#phylodynamics-jc week 3

Fitting compartment models using coalescent approaches.

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Week 3 goals

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

- Phylodynamics of Infectious Disease Epidemics

In future weeks, we'll expand upon on the methods discussed here using the following two papers.

- 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 individuals is given by

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

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:

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

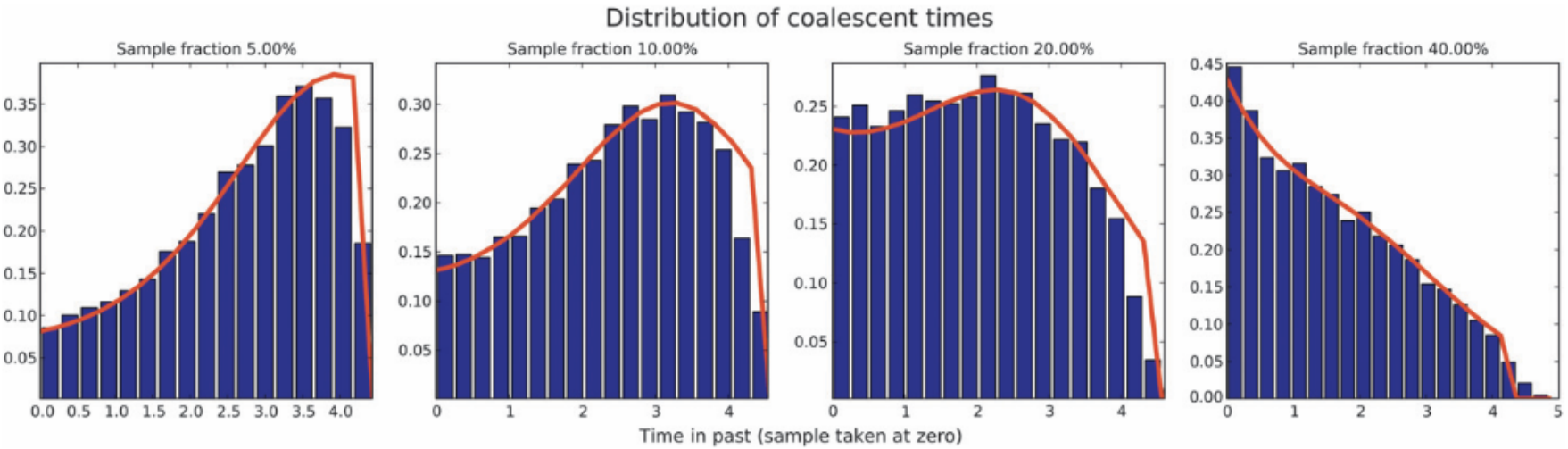
Distribution of coalescent events

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

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

This forms a cumulative distribution function of coalescent times. Differentiating gives the corresponding 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

