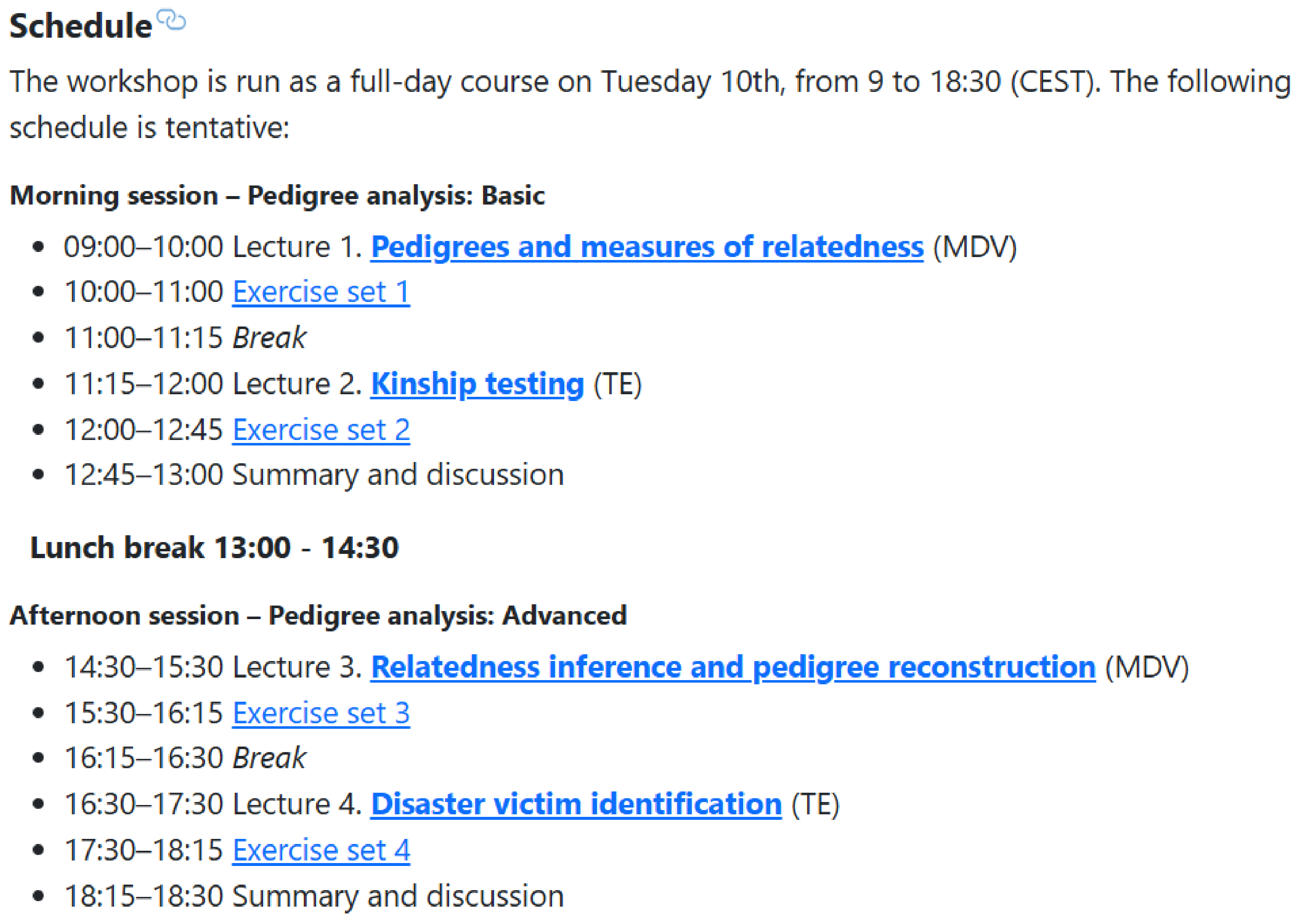
ISFG 2024 Pre-congress Workshop
Santiago de Compostela
Sept 10th 2024

Kinship Statistics and Pedigree Analysis

Teachers

Thore Egeland

Magnus Dehli Vigeland



Schedule

The workshop is run as a full-day course on Tuesday 10th, from 9 to 18:30 (CEST). The following schedule is tentative:

Morning session – Pedigree analysis: Basic

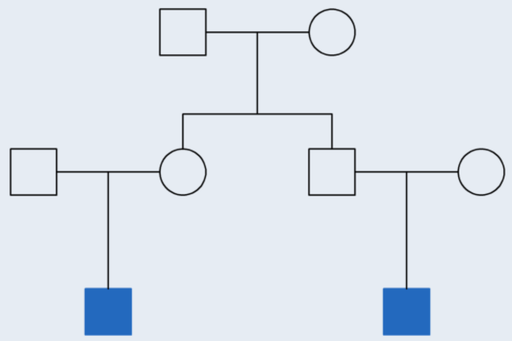
- 09:00–10:00 Lecture 1. **Pedigrees and measures of relatedness** (MDV)
- 10:00–11:00 Exercise set 1
- 11:00–11:15 *Break*
- 11:15–12:00 Lecture 2. **Kinship testing** (TE)
- 12:00–12:45 Exercise set 2
- 12:45–13:00 Summary and discussion

Lunch break 13:00 - 14:30

Afternoon session – Pedigree analysis: Advanced

- 14:30–15:30 Lecture 3. **Relatedness inference and pedigree reconstruction** (MDV)
- 15:30–16:15 Exercise set 3
- 16:15–16:30 *Break*
- 16:30–17:30 Lecture 4. **Disaster victim identification** (TE)
- 17:30–18:15 Exercise set 4
- 18:15–18:30 Summary and discussion

Home page
https://magnusdv.github.io/pedsuite/articles/web_only/course-isfg2024.html



Lecture 2: Relatedness inference and pedigree reconstruction

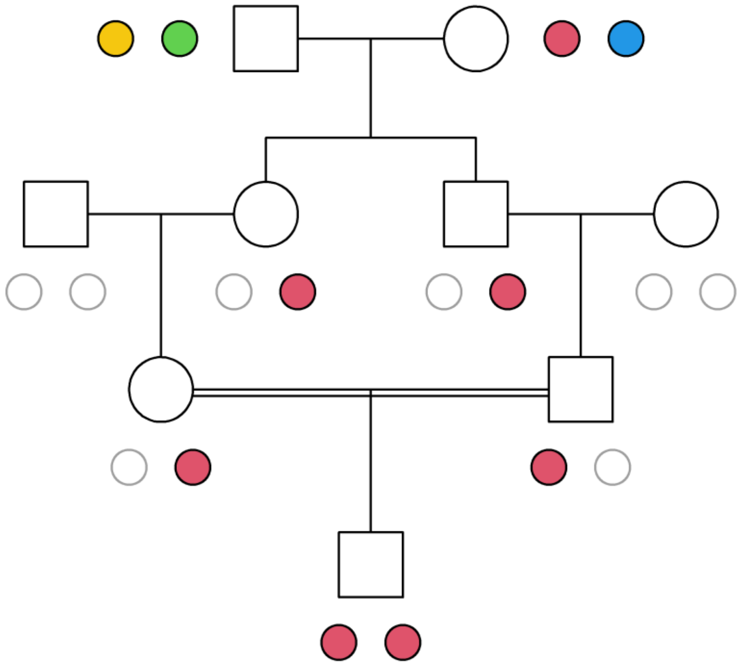
ISFG 2024 Pre-congress Workshop

Kinship Statistics and Pedigree Analysis: Advanced

Magnus Dehli Vigeland

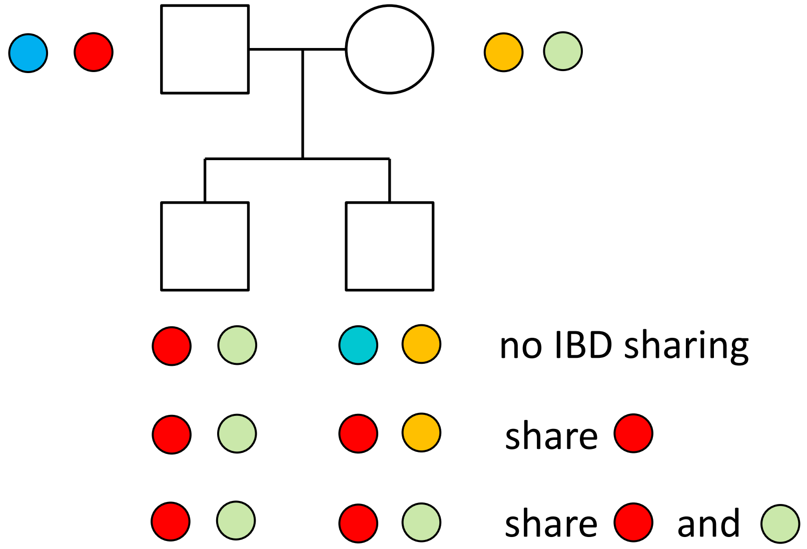
Part I: Inference of ***pairwise*** relatedness

Recap: Identity by descent (IBD)



Recap: IBD coefficients

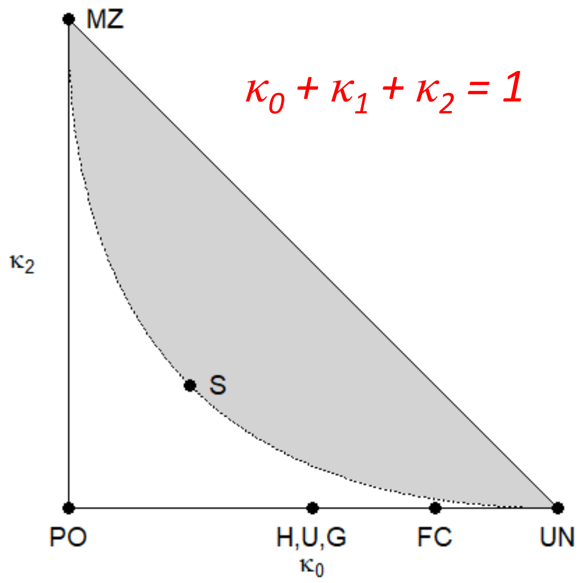
- How many alleles are IBD in each locus?



