Population Genetics using Trees

Peter Beerli
Genome Sciences
University of Washington
Seattle WA
Outline

1. **Introduction to the basic coalescent**
   - Population models
   - The coalescent
   - Likelihood estimation of parameters of interest
   - Why do we need Markov chain Monte Carlo

2. **Extensions and examples**
Population genetics can help us to find answers

- the PCR revolution allows us to generate lots of data from many individuals and many loci
- We are still interested in questions like
  - Where are we or other species coming from?
  - How big are populations?
  - Are these populations species?
  - What is the recombination rate in species x?
Population genetics in the age of genomics

Why do we need theoretical population genetics when we can have the complete sequences of our favorite organism?
Basics: Wright-Fisher population model

All individuals release many gametes and new individuals for the next generation are formed randomly from these.
Basics: Wright-Fisher population model

All individuals release many gametes and new individuals for the next generation are formed randomly from these.
Basics: Wright-Fisher population model

All individuals release many gametes and new individuals for the next generation are formed randomly from these.
Basics: Wright-Fisher population model

All individuals release many gametes and new individuals for the next generation are formed randomly from these.
All individuals release many gametes and new individuals for the next generation are formed randomly from these.
Basics: Wright-Fisher population model

All individuals release many gametes and new individuals for the next generation are formed randomly from these.
Wright-Fisher population model

- Population size $N$ is constant through time.
- Each individual gets replaced every generation.
- Next generation is drawn randomly from a large gamete pool.
- Only genetic drift is manipulating the allele frequencies.
Sewall Wright showed that the probability that 2 gene copies come from the same gene copy in the preceding generation is

$$\text{Prob (two genes share a parent)} = \frac{1}{2N}$$
In every generation, there is a chance of \(1/2N\) to coalesce. Following the sampled lineages through generations backwards in time we realize that it follows a geometric distribution with

\[E(u) = 2N\]  
[the expectation of the time of coalescence \(u\) of two tips is \(2N\)]
JFC Kingman generalized this for $k$ gene copies.

$$\text{Prob (}k\text{ copies are reduced to } k-1\text{ copies) } = \frac{k(k - 1)}{4N}$$
Kingman’s $n$-coalescent
Kingman’s $n$-coalescent

The expectation for the time interval $u_k$ is

$$E(u_k) = \frac{4N}{k(k-1)}$$

The probability is

$$p(G|N) = \prod_i \exp(-u_i \frac{k(k-1)}{4N}) \frac{1}{2^N}$$
BUT, what’s this good for????????????????????????????
Naively we could estimate: 1. Time of the most recent common ancestor

For a given population size we can calculate the time of the most recent common ancestor [MRCA].

1. Get a TRUE genealogy (topology and branch lengths) from an infallible oracle.

2. Get the population size from the same oracle.

3. Calculate the time of the MRCA by summing over all time intervals.
1. **Time of the most recent common ancestor [Shortcut]**

1. Get the population size from another oracle

2. Use the expectation for your data type to get an estimate of the time of the MRCA

The expectation for the time of the MRCA is

\[
\mathbb{E}(u) = 4N \quad \text{for diploid organisms}
\]

\[
\mathbb{E}(u) = 2N \quad \text{for haploid organisms}
\]

\[
\mathbb{E}(u) = N \quad \text{for maternally transmitted mtDNA, paternally transmitted Y-chromosome}
\]

[assumption: sex-ratio is 1:1]
2. Calculate the size of the population

1. We get THE genealogy from our oracle

2. We know that we can calculate $p(\text{Genealogy}|N)$
2. Calculate the size of the population

1. We get THE genealogy from our oracle

2. We remember the probability calculation

\[
p(G|N) = p(u_1|N, k) \frac{1}{2N} \times p(u_2|N, k - 1) \frac{1}{2N} \times .....\]
2. Calculate the size of the population

1. We get THE genealogy from our oracle

2. We remember the probability calculation

\[
p(Genealogy|N) = \prod_j e^{-u_j \frac{k_j(k_j-1)}{4N}} \frac{1}{2N}
\]
2. Calculate the size of the population
2. Calculate the size of the population
2. Calculate the size of the population

\[ \text{Prob( G | N) } \cdot 10^{-43} \]

