Trait genetic architecture and population structure determine model selection for genomic prediction in natural *Arabidopsis thaliana* populations.

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Abstract

In plants, genomic prediction is used to predict agronomically relevant traits of varying trait ontology and genetic architecture. Selecting the most appropriate model for a trait's genetic effects distribution and the population's allele frequencies is crucial. Linear regression models are typically preferred for genomic prediction given the number of genome-wide markers are usually much greater than the number of observations. However, additive models may not suit all genetic architectures and ancestral populations. Machine learning (ML) has been suggested to improve genomic prediction by modelling complex biology, such as epistasis, though has underperformed in past studies. This study evaluates (1) genomic prediction model sensitivity to trait ontology and (2) the impact of ancestral population-specific selection on prediction and model choice. Examining 35 quantitative traits in *Arabidopsis thaliana* with ~1000 observations across Europe, we assessed penalised regression, random forest, and multilayer perceptron performance. Regression models were generally most accurate, except in some biochemical traits where random forest excelled. We link this result to the genetic architecture of each trait – notably that biochemical traits have simpler genetic architecture than macroscopic traits like flowering time. Moreover, complex macroscopic traits, especially related to flowering and yield were strongly correlated with population structure and demography, while molecular traits required individual marker resolution. The study thus highlights the relevance of machine learning approaches for simple molecular traits in crop breeding and underscores the need to consider differential ancestral selection when designing association panels.

1. Introduction

In plants, genomic prediction is used to predict agronomically relevant traits such as yield, phenology, metabolite concentrations or the response to stresses, which all have different genetic basis. Heritable traits, whether simple and controlled by a few loci, or complex and controlled by many variants, can be predicted based on the information from dense, genome-wide markers. Genomic prediction models are often fitted to training populations designed to maximise diversity, often including genotypes with varying levels of co-ancestry and different evolutionary histories (Fodor et al., 2014). Therefore, critical

in genomic prediction is the choice of model most appropriate for a population's allele frequencies and distribution of effects for a particular trait.

The number of genome-wide markers (p) being typically much larger than the number of individual observations (n), overfitting is a major challenge in genomic prediction. A common solution is to use penalised linear regression models (Meuwissen et al., 2001). Penalised regression reduces overfitting by shrinking the effect of each marker. Most penalisation functions assume a prior distribution of the marker effects, which relates to the trait's assumed genetic architecture. Linear models also assume that genetic factors influence the phenotype independently and additively. This simplification allows many predictors to be incorporated parsimoniously but excludes interactive effects such as dominance and epistasis. Indeed, an additive model with a fixed prior distribution may not be an optimal approach when the development and regulation of traits are a complex function of genetic and environmental variables (Meuwissen, 2009; Morgante et al., 2018; Putra et al., 2023).

Machine learning has been proposed as a means to better accommodate biological complexity in genomic prediction (Carlborg & Haley, 2004). Non-linear/nonparametric models can account for dominance and epistasis and have fewer assumptions about the distribution of genetic effects. It is thus reasoned that genomic prediction should be effective under increased model complexity, as is the case for other biological modelling problems like the prediction of protein structure (Jumper et al., 2021). However, the performance of nonlinear machine learning models has been largely underwhelming in genomic prediction. Multiple studies have shown machine learning techniques to be no more accurate than linear regression for complex polygenic traits (Abdollahi-Arpanahi et al., 2020; Azodi et al., 2020; Bellot et al., 2018). One explanation for the underperformance of machine learning models is that the number genetic variants used as predictors is two high compared to the number of observations in current association panels. For example there may be many genetic interactions contributing to the development of a complex trait such as crop yield. If the effect of each interaction is small, it is difficult to parameterise them with low statistical power. Simulation studies have shown that machine learning models might be suited to simpler traits controlled by a small number (<100) of causal loci (Abdollahi-Arpanahi et al., 2020). Indeed, nonlinear models have been most successful for predicting the occurrence of human autoimmune diseases, where most of the genetic variance can be attributed to a discrete number of loci of the major histocompatibility complex (Abraham et al., 2014). As such, rather than attempting to apply machine learning to genomic prediction generally, machine learning models might be specifically suited to simpler traits with strong epistatic effects (Abdollahi-Arpanahi *et al*., 2020). This hypothesis is agronomically relevant. In crops, it can be desirable to select biochemical traits *i.e.* the concentration of minerals or metabolites (Šimić et al., 2012), which often have simpler genetic architectures (Riedelsheimer et al., 2012). On the other hand, macroscopic traits such as those relating to yield combine many endophenotypes and tend to be complex.

