NC STATE UNIVERSITY

Coalescent theory and the population genetics of molecular evolution

Molecular Epidemiology of Infectious Diseases

Lecture 5

February 9th, 2026

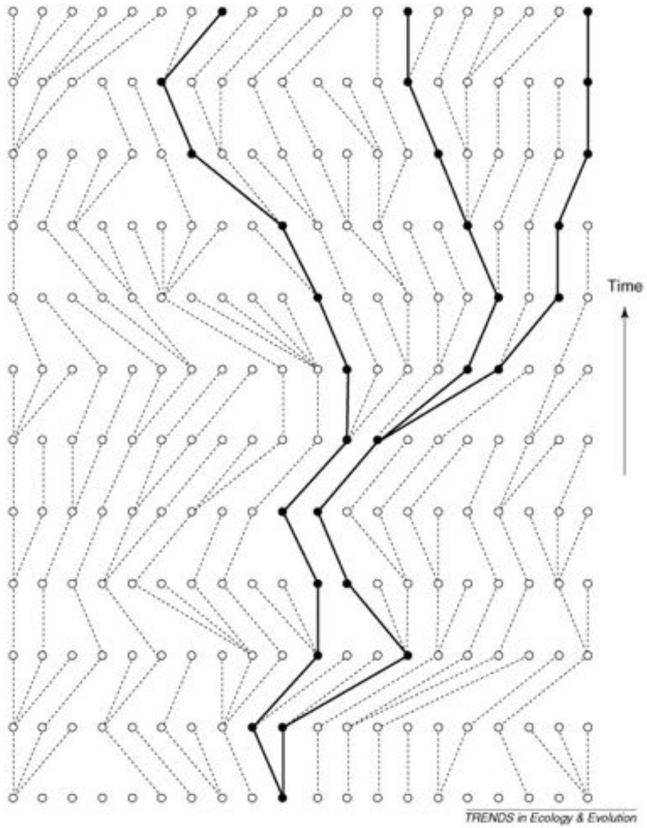
Coalescent models track the ancestry of sampled lineages backwards through time.

John Goddard, The Tree of Man’s Life (1649)

Basic coalescent theory

Coalescent theory describes the ancestral relationships (i.e. genealogy) of idealized individuals sampled from a larger population.

We envision these sampled lineages are embedded within the full ancestral history of the population.



Kuhner *et al.* (2008)

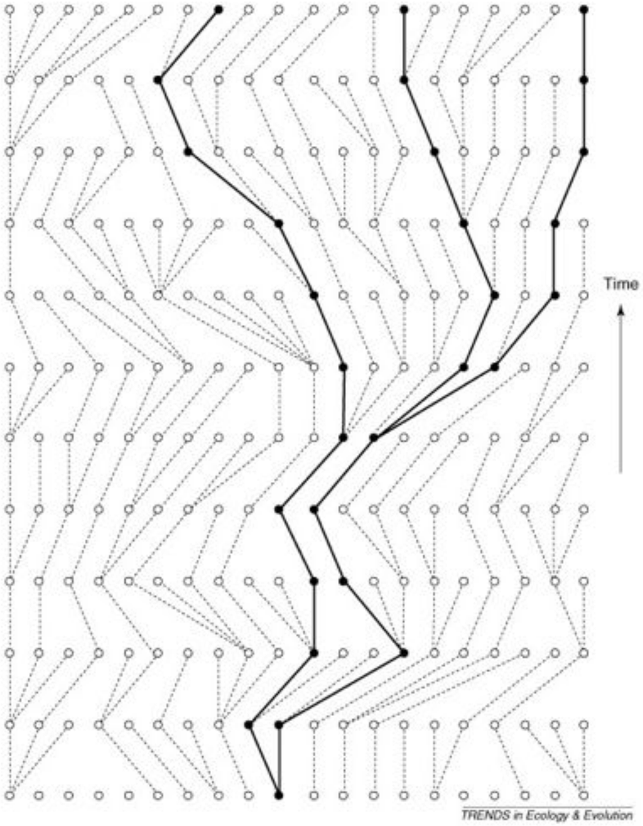
Wright-Fisher assumptions

Coalescent theory is largely based on simple demographic models like the Wright-Fisher model

Constant population size of *N* haploid individuals

Discrete, non-overlapping generations

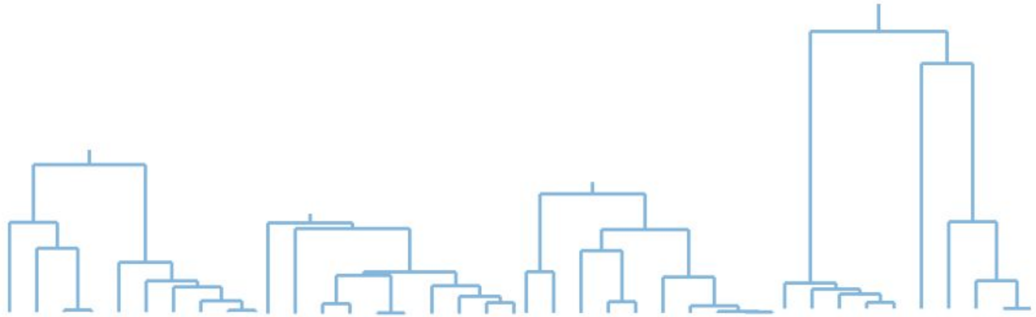
Reproduction is a stochastic process such that individuals leave a random number of offspring.



Kuhner *et al.* (2008)

Basic coalescent theory

Because reproduction is random, the ancestral relationships among individuals is also viewed as a stochastic process that generates random coalescent trees.



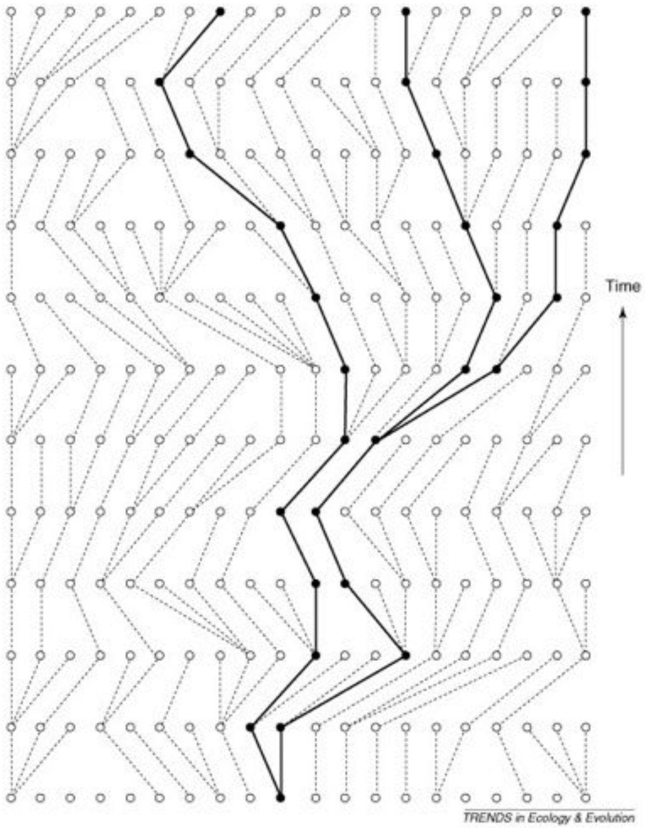
However, we can use these random trees to compute the expected value of other statistical properties, such as the time between coalescent events.

