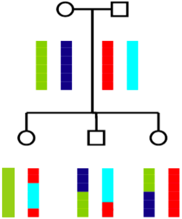
Inference of pairwise relatedness

Ida Moltke, Naples, May 2017



Outline

1. Introduction
   - Goal and motiviation
   - Definition of key concepts
   - Overview of current methods for inference
2. A simple maximum likelihood solution for called genotypes
   - Overview and intuition
   - Model
   - ML inference
3. Problems and more advanced methods
   - Problems with the standard methods
   - NGSrelate (for NGS data)
   - Methods for ancient DNA
   - RelateAdmix (for admixed individuals)
4. Exercises

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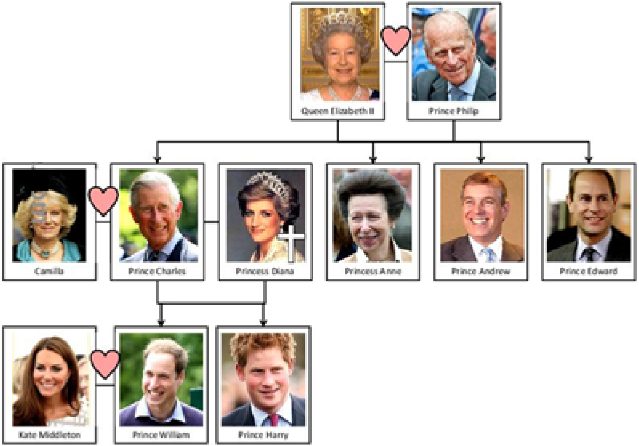
Goal

- We want to infer how two individuals are related based on DNA
- For example:



Motivation

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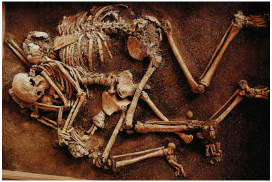
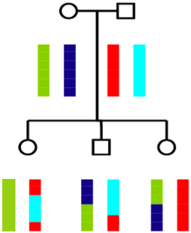
    - can reveal cultural practices in the past



Key concept: Identity-By-Descent

- One definition: DNA sequence **identity due to recent common ancestry**



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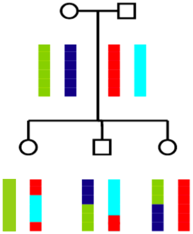

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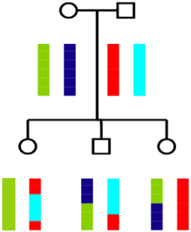

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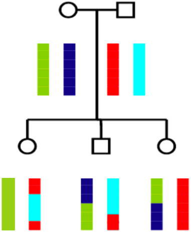

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  - IBD sharing cannot be observed, **so needs to be inferred**
  - Any non-inbred pair will in a locus **share 0, 1 or 2 alleles IBD**.
  - Importantly: **the closer related, the more IBD sharing**

IBD and relatedness coefficients (R)

- $\mathbf{R} = (\mathbf{k_0}, \mathbf{k_1}, \mathbf{k_2})$: fractions of genome with 0, 1 and 2 alleles IBD

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Relationship	k_0	k_1	k_2
Monozogotic twins	0	0	1
Parent-offspring	0	1	0
Siblings	0.25	0.5	0.25
Halfsiblings/Uncle-nephew/grandparent-child	0.5	0.5	0
First cousins	0.75	0.25	0
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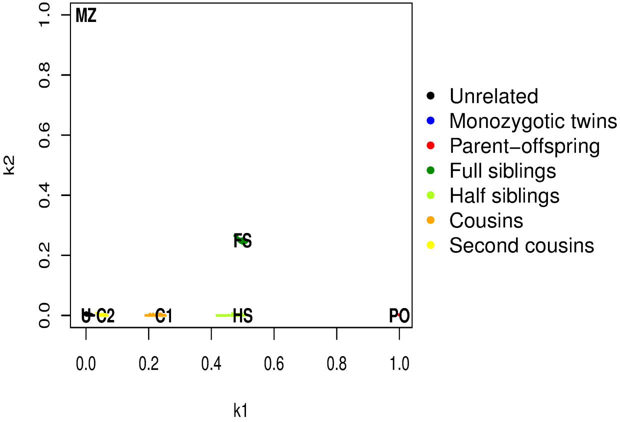
- Hence we can (often) use R to infer how two individuals are related
- There are other measures like kinship
- But they are all functions of R so we will focus on that

How?

