

Lecture 5: Recombination, IBD distributions and linkage

Magnus Dehli Vigeland

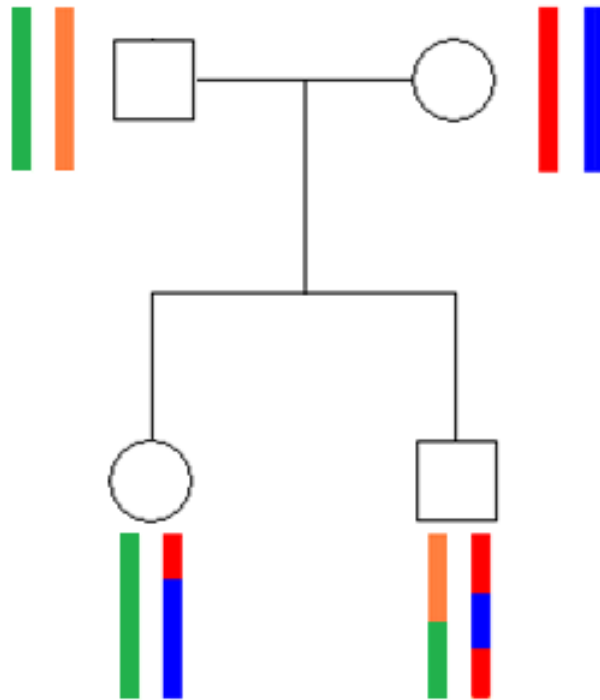
Statistical methods in genetic relatedness and pedigree analysis

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

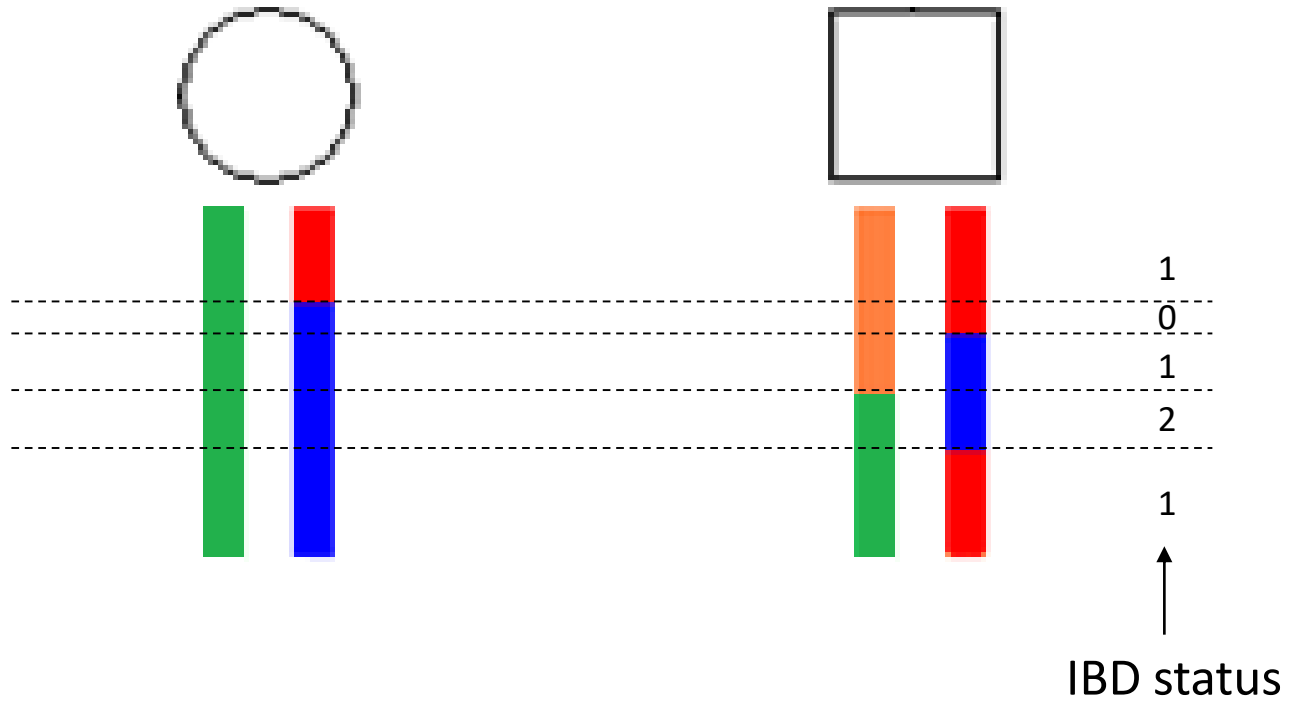
Outline

- Review from yesterday:
 - Meiotic recombination
 - IBD *segments*
- Consequences of the discrete nature of recombination
- Measuring distance in the genome
 - 1) Physical distance
 - 2) Genetic map distance (= crossover rate)
 - 3) Recombination rate
- Map functions: Translating between 2) and 3)
- Using linked markers for relatedness

Recombination and IBD



IBD segments



Consequences of the discrete nature of recombination

- Distant relatives: Possible to have no IBD sharing!
- 100 % inbred?
- Indistinguishable relationships - or not?
 - Half siblings
 - Grandparent/grandchild
 - Aunt/nephew

METRO

HOME NEWS SPORT ENTERTAINMENT LIFESTYLE
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FASHION CULTURE

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

By Meghan McKenna Date November 2, 2017

FASHION BEAUTY GIFT GUIDE

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

Brigitte

SPIELE NEWSLETTER VIDEO GEWINNSPIELE FORUM F-MAG ACADEMY SHOPPING ABC
Aktuell Mode Beauty Rezepte Gesund Liebe Familie Leben Horor

Stammbaum erforscht: Prinz Harry und Meghan Markle sind Cousins!

