THE COALESCENT

INTRODUCTION TO THE COALESCENT

READING: Nielsen & Slatkin pp. 35-57

– Often want to use patterns of genetic variability to estimate parameters such as mutation and migration rates.

– e.g., Under infinite-alleles model saw that $\hat{H} = \frac{4Nu}{1+4Nu} = \frac{\theta}{1+\theta}$, where $\hat{H}$ is the expected equilibrium heterozygosity and $\theta = 4Nu$.

• estimate θ by replacing $\hat{H}$ with sample heterozygosity (H_{observed}) and solving equation for θ: $\theta_{\text{estimated}} = \frac{H_{\text{observed}}}{1 - H_{\text{observed}}}$

– This illustrates a **prospective** approach, since estimate is based on a forward-looking model

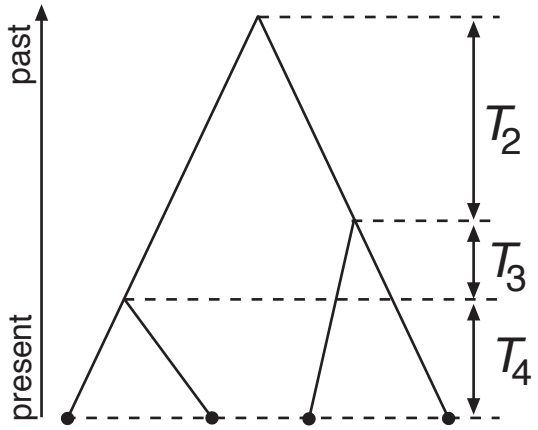
• H_{observed} is also assumed representative of entire population's true heterozygosity

– Alternatively, can develop estimates based on models that look backwards in time (i.e., are **retrospective**) and focus entirely on the set of samples alleles (rather than entire population)

• Called **coalescent** approaches.

– Main assumption behind coalescent: all alleles at a locus in a sample can be traced back to a single ancestral allele.

– **The coalescent** = lineage (genealogy) of sampled alleles traced back to their common ancestor.



• T_k = amount of time there are k distinct lineages.

– each T_k is an independent random variable

– Are interested in $\boldsymbol{T_{tot}}$, the total time in all branches of the genealogy until the entire set of alleles coalesces (i.e., can be traced back to a single common ancestor allele).

• For above example, $T_{tot} = 4T_4 + 3T_3 + 2T_2$

• Since the T_k's are random variables, so is T_{tot}

– If u = mutation rate/generation, then E[different alleles in sample] = E[# mutations in genalogy from the common ancestor] = uE[T_{tot}]

– Coalescent approach often used to estimate $\theta = 4Nu$ based on the **infinite-sites model**.

• assumes each allele is an infinitely long DNA or polypeptide sequence

• every mutation occurs at a different site

– Note: infinite-sites model like infinite-alleles model except in IAM, don't know *how* different the alleles are.

• Will see that S = number of segregating sites (i.e., variable sites) can be used to estimate θ since E[S] = uE[T_{tot}]:

• In fact, will show that $\mathrm{E}[T_{tot}] = 4N\sum_{i=2}^{n}\frac{1}{i-1} = 4N\left(1+\frac{1}{2}+\frac{1}{3}+\cdots+\frac{1}{n-1}\right)$ where n = number of alleles in sample.

– So E[S] = $u\left(4N\sum_{i=2}^{n}\frac{1}{i-1}\right) = 4Nu\left(\sum_{i=2}^{n}\frac{1}{i-1}\right) = \theta\sum_{i=2}^{n}\frac{1}{i-1}$

–Suggests: $\boxed{\theta_{\text{estimated}} = \frac{S_{\text{observed}}}{\sum_{i=2}^{n}\frac{1}{i-1}}}$

• Logic behind formula for E[T_{tot}] = expected time to coalescence for a sample of n alleles:

– Consider the probability of "no coalescence" in previous generation:

* 1st allele's ancestor in previous generation is one of $2N$ possible alleles

* 2nd allele has *different* ancestor in previous generation with probability $1-\frac{1}{2N}$

* 3rd allele has different ancestor from first two alleles with probability $1-\frac{2}{2N}$

⋮

* nth allele has different ancestor from first n–1 alleles with probability $1-\frac{n-1}{2N}$

– So… P(no coalescence in previous generation) = P(alleles have n distinct ancestors in previous generation) = $\left(1-\frac{1}{2N}\right)\left(1-\frac{2}{2N}\right)\cdots\left(1-\frac{n-1}{2N}\right) \approx 1-\frac{1}{2N}-\frac{2}{2N}-\cdots-\frac{n-1}{2N}$

– Finally: P(at least one coalescence in previous generation) = 1 – P(n distinct ancestors) = $\frac{1}{2N}+\frac{2}{2N}+\cdots\frac{n-1}{2N} = \frac{1+2+\cdots(n-1)}{2N} = \frac{n(n-1)/2}{2N} = \frac{n(n-1)}{4N}$

– Implies time to first coalescence in a sample of n alleles, T_n, is "geometrically distributed":

* Geometric distribution is well studied. E.g., know that $E[T_n] = \frac{4N}{n(n-1)}$.

