

JULIUS-MAXIMILIANS UNIVERSITÄT
WÜRZBURG

DOCTORAL THESIS

**Quantitative genetics - from
genome assemblies to neural
network aided omics based
prediction of quantitative traits**

Author:

Jan Alexander
FREUDENTHAL

Supervisor:

Prof. Arthur KORTE

*A thesis submitted in fulfillment of the requirements
for the degree of Ph.D.*

in the

Research group for evolutionary genomics
GSLs

October 20, 2019

Declaration of Authorship

I, Jan Alexander FREUDENTHAL, declare that this thesis titled, “Quantitative genetics - from genome assemblies to neural network aided omics based prediction of quantitative traits” and the work presented in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed:

Date:

“Wit beyond measure is men’s greatest treasure”

Rawenclaw

JULIUS-MAXIMILIANS UNIVERSITÄT WÜRZBURG

Abstract

Faculty Name

GSLs

Ph.D.

**Quantitative genetics - from genome assemblies to neural network aided
omics based prediction of quantitative traits**

by Jan Alexander FREUDENTHAL

The Thesis Abstract is written here (and usually kept to just this page). The page is kept centered vertically so can expand into the blank space above the title too...

Acknowledgements

The acknowledgments and the people to thank go here, don't forget to include your project advisor. . .

Contents

Declaration of Authorship	iii
Abstract	vii
Acknowledgements	ix
1 Benchmarking of Chloroplast Genome Assembly tools	1
1.1 Introduction	1
1.2 Material and Methods	1
1.3 Results	1
1.3.1 Performance metrics	3
1.3.2 Qualitative	3
1.3.3 Simulated data	3
1.3.4 Real data sets	3
1.3.5 Consistency	3
1.4 Disucssion	3
2 Understanding the hapoltype structure of Arabidopisis thaliana	5
2.1 Introduction	5
2.2 Haplotyping of A. thaliana	5
2.3 Results	5
2.4 Disucssion	5
3 GWAS Flow a gpu-accelerated software for large-scale genome-wide association studies	13

3.1	Introduction	13
3.2	Methods	15
	GWAS Model	15
	The GWAS-Flow Software	15
	Calculation of permutation-based thresholds for GWAS	16
	Benchmarking	17
3.3	Results	18
3.4	Disucssion	19
4	Genomic prediction of phenotypic values of quantitative traits using Artificial neural networks	23
4.1	Introduction	23
	4.1.1 A brief history of machine learning	23
	4.1.2 On the nature of quantitative traits	25
	4.1.3 Artificial selection in plant and animal breeding in the genomics era	29
	4.1.4 Genomic selection using artificial neural networks	30
4.2	Proof of concept on ANN-based genomic selection	33
4.3	Material	34
	4.3.1 DH populations derived from MAZE landraces	34
	4.3.2 <i>A. thaliana</i>	34
4.4	Methods	34
	4.4.1 ANN	34
	4.4.2 GBLUP	34
4.5	Results	34
4.6	Discussion	34
5	GWAS	35
5.1	Reevalulation of 463 phenotypes from the AraPheno database	36
	5.1.1 Introduction	36

5.1.2	Material and Methods	36
5.1.3	Results	36
5.1.4	Results	36
5.1.5	Disucssion	36
5.2	GWAS in DH landrace populatios of maze across and within environments	36
5.2.1	Introduction	36
5.2.2	Material and Methods	36
5.2.3	Results	36
5.2.4	Results	36
5.2.5	Disucssion	36
A	Source code GWAS-Flow	37
A.1	gwas.py	37
A.2	main.py	40
A.3	herit.py	45
	Bibliography	47

List of Figures

1.1	An Electron	2
2.1	Haplotype strutcure of chromosome 1 of <i>A. thaliana</i>	6
2.2	Haplotype strutcure of chromosome 2 of <i>A. thaliana</i>	7
2.3	Haplotype strutcure of chromosome 3 of <i>A. thaliana</i>	8
2.4	Haplotype strutcure of chromosome 4 of <i>A. thaliana</i>	9
2.5	Haplotype strutcure of chromosome 5 of <i>A. thaliana</i>	10
2.6	blabl	11
3.1	Computation time vs number of markers	19
3.2	Computations time vs accessions	20
3.3	Computational time of GWA Analyses on real <i>A. thaliana</i> data sets	22
4.1	Basic perceptron model	24
4.2	Schematic layout of a simple mulit-layer perceptron	25

List of Tables

1.1	The effects of treatments X and Y on the four groups studied. .	2
4.1	The effects of treatments X and Y on the four groups studied. .	33
4.2	The effects of treatments X and Y on the four groups studied. .	33

List of Abbreviations

ANN	Artificial Neural Network
BLUP	Best Linear Unbiased Predictor
BLUE	Best Linear Unbiased Estimator
CPU	Core Processing Unit
EMMA	Efficient Mixed Model Associations
FCL	Fully Connected Layer
GP	Genomic Prediction
GPU	Graphical Processing Unit
GS	Genomic Selection
GWAIS	Genome Wide Interaction Association Studies
GWAS	Genome Wide Association Studies
HDF	Hierarchical Data Format
LCL	Locally Connected Layer
LD	Linkage Disequilibrium
LMM	Linear Mixed Model
MLP	Multi Layer Perceptron
ML	Machine Learning
QTL	Quantitative Trait Locus
RKHS	Reproducing Kernel Hilbert Spaces
RSS	Residual Sum of Squares
SNP	Single Nucleotide Polymorphism
TRN	TRaiNing subset
TST	TeSTing subset

WGS	Whole Genome Sequencing
LSC	Large Single Copy
SSC	Small Single Copy
IR	Inverted Repeat
DNA	DeoxyriboNucleic Acid
DNA	RiboNucleic Acid
GUI	Graphical User Interface
BP	Base Pair
DH	Doubled Haploid
GBLUP	Genomic Best Linear Unbiased Predictor

For/Dedicated to/To my...

Chapter 1

Benchmarking of Chloroplast Genome Assembly tools

1.1 Introduction

Here I will but the introduction to from the paper

1.2 Material and Methods

1.3 Results

$$score = \frac{1}{4} \cdot \left(cov_{ref} + cov_{qry} + \min \left\{ \frac{cov_{qry}}{cov_{ref}}, \frac{cov_{ref}}{cov_{qry}} \right\} + \frac{1}{n_{contigs}} \right) \cdot 100 \quad (1.1)$$



FIGURE 1.1: An electron (artist's impression).

TABLE 1.1: The effects of treatments X and Y on the four groups studied.

Groups	Treatment X	Treatment Y
1	0.2	0.8
2	0.17	0.7
3	0.24	0.75
4	0.68	0.3

1.3.1 Performance metrics

1.3.2 Qualitative

1.3.3 Simulated data

1.3.4 Real data sets

1.3.5 Consistency

1.4 Disucssion

Chapter 2

Understanding the hapoltype structure of Arabidopisis thaliana

2.1 Introduction

2.2 Haplotyping of A. thaliana

2.3 Results

2.4 Disucssion

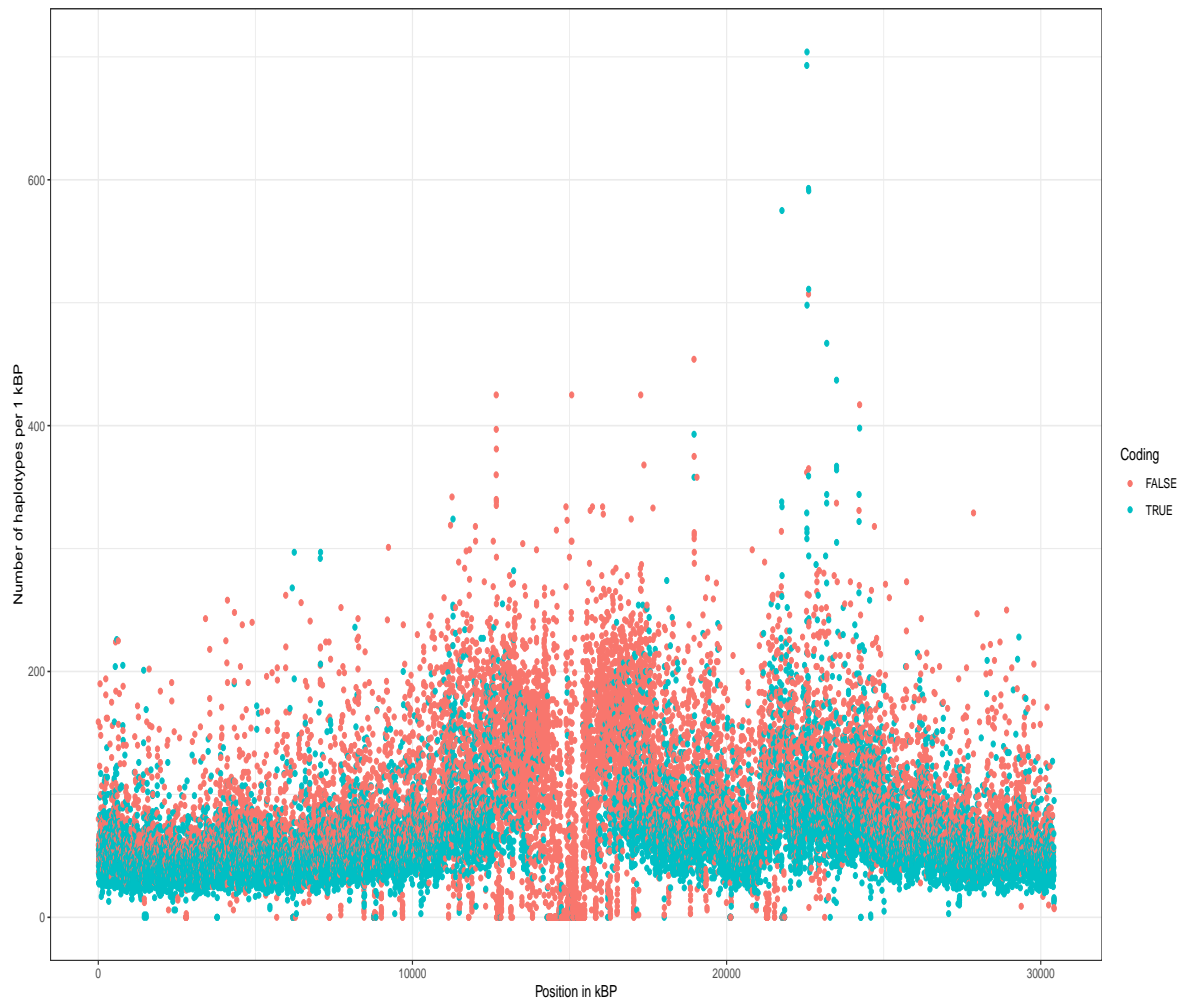


FIGURE 2.1: The number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.



