

JULIUS-MAXIMILIANS UNIVERSITÄT WÜRZBURG

DOCTORAL THESIS

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

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*A thesis submitted in fulfillment of the requirements*

*for the degree of Ph.D.*

*in the*

Research group for evolutionary genomics

GSLs

October 21, 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:

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- 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.

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*“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. . .

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# List of Abbreviations

<b>ANN</b>	<b>Artificial Neural Network</b>
<b>BLUP</b>	<b>Best Linear Unbiased Predictor</b>
<b>BLUE</b>	<b>Best Linear Unbiased Estimator</b>
<b>CPU</b>	<b>Core Processing Unit</b>
<b>EMMA</b>	<b>Efficient Mixed Model Associations</b>
<b>FCL</b>	<b>Fully Connected Layer</b>
<b>GP</b>	<b>Genomic Prediction</b>
<b>GPU</b>	<b>Graphical Processing Unit</b>
<b>GS</b>	<b>Genomic Selection</b>
<b>GWAIS</b>	<b>Genome Wide Interaction Association Studies</b>
<b>GWAS</b>	<b>Genome Wide Association Studies</b>
<b>HDF</b>	<b>Hierarchical Data Format</b>
<b>LCL</b>	<b>Locally Connected Layer</b>
<b>LD</b>	<b>Linkage Disequilibrium</b>
<b>LMM</b>	<b>Linear Mixed Model</b>
<b>MLP</b>	<b>Multi Layer Perceptron</b>
<b>ML</b>	<b>Machine Learning</b>
<b>QTL</b>	<b>Quantitative Trait Locus</b>
<b>RKHS</b>	<b>Reproducing Kernel Hilbert Spaces</b>
<b>RSS</b>	<b>Residual Sum of Squares</b>
<b>SNP</b>	<b>Single Nucleotide Polymorphism</b>
<b>TRN</b>	<b>TRaiNing subset</b>
<b>TST</b>	<b>TeSTing subset</b>
<b>WGS</b>	<b>Whole Genome Sequencing</b>
<b>LSC</b>	<b>Large Single Copy</b>
<b>SSC</b>	<b>Small Single Copy</b>
<b>IR</b>	<b>Inverted Repeat</b>
<b>DNA</b>	<b>DeoxyriboNucleic Acid</b>
<b>DNA</b>	<b>RiboNucleic Acid</b>
<b>GUI</b>	<b>Graphical User Interface</b>
<b>BP</b>	<b>Base Pair</b>
<b>DH</b>	<b>Doubled Haploid</b>
<b>GBLUP</b>	<b>Genomic Best Linear Unbiased Predictor</b>
<b>XOR</b>	<b>eXclusive OR</b>
<b>ReLU</b>	<b>Rectified Linear Units</b>

*For/Dedicated to/To my...*

# 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

### 1.2.1 Methods

### 1.2.2 Tools

### 1.2.3 Evaluation

#### Quantitative

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

## Qualitative

## Consistency

### 1.2.4 Data

## Simulated

## Real data set

## Novel data set

## 1.3 Results

### 1.3.1 Qualitative

### 1.3.2 Quantitative

## Simulated data

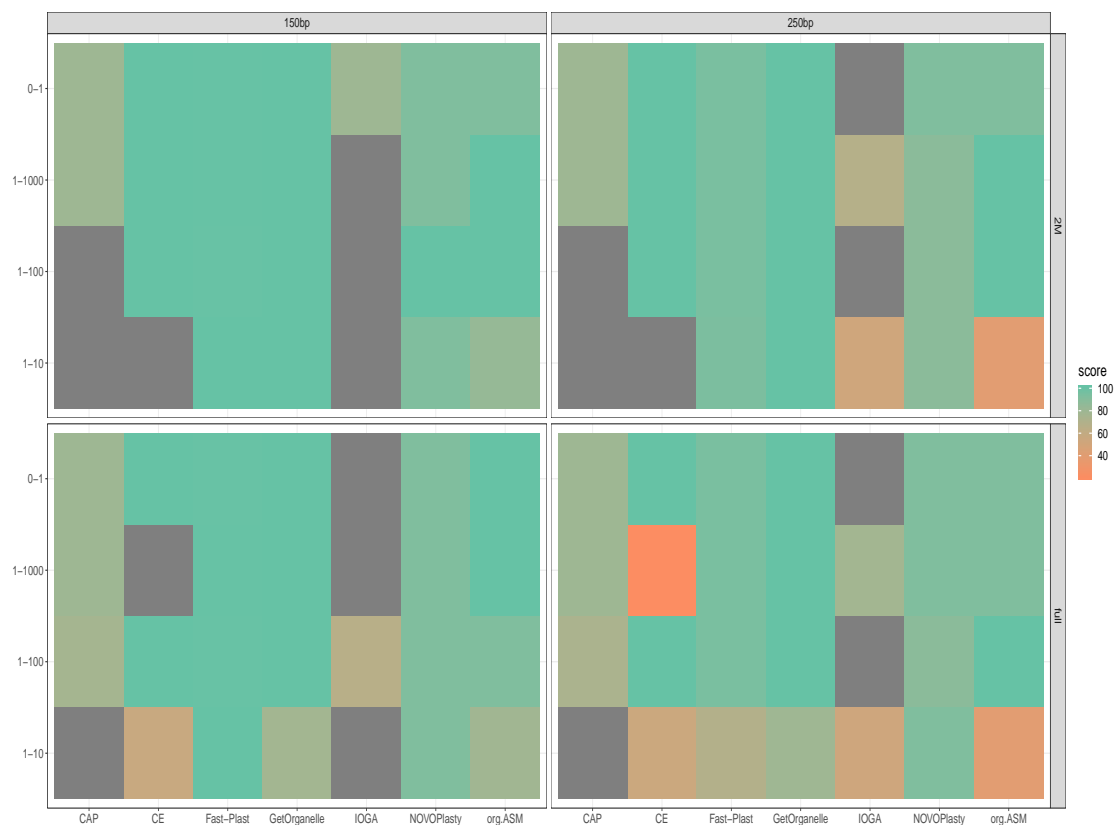


FIGURE 1.1: Results of assemblies executed with simulated data sets.