In addition to biological complexity, different evolutionary histories and patterns of selection in the ancestral populations of association panels between traits could also have an important role in model selection (Fodor et al., 2014; Guo et al., 2014). Population-specific selection on a trait leads to covariance between trait value and population structure, confounding causal variants. Thus within one association panel, traits may be confounded to different degrees by historical patterns of selection. The degree of selection on a trait, the traits phenotypic ontology, and its architecture are likely linked (Zhang, 2018). For

example, in plants flowering time is known to be both complex in genetic architecture and selected along environmental clines (Zan & Carlborg, 2019).

To design and interpret genomic prediction studies, it is important to understand how genetic architecture and evolutionary history interact with genomic prediction models. However, there has been no sensitivity analysis comparing linear and machine learning models for different genetic architectures in natural or outbreeding plant populations. This study aims to address this gap by testing machine learning and linear models for the prediction of 35 *Arabidopsis thaliana* traits. We specifically test the sensitivity to (a) the phenotypic ontology of each trait (b) The genetic architecture of each trait and (c) How each trait relates to population structure and demography. Here we argue these three sensitivities are intertwined. Linear statistical models perform best for macroscopic traits, which were complex in genetic architecture and stratified along environmental gradients. On the other hand, Machine learning approaches improved prediction only in biochemical traits, which had a more simple genetic architecture, and varied uniformly between environments.

2. Methods

2.1 Data Set

We used 10,709,466 genome markers genotyped across 2029 inbred homozygous *Arabidopsis thaliana* accessions from the 'K2029' public data set (Arouisse et al., 2020) including genotypes from the RegMap Panel (Horton et al., 2012) and the 1001 genome project (Alonso-Blanco et al., 2016). We downloaded all available phenotypes measured in all or a subset of these accessions from the AraPheno database (Seren et al., 2017). In addition to the traits listed on the Arapheno database, we also download 22 metabolic traits, which are the concentration of glucosinolates involved in the *Arabidopsis thaliana* herbivory stress response (Brachi et al., 2015). No phenotype was measured across all genotyped accessions, meaning experiments always had less than 2029 observations. For traits where measures were replicated within an accession, we used the breeding value estimated across the replicates as the truth value for our genomic prediction experiments. We estimated these breeding values using the best linear unbiased predictor (BLUP). Using a phenotypic value derived from multiple measures of the same accession further minimises the effect of the environment in this study. From all traits available in the AraPheno database, we retained only studies with 150 or more phenotyped accessions. When two traits were correlated with Pearson's correlation $r^2 > 0.75$, we only retained one arbitrarily, and subsequently only considered traits where at least one genomic prediction model could explain 20% of the phenotypic variance. This filtering process reduced the pool of traits from 551 to 35. We then grouped these 35 traits by their associated trait ontology terms (Cooper et al., 2024)

The total number of markers needed was filtered to keep computation time within a practical range. For each trait, markers with minor allele frequencies (MAF) < 5% were discarded. We used 'plink thin' to prune correlated markers within a sliding window along the genome, using a window size of 200kb, removing one of each pair of markers with LD $r^2 > 0.6$ Due to each trait having a different set of

phenotyped accessions, we conducted this filtering strategy independently for each trait. The total number of markers used for the refined set of 35 traits was in the range 218128-366534.

2.2 Analysis of Genetic Architecture

We investigated the genetic architecture of each trait using genome wide association studies (GWAS). GWAS were conducted in 'VCFtoGWAS' (Vogt et al., 2022) using a 'GEMMA' model (Zhou & Stephens, 2012), where the effect of pairwise relationships (estimated with identity by state) is modelled as random, and the effect of individual markers are modelled as fixed and tested using a Wald test. Polygenic traits were characterised by having a high heritability while lacking substantial GWAS peaks, oligogenic traits had multiple GWAS peaks, and monogenic traits showed a single associated locus (Atwell et al., 2010). Trait complexity was thus determined quantitatively by the kurtosis of the distribution of GWAS p-values, and qualitatively validated through the inspection of Manhattan plots.

