Relatedness 1:
IBD and coefficients of relatedness

or

What does it mean to be related?

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Statistical methods in genetic relatedness and pedigree analysis

NORBIS course, 6th – 10th of January 2020, Oslo

Plan

- Introduction
  - What does it mean to be related?

- Pedigree-based meassures of relatedness:
  - The concept of IBD (identical by descent)
  - Coefficient of kinship/inbreeding
  - The IBD coefficients κ_0, κ_1, κ_2
  - Jacquard's 9 *identity coefficients*

- Relatedness coefficients in R

What does it mean to be related?

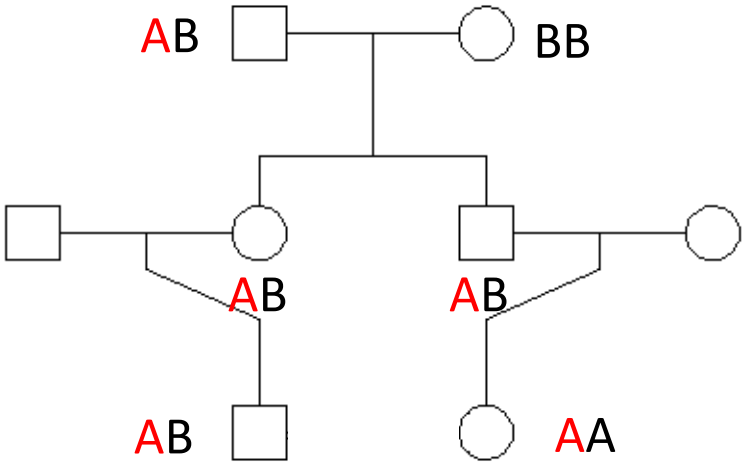
- Social anthropology "definition":
  - being connected through a pedigree
  - having a common ancestor...not too far back
- Genetic "definition":
  - sharing DNA?
  - (more than unrelated people)
- To make all this precise, we need some terminology.....

IBD and autozygosity

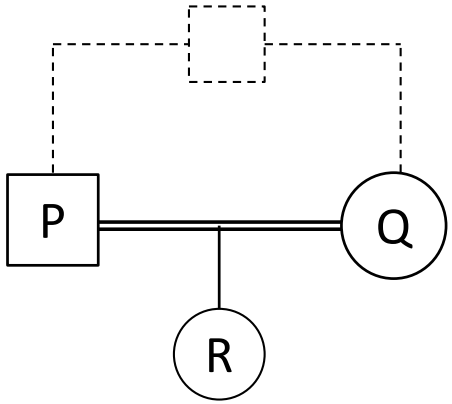
- IBD = "*Identical by descent*"
  = identical alleles with a common origin **in the given pedigree**

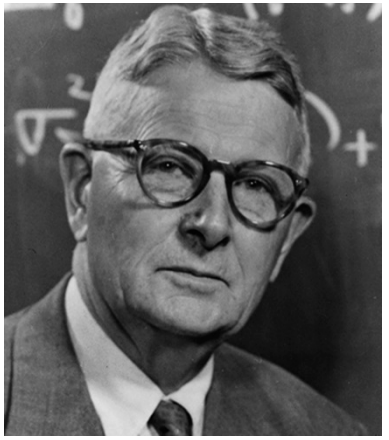
- IBS = "*Identical by state*"
  = identical alleles

- autozygous = homozygous + IBD



Relatedness yellow belt: Coefficient of kinship/inbreeding





Sewall Wright
(1889 - 1988)

- Wright (1921): The kinship coefficient φ between P and Q

$\varphi_{P,Q}$ = *P*(random allele of P is IBD with random allele of Q)

Mendel's 1. law! →

= *P*(R receive IBD alleles from her parents)

= *P*(R is autozygous)

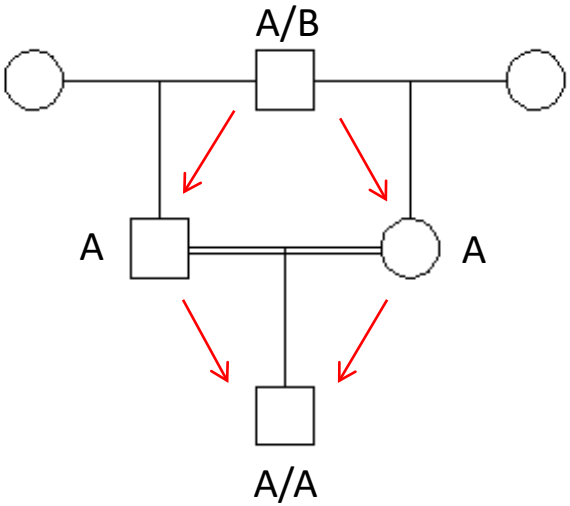
= f_R **the inbreeding coefficient of R**

