

# **Bachelor Thesis**

## **Using Approximate Bayesian Computation to Infer the Number of Populations from SNP Genotype Data**

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# 1 Introduction

In population genetics theoretical models are constructed according to devised hypotheses to investigate the population structure and its evolution for some organisms at interest. Usually for this purpose the validity of a certain model is evaluated by analysing the underlying genotype data of the organisms. Models are often susceptible to the realistic choice of hyperparameters, such that for example the likelihood of a model with a certain hyper parameter greater is than for a much more realistic hyper parameter. Since for many models the declaration of the number of populations in the given data is crucial to infer the remaining parameters, a successful and stable technique for determining this parameter would lead to a significant facilitation for the inference process. However, so far no automated solution exists that satisfyingly alleviate this concern.

Throughout the following pages an approximate bayesian computation method will be presented that intends to deliver a reasonable estimate for the number of populations in SNP genotype data. It is based on a generalisation of currently used approaches, that attempt to exploit the behaviour of the spectrum of a clustered data matrix. The eigenvalues will moreover also make up the utilised summary statistics. The likelihood function for this problem is elusive, therefore a gradient boosting technique with decision trees will be employed to bypass its explicit computation.

Gradient Boosting is a supervised machine learning method, thus it requires a significant amount of data for training and testing. Real world genotype data however is too extensive to acquire in such a magnitude as is necessary, therefore an artificial data set is simulated and used. The generation of the artificial data follows commonly accepted theories for the simulation of population structure.

## 1.1 Problem

Given the genotype data of individuals, organised in a matrix  $X$  where each row corresponds to an individual, the task is to infer how many populations  $K$  are present in  $X$ . A population is a "group of organisms of the same species living within a sufficiently restricted geographical area so that any member can potentially mate with any other member of the opposite sex" Hartl, Clark, and Clark 1997. Especially due to genetic drift, the change of the allele frequencies in a population that occurs because of finite random sampling from the available gene pool, populations are distinguishable in their genetic information, although they might have split from a single population a reasonable amount of generations ago. For further information the reader is referred to Hartl, Clark, and Clark 1997. Therefore, if a sufficient amount of genetic information is used to span the feature space, usually in the form of genetic variations found at genetic markers, individuals should cluster together with other individuals of the same population as their genetic data is more homogenous **add more reasoning???, law of large numbers???**. The number of populations  $K$  should accord with  $K$  clusters found in the feature space, so the problem simplifies to identifying the number of clusters found in the data matrix  $X$ . **give a definition for clusters???, measure of genetic distance???**

## 1.2 Approaches currently used

A natural approach for problems involving clustering, would be to use a well established method and adapting it to infer the number of clusters, such as by maximising the likelihood of an expectation maximisation in combination with a model quality estimator like the Bayesian Information Criterion to avoid overfitting. In general bayesian approaches, such as maximising

the likelihood with regard to a theoretical model of the population structure is always a possible approach, however makes the estimation of the number of populations highly dependable on the a-priori assumptions of the model for what determines mathematically a new population Falush, Stephens, and Pritchard 2003. Fitting a hierarchical tree model with bayesian methods has also been attempted **corander2004baps**. Different assumptions from different models could lead to different estimations, which would undermine their comparability. Nevertheless, a maximum-likelihood approach was implemented in the software STRUCTURE Pritchard, Stephens, and Donnelly 2000 Falush, Stephens, and Pritchard 2003 and widely applied Rosenberg, Pritchard, et al. 2002 Harter et al. 2004 Rosenberg, Burke, et al. 2001. Furthermore, in some cases, especially for data that involves a high number of populations, a very distinctive maximum is not obtained, for the maximum-likelihood function tends to be smoother as higher values are examined **more explanation???**. Some approaches add further heuristics, such as also taking the second order rate of change of the likelihood function into consideration Evanno, Regnaut, and Goudet 2005, which however appears more like mending the performance of an approach that was solely conceived as preliminary remedy Pritchard, Stephens, and Donnelly 2000.

A more "modern" approach involves the insight that a cluster structure is also resembled in a structured form in the spectrum of the respective data matrix. The connection between the spectrum and a matrix was first discovered in graph theory Donath and Hoffman 1973 Fiedler 1973 and later introduced into machine learning Shi and Malik 2000 Meila and Shi 2001 Ng, Jordan, and Weiss 2002, for further information see Von Luxburg 2007. In general the relevant insight states that: suppose  $K$  clusters can be observed in the data matrix  $X$  (w.l.o.g.  $X$  is a square matrix), then the first  $k - 1$  eigenvalues  $\lambda_1 \geq \lambda_2 \geq \dots \geq \lambda_{k-1}$  are significantly larger than the remaining eigenvalues, also the corresponding eigenvectors **span a subspace that approximates a simplex with the clusters as vertices???**. The number of clusters can thus be inferred by examining the eigenvalues of the data, firstly detected and applied in the context of population genetics by Patterson, Price, and Reich 2006.

#### examples

Approaches have been made with random matrix theory (RMT) to concretise the behaviour of the first  $k - 1$  eigenevalues Patterson, Price, and Reich 2006, including a mathematical threshold that distinguishes significantly larger eigenvalues from lower ones K. Bryc, W. Bryc, and Silverstein 2013. Utilising insights from random matrix theory furtherly remains its beginnings, so far no well performing method based on RMT has been developed. **cite ???**

## 2 Biological Background

### ADD MORE !!!

#### 2.0.1 Key words

- **Chromosome:** A DNA molecule that encodes genetic information.
- **Gene:** A DNA (or RNA) sequence that specifies the structure of a particular functional molecule.
- **Locus:** A particular position on the chromosome, like the position of a specific gene.
- **Allele:** A variant form of a given gene. Different alleles can lead to distinct phenotypic traits.