FIGURE 2.2: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

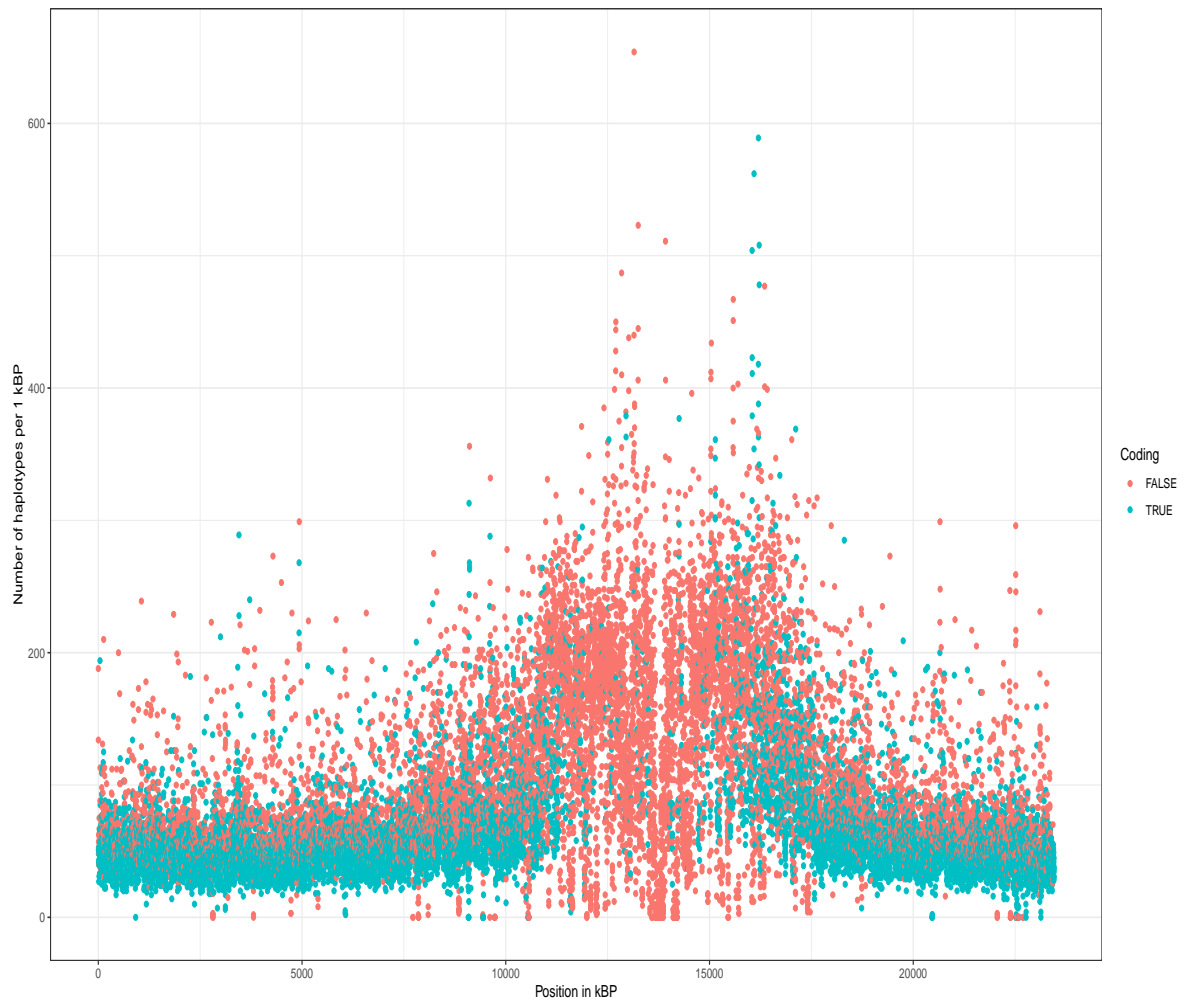


FIGURE 2.3: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

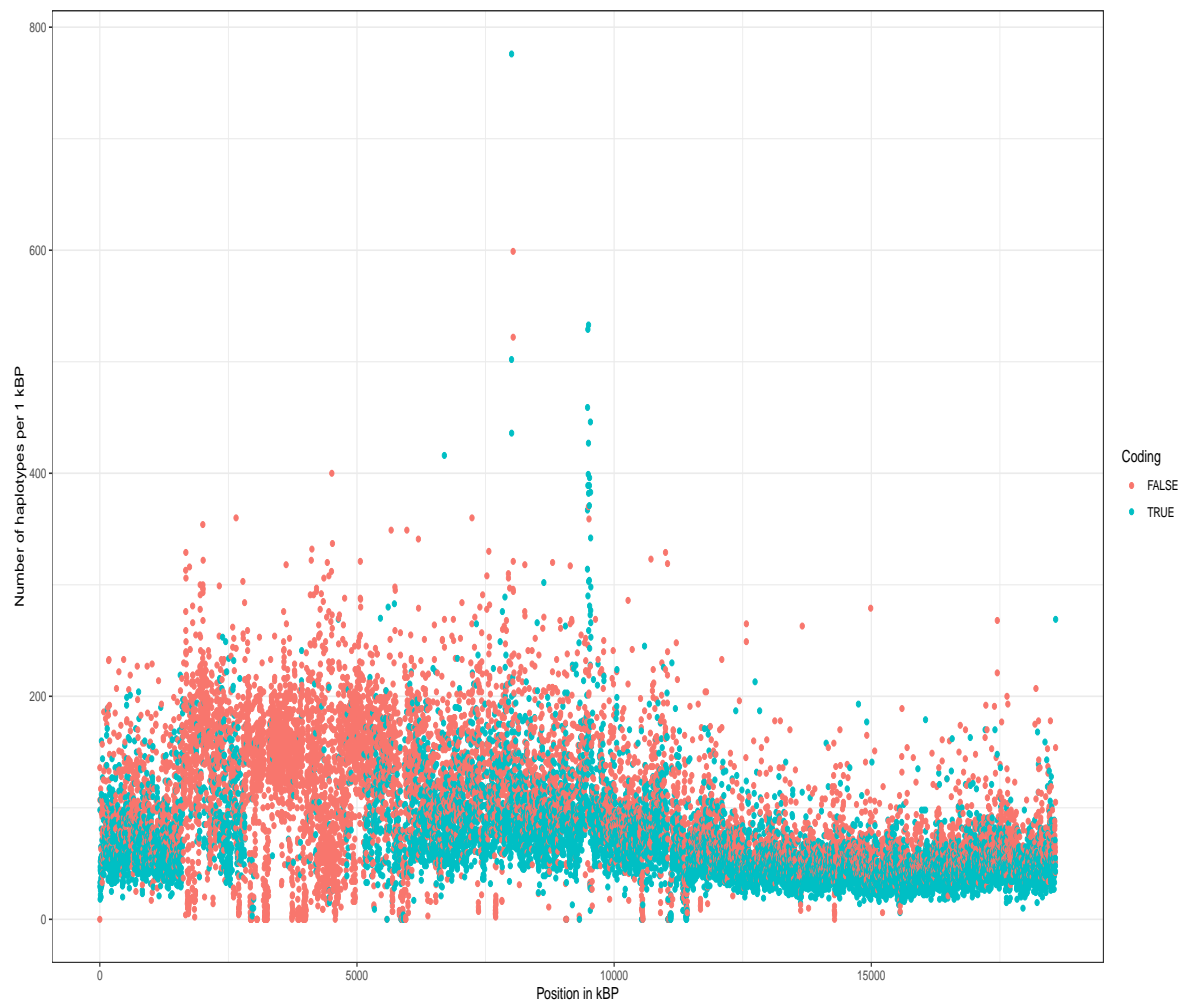


FIGURE 2.4: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

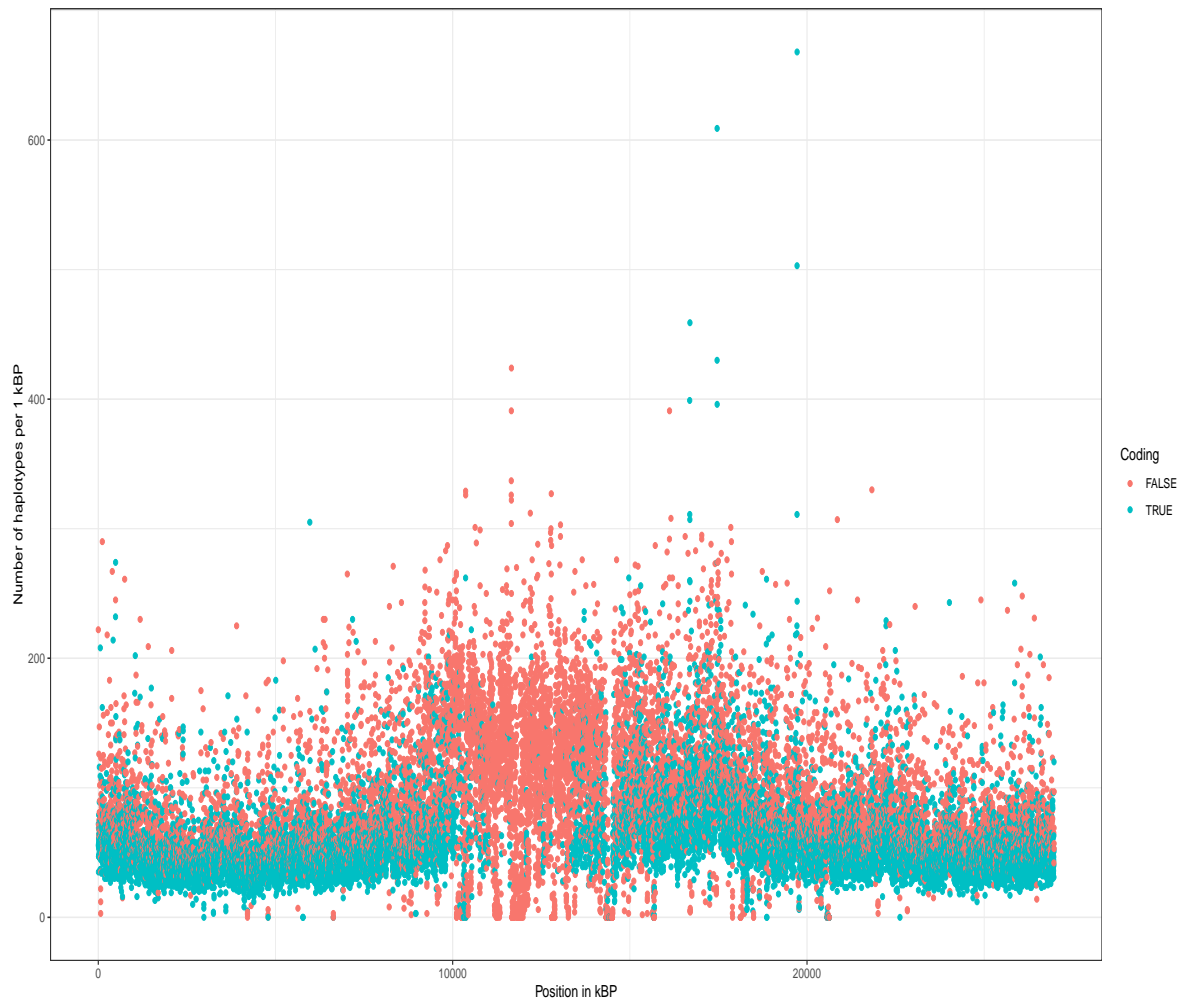


FIGURE 2.5: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

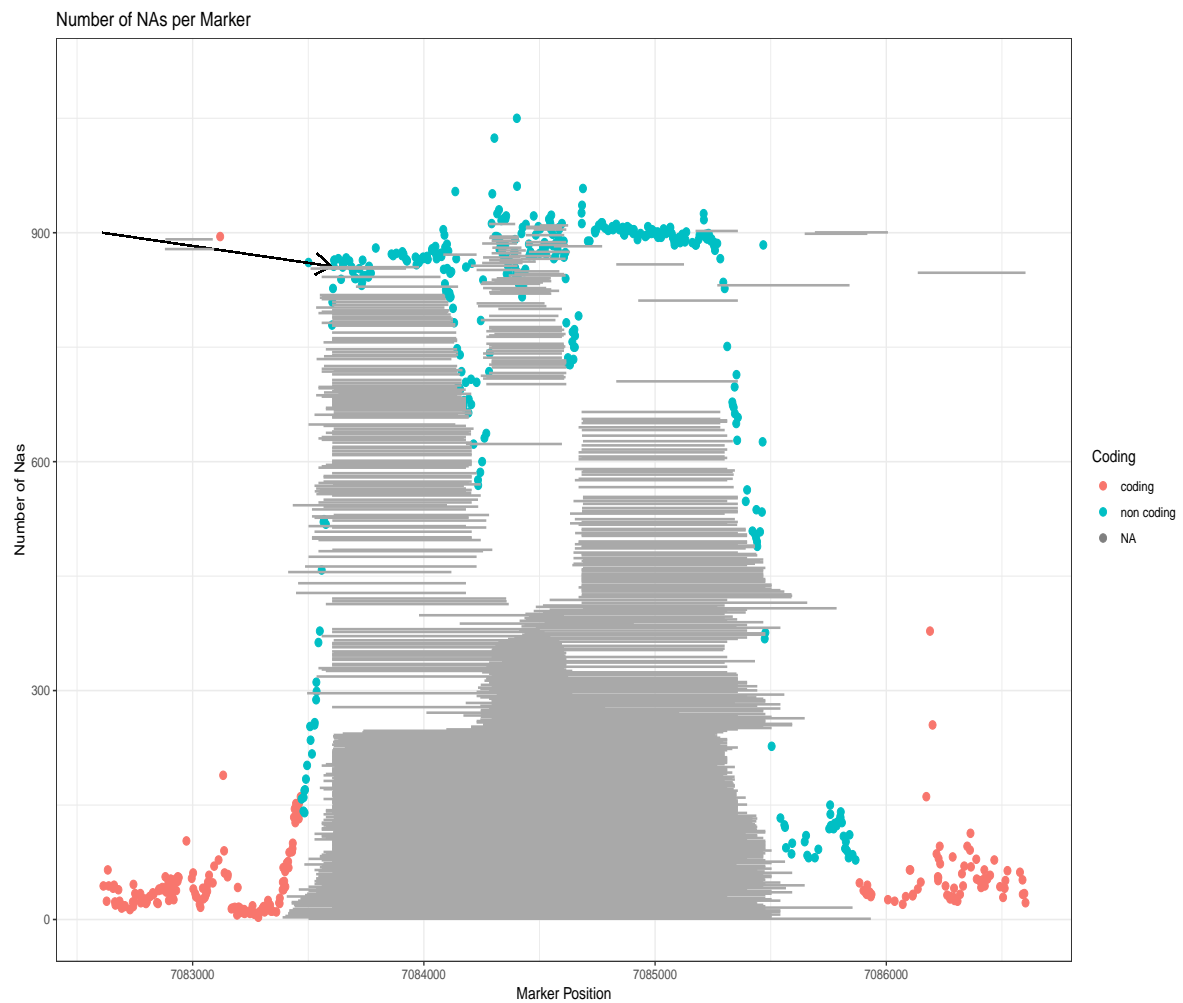


FIGURE 2.6: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

Chapter 3

GWAS Flow a gpu-accelerated software for large-scale genome-wide association studies

