Relatedness 1:
IBD and coefficients of relatedness

or

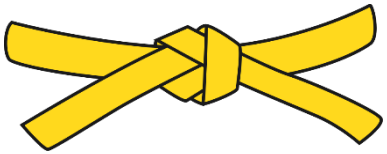
What does it mean to be related?

Magnus Dehli Vigeland

Statistical methods in genetic relatedness and pedigree analysis

NORBIS course, 13th – 17th of June 2022, Oslo

Plan



Kinship/inbreeding coefficient

IBD coefficients & IBD triangle

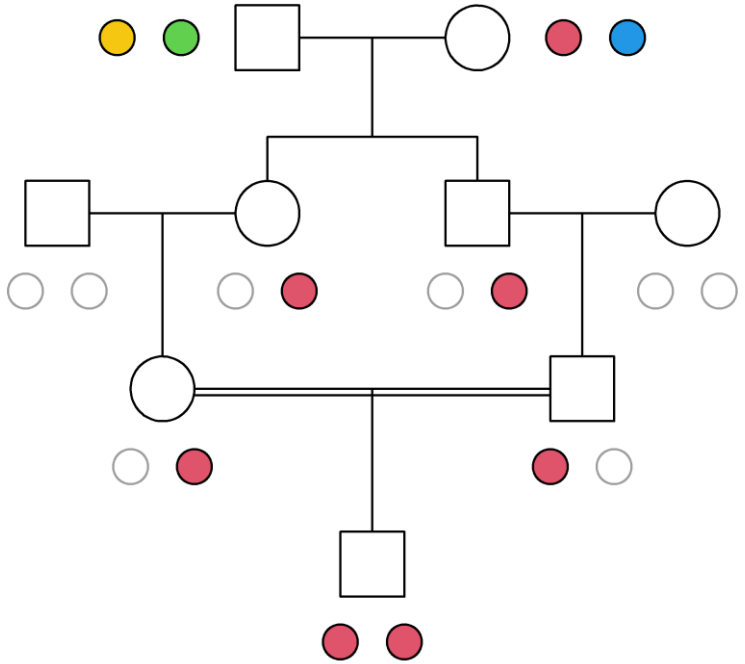
Jacquard's identity coefficients

- Attempt 1
  - being connected through a pedigree
  - having a common ancestor...not too far back
- Attempt 2 - genetic
  - sharing DNA?
  - (more than unrelated people)
- To make this precise, we need some terminology!

IBD and autozygosity

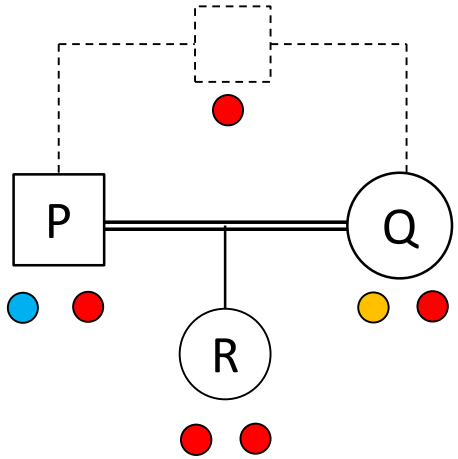
- IBD = Identical by descent
  = identical alleles with a common origin **in the given pedigree**

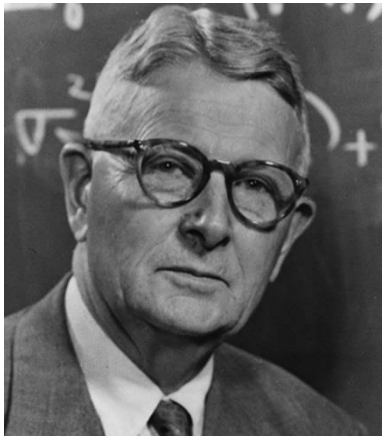
- autozygous = homozygous + IBD



Inbreeding coefficient
$f = P(autozygosity)$

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)

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

= *P*(R is autozygous)