2.3 Prediction Models

2.3.1 Penalised Linear Regression

For the linear models, we implemented *Ridge regression/GBLUP* (genomic best linear unbiased predictor), Lasso, and Elastic Net. Briefly these model fit a weighted linear combination of regression coefficients for the predictors (denoted $\boldsymbol{\beta}$) by minimising the following objective function:

$$\beta = argmin_{\beta}((||y - \hat{y}||_2)^2 + \lambda(\alpha||\beta||_1 + (1 - \alpha)(||\beta||_2)^2)$$

where y is a vector of observed phenotypes and $\hat{y}$ is the predicted phenotype, λ controls the penalisation and α weights L1 and L2 penalisation. When α is zero the model is equivalent to Ridge regression, when α is 1 the model is equivalent to Lasso regression, and when $0 < \alpha < 1$ the model is termed Elastic Net regression (Tibshirani, 1996; Zou & Hastie, 2005).

In our implementation of these models, the meta-parameters λ, and α in the case of Elastic Net, were chosen via cross validation in the training partition of the dataset within the following domains: $\lambda \in \{2^{-20}, 2^{19} \ldots 20^{20}\}$, $\alpha \in \{0.01, 0.1, 0.5, 0.85, 0.9, 0.97, 0.99, 0.995\}$. Ridge and Lasso regressions were implemented using the 'RidgeCV' and 'LassoCV' functions of the scikit-learn package (Pedregosa et al., 2011). Elastic Net regression was implemented using 'glmnet' with the coordinate descent algorithm (Friedman et al., 2010). All other parameters were kept to default values.

2.3.2 Multilayer Perceptron

A Multilayer Perceptron (MLP) is a simple ANN model where perceptrons are organised in fully connected layers. In our implementation, we used the rectified linear unit (ReLU) activation function. Preliminary tests showed that other sigmoidal activation functions (such as *tanh*) had similar prediction accuracy. We optimised {1,2,3} hidden layers in the network, each width equal to two-thirds the number of input predictors. We also incorporated L2 penalisation where λ is a scalar optimised over {0, 0.01, 0.1, 1}. Weights were fitted iteratively using the Adam optimizer (Kingma & Ba, 2014). To determine when to

cease the training of the neural network model we used an early stopping approach (Prechelt, 1998). Briefly, we held out 10% of observations, and training was stopped when either out of sample MSE did not decrease by at least some *tolerance* value for 10 consecutive epochs (iterations over the dataset), or 1000 epochs were reached. The tolerance value was optimised over {0.05, 0.01, 0.005}, noting here that each phenotype was standardised to have a variance of 1. We also added dropouts (Srivastava et al., 2014). Dropouts are a type of regularisation specifically for ANNs which works by randomly deactivating, or "dropping out" a certain percentage of weights between layers during each training iteration. This prevents the model from becoming too reliant on any specific perceptron or connection. We optimised over using no dropout or dropping out 10% of edges in the network in training. Due to the computationally heavy requirement for fitting ANNs, we applied an additional filtering to the number of markers used to fit this model. For additional filtering we fitted a linear lasso regression then filtered out markers with a regression coefficient equal to 0. Here, the penalty terms were determined via 5-cross validation alongside the other meta-parameters specified in this section.

2.3.3 Random forest

Random forest is a tree based ensemble model that fits decision trees to boot strapped samples of the data, then makes predictions by averaging the output of each tree. We implemented the 'RandomForest' sci-kit learn function (Pedregosa et al., 2011). Five-hundred decision trees were used across experiments, further increasing the number of decision trees that did not affect performance. All other parameters were kept as default.

2.3 Model benchmarking and meta-parameter selection

We compared the accuracies and residual errors of each of the models described using nested 10-fold cross validation. This framework consists of an inner loop and an outer loop. The outer loop is a canonical 10-fold cross validation and measures generalizability. The inner loop takes each training partition from the outer loop and uses 5-fold cross validation to evaluate each meta-parameter configuration of the tested model.

2.3 Analysis of Spatial Clines

To understand differential selection in the environment we quantified the strength of spatial clines for each trait. To do this, we used the following model of the phenotypic values in terms of the latitude and longitude of where each accession was originally sampled from.

$$phenotype \sim \beta_0 + lat + \beta_2 long + \beta_3 lat \cdot long + \beta_4 lat^2 + \beta_5 long^2$$

We quantified the strength of a spatial cline based on the phenotypic variance that was captured by this model. We applied this model only to accessions sampled within Europe (latitude -40–60, longitude 20–70), excluding the small number of accessions sampled from within the American continent.