## Real data sets

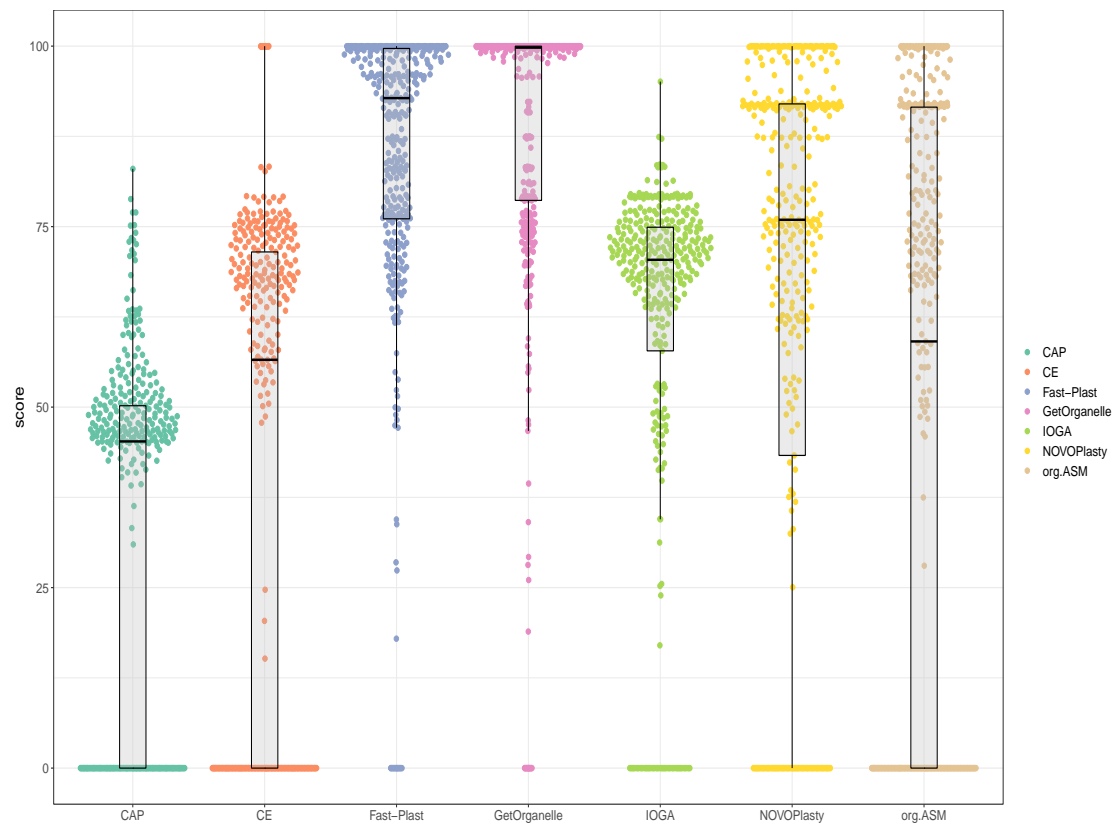


FIGURE 1.2: Box and swarm plots depict the results from the scoring shown in 1.1

Consistency

Real data sets

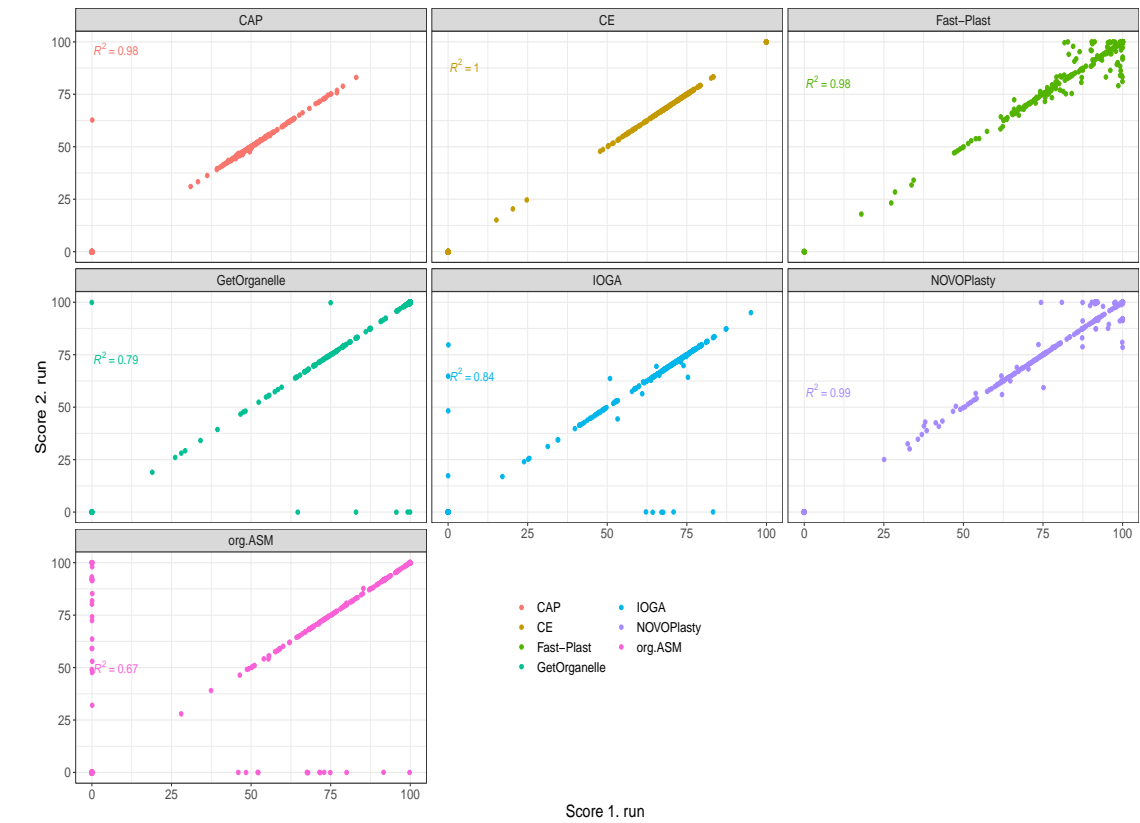


FIGURE 1.3: Swarm plots depict the results from the scoring shown in ??

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

Novel

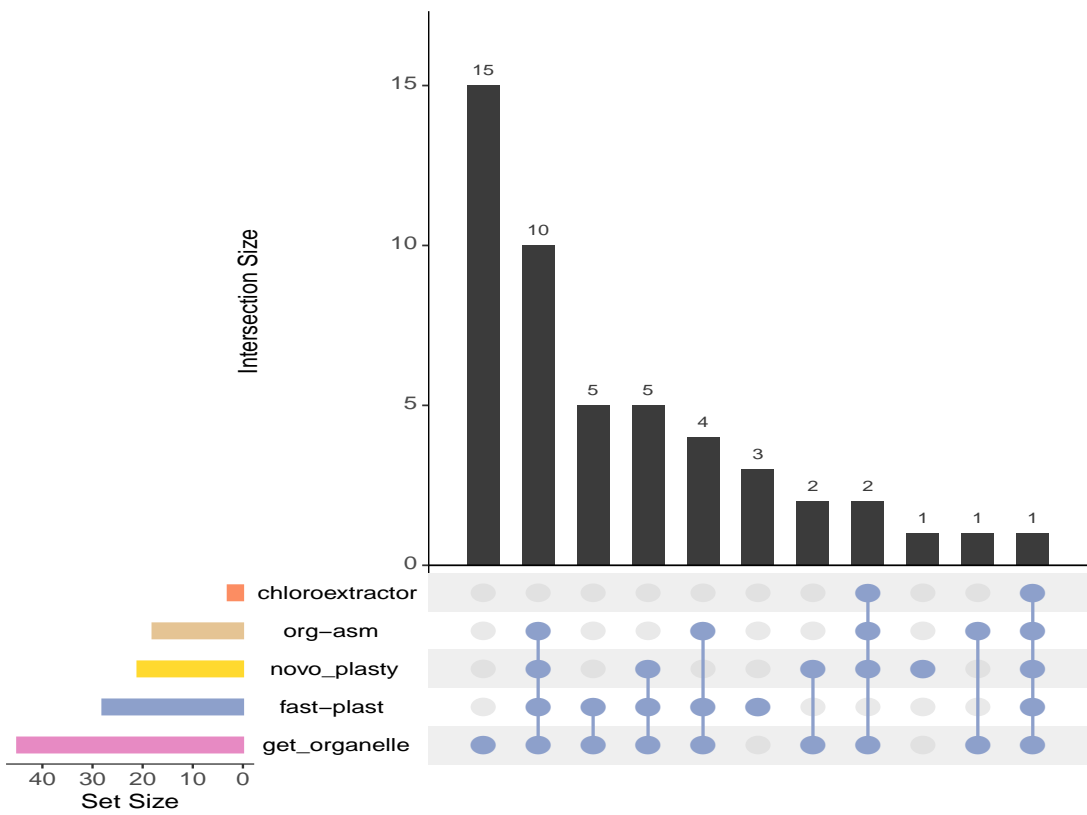


FIGURE 1.4: nls

## 1.4 Disucssion

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FIGURE 1.5: Upset plot showing the intersections of sucess rates between assemblers. A successful assembly was defined with a score > 99 according to equation 1.1

