Lecture 2:
Measures of relatedness

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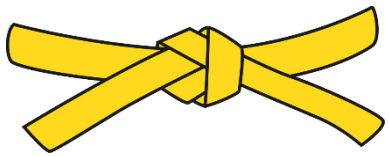
Young Investigator Day 2024

Plan



Kinship/inbreeding coefficient

The relatedness triangle

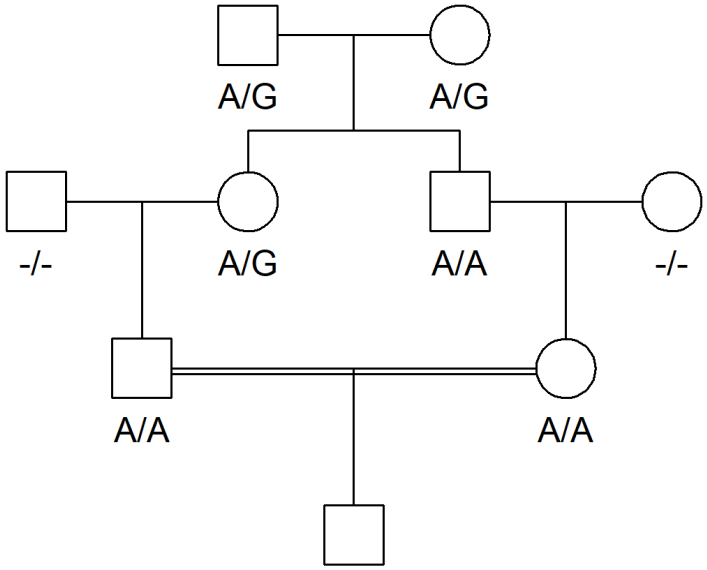
Realised relatedness

- 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!

Identity by descent (IBD)

Identity by *state*

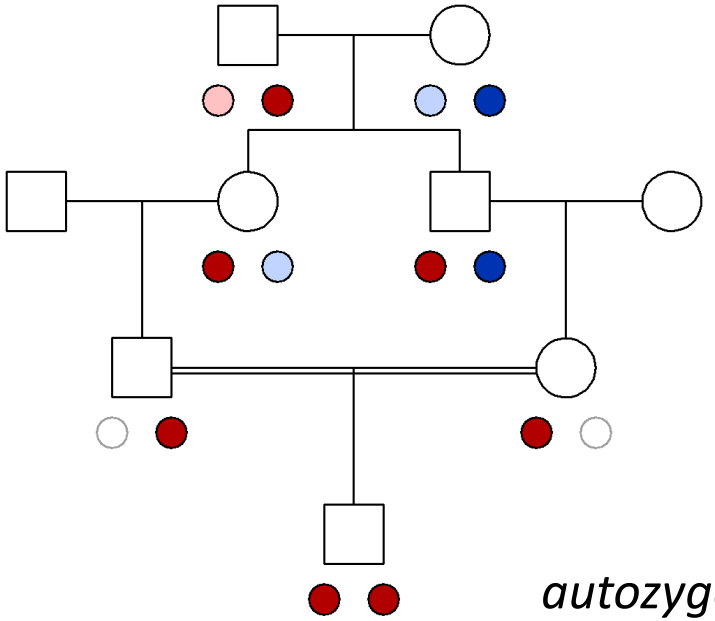
= equal alleles



homozygous

Identity by *descent*

= same origin in the pedigree

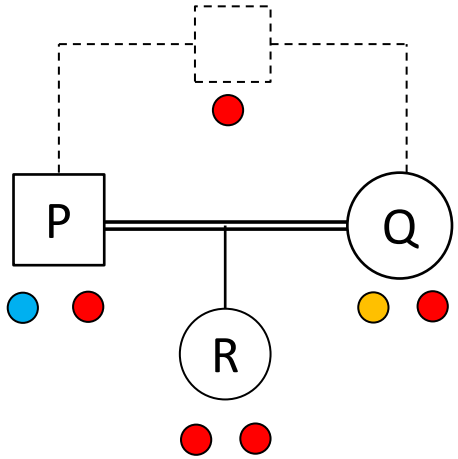


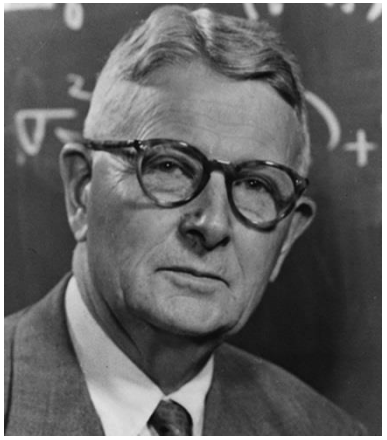
autozygous

Inbreeding coefficient

$f = Pr(autozygosity)$

Coefficient of kinship/inbreeding





Sewall Wright
(1889 - 1988)

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

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

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

= *Pr*(R is autozygous)

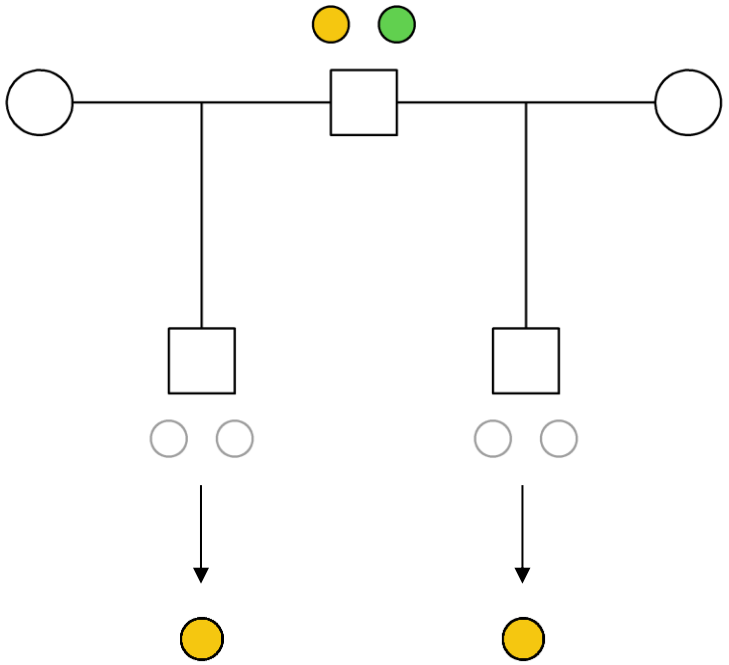
= f_R the inbreeding coefficient of R

P and Q related

$\Updownarrow$

$\varphi_{P,Q} > 0$

Example: Kinship coefficient of half siblings



Kinship coefficient

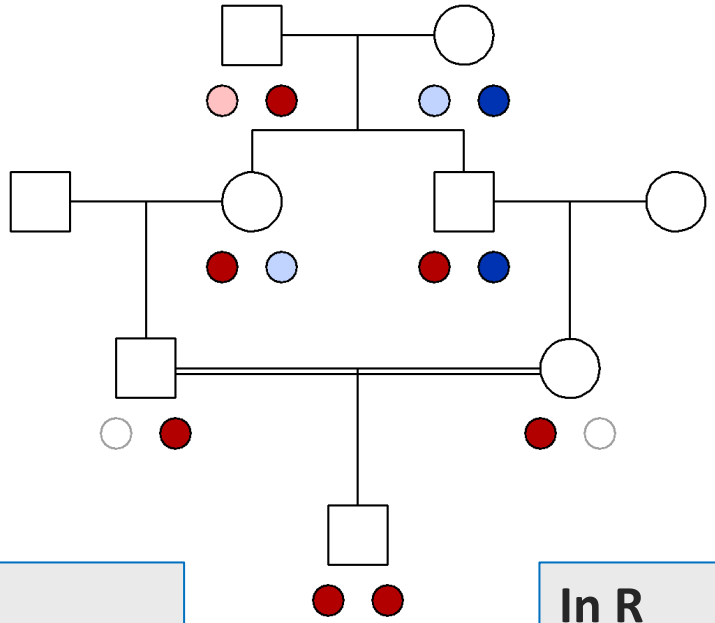
$$\varphi = P(\text{ from both}) \cdot 2$$
$$= 0.5^4 \cdot 2$$
$$= 1/8$$