### 3 Modelling

The genetic information to evaluate individuals is gathered from specific locations in the genom (loci) that can exhibit known genetic variants (alleles). These specific locations are called markers allow for an easier handling of the dimensionality and complexity of a genom for certain tasks, such as classeeification. To detect properly the magnitude of difference between the genotypes of two individuals from the same species, a sufficient amount of loci that carry genetic variation have to be used. For modelling SNP variations will be used. The biological meaning of the loci generated by the following model for the task of inferring the number of populations is irrelevant, solely necessary is the fact that at each loci different alleles should exist. Each population expresses the alleles at different frequencies, such that, by the law of large numbers, the more loci are simulated the more seperable the populations should be from another and individuals easierly assignable to a population. From a modelling view, it is the different allele frequencies that define a population.

The allele frequencies of a population  $k$  at a locus  $l$  for an allele  $a$  will be denoted as  $p_k(l_a)$ . For simplification purposes each loci in the model can be interpreted as having only two alleles. The model assumes a point in time where **no different alleles existed??? or alleles where considered the same???** and overtime mutations introduced new alleles that could asser themselves. However the model does not distinguish between the new alleles, only if an individual carries a mutant variant or not (furthermore ploidity is also ignored). The notation therefore also simplifies for the modell to  $p_k(l)$  (probability of having a mutant allele at locus  $l$  if from population  $k$ ).

#### 3.1 Further Model assumptions

The model assumes several properties:

- Hardy-Weinberg Equilibrium: Relevant to the modelling is that, wiht a Hardy-Weinberg Equilibrium the allele frequencies within a population do not change, the populations are "stationary".
- Linkage equilibrium: Loci are independent from one another.
- **No hierarchical clusters present, like families in a population???**
- **further assumptions ???**

#### 3.2 F-Layer

Distinct populations within a species form mainly due to random genetic drift when there is a fragmentation of the general population into subgroups present. Genetic random drift can be interpreted as a stochastic process where the allele frequencies of a gene change randomly over time. The first modelling atempts applied a markov chain cite, where a transition models the change of allele frequencies from one generation to the next. Further refinements have been added over time, such as converting the simplification of discrete populations to the continous case and adding biological idiosyncrasies cite. The random change in the stochastic process stems from the fact that a population has a finite amount of members, whose genetic makeup was "drawn" from a pool with probabilities according to the allele frequencies of the population at the time of the conception of the members, therefore it is likely that the allele frequencies in a population are not passed on exactly. Considering the law of large numbers inversely, the

smaller a population is the faster genetic drift will make an impact. The allele frequencies change until one allele is able to assert to fixation, meaning no other variants are substantially left and only the one allele is passed on.

All  $K$  populations in the model emerged from a single ancestral population  $A$ . This is founded on the biological background that for various reasons such as migration, geography, climate, sub populations form within a single population and as mating between subpopulations decreases or even ceases the populations are effected by distinct random genetic drifts, as a consequence their genetic makeups diverge from another until they can be considered distinct populations. Random mutations and natural selection, if environments are substantially different, in addition support the divergence. **Nonetheless, the fixation of most genes is mostly due to genetic drift???** As certain alleles become more dominant in populations the genetic variation declines and more individuals become homozygous (so less are heterozygous). Using this insight, a divergence statistics that is widely used measures the decrease in heterozygosity between the original population and the newly emerged subpopulation.

Let  $H_S$  denote the heterozygosity of the original population and  $H_T$  the heterozygosity of the subpopulation. Then

$$F_{ST} = \frac{H_S - H_T}{H_S}$$

gives a percentage by how much heterozygosity decreased.

**what is the connection to the F-model??? how to get to  $\frac{1-F^k}{F^k}$**

This divergence measure, or F-statistic, is used analogously to parametarise the genetic drift from the ancestral population, like following citefalush2003inference:

$$Dir(p_{l_1}^A \frac{1-F^k}{F^k}, p_{l_2}^A \frac{1-F^k}{F^k}, \dots, p_{l_{a_l}}^A \frac{1-F^k}{F^k}) \quad (1)$$

Where  $p_{l_i}^A$  is the allele frequency from the ancestral population of the allele  $i$ , from  $a_l$  alleles, at locus  $l$  and  $F^k$  is the drift value of population  $k$ . At a very low  $F^k$  (like 0.05) the fraction  $\frac{1-F^k}{F^k}$  is considerably above 1, thus the probability mass is mostly concentrated around ancestral allele frequencies. As the value of  $F^k$  increases:

- for a moderate value (like 0.3) the probability mass spreads out further, such that more loci will have different allele frequencies and a divergence to the ancestral population is observable (for a sufficient amount of loci).
- for a high value (like 0.5) the probability mass concentrates itself at the vertices of the  $k-1$  simplex. This corresponds to a high chance of allele fixation. The fixation will be more likely for the allele that was dominant, mathematically because of the multiplication with  $p_{l_i}^A$  in the ancestral population, to begin with.