## **2 Understanding the hapoltype structure of Arabidopisis thaliana**

### **2.1 Introduction**

### **2.2 Haplotyping of A. thaliana**

### **2.3 Results**

### **2.4 Disucssion**

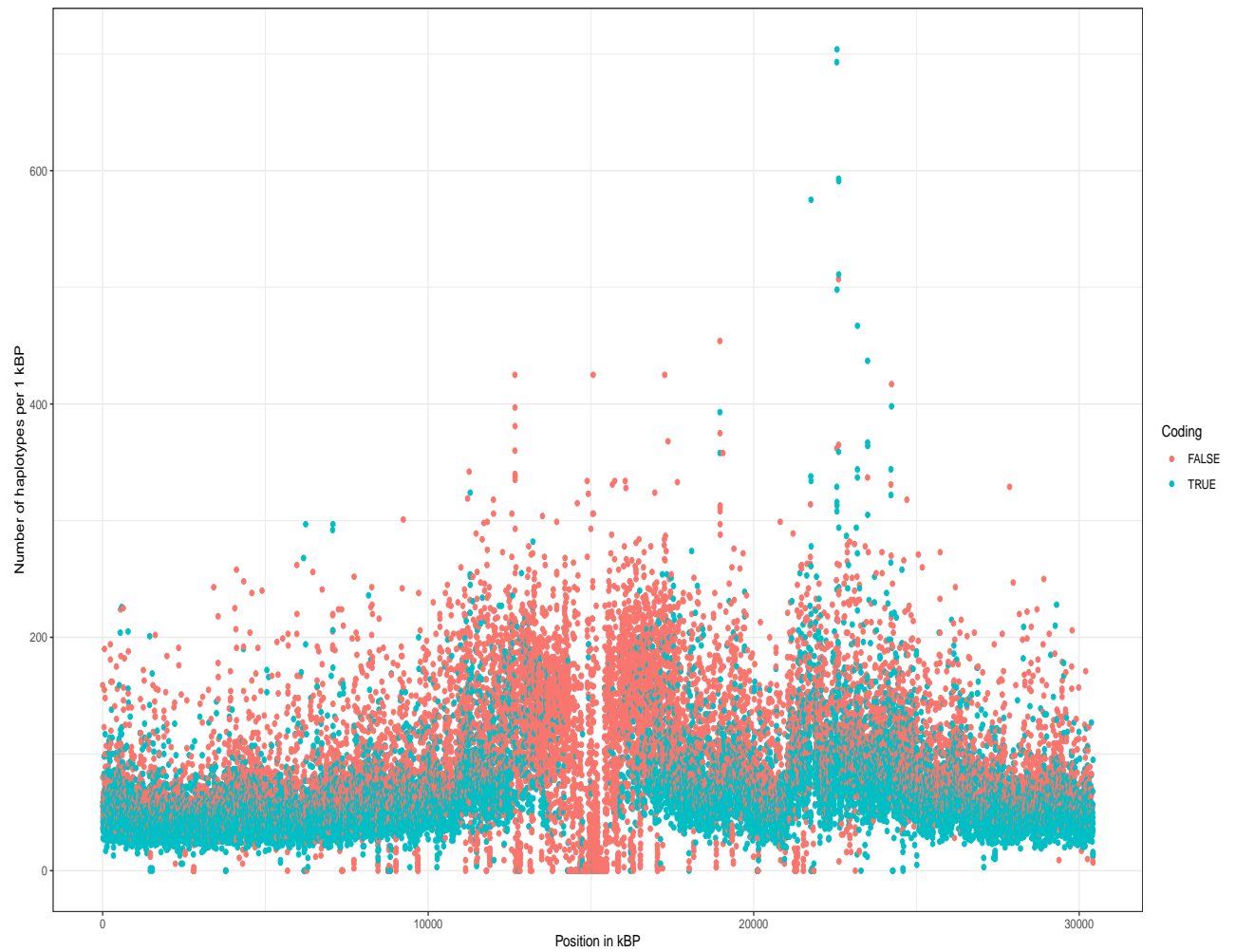


FIGURE 2.1: The number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

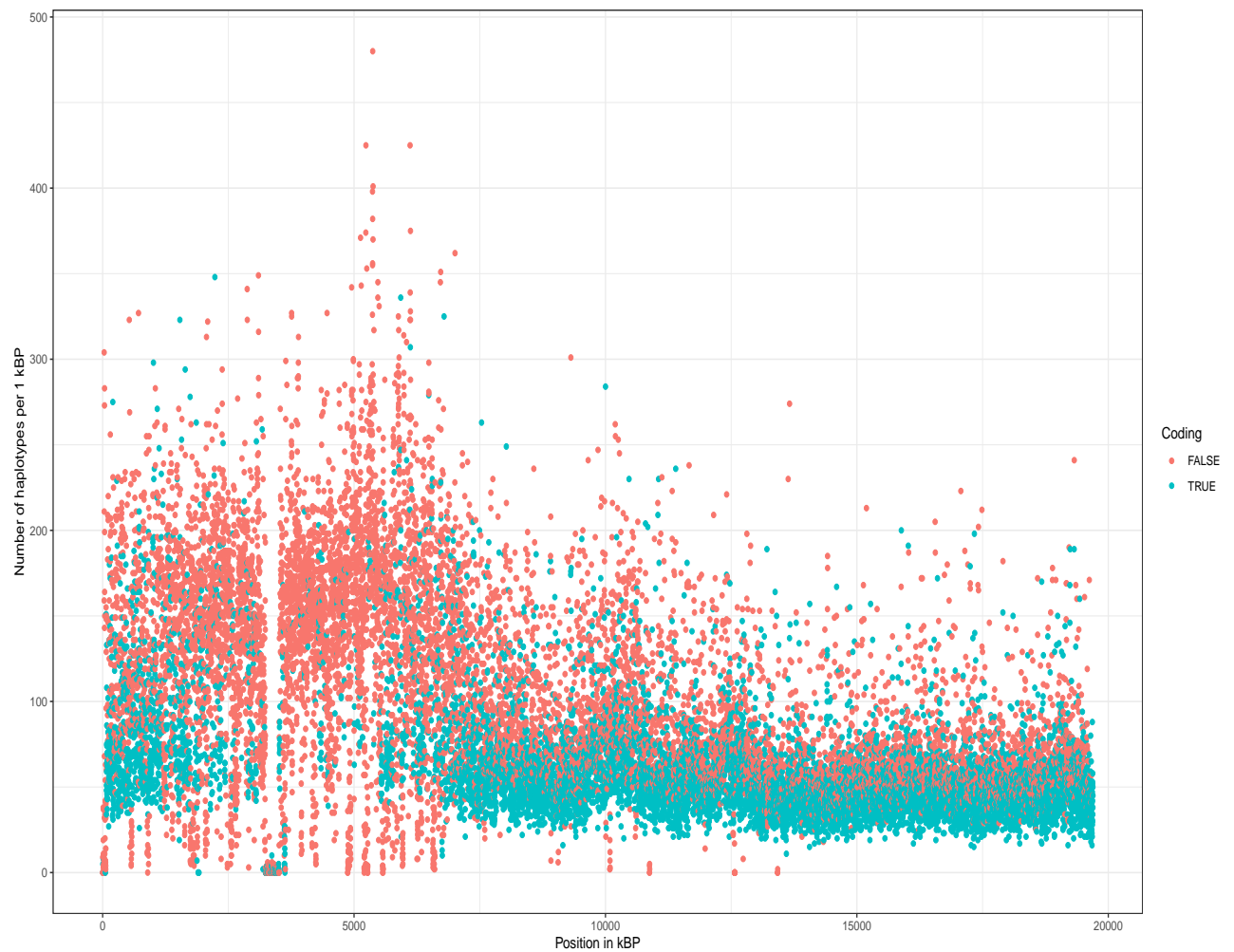


FIGURE 2.2: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

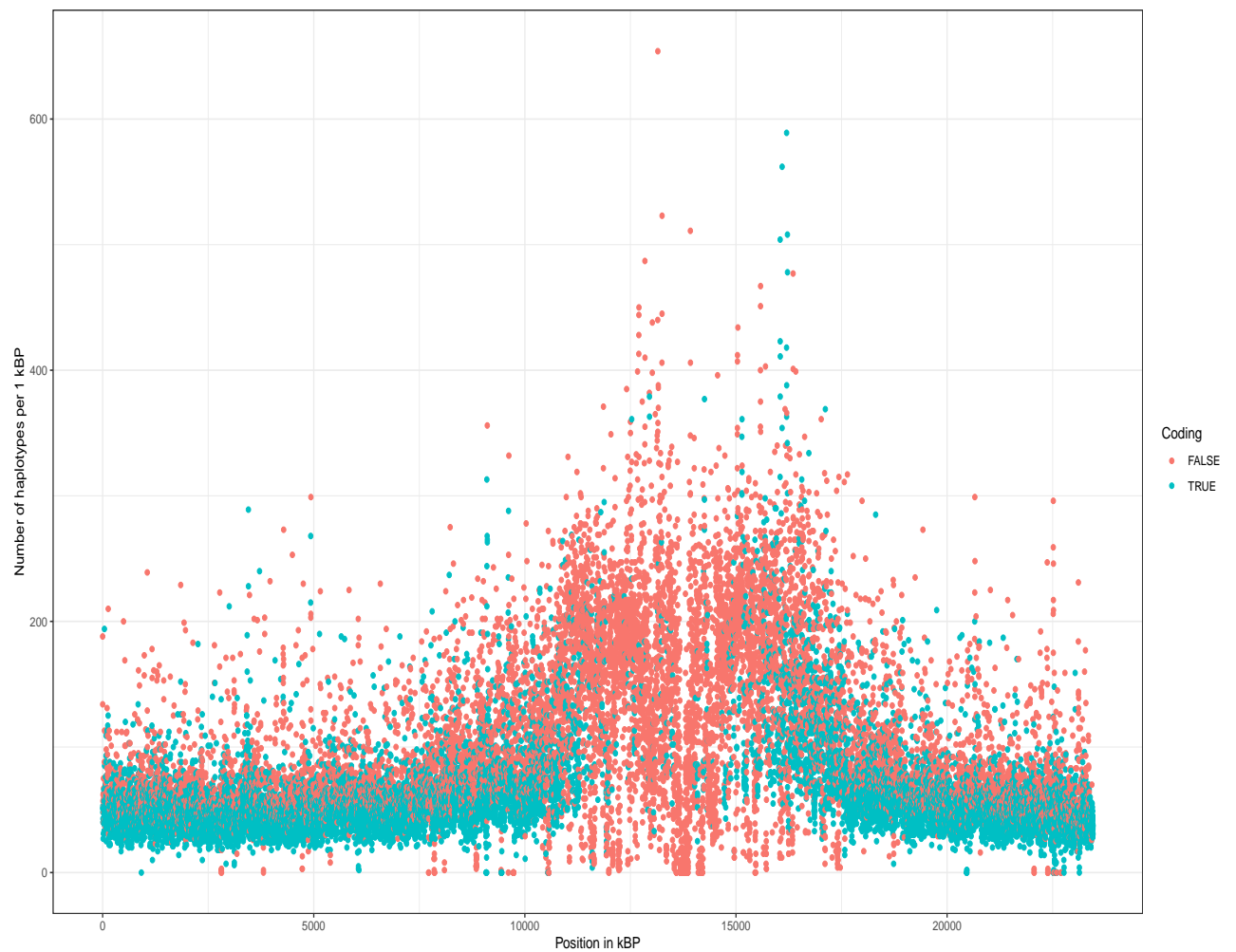


FIGURE 2.3: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.