Rosenberg & Nordborg (2002)

Basic coalescent theory

The probability of two lineages coalescing per generation is:

$$p_{coal} = \frac{1}{N}$$



Kuhner *et al.* (2008)

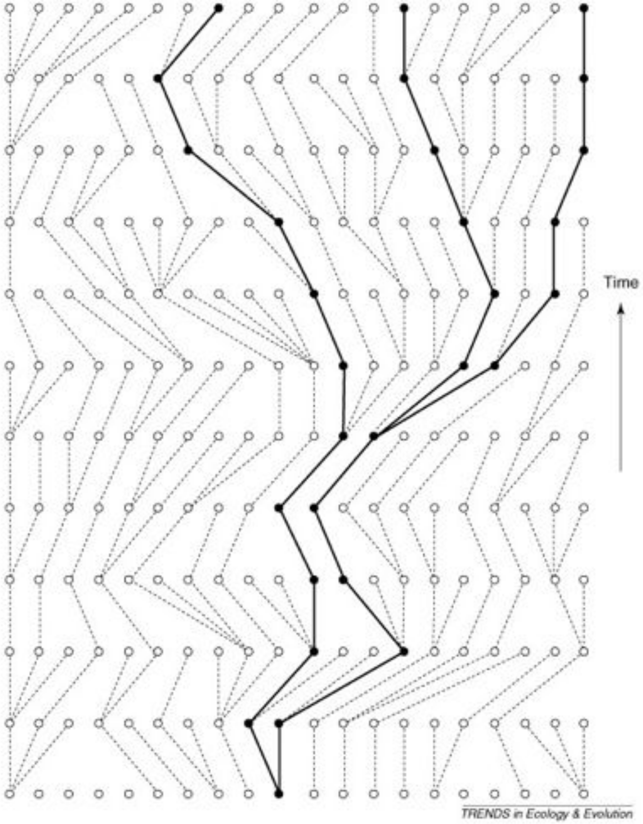
Basic coalescent theory

The probability of two lineages coalescing per generation is:

$$p_{coal} = \frac{1}{N}$$

The probability of coalescing after *n* generations is:

$$Pr(X = n) = (1 - p_{coal})^{n-1} p_{coal}$$



Kuhner *et al.* (2008)

Basic coalescent theory

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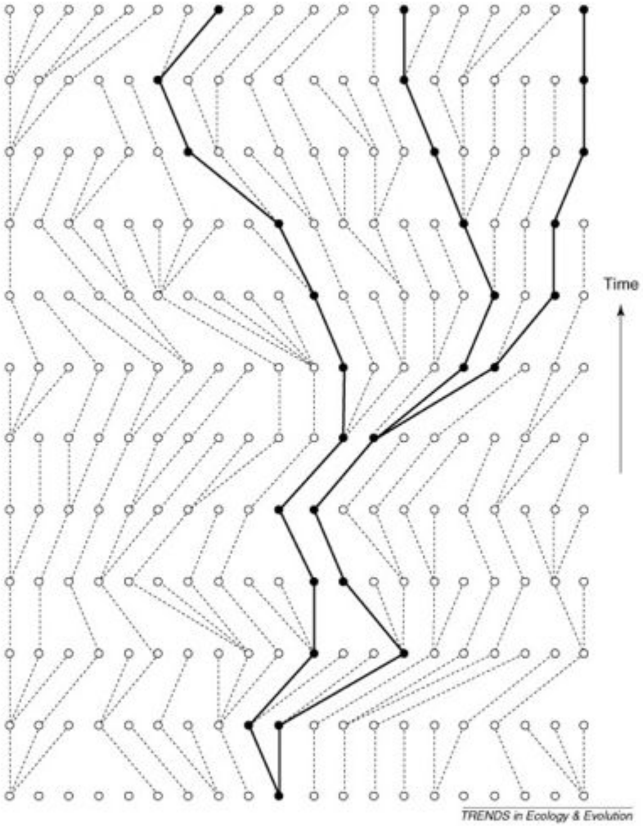
The probability of coalescing after *n* generations is:

$$Pr(X = n) = (1 - p_{coal})^{n-1} p_{coal}$$

In continuous time:

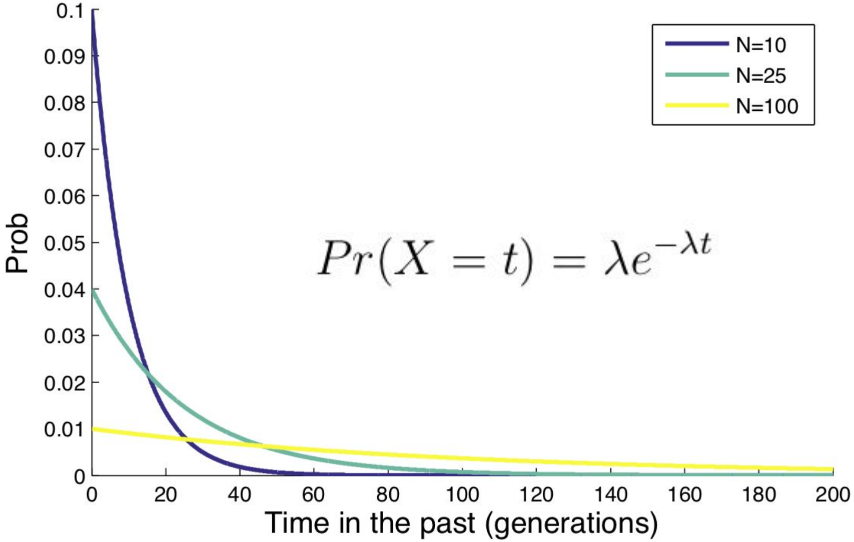
$$Pr(X = t) = \lambda e^{-\lambda t} \qquad \lambda = p_{coal} = \frac{1}{N}$$



Kuhner *et al.* (2008)

Basic coalescent theory

The waiting time for a pair of lineages to coalesce is exponentially distributed.



$$Pr(X = t) = \lambda e^{-\lambda t}$$

A slightly more general coalescent model

The coalescent rate increases with the the amount of reproductive variance σ^2 in the population:

$$\lambda_{coal} = \frac{\sigma^2}{N}$$

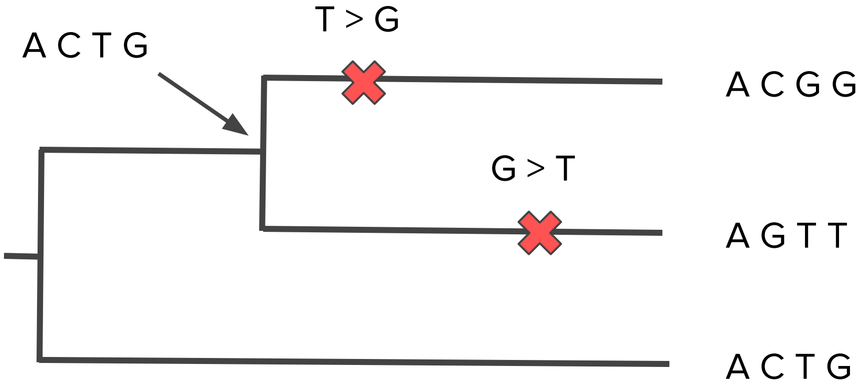
We can define an **effective population size N$_e$**:

$$N_e = \frac{N}{\sigma^2}$$

More generally then, the coalescent rate is:

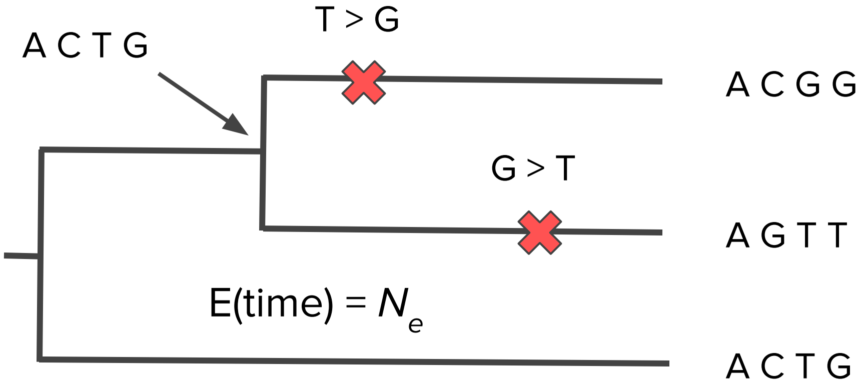
$$\lambda_{coal} = \frac{1}{N_e}$$

Coalescent trees with mutations



Most coalescent models assume mutations are neutral such that mutations occur independently of the coalescent process.