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

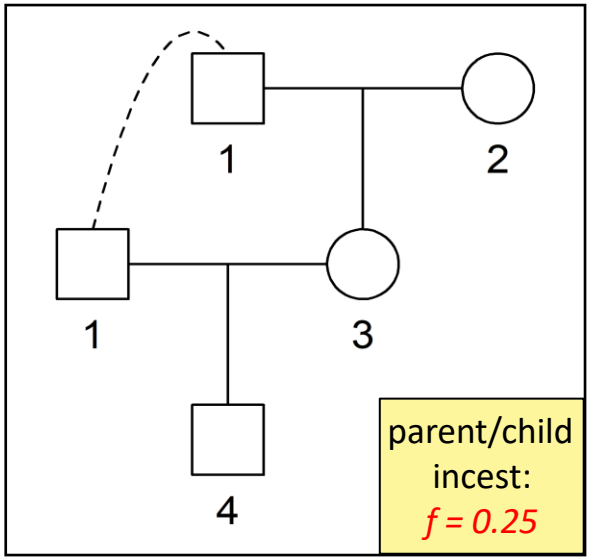
In R

```
>   library(pedsuite)

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

More kinship & inbreeding coefficients

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

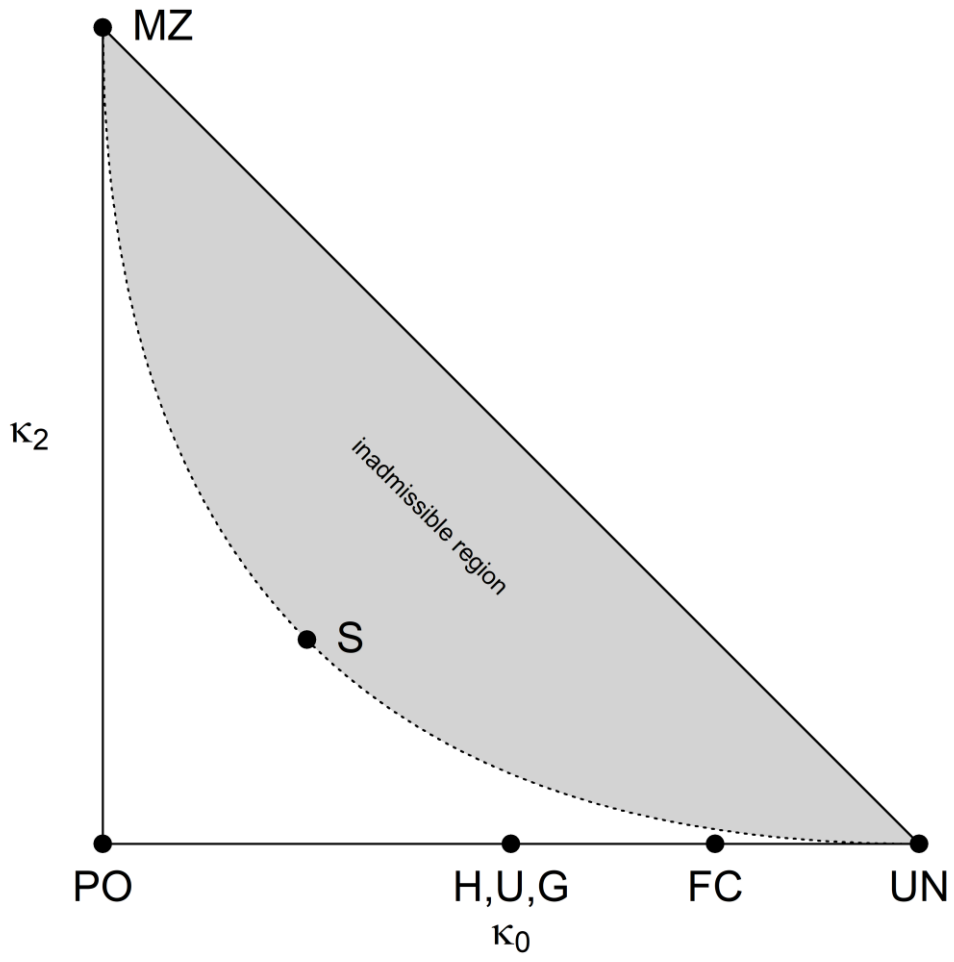
Challenge
Different relationships with the same kinship!




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

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

The relatedness triangle

(or: *the IBD triangle*)

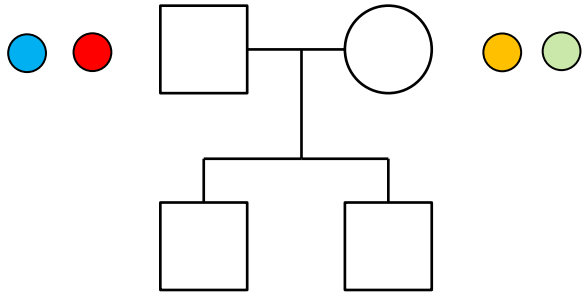


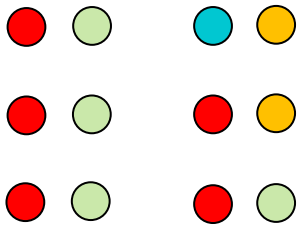
Charles Cotterman
(1914-1989)

