Inbreeding: the preferential mating of closely related individuals

Consider a finite population of diploids:

What size is needed for every individual to have a separate ancestor?

- every individual must have 2 parents, 4 grandparents, 8 great grandparents...
- \( t \) generations: \( 2^t \) ancestors
- natural population sizes are not big enough to avoid inbreeding

Conclusions:

1. even with complete random mating, finite populations will have some level of inbreeding!
2. inbreeding will depend on population size

Above definition is not good enough for us!
Identical by descent (IBD): genes that originated by replication of a single gene in a previous generation.

Coefficient of inbreeding (F): the probability that any two alleles at a randomly chosen locus within a single individual are IBD.

Inbreeding:

1. Individual inbreeding in a pedigree sense
2. Inbreeding as a population deviation from HWE
3. Inbreeding arising from a finite population size
I. Individual inbreeding in a pedigree sense

Conventional pedigree

First cousin mating

Males

Females

IBD
I. Individual inbreeding in a pedigree sense:

Inbreeding coefficient for individual 1 ($F_1$) via "path analysis":

1. Find each path that alleles might take to become IBD.
2. Count the number of lines ($n$) in each path (path segments).
3. Compute the probability of the path.
4. Sum the probabilities over all possible paths

NOTE: $F_{CA}$ is the inbreeding coefficient of the common ancestor (CA)

1. Individual inbreeding in a pedigree sense:

Conventional representation: $A$ is the CA

Path 1: 6 segments
Path 2: 6 segments
A note about the common ancestor (CA)

<table>
<thead>
<tr>
<th>Segment 1</th>
<th>Segment 2</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>X₁</td>
<td>X₁</td>
<td>1/2 × 1/2 = 1/4</td>
</tr>
<tr>
<td>X₂</td>
<td>X₂</td>
<td>1/4</td>
</tr>
<tr>
<td>X₁</td>
<td>X₂</td>
<td>1/4</td>
</tr>
<tr>
<td>X₂</td>
<td>X₂</td>
<td>1/4</td>
</tr>
</tbody>
</table>

Source 1 for IBD: same allele passed down both segments

Genotypes: X₁ X₁ or X₂ X₂

1/4 + 1/4 = 1/2

Source 2: It is also possible that X₁ and X₂ are IBD

x₁ & x₂ = 1/4
x₂ & x₁ = 1/4

(1/4)F_CA + (1/4)F_CA = (1/2)F_CA

Prob that CA transmitted identical alleles down both paths

1/2 + (1/2)F_CA

Prob that CA transmitted different alleles that were IBD

I. Individual inbreeding in a pedigree sense:

**Step 3:** Compute the probability of the path (in our case 2 paths, each with n = 6 segments).

Probability of a path:

\[
\left(\frac{1}{2}\right)^{n-2} \times \left(\frac{1}{2} + \frac{1}{2}F_CA\right)
\]

Probability for n-2 segments not connected to CA

\[
\left(\frac{1}{2}\right)^{n-2} \times \left(\frac{1}{2}\right)(1 + F_CA)
\]

Probability for two CA segments; i.e., from last slide

\[
\left(\frac{1}{2}\right)^{n-1}(1 + F_CA)
\]
I. Individual inbreeding in a pedigree sense:

**Step 4:** Sum over all possible paths for IBD in pedigree

\[
F_i = \sum_i \left( \frac{1}{2} \right)^{n_i-1} \left( 1 + F_{CA} \right)
\]

paths in pedigree are indexed by \( i \)

---

Example: first cousin mating

**Case 1:** Outbred ancestors
- \( F_{CA} = 0 \)
- \( F_i = \left( \frac{1}{2} \right)^{n_i-1} (1+0) + \left( \frac{1}{2} \right)^{n_i-1} (1+0) = 0.062 \)

**Case 2:** Inbred ancestors
- \( F_{CA} = 0.375 \)
- \( F_i = \left( \frac{1}{2} \right)^{n_i-1} (1+0.375) + \left( \frac{1}{2} \right)^{n_i-1} (1+0.375) = 0.09 \)
II. Inbreeding as a population deviation from HWE

Now let’s consider the affect of inbreeding on HWE:

- let \( F \) = probability of IBD beyond random mating expectations.
- let \( p \) = frequency of the A allele

**HWE:** \( f_{AA} = p^2 \)

**Inbreeding:** \( f_{AA} = \frac{p}{\begin{bmatrix} p(1-F) + F \\ \text{The prob of A by mating with a relative} \end{bmatrix}} \)
II. Inbreeding as a population deviation from HWE:

For AA, the frequency is:

\[ p[p(1-F) + F] \]
\[ p[p - pF + F] \]
\[ p^2 - p2F + pF \]
\[ p^2 + pF (1 - p) \]
\[ p^2 + pqF \]

What does this tell us about genotype frequencies under inbreeding?
II. Inbreeding as a population deviation from HWE:

Genotype frequencies under inbreeding

\[
\begin{align*}
AA &= p^2 + pqF \\
Aa &= 2pq (1 - F) \\
aa &= q^2 + pqF
\end{align*}
\]