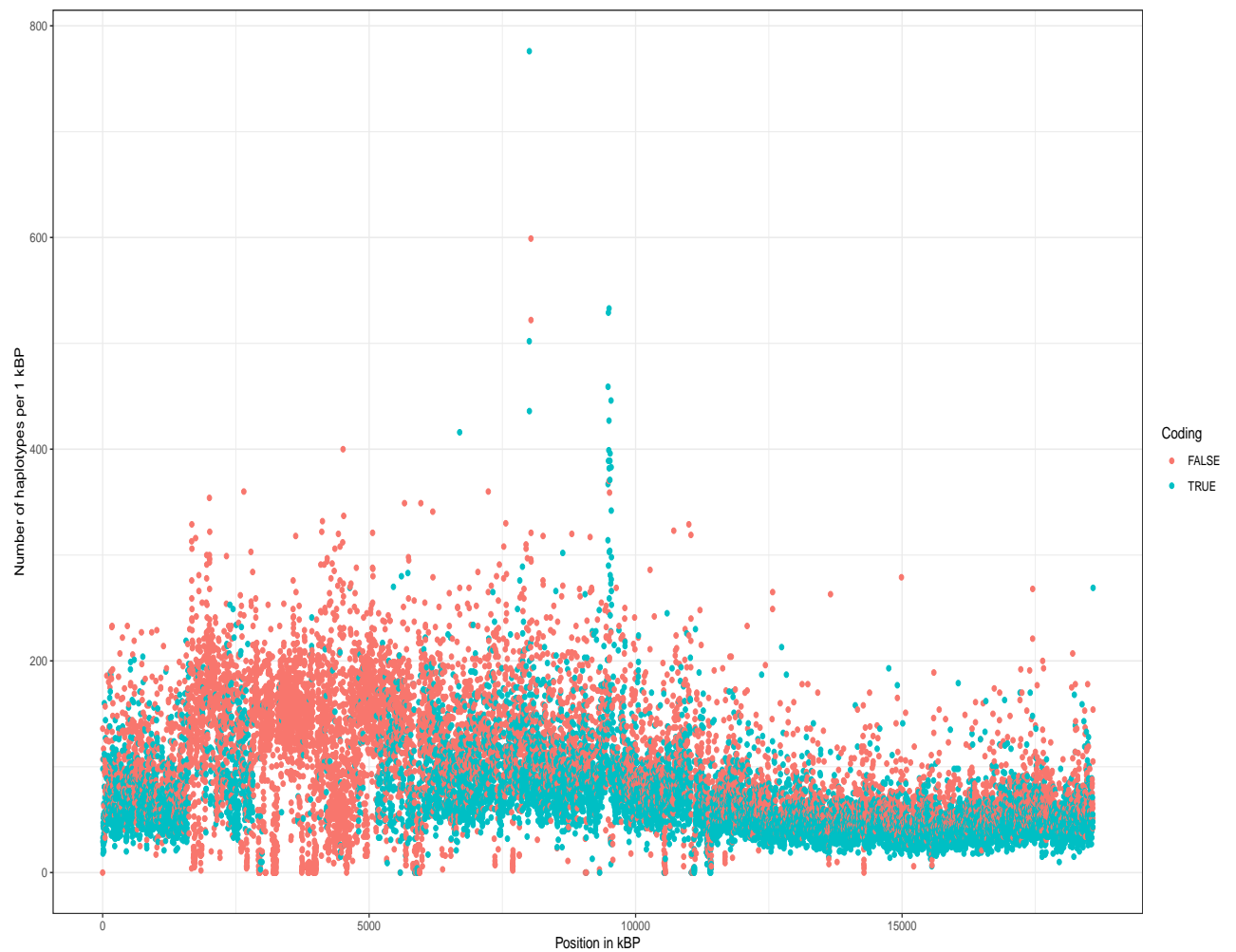


FIGURE 2.4: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

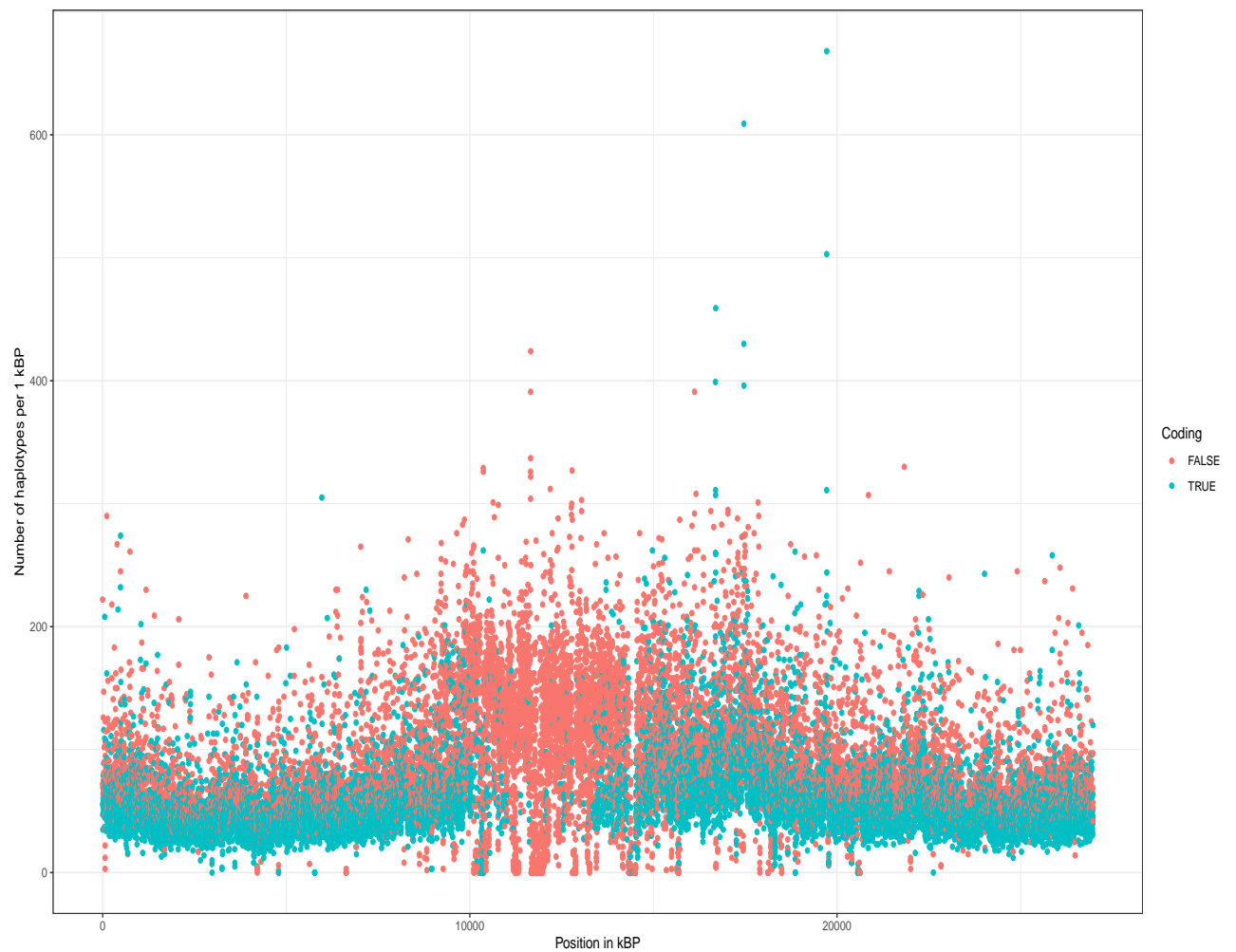


FIGURE 2.5: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

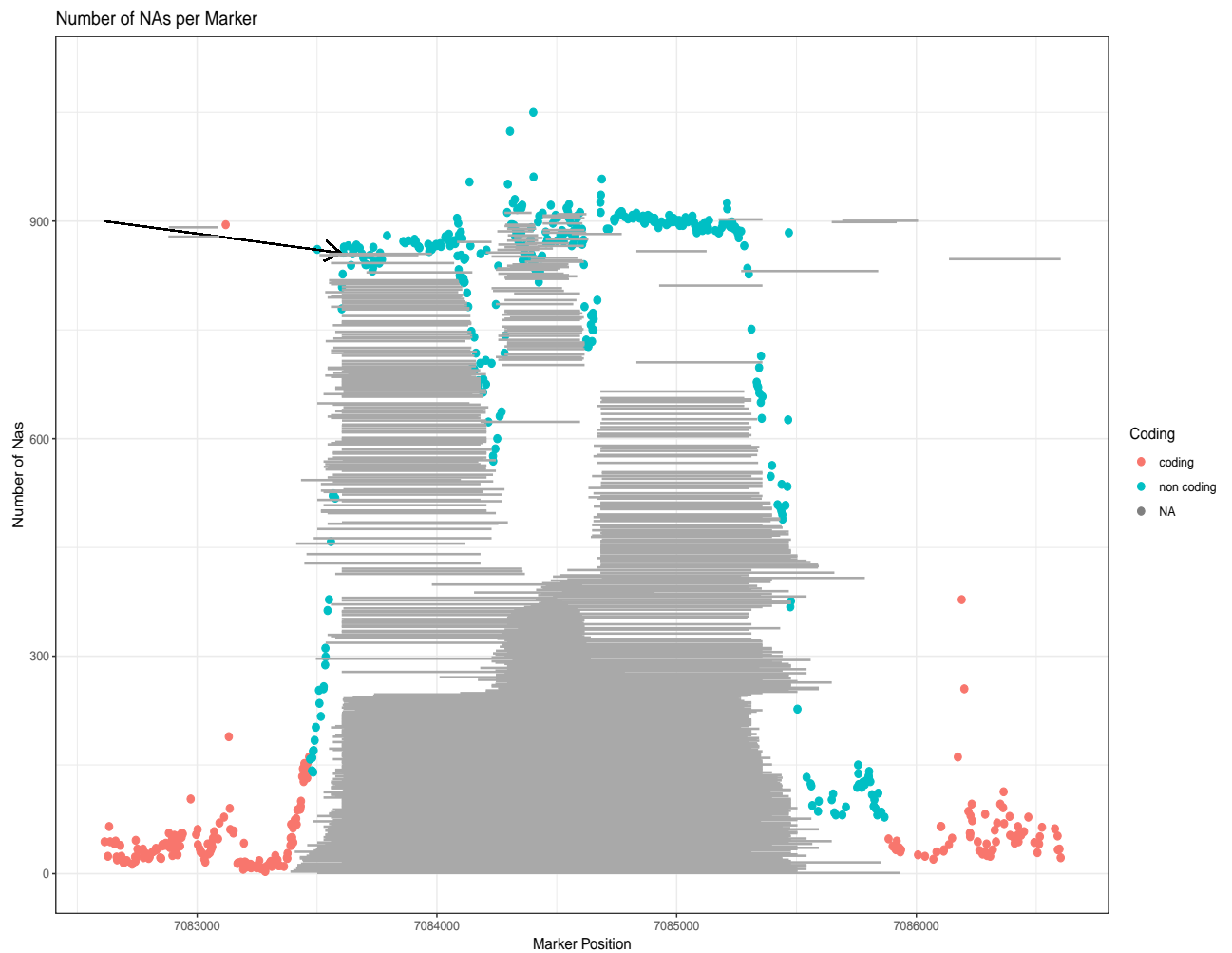


FIGURE 2.6: Number of segregating haplotypes with a polymorphism in at least one position over a stretch of 1 kBP.

## 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  $\sigma_g$  and  $\sigma_e$  