

# Inbreeding

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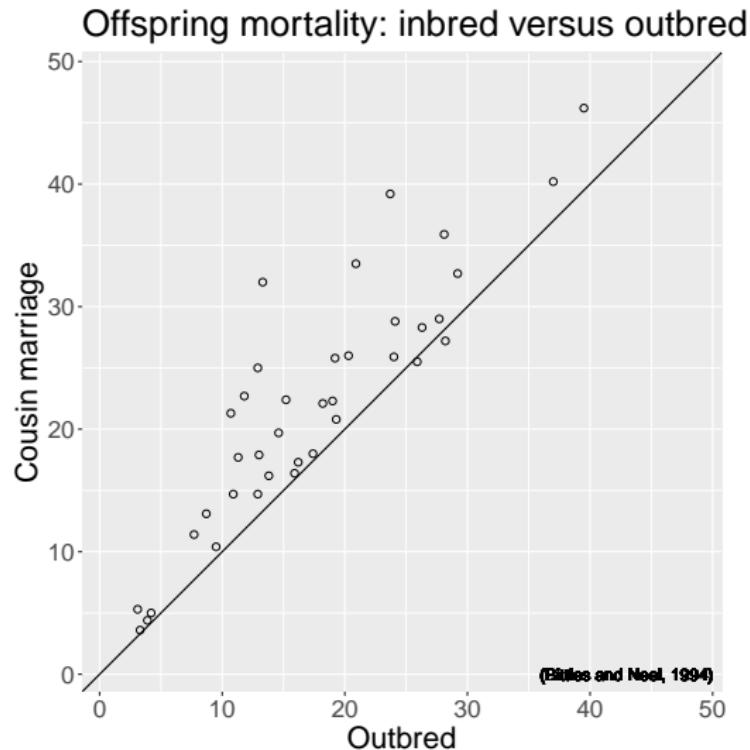
# Inbreeding depression in corn



(JONES 1924)

- ▶ Two plants on left are from inbred homozygous strains.
- ▶ Next: the  $F_1$  offspring of these strains
- ▶ Then offspring ( $F_2$ ) of two  $F_1$ s.
- ▶ Then  $F_3$
- ▶ And so on.

# Inbreeding depression in humans



Offspring of cousin marriages are less likely to survive.

(BITTLES AND NEEL 1994)

## Genotype frequencies without random mating

Genotype	Frequency
$A_1A_1$	$p^2 + pqF$
$A_1A_2$	$2pq(1 - F)$
$A_2A_2$	$q^2 + pqF$

Describes any bi-allelic locus.

$F = 0$  under random mating.  
Reduces to Hardy-Weinberg.

$F > 0$  under inbreeding. Gives excess of homozygotes.

$F$  is the *coefficient of inbreeding*.

## Example

Assume  $p = 1/2$

Genotype	Frequency	
	$F = 0$	$F = 0.1$
$A_1A_1$	0.25	0.275
$A_1A_2$	0.50	0.450
$A_2A_2$	0.25	0.275

Inbred population has more homozygotes.

Suffers if either

- ▶ Heterozygotes tend to have high fitness
- ▶ deleterious alleles tend to be recessive.

## Outline of theory

Inbreeding increases  $F$ , which increases homozygosity, which decreases fitness.

## Decay of heterozygosity under selfing

Gen.	$A_1A_1$	$A_1A_2$	$A_2A_2$
0		$N$	
1	$\frac{1}{4}N$	$\frac{1}{2}N$	$\frac{1}{4}N$
2	$\frac{3}{8}N$	$\frac{1}{4}N$	$\frac{3}{8}N$

## Decay of heterozygosity under selfing

Half of heterozygosity is lost each generation.

## What about cousin mating, or mating between sibs?

It is *extremely* difficult to work this out, using the method we just used.

Between 1903 and 1915, no one could get it right.

Pearl (1913): Only for brother-sister matings does inbreeding reduce heterozygosity. [Wrong!]

Solution: build theory looking backwards in time, not forwards.