P and Q related

⇕

$\varphi_{P,Q} > 0$

Examples

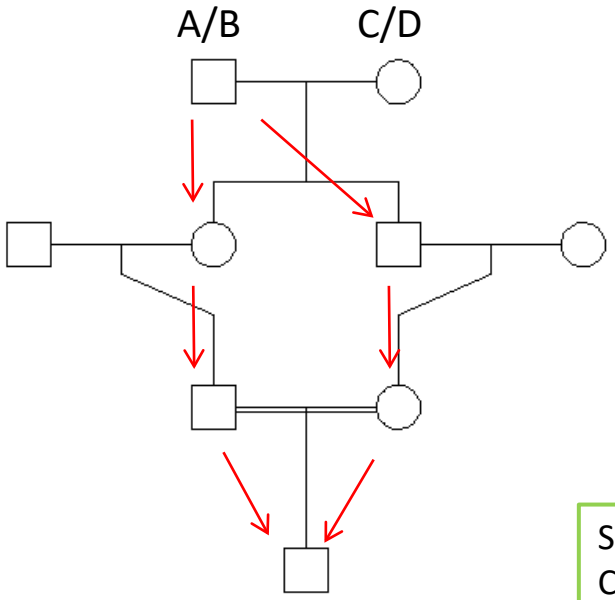


$$f = P(\text{A/A autozygous}) \cdot 2$$

$$= 0.5^4 \cdot 2$$

$$= \frac{1}{8}$$

A or B



Same for C and D

$$f = P(\text{A/A autozygous}) \cdot 2 \cdot 2$$

$$= 0.5^6 \cdot 2 \cdot 2$$

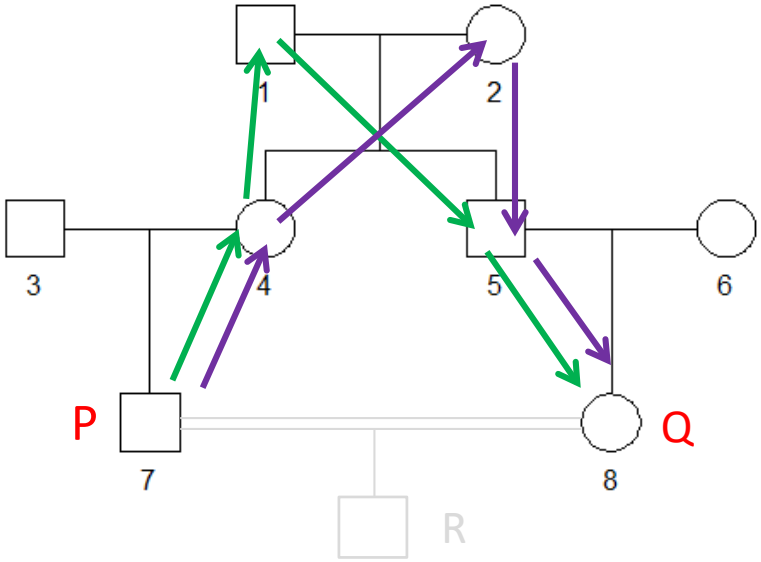
$$= \frac{1}{64} \cdot 4 = \frac{1}{16}$$

A or B

Wright's path formula

- Simple form works in most cases:

$$f_R = \varphi_{P,Q} = \sum_v \left(\frac{1}{2}\right)^{|v|+1}$$



- Translation:
  - Find all paths *v* between *P* and *Q*
  - For each path compute $0.5^{|v|+1}$
  - Take the sum!

- Example: 2 paths
  - 7-4-1-5-8 (length = 4)
  - 7-4-2-5-8 (length = 4)

⇨ $\varphi = 0.5^5 + 0.5^5 = \frac{1}{16} = 0.0625$

Wright's path formula in full generality

$$\varphi_{P,Q} = \sum_A \sum_v \left(\frac{1}{2}\right)^{|v|+1} (1 + f_A)$$

- sum over all common ancestors *A* of *P* and *Q* ...
- ... and all non-collapsing paths *v* fra *P* til *Q* via *A*
- $|v|$ is the length of *v*
- f_A is the inbreeding coefficient of *A*

Applicable to any pairwise relationship, however complex!

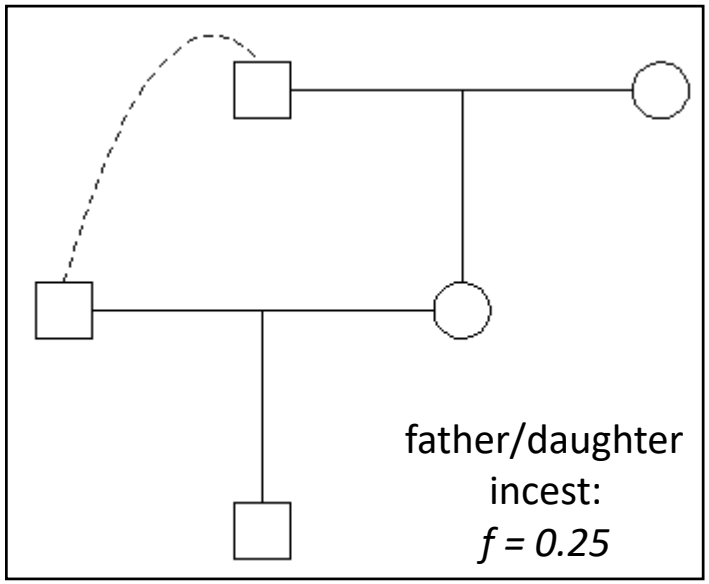
Interpretations of the inbreeding coefficient