3.1 Introduction

Genome-wide association studies, pioneered in human genetics Hirschhorn and Daly, 2005 in the last decade, have become the predominant method to detect associations between phenotypes and the genetic variations present in a population. Understanding the genetic architecture of traits and mapping the underlying genomic polymorphisms is of paramount importance for successful breeding both in plants and animals, as well as for studying the genetic risk factors of diseases. Over the last decades, the cost for genotyping have been reduced dramatically. Early GWAS consisted of a few hundred individuals which have been phenotyped and genotyped on a couple of hundreds to thousands of genomic markers. Nowadays, marker density for many species easily exceed millions of genomic polymorphisms. Albeit commonly SNPs are used for association studies, standard GWAS models are flexible to handle different genomic features as input. The *Arabidopsis* 1001

genomes project features for example 1135 sequenced *Arabidopsis thaliana* accessions with over 10 million genomic markers that segregate in the population Alonso-Blanco et al., 2016. Other genome projects also yielded large amounts of genomic data for a substantial amount of individuals, as exemplified in the 1000 genomes project for humans Siva, 2008, the 2000 yeast genomes project or the 3000 rice genomes project Li, Wang, and Zeigler, 2014. Thus, there is an increasing demand for GWAS models that can analyze these data in a reasonable time frame. One critical step of GWAS is to determine the threshold at which an association is termed significant. Classically the conservative Bonferroni threshold is used, which accounts for the number of statistical tests that are performed, while many recent studies try to use significance thresholds that are based on the false-discovery rate (FDR) Storey and Tibshirani, 2003. An alternative approach are permutation-based thresholds Che et al., 2014. Permutation-based thresholds estimate the significance by shuffling phenotypes and genotypes before each GWAS run, thus any signal left in the data should not have a genetic cause, but might represent model mis-specifications or uneven phenotypic distributions. Typically this process is repeated hundreds to thousands of times and will lead to a distinct threshold for each phenotype analyzed Togninalli et al., 2017. The computational demand of permutation-based thresholds is immense, as per analysis not one, but at least hundreds of GWAS need to be performed. Here the main limitation is the pure computational demand. Thus, faster GWAS models could easily make the estimation of permutation-based thresholds the default choice.

3.2 Methods

GWAS Model

The GWAS model used for GWAS-Flow is based on a fast approximation of the linear-mixed-model described in Kang et al., 2010; Zhang et al., 2010, which estimates the variance components σ_g and σ_e only once in a null model that includes the genetic relationship matrix, but no distinct genetic markers. These components are thereafter used for the tests of each specific marker. Here, the underlying assumption is, that the ratio of these components stays constant, even if distinct genetic markers are included into the GWAS model. This holds true for nearly all markers and only markers which possess a big effect will alter this ratio slightly, where now σ_g would become smaller compared to the null model. Thus, the p-values calculated by the approximation might be a little higher (less significant) for strongly associated markers.

The GWAS-Flow Software

The GWAS-Flow software was designed to provide a fast and robust GWAS implementation that can easily handle large data and allows to perform permutations in a reasonable time frame. Traditional GWAS implementations that are implemented using Python Van Rossum and Drake Jr, 1995 or R R Core Team, 2019 cannot always meet these demands. We tried to overcome those limitations by using TensorFlow Abadi et al., 2015, a multi-language machine learning framework published and developed by Google. GWAS calculations are composed of a series of matrix computations that can be highly parallelized, and easily integrated into the architecture provided by TensorFlow. Our implementation allows both, the classical parallelization of code on multiple processors (CPUs) and the use of graphical processing units (GPUs). GWAS-Flow is written using the Python TensorFlow API. Data import is done with *pandas* McKinney, 2010 and/or *HDF5* for Python Collette,

2013. Preprocessing of the data (e.g filtering by minor Allele count (MAC)) is performed with *numpy* Oliphant, 2006. Variance components for residual and genomic effects are estimated with a slightly altered function based on the Python package *limix* Lippert et al., 2014. The GWAS model is based on the following linear mixed model that takes into account the effect of every marker with respect to the kinship:

$$Y = \beta_0 + X_i\beta_i + u + \epsilon, u \sim N(0, \sigma_g K), \epsilon \sim N(0, \sigma_e I) \quad (3.1)$$

From this LMM the residual sum of squares for marker i are calculated as described in 3.2

$$RSS_i = \sum Y - (X_i\beta_0 + I_i\beta_1) \quad (3.2)$$

The residuals are used to calculate a p-value for each marker according to an overall F-test that compares the model including a distinct genetic effect to a model without this genetic effect:

$$F = \frac{RSS_{env} - R1_{full}}{\frac{R1_{full}}{n-3}} \quad (3.3)$$

Apart from the p-values that derive from the F-distribution, GWAS-Flow also report summary statistics, such as the estimated effect size (β_i) and its standard error for each marker.

Calculation of permutation-based thresholds for GWAS

To calculate a permutation-based threshold, we essentially perform n repetitions ($n > 100$) of the GWAS on the same data with the sole difference that before each GWAS we randomize the phenotypic values. Thus any correlation between the phenotype and the genotype will be broken and indeed for over 90% of these analyses the estimated pseudo-heritability is close to zero.

On the other hand, the phenotypic distribution will stay unaltered by this randomization. Hence, any remaining signal in the GWAS has to be of a non-genetic origin and could be caused by e.g. model mis-specifications. Now we take the lowest p-value (after filtering for the desired minor allele count) for each permutation and take the 5% lowest value as the permutation-based threshold for the GWAS.

Benchmarking

For benchmarking of GWAS-Flow we used data from the *Arabidopsis* 1001 Genomes Project Alonso-Blanco et al., 2016. The genomic data we used were subsets between 10,000 and 100,000 markers. We chose not to include subsets that exceed 100,000 markers, because there is a linear relationship between the number of markers and the computational time demanded, as all markers are tested independently. We used phenotypic data for flowering time at ten degrees (FT10) for *A. thaliana*, published and downloaded from the AraPheno database Seren et al., 2016. We down- and up-sampled sets to generate phenotypes for sets between 100 and 5000 accessions. For each set of phenotypes and markers we ran 10 permutations to assess the computational time needed. All analyses have been performed with a custom R script that has been used previously Togninalli et al., 2017, GWAS-Flow using either a CPU or a GPU architecture and GEMMA Zhou and Stephens, 2012. GEMMA is a fast and efficient implementation of the mixed model that is broadly used to perform GWAS. All calculations were run on the same machine using 16 i9 virtual CPUs. The GPU version ran on an NVIDIA Tesla P100 graphic card. Additionally to the analyses of the simulated data, we compared the times required by GEMMA and both GWAS-Flow implementations for > 200 different real datasets from *A. thaliana* that have been downloaded from the AraPheno Seren et al., 2016 database and have been analyzed with the available fully

imputed genomic dataset of ca. 10 million markers, filtered for a minor allele count greater five.

3.3 Results

The two main factors influencing the computational time for GWAS are the number of markers incorporated in such an analysis and the number of different accessions, while the latter has an approximate quadratic effect in classical GWAS implementations Zhou and Stephens, 2012. Figure 1A shows the time demand as a function of the number of accessions used in the analysis with 10,000 markers. The quadratic increase in time demand is clearly visible for the custom R implementation, as well as for the CPU-based GWAS-Flow implementation and GEMMA. The GWAS-Flow implementation and GEMMA clearly outperforms the R implementation in general, while for a small number of accessions GWAS-Flow is slightly faster than GEMMA. For the GPU-based implementation the increase in run-time with larger sample sizes is much less pronounced. While for small ($< 1,000$ individuals) data, there is no benefit compared to running GWAS-Flow on CPUs or running GEMMA, the GPU-version clearly outperforms the other implementations if the number of accessions increases. Figure 1B shows the computational time in relation to the number of markers and a fixed amount of 2000 accessions for the two different GWAS-Flow implementations. Here, a linear relationship is visible in both cases. To show the performance of GWAS-Flow not only for simulated data, we also run both implementations on more than 200 different real datasets downloaded from the AraPheno database. Figure 1C shows the computational time demands for all analyses comparing both GWAS-Flow implementation to GEMMA. Here, the CPU-based GWAS-Flow performs comparable to GEMMA, while the GPU-based implementation outperforms both,

if the number of accessions is above 500. Importantly all obtained GWAS results (p-values, beta estimates and standard errors of the beta estimates) are nearly (apart from some mathematical inaccuracies) identical between the three different implementations.

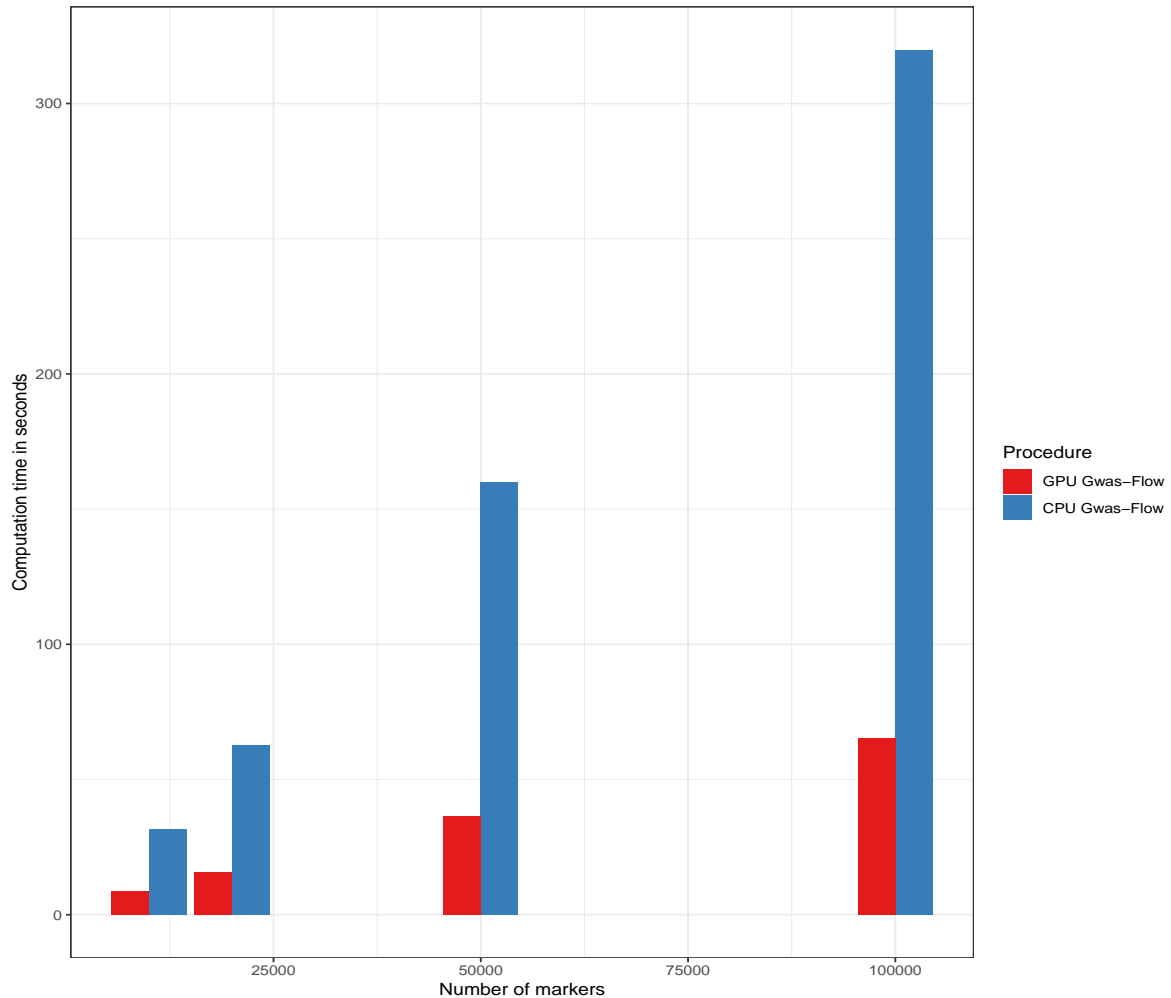


FIGURE 3.1: Computational time as a function of the number of genetic markers with constantly 2000 accessions for both GWAS-Flow versions