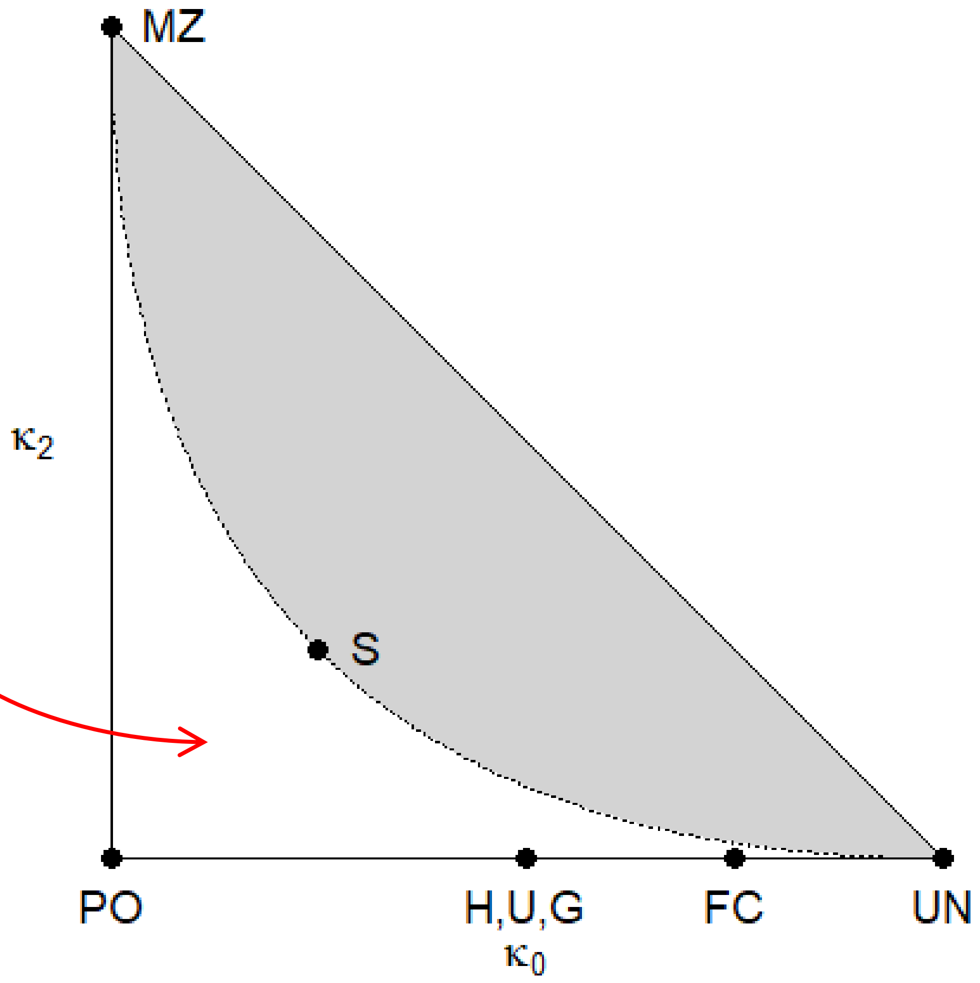
Definition

- $\kappa_0 = Pr(0 \text{ alleles IBD})$
- $\kappa_1 = Pr(1 \text{ alleles IBD})$
- $\kappa_2 = Pr(2 \text{ alleles IBD})$

(at random autosomal locus)



where??



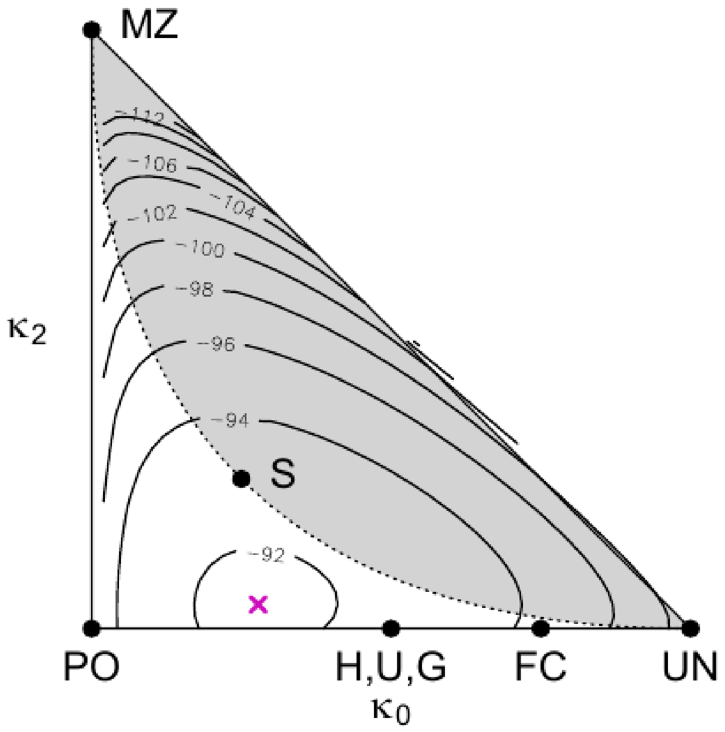
Maximum likelihood estimation of $\kappa = (\kappa_0, \kappa_1, \kappa_2)$

- Thompson (1975)
  - Given: marker genotypes for two individuals
  - The likelihood function

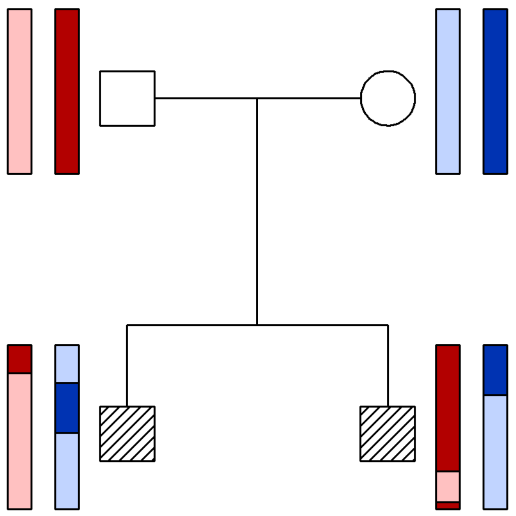
$$L(\kappa) = P(genotypes \mid \kappa)$$

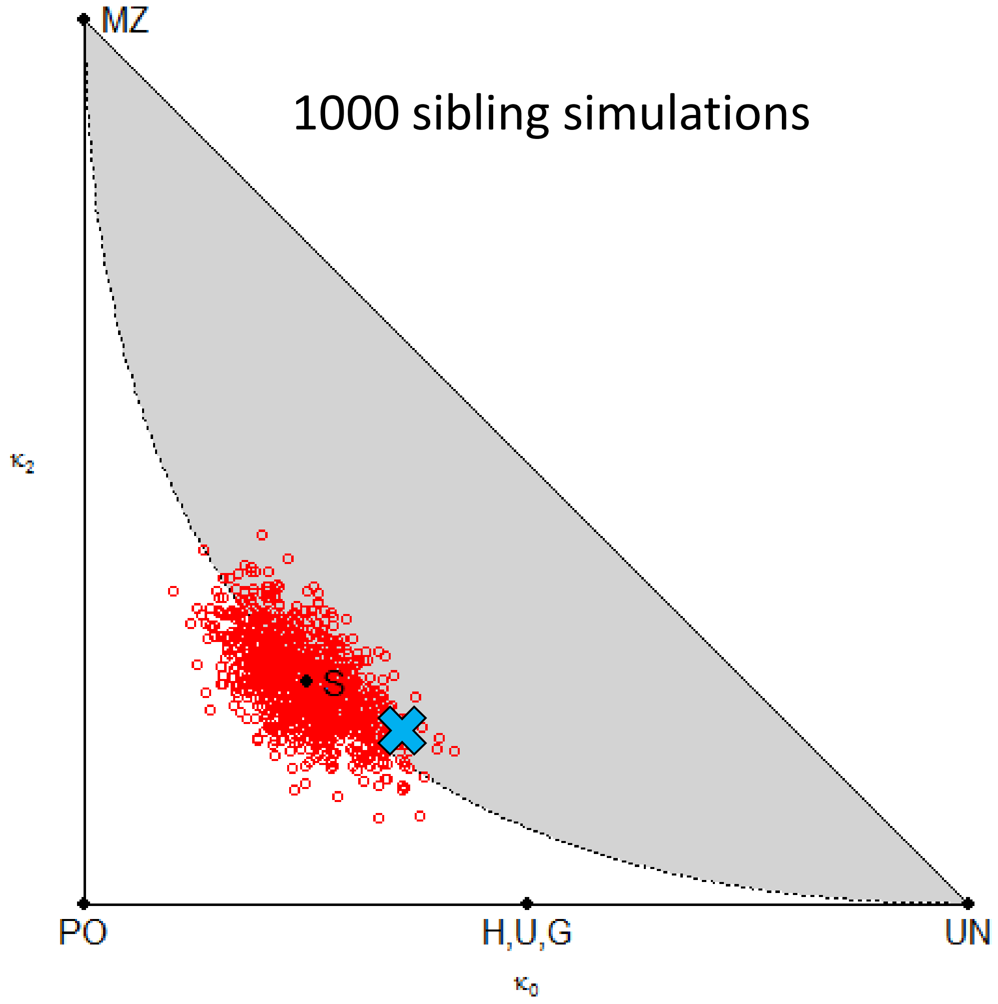
- Find the point *k* which maximizes *L*!
  - Called the maximum likelihood estimate (MLE)

- Assumptions:
  - known allele freqs
  - HWE
  - no inbreeding



What are we estimating?



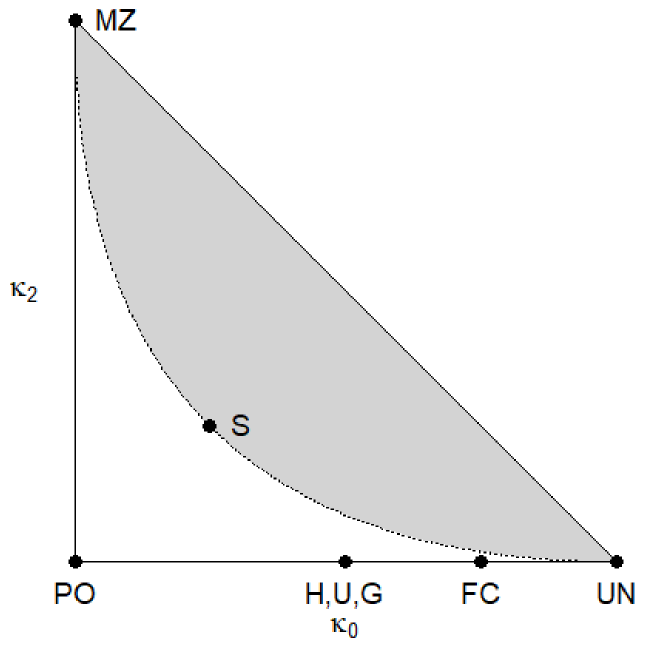


Answer: The *realised* coefficients!