autosomal

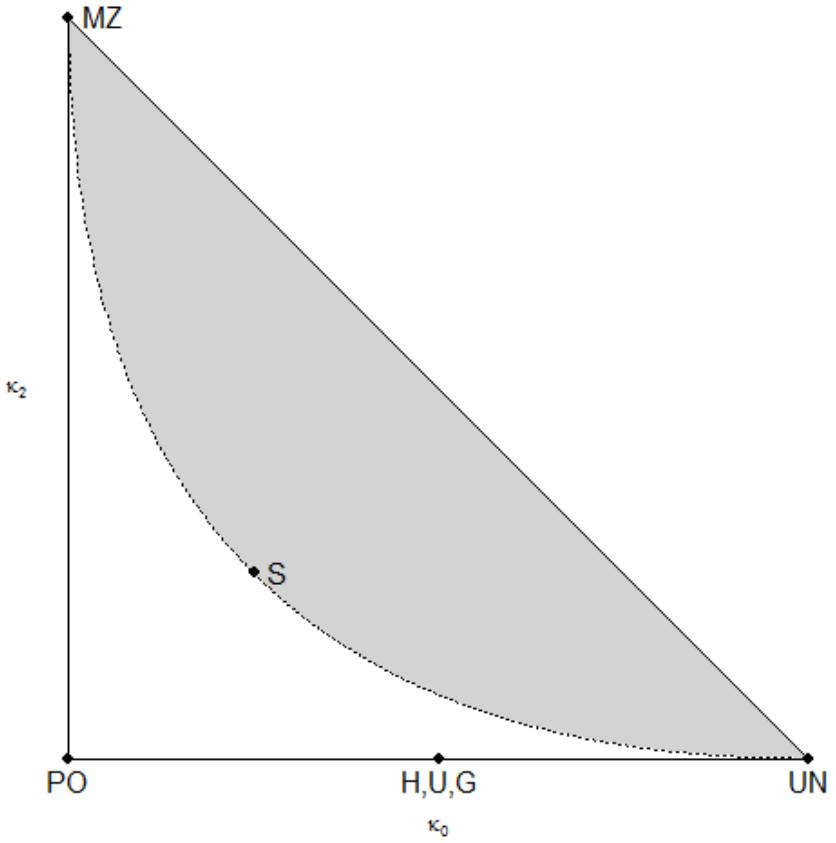
$f = P($ random locus autozygous $)$

= expected fraction of the genome that is autozygous

Parents	f (of child)
father/daughter full sibs	1/4
uncle/niece	1/8
first cousins	1/16
second cousins	1/64
third cousins	1/256



Red belt: The IBD triangle

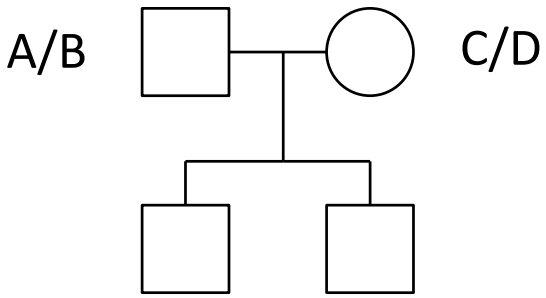


Charles Cotterman
(1914-1989)

Elisabeth Thompson
(1949 -)

IBD coefficients: Warm-up

- Summary so far:
  - Two individuals are related if they can have IBD alleles
  - Their kinship coefficient meassures the amount of IBD sharing
- Natural generalisation:
  - How *many* alleles are IBD in each locus?



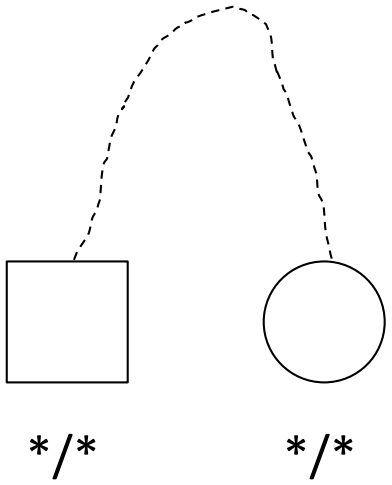
Humans are diploid

IBD = 0, 1 or 2

A/C	A/D	← 1 allele IBD
A/C	A/C	← 2 alleles IBD
A/C	B/D	← 0 alleles IBD

IBD coefficients: Definiton

- Given two (non-inbred) individuals



- For a random autosomal locus

  κ_0 = *P*(0 alleles IBD)

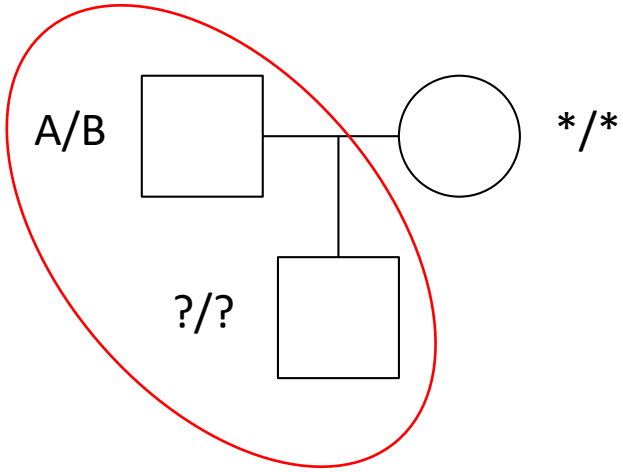
  κ_1 = *P*(1 alleles IBD)