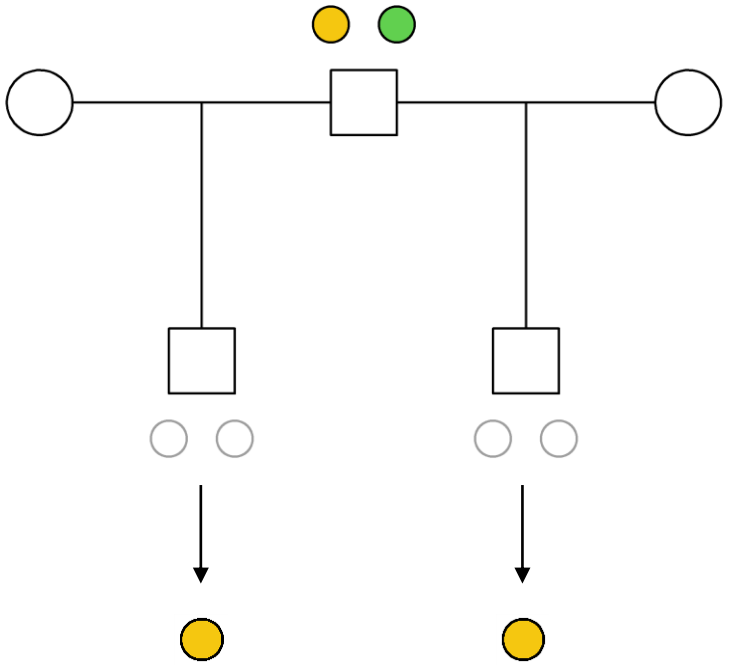
= f_R the inbreeding coefficient of R

P and Q related

$\Updownarrow$

$\varphi_{P,Q} > 0$

Example: Kinship coefficient of half siblings



Kinship coefficient

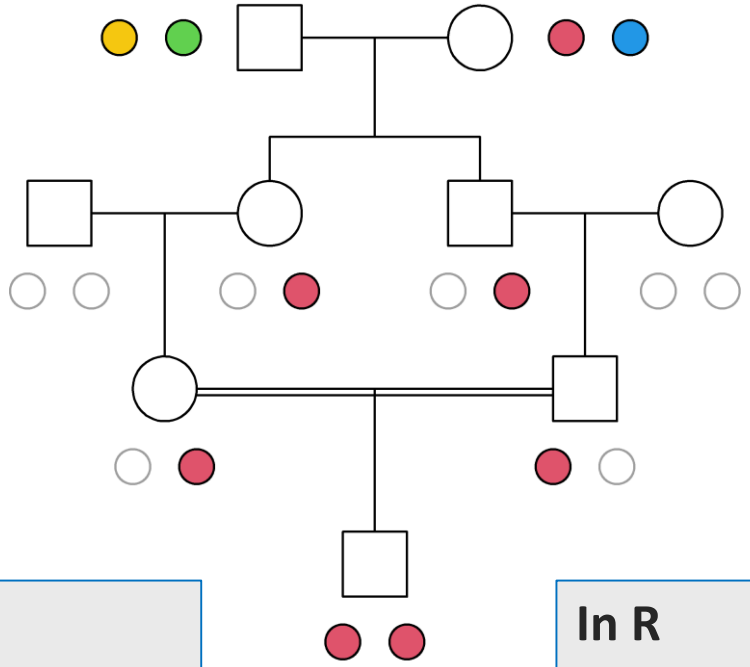
$$\varphi = P(\text{● from both}) \cdot 2$$
$$= 0.5^4 \cdot 2$$
$$= 1/8$$

green

Inbreding coefficient: Example

Wright's path formula:

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



By hand

$$f = P(\text{● autozygous}) \cdot 4$$
$$= 0.5^6 \cdot 4$$
$$= 1/16$$

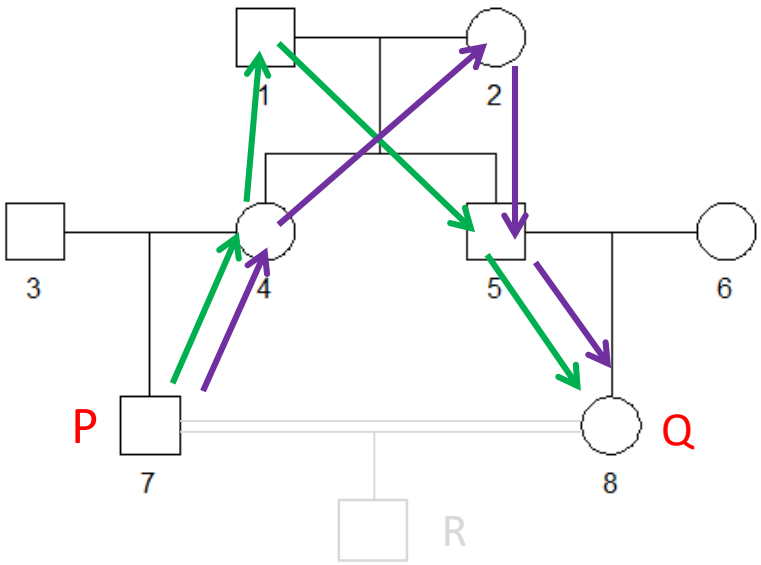
↑ other colors

In R

```
>   library(pedsuite)

>   x = cousinPed(1, child = T)
>   inbreeding(x, ids = 9)
[1] 0.0625
```

Wright's path formula - simple form

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



- In practice:
  - Find all paths between *P* and *Q*
  - For each path
    - count the number of steps S
    - compute 0.5^{S+1}
  - Take the sum!

- 2 paths of length 4

$$\Rightarrow \quad \varphi = 0.5^5 + 0.5^5 = 0.0625$$

Wright's path formula in full generality

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

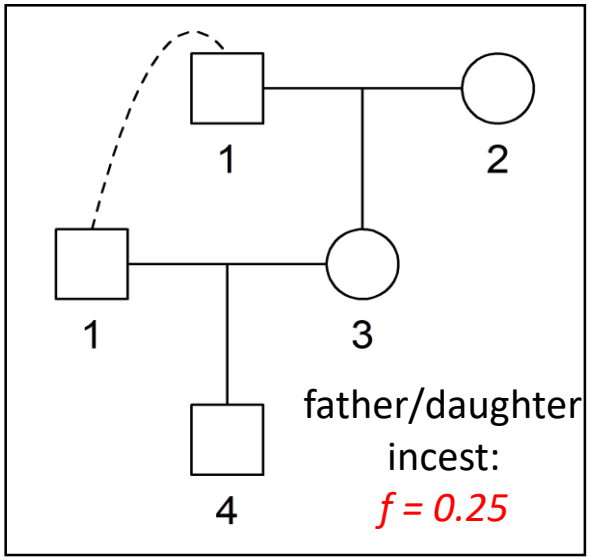
Explanation

- 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!