## Kinds of gene identity

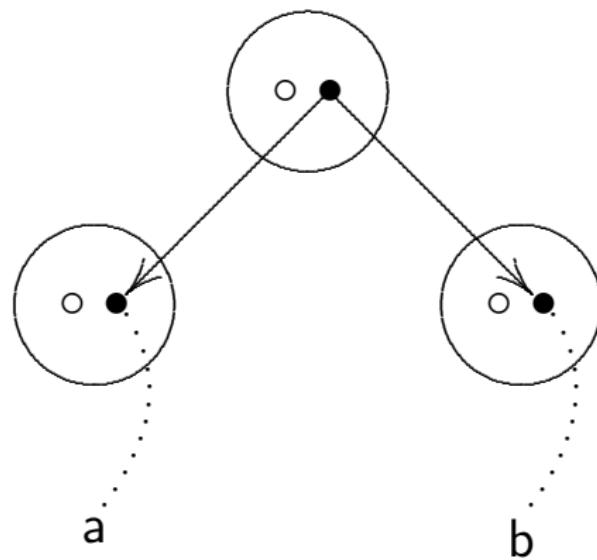
There are two senses in which a pair of gene copies may be “identical:”

identity in state : copies of same allele

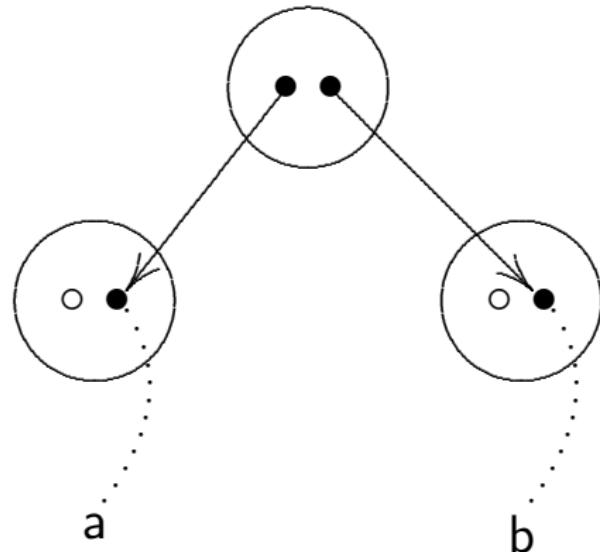
identity by descent : copies of same gene copy in an ancestor

Abbreviation: IBD = Identity by Descent

Gametes *a* and *b* are identical by descent



## Identical in state, not by descent

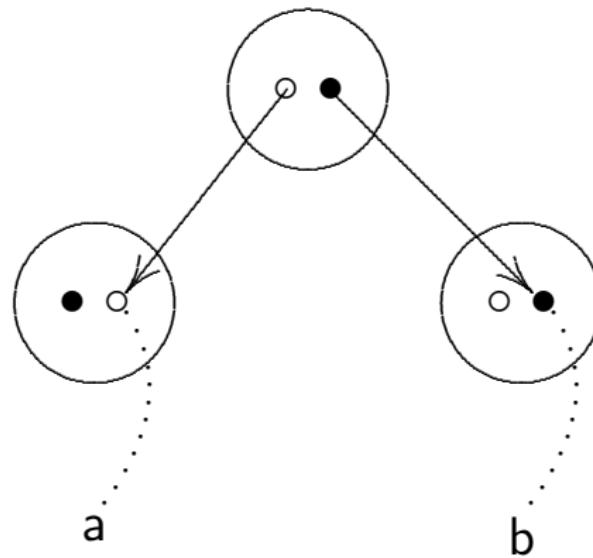


May be IBD relative  
to an earlier  
generation.

Not IBD relative to  
the pedigree shown  
here.

IBD is always  
relative to a  
particular  
generation.

Identical neither in state nor by descent



## Uniting gametes

Consider the two gametes that unite to form an individual.

- ▶  $F$ , is the probability that they are IBD
- ▶ What is the probability that they both carry  $A_1$ ?