  κ_2 = *P*(2 alleles IBD)

IBS = *Identical by state*
IBD = *Identical by descent*

- Note: $\kappa_0 + \kappa_1 + \kappa_2 = 1$

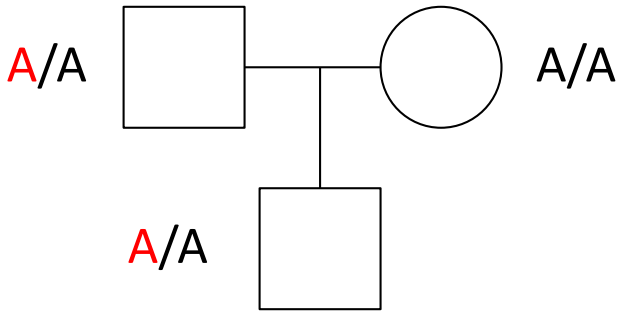
Example 1: Parent vs child



$\kappa_0 = 0$
$\kappa_1 = 1$
$\kappa_2 = 0$

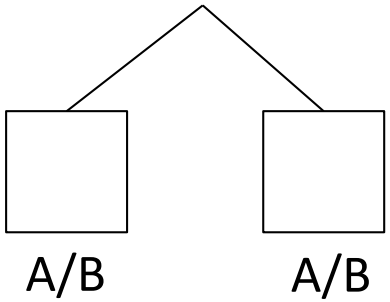
- Note the difference between IBD and IBS:

  Don't be deceived by appearences!



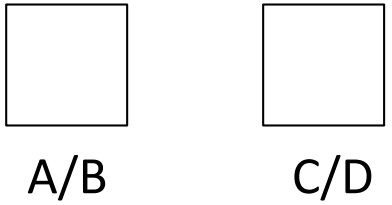
More "trivial" examples

- MZ twins



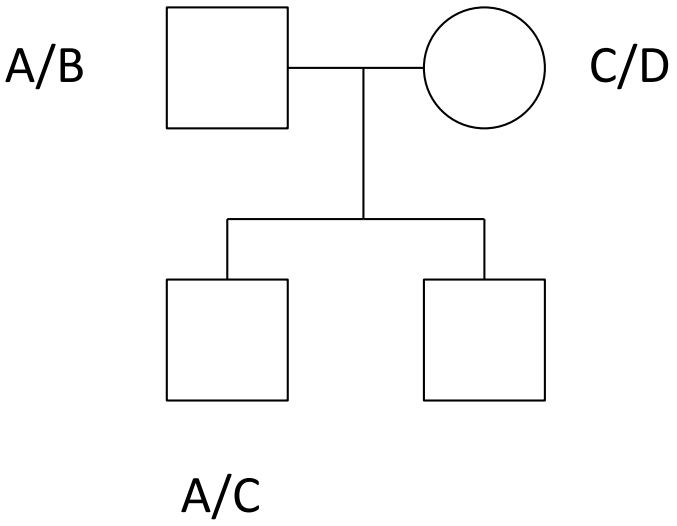
$\kappa_0 = 0$
$\kappa_1 = 0$
$\kappa_2 = 1$