Implementations

- **R**
  - **pedsuite (forrel)**
  - SNPrelate, GWASTools (optimized for association studies)
  - CrypticIBDcheck (as above, slow with many markers)
  - +++

- Other
  - PLINK
  - KING
  - Beagle
  - +++



Pairwise inference in R

- Key functions

```
> ibdEstimate()        # estimate kappa
> showInTriangle()     # visualize!
> ibdBootstrap()       # bootstrap confidence
> checkPairwise()      # detect pedigree errors
```

- Simulation

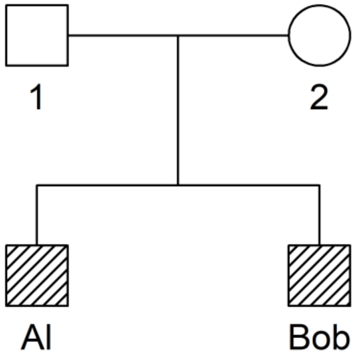
```
> markerSim()          # iid markers
> profileSim()         # complete profiles
```

(Both of these support conditioning on known genotypes)

Pairwise inference in R: Example

Simulate 100 SNPs for a pair of siblings

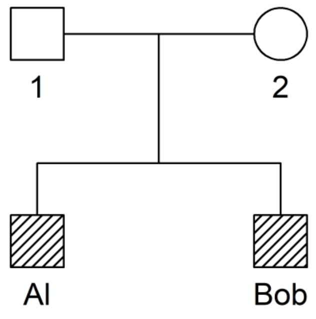
```
>   library(pedsuite) # includes forrel

>   ids = c("Al", "Bob")
>   x = nuclearPed(children = ids)

>   x = markerSim(x, N = 100, ids = ids,
              alleles = 1:2, seed = 1234)
>   x
  id fid mid sex <1> <2> <3> <4> <5>
   1   *   *   1 -/- -/- -/- -/- -/-
   2   *   *   2 -/- -/- -/- -/- -/-
  Al   1   2   1 1/1 1/2 1/1 1/2 2/2
 Bob   1   2   1 1/1 1/2 1/1 1/2 2/2
Only 5 (out of 100) markers are shown.

>   dat = list(subset(x, "Al"),
               subset(x, "Bob"))
```

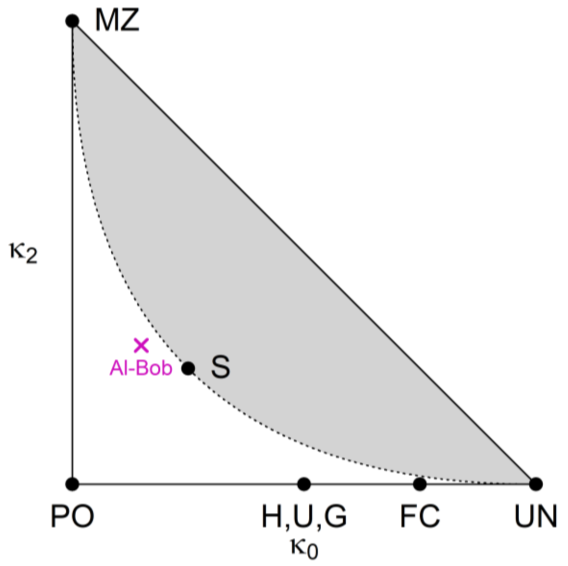


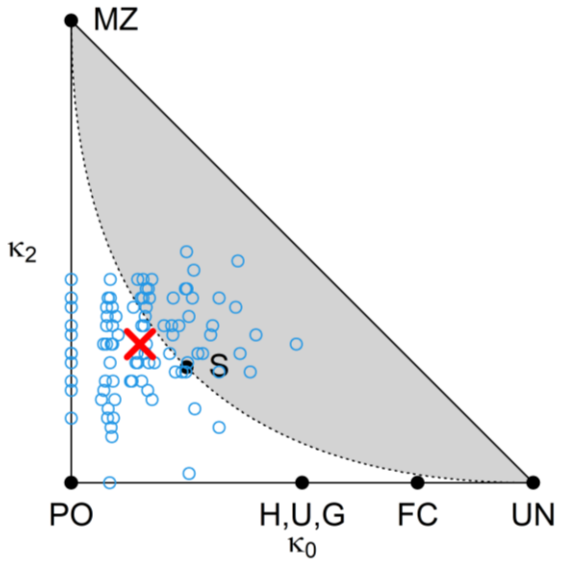
Pairwise inference in R: Example

Estimate kappa from the data

```
>   k = ibdEstimate(dat)
>   k
  id1 id2   N      k0       k1       k2
1  Al Bob 100 0.1486 0.55139 0.30002
>   showInTriangle(k, labels = T)
>   bs = ibdBootstrap(dat, ids, N = 100,
                        param = "kappa")
```