Elisabeth Thompson
(1949 -)

IBD coefficients

- 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?





0 alleles IBD. Prob = 0.25

1 allele IBD. Prob = 0.25 + 0.25 = 0.5

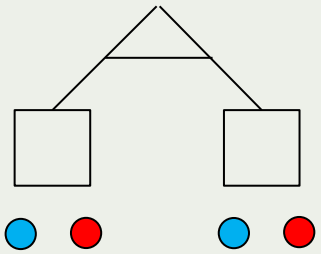
2 alleles IBD. Prob = 0.25

Definition

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

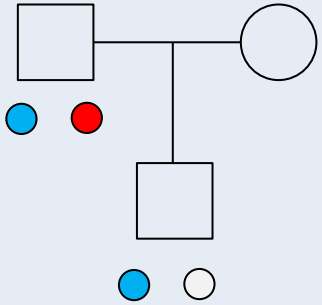
(at random autosomal locus)

Three trivial relationships



Monozygotic twins (MZ)

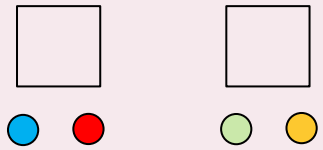
$(\kappa_0, \kappa_1, \kappa_2) = (0,0,1)$



Parent-offspring (PO)

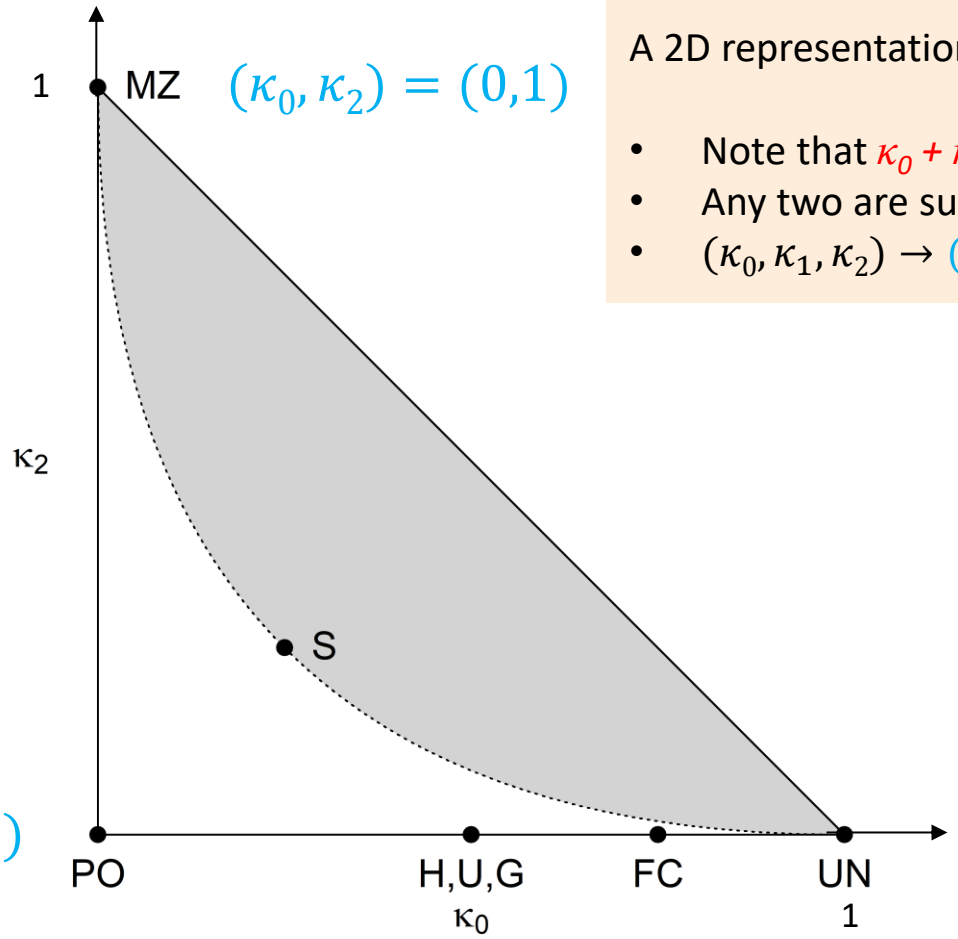
$(\kappa_0, \kappa_1, \kappa_2) = (0,1,0)$

Unrelated (UN)



