7.1 Introduction

Deoxyribonucleic Acid or DNA is commonly known to be responsible for encoding the information of life. Through sexual reproduction, DNA is passed on as hereditary material to offspring. During the replication of genes, sometimes ‘mistakes’ might occur. These mistakes cause the DNA, instead of being identical to the parent DNA, to change a little (one or more of the bases in the strand might have been changed). Such ‘mistakes’ are known as mutations. Through many generations of reproductions, with mutations going on between every generation, bringing about little changes each time in the offspring, different species emerge (or evolve). This is where phylogenetic comes in. Phylogenetic is the study of the genetic relationship among different species.

7.1.1 Mitochondrial DNA and Inheritance

The evolution of modern man is one of the interesting topics in phylogenetics. Before going further into details on the evolution of modern man, a particular aspect which has proven to be significant in this study will be discussed - mitochondrial DNA (mtDNA). mtDNA is located in the mitochondria of the cell. The mitochondria are organelles located outside the nucleus in the cytoplasm of the cell. These organelles are responsible for energy transfer and are basically the ‘powerhouses’ of the cell. There are about 1,700 mitochondria in every human cell, each includes an identical circular DNA of about 16,000 base pairs long containing 37 genes. This form of DNA is in short strands and therefore does not mutate very quickly - it is relatively unchanged and can be compared across several generations. Whenever an egg cell is fertilized, nuclear chromosomes from a sperm cell enter the egg and combine with the egg’s nuclear DNA, producing a mixture of both parents’ genetic code. The mtDNA from the sperm cell, however, is left behind, outside of the egg cell. So the fertilized egg contains a mixture of the father and mother’s nuclear DNA and an exact copy of the mother’s mtDNA, but none of the father’s mtDNA. The result is that mtDNA is passed on only
along the maternal line. This means that the mtDNA in the cells of a person’s body are copies of his or her mother’s mtDNA, and all the mother’s mtDNA is a copy of her mother’s, and so on.

7.1.2 The Constant Molecular Clock

Even though everyone in the Earth today has inherited his or her mtDNA from one person who lived long ago, our mtDNA is not exactly alike. Random mutations have altered the genetic code over the millennia. But these mutations are organized, in a way. For example, let’s say that 10,000 years after the most recent common ancestor, one of the mtDNA branches experienced a mutation. From that point on, that line of mtDNA would include that alteration.

Another branch might experience a mutation in a different location. This alteration would also be passed on. By looking at the similarities and differences of the mtDNAs of the nowadays individuals, researchers try to reconstruct where the branching took place. From an original 1987 Nature article, the three authors (Rebecca Cann, Mark Stoneking, and Allan Wilson) looked at the mtDNA of 147 people from continents around the world (though for Africans, they relied on African Americans). Later, with the help of a computer program, they put together a sort of family tree, grouping those with the most similar DNA together, then grouping the groups, and then grouping the groups of groups. The tree they ended up showed that one of the two primary branches consisted only of African mtDNA and that the other branch consisted of mtDNA from all over the world, including Africa. From this, they inferred that the most recent common mtDNA ancestor was an African woman. This study was done under the assumption of a constant molecular clock. Such a theory supports the idea that rates of change in genes and proteins are constant over time. It claims that in any given DNA sequence, mutations accumulate at an approximately constant rate as long as the DNA sequence retains its original functions. The difference between the sequences of a DNA segment (or protein) in two species would then be proportional to the time since the species diverged from a common ancestor (coalescence time). This time may be measured in arbitrary units and then it can be calibrated in millions of years for any given gene if the fossil record of that species happens to be rich. Moreover, such a theory does not hold in general.

Molecular clocks do not behave metronomically, i.e., neutral mutations do not yield literally constant rates of molecular change but are expected to yield constant average rates of change over a long period of time (known as ‘stochastically constant’ rates). In general, rRNA evolves slowly and mtDNA rapidly. Fast mutating sequences cannot be used to go back in evolutionary time because the mutations effectively randomize the sequences. It is also possible that reverse mutations will occur and the comparisons will be very difficult. These facts along with further research have that Wilson’s clock is not accurate and that the analysis only support the common ancestor of modern man appear from 100,000 to
1 million years ago.