Population size N
2. Calculate the size of the population

\[
\text{Prob}( G \mid N) = 10^{-43}
\]

![Graph showing the relationship between population size and probability](image)
2. Calculate the size of the population

\[ \text{Prob}(G \mid N) \times 10^{-43} \]

- Population size N

![Graph showing the distribution of \text{Prob}(G \mid N) for different population sizes N. The graph has a y-axis labeled \text{Prob}(G \mid N) with values ranging from 0.5 to 2.0, and an x-axis labeled Population size N with values ranging from 1000 to 40000. Two data points are marked on the graph.]
2. Calculate the size of the population
2. Calculate the size of the population
2. Calculate the size of the population

\[
\text{Prob}(G \mid N) \times 10^{-43}
\]
2. Calculate the size of the population

Prob( G | N) 
[\cdot 10^{-43}]
2. Calculate the size of the population
2. Calculate the size of the population

\[ N = 2270 \]

\[ N = 12286 \]
Problems with these very naive approaches

We assume we know the TRUE genealogy: topology and branch length.
Variability of the coalescent

10 coalescent trees generated with the same population size, $N = 10,000$
Variability of mutations
How many samples do we need?
Summary of the basic *Coalescent*

- Mathematically tractable way to calculate probabilities of genealogies in a population.

- The coalescent is a very noisy distribution of times on a tree.

- Variability because of mutation increases the uncertainty of these times.

- The population size is correlated with the depth of the tree.

- Estimations of population size or the time of the MRCA from a single tree are very error-prone.
Variable population size

- In a small population lineages coalesce quickly
- In a large population lineages coalesce slowly

This leaves a signature in the data. We can exploit this and estimate the population growth rate $g$ jointly with the population size $\Theta$. 
Exponential population size expansion or shrinkage
Grow a frog

<table>
<thead>
<tr>
<th>Mutation Rate</th>
<th>Population sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-10000 generations</td>
</tr>
<tr>
<td>$10^{-8}$</td>
<td>8,300,000</td>
</tr>
<tr>
<td>$10^{-7}$</td>
<td>780,000</td>
</tr>
<tr>
<td>$10^{-6}$</td>
<td>40,500</td>
</tr>
</tbody>
</table>
Parameter estimation using *maximum likelihood*

- Mutation model: Nucleotide mutation model, ...
- Population genetics model: the Coalescent
Parameter estimation using maximum likelihood

- Mutation model: Nucleotide mutation model, ...
- Population genetics model: the Coalescent

\[ \text{Prob} \ (N, \mu | \text{data}) \]
Parameter estimation using *maximum likelihood*

- Mutation model: Nucleotide mutation model, ...
- Population genetics model: the Coalescent

\[
\text{Prob} \left( \mathbf{N}, \mu \mid \text{data} \right) = \frac{\text{Prob} \left( \text{data} \mid \mathbf{N}, \mu \right) \text{Prob} \left( \mathbf{N}, \mu \right)}{\text{Prob} \left( \text{data} \right)}
\]
Parameter estimation using maximum likelihood

- Mutation model: Nucleotide mutation model, ...
- Population genetics model: the Coalescent

\[
\text{Prob} \left( N, \mu | \text{data} \right) = \frac{\text{Prob} \left( \text{data} | N, \mu \right) \text{Prob} \left( N, \mu \right)}{\text{Prob} \left( \text{data} \right)}
\]

\[
L(N, \mu) = \text{Prob} \left( \text{data} | N, \mu \right) = c \text{ Prob} \left( N, \mu | \text{data} \right)
\]
Parameter estimation using *maximum likelihood*

\[ L(N, \mu) = \text{Prob} \ (\text{data}|N, \mu) \]
Parameter estimation using *maximum likelihood*

\[ L(N, \mu) = \text{Prob} \left( \text{data} | N, \mu \right) = \int_G p(G|N, \mu) \text{Prob} \left( \text{data} | G, \mu \right) \]
Parameter estimation using *maximum likelihood*

\[
L(N, \mu) = \text{Prob} \ (\text{data}|N, \mu) = \int_G p(G|N, \mu) \ \text{Prob} \ (\text{data}|G, \mu)
\]

