

Bachelor Thesis

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

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1 Introduction

1.1 Biological Background

1.1.1 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.

2 Modelling

The subsequent admixture model, follows a model proposed by **pritchard2000inference**.

A population is defined by its allele probabilities, which is a categorical distributions over the possible alleles at each locus. The distributions are observed as the size of a population tends to infinity. **mention linkage disequilibrium and hardy-weinberg equilibrium** 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. Furthermore, ploidity is also neglected, so it is assumed the genetic data is aploidic, since **ploidity adds nothing unique for the means of inference. citation needed**

The allele probabilities used in the following modell, are derived from an unseen ancestral population. Let p_l^A 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 by **falush2003inference** established F-model, for each population k an F-value F^k is sampled from a **add distribution**. These are used to derive the mutation probabilities of population k at locus l :

$$p_l^k = \text{beta}(p_l^A \frac{1 - F^k}{F^k}, (1 - p_l^A) \frac{1 - F^k}{F^k})$$

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 locus, such that each column of \mathbf{F} gives the probabilities of each population for a specific locus l .

explain reasoning for F-values

To introduce the prospect of mating between individuals from different populations, possibilities of simulating admixed individuals and even whole admixed populations are added according to the admixture model presented in **pritchard2000inference**. 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 weights q_i are sampled from a dirichlet distribution with K influence paramaters 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 $M \times K$.

add description of influencing parameters

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 $\mathbf{P} = \mathbf{Q}\mathbf{F}$. 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 **why bernoulli???** distribution, the simulated SNP genotype data for each individual is obtained.

add modell relevance to real life ???

3 Theory

3.1 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.

3.2 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 **cover2012elements**.

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

3.2.1 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 expressed by 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 $S = \frac{1}{N}XX^T - \bar{X}\bar{X}^T$ 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 .

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

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 λ is the eigenvalue of u . Since u should be maximised, the overall solution is the eigenvector belonging to the largest eigenvalue.

3.2.2 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 sampled from allele probability values that are subject to a weighting of the allele probability values of the non-admixed populations according to their involvement in the admixture **refer back to modell**. This is simply a linear combination, restricted to the coefficients being proportions, 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 - proof ???.** If a cluster lies within the simplex it is admixed (No cluster can lie outside the simplex). Since admixed clusters lie in between the non-admixed clusters, their influence concerning the maximisation of the variance is negligible **further explanation needed???**

3.3 Difficulties

3.4 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 σ^2 is the variance of the random variables.