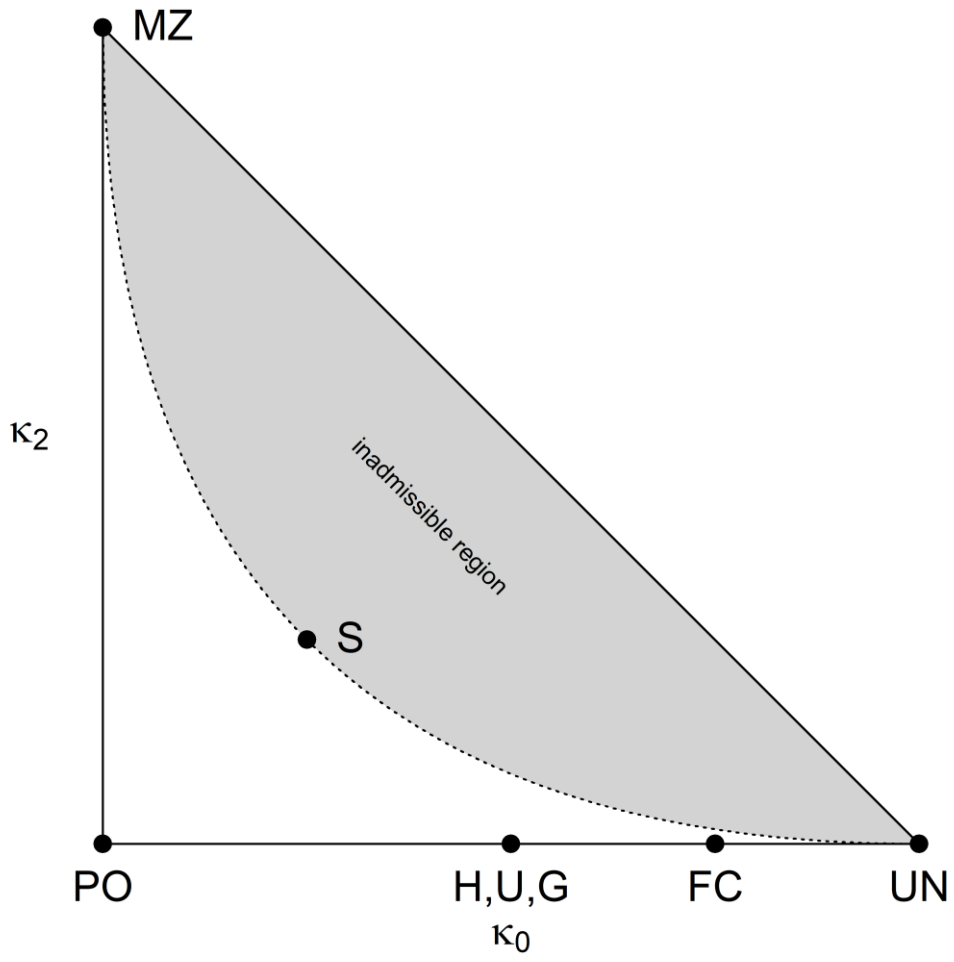
More kinship & inbreeding coefficients

Relationship	kinship φ	f (child)
Parent-child	1/4	1/4
Full siblings	1/4	1/4
Half siblings	1/8	1/8
Grandparent-grandchild	1/8	1/8
Avuncular (uncle/aunt)	1/8	1/8
1st cousins	1/16	1/16
2nd cousins	1/64	1/64
3rd cousins	1/256	1/256




```
>   x = nuclearPed(1, sex = 2)
>   x = addSon(x, c(1, 3))

>   kinship(x, ids = c(1, 3))
[1] 0.25
>   inbreeding(x, id = 4)
[1] 0.25
```

The IBD triangle



Charles Cotterman
(1914-1989)

Elisabeth Thompson
(1949 -)

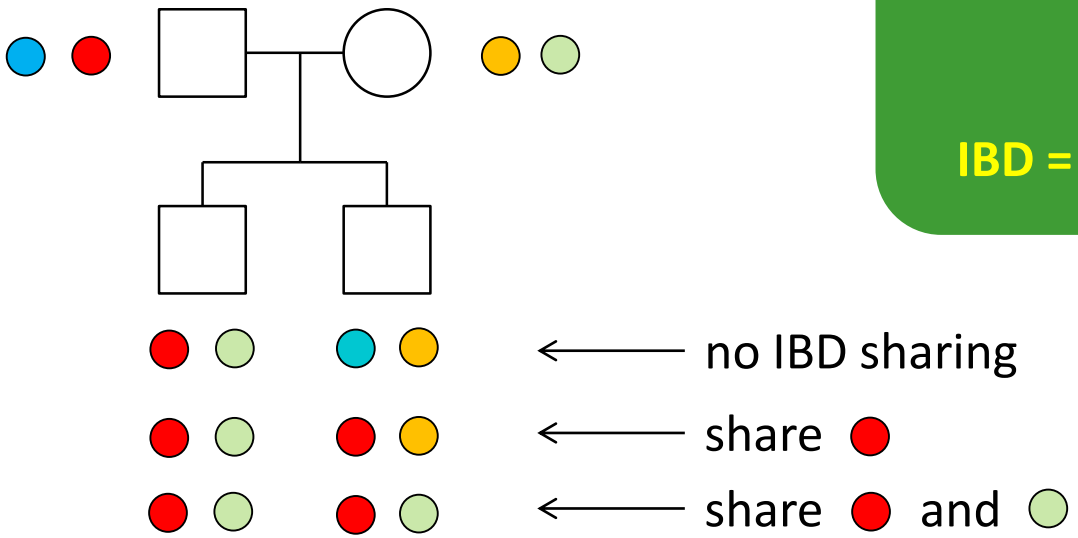
IBD coefficients: Warm-up

- 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?