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  $\sigma_g$  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 ( $\beta_i$ ) 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 Ara-Pheno 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.

### 3.4 Disucssion

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

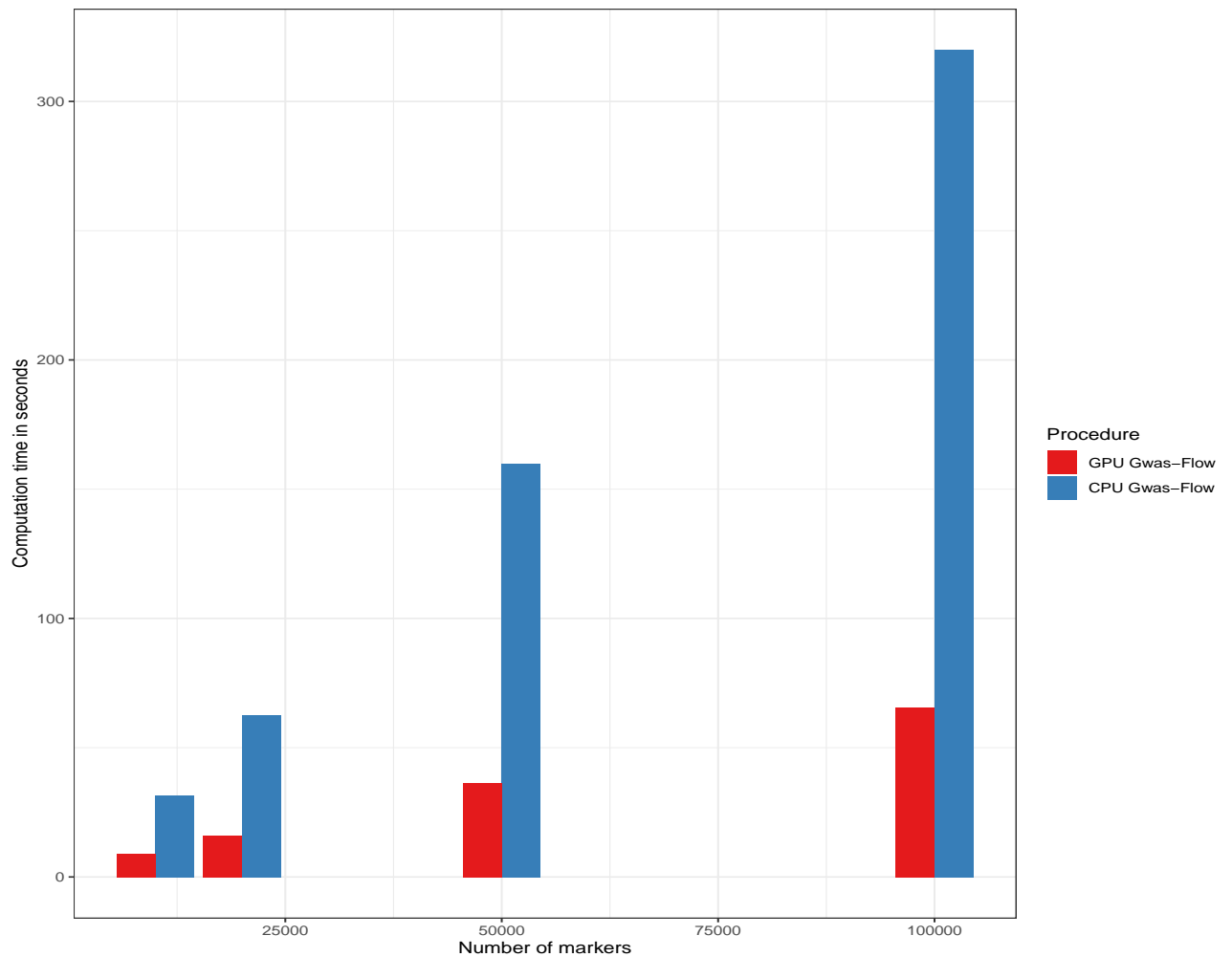


FIGURE 3.1: Computational time as a function of the number of genetic markers with constantly 2000 accessions for both GWAS-Flow versions