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

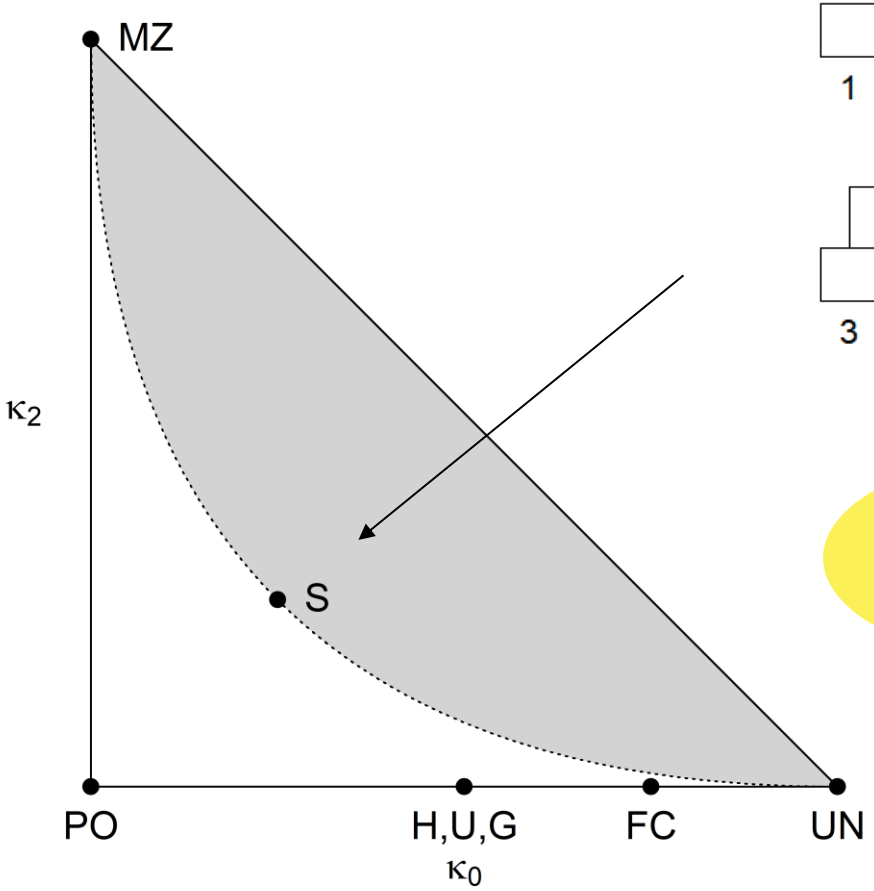
The relatedness triangle

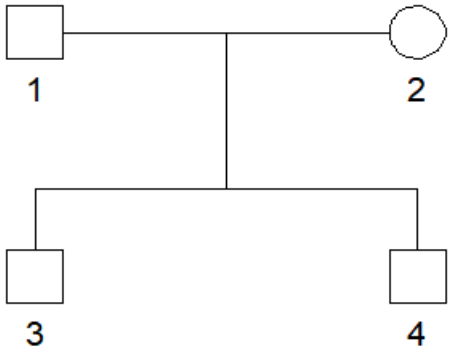


A 2D representation of $(\kappa_0, \kappa_1, \kappa_2)$

- Note that $\kappa_0 + \kappa_1 + \kappa_2 = 1$
- Any two are sufficient
- $(\kappa_0, \kappa_1, \kappa_2) \rightarrow (\kappa_0, \kappa_2)$

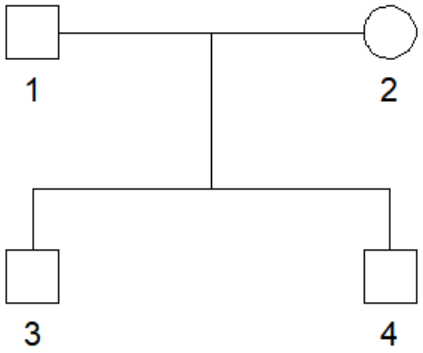
What are the coefficients of full sibs

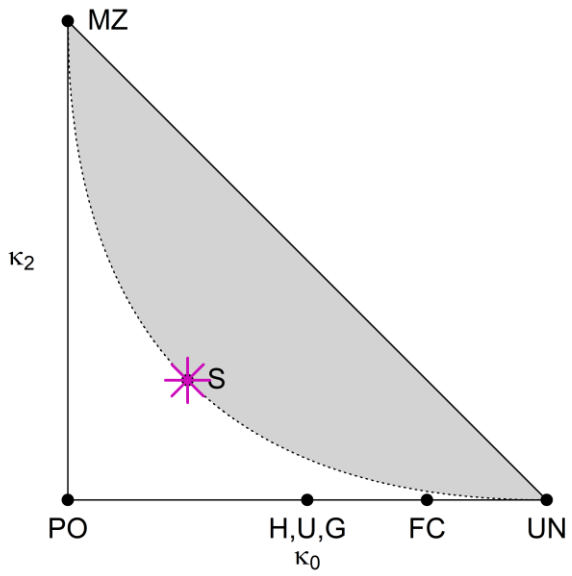




Let's do this in R!

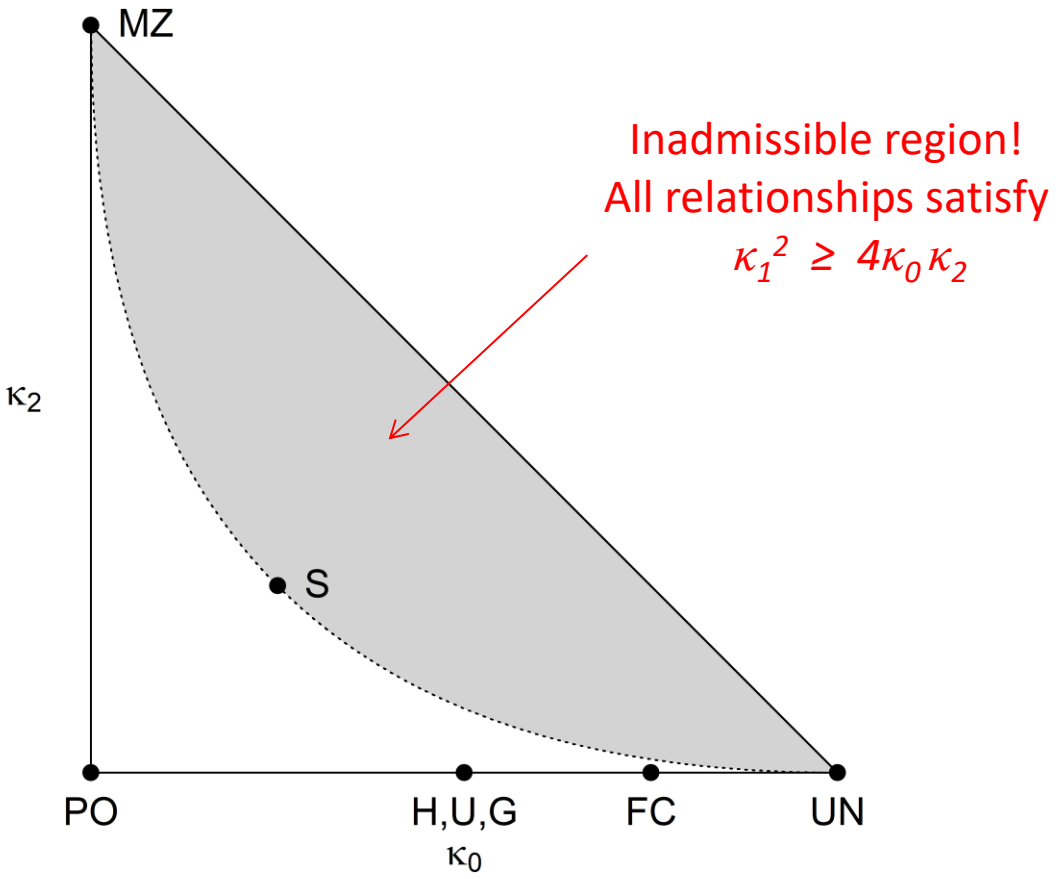
ribd: Pedigree-based relatedness coefficients



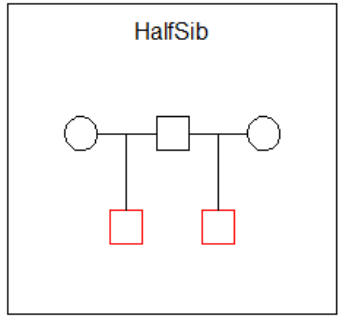


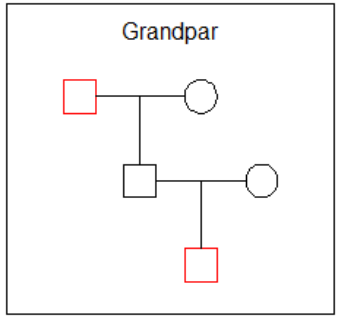