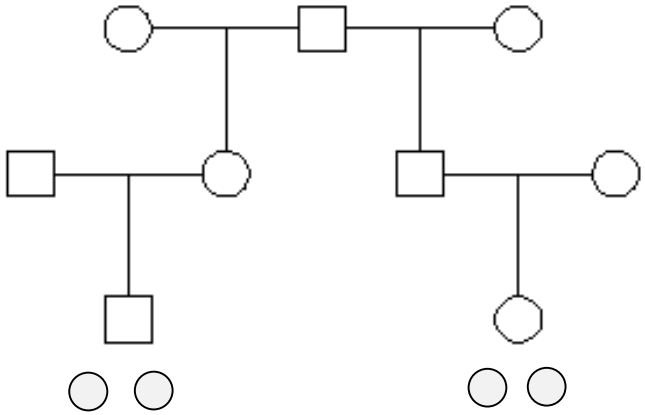
Humans are diploid

↓

IBD = 0, 1 or 2



IBD coefficients: Definition



- Given two (non-inbred) individuals

- For a random autosomal locus

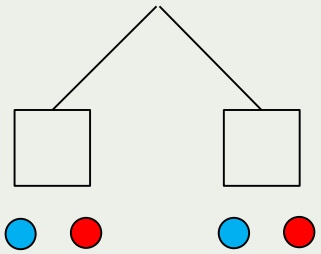
  κ_0 = *P*(0 alleles IBD)

  κ_1 = *P*(1 alleles IBD)

  κ_2 = *P*(2 alleles IBD)

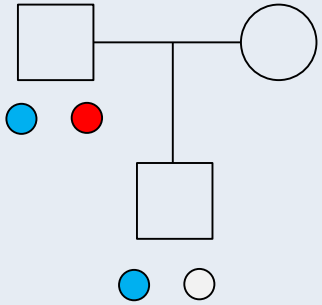
- We always have: $\kappa_0 + \kappa_1 + \kappa_2 = 1$

The three extremes



Monozygotic twins (MZ)

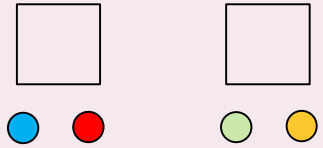
$(\kappa_0, \kappa_1, \kappa_2) = (0,0,1)$



Parent-offspring (PO)

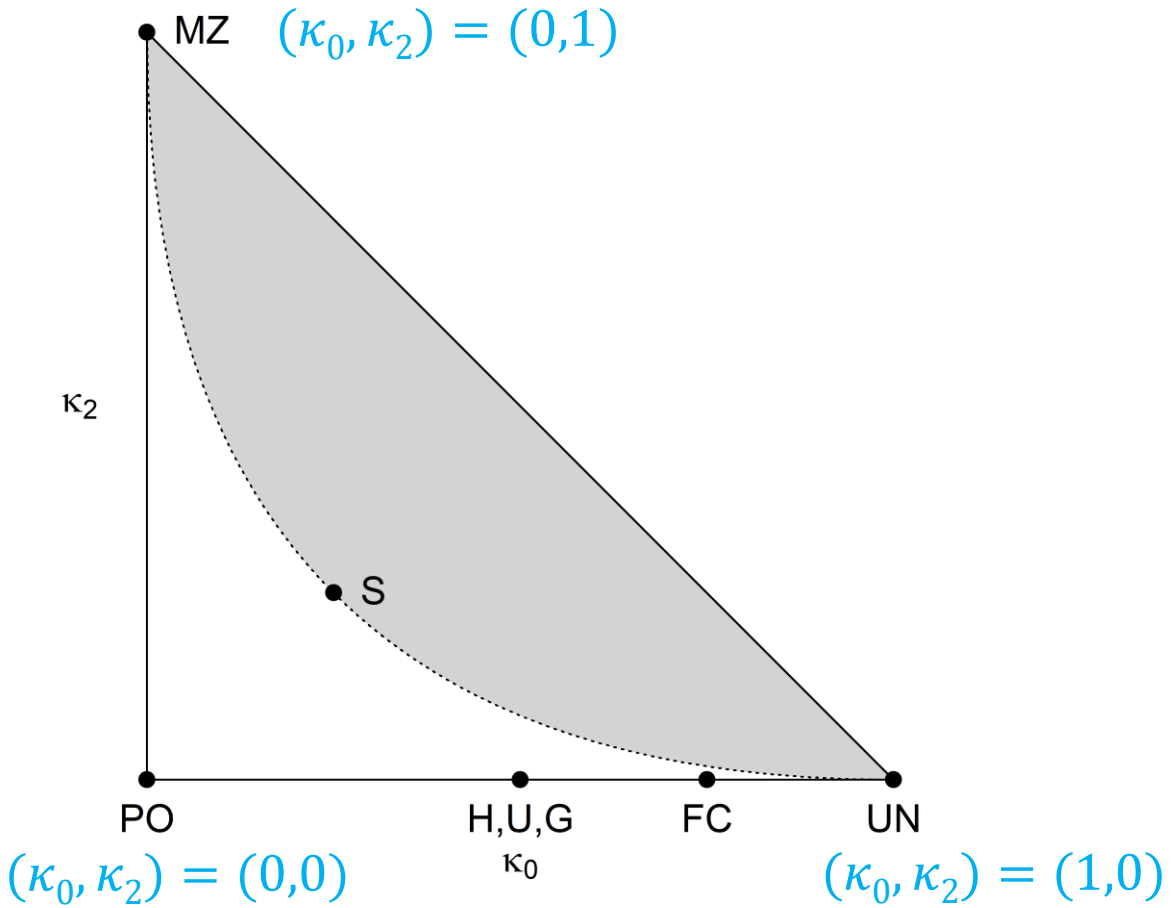
$(\kappa_0, \kappa_1, \kappa_2) = (0,1,0)$