A population is defined by its allele probabilities, whereby the members of the population are approximately homogenous. The allele probabilities are a categorical distributions over the possible alleles at each locus, so how often a genetic variant appears in a population. So at principal, to simulate a new population, its allele probabilities have to be determined. The simulated data the modell produces is supposed to resemble SNP data, where no distinction is made between the different variants of a mutation, but solely if a mutation at  $l$  exists compared to an undetermined hypothetical origin population.

The model has a hierarchical structure starting with allele probabilities that are derived from an unseen ancestral population. Let  $p_A(l)$  denote the probability, sampled from a uniform distribution, of an individual from the ancestral population  $A$  having a variation at locus  $l$ . Subsequently, following the genetic drift modelling from (1) by Falush, Stephens, and Pritchard 2003, for each population  $k$  an F-value  $F^k$  is chosen to introduce the magnitude of genetic drift from the ancestral population. These are used to derive the mutation probabilities of population  $k$  at locus  $l$ :

$$p_k(l) = \text{beta}(p_A(l) \frac{1 - F^k}{F^k}, (1 - p_A(l)) \frac{1 - F^k}{F^k}) \quad (2)$$

The dirichlet distribution from (1) degenerates to a beta distribution as effectively only two alleles are considered for each locus.

Proceeding, the probability values are joined to a vector  $p_k$  and then merged with all other  $K$  populations to a matrix  $\mathbf{F} = [p_1 p_2 \dots p_K]^T$  of size  $K \times L$ , where  $L$  is the number of loci, such that each column of  $\mathbf{F}$  gives the probabilities of each population for a specific locus  $l$ .

### 3.3 Admixture Layer

Apart from populations drifting from another apart, individuals of populations also migrate and mate with other individuals of other populations. Another modelling layer, according to the admixture model presented in Pritchard, Stephens, and Donnelly 2000, introduces the prospect of modelling their admixed offspring, whereby the flexibility, by determining the hyperparameters of a dirichlet distribution, allows to specify the probabilities of how populations partake to what degree in the admixture.

An admixed individual is defined by possessing a mixture of genetic data from various populations. The mixture is a weighting modeled by a categorical distribution according to the influence of each population on the individual. For an individual  $i$  the mixture weights  $q_i$  are sampled from a dirichlet distribution with  $K$  influencing hyperparameters  $j_1, j_2, \dots, j_K$  each corresponding to a population, thus  $q_i \sim \text{dir}(j_1, j_2, \dots, j_K)$ . A non admixed individual  $j$  also receives mixing parameters with the difference that the only non-zero value is a one at position  $k$ , indicating that the individual belongs to population  $k$ , so  $q_j = [0_1, \dots, 1_k, \dots, 0_K]^T$ . All  $M$  individuals are combined to a mixing matrix  $\mathbf{Q} = [q_1, q_2, \dots, q_M]^T$  of dimensions  $M \times K$ .

### 3.4 Combining the Layers

The mixing weights of each individual are subsequently applied over the mutation probabilities of all populations at each locus, which equals to the multiplication of both established matrices  $\mathbf{P} = \mathbf{QF}$ . The resulting matrix  $\mathbf{P}$  of dimension  $N \times L$  holds the mutation probabilities of each individual for each locus. By using each entry of  $\mathbf{P}$  to sample a value from a bernoulli distribution, for either an individual has a mutant allele or not, the simulated SNP genotype data for each individual is obtained. Furthermore, ploidy is neglected, so it is assumed the genetic data is aploidic, since **ploidy adds nothing unique for the means of inference. citation needed???**, each loci of an individual requires only one sample from the bernoulli distribution.

### 3.5 Summary

In summary the generation of a new population setting for which the number of populations  $K$  is known proceeds as following:

1. Sample the ancestral allele frequencies  $p_A(l) \sim \text{Uniform}(0, 1)$
2. Determine the F-values  $F^k$  ???
3. For each of the  $K$  populations:
  - (i) Sample  $p^k(l) \sim \text{beta}(p_l^A \frac{1-F^k}{F^k}, (1 - p_l^A) \frac{1-F^k}{F^k})$
  - (ii) Combine allele probabilities into matrix  $\mathbf{F}$
4. For each individual  $i$ :
  - (i) Choose admixture coefficients  $q_i \sim \text{Dir}(\alpha_1, \dots, \alpha_K)$
  - (ii) Combine admixture coefficients into matrix  $\mathbf{Q}$
5. Calculate admixture  $\mathbf{P} = \mathbf{QF}$
6. Convert each value  $p$  of  $\mathbf{P}$  by sampling  $\text{bernoulli}(p)$

### 3.6 Looking at Admixture

The admixture of an individual is determined by the Dirichlet distribution. The dirichlet distribution is parameterised by  $K$  hyperparameters  $\alpha_1, \alpha_2, \dots, \alpha_K$ .  $K$  corresponds to the desired dimension of the output. The probability density function

$$f(x_1, \dots, x_K, \alpha_1, \dots, \alpha_K) = \frac{1}{\Gamma(\sum)} \dots$$

where  $\sum_{i=1}^K x_i = 1$  and all  $x_i \geq 0$ . So the Dirichlet distribution therefore defines a probability density on the  $K - 1$ -simplex and is therefore a natural choice for sampling admixture coefficients.