```
>   library(pedsuite)
>   x = nuclearPed(2)

>   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)
```

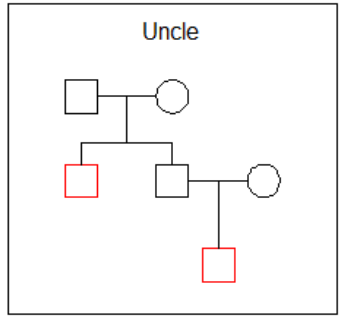
The relatedness triangle



The relatedness triangle



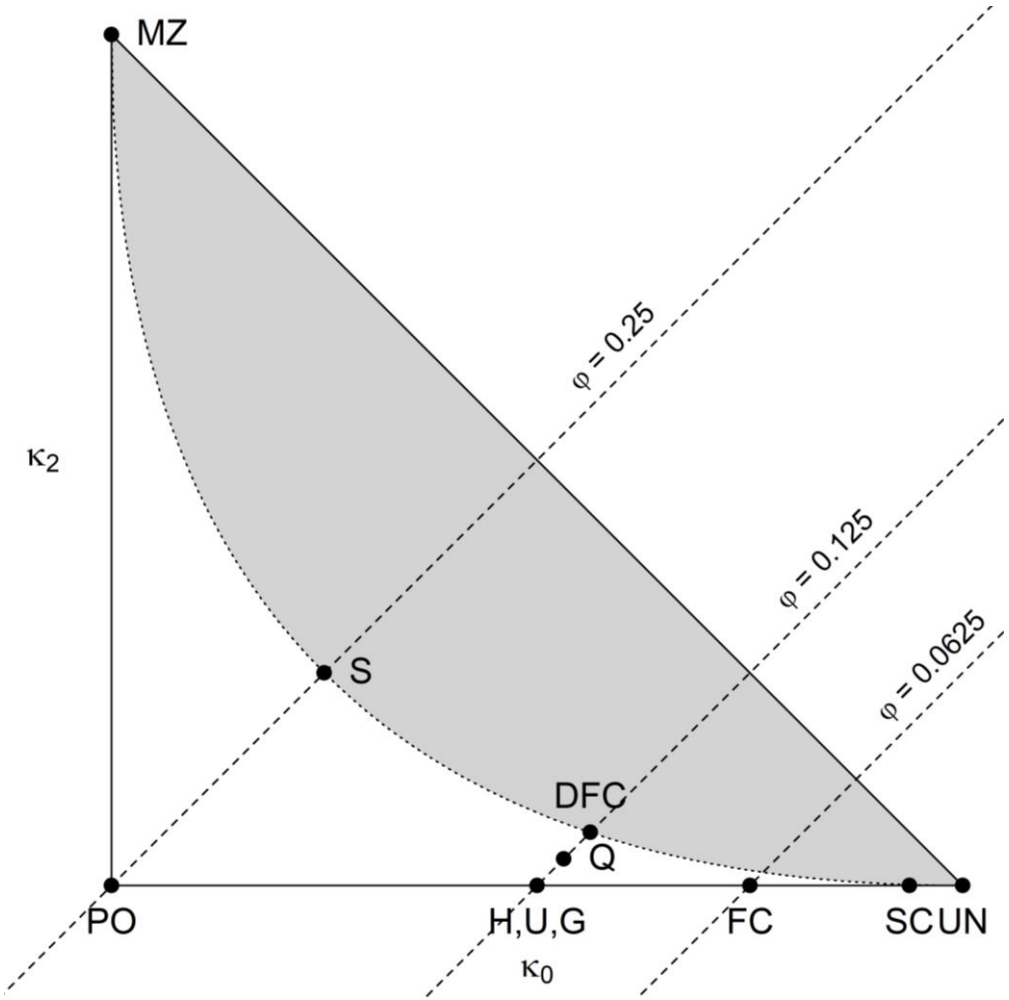




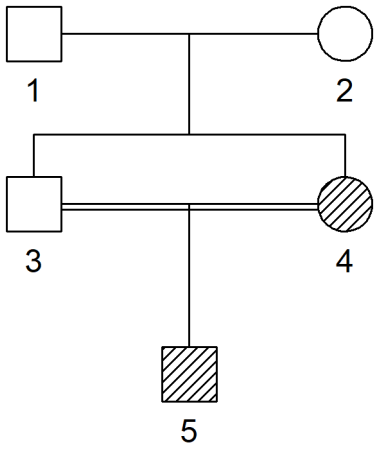
All have $\kappa_0 = \kappa_1 = \frac{1}{2}$

Some relationships coincide!

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



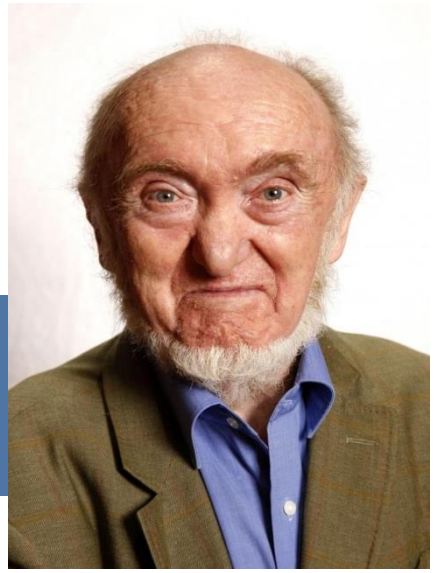
A word of caution



κ is only defined for non-inbred individuals.
For the whole story, we need 9 coefficients!

Jacquard's identity coefficients

Not suitable for a basic course ...



Albert Jacquard
(1925 - 2013)

https://magnusdv.shinyapps.io/quickped/

QuickPed: An Interactive Pedigree Creator

New app design!
Discover the new features
Or stay with the old version: QuickPed3

Purpose: QuickPed lets you rapidly create attractive pedigree plots, save them as images or text files, and analyse the relationships within them.