- This can e.g. be done by plotting k_1 against k_2:



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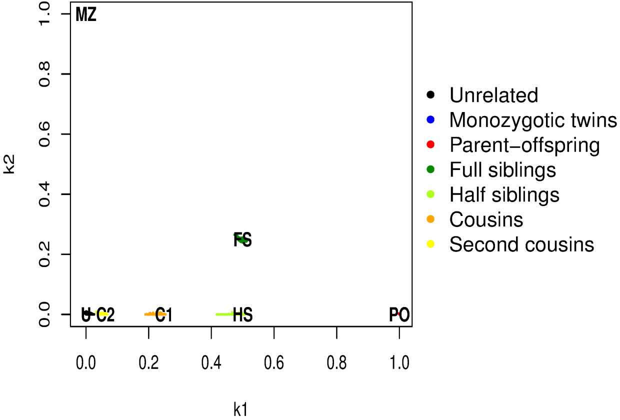

- However, we need to estimate R (because it can't be observed)!

How do we infer R?

There are a number of estimators:

- several method of moments estimators (e.g. PLINK)
- some maximum likelihood (ML) estimators (e.g. Thompson, 1975)
- most used program is probably PLINK

Importantly, all of them are based on several assumptions

- that the individuals are from a **diploid** species

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- that the individuals are **not inbred**
- that we have **called genotypes** for the two individuals in L loci
- that the individuals are from the same **homogenous population**
- that the population **allele frequencies** are known
  (or that you provide enough samples to estimate them)

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A simple ML approach (overview)

1. Define a model that allows us to calculate $P(data|R)$ (likelihood)
2. Estimate R by finding the R value the maximises $P(data|R)$ (MLE)

Intuition behind (what information is used)

Although we cannot observe IBD, only genotypes, we note that

- **If alleles are not identical they cannot be IBD**
- If alleles are identical it could be due to either IBD or chance
- If an allele is frequent, identity will occur often simply by chance
- If an allele is rare, identity will occur rarely by chance
- **So the rarer the allele, the more identity makes us believe the individuals are IBD**

Model

- We want a model that allows us to calculate $P(data|R)$
- Notation: for a pair of non-inbred individuals genotyped in L loci we let
    - G_j be their genotypes in locus j, e.g. $G_j = (AA, aa)$
    - Z_j indicate how many alleles they share IBD in locus j (unobserved)

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$$\begin{aligned} P(G_j|R) = {} & P(Z_j = 0|R)P(G_j|Z_j = 0)+ \\ & P(Z_j = 1|R)P(G_j|Z_j = 1)+ \\ & P(Z_j = 2|R)P(G_j|Z_j = 2) \qquad = \textstyle\sum_{i=0}^{2} P(Z_j = i|R)P(G_j|Z_j = i) \end{aligned}$$

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- Note that $P(Z_j = i|R)$ is simply k_i for all $i \in \{0, 1, 2\}$, so we get

$$P(G_j|R) = \textstyle\sum_{i=0}^{2} k_i P(G_j|Z_j = i)$$

Model ($P(G_j|Z_j = i)$)

- Assuming Hardy-Weinberg Equilibrium we can derive $P(G_j|Z_j = i)$:

G_j	Z_j=0	Z_j=1	Z_j=2	
AA,AA	f_A^4	f_A^3	f_A^2	$\forall A$
AA,aa	$2f_A^2f_a^2$	0	0	$A \neq a$
AA,Aa	$4f_A^3f_a$	$2f_A^2f_a$	0	$A \neq a$
Aa,Aa	$2f_A^2f_a^2$	$f_A^2f_a + f_Af_a^2$	$2f_Af_a$	$A \neq a$

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- Captures connection between IBD, genotypes and allele frequencies:
  - 3) captures that alleles have to be identical to be IBD
  - 1) and 2) captures that the rarer an allele is, the more will observing identity make us believe the individuals are IBD