Coalescent trees and genetic diversity



Genetic diversity depends directly on both the mutation rate µ and the coalescent rate. The expected average pairwise diversity is: $\theta = 2N_e\mu$

Now with more than two lineages

With *k* lineages present, the coalescent rate becomes:

$$\lambda_{coal} = \frac{\binom{k}{2}}{N_e}$$

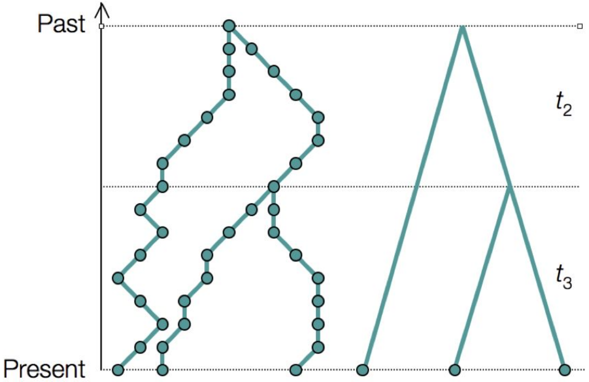
The binomial coefficient gives the total number of lineage pairs that could have coalesced:

$$\binom{k}{2} = \frac{k(k-1)}{2}$$

The coalescent likelihood

For a tree with *n* samples and *n-1* coalescent events we can compute the likelihood of the tree as:

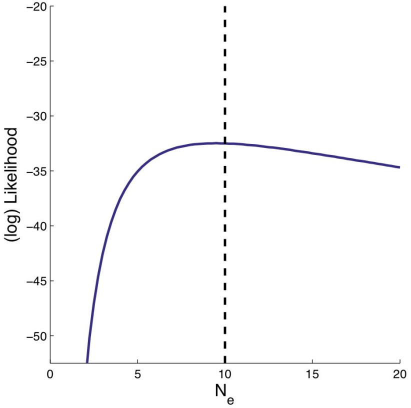
$$L(T|N_e) = \frac{1}{N_e^{(n-1)}} \prod_{k=2}^{n} \exp\Big(-\frac{\binom{k}{2}}{N_e} t_k\Big)$$

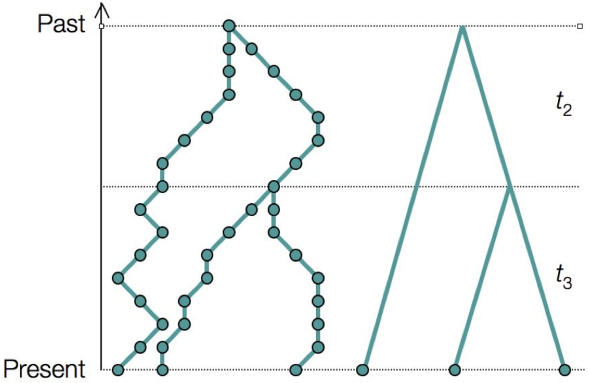


Coalescent-based inference

We can therefore infer demographic parameters like N_e from a known phylogeny.

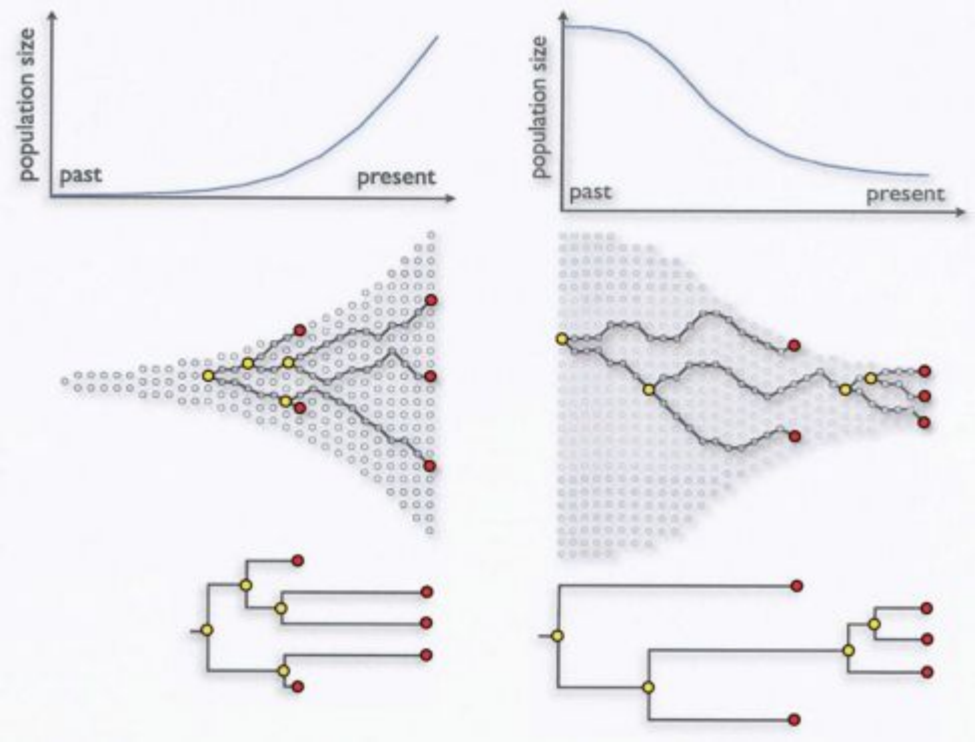
$$L(T|N_e) = \frac{1}{N_e^{(n-1)}} \prod_{k=2}^{n} \exp\left(- \frac{\binom{k}{2}}{N_e} t_k \right)$$





We can therefore use coalescent models to infer the demographic history of a population.

The signal of population size change



Modeling population size changes

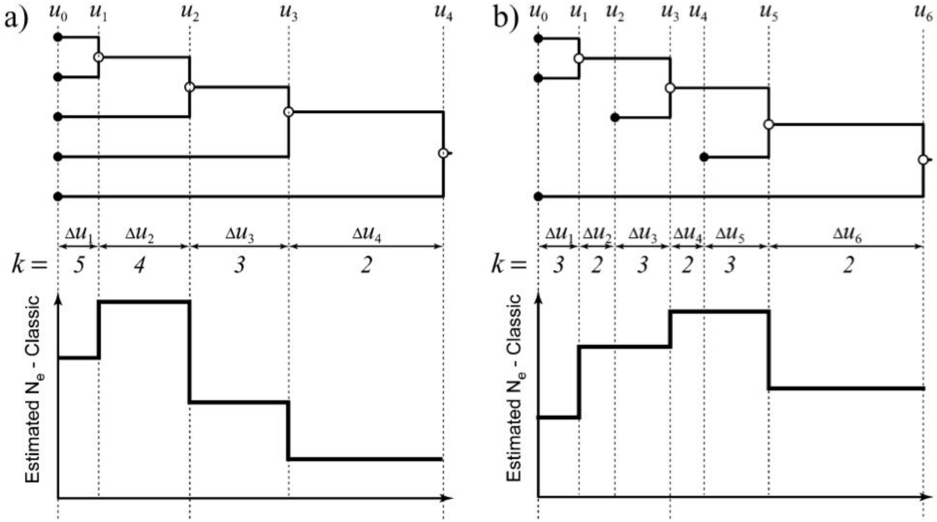
Parametric models assume population sizes change according to some population dynamic model (e.g. exponential growth)

Nonparametric methods allow population sizes to change over time in a flexible manner.