Of particular interest for the described modell are the hyperparameters, also called concentration parameters, as they control the mode and the variance around it. For values  $a_i \geq 1$  the distribution has a single mode, whose coordinates at the maximum  $x$  is given by Bishop 2006:

$$x_i = \frac{\alpha_i - 1}{\sum_{k=1}^K \alpha_k - K}$$

The mode moves therefore more towards those directions, simplex vertices that have a relatively higher valued corresponding hyperparameter compared to the other hyperparameters. In addition, the variance  $\sigma$ , given by

$$\sigma_i = \frac{\alpha_i(\alpha_0 - \alpha_i)}{\alpha_0^2(\alpha_0 + 1)}$$

where  $\alpha_0 = \sum_{i=1}^K \alpha_i$ , reveals that higher values of hyperparameters leads to a decrease of the variance, meaning a higher concentration around the mode.

These two properties can be exploited to control the probability of sampling certain admixture

coefficients. Furthermore, by sampling from the same dirichlet distribution one is able to simulate various population scenarios, such as a detached admixed cluster, which would correspond to a mode with high concentration parameters, or a population that experienced migration, which would coincide with a degenerated dirichlet distribution that only has two nonzero, concentration values for the two involved population, which is in the end a beta distribution.

### 3.7 Analysis

**calculate centroids** The population centroids given by the population allele frequencies (they are the probabilities used for the bernoulli sampling and thus the mean) construct the vertices of a simplex in which the individuals approximately lie. Outliers are solely due to the natural variance created by sampling at the end from a bernoulli distribution. The probabilities the genetic information from each individual is sampled from however would always combine to a vector that lies within the simplex, for the probabilities are through the admixture coefficients a linear combination of the population allele frequencies or, in other words, of the simplex vertices.

For further assessment a mean of quantifying the dissimilarity between two individuals is necessary. As a measure of genetic distance between two individuals  $i$  and  $j$  a natural choice is to use a normalised manhattan distance because the possible values of the genetic information of an individual lies on a lattice of values zeros and ones. Or more concrete, let  $N$  be the number of loci used as genetic markers, then  $\{0, 1\}^N \subseteq \mathbb{R}^N$  is the set containing all possible values for the genetic information of an individual. The measure of genetic distance is

$$D = \frac{1}{N} \sum_{n=1}^N |l_n^i - l_n^j|$$

where  $l_n^i$  and  $l_n^j$  are the values of individual  $i$  and  $j$  respectively at locus  $l_n$ . The normalisation keeps the measure invariant to the number of loci used, as recovering more genetic information should not increase the genetic distance per se. The measure ranges from 0, as two individuals are genetically similar, to 1, meaning genetic dissimilarity.

Suppose two individuals  $i$  and  $j$  are generated by the described model, so sampling from a bernoulli distribution for each loci  $l$  with the respective allele frequencies  $p_i(l)$  and  $p_j(l)$ . The expected genetic difference of both individuals then is:

$$\begin{aligned} \mathbb{E}[D] &= \frac{1}{N} \sum_{n=1}^N \mathbb{E}[|l_n^i - l_n^j|] \\ &= \frac{1}{N} \sum_{n=1}^N p_i(l)(1 - p_j(l)) + p_j(l)(1 - p_i(l)) \end{aligned}$$

The result is intuitive. It is the empirical mean of sampling different allele values. For individuals sampled from the same probabilities the expectation equates to:

$$\frac{2}{N} \sum_{n=1}^N (p(l) - p(l)^2)$$

the further apart allele frequencies  $\rightarrow$  not always higher genetic difference. measure bad ?!



By investigating the variance of two individuals sampled from the same allele frequencies a better impression of the cluster (population) density can be obtained. Also the expected severity of individuals lying outside the simplex can be assessed.

But before calculating the variance, for simplicity reasons the expectation of the genetic difference squared is calculated:

$$\begin{aligned}
\mathbb{E}[D^2] &= \frac{1}{N^2} \mathbb{E}\left[\left(\sum_{n=1}^N |l_n^i - l_n^j|\right)^2\right] \\
&= \frac{1}{N^2} \sum_{n=1}^N \sum_{m=1}^N \mathbb{E}[|l_n^i - l_n^j| |l_m^i - l_m^j|] \\
&= \frac{1}{N^2} \left( \sum_{n=1}^N \mathbb{E}[|l_n^i - l_n^j|^2] + \sum_{n=1}^N \sum_{\substack{m=1 \\ m \neq n}}^N \mathbb{E}[|l_n^i - l_n^j| |l_m^i - l_m^j|] \right) \\
&= \frac{1}{N^2} \left( \sum_{n=1}^N 2(p(l_n) - p(l_n)^2) + \sum_{n=1}^N \sum_{\substack{m=1 \\ m \neq n}}^N 4(p(l_n) - p(l_n)^2)(p(l_m) - p(l_m)^2) \right)
\end{aligned}$$

and since

$$\mathbb{E}[D]^2 = \frac{4}{N^2} \left( \sum_{n=1}^N \sum_{m=1}^N (p(l_n) - p(l_n)^2)(p(l_m) - p(l_m)^2) \right)$$

The variance simplifies to

$$\begin{aligned}
\text{Var}(D) &= \mathbb{E}[D^2] - \mathbb{E}[D]^2 \\
&= \frac{2}{N^2} \left( \sum_{n=1}^N (p(l_n) - p(l_n)^2) - 2 \sum_{n=1}^N (p(l_n) - p(l_n)^2)^2 \right) \\
&= \frac{2}{N^2} \left( \sum_{n=1}^N p(l_n) - 3p(l_n)^2 + 4p(l_n)^3 - 2p(l_n)^4 \right)
\end{aligned}$$

This reveals that the variance decreases significantly of the order  $\mathcal{O}(N^{-2})$  with the number of loci. Therefore, less severe outliers and better observable clusters are to be expected the more loci are simulated.