Example: \( A = p = 0.6, \) and \( a = q = 0.4 \)

<table>
<thead>
<tr>
<th>( F = 0 )</th>
<th>( F = 0.5 )</th>
<th>( F = 1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA = 0.36</td>
<td>AA = 0.48</td>
<td>AA = 0.6 [( = p )]</td>
</tr>
<tr>
<td>Aa = 0.48</td>
<td>Aa = 0.24</td>
<td>Aa = 0</td>
</tr>
<tr>
<td>aa = 0.16</td>
<td>aa = 0.28</td>
<td>aa = 0.4 [( = q )]</td>
</tr>
</tbody>
</table>

F = 0 is HWE
F > 0 leads to a deficiency in heterozygotes (excess of homozygotes)
F = 1 leads to a completely homozygous population

---

II. Inbreeding as a population deviation from HWE:

1. **Inbreeding yields change in the genotype frequencies of the population, but does not alter the allele frequencies.**
2. Hence “losing variation to inbreeding” is only a loss of heterozygosity; there is no loss of allelic variation!
3. **Inbreeding affects all loci in a genome.**
4. **Inbreeding slows the approach to equilibrium among loci; i.e., the decay of LD**
II. Inbreeding as a population deviation from HWE:

Hierarchical F statistics:

\[ F = \frac{H_{\text{HW}} - H}{H_{\text{HW}}} \]

\[ H = H_{\text{HW}} - (H_{\text{HW}} \times F) \]

\[ H = 2pq \]

\[ H = 2pq (1 - F) \]

\[ F_{\text{ST}} = \frac{H_{\text{T}} - H_{\text{S}}}{H_{\text{T}}} \]

Also called the \textbf{fixation index}.

\[ H_{\text{T}} = \text{The expected heterozygosity of an individual in a total population that is random mating} \]

\[ H_{\text{S}} = \text{The expected heterozygosity of an individual in a subpopulation that is random mating} \]

OK, that checks out

III. Inbreeding arising from a finite population size
III. Inbreeding arising from a finite population size:

Let’s set up an idealized population with the following characteristics:

1. A finite population with N individuals
2. Each individual produced equal numbers of sperms and eggs
3. Sperm and eggs unite at random

Let’s start out (generation = 0) with completely out-bred population:

\[
F_0 = \frac{1}{2N}
\]

The probability of randomly picking one’s own allele from the gamete pool is its frequency in the gamete pool.

Let’s consider a second generation (generation = 1):

\[
F_1 = \frac{1}{2N} \cdot \frac{1}{\text{prob of IBD by sampling one's own gamete in current generation}} + \left(1 - \frac{1}{2N}\right) F_0 \cdot \frac{1}{\text{prob of IBD from inbreeding in previous generations}}
\]

We can extend this any number of generations (generation = g):
III. Inbreeding arising from a finite population size:

\[ F_g = \frac{1}{2N} + \left( 1 - \frac{1}{2N} \right) F_{g-1} \]

\[ \Delta F = \frac{1}{2N} \quad \text{There is an incremental increase in inbreeding due to finite population size.} \]

We can think of this as "the rate at which inbreeding accumulates".

We have a problem:

- idealized populations do NOT exist!
- natural populations will not behave according to the above formulas!
- real populations have high variance in reproduction

Inbreeding effective size \((N_e)\): the number of an otherwise ideal population which accumulates inbreeding effects at the same rate as the actual (non-ideal) population.

\[ \Delta F = \frac{1}{2N_e} \]
III. Inbreeding arising from a finite population size:

Any factor that affects the variance in reproductive success will impact the $N_e$

Some important cases:
1. Fluctuating population sizes in successive generations
2. Different numbers of males and females
3. Variance in reproductive success (other than male versus female)

\[
\frac{1}{N_e} = \frac{1}{g} \left[ \frac{1}{N_1} + \frac{1}{N_2} + \frac{1}{N_3} + \ldots + \frac{1}{N_g} \right] \quad \text{(approx.)}
\]

Harmonic mean because of the “residual” effect of historical levels of inbreeding
- sensitive to bottleneck effect
- census size could be very different from effective size

Droughts, floods, etc. are examples of stochastic events that ensure the variance in $N$ will be high over time
III. Inbreeding arising from a finite population size:

Effective population size is dominated by historical lows and can be very much lower than current census size.

1. Very high variance in reproductive success among individuals
2. Very high variance in reproductive success among successive generations
III. Inbreeding arising from a finite population size:

2. Different numbers of males and females

\[ N_m = \text{the number of males in the population} \]
\[ N_f = \text{the number of females in the population} \]
\[ N = N_m + N_f \]

The effective number will be a harmonic mean sensitive to the less numerous sex.

\[ \frac{1}{N_e} = \frac{1}{4N_m} + \frac{1}{4N_f} \] (approx.)

\[ N_e = \frac{4N_mN_f}{N_m + N_f} \] (approx.)

III. Inbreeding arising from a finite population size:

Effective population size is sensitive to variance in reproductive success due to unequal sex ratio.

