

Statistical methods in genetic relatedness and pedigree analysis

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Exercise set VI. Relatedness inference and pedigree reconstruction

Before you start, load the packages needed in the exercises.

```
library(pedsuite)
library(pedbuildr) # not a core package so must be loaded separately
```

If you haven't done it already, you should also download the `data` folder containing the datasets:

```
download.file("https://magnusdv.github.io/pedinr/datasets/data.zip", dest = "data.zip")
unzip("data.zip")
```

Exercise VI-1 (Pairwise estimates)

This exercise uses the dataset `reconstruct-example.ped` in the `data` folder.

- a) Use the following code to load and inspect the data. How many individuals are there? what is their sex? How many markers?

```
w = readPed("data/reconstruct-example.ped", locus = "snp-12")
summary(w)
```

- b) Use `ibdEstimate()` to estimate kappa between individuals 2 and 4, and plot the corresponding point in the IBD triangle. How do you think they are related? How confident are you?
- c) Use the code below to compute and plot 200 bootstrap simulations of the kappa coefficients.

```
ibdBootstrap(w, ids = c(2,4), param = "kappa", N = 200)
```

Comment on the uncertainty of the estimate in b).

- d) Now estimate and plot the kappa coefficients between all pairs of individuals in the dataset. For each pair, explain what the kappa estimate tells us about their relationship.
- e) Use the pairwise estimates to reconstruct the pedigree. (Hint: Start with the parent-offspring pairs.)

Exercise VI-2 (Pedigree reconstruction)

Use the following `pedbuildr` command to reconstruct the pedigree from the previous exercise.

```
# Reconstruct
r = reconstruct(w, inferPO = TRUE, linearInb = FALSE)

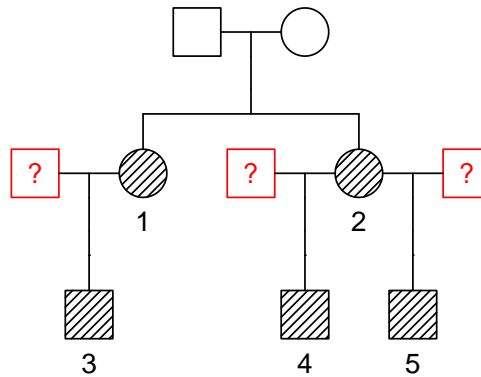
# Plot the most likely pedigrees
plot(r)
```

- a) Explain the meaning of each argument in the function call.
- b) Study the verbose output of the function. How many pedigrees did it consider?
- c) What is the most likely pedigree? How much more likely is it compared with the runner-up?

Exercise VI-3 (A question about fathers)

The following is based on a true case from Australia. Genotypes are available from two sisters and their children. The first sister has one child, the other has two children. The question we must answer is: *Do any of the children have the same father?*

The data are given in the files `reconstruct-fathers.ped` and `reconstruct-fathers.freq`.



- a) Load the data with the commands below, and use `summary()` to inspect the data. Check that the labels and sexes match the figure. How many markers are used?

```
x = readPed("data/reconstruct-fathers.ped")
x = setFreqDatabase(x, "data/reconstruct-fathers.freq")
summary(x)
```

- b) Use **pedbuildr** to perform a pedigree reconstruction on the data set. *Hint:* Use undisputed parts of the family to restrict the search space. For example, the parameters `knownPO` and `noChildren` might be useful. You should also add `linearInb = F` to exclude parent-child incest etc.
- c) Plot the six most likely pedigrees and describe the paternity constellations. What is your conclusion?

Exercise VI-4 (Bonus exercise for the mathematically inclined: ML-estimation by hand!)

This exercise walks you through the computations of a maximum likelihood estimation of the relationship between two non-inbred individuals. To enable hand calculation, the data is the simplest possible: Genotypes from a single marker, for which both individuals are homozygous A/A . Denote by p the population frequency of the A allele, and assume $0 < p < 1$.



- a) What do you think is the most likely relationship given this data?

Recall that maximum likelihood estimation of pairwise relatedness works by finding the value of $k = (k_0, k_1, k_2)$ that maximises the likelihood function

$$L(k) = P(data | k) \quad (1)$$

$$= P(data | UN) \cdot k_0 + P(data | PO) \cdot k_1 + P(data | MZ) \cdot k_2, \quad (2)$$

where the *data* are the observed genotypes, and *UN*, *PO* and *MZ* denote the relationships of unrelated, parent-child and MZ twins, respectively.

- b) Show that the likelihood function in this case becomes

$$L(k) = P(AA, AA | k) = p^4 k_0 + p^3 k_1 + p^2 k_2. \quad (3)$$

- c) Explain that for optimisation purposes you can get rid of a factor p^2 . Furthermore, use the relation $k_0 + k_1 + k_2 = 1$ to eliminate k_1 , giving the simpler function

$$L_1(k_0, k_2) = (p^2 - p)k_0 + p + (1 - p)k_2. \quad (4)$$

- d) Remove another factor, $(1 - p)$, and conclude that all we have to do is to maximize the function

$$L_2(k_0, k_2) = k_2 - pk_0 + C, \quad (5)$$

where C is a constant.

- e) Which point (k_0, k_2) in the IBD triangle gives the highest value of the function L_2 obtained in the previous step? What is the estimated relationship?