### 7.1.3 Phylogeny

In Wilson’s project, the tree they built is known as phylogeny. Phylogeny is defined as the reconstruction of the evolutionary history of a set of species. It is usually represented by a leaf-labeled tree where the internal nodes refer the hypothetical ancestors and the leaves are labeled by the species. Two species that look alike will be represented as neighboring external branches and will be joined to a common parent branch. The objective of phylogenetic analysis is to analyze all the branching relationships in a tree and their respective branch lengths. As an example, we can look at the phylogeny of lizards as illustrated in Figure 7.1.

![Figure 7.1: Phylogeny of lizards](image)

Let us observe the phylogenetic tree in Figure 7.1, also known as a cladogram or a dendrogram. It is a tree of several life forms and their relations. In the figure, time is the vertical dimension with the current time at the bottom and earlier times above it. There are five extant species (species currently living) with their respective names stated. The lines above the extant species represent the same species, just in the past. When two lines converge to a point, that should be interpreted as the point when the two species diverges from a common ancestral species, the point being the common ancestral species. And so it goes until eventually, some time in the past, all the species derived from just one species, the one displayed as the top point.

When performing analysis of phylogenetic trees, one has to understand that the genomes of most organisms have a complex origin. Through reproduction of species, some parts of the genome are passed on by a vertical descent. Other parts may have arisen by horizontal transfer of genetic material between species
through a virus, DNA transformation, symbiosis(living together), or some other horizontal transfer mechanism.

7.1.4 Applications of Phylogeny

Aside from the more obvious applications of understanding the history of life and analyzing rapidly mutating viruses such as HIV, phylogeny has several other uses. One example is multiple sequence alignment. Most multiple sequence alignment programs used in practice rely on a phylogenetic tree in order to speed up the computation. In addition to that, phylogeny also helps in the prediction of the structure of proteins and RNA, helps to explain and predict gene expression, ligand structure for drug design and helps to design enhanced organisms such as rice and wheat. The most significant of these applications is the use of phylogenetic analysis in sequence alignment. When the sequences of two nucleic acid or protein molecules found in two different organisms are similar, they are likely to have been derived from a common ancestor sequence. Sequence alignments reveal conserved, and non-conserved regions between evolutionarily related sequences. When an evolutionary relationship is seen to exist between any two sequences, they are known as homologous. Therefore, one can say that sequence homology is a function of similarity. The analysis of sequences that are similar along their entire length is relatively simple. However, alignment of most sequences requires the positioning of gaps in the sequences involved. The fact that a gap of any length can occur within a sequence introduces the problem of judging how many individual changes have occurred within the organism and in what order. These gaps can thus be used as phylogenetic markers. Knowledge of changes within an organism through mutation over time give us knowledge of regions within a sequence that have not changed. These conserved regions, that may be present in a particular protein might therefore give away the function of this protein. Focusing on the conserved regions of sequences obtained from different levels in the phylogenetic tree, one might thus be able to predict the structure through homology modeling with another known protein with a similar function. Structural similarity will then aid in the rational design of ligands as drug compounds which might prove to have a high binding affinity with these structurally conserved regions, thus helping produce more efficacious and specific drug compounds.

7.1.5 Phylogenetic Tree Reconstruction

Phylogenetic analyses have their own set of problems though. One of the main ones is that of phylogenetic tree reconstruction. The main purpose of phylogenetic tree reconstruction is to predict or make an estimate on the phylogeny for some input data. For any collection of data, there will be some ancestral relationship among the sampled sequences. The data itself contains information that can
be used to reconstruct or to infer these ancestral relationships. This involves the reconstruction of the phylogenetic tree which illustrates the relationship among the sequences. There are two types of input methods that can be used to reconstruct the phylogenetic tree, one is character based (Maximum parsimony, compatibility and maximum likelihood) and the other is distance based (Un-weighted Pair Group with Arithmetic Mean - UPGMA, Transformed Distance Methods and Neighbour Relation Methods). Only the character based methods will be explained in this script.

For character based method, each species is described by a set of characters (i.e. traits). A character can be a base in a specific position in its DNA sequence, morphological features like walks on knuckles, have feathers, etc. These serve as input and the methods seek to build a tree which best explain the input.

### 7.1.6 Rooted and Unrooted Trees

Most methods for the inference of phylogeny yield trees that are unrooted, i.e. the common ancestor is unknown. Thus from a tree itself, it is impossible to tell which species branched off before the others. Examples of a rooted and an unrooted tree are illustrated in Figure 7.2.

To root a tree one should add an outgroup to the data set. An outgroup is a species for which external information (e.g. paleontological information) is available that indicates that the outgroup branched off before all other species. Using more than one outgroup (they must not be closely related), we can improve the estimate of the final tree topology.