**add modell relevance to real life ???**

### 3.8 Relationship to LDA

The presented modell is strongly related to a modell more commonly known under the name latent dirichlet allocation (LDA) Blei, Ng, and Jordan 2003. LDA uses in the setting of natural language processing (NLP) an ensemble of words that are probabilistically associated with certain topics, in order to determine which topics are exhibited by analysed documents, that preferably possess some associated words. Since not all existing words are associated with topics

but only a selection, the selected words can be perceived as reasonable indicators of the topic context, as are the used genetic markers to determine population affiliation. A one hot encoding of whether a word is present in a document or not is the respective equivalent of whether an individual possess a gene variant at a genetic marker or not. The encoding of the selected words or respectively of the genetic markers span the feature space in which the topics/populations lie. The topics/populations then span a simplex in which the documents/individuals are mapped according to the admixture.

## 4 Theory

### 4.1 ABC

To infer the number of populations  $K$  expressed in a given dataset  $X$  the conditional probability  $P(K|X)$  with respect to  $K$  is maximized. Since the large dimensionalities of the used datasets pose substantial computational difficulties, the datasets are summarized in an effective manner, such that the approximation  $P(K|X) \approx P(K|\text{sum}(X))$  is sufficient for the intended inference. Bayes' theorem then yields

$$P(K|\text{sum}(X)) = \frac{P(\text{sum}(X)|K)P(K)}{P(\text{sum}(X))}$$

The calculation of the likelihood  $P(\text{sum}(X)|K)$  however is intractable because ??? To circumvent this problem the likelihood is implicitly calculated by employing a supervised learning method to estimate the posterior, such as a neural network or boosting decision trees. These methods are trained by trying to link summary statistics of datasets to the corresponding values for the number of populations. The prior  $P(K)$  can be implicitly adjusted by changing the proportions of  $K$  in the training data. Gradient boosting with decision trees is chosen in this case, for it has demonstrated good results for various classification problems citation needed. **??? Furthermore, some intuitive reasoning exists, as explained later on, for the use of decision trees in this particular case.**

### 4.2 Choosing the Summary Statistics

The choice of an adequate summary statistics is essential to obtain significant results. On the one hand a summary of the data is necessary to handle its large dimensionality, on the other hand the manner of summarisation has to be chosen carefully to sustain the vital information necessary for the inference, because each summarisation consequently forfeits some of the principal information.

$$\begin{aligned} h(x) &= - \int_{-\infty}^{\infty} N(x|\mu, \Sigma) \ln(N(x|\mu, \Sigma)) dx \\ &= E[\ln(N(x|\mu, \Sigma))] \\ &= E[\ln(\det(2\pi\Sigma)^{-\frac{1}{2}} e^{-\frac{1}{2}(x-\mu)^T \Sigma^{-1}(x-\mu)})] \\ &= \frac{1}{2} \ln(\det(2\pi\Sigma)) + \frac{1}{2} E[(x-\mu)^T \Sigma^{-1}(x-\mu)] \\ &= \frac{1}{2} \ln(\det(2\pi\Sigma)) + \frac{1}{2} E[\text{trace}(\Sigma^{-1}(x-\mu)^T(x-\mu))] \\ &= \frac{1}{2} \ln(\det(2\pi\Sigma)) + \frac{1}{2} E[\text{trace}(I)] \\ &= \frac{1}{2} \ln(\det(2\pi e \Sigma)) \end{aligned}$$

The only non-constant factor influencing the entropy of a multivariate gaussian is the determinant of the respective correlation matrix. Since any real symmetric matrix is diagonalisable,  $\det(\Sigma)$  breaks down to  $\det(\Sigma) = \det(\mathbf{Q}^{-1}) \cdot \det(\mathbf{\Lambda}) \cdot \det(\mathbf{Q}) = \prod_{i=1} \lambda_i$ , thus revealing that actually the eigenvalues of the correlation matrix are responsible for the magnitude of the entropy. Furthermore, the multivariate Gaussian for a given mean and variance is the maximum entropy distribution, for a proof the reader is referred to Cover and Thomas 2012.

## Assume Data is linearly correlated??? connection of normal distribution to PCA

### 4.2.1 PCA - Introduction

**introduction** Principle component analysis is a statistical method that performs a basis transformation on a given data set, such that no linear correlations are anymore present in the data. Since the direction of a linear correlation corresponds to the direction of the highest variance in a concerning subspace, a new axis must be aligned according that particular direction. **citation needed ???** This construction of the axes is done by requiring in an iterative manner each new axis to align with the direction that captures the most variance in the data, which however has not been captured by already established axes.

The differences between data points makes them distinguishable, but also determines the magnitude of the observed variance. Decreasing the variance in a data set by projecting it into a subspace, thus endangers distinguishability (in certain features or even in total), which is information. The amount of sustained variance after projecting the data into a subspace can, therefore act as an indicator for how much information was retained. So by always maximizing the captured variance of a newly added axis to the transformation, which is a subspace of the principal data set, the highest possible amount of information is retained for a projection into a subspace with a particular rank  $K$  (under the assumption that variance corresponds to information). The subspace is spanned by the  $K$  largest Eigenvectors **singular values ???** of the empirical covariance matrix, as is subsequently shown.