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



STJERNER: 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

universitetssykehus

1.1K shares

View c

(Picture: Mail Online)

Ralph BOWES
(1480–1516)
of Streatlam, Co Durham
High Sheriff

GRANDCHILDREN

Sir George BOWES
Loyal to Queen Elizabeth I
during the rising of the North, 1596

Bridget BOWES
Married John Hussey
of Dorking

GREAT-GRANDSON

Sir William BOWES MP
(1657–1707)
During reign of Charles II
Royalist

GRANDSON

Captain Christopher HUSSEY
(1598/9–1686)
A founder of Nantucket, Massachusetts

Sir George BOWES MD
(1707–1770)

Huldah HUSSEY
(1643–1740)
Married Lieutenant John SMITH

Married John

$P(\text{any IBD}) \approx 0$

FOUR

Claude George
(1854–1941)
14th Earl of Strathmore

Lee MERRILL

Lady Elizabeth BOWES LYON
(1900–2001)
HM Queen Elizabeth
The Queen Mother

George David MERRILL
(1861–1924)

Gertrude May MERRILL
(1887–1938)
Married Frederick George SANDERS

HM The Queen
(1926–)

Doris SANDERS
(1921–)
Married Gordon Arnold Markle

Lady Diana Spencer
(1961–1997)

HRH Prince of Wales
(1948–)

Thomas Wayne Markle
(1944–)

Doria L. Ragland
(1956–)

PRINCE HARRY

(RACHEL) MEGHAN MARKLE

~~15th Cousins~~



- 14
- 13
- 10
- 9
- 8
- 4
- 3
- 2
- 1

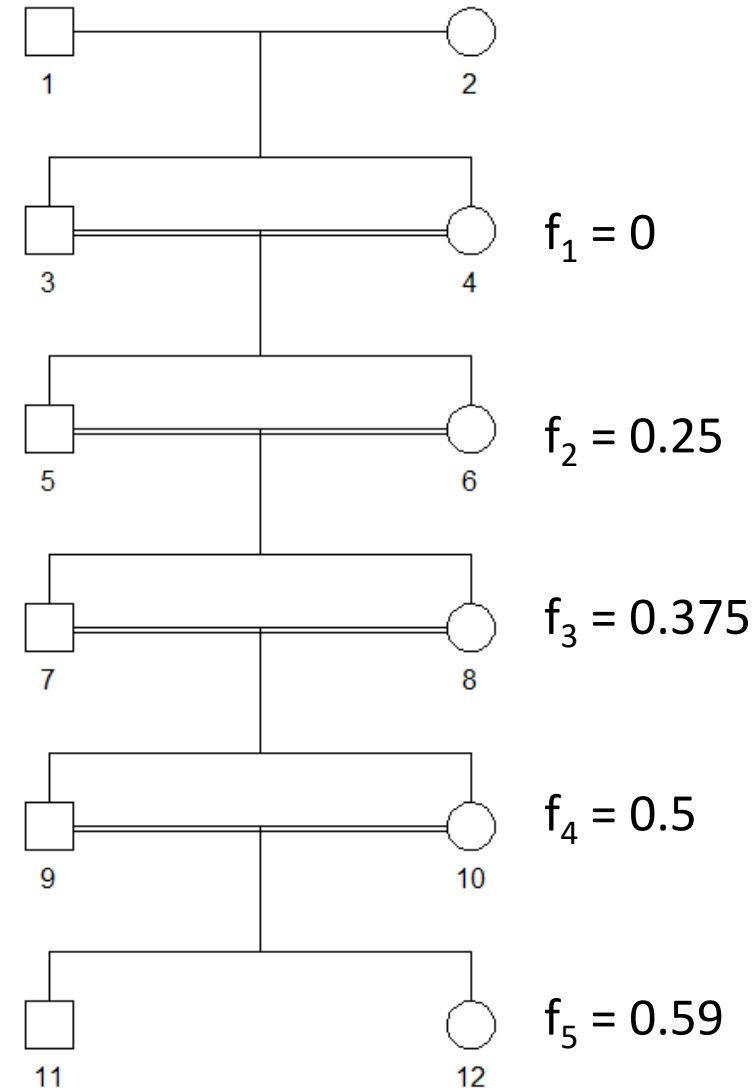
- 15
- 13
- 11
- 10
- 9
- 5
- 4
- 3
- 2
- 1

13th cousins once removed

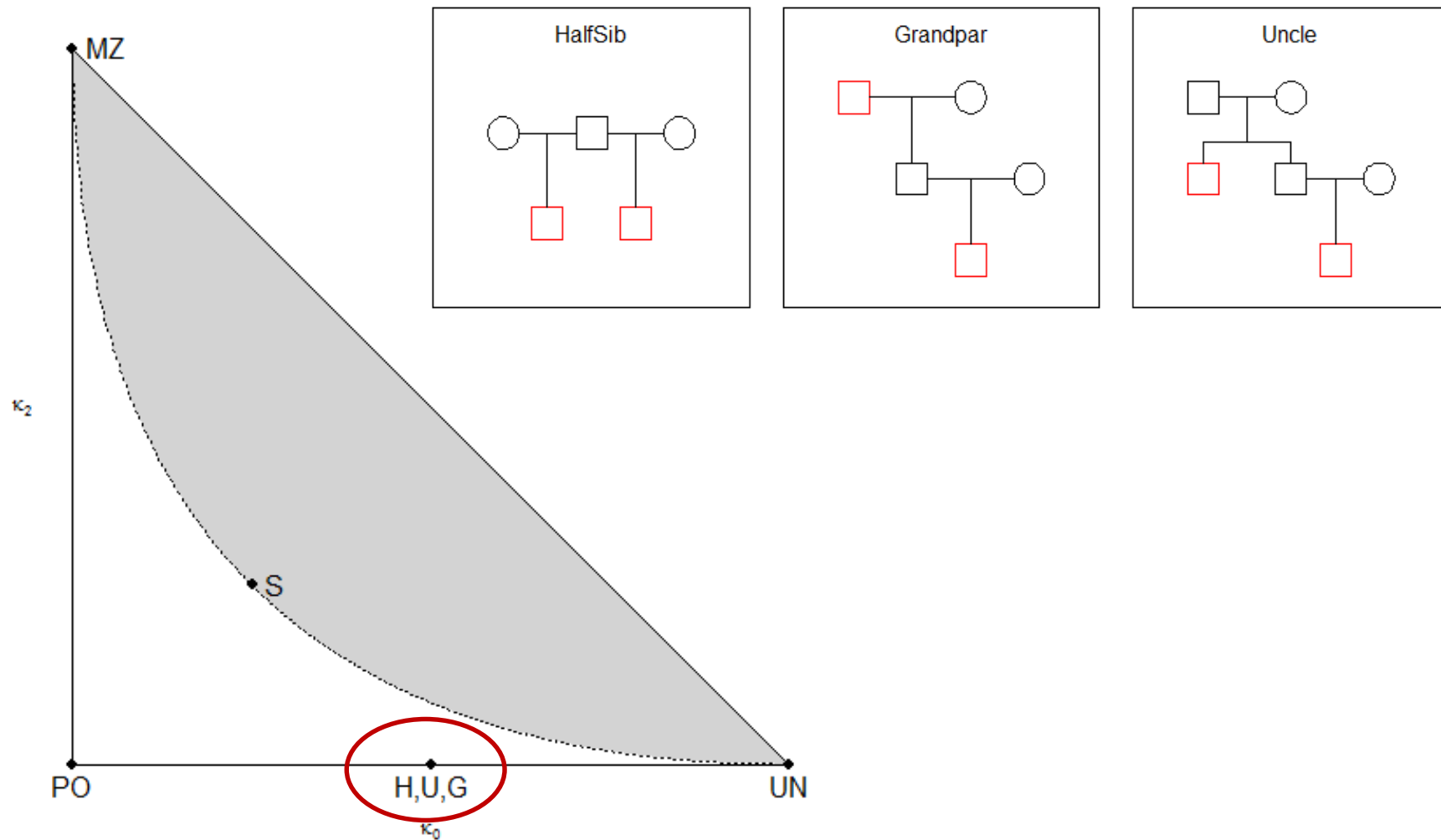
Is 100 % inbreeding possible?