Instructions: Choose a suitable start pedigree and modify it by clicking on individuals and using appropriate buttons. For example, to add a male child, select the parent(s) and press the icon. Check out the online user manual for various tips and tricks, including an introduction to relatedness coefficients.

Citation: If you use QuickPed in a publication, please cite this paper: Vigeland MD (2022). QuickPed: an online tool for drawing pedigrees and analysing relatedness. *BMC Bioinformatics*, **23**. DOI:10.1186/s12859-022-04759-y.

Quick start

Built-in pedigree: Trio

or

Load a ped file

or

Random pedigree

Reset all

Modify

Add

Sex

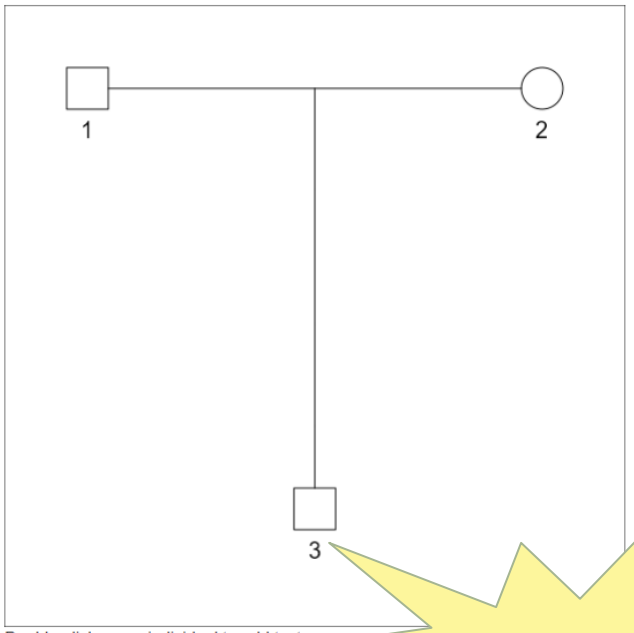
Style

Fill

Twins: MZ / DZ

Remove

Undo



Double-click on an individual to add text

Labels

1, 2, 3, .. I-1, I-2, ..

Show all Hide all

1
2
3

Update

Plot settings

Width: 430
Height: 430
Cex: 1,4
Symbols: 1
Margins: 3