Event	Probability
IBD from $A_1$ -bearing ancestor	$Fp$
Descend from two random ancestors who both carry $A_1$	$(1 - F)p^2$

$$\begin{aligned} P_{11} &= Fp + (1 - F)p^2 \\ &= p^2 + pqF \end{aligned}$$

## All three genotypes

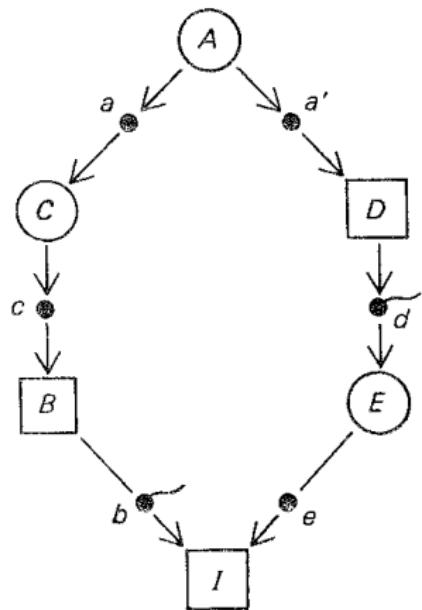
Genotype	Frequency
$A_1A_1$	$p^2 + pqF$
$A_1A_2$	$2pq(1 - F)$
$A_2A_2$	$q^2 + pqF$

Same formulas as before.

$F$  is no longer arbitrary.

$F$  is probability that uniting  
gametes are IBD.

## Calculating $F$ from a pedigree



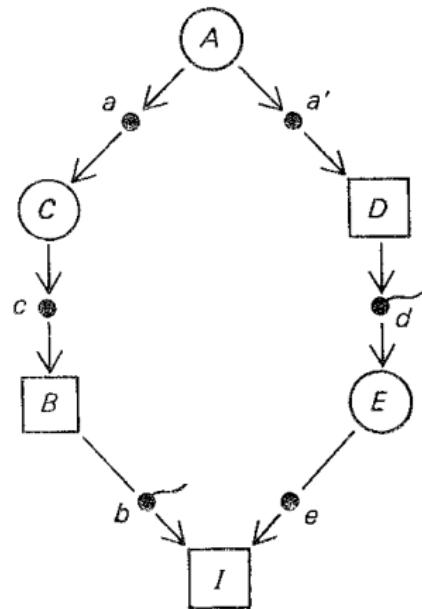
$F$  is probability that  $b$  and  $e$  are IBD,  
which I abbreviate as  $\Pr[b = e]$ .

$$F = \Pr[b = c] \times \Pr[c = a] \times \Pr[a = a'] \times \Pr[a' = d] \times \Pr[d = e].$$

$\Pr[b = c] = 1/2$ , because  $b$  has an equal chance of coming from  $C$  or from  $B$ 's other parent.

Ditto  $\Pr[c = a]$ ,  $\Pr[a' = d]$ , &  
 $\Pr[d = e]$ .

$\Pr[a = a']$  is also  $1/2$

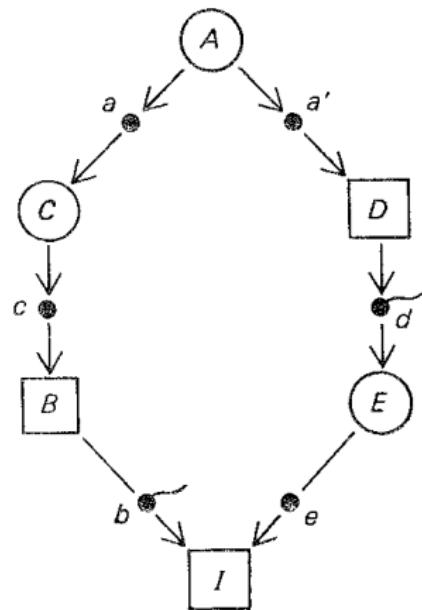


Let  $\oplus$  and  $\otimes$  represent the two gene copies in  $A$ . There are four equally likely possibilities for gametes  $a$  and  $a'$ :  $(\oplus, \oplus)$ ,  $(\oplus, \otimes)$ ,  $(\otimes, \oplus)$ , or  $(\otimes, \otimes)$ .

$a = a'$  in half of these possibilities, so  
 $\Pr[a = a'] = 1/2$ .

Regardless of which gene copy  $A$  contributes to  $C$ , there is a 50% chance that he contributes the same one to  $D$ .