- Full sibs mating scheme
- Easy to show:
 - inbreeding coefficient $f \rightarrow 1$
- But *never* $f = 1$! (in a finite pedigree)

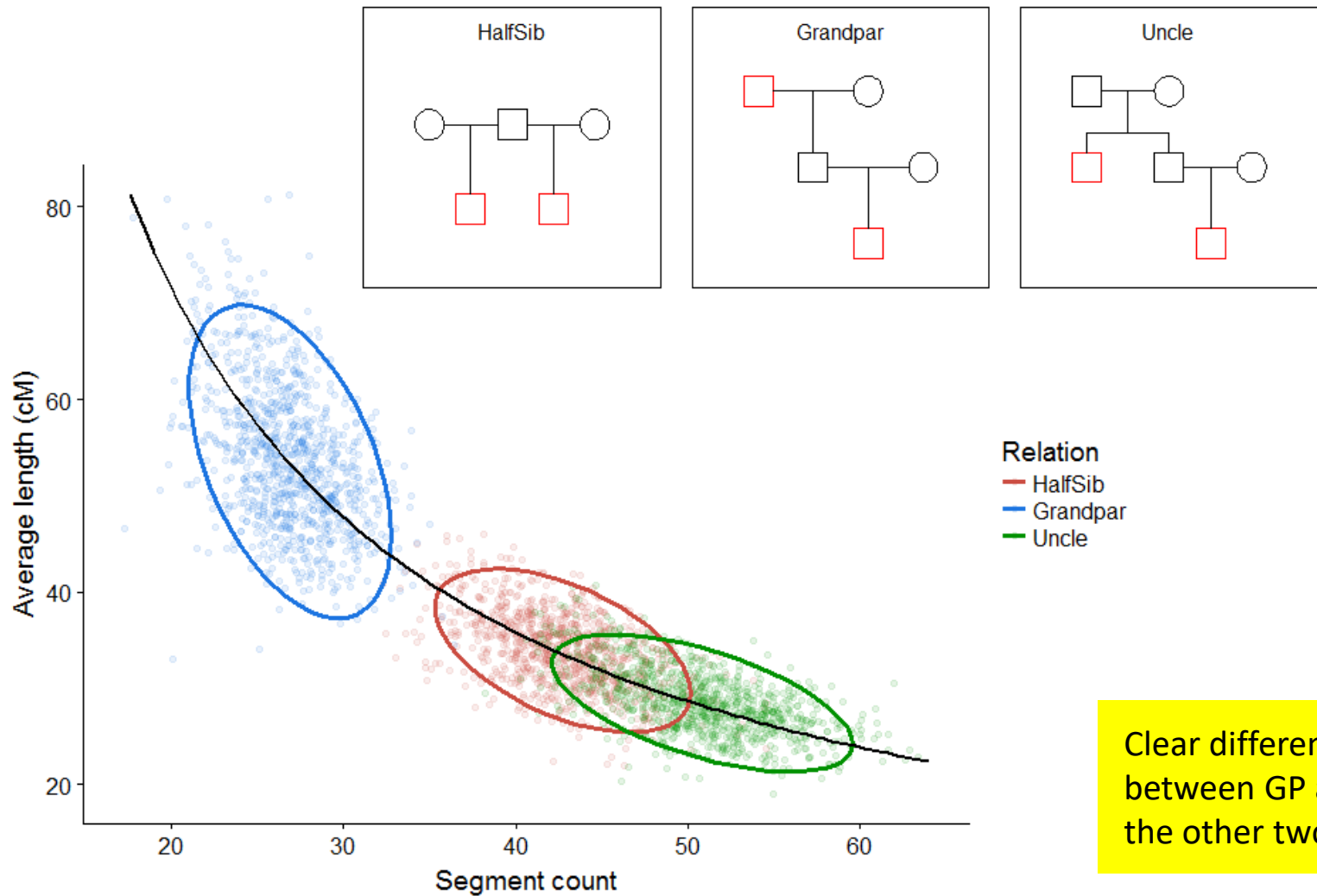
Realised inbreeding
After ~30 generations,
usually $f_{\text{real}} = 1$.



Indistinguishable relationships?