Let  $S = \frac{1}{N}XX^T - \overline{X}\overline{X}^T$  denote the empirical covariance matrix of the data matrix  $X$ . Then the expression  $u^T Su$  is the empirical variance of  $u^T X$ , which is the data  $X$  projected on to the vector  $u$ .

$$\begin{aligned} u^T Su &= \frac{1}{N} u^T XX^T u - u^T \overline{X}\overline{X}^T u \\ &= \frac{1}{N} u^T X (u^T X)^T - \overline{u^T X} (\overline{u^T X})^T \\ &= \frac{1}{N} (u^T X)^2 - (\overline{u^T X})^2 \end{aligned}$$

The empirical variance is maximised with the restriction  $\|x\| = 1$  because  $u$  is supposed to be part of a new standard basis. **mention orthogonality ???**. By using a lagrange multiplier to add this restriction, the equation  $\max_u u^T \Sigma u - \lambda(u^T u - 1)$  is obtained.

$$\begin{aligned} \frac{d}{du} (u^T \Sigma u - \lambda(u^T u - 1)) &= 0 \\ \Sigma u - \lambda u &= 0 \\ \Sigma u &= \lambda u \end{aligned}$$

The solution coincides with the definition of the Eigenvectors, where  $\lambda$  is the eigenvalue of  $u$ . Since  $u$  should be maximised, the overall solution is the eigenvector belonging to the largest eigenvalue.

**Add explanation of SVD??**

### 4.2.2 In context to clustering

Cluster analysis intends to group similar data points together. **what are the clustering assumptions??? distribution? group criteria? boundaries?** Many connections between PCA

and cluster analysis have been established **cite and give examples**.

Data that exhibits reasonable clustering possess a considerably unique structure. This structure also reveals itself to some degree in the orientation of the eigenvectors and the magnitude of the corresponding eigenvalues, such that they can be utilised to infer certain properties of the data, like the number of clusters as is the current intention.

Intuitively, for inferring the number of clusters, it is assumable **cluster assumptions** in a reasonable setting, including for example that each cluster has a similar amount of members, that the in-between variance between two distinct clusters is significantly greater than the variance within a particular cluster. The in-between variance constitutes itself through the variance of the within variance of both concerning clusters and the distance between the clusters (under the assumption that outliers are possible, so cluster membership is not compulsive). While the within variance of a cluster is solely confined to the space assigned to that cluster, which concludes to a significantly smaller variance, especially considering that the distance from the mean of each data point has a squared impact on the variance (definition of variance). **Moreover, the with-in variance of a cluster is always the same (for  $n \rightarrow \infty$ ) regardless of the vector it is projected on (is this true??? proof necessary - RMT), so each cluster can be summarised to its centroid.** For these reasons a new principal component will orient itself in such a way, that it effectively captures the remaining in-between variance of the clusters.

For  $K$  many different population clusters  $K - 1$  significant PCs are obtained, thus allowing an inference of the number of populations. Considering only two clusters, a single significant PC would be observed that is oriented along a line connecting the two centroids of each cluster, as this would maximise the distance of the clusters after a projection on the PC and therefore maximise the variance after projection. In a general setting with  $K$  clusters, the PCs would arrange themselves as linear combinations of the in-between variances, as the overall variance is maximised so all in-between variances are taken into account. Since every cluster participates in  $K - 1$  in-between variances and capturing these in-between variances corresponds to determining the **exact??? (the centroids??? relative positions of the other cluster, a linear combination of exactly  $K - 1$  vectors are needed to locate the relative positions of the other clusters proof necessary??? less: would mean a cluster is admixed, admixture = linear combination of existing clusters  $\rightarrow$  contradiction | more: some in-between variance was not captured - contradiction to maximising variance, sufficient???. The centroids lie in the span of the first  $K - 1$  PCs ???**

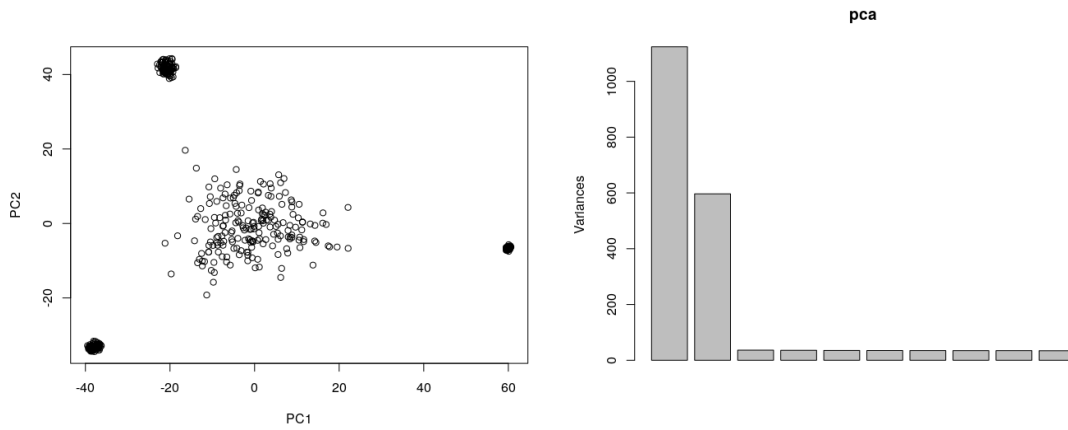
The past mentions of population clusters solely referred to clusters that are not admixed. The introduction of admixed population clusters, however does not alter the previously established theory under certain assumptions. Admixed clusters are several individuals with similar admixed genotypes and are sampled from allele probability values that are subject to a mixture weighting of the allele probability values of the non-admixed populations according to their involvement in the admixture as done in the model (2). This is simply a linear combination, restricted to the coefficients being proportions (summing to one), of the centroids of the other populations, hence it is situated in between non-admixed populations, meaning the centroid of an admixed population lies also in the span of the PCs spanning the non-admixed populations. In general, the centroids of the non-admixed populations constitute the corners of a simplex, that determines if a population cluster is admixed. Since admixed individuals lie in the simplex, which is spanned by the  $K - 1$  first principal components, their influence concerning the maximisation of the variance is negligible. **further explanation needed???**

