# Notes

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# Chapter 1

# Introduction

In epidemiology, it is often desired to be able to reconstruct the history of a pathogen population and it's structure. The problem of reconstructing the hisotry of a pathogen population can be tackles using phylodynamics. Phylodynamics utilises genomic data to assemble phylogenies, which are then used to infer the population size history. This is possible by viewing a phylogeny as a realisation of a coalescent process, wit appropriately rescaled time. This claim can be justified by viewing the coalescent as a Moran model, run backwards in time with the time rate equal to the population size [1].
Within this report we will first introduce the coalescent process for phylodynamic inference, review it's inhomogenous generalisation, and finally introduce the main result of this work, a new model capable of doing local phylodynamic inference, i.e. on a subset of the whole population capable of detecting and modelling clonal expansions.
Clonal expansions are a process in which a particular subsest of a given bacterial strain undergoes explosive population growth that can be traced back to a particular individual [2]. The presence of clonal expansions in bacterial populations have been of long-standing interest and is implicated in epidemic processes, were an outbreak can be traced to a single ancestor [2, 3, 4, 5]. This often happens when a particular strain or individual obtains a variant of a particular gene that confers evolutionary advantange, for example, antibiotic resistance [6, 7, 5].
The presence of clonal expansions leaves an imprint in the overall population structure of a given bacterial strain, the particular topology associated with this often being referred to as star-like [2, 3]. The problem of detecting hidden population structure corresponding to clonal expansions has become a problem of interest in epidemiology and outbreak surveillance [8].
While methods to detect inhomogeneities in the population structure and size have been of interest since the early days of genetic sequencing [2, 3], the interest in the problem increased with whole genome sequencing becoming more accessible and affordable [6, 9, 10].

Despite the problems of inferring population size from a genealogy and detecting heterogeneities in the population size of the entire population being intrinsically tied, all but one method [8], to our knowledge, rely either on manual detection or indirect detection. We aim to propose a simulation for the formation of clonal expansions in genealogy using the structured coalescent process, and devise a fully bayesian method for joint estimation and detection of relative population size and clonal expansions.

# Chapter 2

# Methods

## 2.1 Coalescent Preliminaries

We shall begin with an overview of the standard Kingman's Coalescent process[11]. This process is often used to characterise evolutionary histories of populations [12, 13, 14]. The coalescent is a CTMC defined on the set $\{1...n\}$, parametrised via the coalescent rate, in our case $1/Neg(t)$, where $g$ is a scale parameter and $Neg(t)$ the effective population size at time $t$ [12, 13]. Define $\alpha = Neg$.
The transition rates of the rescaled (phylogenetic) coalescent process are given by

$$\lambda(j, j-1) = \binom{j}{2} \cdot \frac{1}{\alpha(t)}$$

The waiting times in the homogenous case are exponentially distributed

$$P[W_j \leq s] = 1 - \exp\left(-s\frac{\binom{j}{2}}{\alpha(t)}\right)$$

Furthermore, the waiting times for individual coalescent events, conditioned on being less than the time between two consecutive sampling events $\Delta t$ are distributed as follows

$$P[W_j \leq s \mid W_j \leq \Delta t] = \frac{P[W_j \leq s]}{P[W_j \leq \Delta t]} \quad \forall s \leq \Delta t \tag{2.1}$$

In the case of time-inhomogenous effective population size, the waiting times can be derived as follows: For an inhomogenous CTMC, let $E_j(t)$ be the total exit rate from state $j$ at time $t$. By the markov property individual exit events from a given state only depend on the state and given time, i.e. they form a

time-inhomogenous poisson process. As such the probability of no events in an interval $[t, t+s] \quad s \in \mathbb{R}^+$ is

$$\exp\left(-\int_t^{t+s} E_j(\tau)d\tau\right) = \exp\left(-\int_0^s E_j(t+\tau)d\tau\right) \tag{2.2}$$

The waiting times are defined as

$$W_j(t) = \inf\{s : X(t+s) \neq j \mid X(t) = j\} \tag{2.3}$$

As such

$$W_j(t) > s \Rightarrow \forall \tau \in [t, t+s] \quad X(\tau) = j \tag{2.4}$$

Furthermore the above relation holds iff no exit event have occured in the time interval $[t, t+s]$. As such:

$$P[W_j(t) > s] = P[\text{no exit events in } [t, t+s]] = \exp\left(-\int_0^s E_j(t+\tau)d\tau\right)$$

$$P[W_j(t) < s] = 1 - \exp\left(-\int_0^s E_j(t+\tau)d\tau\right)$$

In the case of phylodynamic coalescent this becomes

$$P[W_j(t) \leq s] = 1 - \exp\left(-\int_0^s \frac{\binom{j}{2}}{\alpha(t+\tau)}d\tau\right) \tag{2.5}$$

Note, the waiting times are still memoryless:

$$P\left[W_j(t) > s+u \mid W_j(t) > s\right] = P\left[W_j(t) > s+u \mid X(s) = j\right] \tag{2.6}$$

By markov property

$$P\left[W_j(t) > s+u \mid X(s) = j\right] = P\left[W_j(t+s) > u\right] \tag{2.7}$$

## 2.2 Inhomogenous Coalescent

### 2.2.1 Exponential Growth

## 2.3 Coalescent with Local Population Structure

# Chapter 3

# Results

## 3.1 Implementation Notes

## 3.2 Exponential Growth

### 3.2.1 Phylogeny Simulation

### 3.2.2 MCMC inference

## 3.3 Coalescent with Local Population Structure

### 3.3.1 Phylogeny Simulation

### 3.3.2 MCMC inference

# Chapter 4

# Discussion

# Chapter 5

# Bibliography

# Bibliography


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