Unrelated (UN)

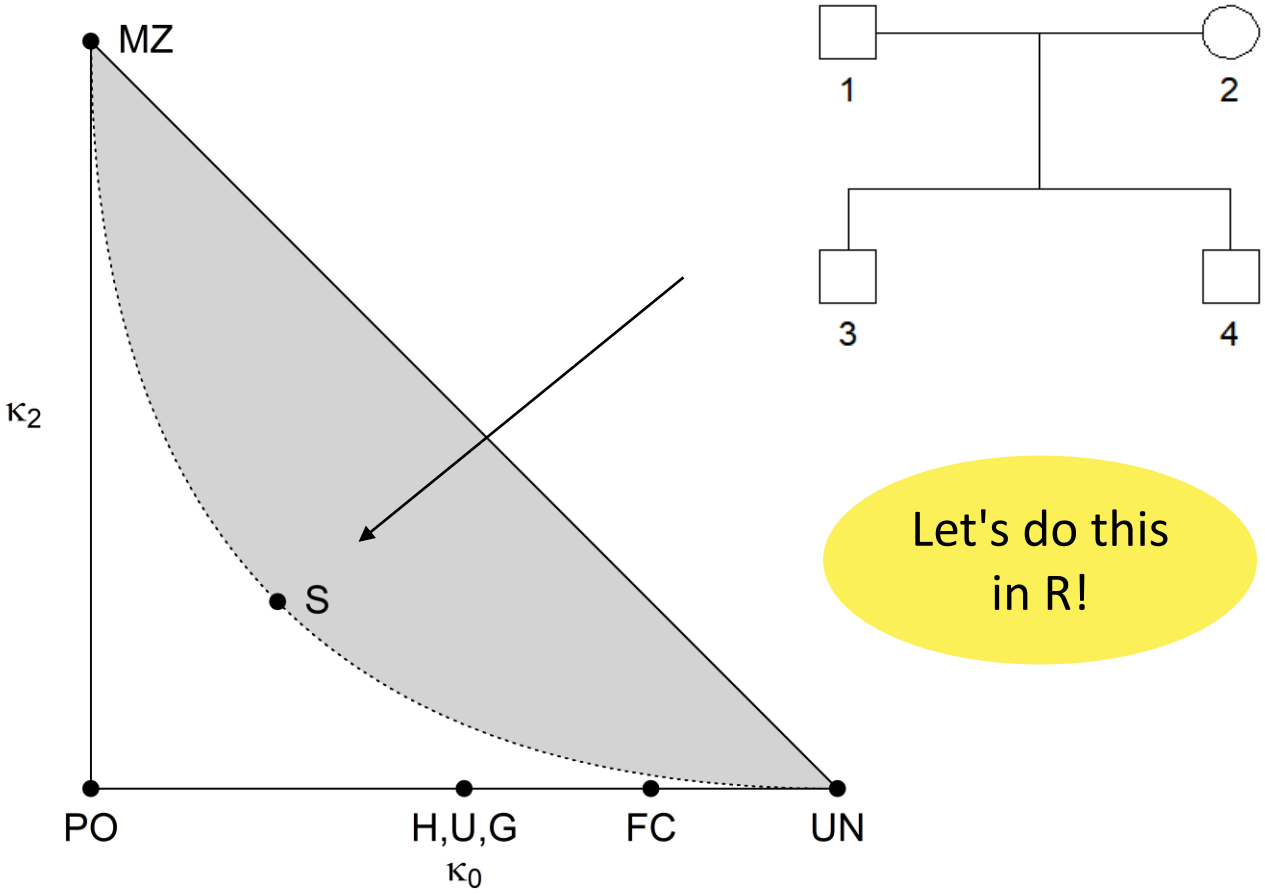


$(\kappa_0, \kappa_1, \kappa_2) = (1,0,0)$

The relatedness triangle

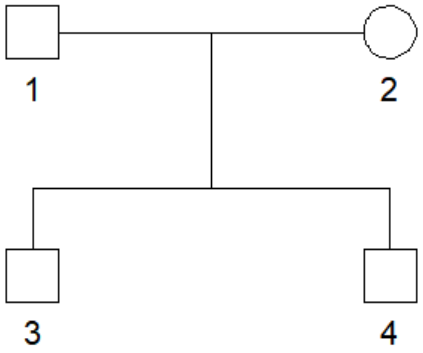


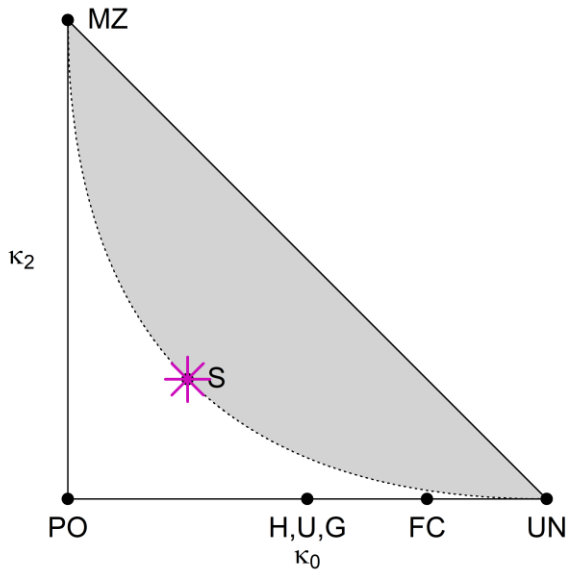
What are the coefficients of full sibs



Let's do this in R!