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

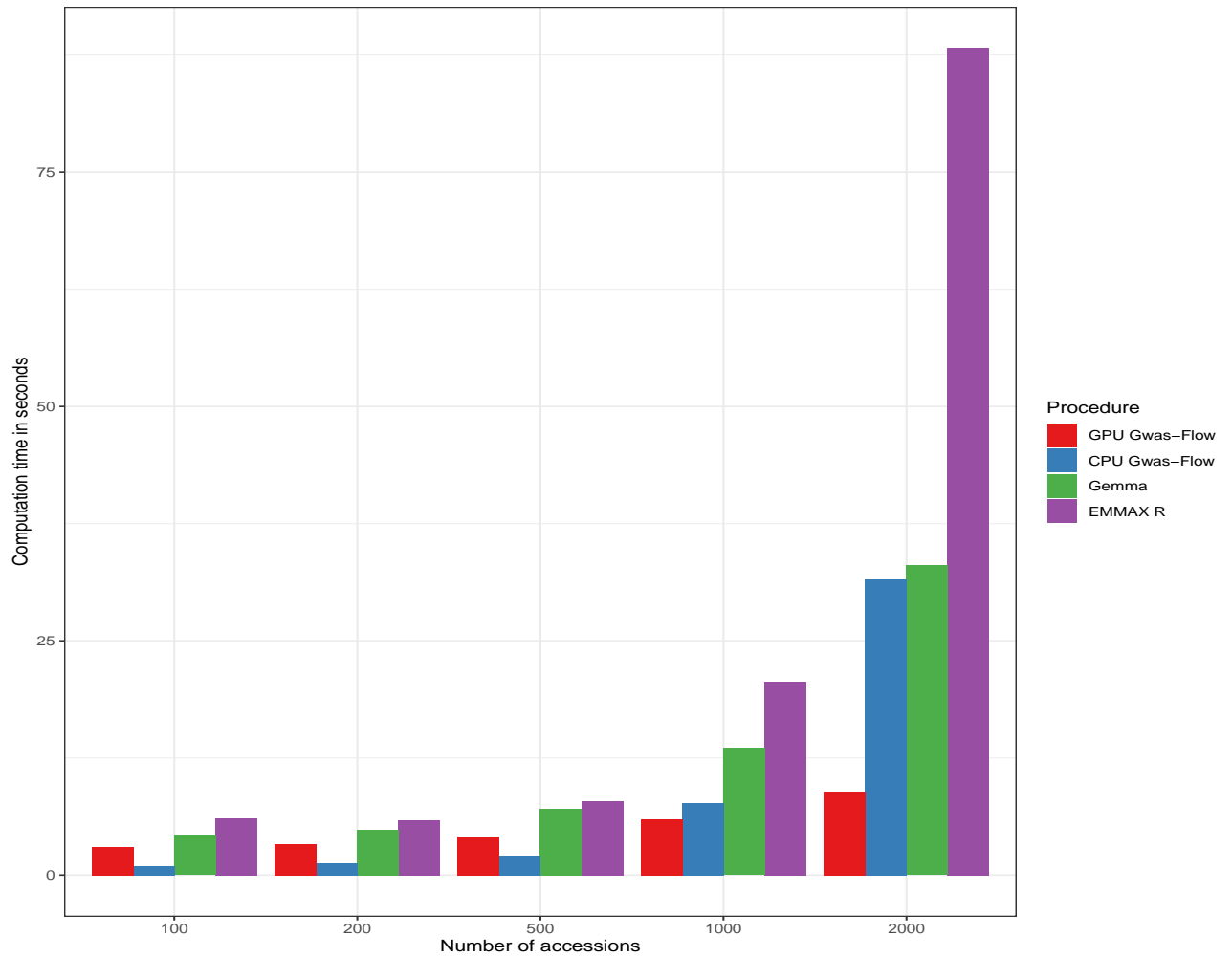


FIGURE 3.2: Computational time as a function of the number of accessions with 10000 markers each.

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.

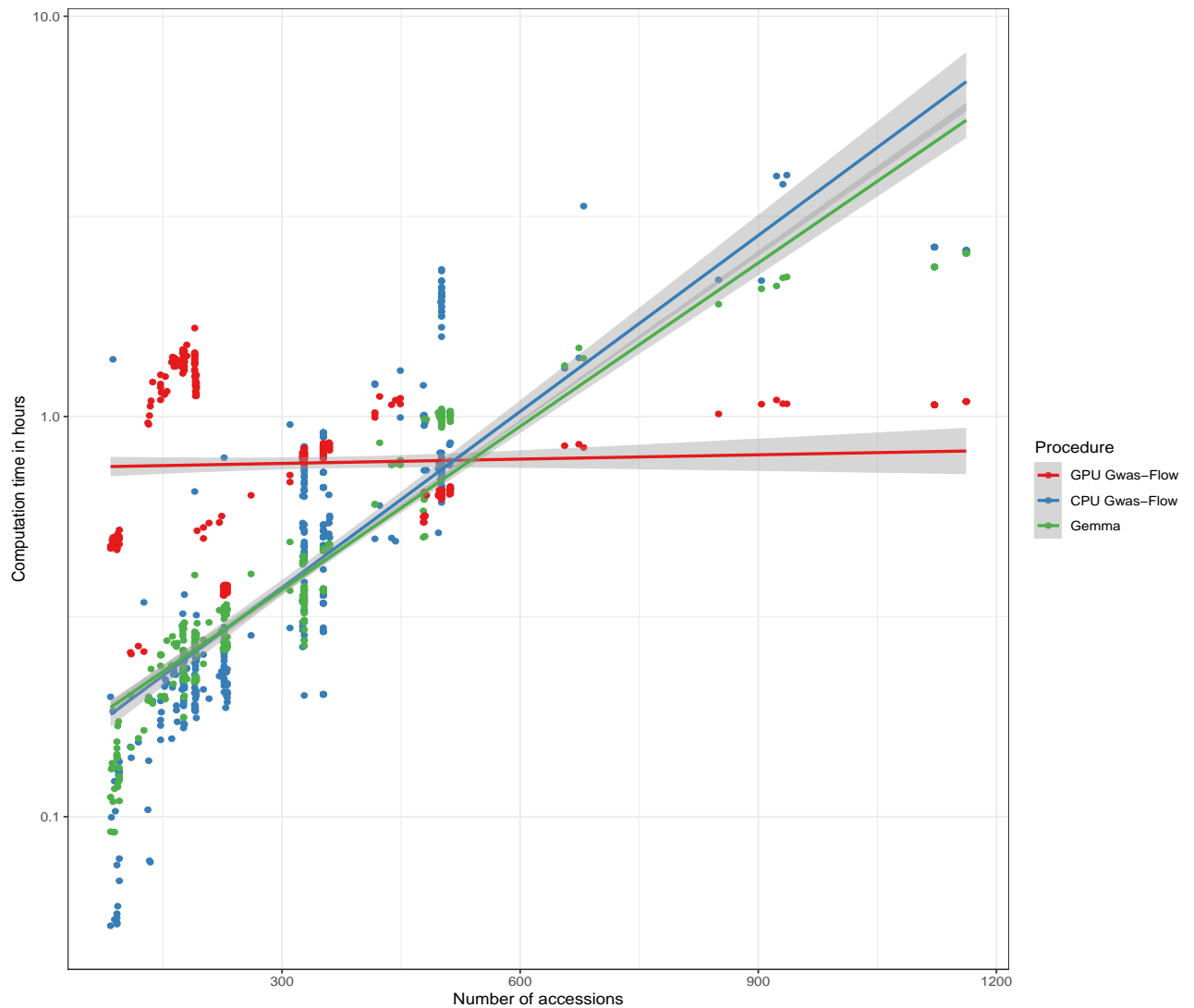


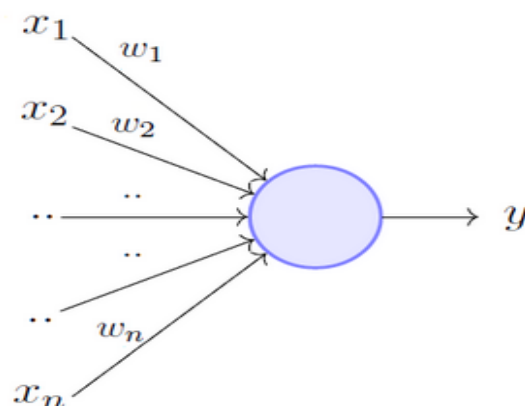
FIGURE 3.3: Comparison of the computational time for the analyses of  $> 200$  phenotypes from *Arabidopsis thaliana* as a function of the number of accessions for GEMMA and the CPU- and GPU-based version of GWAS-Flow. GWAS was performed with a fully imputed genotype matrix containing 10.7 M markers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

# 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



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FIGURE 4.1: Basic perceptron model as proposed by Rosenblatt

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 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  $\theta$  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 still stance in the research of artificial neural networks in the 1970s. This time period as now often referred to as the first AI-winter. Another reason that massively hindered the applications and research of machine learning during that time, was the compared to modern times incredibly small amount of computational power available Nguyen and Widrow, 1990.