ML inference based on the model

- **Assuming loci are independent** we get the full likelihood:

  $P(G_1, G_2, ..., G_L|R) = \prod_{j=1}^{L} P(G_j|R)$

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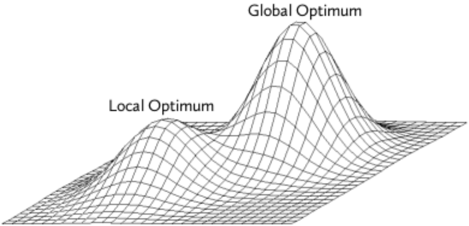
- This function is optimized for R and we get MLE of R
- Most often done using an EM algorithm
- NB does not always give you the MLE!



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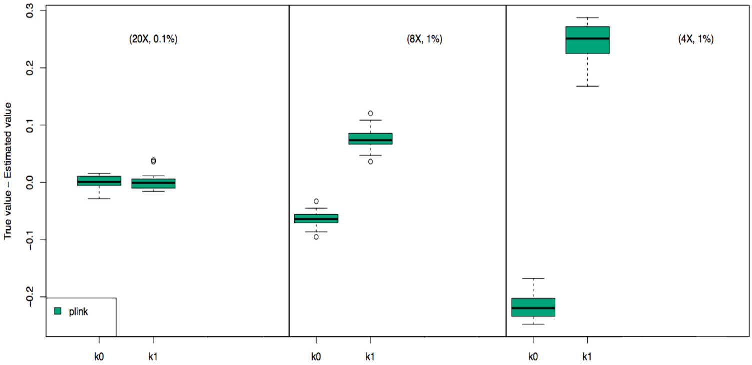
Problems

Most current methods

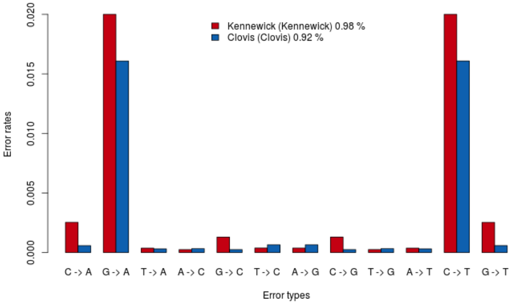
- work on called genotypes and **perform poorly on low depth NGS data**
- E.g. PLINK on simulated data from 20 1st cousins (k0 is overestimated):



Problems (cont.)

For ancient DNA there is a range of additional issues:

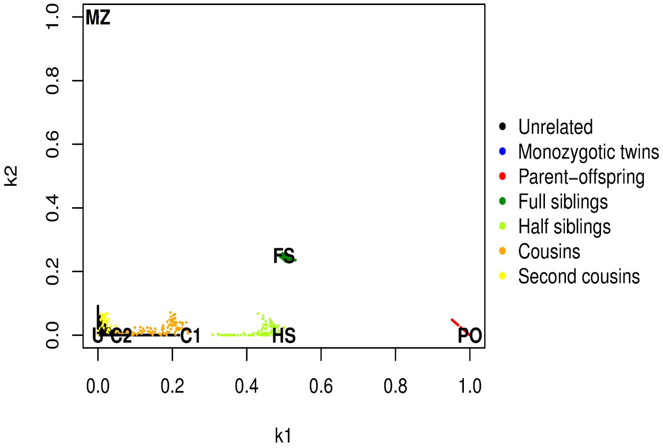
- very low coverage
- increased error rates (especially transitions)



- not enough samples available for proper allele frequency estimation

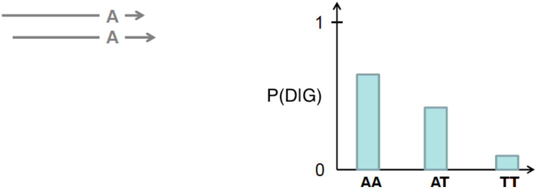
Problems (cont.)