* By similar argument: $E[T_i] = \frac{4N}{i(i-1)}$.

– Know $T_{\text{tot}} = nT_n + (n-1)T_{n-1} + \cdots 2T_2$ so

$$E[T_{\text{tot}}] = \sum_{i=2}^{n} iE[T_i] = \sum_{i=2}^{n}\frac{4N}{i-1} = 4N\left(1+\frac{1}{2}+\cdots+\frac{1}{n-1}\right)$$

– Coalescence-based derivation of equilibrium homozygosity, $\hat{f}$ under IAM:

• Consider P(two alleles not IBD) = $1 - \hat{f}$

• Two alleles will be IBD if they coalesce *before* a mutation occurs on either lineage.

– since P(two gene coalesce) = 1/2N per generation and P(mutation) = 2u per generation

– P(IBD) = $\frac{1/2N}{1/2N + 2u} = \frac{1}{1 + 4Nu} = \frac{1}{1+\theta}$.

– Same result as before, but coalescent approach far easier!

– Example: (Aguadé et al. 1989)

• yellow-achaete-scute region of *D. melanogaster*.

• examined $n = 64$ chromosomes, found 9 polymorphic sites out of 2112 nucleotide sites

• $\theta_{\text{estimated}}(\text{entire region}) = \frac{9}{\sum_{i=2}^{64}(i-1)} = 1.9$

• Implies about 3 "effective alleles" segregating

• $\theta(\text{per site}) = \theta(\text{region})/2112 = 9 \times 10^{-4}$ per site.

– Time to the most recent common ancestor of a sample of size n, T_{MRCA}

• By definition, $T_{\text{MRCA}} = T_n + T_{n-1} + \cdots + T_2$

• $E(T_{\text{MRCA}}) = \sum_{i=2}^{n} E(T_i) = \sum_{i=2}^{n} \frac{4N}{i(i-1)} = 4N\left(1 - \frac{1}{n}\right)$ generations

• Since $E(T_2) = 4N/(2)(2-1) = 2N$ generations and $E(T_{\text{MRCA}}) < 4N$ generations, <u>at least</u> half of the time to coalescence for the sample involves just 2 alleles!

– The coalescent and phylogenetics: "Lineage Sorting"

• Coalescent is a history of genes within a population ("gene tree")
• Phylogeny is a history of relationships among species ("species tree")

• Q: When do gene trees reflect species relationships?

– "Lineage sorting": problem of gene with coalescence time further in past than speciation

• Coalescence theory can help determine if lineage sorting is a problem

• Can show $P\left(T_{\text{MRCA}} > t \text{ generations}\right) \le 3e^{-t/2N_e}$

• Lineage sorting occurs when $T_{\text{MRCA}} > T_{\text{speciation}}$, so $P\left(\text{lineage sorting}\right) \le 3e^{-T_{\text{speciation}}/2N_e}$

• If $3e^{-T_{\text{speciation}}/2N_e}$ is small, lineage sorting is not likely a problem

• Effective Population Size

– The default model for studying and understanding the effects of finite population size is the Wright-Fisher model.

– How do we study drift in organisms with other life cycles and population structures?

• Convenient way is to determine what population size in the Wright-Fisher model would produce the same rate of inbreeding and drift as the system of interest.

• This **effective population size**, N_e, will often be different from the census size of the population, N.

– Examples:

(1) <u>No Selfing</u>

• If no selfing were allowed in the basic Wright-Fisher model, the inbreeding and drift in a population of census size N would proceed as if it were a Wright-Fisher model with size $N_e = N + \frac{1}{2}$.

(2) <u>Two Sexes</u>

• Basic model assumes individuals are hermaphrodites (monoecious). What if a population has two sexes with N_m breeding males and N_f breeding females?

• Turns out $N_e = \dfrac{4N_mN_f}{N_m + N_f}$ = 2 × (harmonic average of N_m and N_f).

• If $N_m = N_f = N/2$, then $N_e = N$

– In all other cases, N_e is closer the number of the less numerous sex.

– Consider:

N_f	N_m	$\approx N_e$
1	99	4
5	95	19
50	50	100
90	10	36

(3) Population Size Fluctuates

- $N_e = \dfrac{1}{\frac{1}{t}\sum_{i=1}^{t}\frac{1}{N_i}}$ = harmonic mean population size through time.

- N_e is never greater (and often is much smaller) than the arithmetic average size: $N_e \leq \frac{1}{t}\sum N_i$.

(4) Variance in Fitness With Non-genetic Basis

- $N_e = \dfrac{4N-2}{2+V_n}$ where V_n = variance in offspring number.

- This N_e can be greater than N (e.g., if all individuals contribute equally), but generally is less than N.

(5) Overlapping Generations

- N_e generally less than N

– **Punch Line**: N_e is generally smaller than census size and can be *much* smaller.