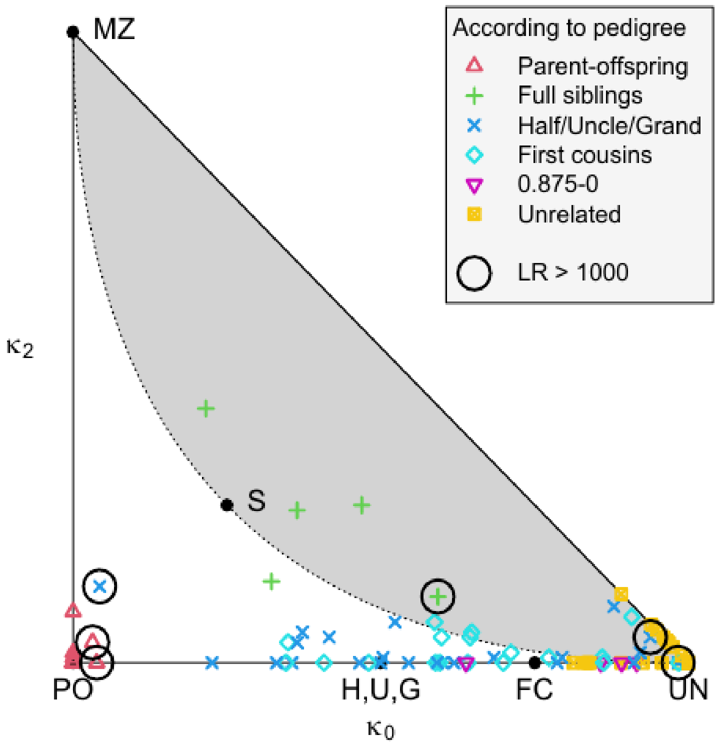




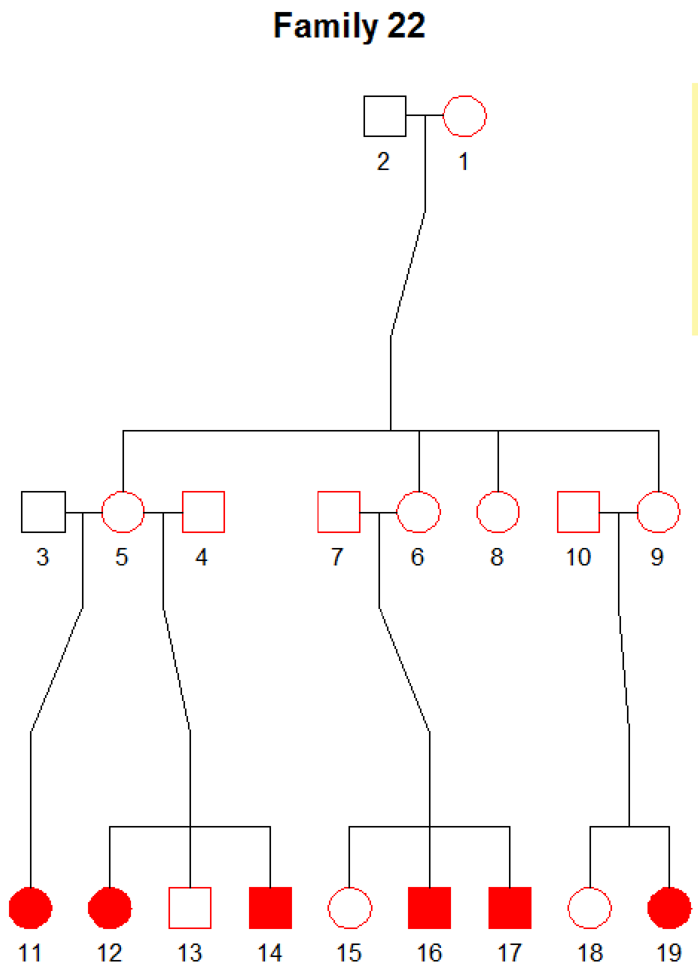


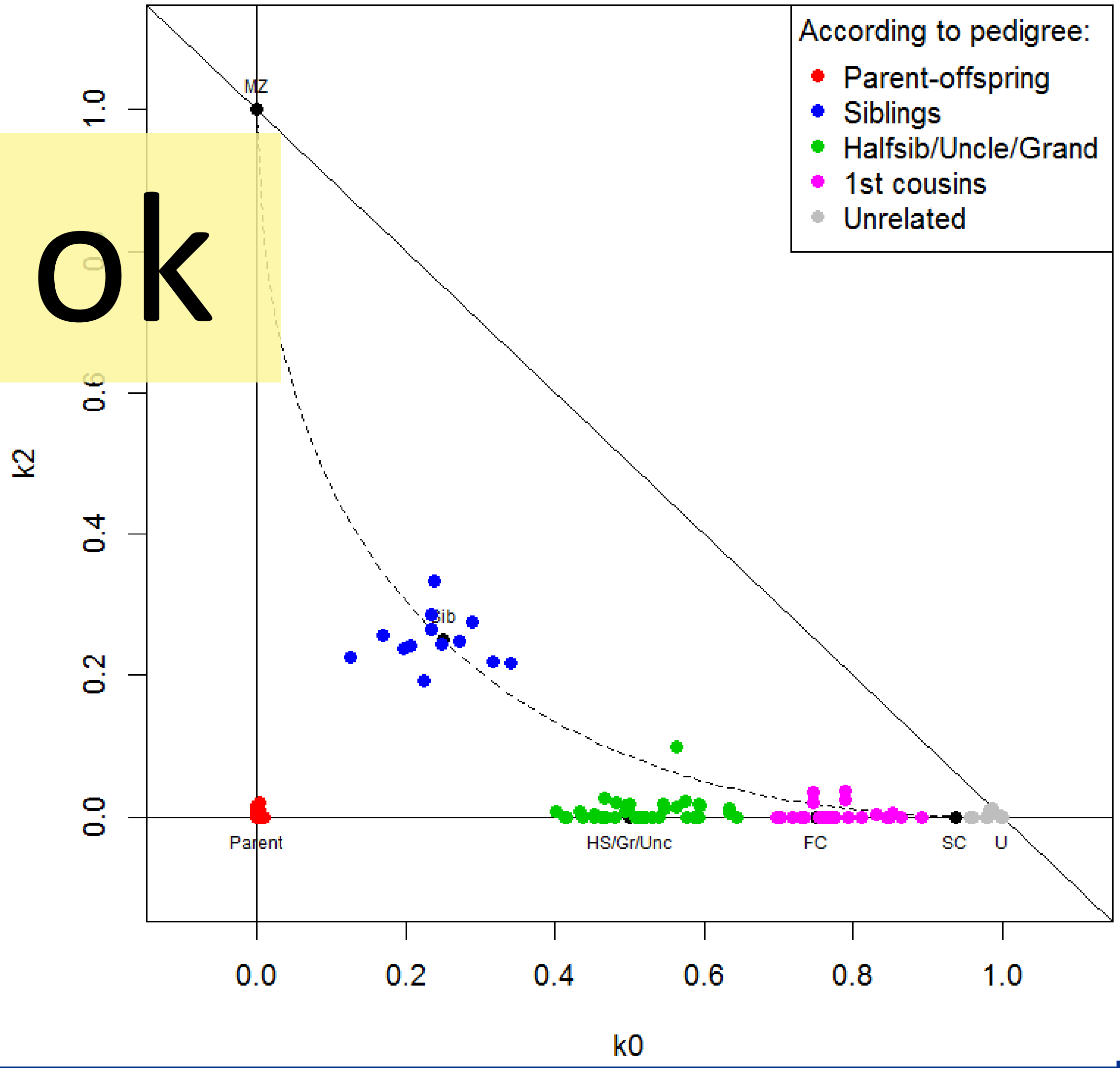
Application: Detecting pedigree errors

- Suppose **`x`** is a pedigree object with attached markers
- The function **`checkPairwise(x)`** computes:
  - pedigree-based kappa for all pairs: **`kappaIBD(x)`**
  - marker-based kappa estimates for all pairs: **`ibdEstimate(x)`**
  - LR comparing the two
  - Color-coded plot according to relationship claimed by pedigree