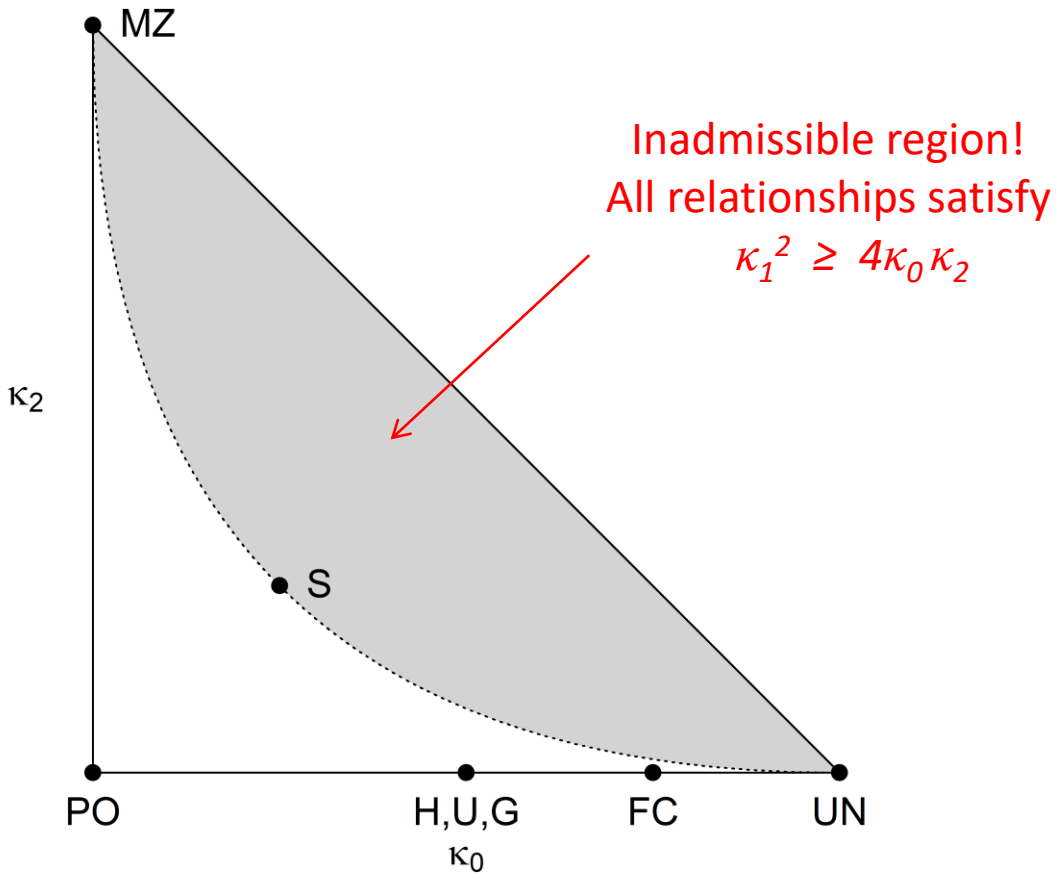
ribd: Pedigree-based relatedness coefficients



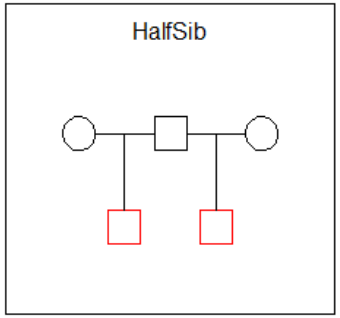


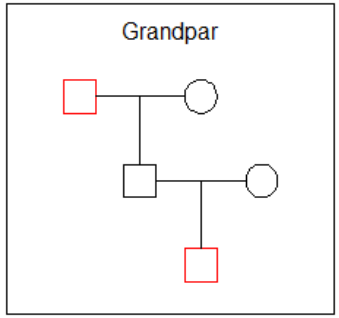

```
>   library(pedsuite)
>   x = nuclearPed(2)

>   kinship(x, ids = 3:4)
[1] 0.25

>   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

>   k = kappaIBD(x, ids = 3:4)
>   showInTriangle(k)
```