## Calculating $F$ from a pedigree (conclusion)

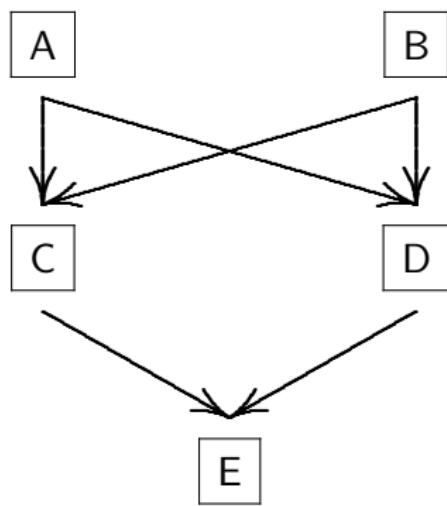


$$F = \Pr[b = c] \times \Pr[c = a] \times \Pr[a = a'] \times \Pr[a' = d] \times \Pr[d = e].$$

Each of the probabilities in this product equals  $1/2$ , so  $F = 1/2^5$ .

In general, each loop in the pedigree contributes  $1/2^n$ , where  $n$  is the number of ancestors in the loop.

## Mating between full siblings



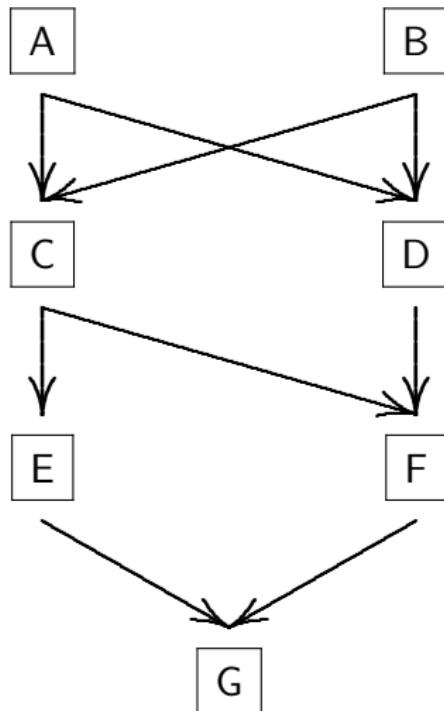
The two loops are mutually exclusive: the two gene copies in *E* cannot be IBD from *A* and also from *B*.

*F* is the sum of the probabilities of the 2 loops.

Each loop contributes  $1/2^3$ .