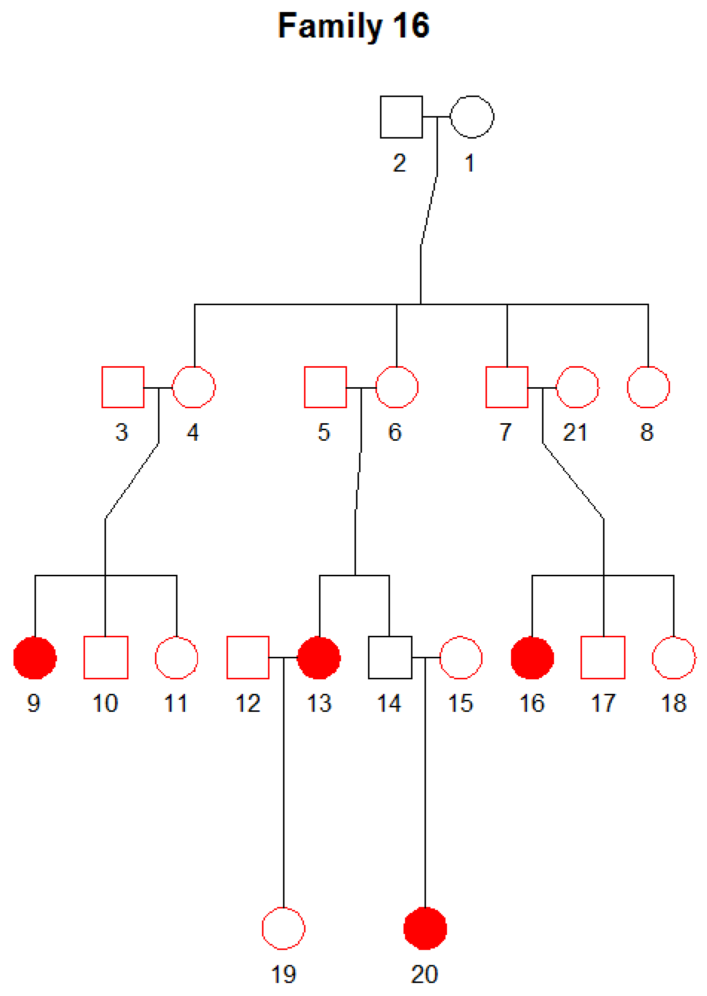
checkPairwise(): Example 1

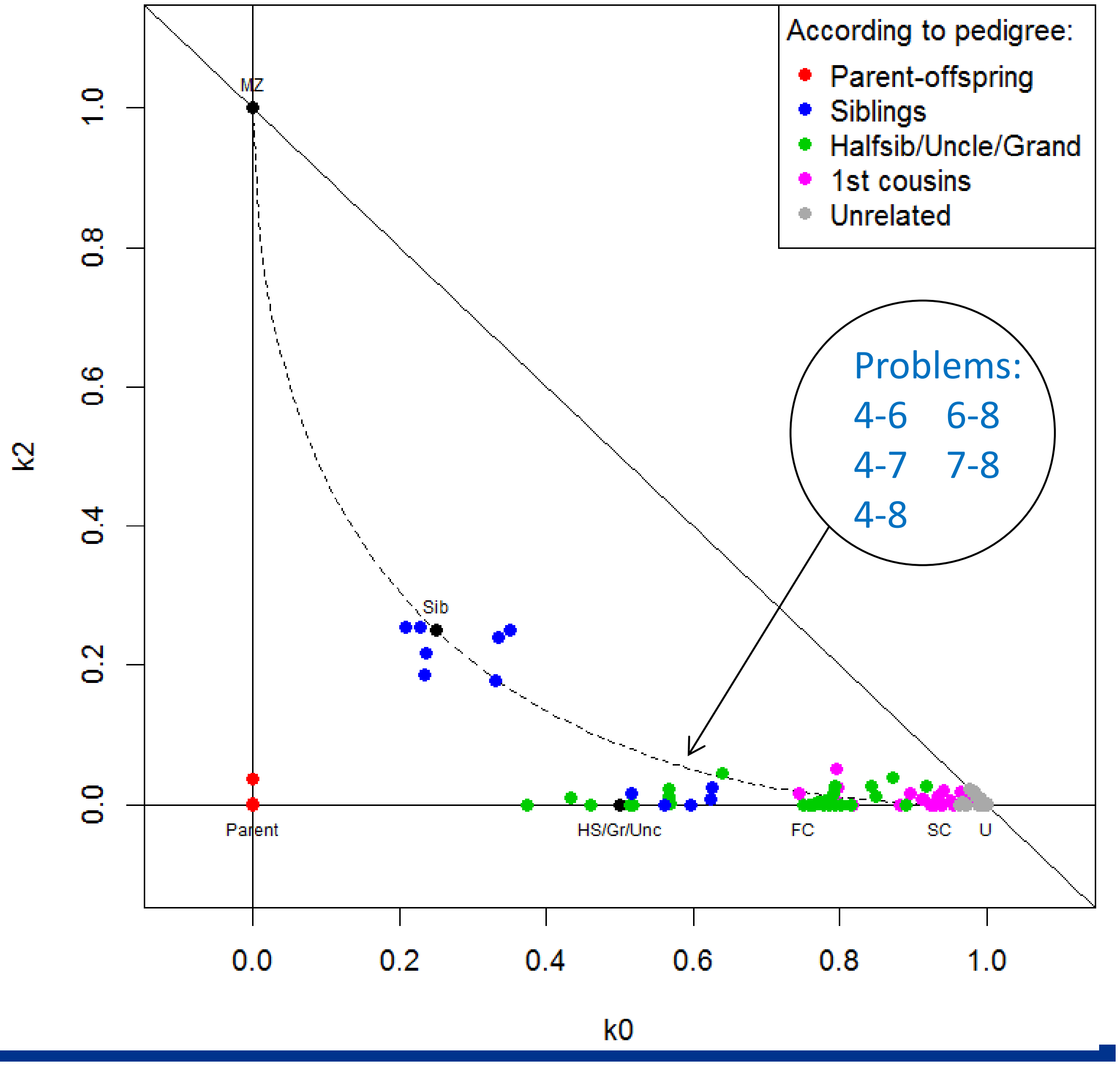




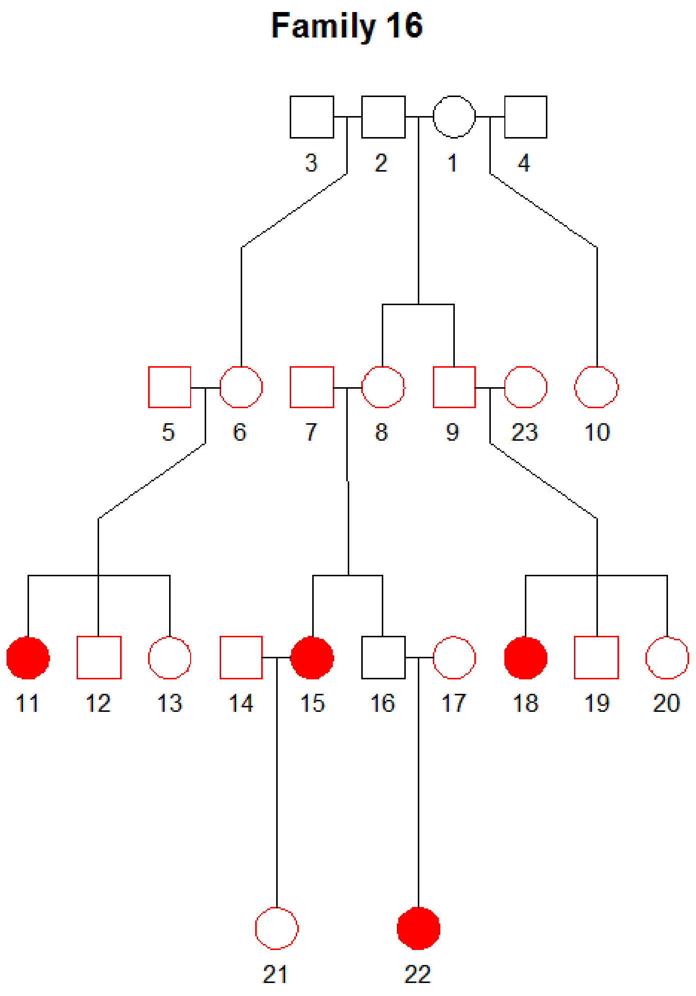
ok

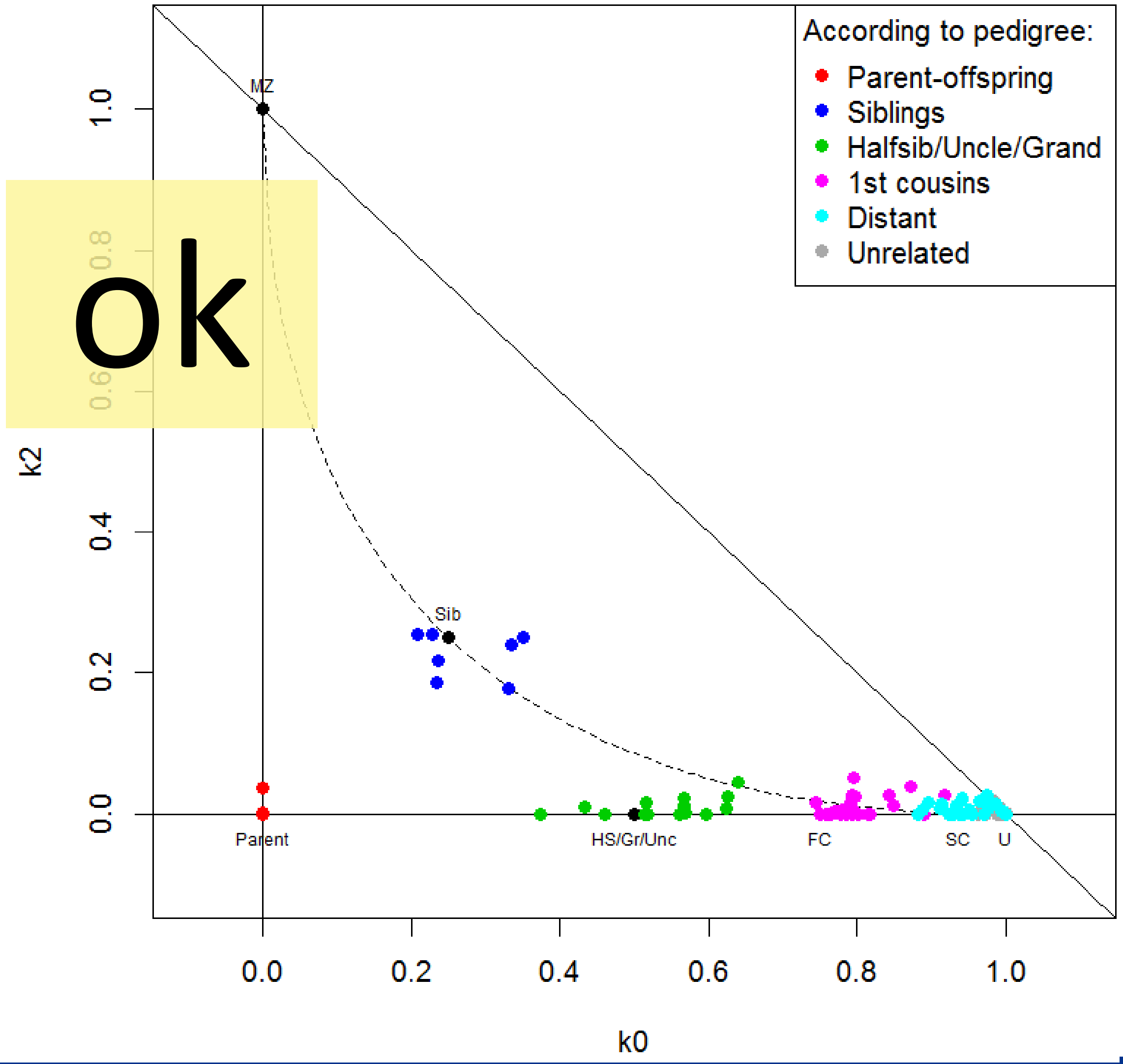
checkPairwise(): Example 2





checkPairwise(): Example 2 - corrected



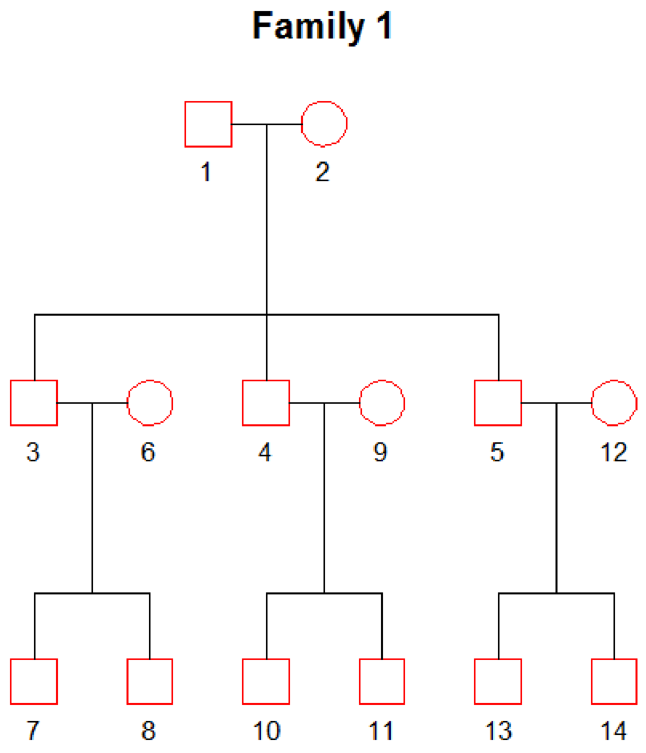


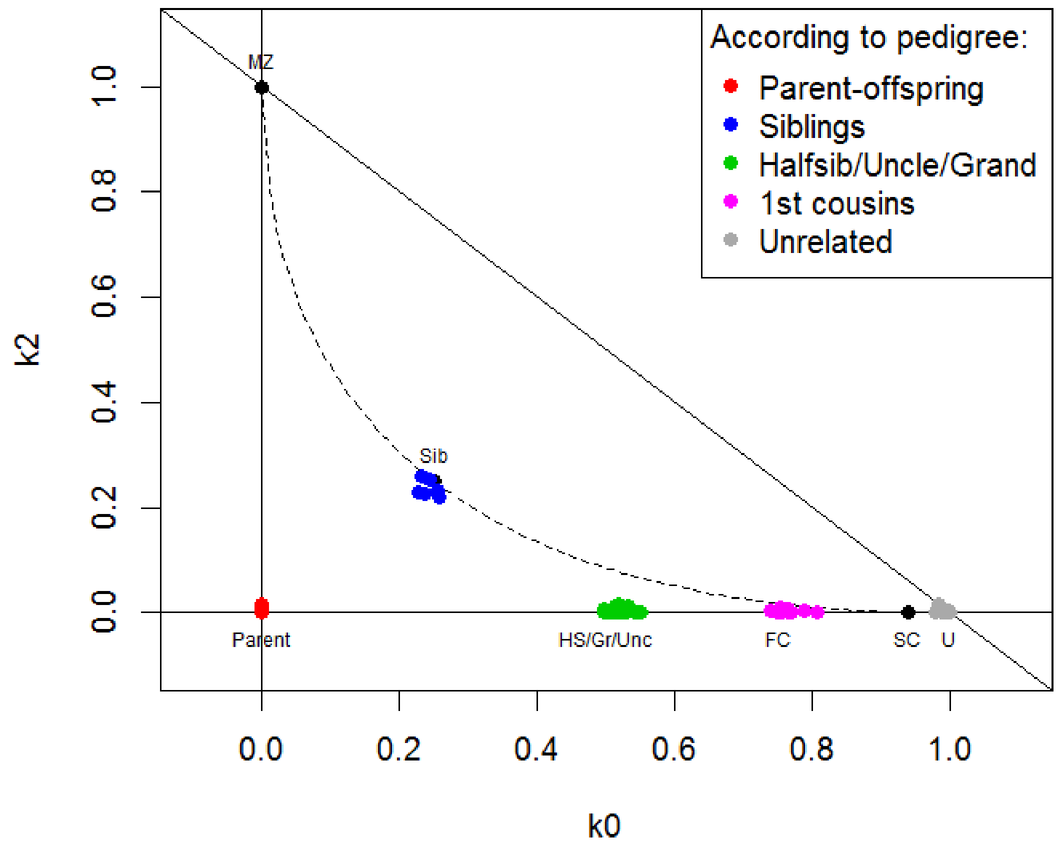
Relatedness inference vs. allele frequencies

- A little simulation experiment!