3. Results

3.1 Optimal genomic prediction model is associated with trait ontology

Of the 551 publicly available traits, 35 traits were independent (correlation between traits $r^2 < 0.75$) and sufficiently heritable to be predicted with an accuracy $r^2 > 0.2$ by one of the genomic prediction models. Of this filtered set of traits, 22 were macroscopic and 13 were biochemical. Penalised regression yielded the most accurate predictions for all 22 macroscopic traits; 21 through ridge regression and one via lasso. In contrast, no single model was superior at predicting the 13 biochemical traits. Noticeably, Random Forest improved prediction above linear models for 7 biochemical traits (Figure 1a). The increase in accuracy was particularly large for allyl concentration, a glucosinolate involved in preventing herbivory, and molybdenum concentration, an essential micronutrient (Figure 1b, paired t-test $p = 9.90 \times 10^{-4}$, $p = 1.41 \times 10^{-5}$ respectively).

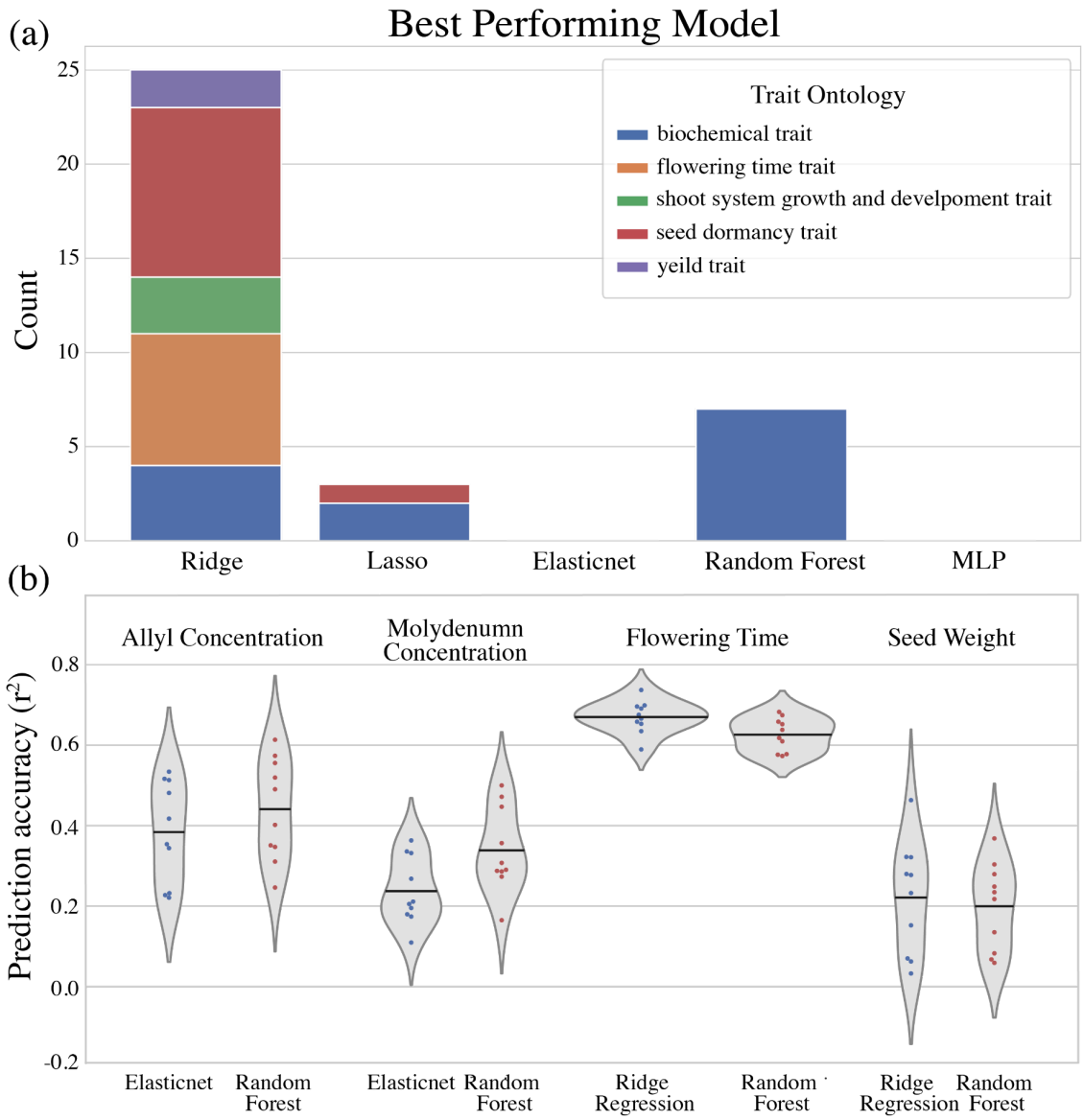

Figure 1: genomic prediction model accuracy depends on trait ontology class. (a) Most accurate genomic prediction model for each trait ontology term. (b) Prediction accuracy of the best linear model compared to Random Forest contrasting for a pair of biochemical traits (the concentration of allyl and molybdenum) and macroscopic traits (number of days to flowering at 10 degrees and average seed weight). Here, each of the 10 points is the prediction accuracy of each partition of 10-fold cross validation.

3.2 The genetic architecture is associated with genomic prediction model choice.

To test the hypothesis that RF outperformance over penalised regression is due to the specific genetic architecture of molecular/biochemical traits, we analysed each trait through GWAS. Biochemical traits had stronger individual associations compared to macroscopic traits (figure 2a). Macroscopic traits