Other options (beta)
- Straight legs
- Arrows

R code

PNG PDF

Relationships

DEMO!

Coefficients!

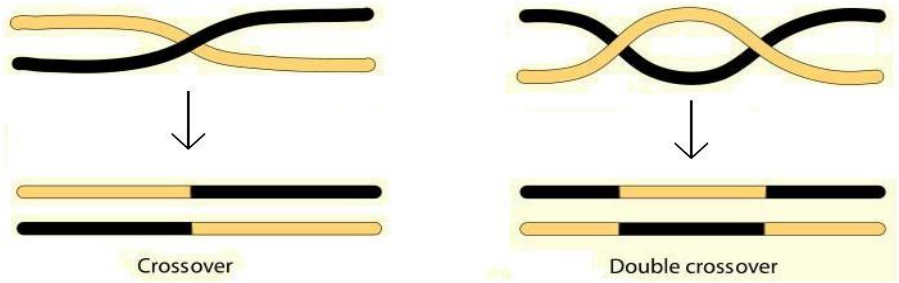
Ped file

Include
- Headers
- Family ID
- Affection status

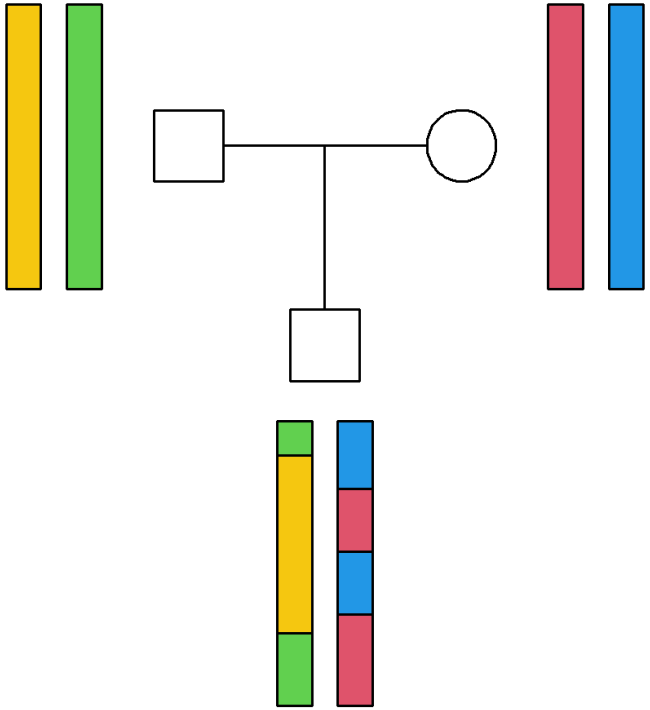
Save ped file

Oslo universitetssykehus

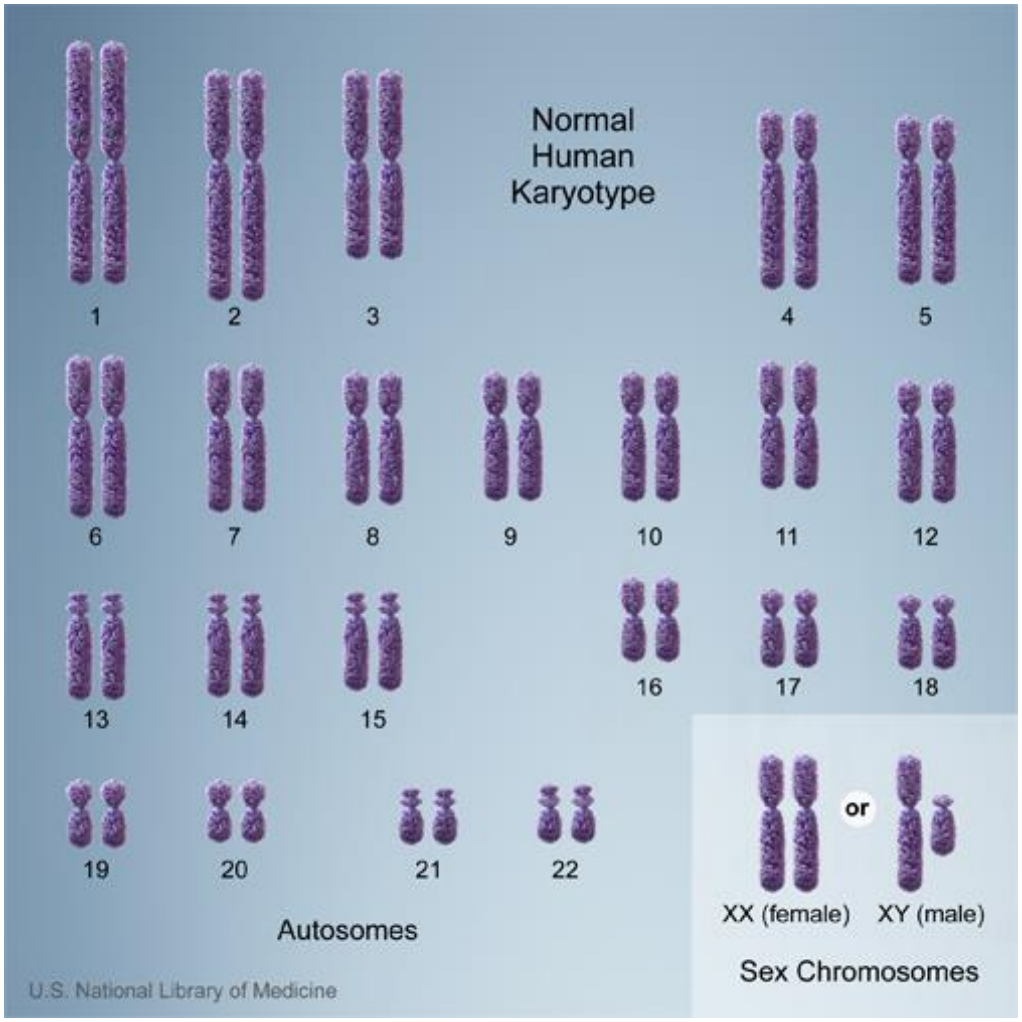
Realised relatedness



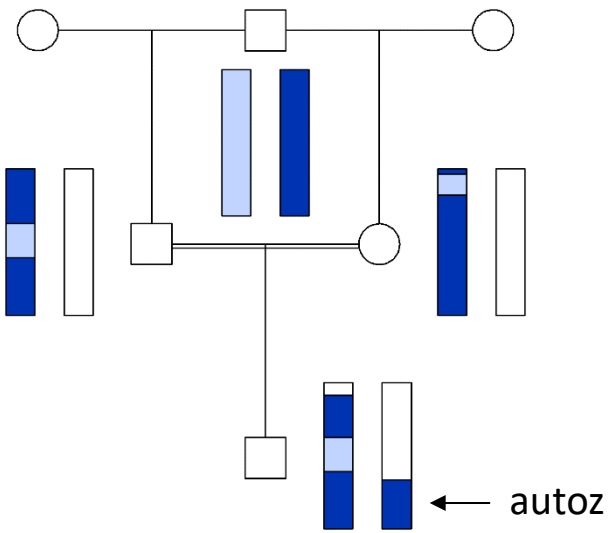
Meiotic recombination



Rule of thumb: One crossover per chromosome arm

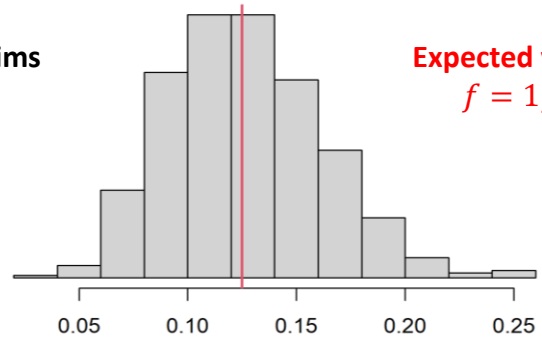


Realised inbreeding

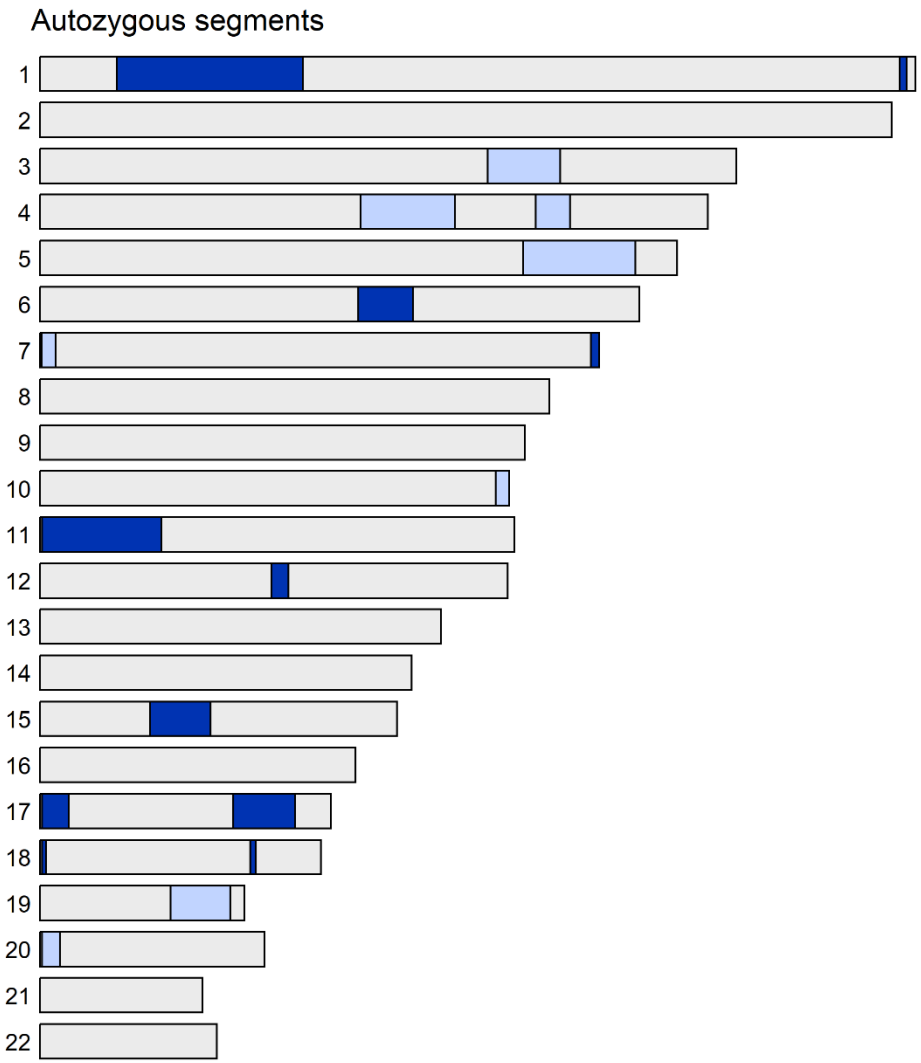


f_R = autozygous fraction of genome

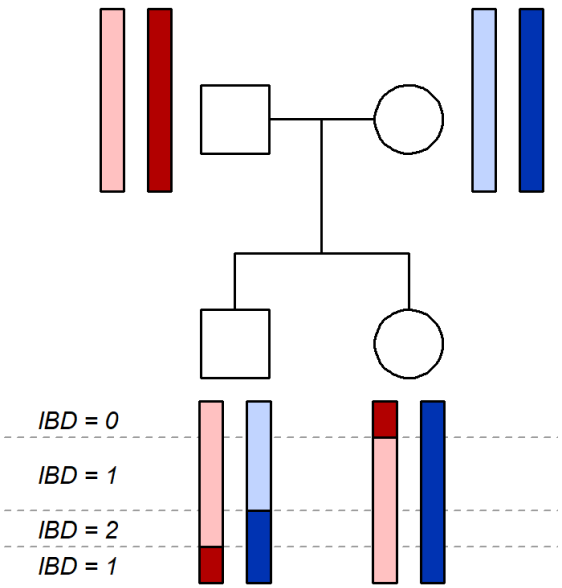
500 sims



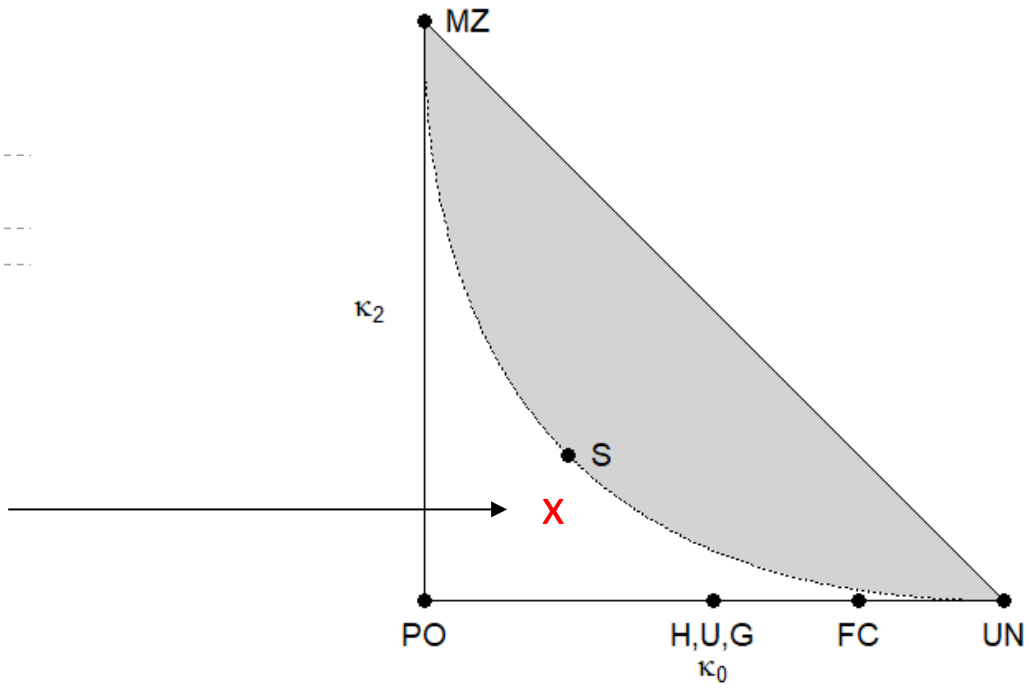
Expected value:
$f = 1/8$



Realised IBD coefficients

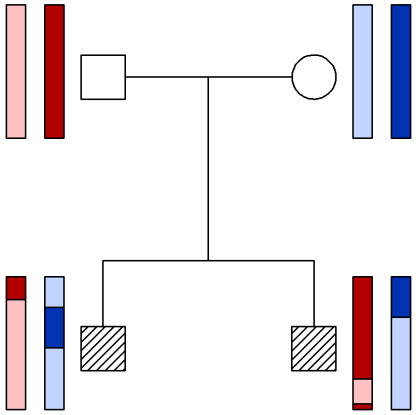


Realised IBD coefficients:
Proportions of genome with IBD = 0, 1, 2

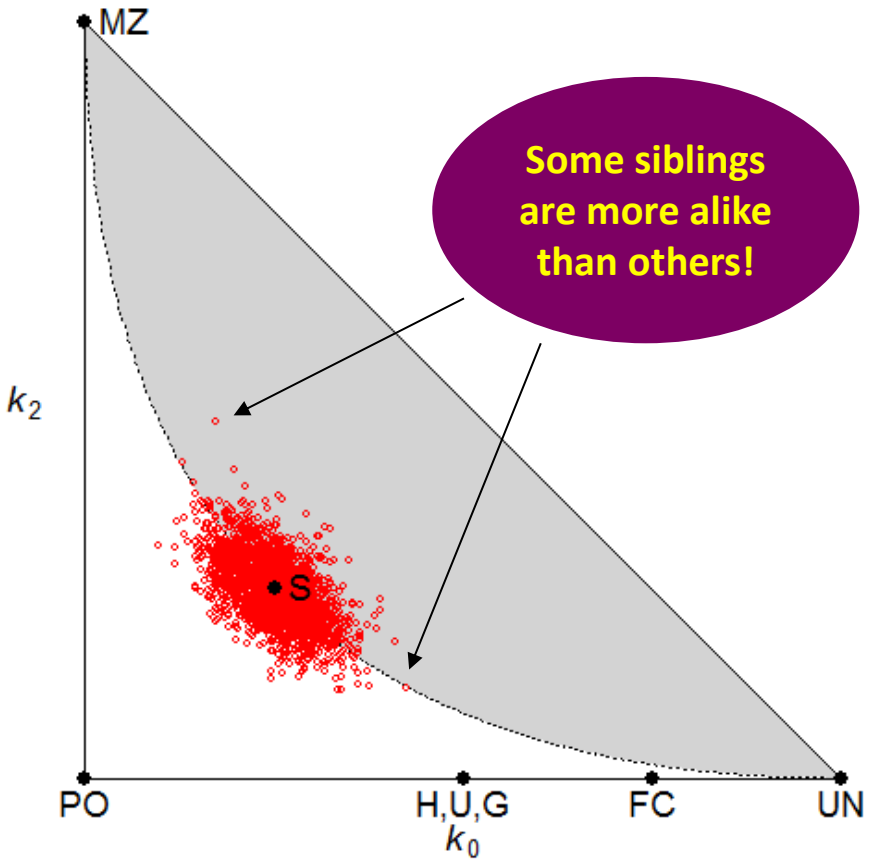


Variation in realised IBD coefficients

1000 simulations