Simulation example

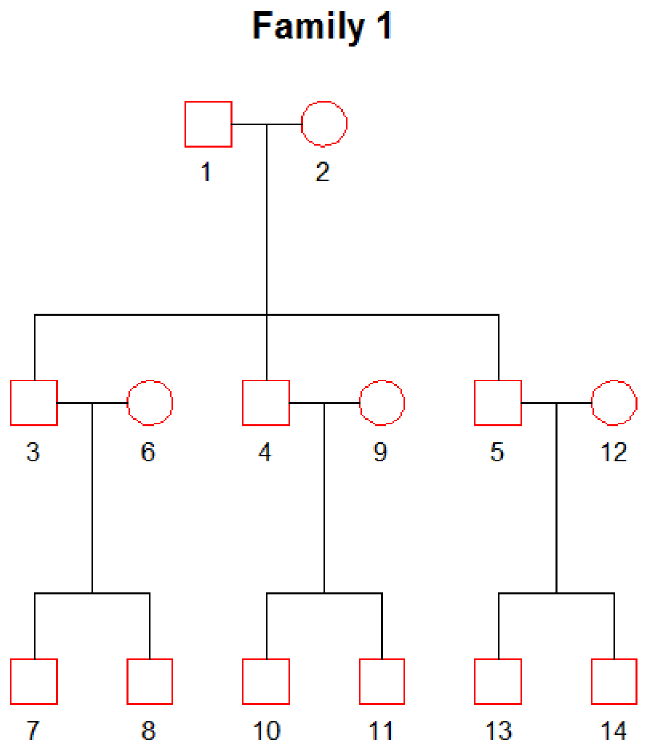
SNPs: 10 000
True frequency distr: Unif(0,1)
Frequencies used: Correct

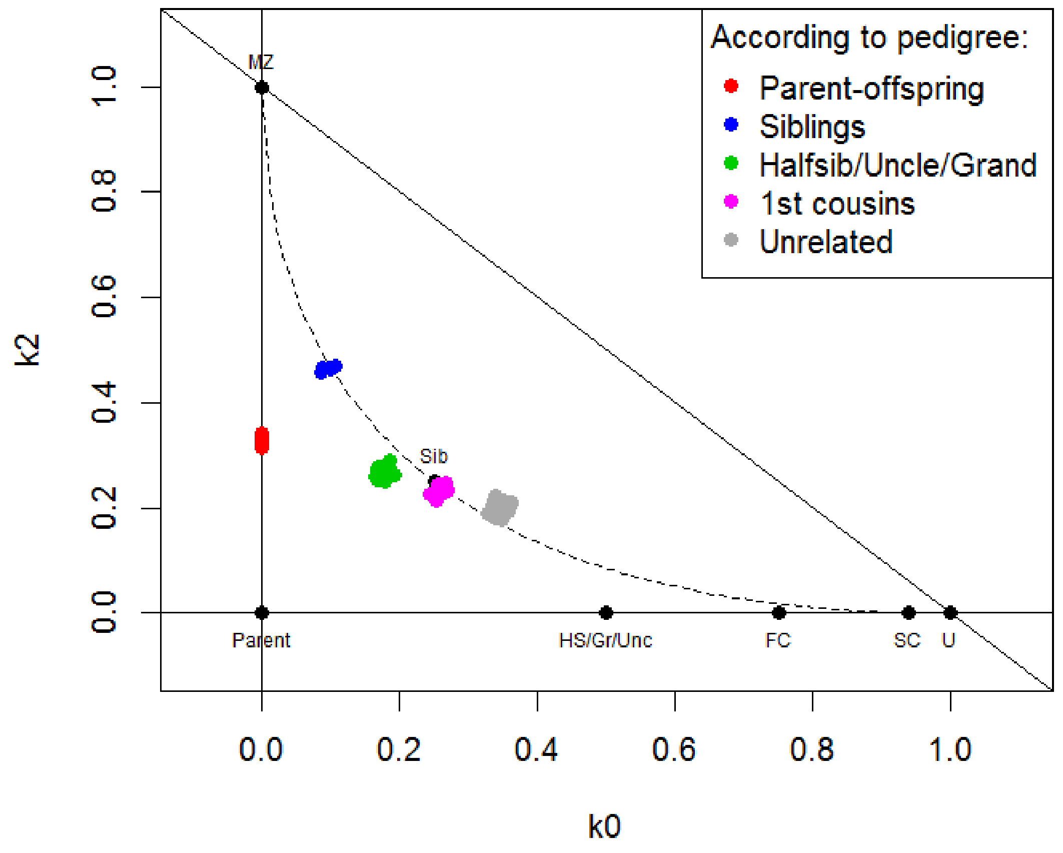




Simulation example

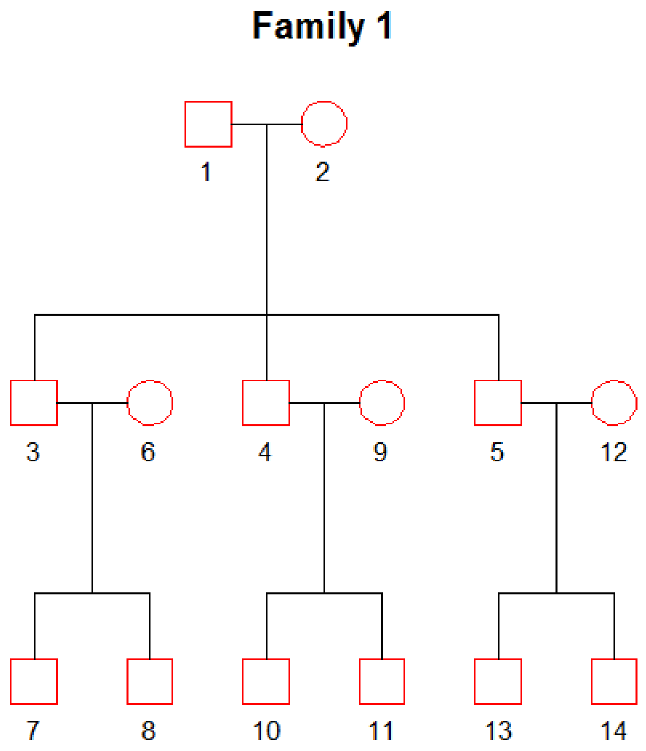
SNPs: 10 000
True frequency distr: Unif(0,1)
Frequencies used: All = 0.5

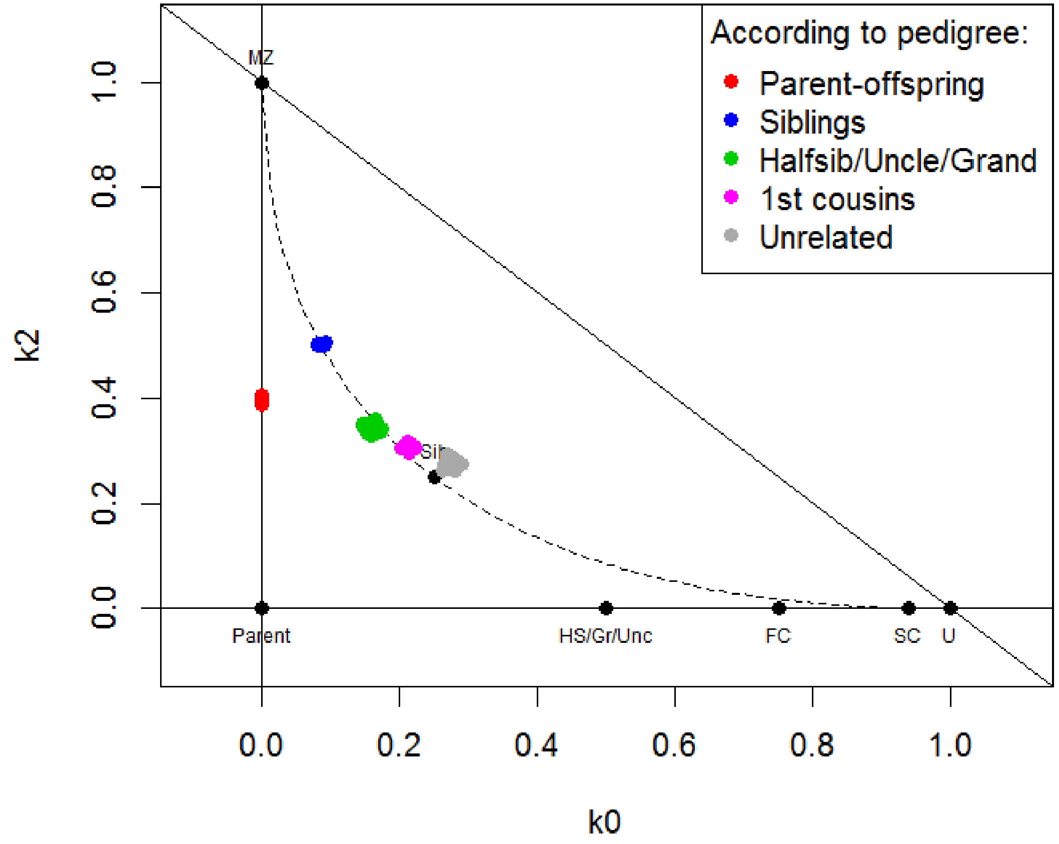




Simulation example

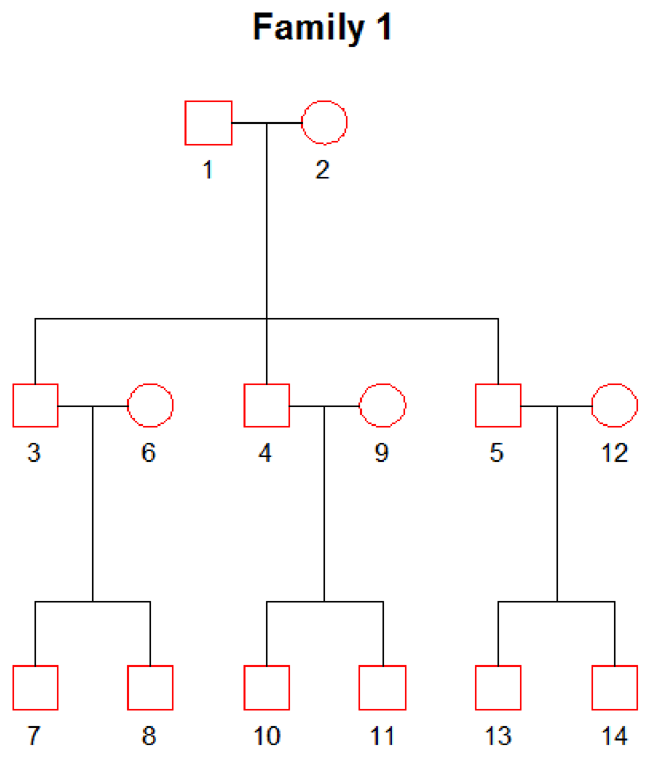
SNPs: 10 000
True frequency distr: Unif(0,1)
Frequencies used: Unif(0,1)