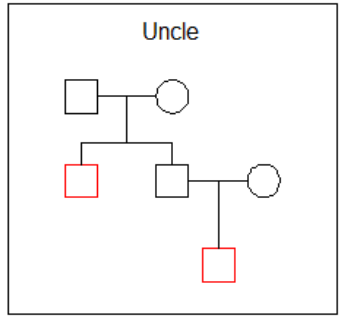
The relatedness triangle



The relatedness triangle



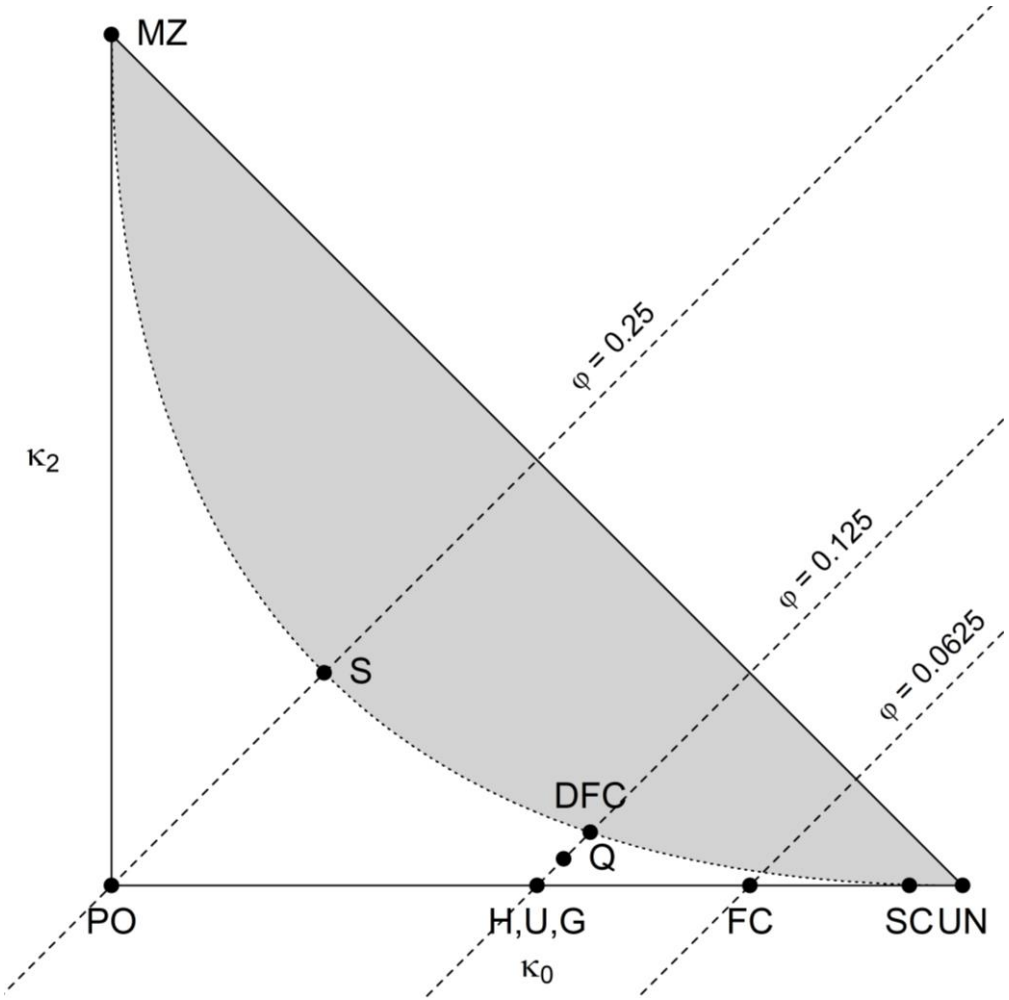




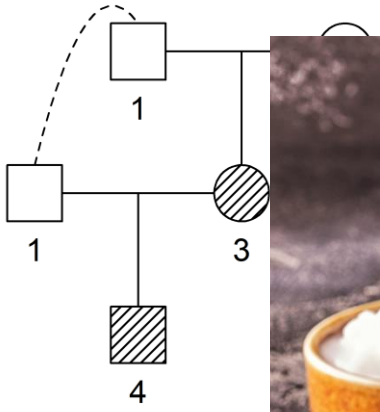
All have $\kappa_0 = \kappa_1 = \frac{1}{2}$

Some relationships coincide!

An important identity: $\varphi = \frac{1}{4}\kappa_1 + \frac{1}{2}\kappa_2$



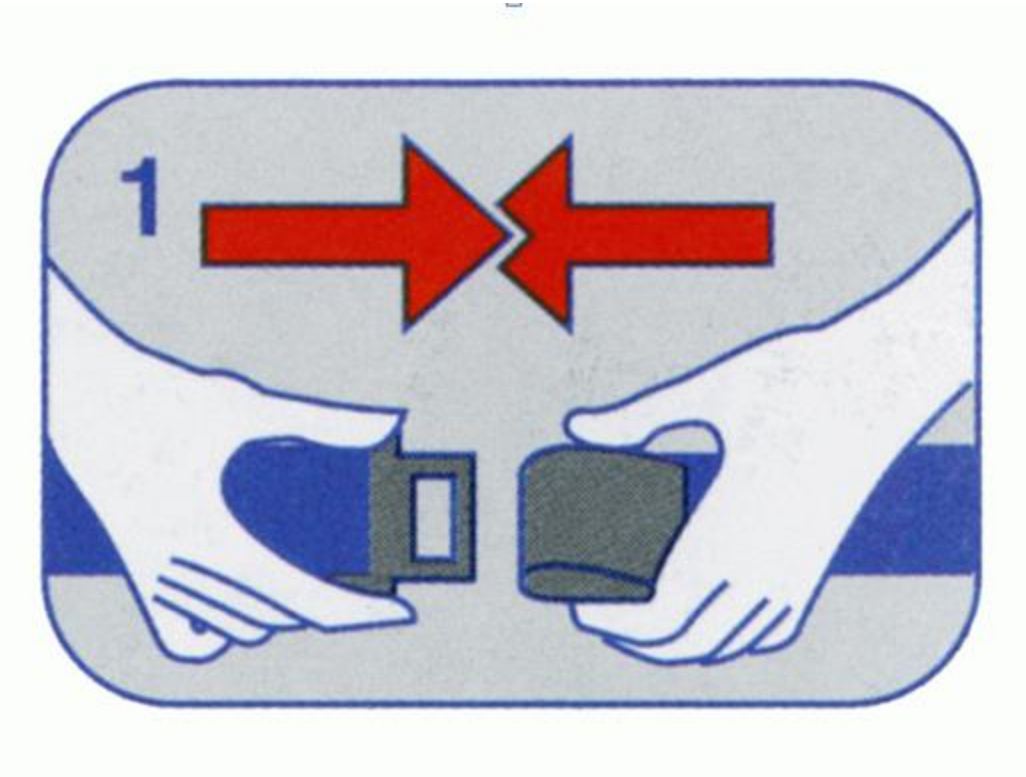
What's missing?



ndividuals.