generally displayed fewer association peaks despite high heritability, indicative of polygenicity. This observation was reflected in the kurtosis of the distribution of p-values, which was on average higher for biochemical traits compared to macroscopic traits (t-statistic=5.37, p=6.12e-06) (figure 2a). Moreover, among all biochemical traits best predicted by random forest, the most accurate linear statistical model was either Elastic Net or Lasso (which assumes sparsity), and never ridge regression (which assumes polygenicity).

3.3 The Effect of genetic architecture and population structure differ across trait ontology.

To better understand how population structure affects prediction accuracy, we used principal components (PCs) computed from genome-wide marker data as predictors instead of the markers themselves. Macroscopic traits were more correlated with this measure of population structure than biochemical traits. For example, when we fitted each model to the PCs explaining 30% of marker variance, the best genomic prediction model fitted to these PCs produced an r^2 value 90% as high as the best marker based model for macroscopic traits compared to 68% as high for biochemical traits (t-statistic=2.60, p=0.0138) (figure 3b).

Finally, we investigated the effect of large spatial gradients. In general, macroscopic traits tended to covary more strongly with latitude/longitude than biochemical traits. A quadratic function of latitude and longitude explained on average 25% of phenotypic variance in macroscopic traits compared to 14% of variance in microscopic traits (t-statistic = 2.61, p = 0.0134). Notable were the extremes. The quadratic spatial model could explain as much as 48% of flowering time traits, yet as little as 1% of variation in biochemical traits (figure 3c).

Critically, the traits with a distribution of genetic effects with a low kurtosis were best predicted by a ridge regression model and explained well by population structure and spatial distribution. While the traits with high kurtosis were best predicted by lasso/random forest and explained poorly by population structure and geography (Figure 2a, 2b, 2c).