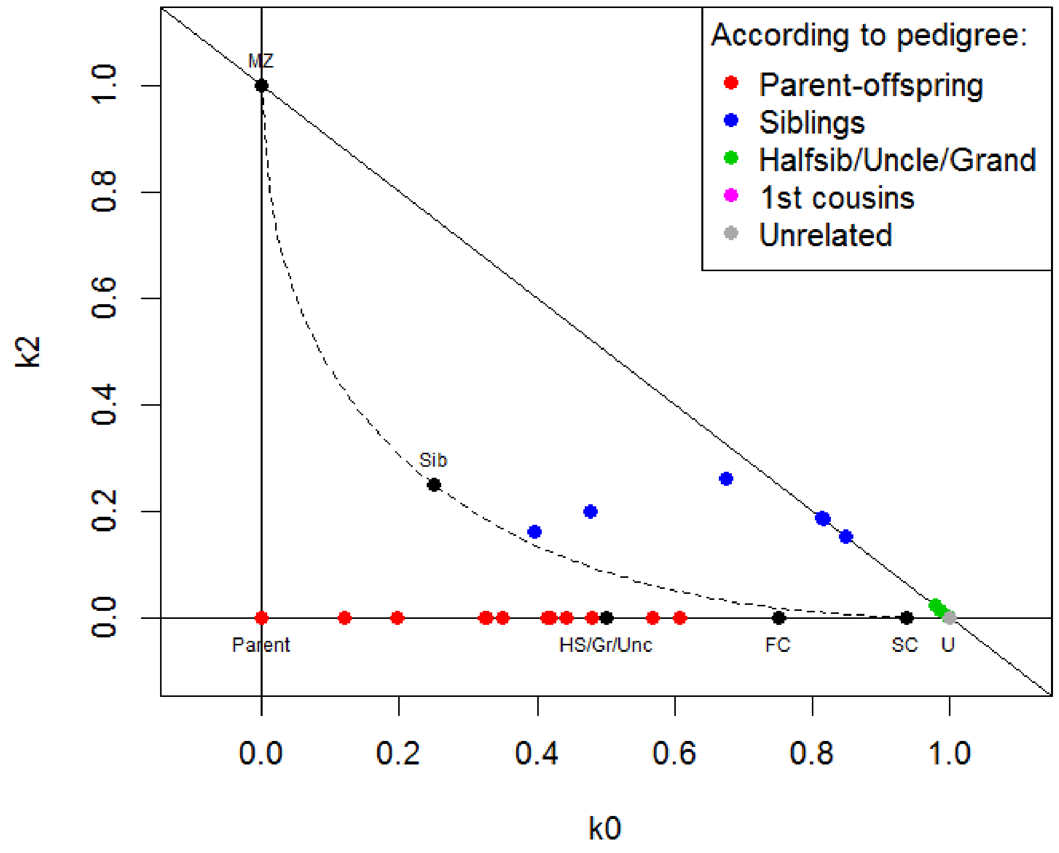




Simulation example

SNPs: 10 000
True frequency distr: Unif(0,1)
Frequencies used: Family estimate

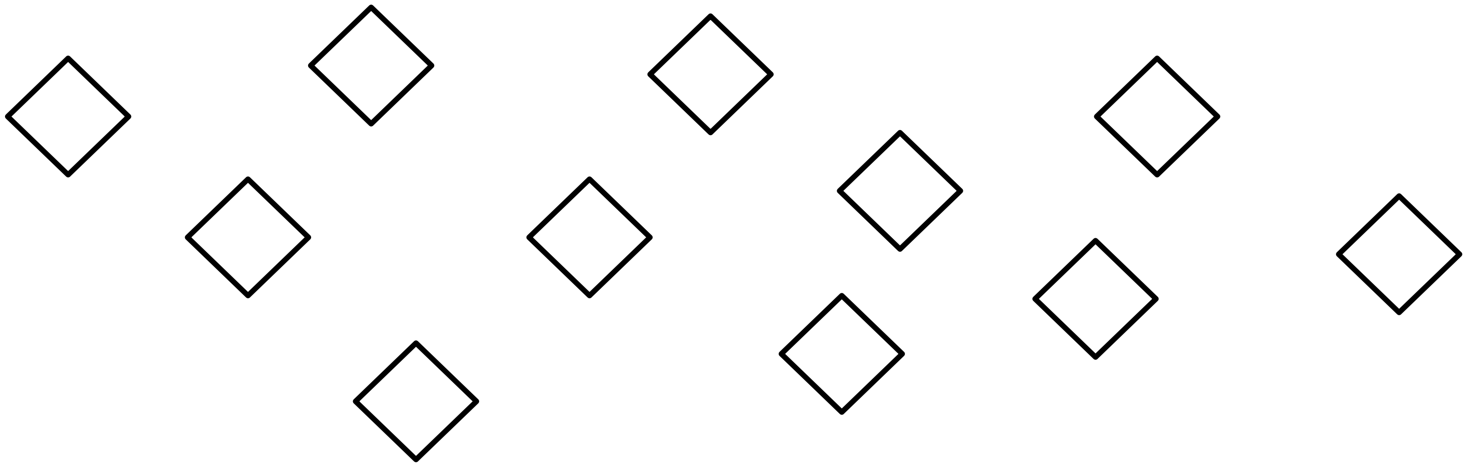




- Conclusion: Pairwise inference can be very sensitive to wrong allele frequencies

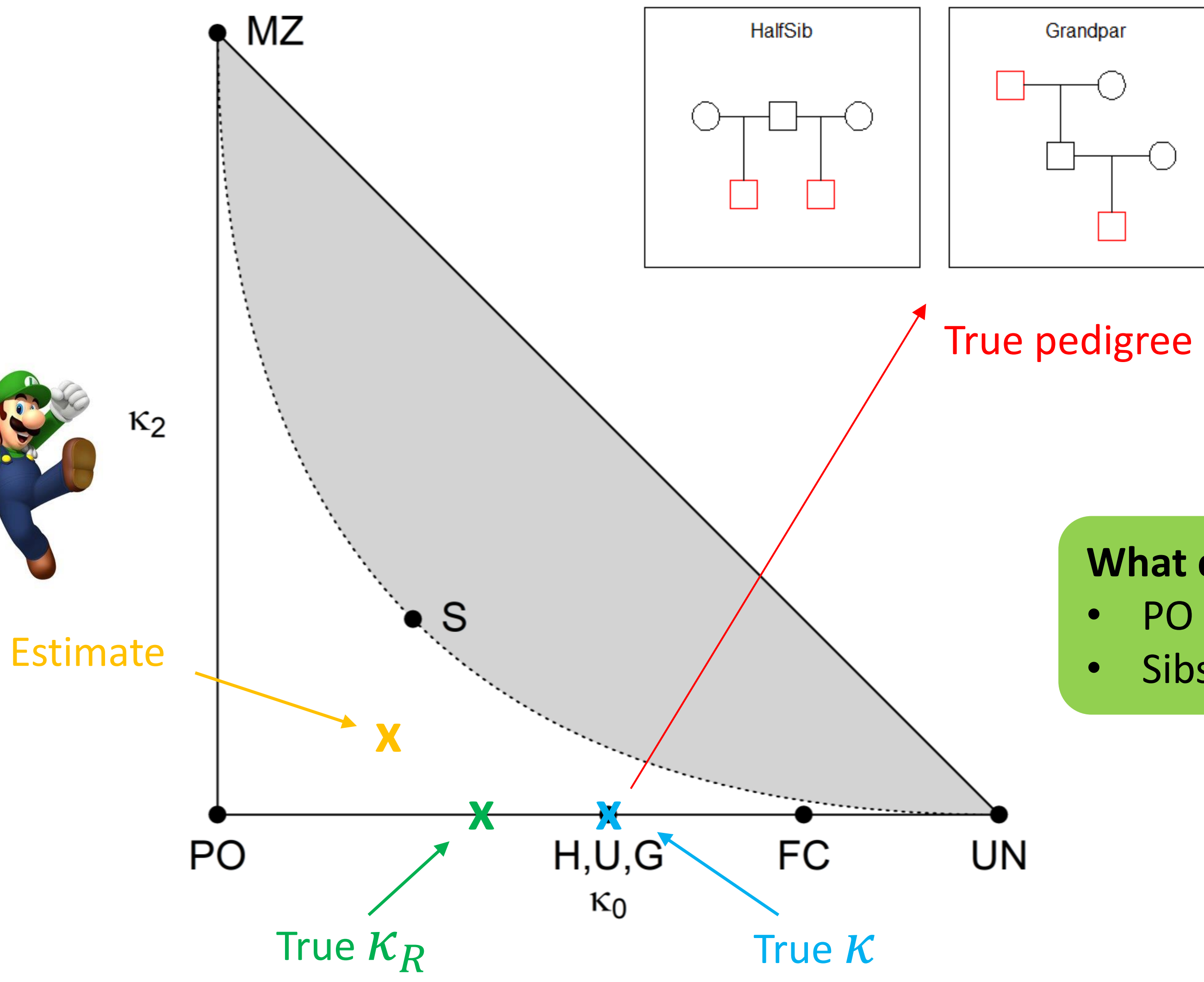
Part II: Pedigree reconstruction

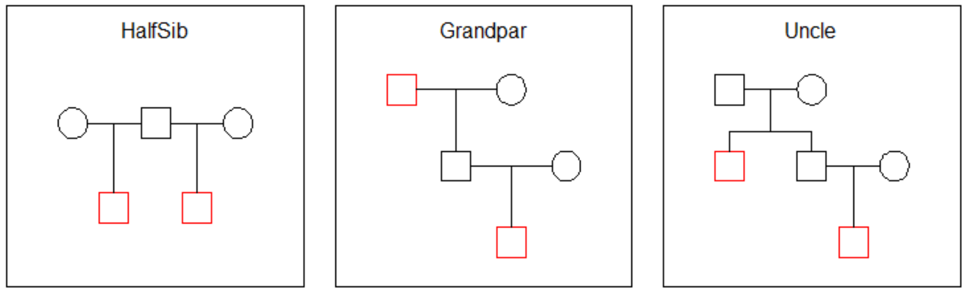
Pedigree reconstruction



Goal: Reconstruct the complete pedigree from genotype data

Impossible - even in theory!