3.4 Disucssion

We made use of recent developments of computational architecture and software to cope with the increasing computational demand in analyzing large

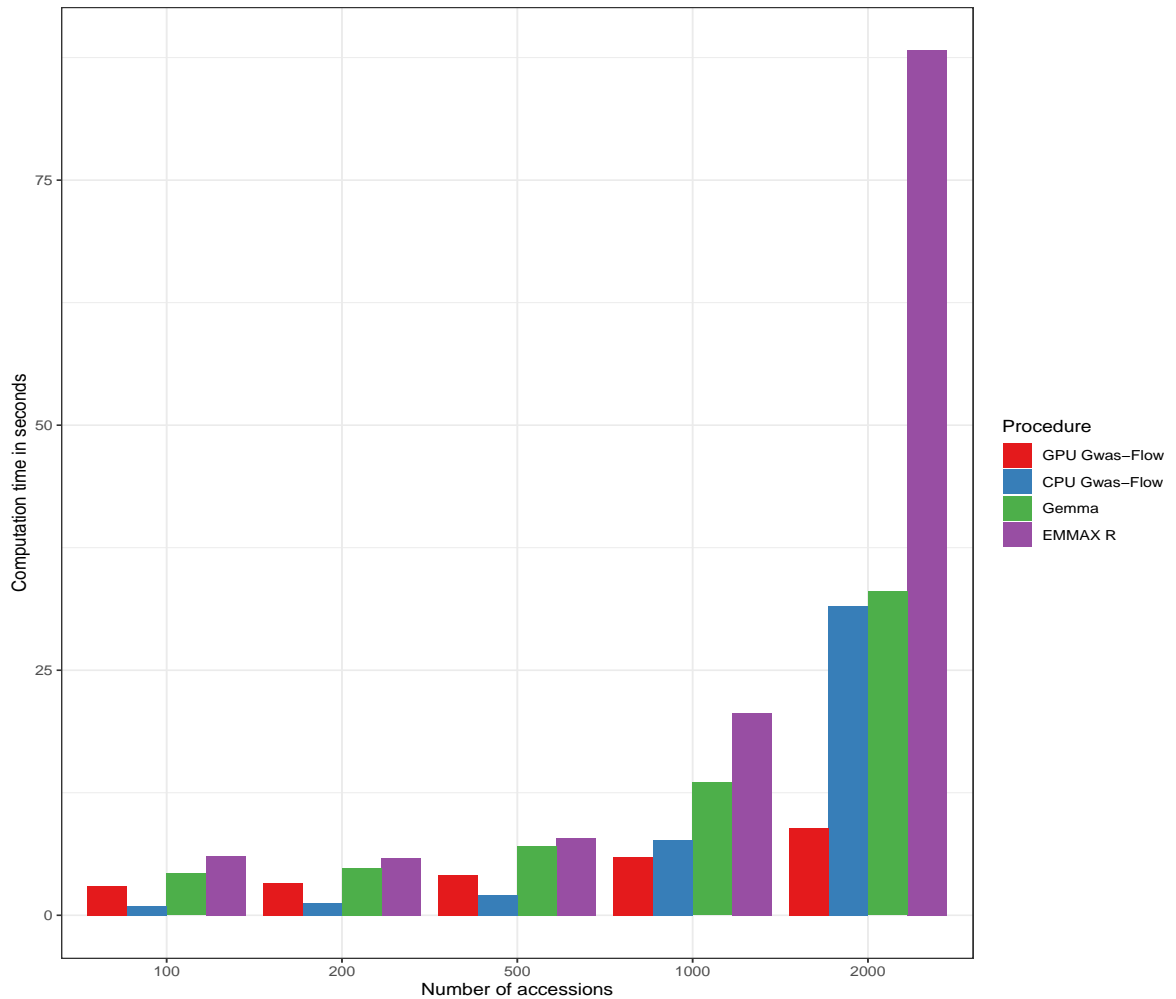


FIGURE 3.2: Computational time as a function of the number of accessions with 10000 markers each.

GWAS datasets. With GWAS-Flow we implemented both, a CPU- and a GPU-based version of the classical linear mixed model commonly used for GWAS. Both implementations outperform custom R scripts on simulated and real data. While the CPU-based version performs nearly identical compared to *GEMMA*, a commonly used GWAS implementation, the GPU-based implementation outperforms both, if the number of individuals, which have been phenotyped, increases. For analyzing big data, here the main limitation would be the RAM of the GPU, but as the individual test for each marker are independent, this can be easily overcome programmatically. The presented GWAS-Flow implementations are markedly faster compared to custom GWAS

scripts and even outperform efficient fast implementations like *GEMMA* in terms of speed. This readily enables the use of permutation-based thresholds, as with *GWAS-Flow* hundred permutations can be performed in a reasonable time even for big data. Thus, it is possible for each analyzed phenotype to create a specific, permutation-based threshold that might present a more realistic scenario. Importantly the permutation-based threshold can be easily adjusted to different minor allele counts, generating different significance thresholds depending on the allele count. This could help to distinguish false and true associations even for rare alleles. *GWAS-Flow* is a versatile and fast software package. Currently *GWAS-Flow* is and will remain under active development to make the software more versatile. This will e.g. include the compatibility with TensorFlow v2.0.0 and enable data input formats, such as PLINK Purcell et al., 2007. The whole framework is flexible, so it is easy to include predefined co-factors e.g. to enable multi-locus models Segura et al., 2012 or account for multi-variate models like the multi-trait mixed model Korte et al., 2012. Standard GWAS are good in detecting additive effects with comparably large effect sizes, but lack the ability to detect epistatic interactions and their influence on complex traits Mckinney and Pajewski, 2012; Korte and Farlow, 2013. To catch the effects of these gene-by-gene or SNP-by-SNP interactions, a variety of genome-wide association interaction studies (GWAIS) have been developed, thoroughly reviewed in Ritchie and Van Steen, 2018. Here, *GWAS-Flow* might provide a tool that enables to test the full pairwise interaction matrix of all SNPs. Although this might be a statistic nightmare, it now would be computationally feasible.

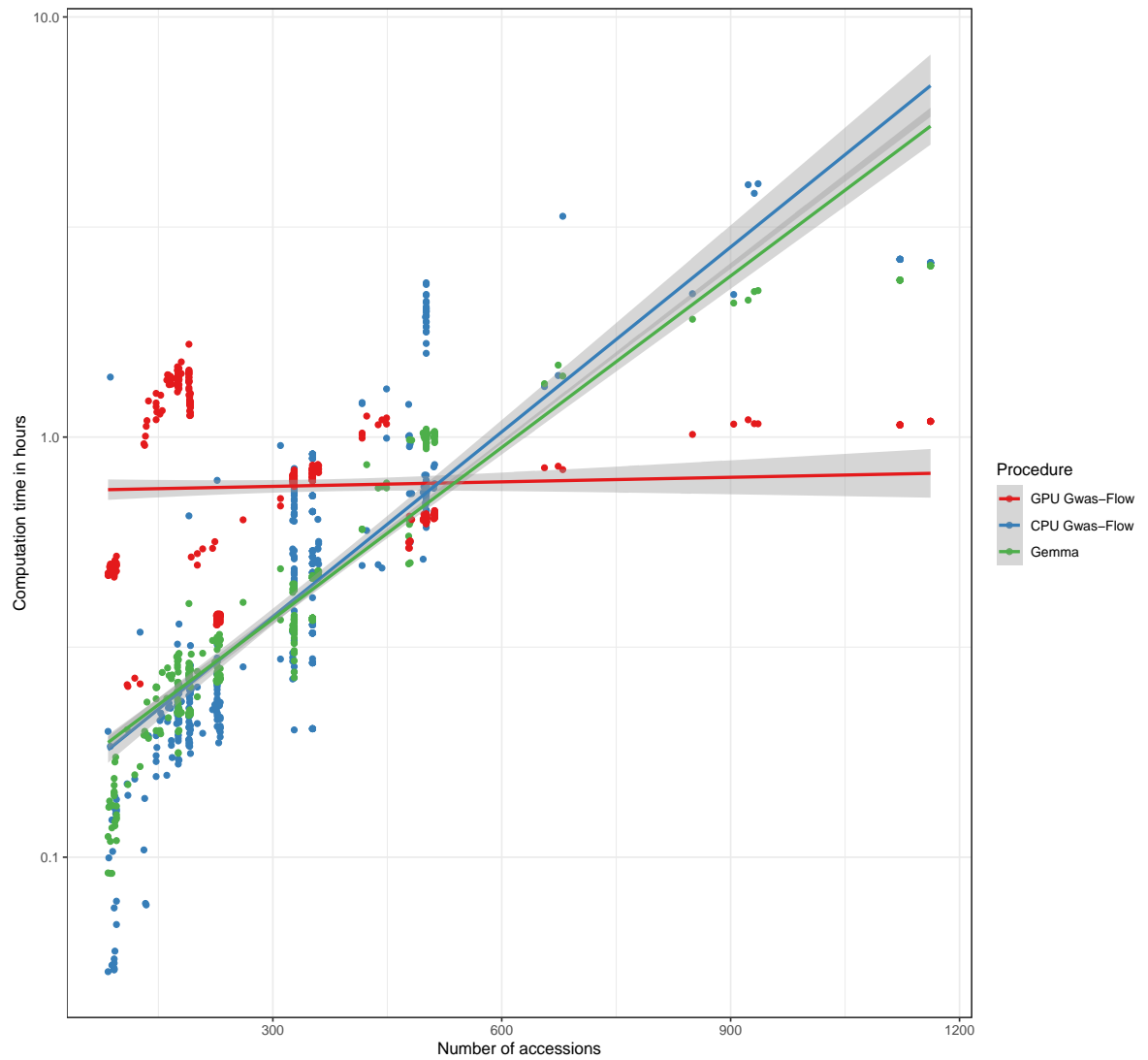


FIGURE 3.3: Comparison of the computational time for the analyses of > 200 phenotypes from *Arabidopsis thaliana* as a function of the number of accessions for GEMMA and the CPU- and GPU-based version of GWAS-Flow. GWAS was performed with a fully imputed genotype matrix containing 10.7 M markers and a minor allele filter of $MAC > 5$

Chapter 4

Genomic prediction of phenotypic values of quantitative traits using Artificial neural networks

4.1 Introduction

4.1.1 A brief history of machine learning

While machine learning, neural networks, deep learning became essential tools for many applications in more recent years, their mathematical principals date back to the early 1950s and 1960s. Figure 4.1 schematically show the basic perceptron model as proposed by Rosenblatt, which was designed to mimic the information flow in biological nervous systems Rosenblatt, 1961

This basic perceptron, which contrary to perceptrons used nowadays does not have an activation function, takes n binary inputs x_1, x_2, \dots, x_n and produces a single, likewise binary, output y after being processed by the perceptron or neuron. To achieve this Rosenblatt introduced the concept of weights which indicated a certain relative importance to the outcome of the output. w_1, w_2, \dots, w_n . The output y is determined by the weighted sum of the weights and biases $\sum_i w_i x_i$. If a certain threshold value is met the neuron is either activated and outputs 1 or not and outputs 0. This is algebraically represented

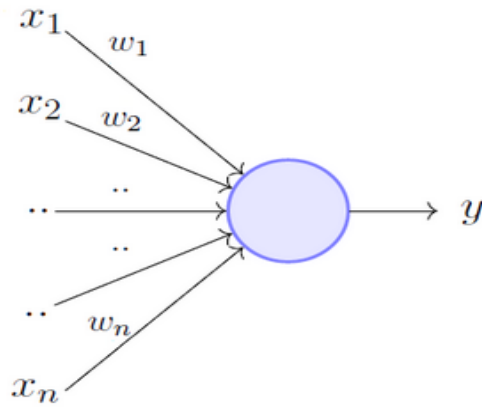


FIGURE 4.1: Basic perceptron model as proposed by Rosenblatt

in 4.1

$$0 = \text{if } \sum_i^n w_i x_i - \theta \leq 0 \quad (4.1a)$$

$$1 = \text{if } \sum_i^n w_i x_i - \theta > 0 \quad (4.1b)$$

Next to the weights w_n and the inputs x_n a third term θ is introduced in equation 4.1 which represents the activation threshold in per definition is negative. A single perceptron is a linear classifier and can only be trained on linearly separable functions and can used as shown by Rosenblatt, 1961 to solve simple logical operations as AND, OR and not. The simple perceptron fails, due to non-linearity, to perform XOR operations as shown by Marvin and Seymour, 1969. This discovery let to a near stillstance in the research of artificial neural networks in the 1970s.