$$F = 2 \times \frac{1}{2^3} = 1/2^2$$

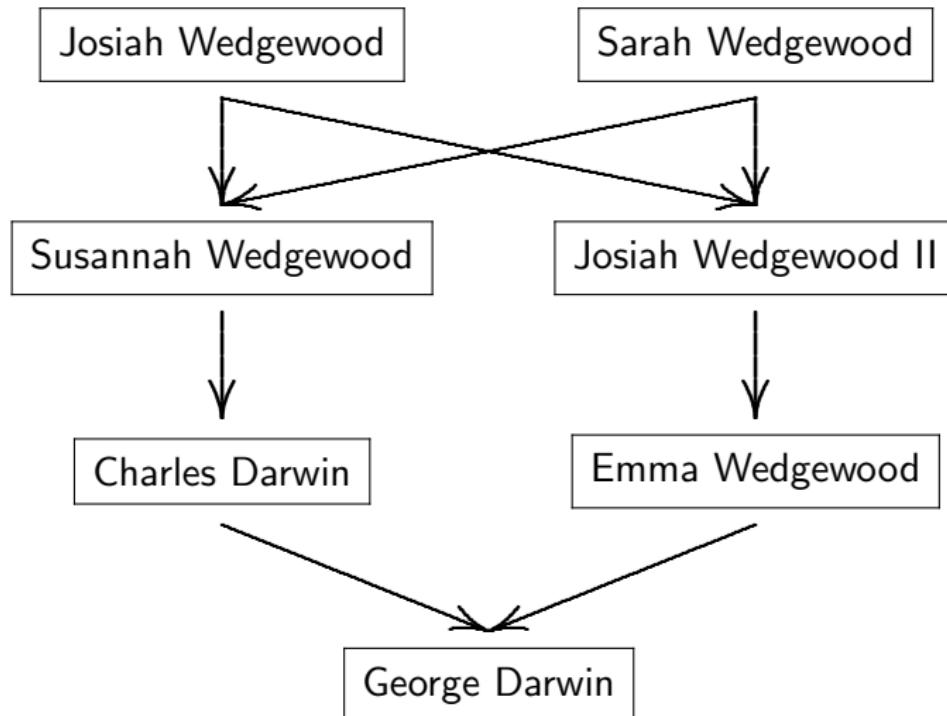
## A complex pedigree



Three loops with probabilities  
 $1/2^3$ ,  $1/2^5$ , and  $1/2^5$ .

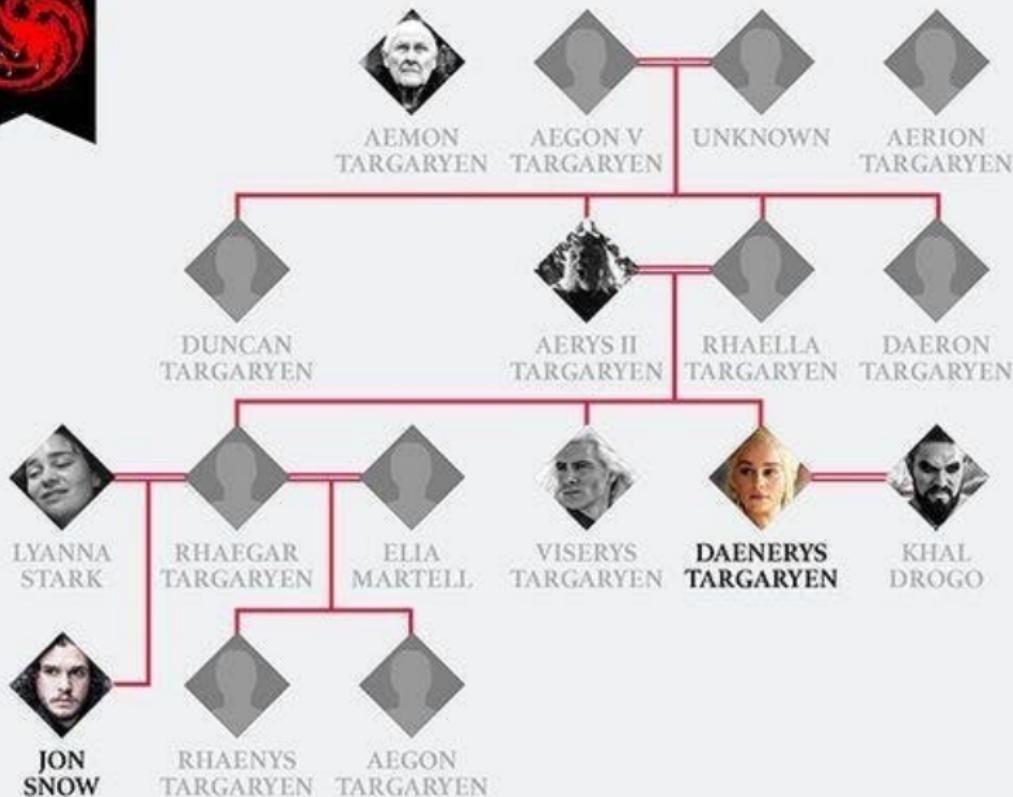
$$F = 1/2^3 + 2 \times \frac{1}{2^5} = 3/2^4$$

# Darwin-Wedgewood Genealogy





# HOUSE TARGARYEN



## Summary

- ▶ The inbreeding coefficient,  $F$ , is the probability that the two gene copies in an individual are IBD from some given generation in the past.
- ▶ Inbreeding subtracts  $2pqF$  from heterozygosity and adds  $pqF$  to the frequency of each of the two homozygous genotypes.
- ▶ Each loop in a pedigree contributes  $1/2^n$  to  $F$ , where  $n$  is the number of ancestors in the loop.
- ▶ Sum across loops to calculate  $F$ .