Distributions of IBD segments

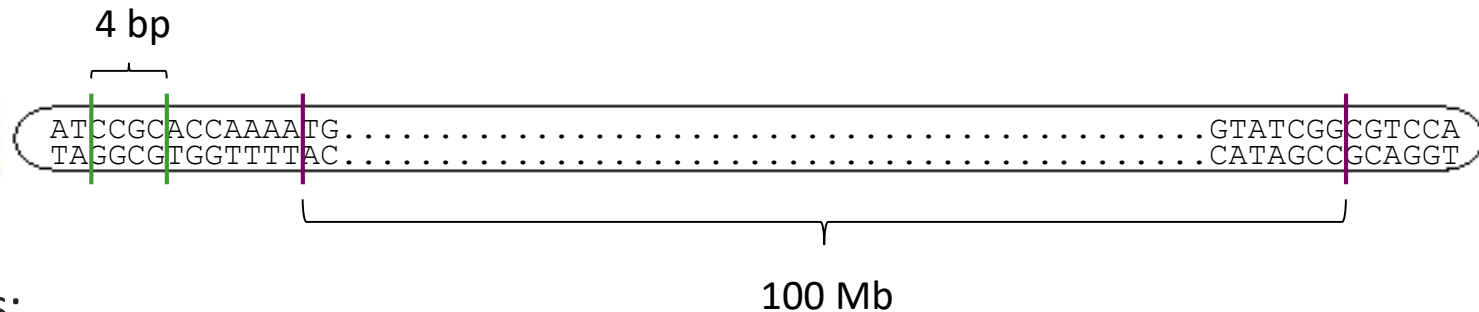


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Physical distance

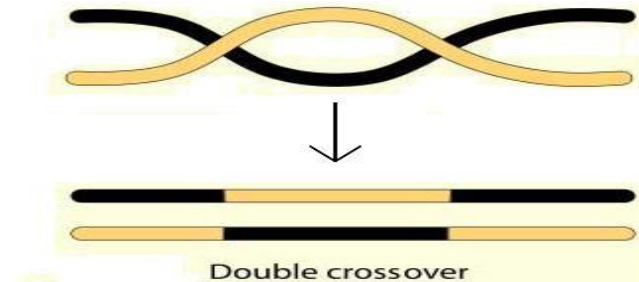
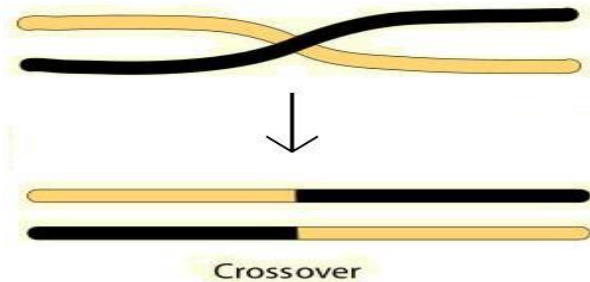
- The **physical distance** between two loci
= number of base pairs between them



- Units:
 - 1 bp (base pair)
 - 1 kb = 1000 bp ("1 kilobase")
 - 1 Mb = 1 000 000 bp ("1 megabase")
- The physical distance/position is often the ultimate goal, but **rarely accessible** by experiments

Map distance

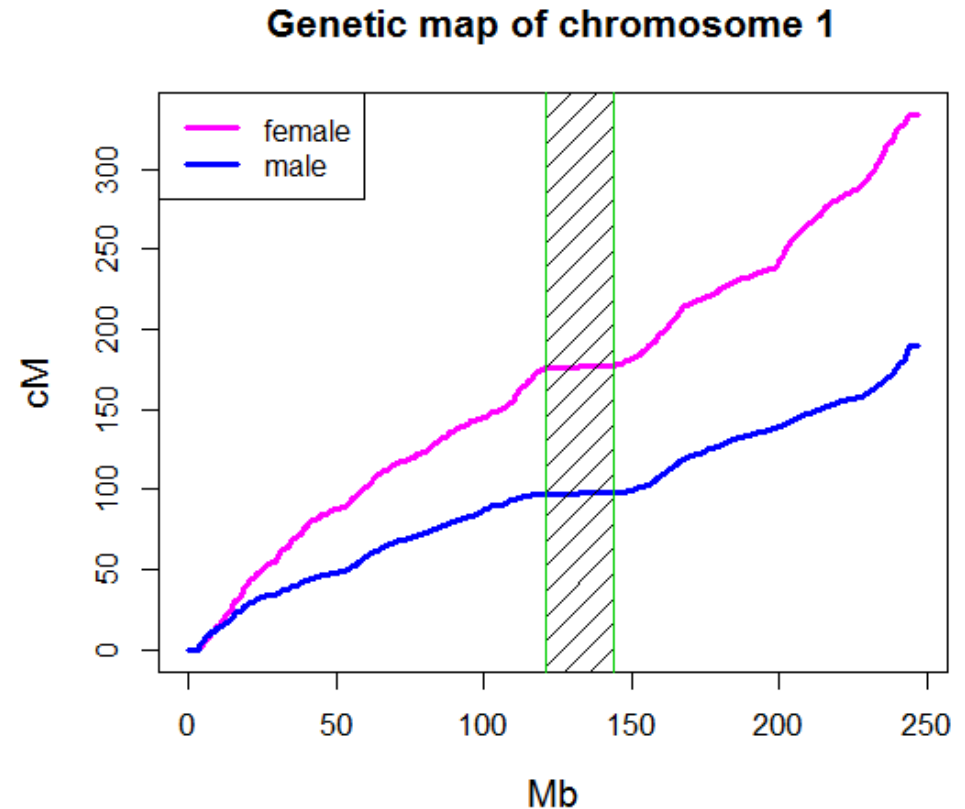
- Chromosomal crossovers:



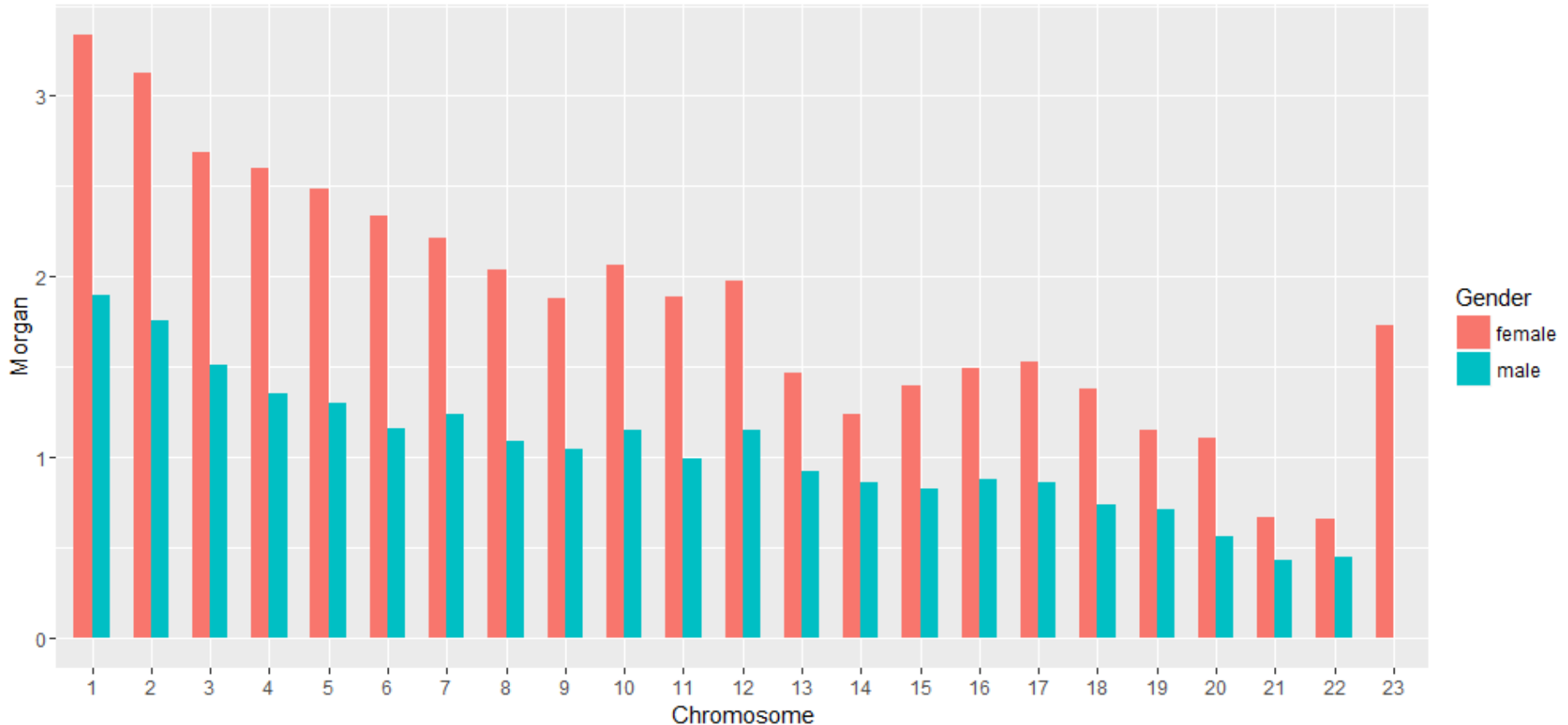
- The **genetic map distance** between two loci
= average number of crossovers between them
- Units:
 - 1 Morgan (M) = average 1 crossover per meiosis
 - 1 centiMorgan (cM) = 0.01 M
- The entire human genome: Ca 30 Morgan

Map distance

- Rule of thumb:
 $1 \text{ cM} \approx 1 \text{ Mb}$
- But: crossover rates vary
 - across the genome
 - males vs. females



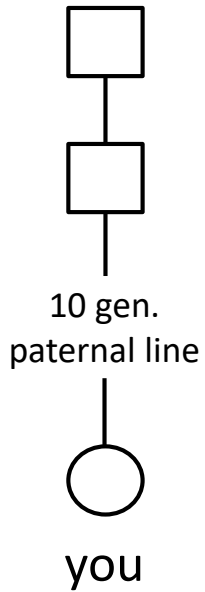
Females have a much longer genome!



Consequences



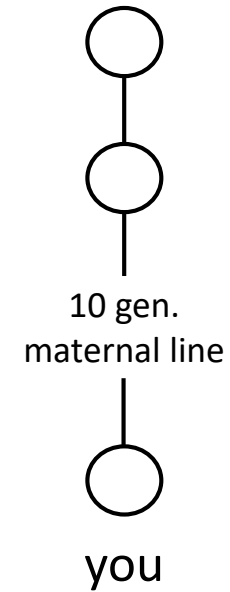
Napoleon Bonaparte (1769 - 1821)



$P(\text{any IBD sharing}) \approx 19 \%$

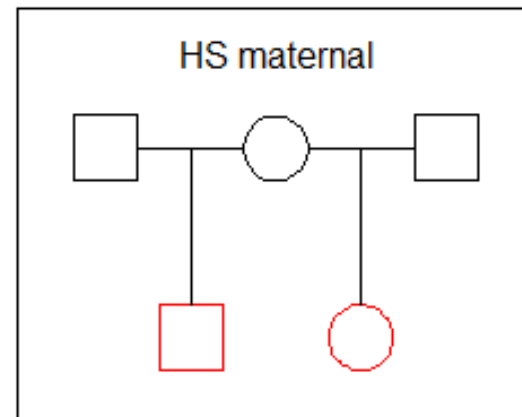
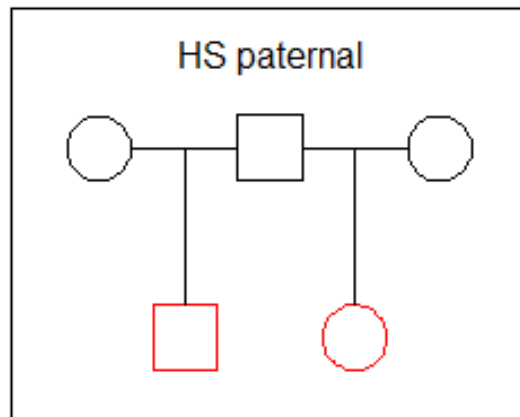


Jane Austen (1775 - 1817)