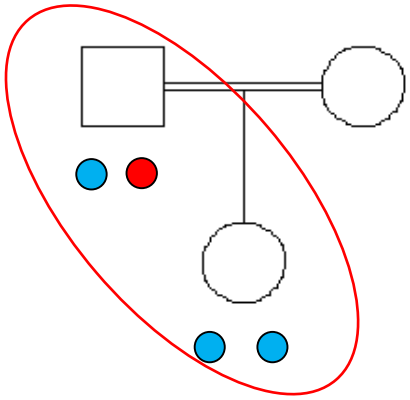
Jacquard

Albert Jacquard
(1925 - 2013)


1

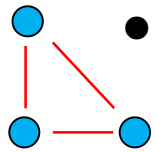
Black belt: Jacquard's identity coefficients

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



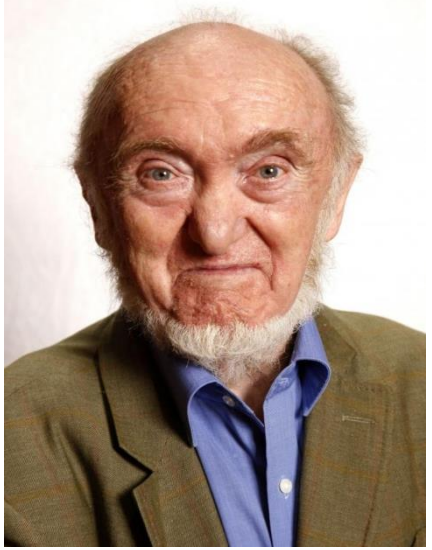
What's the IBD status here??? 1 or 2?
Cannot be summarised in one number.

Configuration:



← father's alleles

← child's alleles



Albert Jacquard
(1925 - 2013)

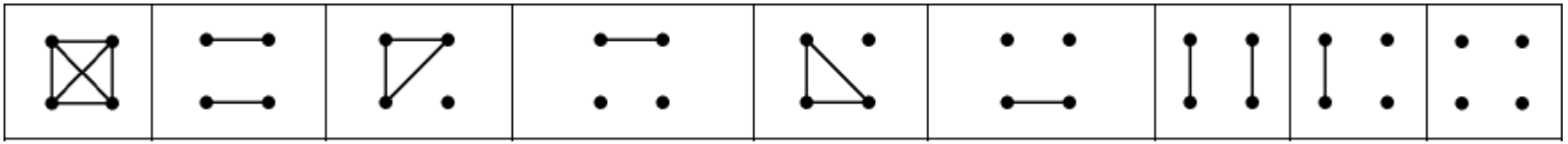
Jacquard's 9 coefficients

- 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:

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

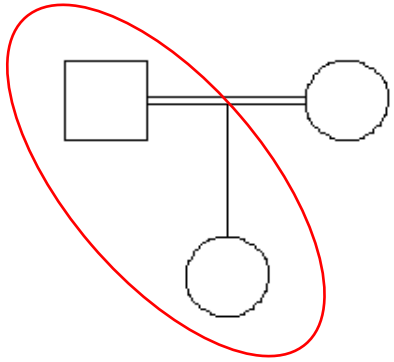
Very simple with non-inbred individuals

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

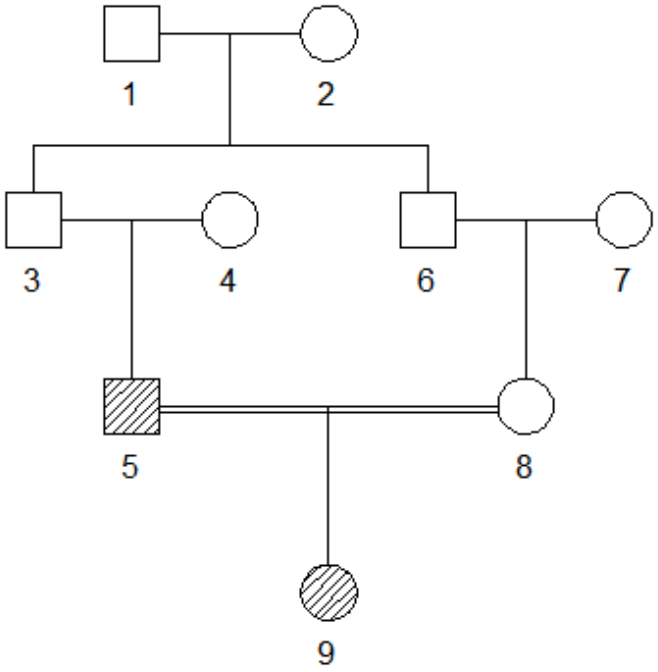


Suppose the parents are first cousins, but not themselves inbred

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

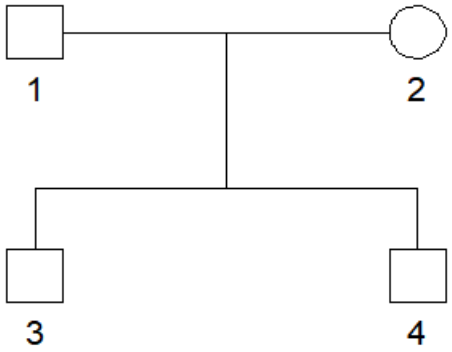


Main functions

- inbreeding(x, ids)
- kinship(x, ids)
- kappaIBD(x, ids)
- identityCoefs (x, ids)

Try it out!

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




```
> inbreeding(x)
1 2 3 4
0 0 0 0
```

```
> 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
```

```
> identityCoefs(x)
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
```