- Bayesian Skyline (Drummond *et al.*, 2005)
- Bayesian Skygrid (Minin *et al.*, 2008)

Nonparametric approaches

Generally assume population sizes change over time in a piecewise-constant manner.



a)
u_0 u_1 u_2 u_3 u_4
Δu_1 Δu_2 Δu_3 Δu_4
$k =$ 5 4 3 2
Estimated N_e - Classic
b)
u_0 u_1 u_2 u_3 u_4 u_5 u_6
Δu_1 Δu_2 Δu_3 Δu_4 Δu_5 Δu_6
$k =$ 3 2 3 2 3 2
Estimated N_e - Classic

Drummond *et al.* (MBE, 2005)

Bayesian skyline

Assumes that the population size can only change at a fixed number of change points.

Uses Bayesian MCMC to integrate (average) over all possible change point positions in addition to N_e within each interval/epoch.

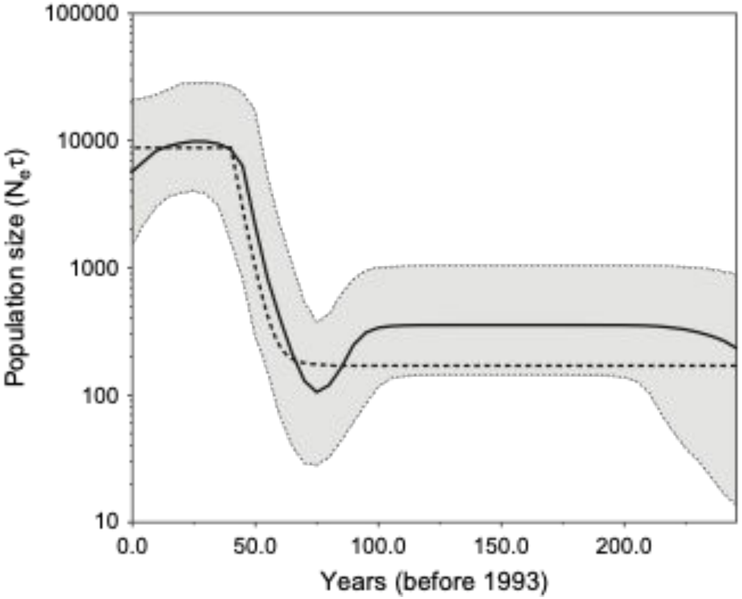
Intervals can contain multiple coalescent events allowing for better estimates of N_e

Produces a smoothed estimate of N_e through time with credible intervals.

Drummond *et al.* (MBE, 2005)

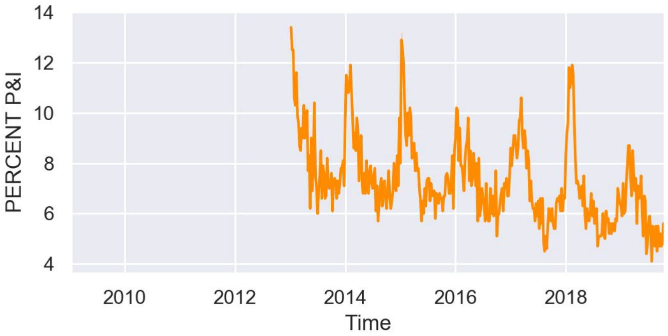
Bayesian skyline plots

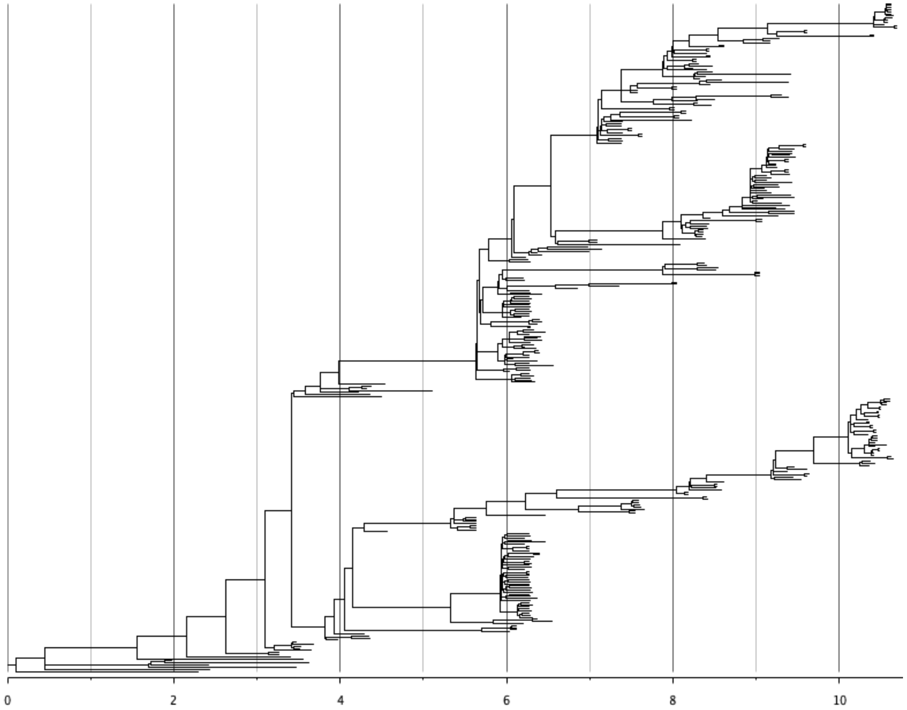
Bayesian skyline estimates of for Hepatitis C virus in Egypt



Drummond *et al.* (2005)

Bayesian skyline plots for the flu in NC





Limitations of simple coalescent models

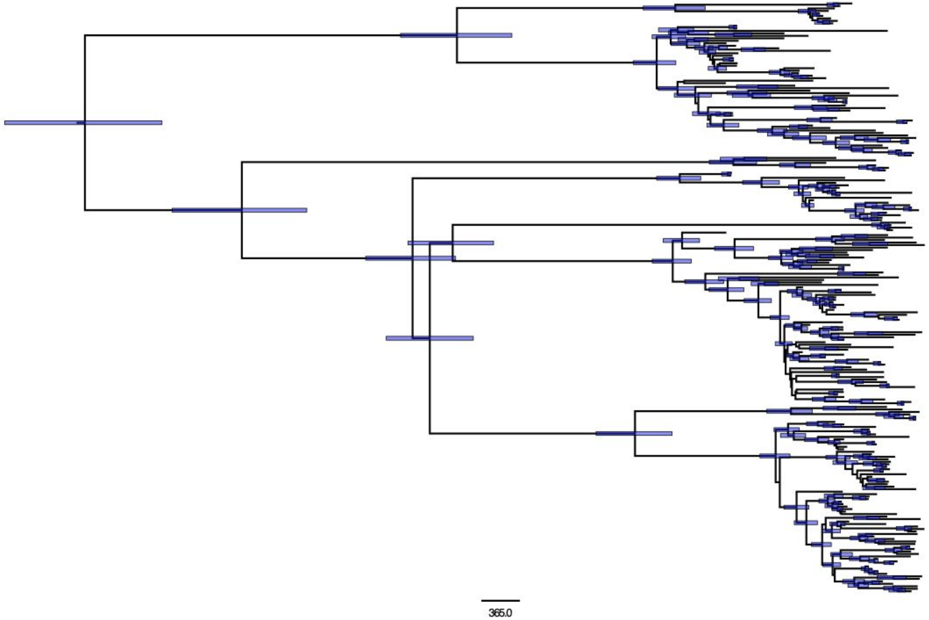
Other forces beyond population dynamics influence coalescent rates and can strongly shape phylogenies:

- Reproductive variance - we infer N_e instead of absolute N
- Selection is difficult to model because reproduction is non-random
- Population/spatial structure

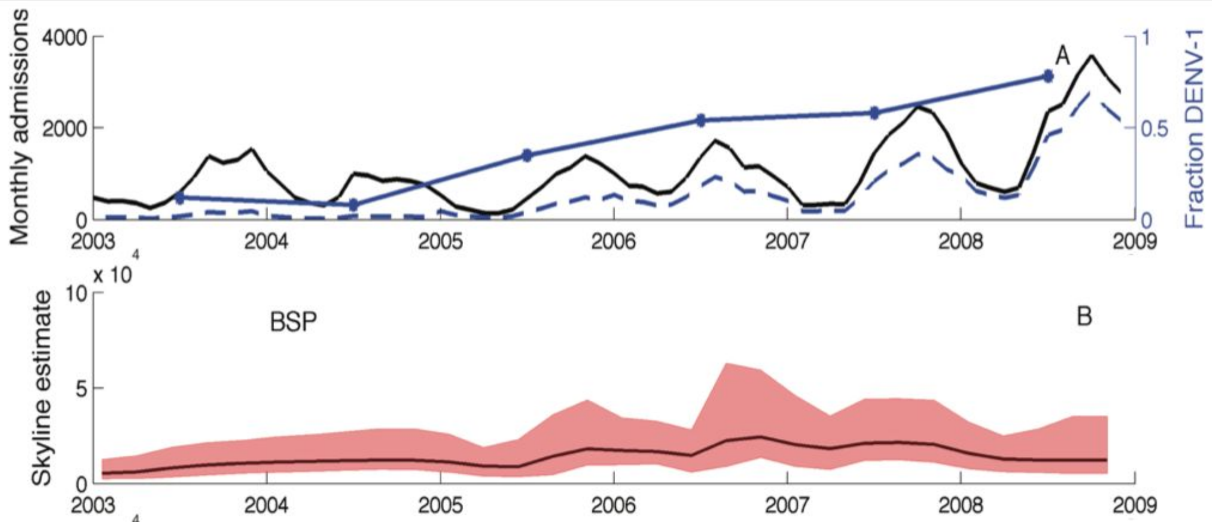
How do we account for population structure?

Dengue in southern Vietnam

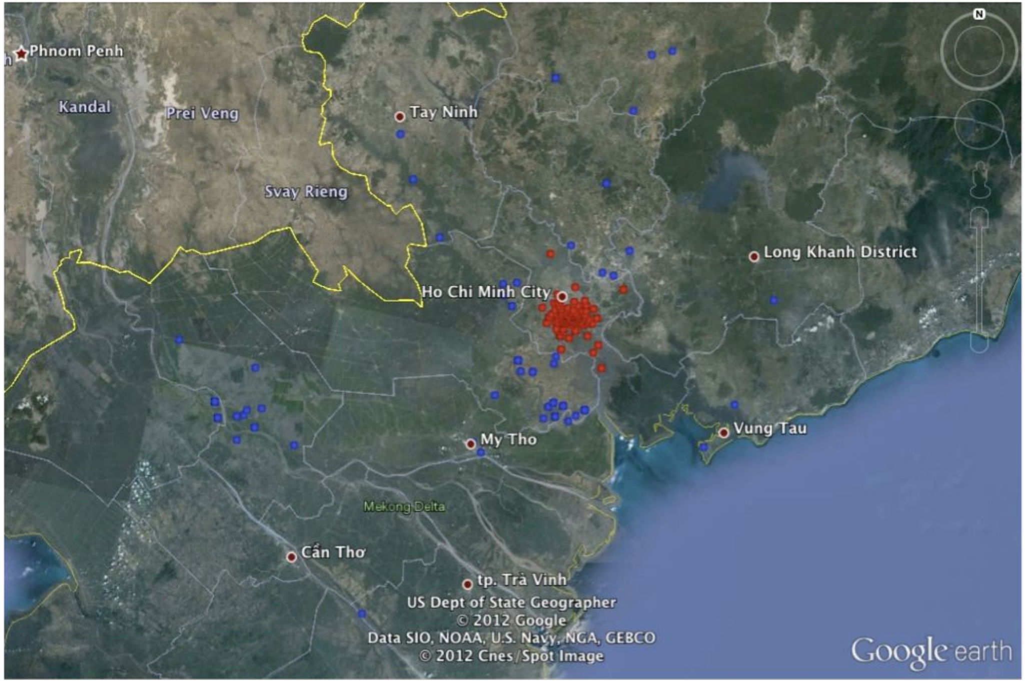
Guangxi
Hà Nội
Hainan
Laos
Vientiane
Thailand
Paracel Isla
Vietnam
Bangkok
Cambodia
Phnom Penh
Hospital for Tropical Diseases
Ho Chi Minh City
Ko Samui
Gulf of Thailand
Pulau Pinang
© 2013 Tele Atlas
© 2013 Mapabc.com
US Dept of State Geographer
© 2013 Google



Bayesian skyline estimates



Spatial structure



The problem with population structure

Standard coalescent models assume that all lineages in the tree are **exchangeable**.

Exchangeability here means that any lineage is equally likely to coalesce with any other lineage in the tree.

Many forms of population structure violate this key assumption.

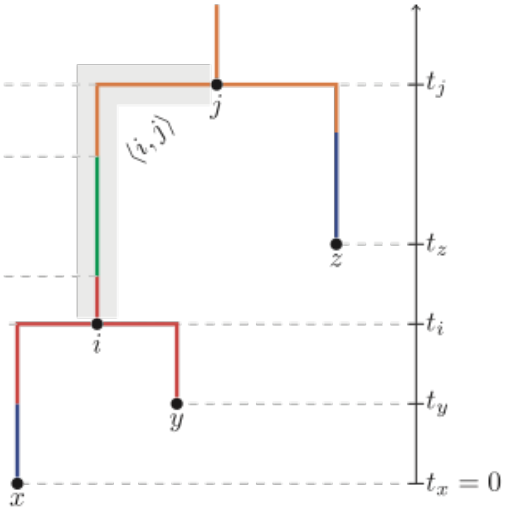
The structured coalescent

Relaxes the exchangeability assumption by letting lineages move between different populations.

The pairwise rate of coalescent between two lineages *i* and *j* will depend on their population states *k* and *l*:

$$\lambda_{ij} = \begin{cases} \frac{1}{N_e^k} & \text{if } k = l \\ 0 & \text{if } k \neq l. \end{cases}$$

Lineages sampled in different populations therefore need to migrate back to the same population before they can coalesce.