### 4.3 Examples

A synthetic problem instance generated by the model, could look like shown in Figure 1, where three populations that span the simplex are observable. The populations have fairly distinct F-values (meaning they drifted away from the ancestral population at quite different magnitudes), therefore the clusters are well separable from one another. Within the simplex is a cluster of several admixed individuals located. They were all sampled from the same dirichlet distribution  $Dir(8, 8, 8)$ , with uniform hyperparameters, so they are concentrated around a central mode and all populations participate on average the same amount to the admixture.

Just by looking at the corresponding biggest eigenvalues, it is fairly easy, with the use of the previously insights, to infer the number of populations. The first two eigenvalues are significantly larger than the rest, thus the number of populations should be three.

Figure 1: Projection of three populations and one admixed on to the first two PCs and corresponding eigenvalues



Three populations with F-values of 0.1, 0.5, 0.9 and 100 individuals each were sampled. The admixed population derived the proportional weightings for its allele probabilities by sampling for each allele from a  $Dir(8, 8, 8)$  distribution. 200 individuals were sampled for the admixed. For this simulation 10000 loci were simulated.

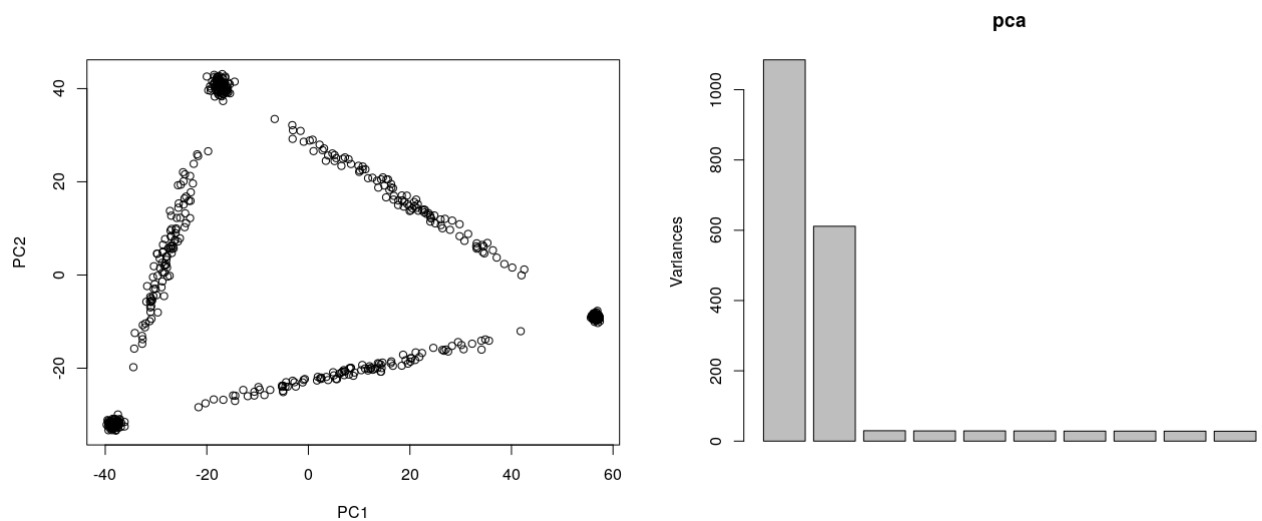
Figure 2 shows a similar scenario as Figure 1, whereby the only difference consists of a different admixture of the admixed individuals. In this example admixed individuals are sampled from three different dirichlet distributions. In turn one of the hyperparameters is set to zero, thus always on population does not partake in the admixture of an individual. As a consequence the individuals are spread along the edges of the simplex, also because the non-zero hyperparameters model a lower concentration than in Figure 1.

Again the eigenvalues feature two significant large eigenvalues, making the inference of the number of populations using solely the eigenvalues once again a simple task. The natural variance of the discretisation of the allele values through the bernoulli distribution, which would allow individuals to lie outside the simplex, only has a neglectable marginal effect on the eigenvalues.

#### 4.3.1 Difficulties

The past examples only demonstrate fairly simple problem instances, for which even a human recognition capabilities suffice. It is also possible to construct more difficult problem instances.