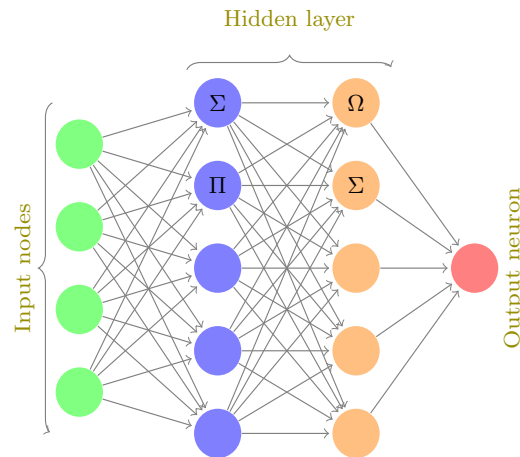


FIGURE 4.2: Schematic layout of a simple multi-layer perceptron

4.1.2 On the nature of quantitative traits

According to the omnigenic model which is an extension of the polygenic model proposed by Boyle, Li, and Pritchard, 2017 and thoroughly reviewed in Timpson et al., 2018 all traits or phenotypic values are influenced by a great number or all genes in the genome. Therefore resulting in traits following certain gradual statistical distributions instead of being binned in classes or even binary. Intuitively this might be contradicting with the foundation of modern Genetics - Mendel's three laws. That were derived from observations with where mainly influenced by one locus. But staying with one of Mendel's examples the round or wrinkled surfaces of peas *Pisum sativum*, an assessment of a couple of thousands peas, would most likely inevitably lead to the conclusion that from the "roundest" to the "wrinkliest" pea any gradual step between those is possible and observable. Mendel's third law of independent segregation also only holds true under certain assumptions. The most simplest one being that the traits under investigation have to be located on different linkage groups. Otherwise for the 7 traits used in Mendel's

initial studies would not have segregated independently. The odds of 7 randomly selected traits being on 7 different linkage groups are rather small, especially taking into account, that the genome of the *P. sativum* consists of only 7 chromosomes itself Kalo et al., 2004. Mendel probably new about traits not following its own law's, as well as being aware of the quantitative nature of traits such as the constitution of surfaces of peas or the color of petals. But being the pioneer of a then rather unexplored field of science, some of which big questions we fail to satisfactory answer today, he did not have the resources or the knowledge to explain behavior's not "mendeling", that were only able to be deciphered in later decades and centuries based on his ground-breaking work.

Initially thought to be contradicting to Mendel's ideas Darwin proposed the concept's of evolution due to natural selection which also introduce the idea of traits following a gradual distribution Darwin, 1859. This contrast led to a long lasting debate in the scientific community in the early 1900s, between the Mendelians and the biometricians who believed in the quantitative nature of continuous traits. This conflict has eventually been solved by Fisher's fundamental work published in 1918 Fisher, 1919. His theories combined the then in all fields of science popular research of distributions with genomics. He he mathematically proved that traits influenced by many genes, with randomly-sampled alleles follow a continuous normal distribution in a population. While this combined the ideas of Mendel and the biometricians it opened an other long debated question of effect size and the overall architecture of complex traits. While in the theory of monogenic traits the effect size of the single gene on the trait is 1 or 100 % with an increasing number of genes influencing a complex traits the *per se* contribution of single gene has to decrease with an increasing number of loci determining the value a given trait. In the 1990s it has been thought, that complex traits are predominantly controlled from few genes with a large to medium effect size, while others

had a minimal influence Zhang et al., 2018.

With the upcoming popularity of GWAS as the favored method to decipher genetic architectures of traits, or having pioneered in human genetics in became clear that the majority of the effect sizes are tiny $< 1\%$ while there are very few loci which have a moderate effect on the phenotypic variance of a population with around 10% or less Korte and Farlow, 2013, Stringer et al., 2011. This nature of quantitative traits present great challenges to animal Goddard and Hayes, 2009 and plant breeding Würschum, 2012, in further improving crop or livestock performances, as well complicating the decomposition of genomic causes for diseases like schizophrenia or autism in human medicine De Rubeis et al., 2014, Purcell et al., 2014.

While the complex nature of the architecture of quantitative traits provide enough challenges as is, all traits will also be influenced by the environment from which an individual originates. Therefore the distribution of trait values in a given population can be expressed as the addition of the variances of its genetic and the environmental effects 4.2.

$$\sigma_P = \sigma_G + \sigma_E \quad (4.2)$$

The genomic and the environmental effects not only influence the phenotypic variance directly, but the environment also has an influence on gene expression methylation of DNA bases etc. and therefore the equation 4.2 needs to be extend by the variance of the gene- environment interactions $\sigma_{G \times E}$?? , Lynch, Walsh, et al., 1998, Walsh and Lynch, 2018.

$$\sigma_P = \sigma_G + \sigma_E + \sigma_{G \times E} \quad (4.3)$$

Equation 4.3 shows the decomposition of the phenotypic variance, to thoroughly understand complex genetic architectures of traits the genetic variance needs to be decomposed further in its additive, dominance and epistatic

components 4.4

$$\sigma_G = \sigma_A + \sigma_D + \sigma_I \quad (4.4)$$

The additive effects are caused by single, for this model mostly homozygous, loci while the variance caused by dominance effects, is caused by heterozygous loci and their resulting interactions being full-, over-, co- or underdominant. And lastly the interaction effects that are a result of two or more genes only having an impact if the involved genes co-occur in a certain state. The resulting variance is commonly known as gene-gene interactions and/or epistasis Falconer and Mackay, 1996.

Since possible interactions in a genome can happen between additive or dominant or a combination of those loci. The variance due to interaction effects σ_I can be further dissembled in the variance resulting from additive-additive σ_{AA} dominant-dominant σ_{DD} and additive-dominant σ_{AD} terms as represented in equation 4.5.

$$\sigma_I = \sigma_{AA} + \sigma_{DD} + \sigma_{AD} \quad (4.5)$$

Knowledge of the variance components involved in the expression of a trait in population, lead up to the estimation of the total influence of all genetic variances and the environmental variance on the phenotypic distribution. This concept is called heritability. The heritability of a trait H^2 accounts for the proportion of the phenotypic variance controlled by the total genetic variance as shown in equation 4.6. This is also referred to as broad sense heritability, because all genetic effects including additive, dominance and epistatic effects are included Brooker, 1999.

$$H^2 = \frac{\sigma_A + \sigma_D + \sigma_I}{\sigma_P} \quad (4.6)$$

The concept of narrow-sense heritability 4.7 is similar to the broad-sense heritability, but only the additive genetic effects are included in the genetic part of the equation. This differentiation is important for natural and artificial selection and thus is commonly used in evolutionary genomics and breeding. Because in diploid species each parent only passes down on a single allele of a given locus. Dominance effects or interaction effects are not commonly inherited from one parent. Therefore it is mainly the additive genetic effects of a parent that influence its offspring. While the dominance and epistatic variances are controlled by the combination of the parents Falconer and Mackay, 1996, Walsh and Lynch, 2018.

$$h^2 = \frac{\sigma_A}{\sigma_P} \quad (4.7)$$

4.1.3 Artificial selection in plant and animal breeding in the genomics era

Genomic prediction has been applied to almost all relevant crop and model species. Including *A. thaliana* Hu et al., 2015, Shen et al., 2013, barley Neyhart, Lorenz, and Smith, 2019, Oakey et al., 2016, Zhong et al., 2009; cassava (*Manihot esculenta*) Elias et al., 2018a, Elias et al., 2018b; cauliflower (*Brassica oleracea* spp) Thorwarth, Yousef, and Schmid, 2018; cotton (*Gossypium* spp. Gapare et al., 2018; maize (*Zea mays*) Moeinizada et al., 2019, Allier et al., 2019, Brauner et al., 2018, Schrag et al., 2018, Schopp et al., 2017b, Sousa et al., 2017, Schopp et al., 2017a, Kadam et al., 2016, Bustos-Korts et al., 2016, Montesinos-López et al., 2015, Owens et al., 2014, Lehermeier et al., 2014, Technow et al., 2014, Peiffer et al., 2014, Riedelsheimer et al., 2013, Guo et al., 2013, Technow, Bürger, and Melchinger, 2013, Windhausen et al., 2012, Rincón et al., 2012; potato (*Solanum tuberosum* Enciso-Rodríguez et al., 2018

4.1.4 Genomic selection using artificial neural networks

Genomic selection (GS) has been successfully applied in animal Gianola and Rosa, 2015, Hayes and Goddard, 2010 and plant breeding Crossa et al., 2010, Desta and Ortiz, 2014, Heffner et al., 2010, Crossa et al., 2017a as well as in medical applications, since it was first reported Hayes, Goddard, et al., 2001a. Since then the repertoire of methods for predicting phenotypic values has increased rapidly e.g. De Los Campos et al., 2009, Habier et al., 2011, Gianola, 2013, Crossa et al., 2017b. The most commonly applied methods include GULP and a set of related algorithms known as the bayesian alphabet Gianola et al., 2009. Genomic prediction in general has repeatedly been shown to outperform pedigree-based methods Crossa et al., 2010, Albrecht et al., 2011 and is nowadays used in many plant and animal breeding schemes. It has also been shown that using whole-genome information is superior to using only feature-selected markers with known QTLs for a given trait Bernardo and Yu, 2007, Heffner, Jannink, and Sorrells, 2011 in some cases. A more recent study Azodi et al., 2019 compared 11 different genomic prediction algorithms with a variety of data sets and found contradicting results, indicating that feature selection can be useful in some cases when the whole genome regression is performed by neural nets. While every new method is a valuable addition to the tool-kits for genomic selection, some fundamental problems remain unsolved, of which the $n \gg p$ problematic stands out. Usually in genomic selection settings the size of the training population (TRN) with n phenotypes is substantially smaller than the number of markers (p) Fan, Han, and Liu, 2014. Making the number of features immensely large, even when SNP-SNP interactions are not considered. Furthermore each marker is treated as an independent observation neglecting collinearity and linkage disequilibrium (LD). Further difficulties arise through non-additive, epistatic and dominance marker effects. The

main problem with epistasis issue quantitative genetics is the almost infinite amount of different marker combinations, that cannot be represented within the size of TRN in the thousands, the same problems arises for example in GWA studies Korte and Farlow, 2013. With already large p the number of possible additive SNP-SNP interactions potentiates to $p^{(p-1)}$. Methods that attempt to overcome those issues are EG-BLUP, using an enhanced epistatic kinship matrix and reproducing kernel Hilbert space regression (RKHS) Jiang and Reif, 2015, Martini et al., 2017.

In the past 10 years, due to increasing availability of high performance computational hardware with decreasing costs and parallel development of free easy-to-use software, most prominent being googles library TensorFlow Abadi et al., 2016 and Keras Chollet et al., 2015, machine learning (ML) has experienced a renaissance. ML is a set of methods and algorithms used widely for regression and classification problems. popular among those are e.g. support vector machines, multi-layer perceptrons (MLP) and convolutional neural networks. The machine learning mimics the architecture of neural networks and are therefore commonly referred to as artificial neural networks (ANN). Those algorithms have widely been applied in many biological fields Min, Lee, and Yoon, 2017, Lan et al., 2018, Mamoshina et al., 2016, Angermueller et al., 2016, Webb, 2018, Rampasek and Goldenberg, 2016.

A variety of studies assessed the usability of ML in genomic prediction González-Camacho et al., 2018, González-Camacho et al., 2016, Ogutu, Piepho, and Schulz-Streeck, 2011, Montesinos-López et al., 2019a, Grinberg, Orhobor, and King, 2018, Cuevas et al., 2019, Montesinos-López et al., 2019b, Ma et al., 2017, Qiu et al., 2016, González-Camacho et al., 2012 Li et al., 2018. Through all those studies the common denominator is that there is no such thing as a gold standard for genomic prediction. No single algorithm was able to outperform all the others tested in a single of those studies, let alone in all.