Beerli and Felsenstein (2001)

The structured coalescent

Each lineage pair is allowed to coalesce at a different rate λ_{ij} based on the locations of lineages *i* and *j*.

However, we can still write down the likelihood of a tree given the rates λ_{ij}

$$L(T|\theta) = \prod_{k=2}^{n} \lambda_{ij} \exp\left[-\sum_{i}^{k} \sum_{j>i}^{k} \lambda_{ij} t_k \right]$$

However, inference is much more difficult because we must also infer the location of each lineage through time.

The Migrate-n model

A structured coalescent model with migration between n subpopulations or demes

Models is parameterized in terms of a migration rate matrix M and a vector of effective population sizes θ:

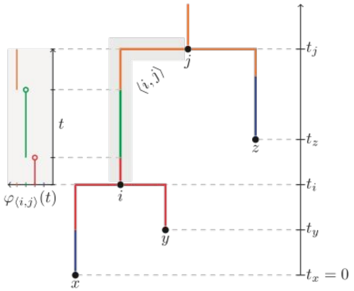
$$M = \begin{bmatrix} 0 & m_{1,2} & \cdots & m_{1,n} \\ m_{2,1} & 0 & \cdots & m_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ m_{n,1} & m_{n,2} & \cdots & 0 \end{bmatrix} \qquad \Theta = \begin{bmatrix} N_e^1 \\ N_e^2 \\ \vdots \\ N_e^n \end{bmatrix}$$

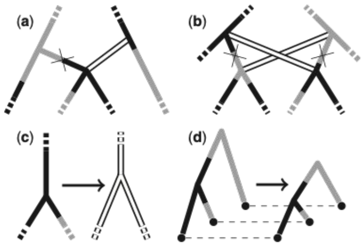
Model allows for likelihood-based inference of M and θ. BUT we need to use MCMC to sample full **migration histories** along each lineage

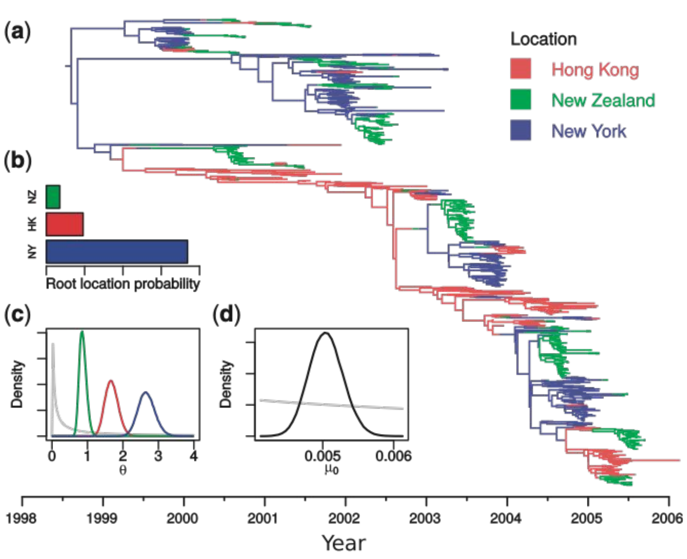
Beerli and Felsenstein (2001)

Migrate-N and MultiTypeTree

MCMC implementations of the structured coalescent like MIGRATE and MultiTypeTree (Vaughan *et al.*, 2014) sample migration histories on trees







Phylogeography with the SC

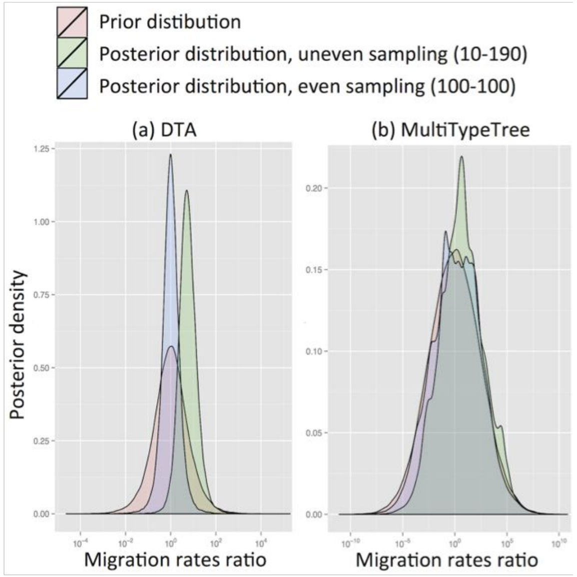
The structured coalescent (SC) has become an attractive alternative to discrete-trait analysis (DTA) for phylogeography

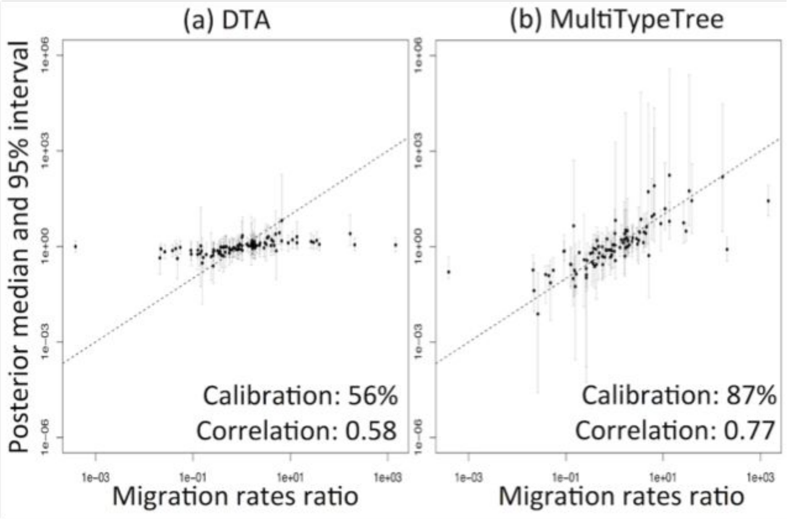
DTA treats sampling locations as informative about the migration process whereas the SC conditions on sampling locations.

DTA can therefore be highly biased by disproportionate sampling while the SC is more robust to uneven sampling.

DTA vs. the SC

Uneven sampling strongly biases DTA but not the structured coalescent.

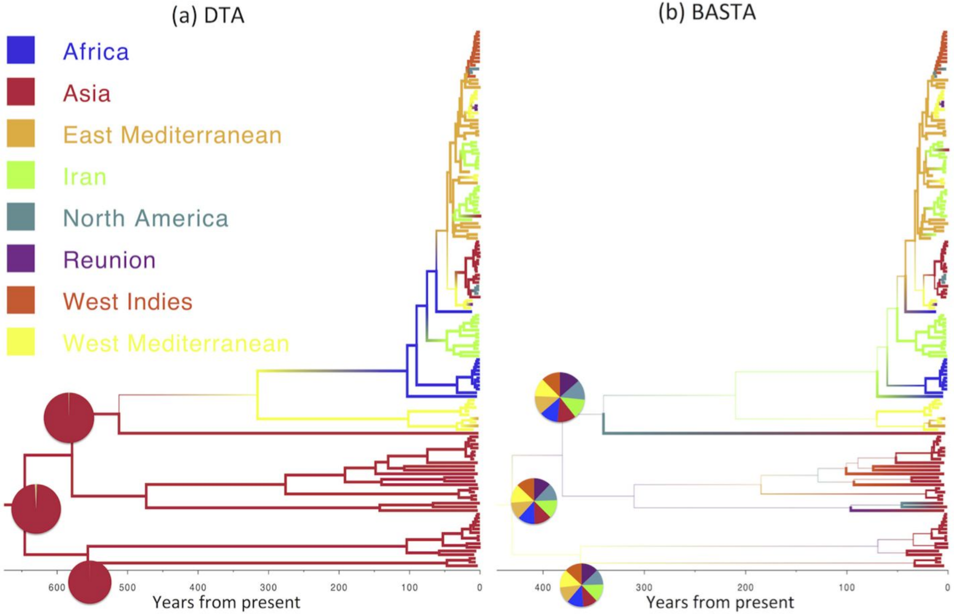




De Maio *et al.* (PLoS Genetics, 2015)

DTA vs. the SC

DTA is also over confident in assigning ancestral state probabilities.