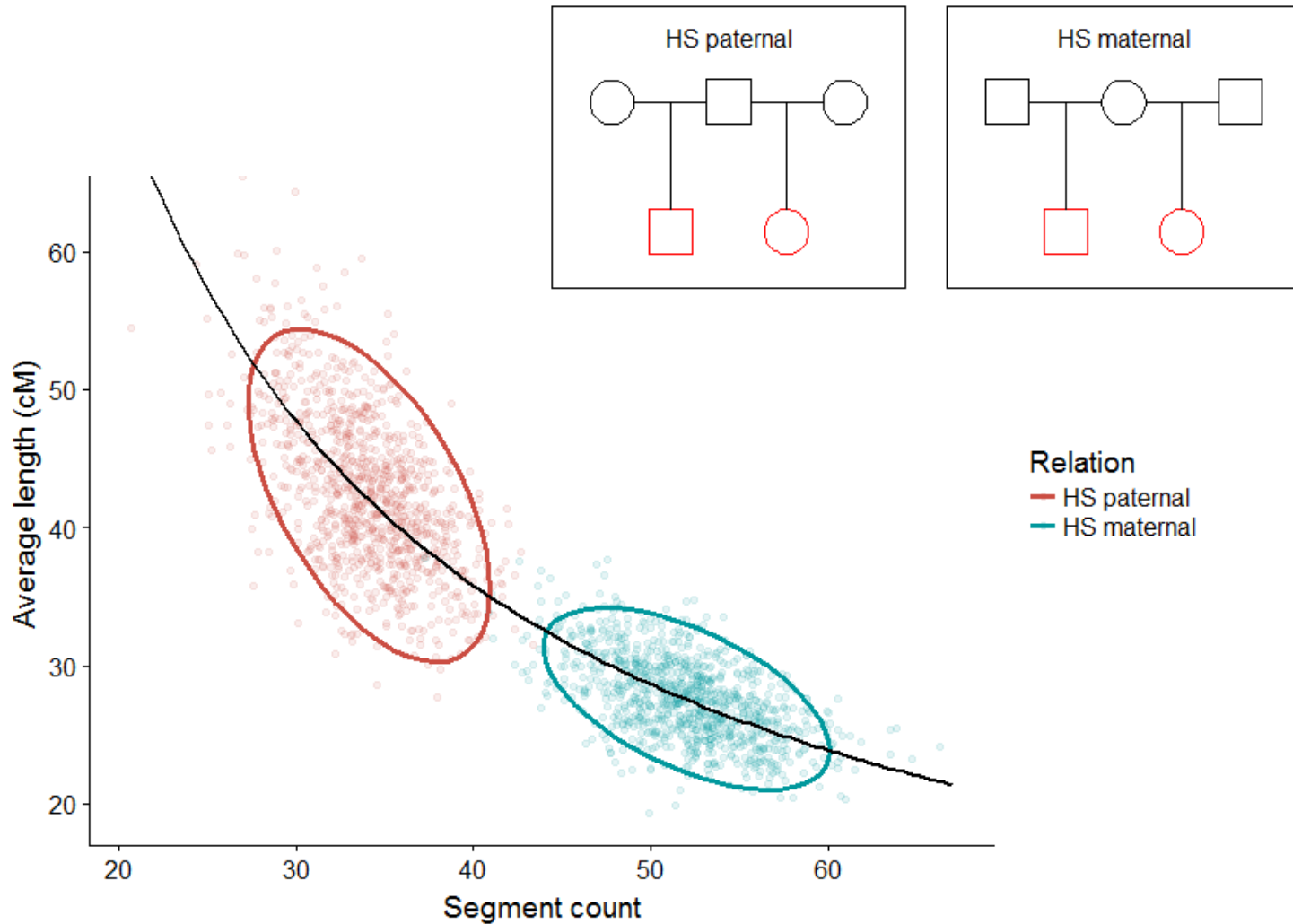


$P(\text{IBD sharing}) \approx 33 \%$

Can we separate these??



Yes!

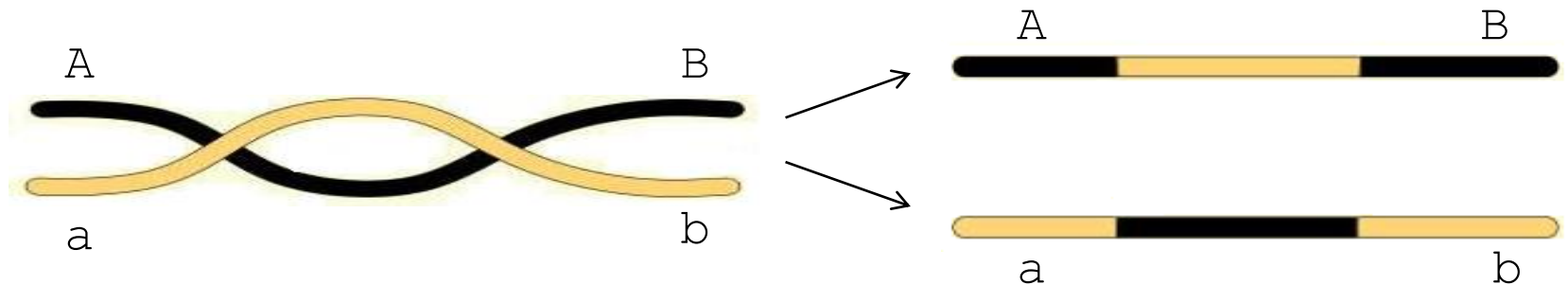


- So far:
 - crossover rates: meiotic process
 - IBD distributions
 - has nothing to do with markers

- Now: Change focus
 - marker genotypes
 - what can we *observe*?