Figure 2: Projection of three populations and one admixed on to the first two PCs

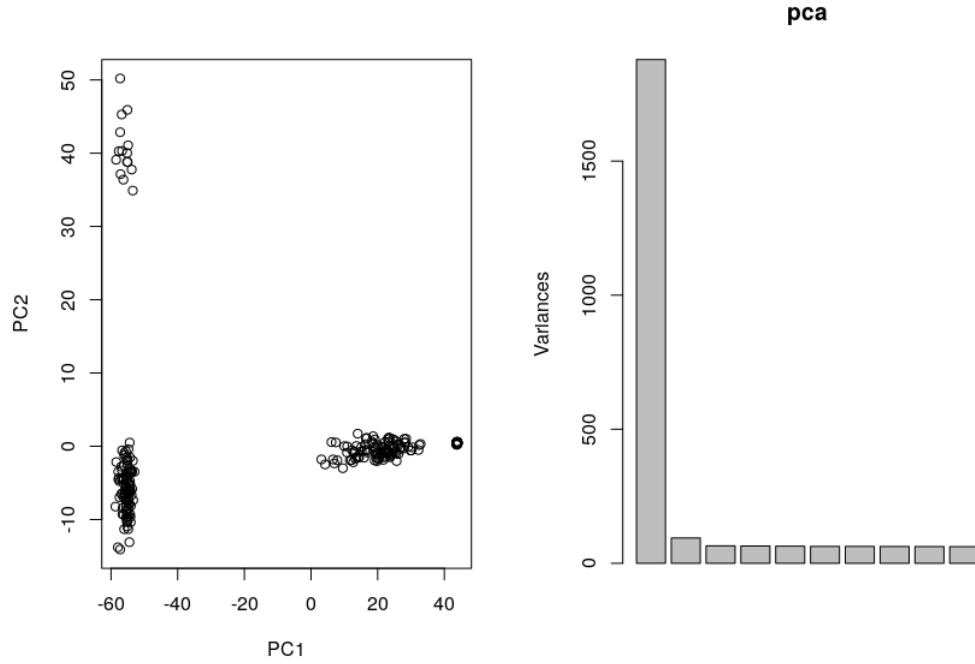


Three populations with F-values of 0.1, 0.5, 0.9 and with 100 individuals each were sampled. Between each pair of population clusters lies an admixed population sampled from a dirichlet with 5s and a 0 for not involved populations, which corresponds to a  $\text{beta}(5, 5)$ . Each admixed cluster holds 200 individuals. The simulation used again 10000 loci.

Figure 3 is an example of such. The ploy is to simulate a setting where most of the variance is already captured by less than  $k - 1$ , hence making it more difficult to recognise the cut-off for significant and insignificant eigenvalues. In figure 3 there are two populations that have similar allele frequencies (F-values 0.05 and 0.1) and one population that has been subject to strong genetic drift and therefore is genetically completely distinct (F-value 0.99). Furthermore, most individuals are distributed over one of the two close populations and the one very far apart. This introduces high a high incentive for the eigenvalues to try to capture the variance of the individuals of the two populations, since a bigger distance accounts for higher variance. Inversely, because the population that holds a fewer amount of individuals is not very far away from the positioning of the first eigenvector, such that the second eigenvector, which has to orient itself perpendicular to the first, does not capture very much variance. Also the low amount of individuals in the smaller population makes the orientation of the second eigenvector susceptible to the variance of the other populations or to any outliers. An admixed population also resides between the two greater populations, giving the first eigenvalue even more weight.

The graph with the biggest eigenvalues reveals the described dilemma. The first eigenvector accounts for almost all of the variance between the populations, rendering the other significant eigenvalue almost insubstantial and undiscernible from the other insignificant eigenvalues. In different scenarios the distance between the populations and the distribution of the individuals over the populations could be even more disadvantageous (although the question could more be of the nature to decide what is considerable to be a population, **this is part of the discussion???**). In addition, the situation becomes even more difficult if even more populations are simulated with "extreme" F-values.

Figure 3: Example of a difficult case



Three populations with F-values of 0.05, 0.01, 0.99. The first population with the smallest F-value has 15 members, while the others have a 100 each. The mixture proportions of the admixed population were sampled from a  $Dir(0, 10, 30)$ . 10000 loci were simulated.

#### 4.4 RMT

Let  $\mathbf{A} = \frac{1}{n}\mathbf{X}\mathbf{X}^T$  be the empirical covariance matrix of  $\mathbf{X}$  with  $\mathbf{X}$  being an  $m \times n$  matrix.  $\lambda_1, \lambda_2, \dots, \lambda_m$  are the corresponding eigenvalues of  $\mathbf{A}$ . The empirical spectral distribution (ESD) for  $\mathbf{M}$  is then given by:

$$F^M(x) = \frac{1}{m} |\{ \lambda_i \leq x \mid i \leq m \}|$$

Whereby  $|\cdot|$  denotes the size of a set.

By assuming a theoretical setting in which  $m, n \rightarrow \infty$  while  $y = \frac{m}{n} \rightarrow (0, \infty)$  the Marchenko-Pastur Law extends the ESD to the continuous case.

Under the assumption that the entries of  $\mathbf{X}$  are random variables iid distributed with mean 0, it states that the probability density of the eigenvalues is given by:

$$p^M(x) = \frac{1}{2\pi xy\sigma^2} \sqrt{(\rho_+ - x)(x - \rho_-)}$$

where  $\rho_{\pm} = \sigma^2(1 \pm \sqrt{y})^2$  and  $\sigma^2$  is the variance of the random variables.

**Insert Plot of distribution**



## 5 Gradient Boosting

## 6 Results

## 7 Discussion

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