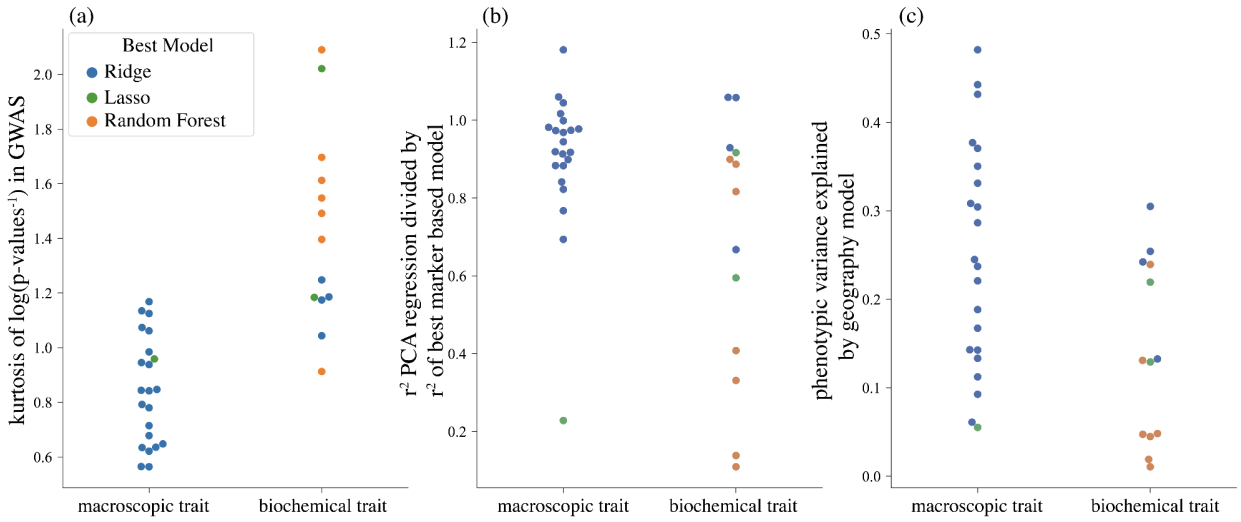

Figure 2: Sensitivity of best genomic prediction model to genetic architecture, population structure and geography. (a) The kurtosis of GWAS log(p-values^{-1}) for each of the 32 traits analysed in this study. (b) the ratio between prediction accuracy (r^2) of the best performing model fit to the principal components of the genome (30% variance explained), to the best model fit onto genome wide markers. (c) The proportion of phenotypic variance described in the geography model given by equation 1 for each trait.