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

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

Fitting epidemic models to sequence data

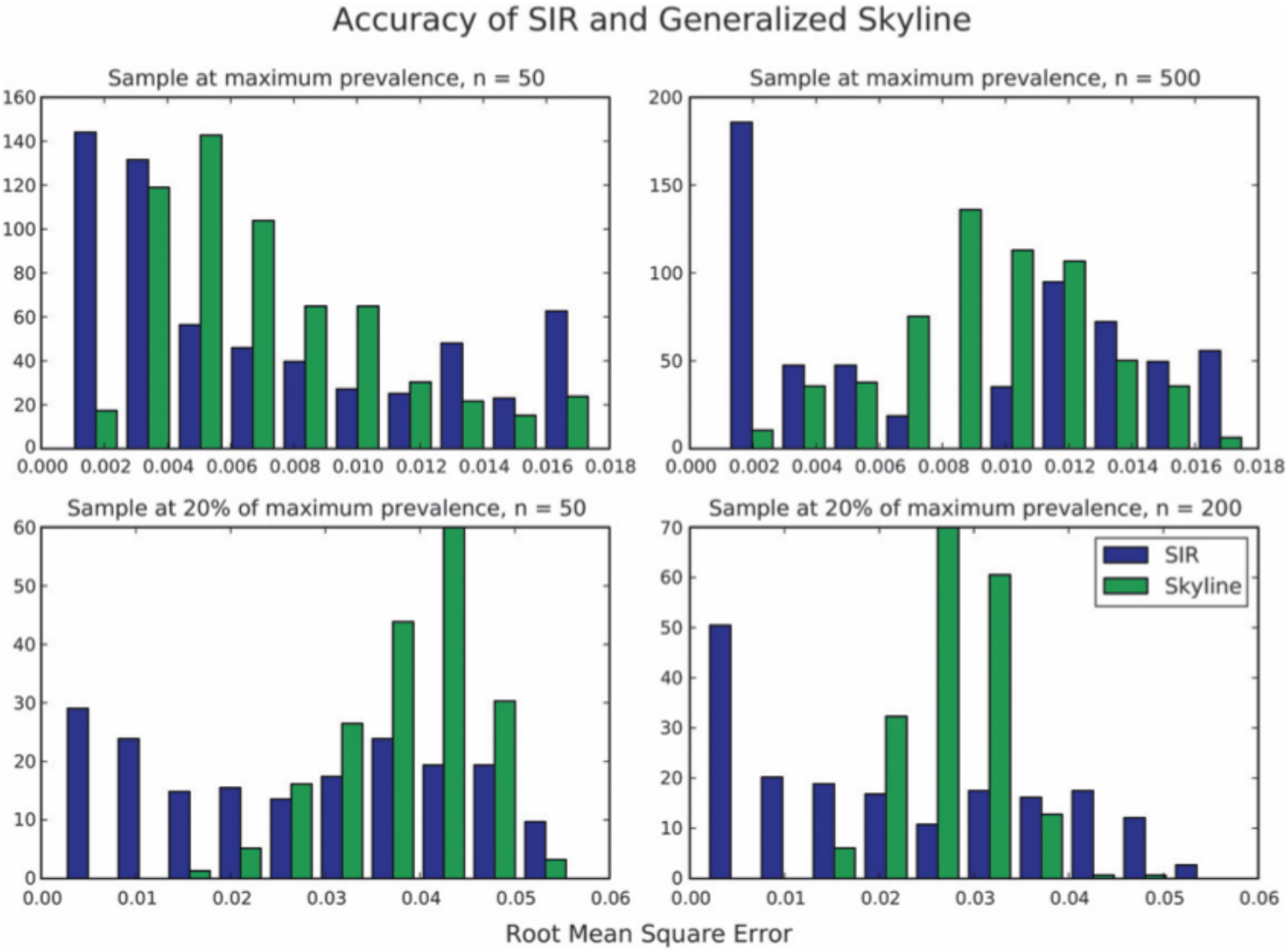


FIGURE 3.—Root mean square error of SIR and generalized skyline estimates of epidemic prevalence. Data are based on 300 simulated epidemics ($R_0 = 2$). RMSE is averaged over 100 time points.

Application: Fitting to HIV-1 sequences

Using the likelihood function defined above, the authors fit an SIR to a phylogeny of 55 HIV-1 sequences sampled in 1993. This involved using modified infection dynamics:

$$\frac{dS}{dt} = \mu - S^{\alpha}(\beta_1 I_1 + \beta_2 I_2) - \mu S \tag{6}$$

$$\frac{dI_1}{dt} = S^{\alpha}(\beta_1 + I_1 + \beta_2 I_2) - \gamma_1 I_1 - \mu I_1 \tag{7}$$

$$\frac{dI_2}{dt} = \gamma_1 I_1 - \gamma_2 I_2 - \mu I_2. \tag{8}$$

Here, $\beta., \gamma.$ are transmission rates and recovery rates respectively. A subscript of 1 refers to those individuals with an acute infection and subscript 2 refers to chronic infection.

Application: Fitting to HIV-1 sequences.

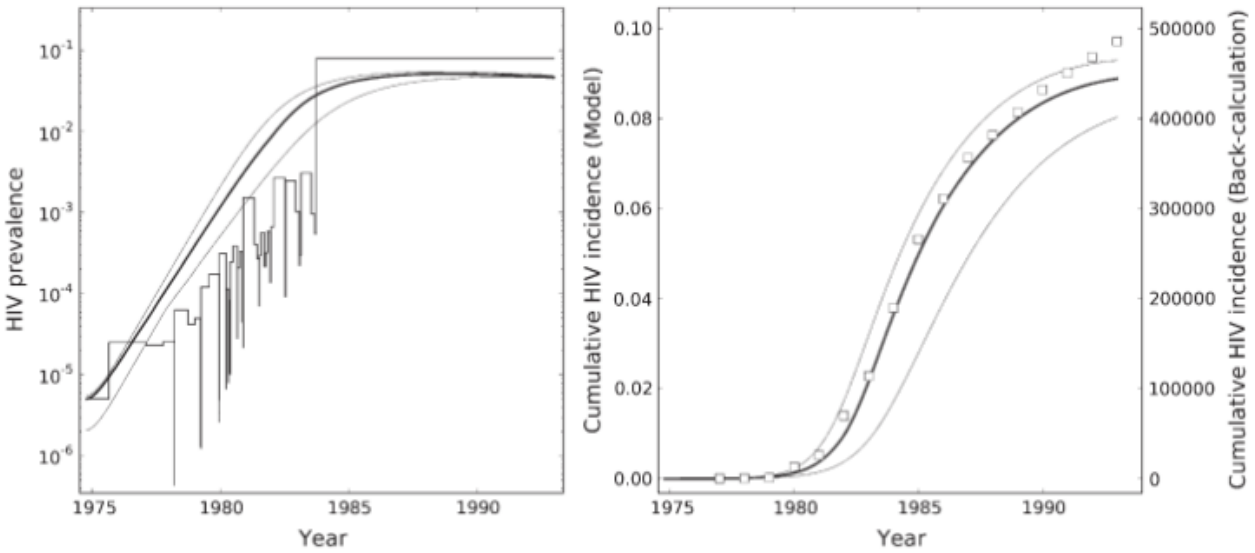


FIGURE 5.—Left: Estimated epidemic prevalence (logarithmic scale) of HIV among MSM in the United States. A solution to Equation 16 is compared to the skyline plot, rescaled such that minimum effective population size equals minimum prevalence. The thin lines show 95% confidence intervals. Right: Estimated cumulative incidence of HIV among MSM *vs.* time (years prior to 1993). A solution to Equation 16 is compared to estimates based on sero-surveillance data (HALL *et al.* 2008).

Figure 3: HIV prevalence and model fit.