Intro Snippets

V6

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).

Quantitative genetics emphasizes traits controlled by many genes and alleles, providing an approximately normal distribution of trait values.

A similar concept, balancing selection, is common in population genetics theory (Charlesworth 2006). The difference lies in the target of selection: under stabilizing selection traits under the control of many genes approach optimum values (Fisher 1930), whereas under balancing selection, the most fit genotypes at a single locus are polymorphic, either through overdominance (heterozygote-advantage) or rare-allele-favored frequency-dependent selection (Charlesworth 2006).

Another limitation lies in the ability of both Continuum-of-Alleles models in predicting observed levels of genetic variation. Selection strengths and mutation rates in both models appear inconsistent with observed heritabilities {Walsh, 2018 #26}. However,

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?

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;

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.

Empirical estimates of VA are notoriously difficult to obtain, however 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

# 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).

Among the distinctions between Gaussian and House-of-Cards models are their assumptions regarding the relative importance of standing genetic variation and mutational variance. Under Gaussian models, standing genetic variation provides most of the genetic variance, owing to higher mutation rates relative to selection, which in turn leads to higher numbers of segregating alleles (Walsh and Lynch 2018). Indeed, our results support this, with House-of-Cards models maintaining lower variation than Gaussian models (Figure 5). It should be noted that it is difficult to ascertain if this trend remains at high additive effect sizes as both model types have considerably fewer adapted populations than under lower additive effect size variance, which fuels large standard errors of means (Table 2).

Both models impose restrictions on which mutations are viable, and the strength of those restrictions defines the distribution of allelic effects. We found that the distribution of allelic effects became significantly wider with increasing additive effect size variance, but only under a Gaussian model, indicating a sensitivity to additive effect variation that is not present under a House-of-Cards model (Figure 8). We believe the mechanism underpinning this sensitivity to additive effect size change lies in the underlying assumptions of the models.

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?

However, even among the adapted subset of populations, very few were directly at the optimum: there was always some level of maladaptation,

Genetic architecture controls ability to adapt and stay there; Gaussian vs HoC are similar in ability to get there, very different from null (16 vs 0.5% chance); among models that are maladapted, there is plenty of variance, to the point where much of the null model distribution overlaps with that of the CoA models; Among the few null models that did get into that adapted range, they never got to the perfect adaptation level, where distance = 0; suggests there is a drift barrier to clear to be able to overcome mutation/drift and reach the optimum; example of barrier (Gardon et al. 2020).

The position of this barrier differs depending on the expectations of where the m/s/d equilibrium is; this is likely different between models, as shown in fig 4A where the distribution of distances is much smaller in HoC vs Gaussian, due to fewer mutations that may cause populations to drift further from their optimum; Among those adapted populations, what was the predictor underpinning that ability? How did these populations adapt? What were then signatures associated with that? HoC and Gaussian were pretty similar in how close they got – but their responses to changes in additive effect size were different; HoC remained unaffected, Gaussian moved further away; insensitivity caused by the relative strengths of selection and mutation swamping of high mutation rates; with high effect sizes and weak selection, Gaussian models fluctuate more around optimum, as selection cannot effectively reduce this standing variation; HoC on the other hand is efficient in removing new mutations that are mostly deleterious, results in lower standing variance and increased reliance on big new mutations to drive further adaptation; trade-off in the case of a changing optimum – Gaussian may be able to get to the general range of an optimum faster, but will not be able to truly get there; HoC needs to wait for the appropriate mutations to arise to drive adaptation, will take longer but the stronger selection means they are more likely to pinpoint their location very close to the optimum; different strategies that are likely to be beneficial in different environments; Gaussian in heterogeneous environments; HoC in homogeneous, stable environments; the models act like ‘hot’ or ‘cold’, with Gaussian being a hot excited molecule dashing around the optimum imprecisely, while HoC are more cold, and move less far from the optimum over the same time; over time, modifiers of mutation rate may be beneficial if you need to react to a new event, then those will slowly go away; example;

Demonstrated that genetic architecture contributes greatly to the ability of populations to adapt, and that the effect of genetic architecture on adaptability depends on the relative strength of mutation to selection, via the HoC vs Gaussian model. Particularly the variation in additive effect size, the ‘precision’ of mutation to drive populations to the optimum, had large influences (Fig. 5, 6, 7, 8). However, HoC models appeared more robust to changes in effect size in general, with variance, distance, and covariance not being perturbed as much as under Gaussian models. Why? Comes down to assumptions of these models

Gaussian assumes mutation > selection, most additive variation comes from standing variation. HC assumes selection > mutation, so mutational variance is greater than standing variance. Because selection strong, the allele with the highest frequency is expected to have a value close to the optimum. So new mutations are deleterious and tend to disappear quickly, resulting in most of the gen var being due to rare alleles with large effects

standing genetic variation (in the Gaussian model, where selection is much weaker than mutation; Figure 2), or new mutational variance (in the House-of-Cards model, where selection is much stronger than mutation).

Very little variation is expected to be maintained by adapted populations, may change with

Why is effect size so important? Introduces mutational variance, increases additive variance which selection can act on to go more efficiently, or in this case, can reduce ability of populations to maintain positions around optima because effects are all over the place – swamping effect. This is why Gaussian vs HoC so important, the relative rates of mutation to selection define the positions of models.

Driver of effect size, importance of mutational variance vs standing variation

Weird outliers in variance and covariance: could be that these populations did have high variance and covariance due to wildly different individual phenotypes, but when you took the mean distance of the population, that mean was somewhere in the middle of all that variation, which happened to be close to the optimum.

Robustness of HoC vs Gaussian to changes in Effect size

Truly adapted ones – at distance = 0

Really rare to be close under null

Estes and Arnold 2007 – 64% populations at least 1 sd from the optimum

Accuracy vs speed of adaptation – we are looking at accuracy

Fig 4A: when you’re far from the optimum there is a lot of stochasticity – Gaussian and HoC overlap with Null distributions indicating they aren’t able to escape the drift barrier (Nes < 1)

Fig 4B: HoC/Gaus pops are very different from null

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

Relative importance of mutational variance vs standing variation drives differences in responses to selection

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

In turn, these changes in variance-covariance structure could affect the ability of populations to adapt to future environmental changes (Arnold *et al.* 2008; Otto 2009).

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