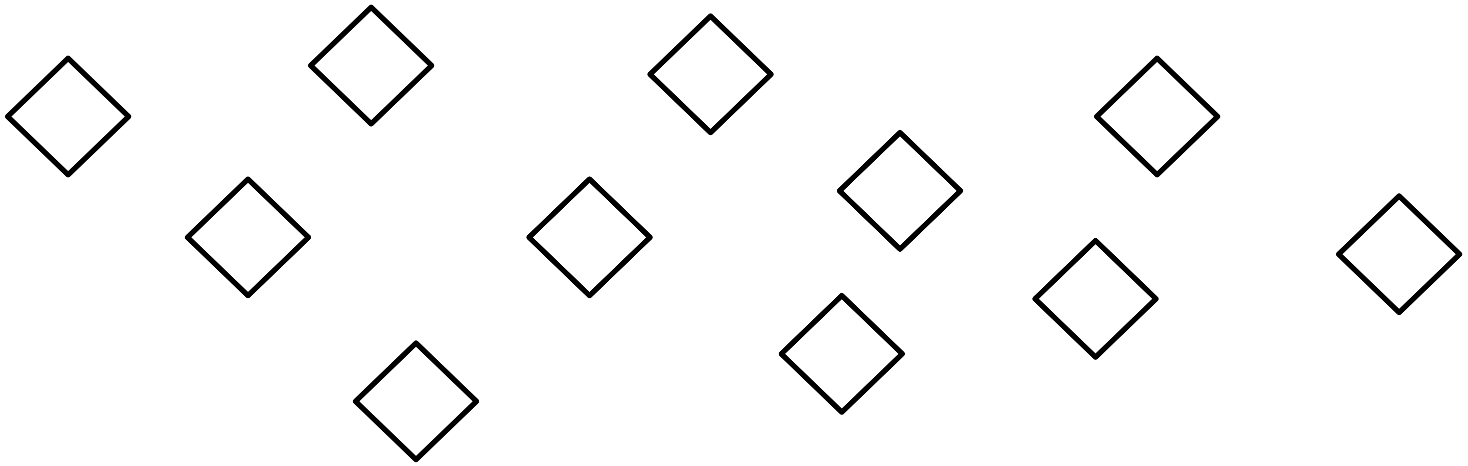




What can we trust?

- PO usually ok
- Sibs if good data

Pedigree reconstruction



Naive approach

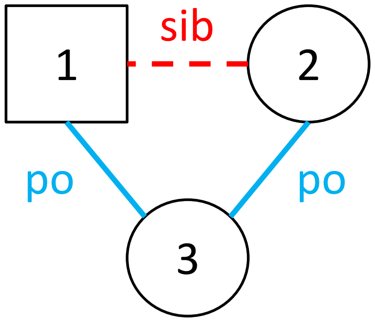
Step 1: Genders

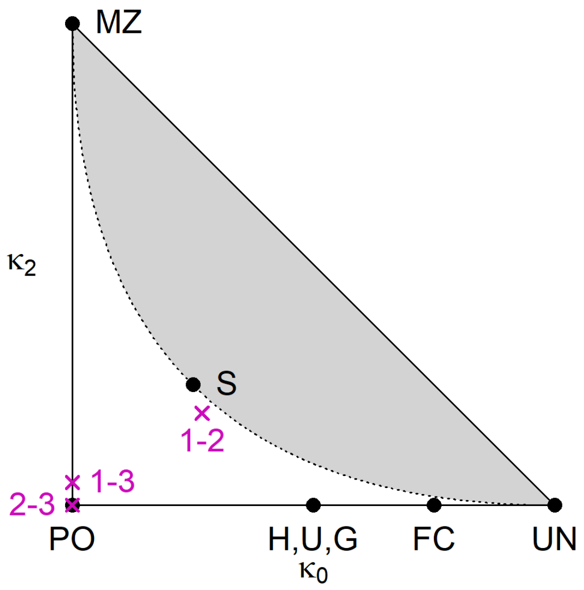
Step 2: Estimate pairwise relationships

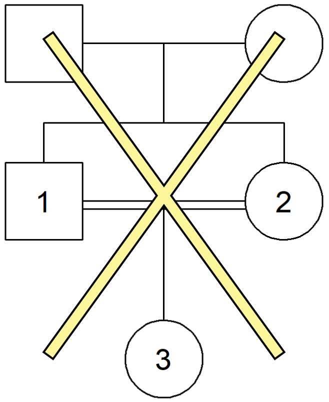
- Connect parent-child
- Exploit siblings

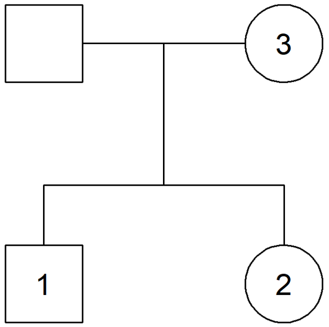
Step 3: Solve the puzzle!

Example









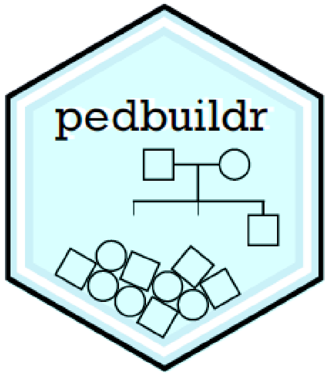
Better approach: Maximum likelihood

Idea:

- Generate a list of "all possible" pedigrees connecting the individuals
- Compute the likelihood of each pedigree
- Sort and output the best pedigrees

Key functions:

```
>  buildPeds()      # generate pedigrees

>  reconstruct()    # main function!
>  plot()           # plot top hits
```

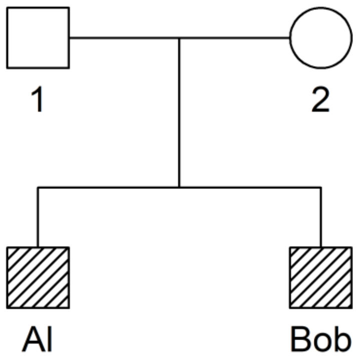


pedbuildr: Example

Same dataset as before:

Simulate 100 SNPs for a pair of siblings

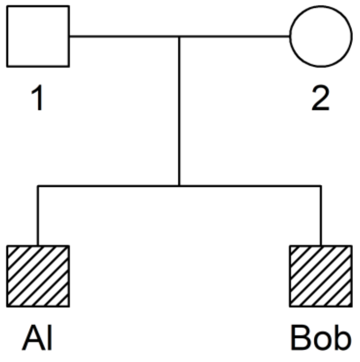
```
>  library(pedsuite)

>  ids = c("Al", "Bob")
>  x = nuclearPed(children = ids)

>  x = markerSim(x, N = 100, ids = ids,
             alleles = 1:2, seed = 1234)
>  x
 id fid mid sex <1> <2> <3> <4> <5>
   1   *   *   1 -/- -/- -/- -/- -/-
   2   *   *   2 -/- -/- -/- -/- -/-
  Al   1   2   1 1/1 1/2 1/1 1/2 2/2
 Bob   1   2   1 1/1 1/2 1/1 1/2 2/2
Only 5 (out of 100) markers are shown.

>  dat = list(subset(x, "Al"),
              subset(x, "Bob"))
```

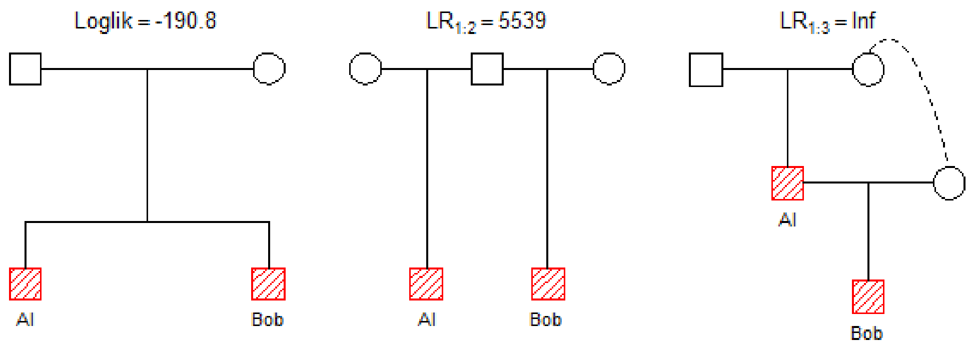


pedbuildr: Example

Reconstruct the most likely

```
>  library(pedbuildr)

>  r = reconstruct(dat)
Pedigree parameters:
  ID labels: Al, Bob
  Sex: 1, 1
  Extra: parents
  Age info: -
  Known PO: -
  ...

Building pedigree list:
  ...
Computing the likelihood of 6 pedigrees.

>  plot(r, top = 3)
```

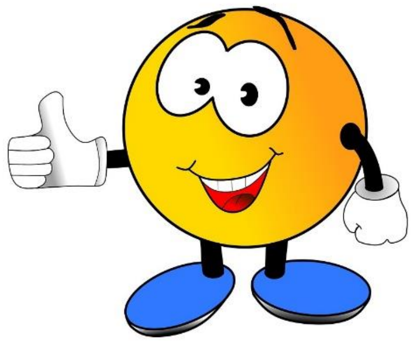


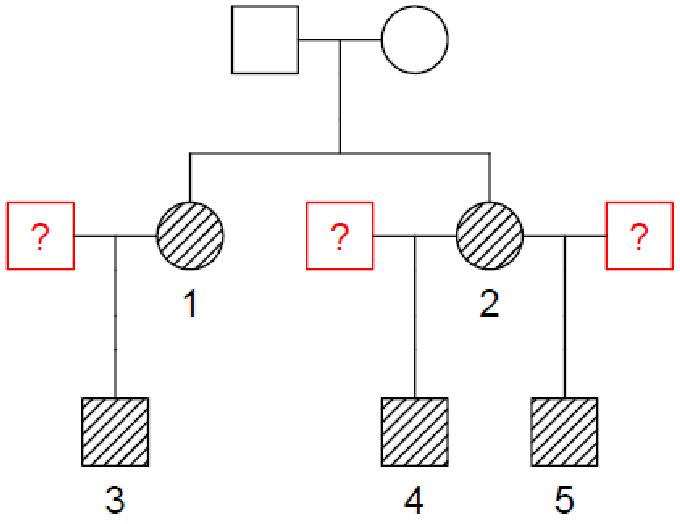


Optional parameters for restricting the search space

- **`extra`**: The max number of connecting individuals
    - default: **`extra = "parents"`** (suitable for small datasets)
- **`maxInbreeding`**: Default: 1/16 (e.g., first cousins)
- **`age`**: A vector of (relative) ages OR age inequalities, e.g. "Al > Bob"
- **`inferPO`**: If TRUE, an initial stage of pairwise IBD estimation is done
- **`knownPO`**: Known parent–offspring pairs
- **`allKnown`**: Is **`knownPO`** the *complete* list of POs?
- **`notPO`**: Pairs known not to be parent–offspring
- **`noChildren`**: Individuals known to have no children
- **`linearInb`**: Max incestuous generation gap (default: 0)
- **`connected`**: Set to FALSE to allow disconnected pedigrees
- **`sexSymmetry`**: Remove 'symmetric' versions. Default: TRUE

Your turn: Exercises!





Q: Do any of the children have the same father?