![Graph showing effective population size (Ne) in relation to number of males (N) with N = 100 constant.](image)
III. Inbreeding arising from a finite population size:

3. Variance in reproductive success (other than male versus female)

![Effective population size is sensitive to anything that yields a variance in reproductive success](image)

Almost all natural populations are expected to have $N_e$ less than $N$

<table>
<thead>
<tr>
<th>Species</th>
<th>$N_e/N$</th>
<th>Species</th>
<th>$N_e/N$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puma</td>
<td>0.64</td>
<td>Moose</td>
<td>0.27</td>
</tr>
<tr>
<td>Florida Panther</td>
<td>0.25</td>
<td>Northern Elephant Seal</td>
<td>0.22</td>
</tr>
<tr>
<td>Rainbow trout</td>
<td>0.90</td>
<td>White-tailed Deer</td>
<td>0.52</td>
</tr>
<tr>
<td>Coho Salmon</td>
<td>0.24</td>
<td>Bighorn Sheep</td>
<td>0.44</td>
</tr>
<tr>
<td>Re-spotted newt</td>
<td>0.07</td>
<td>Grey Squirrel</td>
<td>0.59</td>
</tr>
<tr>
<td>Wood Frog</td>
<td>0.44</td>
<td>Black Bear</td>
<td>0.69</td>
</tr>
<tr>
<td>Red-cockaded Woodpecker</td>
<td>0.63</td>
<td>Grizzly Bear</td>
<td>0.28</td>
</tr>
<tr>
<td>Acorn Woodpecker</td>
<td>0.09</td>
<td>Wild Oats</td>
<td>0.51</td>
</tr>
<tr>
<td>Spotted Owl</td>
<td>0.39</td>
<td>White Spruce</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Note that these estimates were made in different studies and in some cases by using different methods. Comparison is not always straightforward. Data were obtained from review by Frankham (1995)
**Inbreeding depression:** the decrease in the mean fitness of individuals arising from a greater frequency of the homozygous recessive genotypes for deleterious alleles, as compared with outbred individuals

My Dear Lubbock,

...In England and many parts of Europe the marriages of cousins are objected to from their supposed injurious consequences: but this belief rests on no direct evidence. It is therefore manifestly desirable that the belief should be either proved false, or should be confirmed, so that in this latter case the marriages of cousins might be discouraged ...

It is moreover, much to be wished that the truth of the often repeated assertion that consanguineous marriages lead to deafness and dumbness, blindness, &c, should be ascertained: and all such assertions could be easily tested by the returns from a single census.

Believe me,
Yours very sincerely,
Charles Darwin
Inbreeding depression:

Let’s use our knowledge of populating genetics to determine if inbreeding will lead to an increased chance of the CF allele appearing as a homozygous recessive.

Random mating:
Frequency of CF = \( q = \frac{1}{2500} \)
Risk of CF under random mating = \( q^2 = 0.00000016 \)  
(risk projected over all genes = .4%)

First cousin mating:
Remember that \( F \) for the offspring of a first cousin mating = 1/16 (assuming that the great grandparents were unrelated)
Risk of CF in children of a first cousin mating = \( q(q(1-F) + F) = 0.00002515 \)  
(risk projected over all genes = 60%)

The risk of CF in the offspring of a first cousin marriage is 157 times larger than in the offspring of a random mating.

Effects of inbreeding in captivity:

![Weekly survivorship of inbred and non-inbred white-footed mice in their natural habitat](image-url)
Effects of inbreeding in captivity:

<table>
<thead>
<tr>
<th>Environment</th>
<th>Non-inbred</th>
<th>Inbred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captive</td>
<td>1</td>
<td>( w_f )</td>
</tr>
<tr>
<td>Natural</td>
<td>( w_N )</td>
<td>( w_f w_N )</td>
</tr>
<tr>
<td>Mouse data</td>
<td>Captive</td>
<td>( w_f = 0.935 )</td>
</tr>
<tr>
<td>Natural</td>
<td>( w_N = 0.221 )</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Hedrick and Kalinowski 2000

Inbreeding depression in a wild population:

![Breeding success in Red Deer in relation to heterozygosity](image)

Adapted from Slate et al. 2000
Keynotes on inbreeding depression and captive breeding

- Inbreeding depression can significantly affect fitness.
- The effects of inbreeding on fitness will vary among species.
- The effects of inbreeding are likely to be variable over populations, traits and environments.
- Species that typically have low effective population sizes in natural populations will have few deleterious alleles to contribute to inbreeding depression.
- The negative effects of inbreeding might be greater than predicted by measurements in the benign environments of captive populations.
- Detecting inbreeding depression is difficult. Statistical power might be a particularly important issue in the benign environments of captive populations.
- Severe inbreeding depression does not mean that a population is beyond hope. Cases such as Speke’s gazelles (4 founders), Przewalski’s horses (13 founders) and Black footed ferrets (6 founders) demonstrate that stable and successful captive breeding programs can be established.
- Sometimes alleles with detrimental affects can be purged from a captive population in an attempt to reduce inbreeding depression. While this is clearly possible in theory, the often cited example of Speke’s gazelles has recently been questioned.