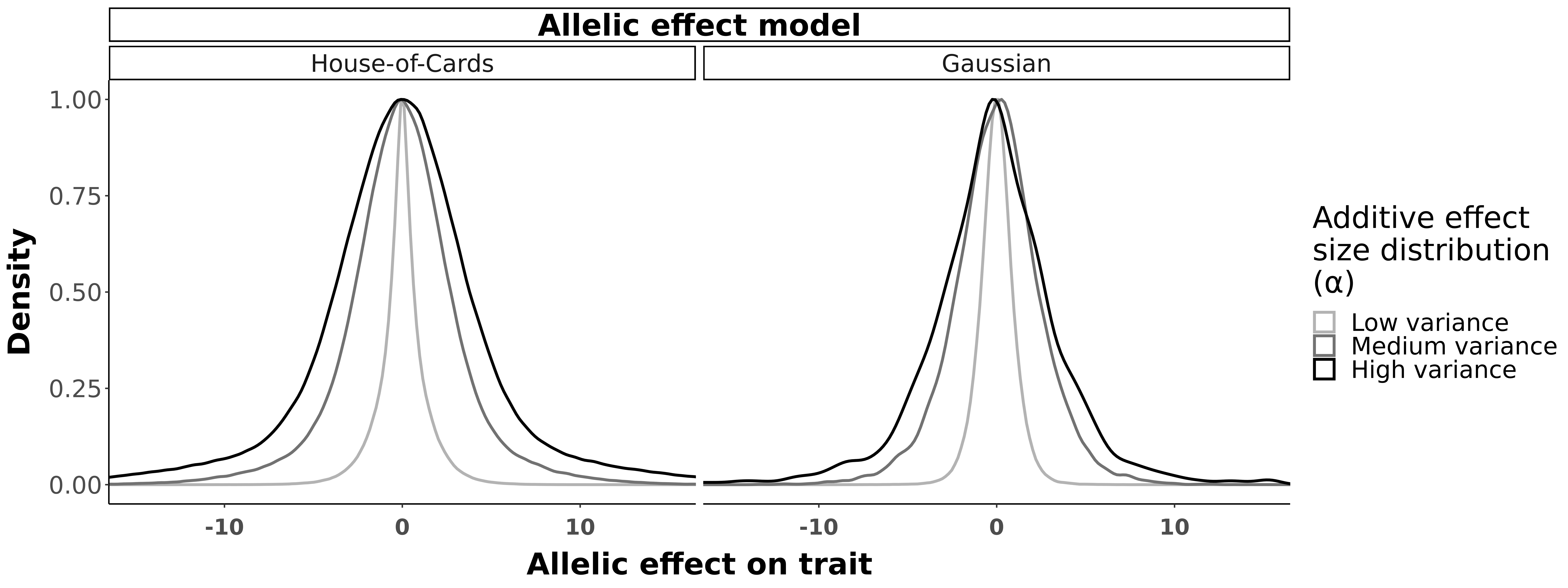


Figure 8: Density estimates of mutational effect sizes for adapted populations at generation 100,000 under different Continuum of Alleles models, with additive effect size distribution.

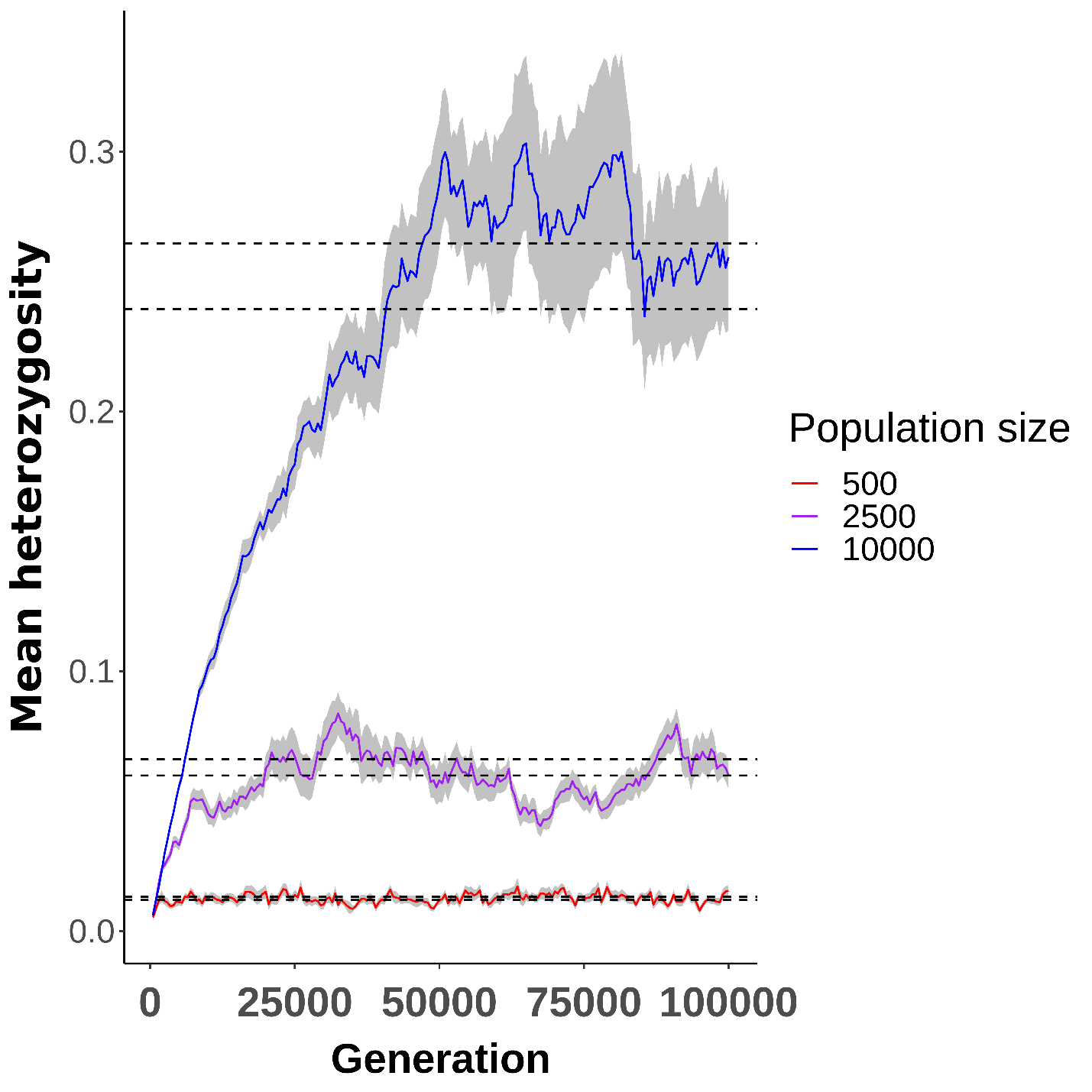


Figure S1: Mean population heterozygosity over time. Lines represent mean trajectories of 20 replicates, with ribbons representing standard errors. Dotted lines represent expected heterozygosities ± 5%, given by .

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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