Tomato yellow leaf curl virus

De Maio *et al.* (PLoS Genetics, 2015)

DTA vs. the SC

Structured coalescent models improve statistical performance but are fundamentally limited by the need to sample migration histories on trees.

This does not allow for very efficient MCMC sampling due to strong correlations between the migration histories and model parameters. Generally limited to about 5 or 6 states and trees with < 1000 tips.

But what if there was a way to efficiently “integrate over” migration histories and therefore average over all possible paths a lineage could have taken?

The Volz (2012) Structured Coalescent

Rather than sampling migration histories, we can probabilistically track the movement of each lineage back through time.

We can then write pairwise coalescent rates in terms of lineage state probabilities p_{ik}. Assuming lineage pairs can only coalesce if they're in the same population:

$$\lambda_{ij} = \sum_{k}^{m} \frac{p_{ik} p_{jk}}{N_k}$$

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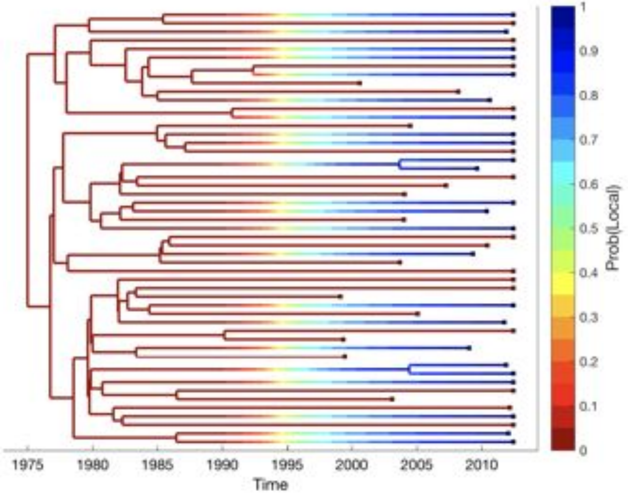
The theory in Volz (2012) is actually more general and allows birth/coalescent events to occur between populations at rate f_{kl}. But we'll return to this later.

$$\lambda_{ij} = \sum_{k}^{m} \sum_{l}^{m} \frac{f_{kl}}{y_k y_l} \left(p_{ik} p_{jl} + p_{il} p_{jk} \right)$$

The Volz (2012) Structured Coalescent

Lineage state probabilities p_{ik} can then be tracked backwards in time using a system of master equations (ODEs) based on the transition rates g_{kl}:



$$\frac{d}{dt}p_{ik} = \sum_{l}^{m} \left(p_{il}g_{kl} - p_{ik}g_{lk}\right)$$

Volz (Genetics, 2012)

The Volz (2012) Structured Coalescent

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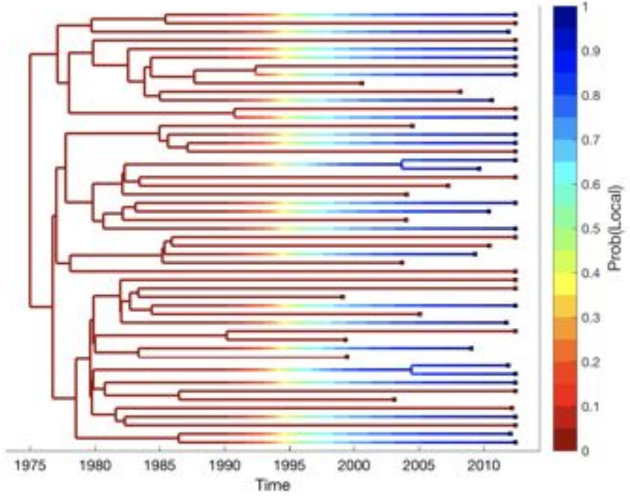


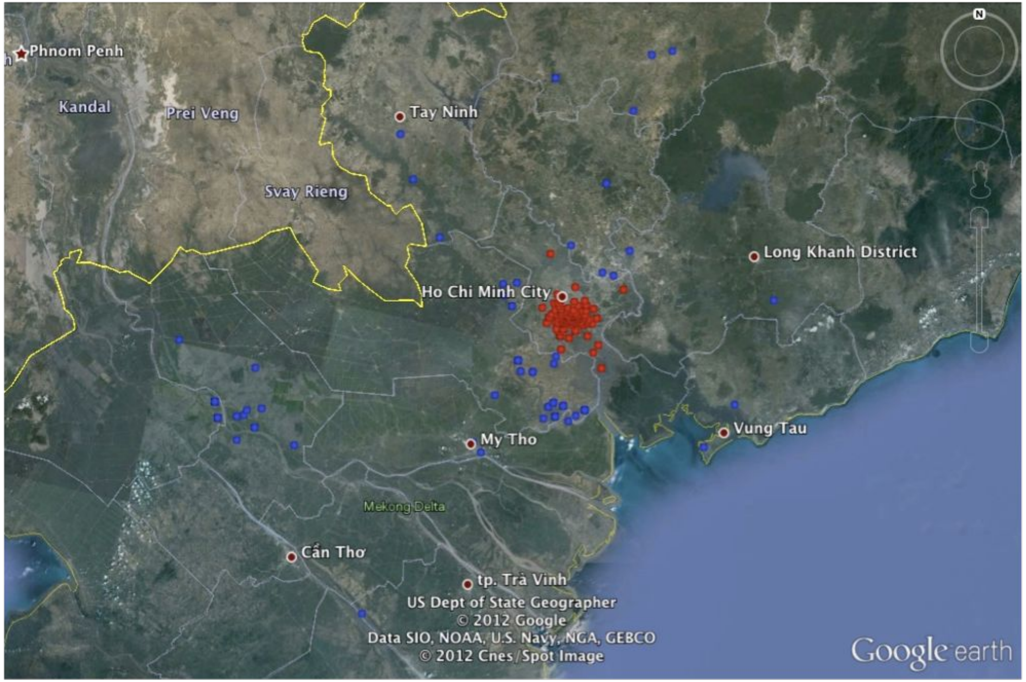
$$\frac{d}{dt}p_{ik} = \sum_{l}^{m} \left(p_{il}g_{kl} - p_{ik}g_{lk}\right)$$