Map distance

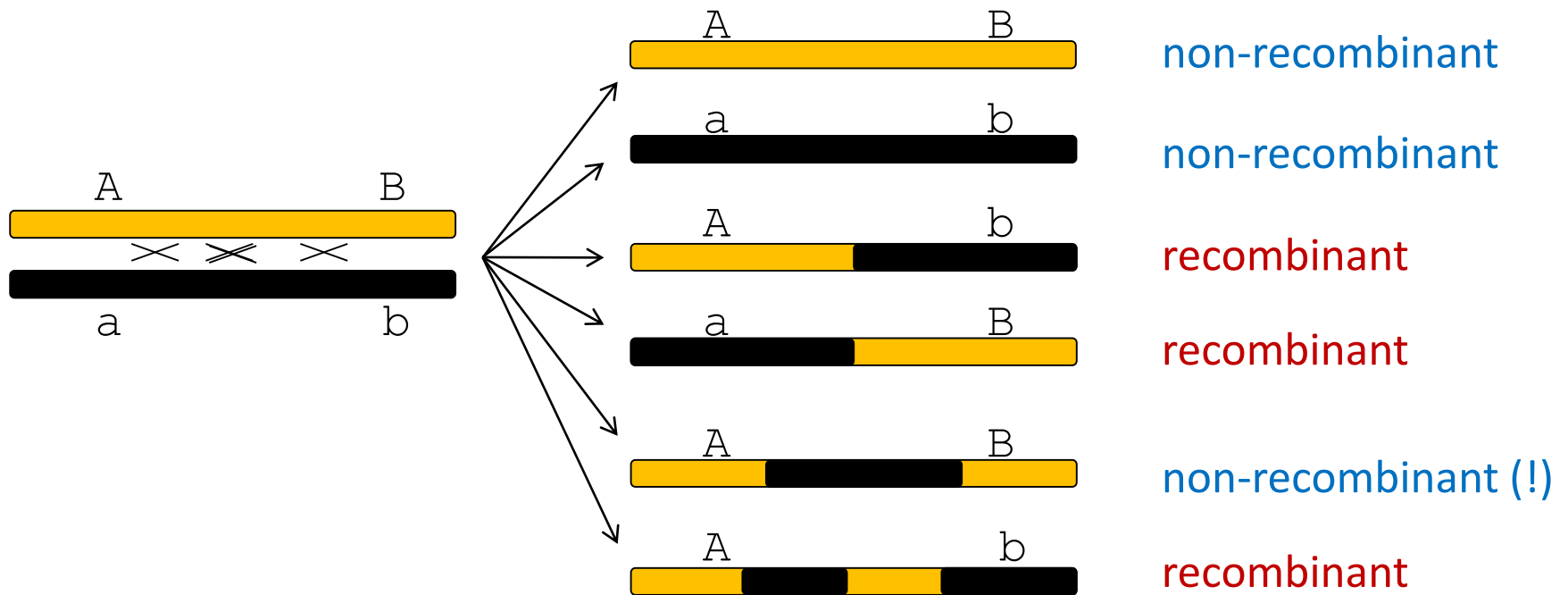
- Crossovers (and thus map distances) are not directly observable with markers
- Reason: multiple crossovers between markers



- Remember: We don't observe the meioses themselves, only their outcome (the gametes)
- What can we observe directly?
 - Answer: **Recombination rates between markers**

Recombination rate

- The **recombination rate** between two loci
= average number of recombinant gametes



Recombination rate

- Loci on different chromosomes: $\theta = 0.5$
- Loci far apart on the same chromosome: $\theta \approx 0.5$
- Loci right next to each other: $\theta = 0$

- Definition: Two loci are linked \longleftrightarrow $\theta < 0.5$

(In plain language: "On the same chromosome, not too far apart")

Crossover rate vs. recombination rate

Map distance: Crossover rate

$$d = E[\text{\#crossovers}]$$

- Based on a fundamental property of the meiosis
- Very natural measure of distance
- But:
Hard to observe directly

Recombination rate:

$$\theta = E[\text{\#recombinant gametes}]$$

- Perhaps not as intuitive
- Relative to markers
- But:
Easy to estimate using genotyping

Can we relate these in some way?

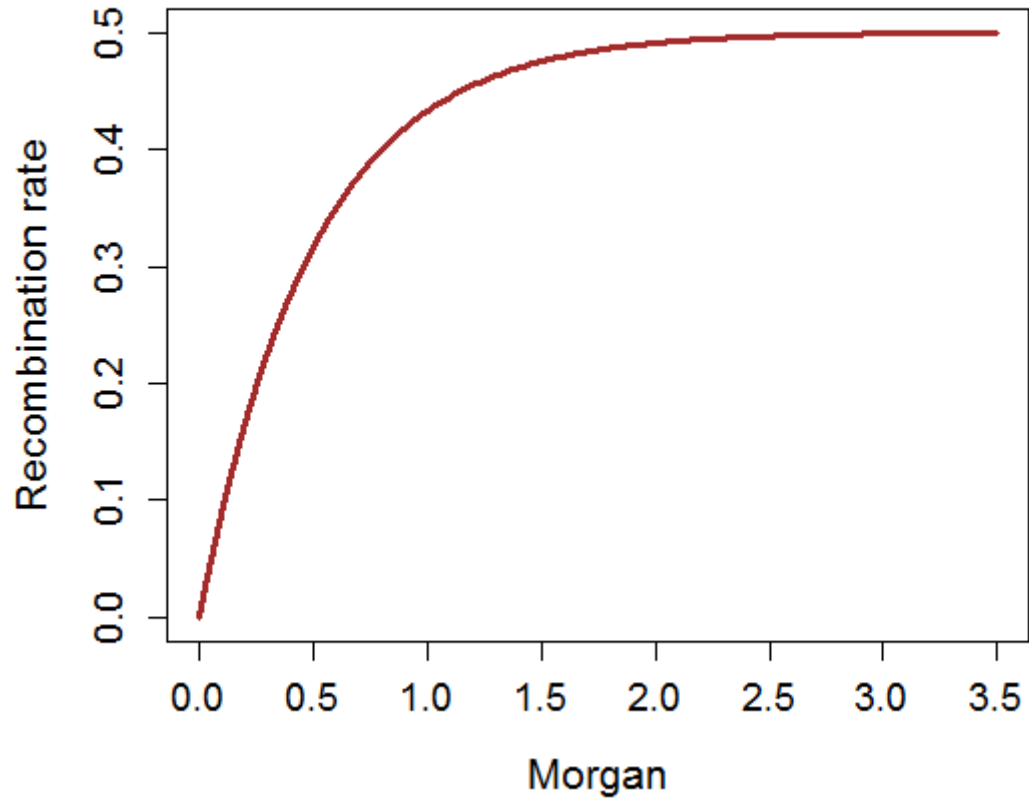
Haldane's map function

- Given observations on recombinations, we would like to compute the crossover rate.
- Requires a *statistical model* of the crossover process
- Haldane's model:
 - Crossover events occur completely at random, with fixed rate 1.
 - Events are independent (in reality not true: cannot be too close)
 - Poisson process!
- From this easy to compute the recombination rate, using that
 $\theta = P(\text{odd number of crossovers})$