Finally, most current methods have problems with admixed individuals. E.g. PLINK:



Handling NGS data (NGSrelate)

- A solution is to use genotype likelihoods (GLs) instead of called genotypes



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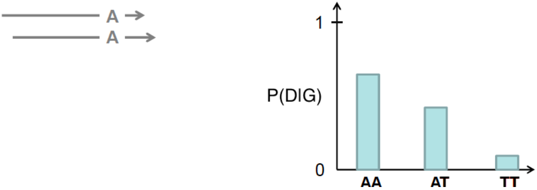

- Quantifies the uncertainty in what the genotype is
- We can write a new likelihood for a locus j which takes this uncertainty into account using these:

$$P(D_j|R) = \sum_{G_j \in \{\text{all possible genotype pairs}\}} P(D_{j,i1}|G_{j,i1})P(D_{j,i2}|G_{j,i2})P(G_j|R)$$

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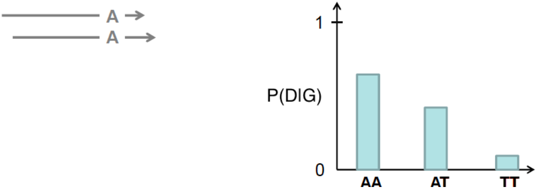

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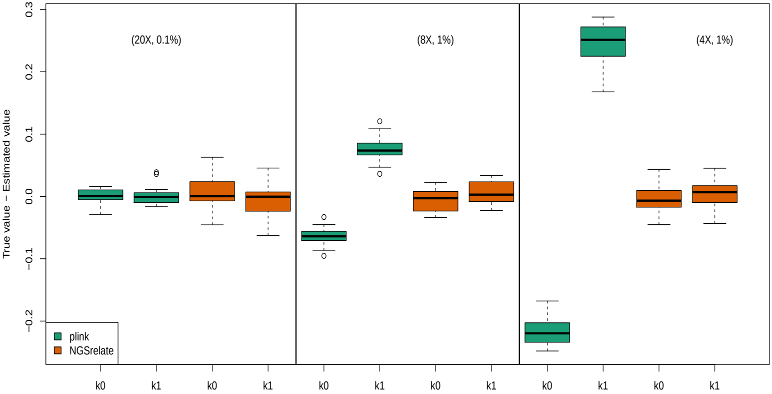
- NB when genotypes are known the GLs are 0 for all but the true genotype, so the likelihood becomes the same as before!

Handling NGS data (NGSrelate)

- NGSrelate vs PLINK:

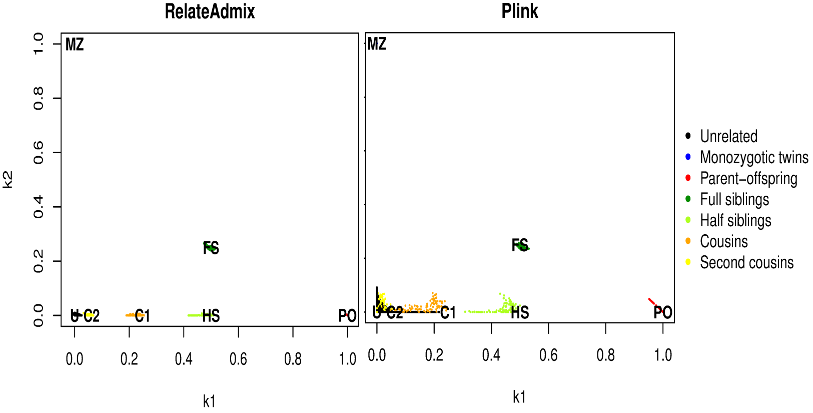


Methods for ancient DNA

- In some cases methods like NGSrelate can be used
(if frequency info is available and one removes transitions)
- In other cases you need special methods
(e.g. due to lack of allele frequencies)
- Still highly active research field, this year at least 2 new methods came out
(Kuhn et al. BioRXiv and Theunert et al. Genetics)

Handling admixture

- the likelihood can also be adjusted to take admixture into account
- this is done in the software relateAdmix
- comparison of relateAdmix and PLINK on admixed individuals:



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Exercise

Go to http://popgen.dk/ida/EMBONaples2017/web/ and solve exercise 1 & 2

(run the exercises on the server logged in with ssh -Y)