More complex decision making, like solving XOR problems, requires more complex structures than a single perceptron. Continuing the trend of mimicking human neural networks, multiple artificial neurons are stacked into layers and these layers, are connected to each other allowing communication between the many perceptrons in a such generated network. Figure 4.2 shows schematically the basic structure of

such a network, now contains three types of layers. (i) the input layer, (ii) one or more hidden layers and (iii) one output layer, which in this case only consists of one neuron.

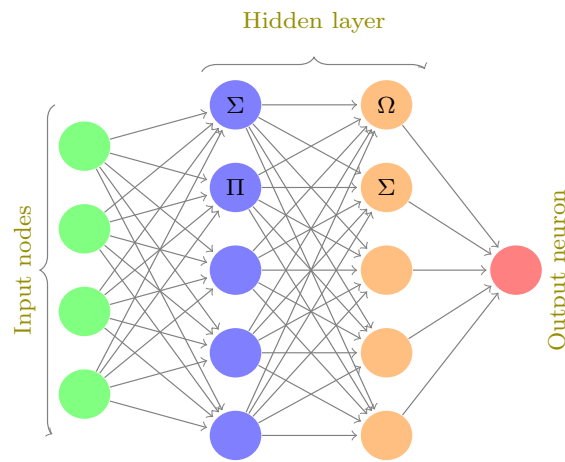


FIGURE 4.2: Schematic layout of a simple multi-layer perceptron

In the sample layout of figure 4.2 the neurons in the first column weigh the inputs and pass those to the neurons on the second layer. In this case all neurons on the first layer are connected to all neurons on the second layer, such layers are referred to as fully-connected layers (FLC), and their resulting networks are often called multi-layer perceptrons (MLP). This architecture enables the network to perform more complex calculations and result in more abstract decisions than single neurons or single layer architectures.

The neurons discussed so far are only capable of outputting binary results. Either 0 or 1, depending on the threshold values being met or not. For more complex estimations it is desirable that small changes in the input also result in small changes of the output. This requirement can not be met with binary outputs. Activation functions for a given node provide rules for the output in accordance to the inputs Žilinskas, 2006.

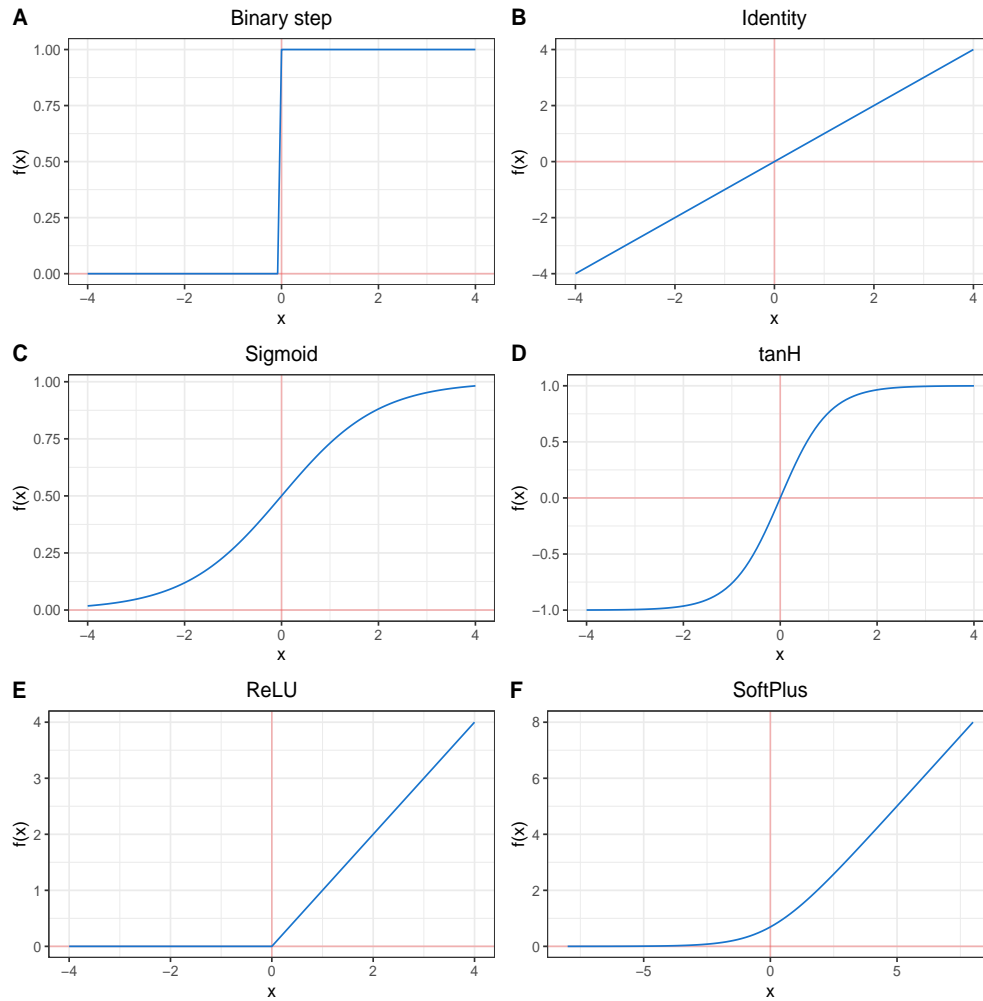


FIGURE 4.3: Popular activation functions used in neural networks. **A** Binary step activation function. **B** Identity activation function. **C** Sigmoid or logistic activation function. **D** tangens hyperbolicus activation function. **E** rectified linear units activation function . **F** SoftPlus activation function.

Figure 4.3 A shows six of the most commonly used activation functions Warner and Misra, 1996. The simplest one was introduced, is the binary step activation function equation 4.2, which properties have been discussed along the perceptron model. All other activation produce continuous outputs from any given input. Basically any mathematical function can serve as an activation function in neural nets, starting with a simple identity function 4.3 , 4.3 B. Sigmoid figure 4.3 C, equation 4.4 and tanh figure 4.3 D, equation 4.5, when  $x \rightarrow \infty$  or  $x \rightarrow -\infty$  they have similar properties to the binary function, but produce continuous output around 0.



$$f(x) = \sigma(x) = \begin{cases} 0 & \text{for } x < 0 \\ 1 & \text{for } x \geq 0 \end{cases} \quad (4.2)$$

$$f(x) = \sigma(x) = x \quad (4.3)$$

$$f(x) = \sigma(x) = \frac{1}{1 + e^{-x}} \quad (4.4)$$

$$f(x) = \sigma(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}} \quad (4.5)$$

$$f(x) = \sigma(x) = \begin{cases} 0 & \text{for } x < 0 \\ x & \text{for } x \geq 0 \end{cases} \quad (4.6)$$

$$f(x) = \ln(1 + e^x) \quad (4.7)$$

ReLU (equation 4.6) and the softplus (equation 4.7) share similar properties as well, the latter one being a smoothed version of ReLU. Rectifiers as activation functions have been introduced in 2000s Hahnloser et al., 2000 and have since then overtaken all others as the most popular activations functions in neural networks and deep learning today LeCun, Bengio, and Hinton, 2015 and they have proven to be superior in deep-learning algorithms that sigmoid or logistic functions Glorot, Borde, and Bengio, 2011.

Backpropagation Rumelhart, Hinton, and Williams, 1988

#### 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 laws, 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 it 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 4.8.

$$\sigma_P = \sigma_G + \sigma_E \quad (4.8)$$

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 4.8 needs to be extend by the variance of the gene- environment interactions  $\sigma_{G \times E}$  ?? , Lynch and Walsh, 1998, Walsh and Lynch, 2018.

$$\sigma_P = \sigma_G + \sigma_E + \sigma_{G \times E} \quad (4.9)$$

Equation 4.9 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 4.10

$$\sigma_G = \sigma_A + \sigma_D + \sigma_I \quad (4.10)$$

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  $\sigma_I$  can be further dissembled in the variance resulting from additive-additive  $\sigma_{AA}$  dominant-dominant  $\sigma_{DD}$  and additive-dominant  $\sigma_{AD}$  terms as represented in equation 4.11.

$$\sigma_I = \sigma_{A \times A} + \sigma_{D \times D} + \sigma_{A \times D} \quad (4.11)$$

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 one 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 4.12. This is also referred to as broad sense heritability, because all genetic effects including additive, dominance and epistatic effects are included Brooker, 1999.

$$H^2 = \frac{\sigma_A + \sigma_D + \sigma_I}{\sigma_P} \quad (4.12)$$

The concept of narrow-sense heritability 4.13 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 influences its offspring. While the dominance and epistatic variances are controlled by the combination of the parents Falconer and Mackay, 1996, Walsh and Lynch, 2018.