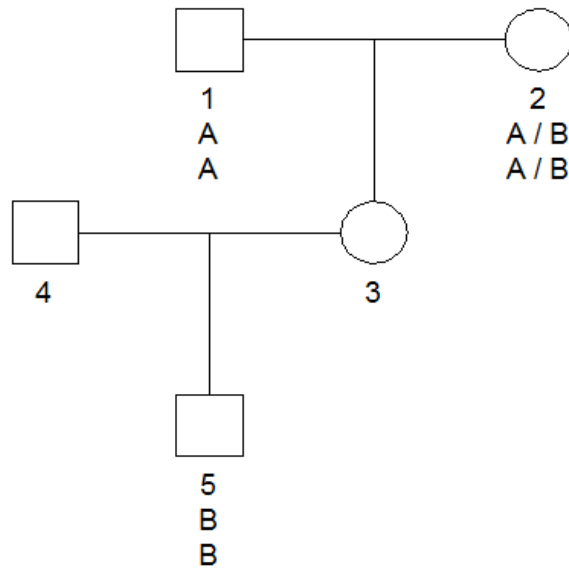
Haldane's map function:

$$\theta = \frac{1}{2}(1 - e^{-2d})$$

Haldane's map function



Likelihood with linked markers



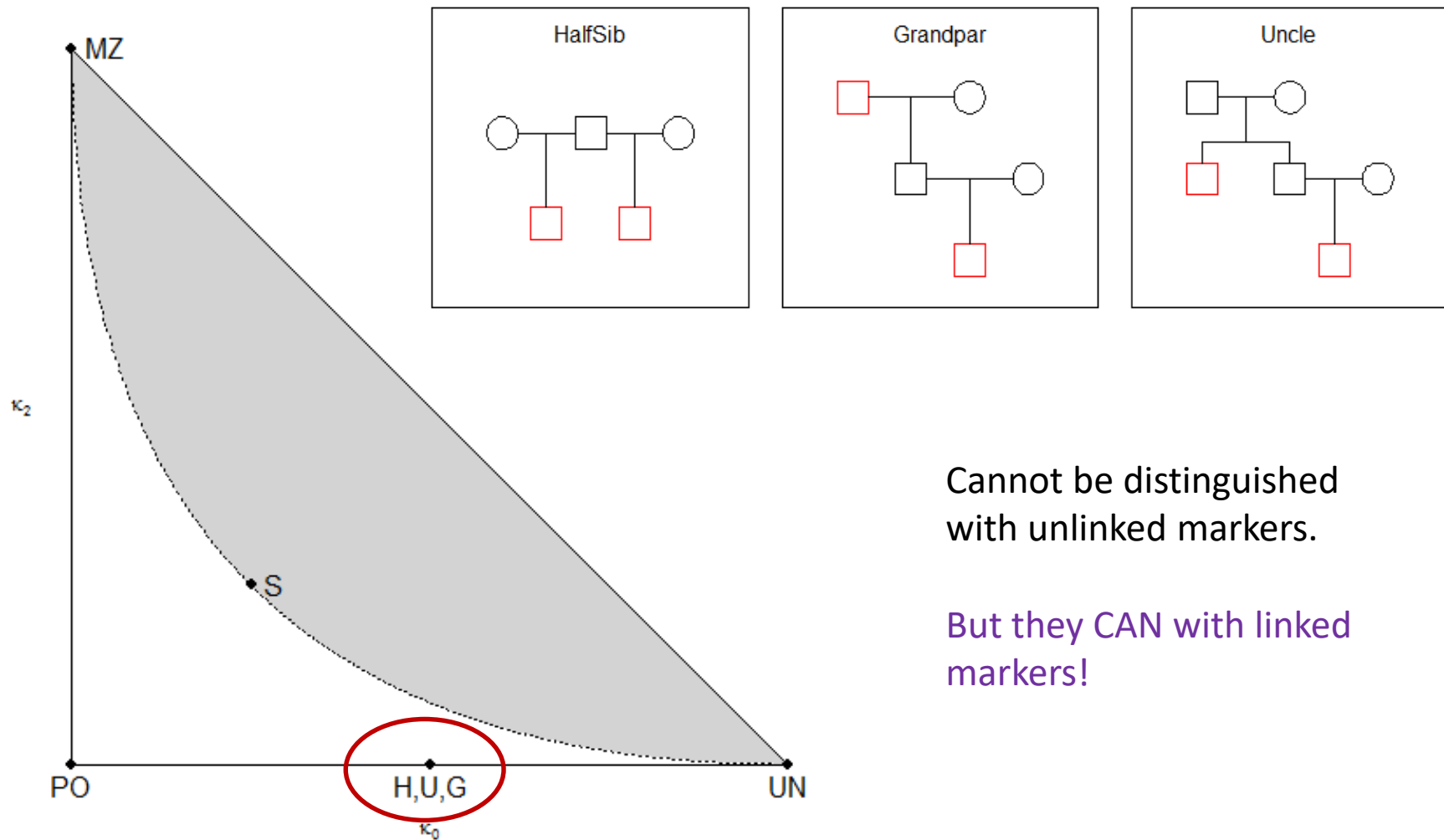
Unlinked markers:

$$L = L_1 \times L_2$$

This does not hold if
the markers are linked!

Ignoring linkage can lead to serious errors

Advantages of linked markers



Summary

- Distributions of IBD segments
- Measures of genomic distance
 - physical
 - genetic distance (= crossover rate):
 - centiMorgan
 - recombination rate
- Haldanes map function
- Marker linkage in relatedness analysis
 - bad (if ignored)
 - good (esp. for distinguished some relationships)