Introduction to fitting compartment models using coalscent approaches.

#phylodynamics-jc week 3

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Week 3 goals

We'll be doing a whirlwind tour of the following three papers in order to paint a picture of the mathematics underlying phylodynamics methods.

- Phylodynamics of Infectious Disease Epidemics
- Complex Population Dynamics and the Coalescent Under Neutrality
- Inferring the Source of Transmission with Phylogenetic Data

Section 1

Volz 2009: Phylodynamics of Infectious Disease Epidemics

Takeaways

We present a formalism for unifying the inference of infected population sizes from genetic sequences and mathematical models of infectious disease in populations.

In practice, we are able to fit epidemiological models to a phylogeny of viral sequences and make inferences regarding the disease dynamics.

Methods

There are several practical questions that we seek to answer with these methods.

- If n individuals from a total infected population of $|I|$ are sampled at time T, how many lineages existed at time $t < T$.
- How many of the lineages at time t have surviving progeny at time T?

Coalescent model for SIR

Suppose that we're given a human population of size N, the SIR dynamics of this population are described by the series of differential equations

$$\frac{dS}{dt} = -\beta SI \tag{1}$$

$$\frac{dI}{dt} = \beta SI - \gamma I \tag{2}$$

$$\frac{dR}{dt} = \gamma I, \tag{3}$$

where S, I, R denote the fraction of the population which are susceptible, infected, and recovered respectively.

Probability of observing coalescence

Given a population of size N with k lineages, the probability that these lineages merge is well approximated by $\binom{k}{2} = \frac{k(k-1)}{2}$ if N is large relative to k. Therefore, given a coalescent event occurs between the infected individuals, the probability of observing this event in the n sampled lineages is given by

$$p_C = \binom{n}{2} / \binom{|I|}{2} = \frac{n(n-1)}{|I|\left(|I|-1\right)}.$$

TO-DO: FIGURE ON k lineages merging

Probability of sampled ancestors

If we define a function $A(t, T)$ which describes the fraction of the individuals at time t with sampled progeny at T. We'll use this definition alongside our early computation to find the probability of a transmission causing us to observe a coalescent event.

$$p_c(t, T) = \left(\frac{A(t, T)}{I(t)} \right)^2,$$

since the total number of lineages in a population with total size N is given by $A(t, T)N$ and the number of infected individuals is $I(t)N$. Therefore, we can compute the function $A(t, T)$ using the following ODE:

$$-\frac{dA}{dt} = -\beta SI \cdot \left(\frac{A(t, T)}{I(t)} \right)^2.$$

Distribution of coalescent events

Using this ancestor equations allows us to fit epidemic models to a fixed genealogy with no uncertainty. This can be extended to allow for uncertainty in branching times.

The ancestor function allows us to define the fraction of coalescent events which have occurred by time τ between times t and T as

$$F(\tau) = \frac{A(T,T) - A(\tau,T)}{A(T,T) - A(t,T)}.$$

This serves as a cumulative distribution function for the coalescent times. Differentiating this allows us to find the probability density function

$$f(\tau) = -\frac{dA}{dt}(\tau) \cdot \frac{1}{A(T,T) - A(t,T)}.$$

Fitting epidemic models to sequence data

Suppose we're given branching times $t_1, t_2, \ldots, t_{n-1}$ for a phylogeny of n sequences. Then, we can write a log-likelihood for our branching times as

$$\Lambda(t_1, \ldots, t_{n-1} \mid \theta) = \sum_{i=1}^{n-1} \log(f(\tau)) \tag{4}$$

$$= \sum_{i=1}^{n-1} \log\left(-\frac{dA}{dt}(t_i)\right) - (n-1)\log(A(T,T) - A(t,T)) \tag{5}$$

Section 2

Volz 2012: Complex Population Dynamics and the Coalescent Under Neutrality

Takeaways

A coalescent model is developed for a large class of populations such that the demographic history is described by a deterministic nonlinear dynamical system of arbitrary dimension. This class of demographic model differs from those typically used in population genetics. Birth and death rates are not fixed, and no assumptions are made regarding the fraction of the population sampled.

Approaching this from the perspective of a birth-death process. Useful for generating lineages.

As shown in Volz 2009, the rate of of coalescence for two extant lineages is:

$$\lambda_2(t) = \frac{2f(t)}{I(t)^2}$$

In the case of the simple SIR, this reduces to the familiar

$$\lambda_2(t) = \frac{2\beta S(t)}{I(t)}$$

Varying birthrate: Skyline estimates of effective population size will be biased for true population size

This is section “The effective number of infections”

Calculating the likelihood of a genealogy condition on f(s) and I(s)

Test

We can...

Test