Flow in from other pops

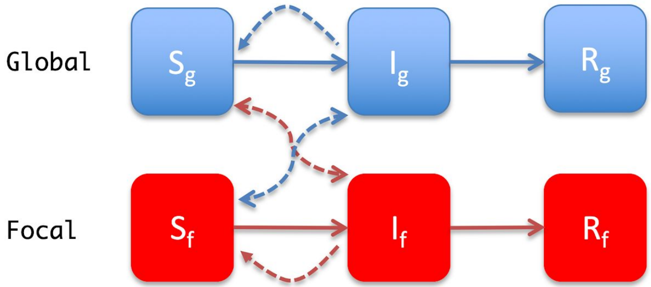
Flow out to other pops

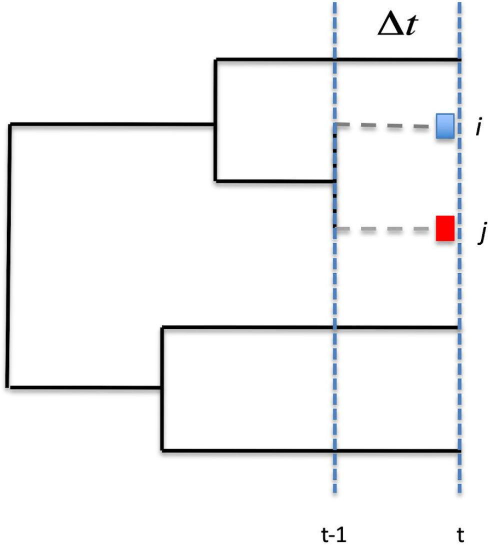
Volz (Genetics, 2012)

Spatial structure



Spatial SIR model

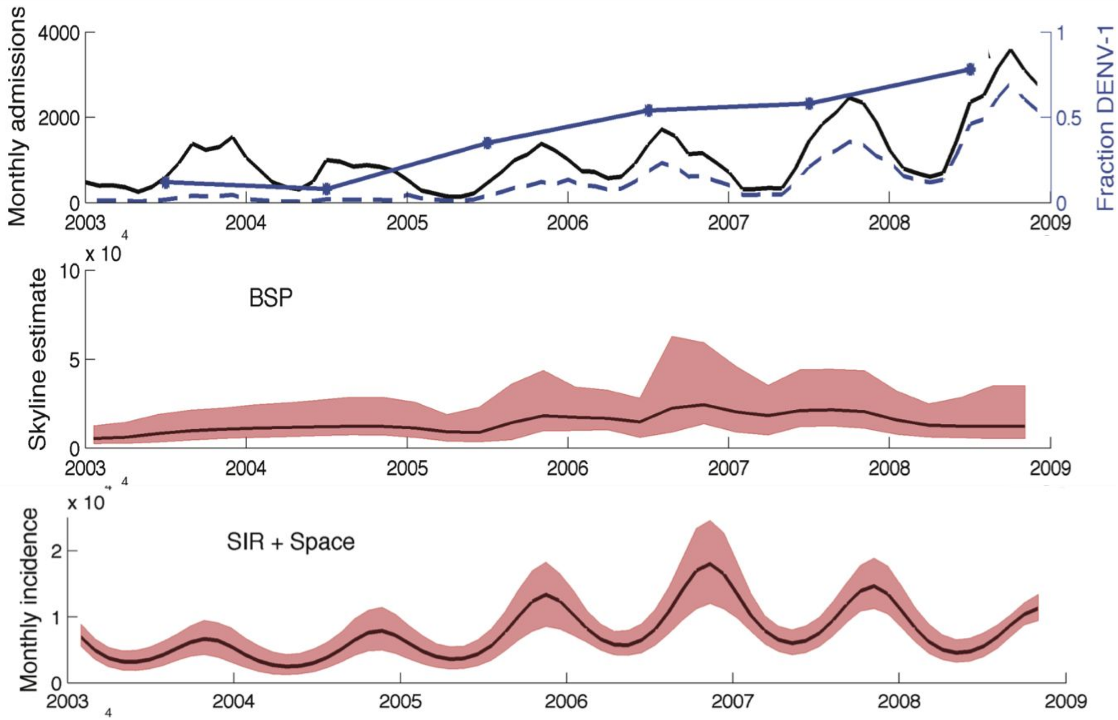




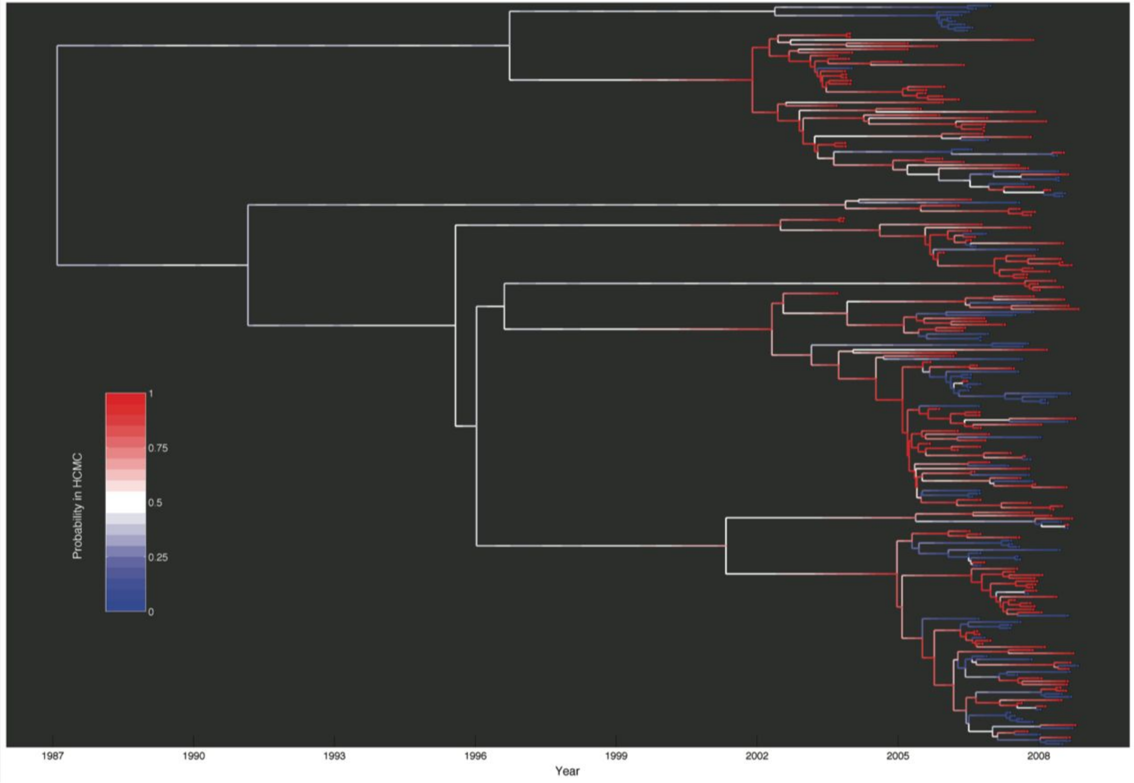
Structured coalescent model:

$$\lambda_{ij} = \sum_{k}^{m} \sum_{l}^{m} \frac{\beta_{kl}\frac{S_l}{N_l}I_k}{I_k I_l}\left(p_{ik}p_{jl} + p_{il}p_{jk}\right)$$

Estimates accounting for spatial structure



Movement of lineages



Conclusions

Coalescent models relate phylogenies of sampled lineages back to the larger demographic history of a population.

Coalescent methods can be used to reconstruct past population dynamics but other forces, especially population structure, also shape trees.

Structured coalescent models generalize coalescent models and are very useful for modeling different forms of population structure.

SC models improve upon earlier discrete-trait phylogeographic methods but are less computationally efficient. Newer approaches like MASCOT that approximate lineage state probabilities offer a promising alternative.

Bonus lab: MASCOT

The MASCOT package for BEAST 2 implements a structured coalescent model that tracks lineage states probabilistically as in Volz (2012).

Uses an improved approximation to track lineage state probabilities

Allows for inference of pop sizes, migration rates and ancestral states

Can also use GLMs to predict migration rates based on explanatory variables

Müller et al. (Bioinformatics, 2017)