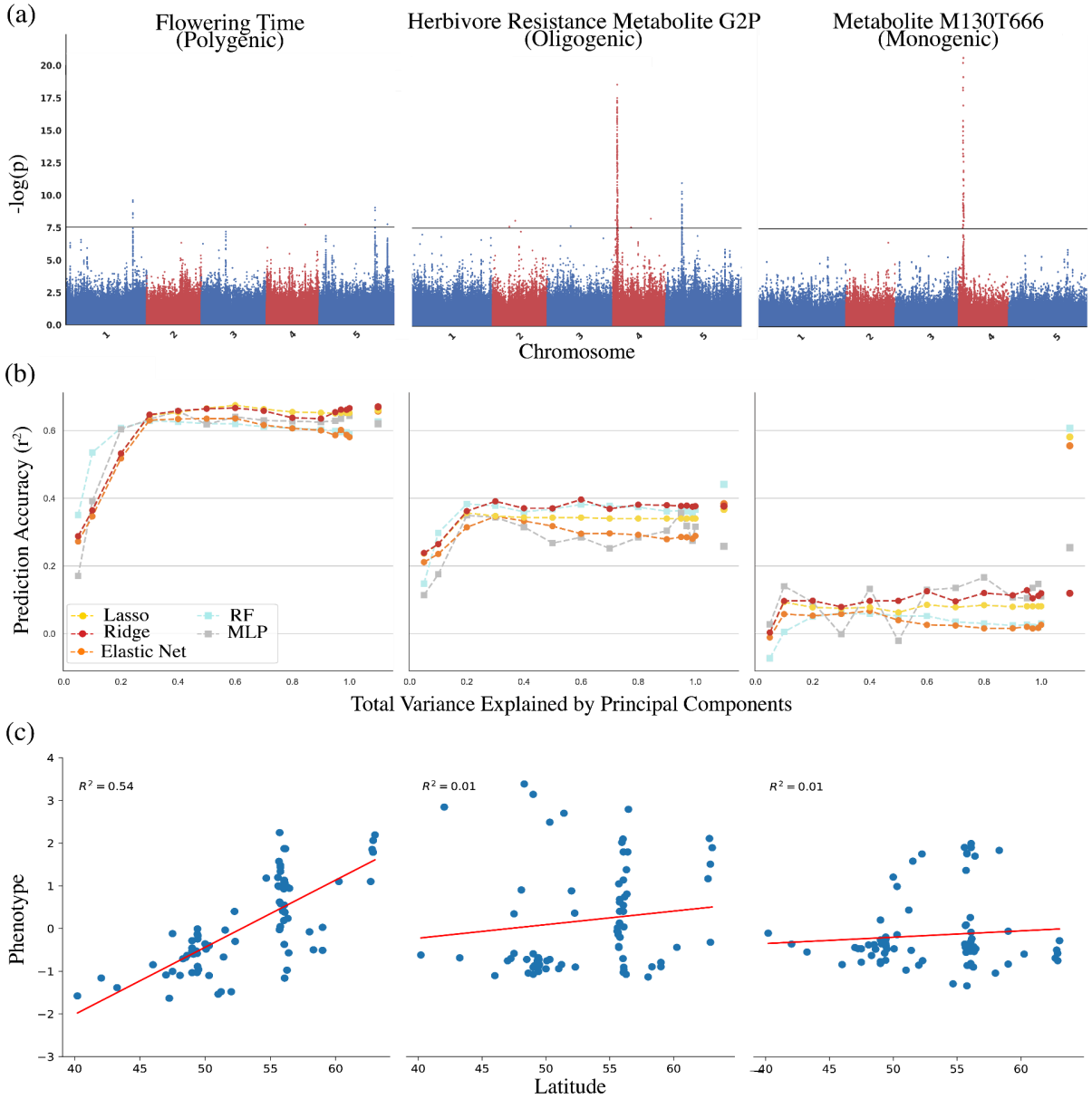

Figure 3: The relationship between genetic architecture, genomic prediction model, population structure and geography illustrated through 3 traits in detail. (a) Manhattan plots for GWAS illustrating the genetic architecture of 3 traits with contrasted genetic architectures. (b) Sensitivity to dimensionality reduction conducted through principal component (PC) analysis. The x-axis shows the cumulative variance explained by the set of PCs retained in the untransformed feature set. The last tick on the x-axis corresponds to the accuracy achieved using the markers, equivalent to using all PCs. RF: Random Forest; MLP: multilayer perceptron model which uses a single hidden layer. (c) Sensitivity between the phenotype and the latitude of origin of the accessions. *Note* figure shows only the 78 accessions with phenotype data for all 3 traits.

4. Discussion

Genomic prediction is an expanding field of research initially motivated by the opportunity of conducting molecular breeding in animals and plants. Genomic selection can apply to any heritable trait, with very diverse genetic architectures and evolutionary histories. As such, we expected that genomic prediction would rely on different, specific methodologies for each trait. Among the 35 *Arabidopsis thaliana* traits tested, the most accurate genomic prediction model depended on trait ontology, genetic architecture and population structure. These components are interconnected and collectively determine the most suitable prediction models. Specifically, we observed that biochemical traits have sparser genetic architectures and are less influenced by population structure. As a result, different approaches were optimal for biochemical and macroscopic traits. Linear regression was best suited for macroscopic traits, while sparse linear regression or random forest generally worked better for biochemical traits.

Model selection depends on the genetic architecture of the trait

We found that random forest specifically outperformed linear models for molecular traits which showed a monogenic to oligogenic architecture. These findings challenge previous work which has argued that for polygenic traits determined by a complex network of genes, nonlinear models have potential to outperform linear models (Azodi et al., 2019; Momen et al., 2018; Morgante et al., 2018). Instead we support that non linear models are best suited to traits with a small number of effects with strong epistasis (Abdollahi-Arpanahi et al., 2020). Our results also suggest that for association panels gathering broad sources of natural variation, nonlinear/nonparametric prediction can benefit models when targeted to and informed by specific sparse traits. We argue this is more effective than the strategy of developing generalised machine learning frameworks aimed at improving genomic prediction across all traits. This is consistent with recent studies that linked the success of ensemble approaches to evidence of strong epistasis in particular mice traits (Perez et al., 2022; Zingaretti et al., 2020). Our findings particularly expand on a study by Riedelsheimer and colleagues (2012), which compared linear models between molecular and macroscopic traits in maize. Their study found the molecular traits to have a simple genetic architecture, and showed linear models with a sparse prior to best predict them. Consistent with these findings, we generally observed that for biochemical traits the best performing linear models had sparse priors, although random forest delivered higher accuracy for a few of the biochemical traits. Previous motivations for testing machine learning in complex traits has been capturing phenotypic variance underpinned by epistasis. We believe nonparametric models worked specifically for sparser traits because the presence of interaction effects is stronger when fewer genomic regions underpin a trait. Moreover when a trait is sparse, the prior distribution of effect sizes is more difficult to define, which is advantageous to non-parametric models like random forests which rely on fewer prior assumptions. The development and regulation of complex traits may well be underpinned by epistasis, but the effect size of each interaction could be small, or underpinned by very rare variants. As the authors of these past works have noted this would make the effect size of each interaction small, and difficult to be learned from data (Azodi et al., 2019).