- Unrelated inviduals



$\kappa_0 = 1$
$\kappa_1 = 0$
$\kappa_2 = 0$

The case of full siblings

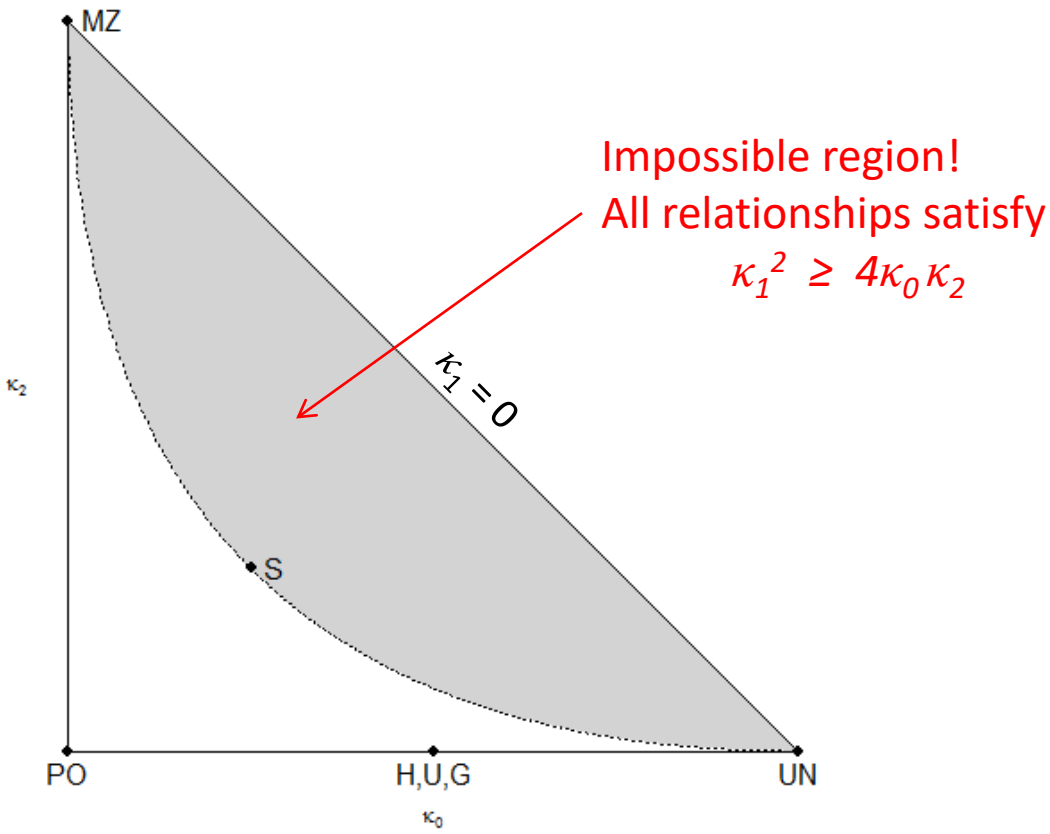


$\kappa_0 = 0.25$

$\kappa_1 = 0.5$

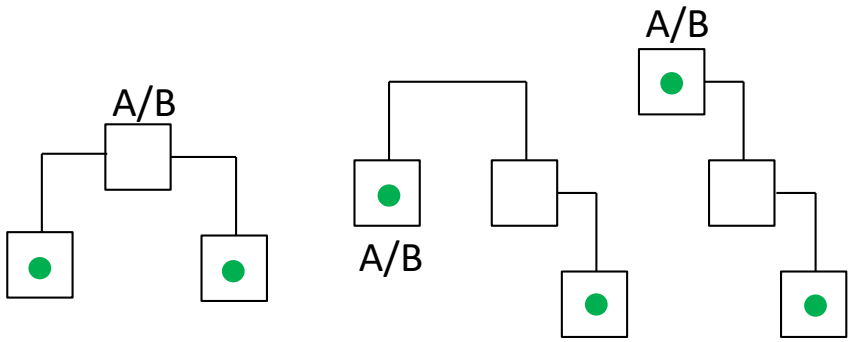
$\kappa_2 = 0.25$