However, in the absence of a good outgroup the root may be positioned by assuming approximately equal evolutionary rates over all the branches. In this way the root is put at the midpoint of the longest pathway between two species. This way of rooting is called mid-point rooting.

### 7.2 Parsimony

#### 7.2.1 What is Parsimony

The principle of parsimony is defined as “a scientific rule which states that if there exists two answers to a problem or a question, and if, for one answer to be true, well-established laws of logic and science must be re-written, ignored, or suspended in order to allow it to be true, and for the other answer to be true no such accommodation need to be made, then the simpler of the two answers is much more likely to be correct.” Putting it in a simpler way, parsimony is a principle that states that the simplest explanation that explains the greatest number of observations is preferred to more complex explanations.
Figure 7.2: Structure of evolutionary

Parsimony is one of the most popular character based method for the phylogeny reconstruction problem. The idea behind parsimony is to build the phylogeny with the fewest point mutations.

**Formal Definition:**

- Let $S$ be a set of (DNA or Protein) sequences.
- Denote $H(x,y)$ be the hamming distance between two sequences $x$ and $y$. (Hamming distance is the number of characters that is different between sequence $x$ and $y$.)
- The most parsimonious tree is a tree $T$ leaf-labeled by $S$ and each internal node is assigned a sequence such that $H(T) = \sum_{(x,y) \in E(T)} H(x,y)$ is minimized. Note that $H(T)$ is called the parsimony length of $T$.

Figure 7.3 shows an example of the most parsimonious tree for four species where each is represented by a sequence of 4 characters.
Example (4 species, each is represented by a sequence of 4 characters)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>A</td>
<td>C</td>
<td>G</td>
<td>T</td>
</tr>
<tr>
<td>X</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td>Y</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>G</td>
</tr>
<tr>
<td>Z</td>
<td>C</td>
<td>C</td>
<td>G</td>
<td>T</td>
</tr>
</tbody>
</table>

This is the most parsimonious tree
Its parsimony length is 3

Figure 7.3: Example of parsimonious tree

**Note:** Although there is no rule that requires nature to follow the simplest path, and results can vary based on which pieces of evidence are used, Parsimony is nonetheless a strong basis for the scientific work of paleontologists.

### 7.2.2 Computational Problems

The computational problems related to the parsimony approach can be categorized in two groups:

- Small Parsimony problem: To find the parsimony length of a given tree topology.
- Large Parsimony problem: To find the most parsimonious tree.

#### 7.2.2.1 Small Parsimony Problem

**Input:** Given a set $S$ of sequences and the topology of a rooted phylogenetic tree $T$ with leave labeled by $S$

**Goal:** Find parsimony length of $T$.

**Problem statement:**

1. What is the minimum number of changes for this topology?
2. What is the optimal labeling of the internal nodes?
This problem can be solved using Fitch's algorithm [F71] in polynomial time. Each character can be solved separately and this can be extended to handle sequences of n characters as characters are mutually independent.

Each sequence has one character (Simple case)

**Input:** a leaf-labeled tree $T$ where each leaf $v$ is labeled by a single character $v_c$.

**Output:** a fully-labeled tree which is also the most parsimonious tree of $T$.

**Algorithm:**
The algorithm first puts all characters at the leaves of the tree and then it tries to label every internal node of tree, such that every node has label equal to one of its children. Formally the algorithm is as follows.

1. For every leaf $v$, let $S_v = \{v_c\}$.
2. For every internal node $v$ with children $u, w$, let $S_v = S_u \cap S_w$ if $S_u \cap S_w \neq \emptyset$; and $S_u \cup S_w$ otherwise.
3. For every node $v$ in preorder,
   - Let $u$ be its parent. If $u_c \in S_v$ set $v_c \leftarrow u_c$; otherwise, assign any character in $S_v$ to $v_c$.

![Diagram of the algorithm](image)

- Each asterisk (*) requires a change in one of the edges to its children.

Figure 7.4: Small parsimony problem (simple case)
Figure 7.4 shows an example for the implementation of the above algorithm. Time complexity of the above algorithm is $O(nk)$ where $n$ is the number of sequences and $k$ is the size of the alphabet.

Each sequence has $m$ characters: To solve the problem with each sequence having $m$ characters, first note that the $i^{th}$ character and the $j^{th}$ character are independent for any $i$ and $j$. The problem of having $m$ characters in a sequence can, thus, be solved using $m$ instance of the simple case problem. Therefore, the time complexity would be $O(mnk)$.