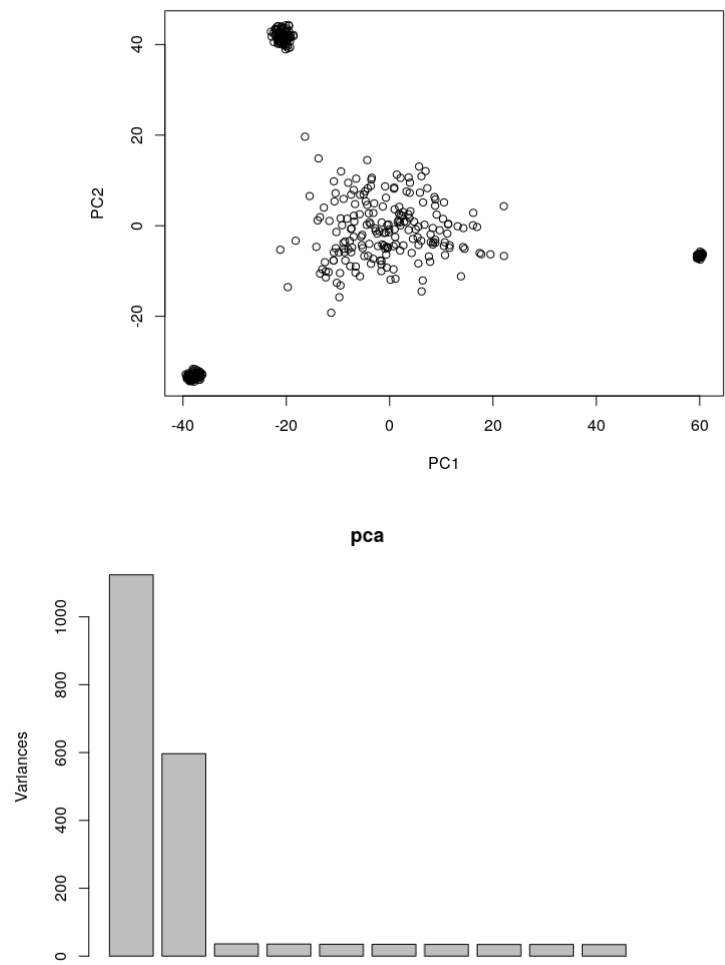
Insert Plot of distribution

4 Gradient Boosting

5 Results

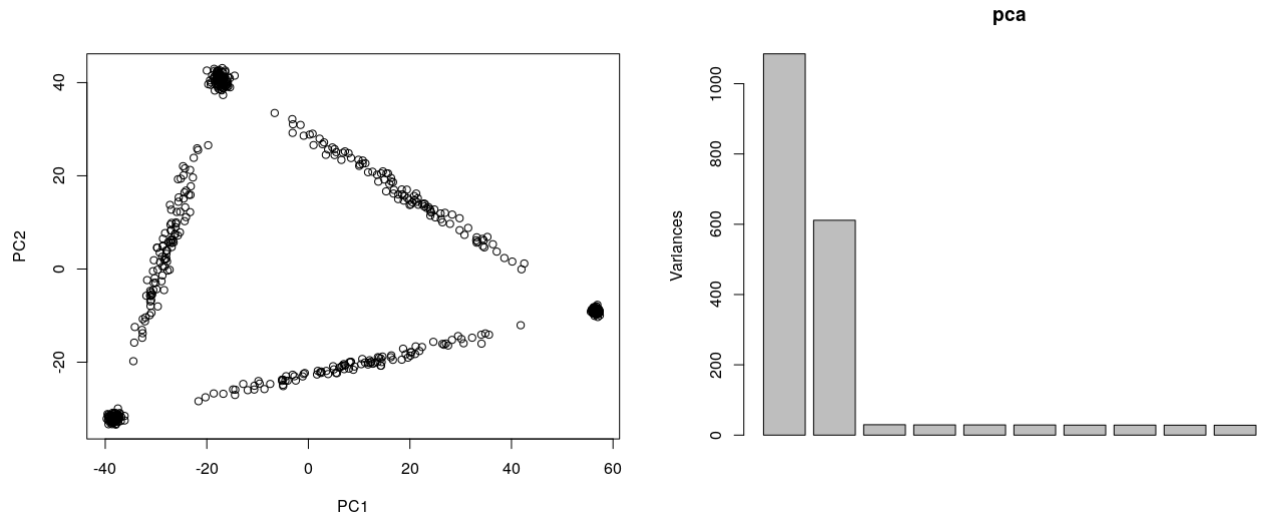
6 Discussion

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



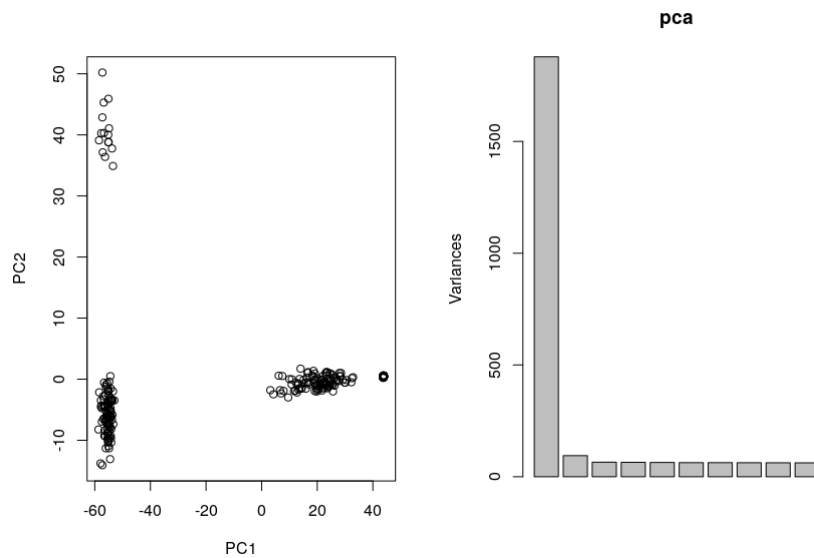
Three populations with F-values of 0.1, 0.5, 0.9 and 100 individuals each were sampled. The admixed population derived the proportional weightings for its allele probabilities by sampling for each allele from a $Dir(8, 8, 8)$ distribution. 200 individuals were sampled for the admixed. For this simulation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

Figure 2: 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 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: 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 $\text{Dir}(0, 10, 30)$. 10000 loci were simulated.