$$h^2 = \frac{\sigma_A}{\sigma_P} \quad (4.13)$$

### 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, alfalfa (*Medicago sativa*) Li and Brummer, 2012; Annicchiarico et al., 2015, Li et al., 2015, Biazzi et al., 2017, Hawkins and Yu, 2018; 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*) Moeiniazade 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., 2016a, 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, Rincént et al., 2012; potato (*Solanum tuberosum*), Enciso-Rodriguez et al., 2018, Endelman et al., 2018; rape seed (*Brassica naps*) . Würschum, Abel, and Zhao, 2014, Jan et al., 2016, Luo et al., 2017, Werner et al., 2018, Snowdon and Iniguez Luy, 2012, Qian, Qian, and Snowdon, 2014; rice (*Oryza sativa*) Momen et al., 2019, Hassen et al., 2018, Xu, 2013, Grenier2015; rye (*Secale cereale*) Auinger et al., 2016, Bernal-Vasquez et al., 2014, Wang et al., 2014, Bernal-Vasquez et al., 2017, Marulanda et al., 2016; soybean (*Glycine max*) Stewart-Brown et al., 2019, Jarquin, Specht, and Lorenz, 2016, Xavier, Muir, and Rainey, 2016; switchgrass (*Panicum virgatum*) Poudel et al., 2019, Ramstein and Casler, 2019, Ramstein et al., 2016; wheat (*Triticum aestivum*) Cuevas et al., 2019a, Howard et al., 2019, Krause et al., 2019, Rincént et al., 2018, Norman et al., 2018, Belamkar et al., 2018, Ovenden et al., 2018, Sukumaran et al., 2016, Bustos-Korts et al., 2016b, Gianola et al., 2016, Crossa et al., 2016, Thavamanikumar, Dolferus, and Thumma, 2015, Lopez-Cruz et al., 2015, Pérez-Rodríguez et al., 2012 and various tree species Almeida Filho et al., 2019, Rincént et al., 2018, Kainer et al., 2018, Ratcliffe et al., 2017, El-Dien et al., 2016, Kumar et al., 2015, Jaramillo-Correa et al., 2014, Zapata-Valenzuela et al., 2013, Holliday, Wang, and Aitken, 2012, Resende et al., 2012

#### 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 and Goddard, 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 in 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 problem 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, 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., 2019b, 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 and Goddard, 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**

## **5 GWAS**

### **5.1 Reevalulation of 463 phenotypes from the AraPheno 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**

# 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
42 csv or hdf5 format of size")
43         print("-y , --phenotype: file container phenotype information
44 in csv format" )
45         print("-k , --kinship : file containing kinship matrix of size
46 k X k in csv or hdf5 format")
47         print("-m : name of columnn containing the phenotype : default
48 m = phenotype_value")
49         print("-a , --mac_min : integer specifying the minimum minor
50 allele count necessary for a marker to be included. Default a = 1"
51 )
52         print("-bs, --batch-size : integer specifying the number of
53 markers processed at once. Default -bs 500000" )
54         print("-p , --perm : single integer specifying the number of
55 permutations. Default 1 == no perm ")
56         print("-o , --out : name of output file. Default -o results.
57 csv ")
58         print("-h , --help : prints help and command line options")
59         quit()
60     else:
61         print('unknown option ' + str(sys.argv[i]))
62         quit()
63
64 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("- "),
74 markers_used)))
75     else:
76         chr_reg = h5py.File(X_file,'r')['positions'].attrs['
chr_regions']
77         mk_index= np.array(range(len(markers)),dtype=int)[macs >=
mac_min]
78         chr_pos = np.array([list(map(lambda x: sum(x > chr_reg[:,1]) +
1, mk_index)), markers_used]).T
79         my_time = np.repeat((time.time()-start),len(chr_pos))
80     pd.DataFrame({
81         'chr' : chr_pos[:,0] ,
82         'pos' : chr_pos[:,1] ,
83         'pval': output[:,0] ,
84         'mac' : np.array(macs[macs >= mac_min],dtype=np.int) ,
85         'eff_size': output[:,1] ,
86         'SE' : output[:,2]}) .to_csv(out_file,index=False)
87 elif perm > 1:
88     min_pval = []
89     perm_seeds = []
90     my_time = []
91     for i in range(perm):
92         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(['accession_id',
17     '']).groupby('accession_id').mean()
18     Y = pd.DataFrame({'accession_id' : Y.index, 'phenotype_value' : Y
19     [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)
40
41     acc_Y = np.asarray(Y[['accession_id']]).flatten()
42     acc_isec = [isec for isec in acc_X if isec in acc_Y]
43
44     idx_acc = list(map(lambda x: x in acc_isec, acc_X))
45     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
48     if type_X == 'hdf5' or type_X == 'h5py' :
49         X = np.asarray(SNP['snps'][0:(len(SNP['snps'])+1)],dtype=np.
50             float32)[: ,idx_acc].T
51         X = X[np.argsort(acc_X[idx_acc]),:]
52         k1 = np.asarray(k['kinship'][:])[idk_acc,:]
53         K = k1[:,idk_acc]
54         K = K[np.argsort(acc_X[idx_acc]),:]
55         K = K[:,np.argsort(acc_X[idx_acc])]
56     else:
57         X = X[idx_acc,:]
58         k1 = k[idk_acc,:]
59         K = k1[:,idk_acc]
60
61     print("data has been imported")
62     return X,K,Y_,markers
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) * K) *
77     K

```

```

77     vg, delta, ve = herit.estimate(Y,"normal",K_stand,verbose = False
78 )
79     print(" Pseudo-heritability is " , vg / (ve + vg + delta))
80     print(" Performing GWAS on ", n , " phenotypes and ", n_marker , "
81 markers")
82     ## Transform kinship-matrix, phenotypes and estimate intercpt
83     Xo = np.ones(K.shape[0]).flatten()
84     M = np.transpose(np.linalg.inv(np.linalg.cholesky(vg * K_stand +
85 ve * np.identity(n))))).astype(np.float32)
86     Y_t = np.sum(np.multiply(np.transpose(M),Y),axis=1).astype(np.
87 float32)
88     int_t = np.sum(np.multiply(np.transpose(M),np.ones(n)),axis=1).
89 astype(np.float32)
90     ## EMMAX Scan
91     RSS_env = (np.linalg.lstsq(np.reshape(int_t,(n,-1)) , np.reshape(
92 Y_t,(n,-1))) [1]).astype(np.float32)
93     ## calculate betas and se of betas
94     def stderr(a,M,Y_t2d,int_t):
95         x = tf.stack((int_t,tf.squeeze(tf.matmul(M.T,tf.reshape(a,(n
96 ,-1))))),axis=1)
97         coeff = tf.matmul(tf.matmul(tf.linalg.inv(tf.matmul(tf.
98 transpose(x),x)),tf.transpose(x)),Y_t2d)
99         SSE = tf.reduce_sum(tf.math.square(tf.math.subtract(Y_t,tf.
100 math.add(tf.math.multiply(x[:,1],coeff[0,0]),tf.math.multiply(x
101[:,1],coeff[1,0])))))
102         SE = tf.math.sqrt(SSE/(471-(1+2)))
103         StdERR = tf.sqrt(tf.linalg.diag_part(tf.math.multiply(SE , tf
104 .linalg.inv(tf.matmul(tf.transpose(x),x)))) [1]
105         return tf.stack((coeff[1,0],StdERR))
106     ## calculate residual sum squares
107     def rss(a,M,y,int_t):
108         x_t = tf.reduce_sum(tf.math.multiply(M.T,a),axis=1)
109         lm_res = tf.linalg.lstsq(tf.transpose(tf.stack((int_t,x_t),
110 axis=0)),Y_t2d)
111         lm_x = tf.concat((tf.squeeze(lm_res),x_t),axis=0)
112         return tf.reduce_sum(tf.math.square(tf.math.subtract(tf.
113 squeeze(Y_t2d),tf.math.add(tf.math.multiply(lm_x[1],lm_x[2:]), tf.
114 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            :
16                data = conform_dataset(y, M=M, K=K)
17                y = data["y"]
18                M = data["M"]
19                K = data["K"]
20                assert_finite(y, M, K)
21                if K is not None:
22                    # K = K / diag(K).mean()
23                    QS = economic_qs(K)
24                else:
25                    QS = None
26                if lik_name == "normal":
27                    method = LMM(y.values, M.values, QS, restricted=True)
28                    method.fit(verbose=verbose)
29                else:
30                    method = GLMMExpFam(y, lik, M.values, QS, n_int=500)

```

```
30         method.fit(verbose=verbose, factr=1e6, pgtol=1e-3)
31     g = method.scale * (1 - method.delta)
32     e = method.scale * method.delta
33     if lik_name == "bernoulli":
34         e += pi * pi / 3
35     v = var(method.mean())
36     return g , v , e
```

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