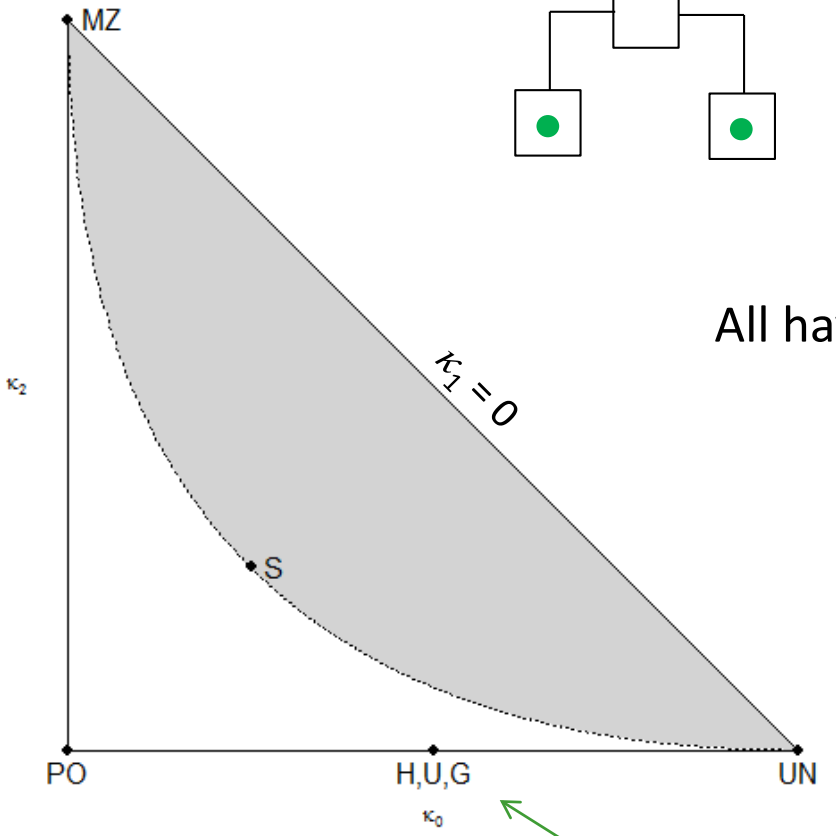
The relatedness triangle



Recall: $\kappa_0 + \kappa_1 + \kappa_2 = 1$

The relatedness triangle





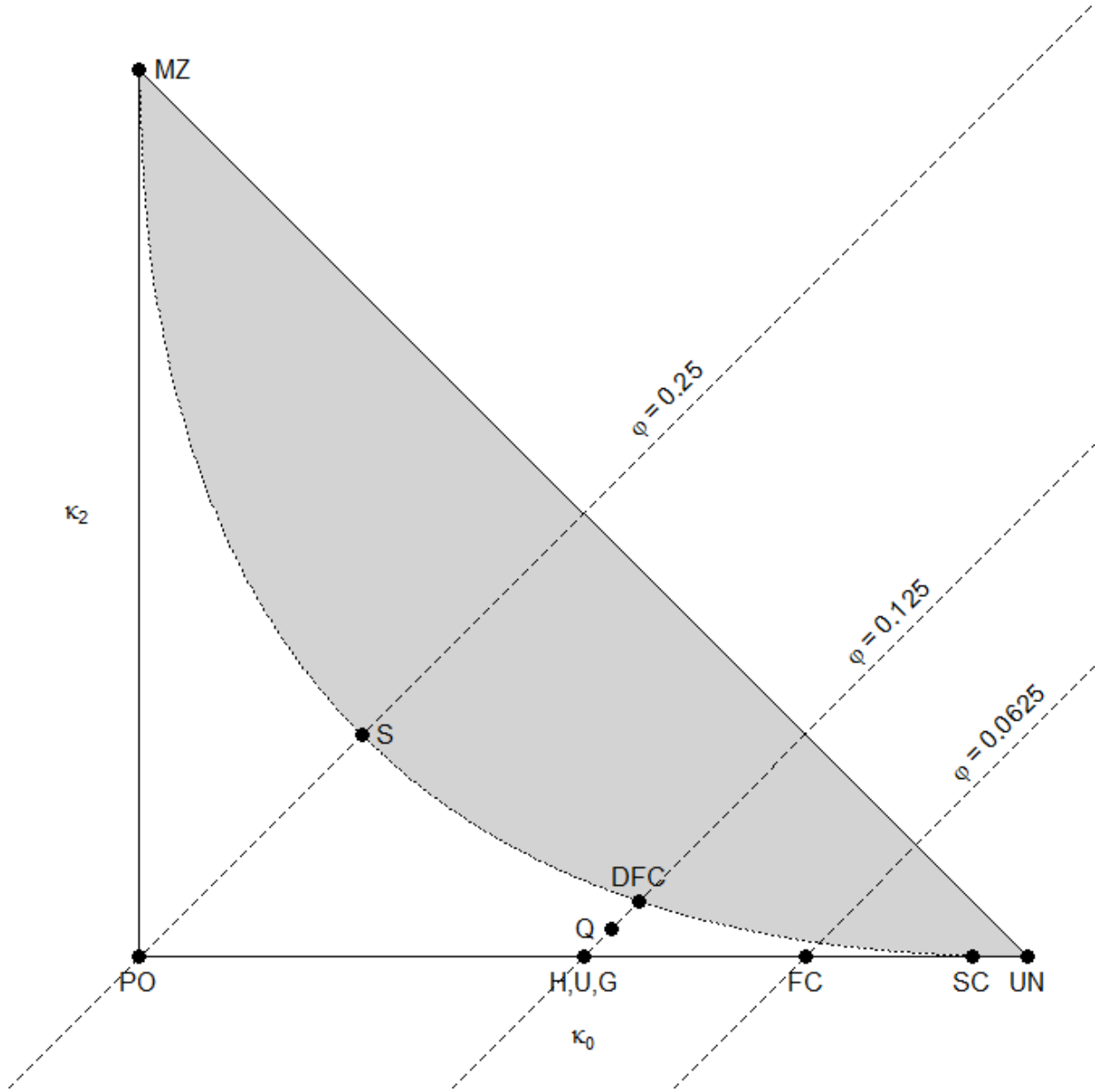
All have κ = (½, ½, 0)

NB: Some relationships coincide!