While the generally aptitude of ML for genomic selection has been repeatedly shown, how no evidence exists that neural networks can outperform or in many cases perform on that same level as mixed-model approaches as GBLUP Hayes, Goddard, et al., 2001b. While in other fields like image classification neural networks have up to 100s of hidden layers He et al., 2016 the commonly used fully-connected networks in genomic prediction of 1 - 3 hidden layers. With 1 layer networks often being the most successful among those. Contradicting to the idea behind machine learning in genomic selection 1 hidden layer networks will be inapt to capture interactions between loci and thus only account for additive effects. As shown in Azodi et al., 2019 convolutional networks perform worse than fully-connected networks in genomic selection, which again is contradicting to other fields where convolutional layers are applied successfully, e.g natural language processing Dos Santos and Gatti, 2014 or medical image analysis Litjens et al., 2017. Instead of using convolutional layers and fully-connected layers only, as show in Pook et al 2019, we also propose to use locally-connected layer in combination with fully-connected layers. While CL and LCL are closely related they have a significant difference. While in CL weights are shared between neurons in LCLs each neuron as its own weight. This leads to a reduced number of parameters to be trained in the following FCLs, and should therefore theoretically lead to a decrease in overfitting a common problem in machine learning. To evaluate the results of Pook et al. 2019 accomplished with simulated data we used the data sets generated in the scope of the 1001 genome project of *Arabidopsis thaliana* Alonso-Blanco et al., 2016

4.2 Proof of concept on ANN-based genomic selection

TABLE 4.1: The effects of treatments X and Y on the four groups studied.

	M_1	M_2	Y_{ADD}	Y_{AND}	Y_{OR}	Y_{XOR}
G_1	0	0	0	0	0	0
G_2	0	1	1	0	1	1
G_3	1	0	1	0	1	1
G_4	1	1	2	1	1	0

TABLE 4.2: The effects of treatments X and Y on the four groups studied.

	M_1	M_2	\hat{Y}_{ADD}	\hat{Y}_{AND}	\hat{Y}_{OR}	\hat{Y}_{XOR}
G_1	0	0	0.01	0.00	0.00	0.01
G_2	0	1	0.99	0.01	0.99	0.98
G_3	1	0	0.99	0.00	0.99	1.01
G_4	1	1	1.99	0.98	1.01	0.02

4.3 Material

4.3.1 DH populations derived from MAZE landraces

4.3.2 A. thaliana

4.4 Methods

4.4.1 ANN

4.4.2 GBLUP

4.5 Results

4.6 Discussion

Chapter 5

GWAS

5.1 Reevaluation of 463 phenotypes from the Ara-Pheno database

5.1.1 Introduction

5.1.2 Material and Methods

5.1.3 Results

5.1.4 Results

5.1.5 Disucssion

5.2 GWAS in DH landrace populatios of maze across and within environments

5.2.1 Introduction

5.2.2 Material and Methods

5.2.3 Results

5.2.4 Results

5.2.5 Disucssion

Appendix A

Source code GWAS-Flow

A.1 gwas.py

```
1 import os
2 import sys
3 import time
4 import numpy as np
5 import pandas as pd
6 import main
7 import h5py
8
9 # set defaults
10 mac_min = 1
11 batch_size = 500000
12 out_file = "results.csv"
13 m = 'phenotype_value'
14 perm = 1
15 mac_min= 6
16
17 X_file = 'gwas_sample_data/AT_geno.hdf5'
18 Y_file = 'gwas_sample_data/phenotype.csv'
19 K_file = 'gwas_sample_data/kinship_ibs_binary_mac5.h5py'
20
21
22
23 for i in range (1,len(sys.argv),2):
24     if sys.argv[i] == "-x" or sys.argv[i] == "--genotype":
25         X_file = sys.argv[i+1]
```

```

26     elif sys.argv[i] == "-y" or sys.argv[i] == "--phenotype":
27         Y_file = sys.argv[i+1]
28     elif sys.argv[i] == "-k" or sys.argv[i] == "--kinship":
29         K_file = sys.argv[i+1]
30     elif sys.argv[i] == "-m":
31         m = sys.argv[i+1]
32     elif sys.argv[i] == "-a" or sys.argv[i] == "--mac_min":
33         mac_min = int(sys.argv[i+1])
34     elif sys.argv[i] == "-bs" or sys.argv[i] == "--batch-size":
35         batch_size = int(sys.argv[i+1])
36     elif sys.argv[i] == "-p" or sys.argv[i] == "--perm":
37         perm = int(sys.argv[i+1])
38     elif sys.argv[i] == "-o" or sys.argv[i] == "--out":
39         out_file = sys.argv[i+1]
40     elif sys.argv[i] == "-h" or sys.argv[i] == "--help":
41         print("-x , --genotype :file containing marker
information in csv or hdf5 format of size")
42         print("-y , --phenotype: file container phenotype
information in csv format" )
43         print("-k , --kinship : file containing kinship matrix
of size k X k in csv or hdf5 format")
44         print("-m : name of columnn containing the phenotype :
default m = phenotype_value")
45         print("-a , --mac_min : integer specifying the minimum
minor allele count necessary for a marker to be included.
Default a = 1" )
46         print("-bs, --batch-size : integer specifying the number
of markers processed at once. Default -bs 500000" )
47         print("-p , --perm : single integer specifying the
number of permutations. Default 1 == no perm ")
48         print("-o , --out : name of output file. Default -o
results.csv ")
49         print("-h , --help : prints help and command line
options")
50         quit()
51     else:
52         print('unknown option ' + str(sys.argv[i]))
53         quit()

```

```

54
55
56
57 print("parsed commandline args")
58
59 start = time.time()
60
61 X,K,Y_,markers = main.load_and_prepare_data(X_file,Y_file,K_file
        ,m)
62
63
64 ## MAF filterin
65 markers_used , X , macs = main.mac_filter(mac_min,X,markers)
66
67 ## prepare
68 print("Begin performing GWAS on ", Y_file)
69
70 if perm == 1:
71     output = main.gwas(X,K,Y_,batch_size)
72     if( X_file.split(".")[ -1] == 'csv'):
73         chr_pos = np.array(list(map(lambda x : x.split("- "),
markers_used)))
74     else:
75         chr_reg = h5py.File(X_file,'r')['positions'].attrs['
chr_regions']
76         mk_index= np.array(range(len(markers)),dtype=int)[macs
>= mac_min]
77         chr_pos = np.array([list(map(lambda x: sum(x > chr_reg
[: ,1]) + 1, mk_index)), markers_used]).T
78         my_time = np.repeat((time.time()-start),len(chr_pos))
79         pd.DataFrame({
80             'chr' : chr_pos[:,0] ,
81             'pos' : chr_pos[:,1] ,
82             'pval': output[:,0] ,
83             'mac' : np.array(macs[macs >= mac_min],dtype=np.int) ,
84             'eff_size': output[:,1] ,
85             'SE' : output[:,2]}).to_csv(out_file,index=False)
86 elif perm > 1:

```

```

87     min_pval = []
88     perm_seeds = []
89     my_time = []
90     for i in range(perm):
91         start_perm = time.time()
92         print("Running permutation ", i+1, " of ", perm)
93         my_seed = np.asscalar(np.random.randint(9999, size=1))
94         perm_seeds.append(my_seed)
95         np.random.seed(my_seed)
96         Y_perm = np.random.permutation(Y_)
97         output = main.gwas(X, K, Y_perm, batch_size)
98         min_pval.append(np.min(output[:, 0]))
99         print("Elapsed time for permuatation", i+1, " with p_min"
, min_pval[i], " is", ":", round(time.time() - start_perm, 2))
100         my_time.append(time.time() - start_perm)
101     pd.DataFrame({
102         'time': my_time,
103         'seed': perm_seeds,
104         'min_p': min_pval }).to_csv(out_file, index=False)
105
106     print("done")
107
108     end = time.time()
109     eltime = np.round(end - start, 2)
110
111     if eltime <= 59:
112         print("Total time elapsed", eltime, "seconds")
113     elif eltime > 59 and eltime <= 3600:
114         print("Total time elapsed", np.round(eltime / 60, 2), "
minutes")
115     elif eltime > 3600 :
116         print("Total time elapsed", np.round(eltime / 60 / 60, 2), "
hours")
117
118

```

A.2 main.py

```

1     import pandas as pd
2     import numpy as np
3     from scipy.stats import f
4     import tensorflow as tf
5     import limix
6     import herit
7     import h5py
8     import limix
9     import multiprocessing as mlt
10
11 def load_and_prepare_data(X_file,Y_file,K_file,m):
12     type_K = K_file.split(".")[1]
13     type_X = X_file.split(".")[1]
14
15     ## load and preprocess genotype matrix
16     Y = pd.read_csv(Y_file,engine='python').sort_values(['
17     accession_id']).groupby('accession_id').mean()
18     Y = pd.DataFrame({'accession_id' : Y.index, '
19     phenotype_value' : Y[m]})
20
21     if type_X == 'hdf5' or type_X == 'h5py' :
22         SNP = h5py.File(X_file,'r')
23         markers= np.asarray(SNP['positions'])
24         acc_X = np.asarray(SNP['accessions'][:,],dtype=np.int)
25     elif type_X == 'csv' :
26         X = pd.read_csv(X_file,index_col=0)
27         markers = X.columns.values
28         acc_X = X.index
29         X = np.asarray(X,dtype=np.float32)/2
30     else :
31         sys.exit("Only hdf5, h5py and csv files are supported")
32
33     if type_K == 'hdf5' or type_K == 'h5py':
34         k = h5py.File(K_file,'r')
35         acc_K = np.asarray(k['accessions'][:,],dtype=np.int)
36     elif type_K == 'csv':
37         k = pd.read_csv(K_file,index_col=0)
38         acc_K = k.index
39         k = np.array(k, dtype=np.float32)

```

```

37
38     acc_Y = np.asarray(Y[['accession_id']]).flatten()
39     acc_isec = [isec for isec in acc_X if isec in acc_Y]
40
41     idx_acc = list(map(lambda x: x in acc_isec, acc_X))
42     idy_acc = list(map(lambda x: x in acc_isec, acc_Y))
43     idk_acc = list(map(lambda x: x in acc_isec, acc_K))
44
45     Y_ = np.asarray(Y.drop('accession_id',1),dtype=np.float32)[
idy_acc,:]
46
47     if type_X == 'hdf5' or type_X == 'h5py' :
48         X = np.asarray(SNP['snps'][0:(len(SNP['snps'])+1)],,
dtype=np.float32)[: ,idx_acc].T
49         X = X[np.argsort(acc_X[idx_acc]),:]
50         k1 = np.asarray(k['kinship'][::])[idk_acc,:]
51         K = k1[:,idk_acc]
52         K = K[np.argsort(acc_X[idx_acc]),:]
53         K = K[:,np.argsort(acc_X[idx_acc])]
54     else:
55         X = X[idy_acc,:]
56         k1 = k[idk_acc,:]
57         K = k1[:,idk_acc]
58
59
60     print("data has been imported")
61     return X,K,Y_,markers
62
63
64 def mac_filter(mac_min, X, markers):
65     ac1 = np.sum(X,axis=0)
66     ac0 = X.shape[0] - ac1
67     macs = np.minimum(ac1,ac0)
68     markers_used = markers[macs >= mac_min]
69     X = X[:,macs >= mac_min]
70     return markers_used, X, macs
71
72 def gwas(X,K,Y,batch_size):

```



```

73     n_marker = X.shape[1]
74     n = len(Y)
75     ## REML
76     K_stand = (n-1)/np.sum((np.identity(n) - np.ones((n,n))/n) *
77                             K) * K
78     vg, delta, ve = herit.estimate(Y,"normal",K_stand,verbose =
79                                   False)
80     print(" Pseudo-heritability is " , vg / (ve + vg + delta))
81     print(" Performing GWAS on ", n , " phenotypes and ",
82           n_marker , "markers")
83     ## Transform kinship-matrix, phenotypes and estimate
84     intercept
85     Xo = np.ones(K.shape[0]).flatten()
86     M = np.transpose(np.linalg.inv(np.linalg.cholesky(vg *
87                                                       K_stand + ve * np.identity(n))))
88       .astype(np.float32)
89     Y_t = np.sum(np.multiply(np.transpose(M),Y),axis=1).astype(
90               np.float32)
91     int_t = np.sum(np.multiply(np.transpose(M),np.ones(n)),axis
92                     =1).astype(np.float32)
93     ## EMMAX Scan
94     RSS_env = (np.linalg.lstsq(np.reshape(int_t,(n,-1)) , np.
95                               reshape(Y_t,(n,-1)))[1]).astype(np.float32)
96     ## calculate betas and se of betas
97     def stderr(a,M,Y_t2d,int_t):
98         x = tf.stack((int_t,tf.squeeze(tf.matmul(M.T,tf.reshape
99             (a,(n,-1))))),axis=1)
100         coeff = tf.matmul(tf.matmul(tf.linalg.inv(tf.matmul(tf.
101             transpose(x),x)),tf.transpose(x)),Y_t2d)
102         SSE = tf.reduce_sum(tf.math.square(tf.math.subtract(Y_t
103             ,tf.math.add(tf.math.multiply(x[:,1],coeff[0,0]),tf.math.
104             multiply(x[:,1],coeff[1,0])))))
105         SE = tf.math.sqrt(SSE/(471-(1+2)))
106         StdERR = tf.sqrt(tf.linalg.diag_part(tf.math.multiply(
107             SE , tf.linalg.inv(tf.matmul(tf.transpose(x),x))))[1]
108         return tf.stack((coeff[1,0],StdERR))
109     ## calculate residual sum squares
110     def rss(a,M,y,int_t):
111         x_t = tf.reduce_sum(tf.math.multiply(M.T,a),axis=1)