7.2.2.2 Large Parsimony Problem

Input: A set $S$ of sequences.
Output: The most parsimonious tree.
Problem statement:

1. What is the optimal phylogeny for these species, i.e., the one minimizing the parsimony score?

The large parsimony problem is a NP-hard problem, i.e. the problem most probably cannot be solved in a polynomial time. However, it can be 2-approximated (not worse than 2x the actual best result) in polynomial time, using the following algorithm.

Approximation algorithm:

- Given a set $S$ of sequences, define $G(S)$ be a weighted complete graph whose nodes are labeled by $S$ and each edge $(i, j)$ has weight $H(i, j)$, where $H(i, j)$ is the hamming distance between sequences $i$ and $j$.

- return the minimum spanning tree, $T$, of $G(S)$.

**Theorem 7.1** Let $T^*$ be a minimum spanning tree of $G(S)$. Then, the parsimony length of $T$ is at most twice that of the most parsimonious tree.

**Proof:**

- Let $T^*$ be the most parsimonious tree.

- Let $C$ be an Euler cycle of $T^*$. (Note that in the Euler cycle $C$ of $T^*$, every edge in $T^*$ appears twice.)

- Let $P$ contains only the nodes of $G(S)$ ordered in the way in which they appear in $C$. 
• Define $w(H)$ to be the sum of the weights of the edges in $H$.
  Thus, $w(C) = 2 \cdot w(T^*)$ since $C$ is Eulerian.
  Furthermore, $w(P) \leq w(C)$ since Hamming distance satisfy the triangle
  inequality.
  Finally, note that if we delete any single edge from $P$, we create a path
  which is also a spanning tree but not necessarily the minimum.
  Therefore, $w(T) \leq w(P) \leq w(C) = 2 \cdot w(T^*)$.

  $\blacksquare$

It is obvious that maximum parsimony does not take into account 'backflips',
that is, a series of mutations that bring a character value back to its ancestor value.
Most importantly, maximum parsimony is statistically inconsistent. As more and
more data become available, the generated trees do not converge to the same tree.

7.3 Compatibility

Compatibility is another attempt to define a target function for the phylogeny
problem: Given a set of characters which represents a set of species, it tries to
find a phylogeny tree which is compatible with as many characters as possible.
In fact, it is a simplification of parsimony approach. In the following discussion,
we assume each character in the sequence can only have binary states, say 0 and
1 without loss of generality.

7.3.1 Problem definition

Let’s have some basic definitions, before defining the compatibility problems:

7.3.1.1 Compatible

A binary character (a sequence of binary bits) $c$ is compatible to a leaf-labeled
tree $T$ if and only if there exist an assignment of states to the internal nodes of
$T$ such that a change of state exists at most in one edge.

Figure 7.5 shows an example of compatibility and non-compatibility. When
only one change is found in the edges of the tree, the character is compatible, oth-
wise, if there are more than one change in the edges of the tree, the character is
incompatible to the tree. In fact, there is another way to express the compatible
property. If a character $c$ is compatible to a tree $T$, then an $edge(u, v)$ can be
identified in $T$, such that

• All the leaves in the subtree rooted by $v$ have state $s$ in the corresponding
  positions in the character $c$. 
One state change!
c is compatible to T

Two state change!
c is not compatible to T

Figure 7.5: compatibility of a character with a tree

Figure 7.6: Compatible example for compatible case

- The other leaves have state \((1 - s)\) for the remaining positions in the character \(c\)

This property can be seen from Figure 7.6. The reason is quite straightforward, since only one edge can have change, say this edge is \((u, v)\), without loss of generality, say \(v\) is a son of \(u\). Then the leaves in the subtree rooted by \(v\) must have the same state, otherwise, other changes will exist. The same reason for the rest of leaves.

7.3.1.2 Perfect Phylogeny

Based on compatibility concept, perfect phylogeny can be defined as follows:

**Input**: Given \(n\) species, each is characterized by \(m\) binary characters. The input can be represented using a binary matrix \(M\) with \(n\) rows and \(m\) columns, where \(M_{ij}\) is the state of character \(j\) of species \(i\).
<table>
<thead>
<tr>
<th>M</th>
<th>X1</th>
<th>X2</th>
<th>X3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species 1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Species 2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Species 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Species 4</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Species 5</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Example: characters 1, 2 and 3 are all compatible!