Recall: $\kappa_0 + \kappa_1 + \kappa_2 = 1$

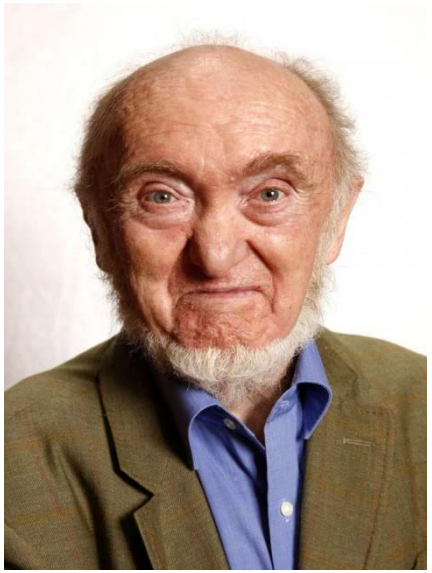
An important identity

$$\varphi = \frac{1}{4}\kappa_1 + \frac{1}{2}\kappa_2$$

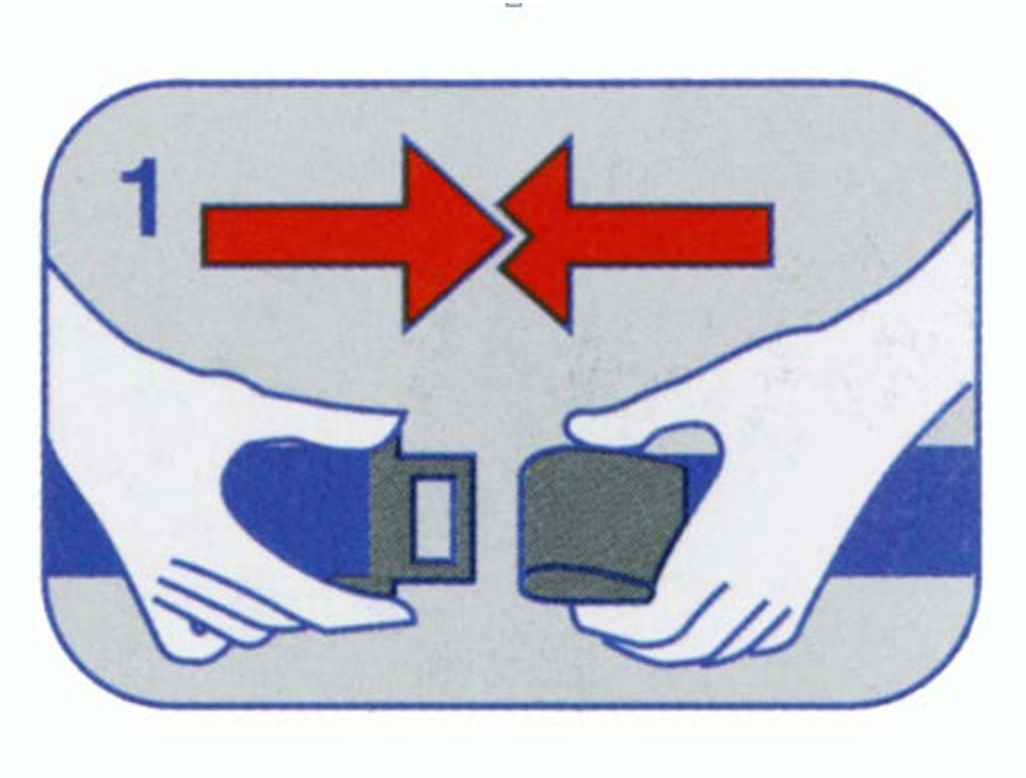

MZ
κ_2
$\varphi = 0.25$
$\varphi = 0.125$
$\varphi = 0.0625$
S
DFC
Q
PO
H,U,G
FC
SC
UN
κ_0

- After a short coffee break:

Black belt: Jacquard's identity coefficients



Albert Jacquard
(1925 - 2013)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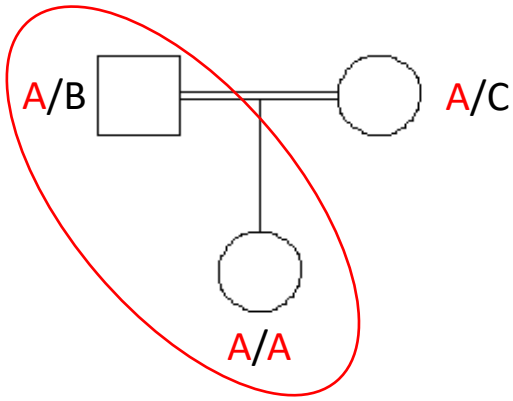
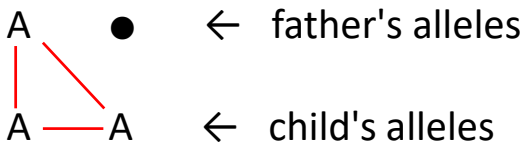
Black belt: Jacquard's identity coefficients

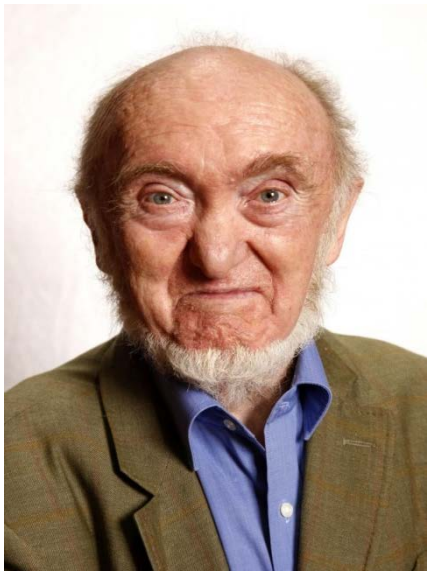
- Jacquard (1970):
  - Structures Génétiques des Populations
- Motivation: Inbred relationships
  - $\kappa_0, \kappa_1, \kappa_2$ are not well defined
- Example:



What's the IBD status here??? 1 or 2?
Cannot be summarised in one number.

Configuration:





Albert Jacquard
(1925 - 2013)

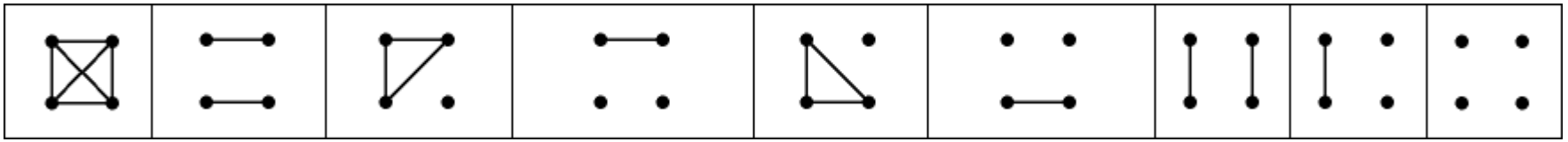
Jacquard's 9 coefficients

- Two individuals, two alleles each:

● ● ← alleles of individual 1

● ● ← alleles of individual 2

9 possible IBD configurations:



- Any pairwise relationship can be summarised by the relative frequencies of each of these.