```

```

98         lm_res = tf.linalg.lstsq(tf.transpose(tf.stack((int_t,
x_t),axis=0)),Y_t2d)
99         lm_x = tf.concat((tf.squeeze(lm_res),x_t),axis=0)
100         return tf.reduce_sum(tf.math.square(tf.math.subtract(tf
.squeeze(Y_t2d),tf.math.add(tf.math.multiply(lm_x[1],lm_x
[2:]), tf.multiply(lm_x[0],int_t)))))
101     ## loop over the batches
102     for i in range(int(np.ceil(n_marker/batch_size))):
103         tf.reset_default_graph()
104         if n_marker < batch_size:
105             X_sub = X
106         else:
107             lower_limit = batch_size * i
108             upper_limit = batch_size * i + batch_size
109             if upper_limit <= n_marker :
110                 X_sub = X[:,lower_limit:upper_limit]
111                 print("Working on markers ", lower_limit , " to
", upper_limit, " of ", n_marker )
112             else:
113                 X_sub = X[:,lower_limit:]
114                 print("Working on markers ", lower_limit , " to
", n_marker, " of ", n_marker )
115             config = tf.ConfigProto()
116             n_cores = mlt.cpu_count()
117             config.intra_op_parallelism_threads = n_cores
118             config.inter_op_parallelism_threads = n_cores
119             sess = tf.Session(config=config)
120             Y_t2d = tf.cast(tf.reshape(Y_t,(n,-1)),dtype=tf.float32)
121             y_tensor = tf.convert_to_tensor(Y_t,dtype = tf.float32)
122             StdERR = tf.map_fn(lambda a : stderr(a,M,Y_t2d,int_t),
X_sub.T)
123             R1_full = tf.map_fn(lambda a: rss(a,M,Y_t2d,int_t),
X_sub.T)
124             F_1 = tf.divide(tf.subtract(RSS_env, R1_full),tf.divide(
R1_full,(n-3)))
125             if i == 0 :
126                 output = sess.run(tf.concat([tf.reshape(F_1,(X_sub.
shape[1],-1)),StdERR],axis=1))

```

```

127         else :
128             tmp = sess.run(tf.concat([tf.reshape(F_1,(X_sub.
shape[1],-1)),StdERR],axis=1))
129             output = np.append(output,tmp,axis=0)
130             sess.close()
131             F_dist = output[:,0]
132             pval = 1 - f.cdf(F_dist,1,n-3)
133             output[:,0] = pval
134             return output
135
136
137

```

A.3 *herit.py*

```

1
2 def estimate(y, lik, K, M=None, verbose=True):
3     from numpy_sugar.linalg import economic_qs
4     from numpy import pi, var, diag
5     from glimix_core.glmm import GLMMExpFam
6     from glimix_core.lmm import LMM
7     from limix._data._assert import assert_likelihoood
8     from limix._data import normalize_likelihoood,
conform_dataset
9     from limix.qtl._assert import assert_finite
10    from limix._display import session_block, session_line
11    lik = normalize_likelihoood(lik)
12    lik_name = lik[0]
13    with session_block("Heritability analysis", disable=not
verbose):
14        with session_line("Normalising input...", disable=not
verbose):
15            data = conform_dataset(y, M=M, K=K)
16            y = data["y"]
17            M = data["M"]
18            K = data["K"]
19            assert_finite(y, M, K)
20            if K is not None:

```

```
21         # K = K / diag(K).mean()
22         QS = economic_qs(K)
23     else:
24         QS = None
25     if lik_name == "normal":
26         method = LMM(y.values, M.values, QS, restricted=True
27     )
28         method.fit(verbose=verbose)
29     else:
30         method = GLMMExpFam(y, lik, M.values, QS, n_int=500)
31         method.fit(verbose=verbose, factr=1e6, pgtol=1e-3)
32     g = method.scale * (1 - method.delta)
33     e = method.scale * method.delta
34     if lik_name == "bernoulli":
35         e += pi * pi / 3
36     v = var(method.mean())
37     return g , v , e
```

Bibliography

- Abadi, Martín et al. (2015). *TensorFlow: Large-Scale Machine Learning on Heterogeneous Systems*. Software available from tensorflow.org. URL: <https://www.tensorflow.org/>.
- Abadi, Martín et al. (2016). “TensorFlow: A System for Large-scale Machine Learning”. In: *Proceedings of the 12th USENIX Conference on Operating Systems Design and Implementation*. OSDI’16. Savannah, GA, USA: USENIX Association, pp. 265–283. ISBN: 978-1-931971-33-1. URL: <http://dl.acm.org/citation.cfm?id=3026877.3026899>.
- Albrecht, Theresa et al. (2011). “Genome-based prediction of testcross values in maize”. In: *Theoretical and Applied Genetics* 123.2, p. 339.
- Allier, Antoine et al. (2019). “Usefulness Criterion and post-selection Parental Contributions in Multi-parental Crosses: Application to Polygenic Trait Introgression”. In: *G3: Genes, Genomes, Genetics* 9.5, pp. 1469–1479.
- Alonso-Blanco, Carlos et al. (2016). “1,135 genomes reveal the global pattern of polymorphism in *Arabidopsis thaliana*”. In: *Cell* 166.2, pp. 481–491.
- Angermueller, Christof et al. (2016). “Deep learning for computational biology”. In: *Molecular systems biology* 12.7, p. 878.
- Azodi, Christina B et al. (2019). “Benchmarking algorithms for genomic prediction of complex traits”. In: *bioRxiv*, p. 614479.
- Bernardo, Rex and Jianming Yu (2007). “Prospects for genomewide selection for quantitative traits in maize”. In: *Crop Science* 47.3, pp. 1082–1090.
- Boyle, Evan A, Yang I Li, and Jonathan K Pritchard (2017). “An expanded view of complex traits: from polygenic to omnigenic”. In: *Cell* 169.7, pp. 1177–1186.
- Brauner, Pedro C et al. (2018). “Genomic prediction within and among doubled-haploid libraries from maize landraces”. In: *Genetics* 210.4, pp. 1185–1196.

- Brooker, Robert J (1999). *Genetics: analysis & principles*. Addison-Wesley Reading, MA.
- Bustos-Korts, Daniela et al. (2016). "Improvement of predictive ability by uniform coverage of the target genetic space". In: *G3: Genes, Genomes, Genetics* 6.11, pp. 3733–3747.
- Che, Ronglin et al. (2014). "An adaptive permutation approach for genome-wide association study: evaluation and recommendations for use". In: *BioData mining* 7.1, p. 9.
- Chollet, François et al. (2015). *Keras*. <https://keras.io>.
- Collette, Andrew (2013). *Python and HDF5*. O'Reilly.
- Crossa, José et al. (2010). "Prediction of genetic values of quantitative traits in plant breeding using pedigree and molecular markers". In: *Genetics*.
- Crossa, José et al. (2017b). "Genomic selection in plant breeding: Methods, models, and perspectives". In: *Trends in plant science*.
- Crossa, José et al. (2017a). "Genomic selection in plant breeding: methods, models, and perspectives". In: *Trends in plant science* 22.11, pp. 961–975.
- Cuevas, Jaime et al. (2019). "Deep Kernel for Genomic and Near Infrared Predictions in Multi-environment Breeding Trials". In: *G3: Genes, Genomes, Genetics* 9.9, pp. 2913–2924.
- Darwin, Charles (1859). *On the Origin of Species by Means of Natural Selection. or the Preservation of Favored Races in the Struggle for Life*. London: Murray.
- De Los Campos, Gustavo et al. (2009). "Predicting quantitative traits with regression models for dense molecular markers and pedigree". In: *Genetics* 182.1, pp. 375–385.
- De Rubeis, Silvia et al. (2014). "Synaptic, transcriptional and chromatin genes disrupted in autism". In: *Nature* 515.7526, p. 209.
- Desta, Zeratsion Abera and Rodomiro Ortiz (2014). "Genomic selection: genome-wide prediction in plant improvement". In: *Trends in plant science* 19.9, pp. 592–601.
- Dos Santos, Cicero and Maira Gatti (2014). "Deep convolutional neural networks for sentiment analysis of short texts". In: *Proceedings of COLING*

- 2014, the 25th International Conference on Computational Linguistics: Technical Papers, pp. 69–78.
- Elias, Ani A et al. (2018a). “Improving genomic prediction in cassava field experiments by accounting for interplot competition”. In: *G3: Genes, Genomes, Genetics* 8.3, pp. 933–944.
- (2018b). “Improving genomic prediction in cassava field experiments using spatial analysis”. In: *G3: Genes, Genomes, Genetics* 8.1, pp. 53–62.
- Enciso-Rodriguez, Felix et al. (2018). “Genomic selection for late blight and common scab resistance in tetraploid potato (*Solanum tuberosum*)”. In: *G3: Genes, Genomes, Genetics* 8.7, pp. 2471–2481.
- Falconer, DS and TFC Mackay (1996). “Introduction to quantitative genetics. 1996”. In: *Harlow, Essex, UK: Longmans Green* 3.
- Fan, Jianqing, Fang Han, and Han Liu (2014). “Challenges of big data analysis”. In: *National science review* 1.2, pp. 293–314.
- Fisher, Ronald A (1919). “XV.—The correlation between relatives on the supposition of Mendelian inheritance.” In: *Earth and Environmental Science Transactions of the Royal Society of Edinburgh* 52.2, pp. 399–433.
- Gapare, Washington et al. (2018). “Historical Datasets Support Genomic Selection Models for the Prediction of Cotton Fiber Quality Phenotypes Across Multiple Environments”. In: *G3: Genes, Genomes, Genetics* 8.5, pp. 1721–1732.
- Gianola, Daniel (2013). “Priors in whole-genome regression: the Bayesian alphabet returns”. In: *Genetics* 194.3, pp. 573–596.
- Gianola, Daniel and Guilherme JM Rosa (2015). “One hundred years of statistical developments in animal breeding”. In: *Annu. Rev. Anim. Biosci.* 3.1, pp. 19–56.
- Gianola, Daniel et al. (2009). “Additive genetic variability and the Bayesian alphabet”. In: *Genetics* 183.1, pp. 347–363.
- Goddard, Michael E and Ben J Hayes (2009). “Mapping genes for complex traits in domestic animals and their use in breeding programmes”. In: *Nature Reviews Genetics* 10.6, p. 381.

- González-Camacho, JM et al. (2012). "Genome-enabled prediction of genetic values using radial basis function neural networks". In: *Theoretical and Applied Genetics* 125.4, pp. 759–771.
- González-Camacho, Juan Manuel et al. (2016). "Genome-enabled prediction using probabilistic neural network classifiers". In: *BMC genomics* 17.1, p. 208.
- González-Camacho, Juan Manuel et al. (2018). "Applications of machine learning methods to genomic selection in breeding wheat for rust resistance". In: *The plant genome* 11.2.
- Grinberg, Nastasiya F, Oghenejokpeme I Orhobor, and Ross D King (2018). "An Evaluation of Machine-learning for Predicting Phenotype: Studies in Yeast, Rice and Wheat". In: *BioRxiv*, p. 105528.
- Guo, Zhigang et al. (2013). "Accuracy of across-environment genome-wide prediction in maize nested association mapping populations". In: *G3: Genes, Genomes, Genetics* 3.2, pp. 263–272.
- Habier, David et al. (2011). "Extension of the Bayesian alphabet for genomic selection". In: *BMC bioinformatics* 12.1, p. 186.
- Hayes, Ben and Mike Goddard (2010). "Genome-wide association and genomic selection in animal breeding". In: *Genome* 53.11, pp. 876–883.
- Hayes, BJ, ME Goddard, et al. (2001a). "Prediction of total genetic value using genome-wide dense marker maps". In: *Genetics* 157.4, pp. 1819–1829.
- (2001b). "Prediction of total genetic value using genome-wide dense marker maps". In: *Genetics* 157.4, pp. 1819–1829.
- He, Kaiming et al. (2016). "Deep residual learning for image recognition". In: *Proceedings of the IEEE conference on computer vision and pattern recognition*, pp. 770–778.
- Heffner, Elliot L, Jean-Luc Jannink, and Mark E Sorrells (2011). "Genomic selection accuracy using multifamily prediction models in a wheat breeding program". In: *The Plant Genome* 4.1, pp. 65–75.
- Heffner, Elliot L et al. (2010). "Plant breeding with genomic selection: gain per unit time and cost". In: *Crop science* 50.5, pp. 1681–1690.