```
> library(ibdsim2)

> x = nuclearPed(2)
> s = ibdsim(x, N = 1000)
> k = realisedKappa(s, ids = 3:4)

> ribd::showInTriangle(k)
```



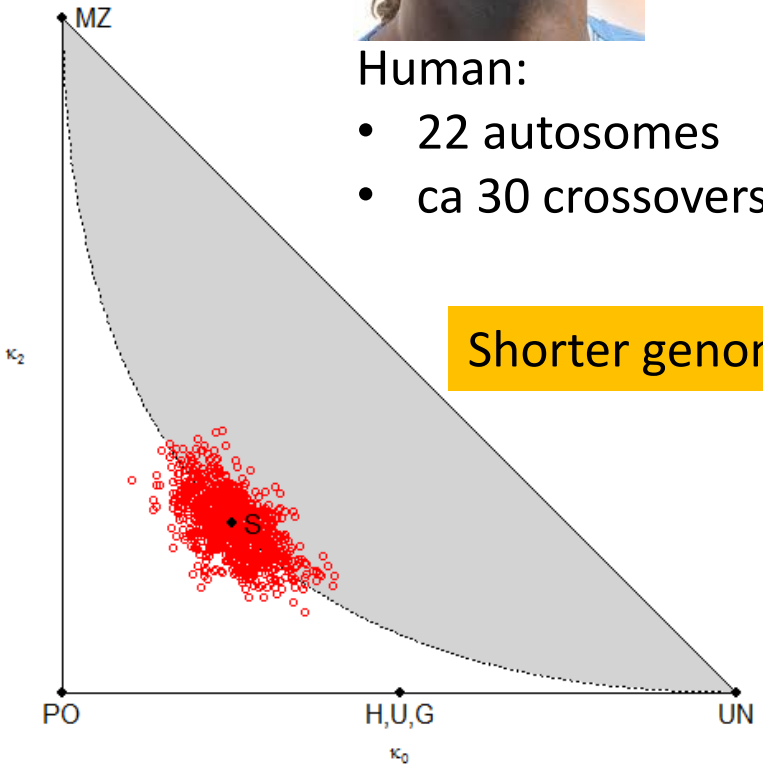
Variation depends on the genome

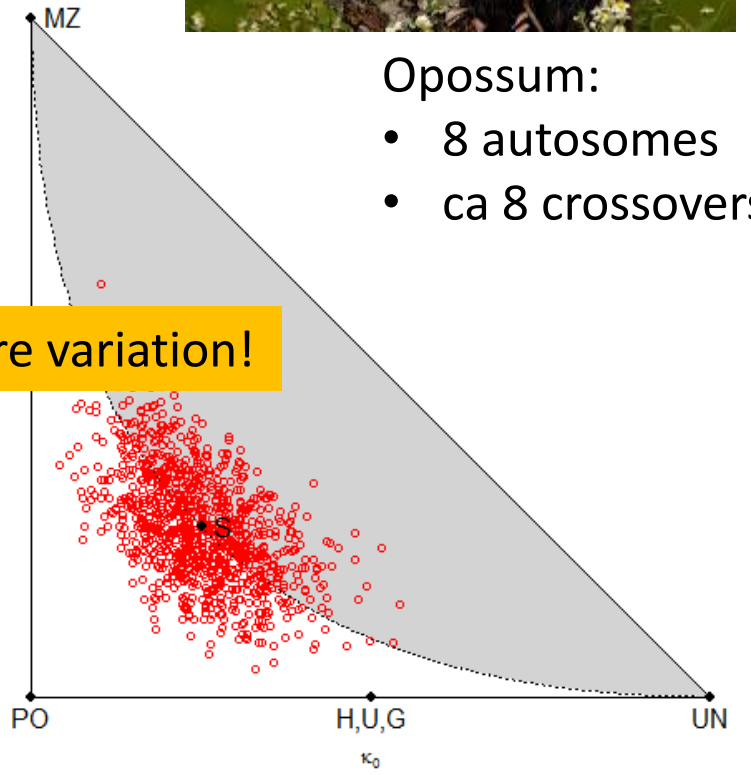
Human:

- 22 autosomes
- ca 30 crossovers

Opossum:

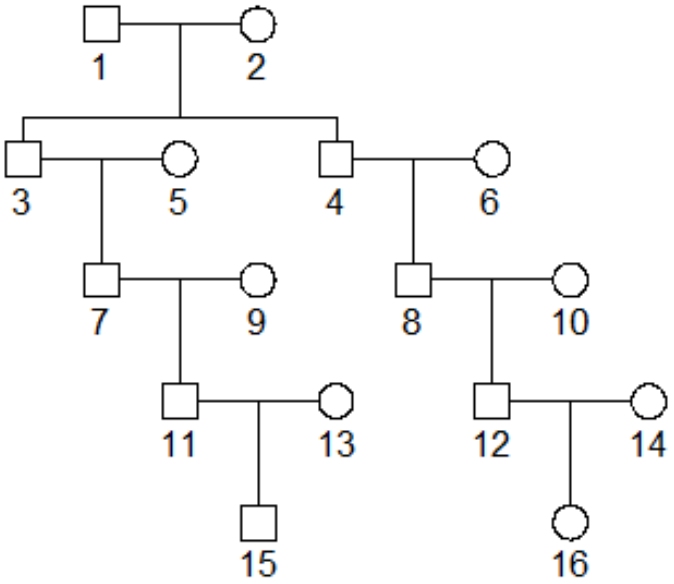
- 8 autosomes
- ca 8 crossovers





Shorter genome = more variation!

The probability of zero IBD



N'th cousins	*P*(zero IBD)
first	0.0 %
second	0.0 %
third	1.5 %
fourth	28 %
fifth	67 %

Third cousins

Expected fraction with IBD = 1:

$$k_1 = \frac{1}{64}$$

Two individuals can have a common ancestor without being genetically related!

METRO

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UK WORLD WEIRD TECH

Let's not forget – Prince Harry and Meghan Markle are actually (very distant) cousins

Richard Hartley-Parkinson for Metro.co.uk Monday 27 Nov 2017 11:35 am

18.8k

FASHION

CULTURE

FASHION BEAUTY GIFT G

Ou, Awkward...Meghan Markle and Prince Harry are Apparently Related

By Meghan McKenna Date November 2, 2017

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ousins!

Brigitte

SPIELE NEWSLETTER VIDEO GEWINNSPIELE FORUM F-MAG ACADEMY SHOPPING ABO

Aktuell Mode Beauty Rezepte Gesund Liebe Familie Leben Horo

Brigitte → Aktuell → Stars und TV → Meghan Markle und Prinz Harry sind "verwandt"

Stammbaum erforscht: Prinz Harry und Meghan Markle sind Cousins!

STJERNEPAR: Meghan Markle og prins Harry viser endelig kjærligheten sin offentlig, etter å ha holdt forholdet svært privat i lang tid. Nå kommer det frem at paret, som er fra to forskjellige kontinenter, faktisk er i slekt. Foto: NTB scanpix

Prins Harry er i slekt med kjæresten

SE OG HØR

1.1K shares

View c

(Picture: Mail Online)

14 13 10 9 8 4 3 2 1

15 13 11 10 9 5 4 3 2 1

13th cousins once removed

Relatedness: Summary

- Measuring relatedness with increasing precision:
  - the kinship/inbreeding coefficient φ
  - the IBD coefficients $\kappa = (\kappa_0, \kappa_1, \kappa_2)$

- Each coefficient is
  - the probability of observing a certain IBD pattern in a random locus
  - the expected proportion of the genome in this state

- IBD is not a pointwise phenomenon: Always in segments
  - determined by meiotic crossovers
  - consequence: Variation in the *realised* IBD!

- Family relation $\not\Rightarrow$ genetic relation

So...what does it mean to be related?

- Pedigree based definition: $\varphi > 0$

  potentially having alleles IBD

- Genomic definition (**realised** relatedness):

  actually having alleles IBD