We cannot observe the mutation events. Instead of estimating \( N \) and \( \mu \) we estimate the product \( \Theta = 4N\mu \) and scale \( G \) with \( \mu \)

\[
L(\Theta) = \int_{G^*} p(G^*|\Theta) \ \text{Prob} \ (\text{data}|G^*)
\]
Parameter estimation using *maximum likelihood*

\[ L(N, \mu) = \text{Prob} \ (\text{data}|N, \mu) = \int_G p(G|N, \mu) \ \text{Prob} \ (\text{data}|G, \mu) \]

We cannot observe the mutation events. Instead of estimating \( N \) and \( \mu \) we estimate the product \( \Theta = 4N\mu \) and scale \( G \) with \( \mu \)

\[ L(\Theta) = \int_{G^*} p(G^*|\Theta) \ \text{Prob} \ (\text{data}|G^*) \]

**Problem:** We need to integrate over all genealogies: all different labelled histories, all different branchlengths
Can we calculate this sum over all genealogies?

We need to integrate over all genealogies: all different topologies, all different branchlengths.

<table>
<thead>
<tr>
<th>Tips</th>
<th>Topologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
</tr>
<tr>
<td>6</td>
<td>2700</td>
</tr>
<tr>
<td>7</td>
<td>56700</td>
</tr>
<tr>
<td>8</td>
<td>1587600</td>
</tr>
<tr>
<td>9</td>
<td>57153600</td>
</tr>
<tr>
<td>10</td>
<td>2571912000</td>
</tr>
<tr>
<td>15</td>
<td>6958057668962400000</td>
</tr>
<tr>
<td>20</td>
<td>564480989588730591336960000000</td>
</tr>
<tr>
<td>30</td>
<td>4368466613103069512464680198620763891440640000000000000</td>
</tr>
<tr>
<td>40</td>
<td>30273338299480073565463033645514572000042939432053862501707888721920000000000000000</td>
</tr>
<tr>
<td>50</td>
<td>3.28632 $\times 10^{112}$</td>
</tr>
<tr>
<td>100</td>
<td>1.37416 $\times 10^{284}$</td>
</tr>
</tbody>
</table>
A solution: *Markov chain Monte Carlo*

**Metropolis recipe**

0. first state

1. perturb old state and calculate probability of new state

2. test if new state is better than old state: accept if ratio of new and old is larger than a random number between 0 and 1.

3. move to new state if accepted otherwise stay at old state

4. go to 1
How do we change a genealogy
Markov chain Monte Carlo

$L(G_1|\Theta)$
Markov chain Monte Carlo

create a new tree
Markov chain Monte Carlo

$L(G_2|\Theta)$

Evaluate

$r < \frac{p(G_2|\Theta)P(D|G_2)P(G_1|G_2)}{p(G_1|\Theta)P(D|G_1)P(G_2|G_1)}$

luckily reduces most often to:

$r < \frac{P(D|G_2)}{P(D|G_1)}$
Markov chain Monte Carlo

Store $G_1$

Make another change to the tree
Markov chain Monte Carlo

$L(G_3|\Theta) < \frac{P(D|G_3)}{P(D|G_2)}$
Markov chain Monte Carlo

Store $G_2$

Make another change to the tree
Markov chain Monte Carlo
Markov chain Monte Carlo
Markov chain Monte Carlo
MCMC walk I
MCMC walk result
MCMC walk result
Improving our MCMC walker: MCMC MCMC or MC$^3$

Metropolis Coupled Markov chain Monte Carlo

- Run several independent parallel chains: each has a different temperature.

- After some sampling of genealogies, swap the genealogies of a pair of chains if the ratio between probabilities in the cold and the hot chain is larger than a random number drawn between 0 and 1.
MCMC walk II
better MCMC walk result