- Hirschhorn, Joel N. and Mark J. Daly (2005). "Genome-wide association studies for common diseases and complex traits". In: *Nature Reviews Genetics* 6.2, pp. 95–108. ISSN: 1471-0064. DOI: [10.1038/nrg1521](https://doi.org/10.1038/nrg1521). URL: <https://doi.org/10.1038/nrg1521>.
- Hu, Yaodong et al. (2015). "Prediction of plant height in *Arabidopsis thaliana* using DNA methylation data". In: *Genetics* 201.2, pp. 779–793.
- Jiang, Yong and Jochen C Reif (2015). "Modeling epistasis in genomic selection". In: *Genetics* 201.2, pp. 759–768.
- Kadam, Dnyaneshwar C et al. (2016). "Genomic prediction of single crosses in the early stages of a maize hybrid breeding pipeline". In: *G3: Genes, Genomes, Genetics* 6.11, pp. 3443–3453.
- Kalo, P et al. (2004). "Comparative mapping between *Medicago sativa* and *Pisum sativum*". In: *Molecular Genetics and Genomics* 272.3, pp. 235–246.
- Kang, Hyun Min et al. (2010). "Variance component model to account for sample structure in genome-wide association studies". In: *Nature genetics* 42.4, p. 348.
- Korte, Arthur and Ashley Farlow (2013). "The advantages and limitations of trait analysis with GWAS: a review". In: *Plant methods* 9.1, p. 29.
- Korte, Arthur et al. (2012). "A mixed-model approach for genome-wide association studies of correlated traits in structured populations". In: *Nature genetics* 44.9, p. 1066.
- Lan, Kun et al. (2018). "A survey of data mining and deep learning in bioinformatics". In: *Journal of medical systems* 42.8, p. 139.
- Lehermeier, Christina et al. (2014). "Usefulness of multiparental populations of maize (*Zea mays* L.) for genome-based prediction". In: *Genetics* 198.1, pp. 3–16.
- Li, Bo et al. (2018). "Genomic prediction of breeding values using a subset of SNPs identified by three machine learning methods". In: *Frontiers in genetics* 9, p. 237.
- Li, Jia-Yang, Jun Wang, and Robert S Zeigler (2014). "The 3,000 rice genomes project: new opportunities and challenges for future rice research". In: *GigaScience* 3.1, p. 8.

- Lippert, Christoph et al. (2014). "LIMIX: genetic analysis of multiple traits". In: *bioRxiv*. DOI: 10.1101/003905. eprint: <https://www.biorxiv.org/content/early/2014/05/22/003905.full.pdf>. URL: <https://www.biorxiv.org/content/early/2014/05/22/003905>.
- Litjens, Geert et al. (2017). "A survey on deep learning in medical image analysis". In: *Medical image analysis* 42, pp. 60–88.
- Lynch, Michael, Bruce Walsh, et al. (1998). *Genetics and analysis of quantitative traits*. Vol. 1. Sinauer Sunderland, MA.
- Ma, Wenlong et al. (2017). "DeepGS: Predicting phenotypes from genotypes using Deep Learning". In: *bioRxiv*, p. 241414.
- Mamoshina, Polina et al. (2016). "Applications of deep learning in biomedicine". In: *Molecular pharmaceuticals* 13.5, pp. 1445–1454.
- Martini, Johannes WR et al. (2017). "Genomic prediction with epistasis models: on the marker-coding-dependent performance of the extended GBLUP and properties of the categorical epistasis model (CE)". In: *BMC bioinformatics* 18.1, p. 3.
- Marvin, Minsky and Papert Seymour (1969). *Perceptrons*.
- Mckinney, Brett and Nicholas Pajewski (2012). "Six degrees of epistasis: statistical network models for GWAS". In: *Frontiers in genetics* 2, p. 109.
- McKinney, Wes (2010). "Data Structures for Statistical Computing in Python". In: *Proceedings of the 9th Python in Science Conference*. Ed. by Stéfan van der Walt and Jarrod Millman, pp. 51–56.
- Min, Seonwoo, Byunghan Lee, and Sungroh Yoon (2017). "Deep learning in bioinformatics". In: *Briefings in bioinformatics* 18.5, pp. 851–869.
- Moeinizade, Saba et al. (2019). "Optimizing Selection and Mating in Genomic Selection with a Look-Ahead Approach: An Operations Research Framework". In: *G3: Genes, Genomes, Genetics*, g3–200842.
- Montesinos-López, Osval A et al. (2015). "Threshold models for genome-enabled prediction of ordinal categorical traits in plant breeding". In: *G3: Genes, Genomes, Genetics* 5.2, pp. 291–300.

- Montesinos-López, Osval A et al. (2019a). “A benchmarking between deep learning, support vector machine and Bayesian threshold best linear unbiased prediction for predicting ordinal traits in plant breeding”. In: *G3: Genes, Genomes, Genetics* 9.2, pp. 601–618.
- (2019b). “New deep learning genomic-based prediction model for multiple traits with binary, ordinal, and continuous phenotypes”. In: *G3: Genes, Genomes, Genetics* 9.5, pp. 1545–1556.
- Neyhart, Jeffrey, Aaron J Lorenz, and Kevin P Smith (2019). “Multi-Trait Improvement by Predicting Genetic Correlations in Breeding Crosses”. In: *bioRxiv*, p. 593210.
- Oakey, Helena et al. (2016). “Genomic selection in multi-environment crop trials”. In: *G3: Genes, Genomes, Genetics* 6.5, pp. 1313–1326.
- Ogut, Joseph O, Hans-Peter Piepho, and Torben Schulz-Streeck (2011). “A comparison of random forests, boosting and support vector machines for genomic selection”. In: *BMC proceedings*. Vol. 5. 3. BioMed Central, S11.
- Oliphant, Travis E (2006). *A guide to NumPy*. Vol. 1. Trelgol Publishing USA.
- Owens, Brenda F et al. (2014). “A foundation for provitamin A biofortification of maize: genome-wide association and genomic prediction models of carotenoid levels”. In: *Genetics* 198.4, pp. 1699–1716.
- Peiffer, Jason A et al. (2014). “The genetic architecture of maize height”. In: *Genetics* 196.4, pp. 1337–1356.
- Purcell, Shaun et al. (2007). “PLINK: a tool set for whole-genome association and population-based linkage analyses”. In: *The American journal of human genetics* 81.3, pp. 559–575.
- Purcell, Shaun M et al. (2014). “A polygenic burden of rare disruptive mutations in schizophrenia”. In: *Nature* 506.7487, p. 185.
- Qiu, Zhixu et al. (2016). “Application of machine learning-based classification to genomic selection and performance improvement”. In: *International Conference on Intelligent Computing*. Springer, pp. 412–421.
- R Core Team (2019). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Vienna, Austria. URL: <https://www.R-project.org/>.

- Rampasek, Ladislav and Anna Goldenberg (2016). "Tensorflow: Biology's gateway to deep learning?" In: *Cell systems* 2.1, pp. 12–14.
- Riedelsheimer, Christian et al. (2013). "Genomic predictability of interconnected biparental maize populations". In: *Genetics* 194.2, pp. 493–503.
- Rincent, Renaud et al. (2012). "Maximizing the reliability of genomic selection by optimizing the calibration set of reference individuals: comparison of methods in two diverse groups of maize inbreds (*Zea mays* L.)" In: *Genetics* 192.2, pp. 715–728.
- Ritchie, Marylyn D and Kristel Van Steen (2018). "The search for gene-gene interactions in genome-wide association studies: challenges in abundance of methods, practical considerations, and biological interpretation". In: *Annals of translational medicine* 6.8.
- Rosenblatt, Frank (1961). *Principles of neurodynamics. perceptrons and the theory of brain mechanisms*. Tech. rep. Cornell Aeronautical Lab Inc Buffalo NY.
- Schopp, Pascal et al. (2017a). "Accuracy of genomic prediction in synthetic populations depending on the number of parents, relatedness, and ancestral linkage disequilibrium". In: *Genetics* 205.1, pp. 441–454.
- Schopp, Pascal et al. (2017b). "Genomic prediction within and across biparental families: means and variances of prediction accuracy and usefulness of deterministic equations". In: *G3: Genes, Genomes, Genetics* 7.11, pp. 3571–3586.
- Schrag, Tobias A et al. (2018). "Beyond genomic prediction: combining different types of omics data can improve prediction of hybrid performance in maize". In: *Genetics* 208.4, pp. 1373–1385.
- Segura, Vincent et al. (2012). "An efficient multi-locus mixed-model approach for genome-wide association studies in structured populations". In: *Nature genetics* 44.7, p. 825.
- Seren, Ümit et al. (2016). "AraPheno: a public database for *Arabidopsis thaliana* phenotypes". In: *Nucleic acids research*, gkw986.
- Shen, Xia et al. (2013). "A novel generalized ridge regression method for quantitative genetics". In: *Genetics* 193.4, pp. 1255–1268.
- Siva, Nayanah (2008). *1000 Genomes project*.

- Sousa, Massaine Bandeira e et al. (2017). "Genomic-enabled prediction in maize using kernel models with genotype \times environment interaction". In: *G3: Genes, Genomes, Genetics* 7.6, pp. 1995–2014.
- Storey, John D. and Robert Tibshirani (2003). "Statistical significance for genomewide studies". In: *Proceedings of the National Academy of Sciences* 100.16, pp. 9440–9445. ISSN: 0027-8424. DOI: [10.1073/pnas.1530509100](https://doi.org/10.1073/pnas.1530509100). eprint: <https://www.pnas.org/content/100/16/9440.full.pdf>. URL: <https://www.pnas.org/content/100/16/9440>.
- Stringer, Sven et al. (2011). "Underestimated effect sizes in GWAS: fundamental limitations of single SNP analysis for dichotomous phenotypes". In: *PloS one* 6.11, e27964.
- Technow, Frank, Anna Bürger, and Albrecht E Melchinger (2013). "Genomic prediction of northern corn leaf blight resistance in maize with combined or separated training sets for heterotic groups". In: *G3: Genes, Genomes, Genetics* 3.2, pp. 197–203.
- Technow, Frank et al. (2014). "Genome properties and prospects of genomic prediction of hybrid performance in a breeding program of maize". In: *Genetics* 197.4, pp. 1343–1355.
- Thorwarth, Patrick, Eltohamy AA Yousef, and Karl J Schmid (2018). "Genomic Prediction and Association Mapping of Curd-Related Traits in Gene Bank Accessions of Cauliflower". In: *G3: Genes, Genomes, Genetics* 8.2, pp. 707–718.
- Timpson, Nicholas J et al. (2018). "Genetic architecture: the shape of the genetic contribution to human traits and disease". In: *Nature Reviews Genetics* 19.2, p. 110.
- Togninalli, Matteo et al. (2017). "The AraGWAS Catalog: a curated and standardized Arabidopsis thaliana GWAS catalog". In: *Nucleic acids research* 46.D1, pp. D1150–D1156.
- Van Rossum, Guido and Fred L Drake Jr (1995). *Python tutorial*. Centrum voor Wiskunde en Informatica Amsterdam, The Netherlands.
- Walsh, Bruce and Michael Lynch (2018). *Evolution and selection of quantitative traits*. Oxford University Press.

- Webb, Sarah (2018). "Deep learning for biology". In: *Nature* 554.7693.
- Windhausen, Vanessa S et al. (2012). "Effectiveness of genomic prediction of maize hybrid performance in different breeding populations and environments". In: *G3: Genes, Genomes, Genetics* 2.11, pp. 1427–1436.
- Würschum, Tobias (2012). "Mapping QTL for agronomic traits in breeding populations". In: *Theoretical and Applied Genetics* 125.2, pp. 201–210.
- Zhang, Yan et al. (2018). "Estimation of complex effect-size distributions using summary-level statistics from genome-wide association studies across 32 complex traits". In: *Nature genetics* 50.9, p. 1318.
- Zhang, Zhiwu et al. (2010). "Mixed linear model approach adapted for genome-wide association studies". In: *Nature Genetics* 42.4, pp. 355–360. DOI: [10.1038/ng.546](https://doi.org/10.1038/ng.546). URL: <https://doi.org/10.1038/ng.546>.
- Zhong, Shengqiang et al. (2009). "Factors affecting accuracy from genomic selection in populations derived from multiple inbred lines: a barley case study". In: *Genetics* 182.1, pp. 355–364.
- Zhou, Xiang and Matthew Stephens (2012). "Genome-wide efficient mixed-model analysis for association studies". In: *Nature Genetics* 44.7, pp. 821–824. DOI: [10.1038/ng.2310](https://doi.org/10.1038/ng.2310). URL: <https://doi.org/10.1038/ng.2310>.