Statistical population genetics

Lecture 2: Wright-Fisher model

Xavier Didelot

Dept of Statistics, Univ of Oxford

didelot@stats.ox.ac.uk

Heterozygosity

- One measure of the diversity of a population is its **heterozygosity**.

  Definition (Heterozygosity)**.**
  Heterozygosity is the probability that two genes chosen at random from the population have different alleles.

- In a biallelic WF model, the heterozygosity is equal to:

$$H_t = 2\frac{X_t}{M}\left(1 - \frac{X_t}{M}\right)$$

- How does this evolve with time in the WF?

Heterozygosity in the WF

Theorem (Heterozygosity under the biallelic WF model)**.**
Under the biallelic WF model, the expected heterozygosity decays approximately at rate $1/M$ *when* M *is large.*

Heterozygosity in the WF

Proof.

$$\begin{aligned}
\mathbb{E}(H_{t+1}) &= \frac{2}{M^2}\mathbb{E}\left(X_{t+1}\left(M - X_{t+1}\right)\right) \\
&= \frac{2}{M^2}\left\{M\mathbb{E}(X_{t+1}) - \mathbb{E}(X_{t+1}^2)\right\} \\
&= \frac{2}{M^2}\left\{M\mathbb{E}(X_{t+1}) - \mathrm{var}(X_{t+1}) - \mathbb{E}(X_{t+1})^2\right\} \\
&= \frac{2}{M^2}\left\{MX_t - X_t + \frac{X_t^2}{M} - X_t^2\right\} \\
&= H_t\left(1 - \frac{1}{M}\right)
\end{aligned}$$

By induction on t we get that:

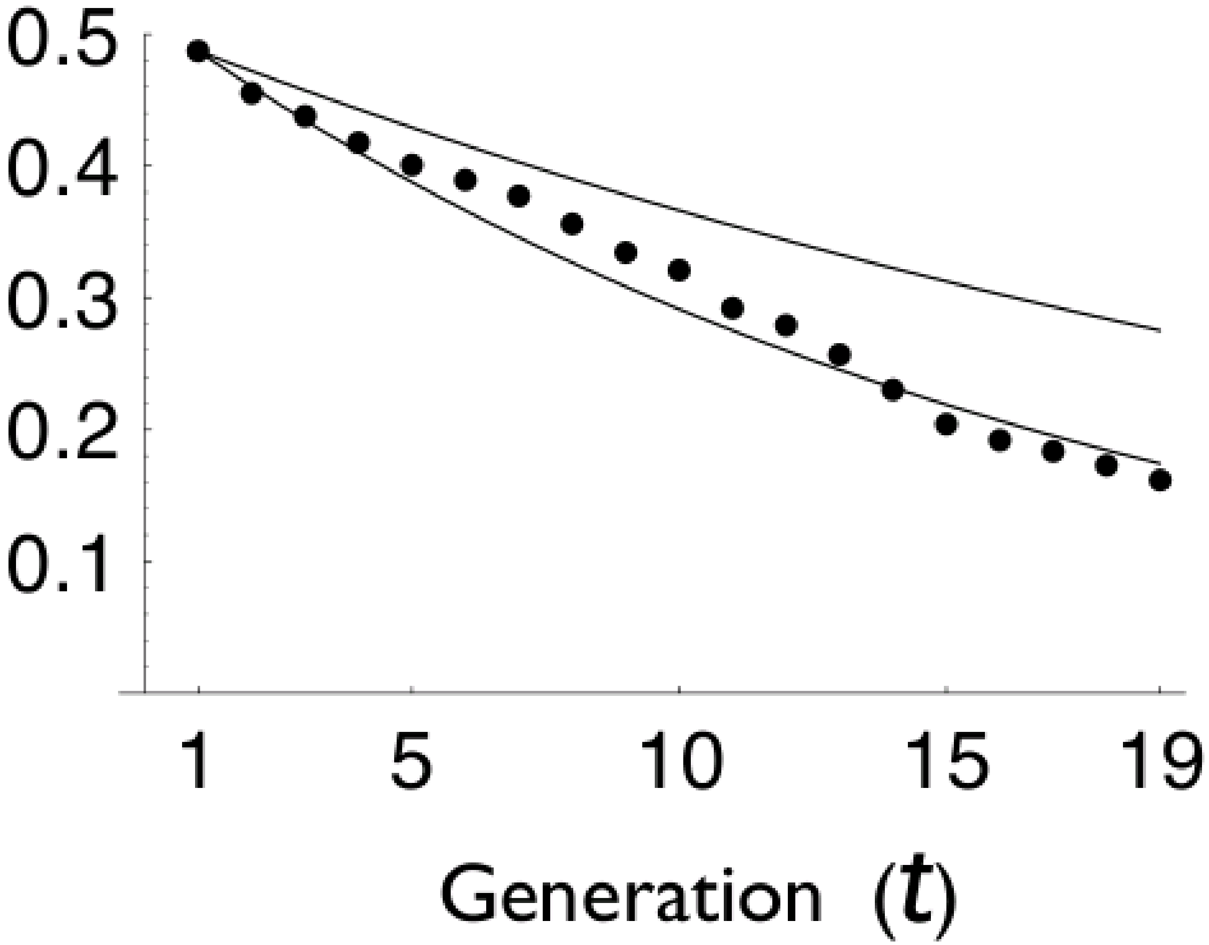
$$\begin{aligned}
\mathbb{E}(H_t) &= H_0\left(1 - \frac{1}{M}\right)^t \\
&\approx H_0 e^{-t/M}
\end{aligned}$$

□

Heterozygosity

- The decay of the **heterozygosity** illustrates how **genetic drift** tends to remove genetic variation from populations.
- Smaller populations loose variation faster than larger populations.
- The rate at which heterozygosity decays can be used to estimate the **effective population size**.