Jacquard's *condensed identity* coefficients:

$\Delta_1, \Delta_2, \ldots, \Delta_9$

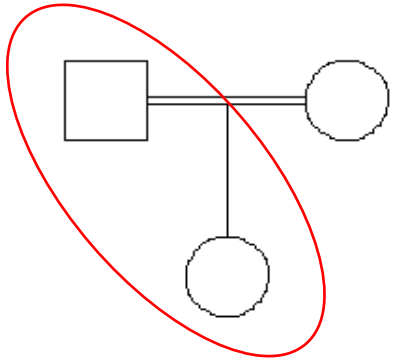
Very simple with non-inbred individuals

A/B C/D

								
0	0	0	0	0	0	κ_2	κ_1	κ_0

- • ← alleles of individual 1
- • ← alleles of individual 2

Non-trivial example

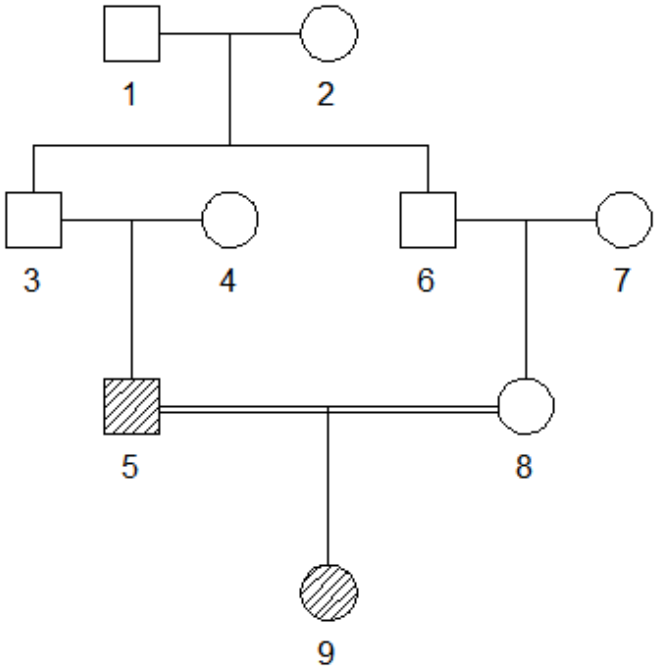


Suppose the parents are first cousins, but not themselves inbred

The Jacquard coefficients for the father vs child:

0	0	0	0	$\frac{1}{16}$	0	$\frac{1}{16}$	$\frac{7}{8}$	0

ribd: Pedigree-based relatedness coefficients



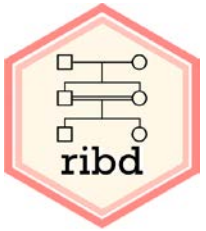
Main functions

- kinship(x, ids)
- kappaIBD(x, ids)
- condensedIdentity(x, ids)

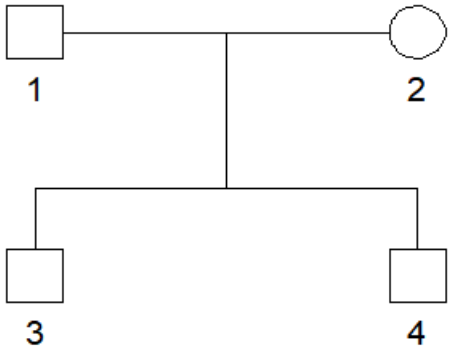
= Jacquard

Try it out!

```
> library(devtools)
> install_github("magnusdv/ribd")
> install_github("magnusdv/forrel")
```




```
> library(ribd)
> x = nuclearPed(2)
> plot(x)
```




```
> kinship(x)
     1    2    3    4
1 0.50 0.00 0.25 0.25
2 0.00 0.50 0.25 0.25
3 0.25 0.25 0.50 0.25
4 0.25 0.25 0.25 0.50
```

```
> kappaIBD(x)
id1 id2 kappa0 kappa1 kappa2
  1   2   1.00    0.0   0.00
  1   3   0.00    1.0   0.00
  1   4   0.00    1.0   0.00
  2   3   0.00    1.0   0.00
  2   4   0.00    1.0   0.00
  3   4   0.25    0.5   0.25
```

```
> condensedIdentity(x, ids = 1:4)
id1 id2 D1 D2 D3 D4 D5 D6   D7  D8   D9
  1   2  0  0  0  0  0  0 0.00 0.0 1.00
  1   3  0  0  0  0  0  0 0.00 1.0 0.00
  1   4  0  0  0  0  0  0 0.00 1.0 0.00
  2   3  0  0  0  0  0  0 0.00 1.0 0.00
  2   4  0  0  0  0  0  0 0.00 1.0 0.00
  3   4  0  0  0  0  0  0 0.25 0.5 0.25
```