In line with previous works we found artificial neural networks (of any design tested) to have lower out of sample prediction accuracy then linear models (Abdollahi-Arpanahi et al., 2020; Azodi et al., 2020; Bellot et al., 2018). MLPs make predictions by building progressively abstract representations from all of the predictors. They have the implicit assumption that every predictor is meaningful, and likely interacts with

other predictors. These assumptions work well for tasks like computer vision, where each pixel contains a small but meaningful amount of information, and an image is best understood in terms of many pixels collectively. We believe the poor results from MLP in genomic prediction is because the way genomic information maps to phenotypic variation poorly matches the assumptions of MLPs. In the case of simpler traits, many SNPs may have no signal, and of those that do, there may only be a small number of interactions. In complex traits, that are hypothesised to be underpinned by a complex network of genes (Carlborg & Haley, 2004), complex models like MLPs suffer from the aforementioned problems of low statistical power and rare variants (Azodi et al., 2019; Bellot et al., 2018).

Effect of the trait evolutionary history on genomic prediction

In addition to the genetic architecture, we found that the population demography and selection history of the trait is also an important determinant of genomic prediction model selection. Particularly, biochemical traits were less correlated with population structure than the macroscopic traits. The principle components of the population's genomic data capture the major axis of genomic variation, and thus provide a concise summary of population structure (Ma & Amos, 2012; Novembre & Stephens, 2008). For example, a linear combination of PCs explaining 30% of genomic variants predicted flowering time as well as any marker based model. On the other hand, PCs could only predict the concentration of metabolite M130T666 22% as well as the best marker based model. Thus in genomic prediction models for the examined population, individual markers are informative for the prediction of simple (typically biochemical) traits while in macroscopic traits, causal variants are confounded by population structure. Indeed a complex trait like flowering time may be underpinned by many epistatic effects, but could be obfuscated by population structure, favouring simpler linear models. Although we do note that we tested an inbred population sampled across a global scale, which is a point of difference to past genomic prediction studies. Thus, the effect of population structure we observed might be less pronounced in crossed study designs. Although, simulation studies using genotypic data from crossed populations have also shown that structure can benefit the prediction of complex traits if the testing partition of the data captures similar variation to the training partition (Fodor et al., 2014).

Our findings suggest that the varying degree of correlation between phenotypic values and population structure observed within this study is explained by selection. We observed that macroscopic traits on average had stronger biological clines across longitudinal and latitudinal gradients compared to biochemical traits. We thus expect that such biological clines occur due to selection pressures changing between environments. For example it is understood that plant flowering is selected for, and adapted to specific environments in Europe (Fournier-Level et al., 2022). The absence of clines in biochemical traits supports the neutral theory of molecular evolution, which posits that selection occurs at the organismal level and that molecular traits are generally more neutral than macroscopic traits (Kimura, 1985). When considering the phenome's hierarchy of biological organisation, it follows that a mutation affecting a trait at a high level will also influence traits at lower levels. Macroscopic traits which are under direct selection combine many endophenotypes. However, individual biochemical traits might not affect the organism at a macroscopic level and thus are inherently more neutral to selection (Zhang, 2018). Indeed we believe that in addition to genetic architecture ensemble approaches were effective for specifically biochemical traits because these traits are more neutral, and thus less confounded by population structure. Importantly this research suggests that within the same population, selection in ancestral populations affects the inference

of causal variants and genomic prediction model choice, and the degree of this effect in a natural population can be understood in terms of the hierarchical organisation of trait ontology.

Conclusion

In light of this study we propose that future implementations of genomic prediction should consider ensemble models in addition to linear statistical models when the genetic architecture is sparse. Notably, we caution that confounding population structure can vary between traits within the same population, likely due to past selection. This has the potential to negatively impact the generalisation and biological interpretability of genomic prediction models. For example we found complex traits to be structured and could be predicted by a small number principle components, while simple traits were less structured and necessitated resolution of individual markers. We also suggest that nonlinear approaches have a role in genomic prediction, however only in specific genetic architectures, with strong associations that are not confounded by population structure, and/or strong differential selection in the ancestral population. Many past works have focused on benchmarking a wide range of genomic prediction models across select complex traits. However, in future works focused on expanding genomic prediction methodology, we recommend further exploration of the phenome to expand the theoretical framework linking trait ontologies, genetic architectures, and population histories to genomic prediction modelling strategies.

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