The Buri experiment



Once again, the data of Buri (1956) does not fit our expectation when $M = 32$ but behaves as if $M = 18$.

Fixation

- $X_t = 0$ and $X_t = M$ are **absorbing states** of the biallelic WF process.
- Genetic drift leads to either A or a being lost from the population.
- When this happens, the surviving allele is said to be **fixed** in the population, and the lost allele is said to be **extinct**.
- What is the probability that A will reach fixation rather than a given its initial frequency?

Fixation

Theorem (Probability of fixation)**.**
The probability that an allele will reach fixation given its initial frequency is equal to its initial frequency.

Fixation

Proof.

- The result is implied by the fact that $\mathbb{E}(X_t)$ remains constant and equal to X_0: If fixation is reached at time t, then:

$$\mathbb{E}(X_t) = \mathbb{P}(\text{A fixed}) \times M + \mathbb{P}(\text{a fixed}) \times 0$$

  so that:

$$\mathbb{P}(\text{A fixed}) = \mathbb{E}(X_t)/M = X_0/M$$

- Genealogical approach: eventually all genes in the population will be descended from one unique gene in generation 0, and this gene has probability X_0/M to be of allele A.
- Markov Chain approach: let q_i be the probability of fixation of A given $X_t = i$, solve:

$$q_i = \sum_{j=0}^{M} q_j P_{i,j}$$

Examples

- In the Buri (1956) experiment, 58 of the 107 populations reached fixation: 28 for allele bw^{75} and 30 for the other allele.
- The probability that a new allele appearing in a population through mutation will eventually become fixed is equal to $1/M$ provided no further mutation occurs.
- What is the expected time before fixation?

Time before fixation

Theorem (Time before fixation)**.**

Let $\tau(p)$ *be the expected time before fixation given that* $X_0 = pM$*. Then:*

$$\tau(p) \approx -2M(p\log(p) + (1-p)\log(1-p))$$

with the approximation being valid for large populations.

Time before fixation

Proof. If $p = 0$ or $p = 1$, fixation is reached so that $\tau(0) = 0$ and $\tau(1) = 0$. Otherwise, $\tau(p)$ is equal to one plus the fixation time in the next step. By summing over all possibilities for the next step, we get:

$$\tau(p) = 1 + \sum_{j=0}^{M} P_{pM,j}\tau(j/M)$$

This expresses τ as the solution of a linear equation. Unfortunately, this equation becomes increasingly difficult to solve as M increases. We therefore use an approximation.

Time before fixation

Let $p_t = X_t/M$. Recall that the variance of p_{t+1} about p_t is of order $1/M$. Thus when M is large, the terms in the sum for which $\mathrm{abs}(pM - j)$ is “large” can be ignored. This suggests a continuous approximation. Let us assume that p is a continuous function in $[0, 1]$.

Then we can rewrite as:

$$\tau(p) = 1 + \int_{\epsilon} \mathbb{P}(p \rightarrow p + \epsilon)\tau(p + \epsilon)\mathrm{d}\epsilon$$

Time before fixation

Since ϵ is small, we can expand $\tau(p+\epsilon)$ as a Taylor series:

$$\begin{aligned}
\tau(p) &\approx 1 + \int_\epsilon \mathbb{P}(p \rightarrow p+\epsilon)(\tau(p) + \epsilon\tau'(p) + \epsilon^2\tau''(p)/2)\mathrm{d}\epsilon \\
&= 1 + \tau(p) + \tau'(p) \int_\epsilon \mathbb{P}(p \rightarrow p+\epsilon)\epsilon\mathrm{d}\epsilon \\
&+ (\tau''(p)/2) \int_\epsilon \mathbb{P}(p \rightarrow p+\epsilon)\epsilon^2\mathrm{d}\epsilon \\
&= 1 + \tau(p) + \tau'(p)\mathbb{E}(\epsilon) + (\tau''(p)/2)\mathbb{E}(\epsilon^2)
\end{aligned}$$

Time before fixation

Since $\mathbb{E}(\epsilon) = \mathbb{E}(p_{t+1} - p_t) = 0$ and $\mathbb{E}(\epsilon^2) = \mathrm{var}(\epsilon) = \mathrm{var}(p_{t+1}) = p(1-p)/M$, we have:

$$\tau(p) = 1 + \tau(p) + \tau''(p)p(1-p)/(2M)$$

or

$$\tau''(p) = \frac{-2M}{p(1-p)}$$

This can be solved with boundary conditions $\tau(0) = 0$ and $\tau(1) = 0$ to give the required result. □.

Time before fixation

- Thus, for the Wright-Fisher model, the expected time to fixation is of order $O(M)$.
- This is the so-called **diffusion approximation** to the mean absorption time, although we have not used diffusion theory explicitly here.
- For example, in the case of a newly appeared mutation, we have $p = 1/M$ and

$$\tau(p) \approx 2 + 2\log(M)$$

- In the case where $p = 1/2$, we have

$$\tau(p) \approx 1.38M$$

Summary

- The pure Wright-Fisher model results in a **decay of genetic variation**.
- This is the effect of **genetic drift**, which is compensated by **mutation**.
- It is straightforward to **extend** the WF model to incorporate mutations.
- Exact calculations are impossible so that we need to use **diffusion approximations** as we did to find the time before fixation.
- This approach was championed in the 50s and 60s by **Kimura**.
- This is one of the most sophisticated branches of applied probability.
- We will avoid these complications!