Figure 7.7: Compatibility example for compatible case

**Definition:** $M$ admits a perfect phylogeny if and only if there exists a rooted tree $T$ for $n$ species such that all $m$ characters are compatible.

Figure 7.7, shows an example for the input matrix $M$. As shown in the figure, the matrix $M$ admits a perfect phylogeny since $X1$, $X2$ and $X3$ are all compatible to the tree $T$.

### 7.3.1.3 Computation Problems based on compatibility

Given $n$ species, each characterized by $m$ binary characters, represented by a binary matrix $M$, there are two classes of problem that we need to address.

- **Compatibility problem** Does this given set of species admit a perfect phylogeny? This is equivalent to answer whether there exists a rooted tree $T$ such that all $m$ characters are compatible to the tree $T$.

- **Large Compatibility Problem (Perfect Phylogeny Problem)** In the event if $M$ can’t admit a perfect phylogeny, one may wish to find the maximum set of mutually compatible characters and recover the corresponding tree.

### 7.3.2 Compatibility Problem

Compatibility problem can be divided into two steps.

- In the first step, check whether $M$ admits a perfect phylogeny.

- In the second step, if $M$ admits a perfect phylogeny, recover the tree.
7.3.2.1 Majority Rule

Observe that if \( M \) admits a perfect phylogeny \( T \), after exchange 0 and 1 in any column, the result matrix \( M \) still admits the same perfect phylogeny \( T \). The transformation, thus, has no effect on compatibility. (See Figure 7.8 for an example.)

Based on the above observation, we can define the **majority rule** as:

For any binary matrix \( M \), if there exists a column such that the number of state 1 > number of state 0, exchange 0 and 1.

7.3.2.2 Main lemma in Compatibility

Before describing the lemma, let’s make some definitions.

- For every character \( i \), let \( O_i \) be the sets of species with state 1. For example, in Figure 7.7, \( O_1 = \{1,5\} \)

- Characters \( i \) and \( j \) are **pairwise compatible** if \( O_i \) and \( O_j \) are disjoint or one of them contains the other. For example, \( O_1 = \{1,5\} \) contains \( O_2 = \{1\} \) in Figure 7.7. Furthermore, \( O_3 = \{2,4\} \) is disjoint with \( O_1 \).

**Lemma 7.2** Let \( M \) be a binary matrix after applying the ”majority rule”. \( M \) admits a perfect phylogeny if and only if for every characters \( i \) and \( j \), they are pairwise compatible.
Proof: $M$ admits a perfect phylogeny \(\Rightarrow\) every characters $i$ and $j$ are pairwise compatible.

- Given that $M$ admits a perfect phylogeny.
- Since we have applied "majority rule" to $M$, $|O_i| \leq n/2$ for every character $i$.
- Assume that $i$ and $j$ are not pairwise compatible, i.e. there exists three species $X$, $Y$, $Z$ such that $Y,Z \in O_i, X \notin O_i$ and $X,Z \in O_j, Y \notin O_j$.
- Since $O_i \cap O_j$ is non-empty, thus, $|O_i \cup O_j| < n$. Thus, there exists a species $W \notin O_i, O_j$.
- By character $i$, without loss of generality, $Y$ and $Z$ are in the same partition in $T$, while $X$ and $W$ are in another partition.
- By character $j$, $X$ and $Z$ are in the same partition in $T$, while $W$ and $Y$ are the same partition in $T$.
- Above situation can never happen in a $T$.
- Therefore, our assumption is wrong.

Proof: Every characters $i$ and $j$ are pairwise compatible \(\Rightarrow\) $M$ admits a perfect phylogeny.

- Given that every character $i$ and $j$ are pairwise compatible.
- Recall that in each phase of the tree reconstruction algorithm presented in lecture, a particular character $i$ for every node $v$ in $T$ was considered. If $N(v)$ contains two groups of species such that one group with state $i$ equal to 0 and another group with state $i$ equal to 1, the node is splitted.
- Assume in a phase for character $i$, there are more than one node, say $u$ and $v$, that can be splitted.
- This means that there exists some character $j$ which splits the species into nodes $u$ and $v$.
- Thus, $O_j \cap O_i \neq \emptyset$.
- Assume that the species in node $u$ belong to $O_j$ while that in node $v$ do not belong to $O_j$.
- Since $i$ splits $u$, this means that some species in $O_j$ does not exist in $O_i$, that is, $O_j \not\subseteq O_i$. 

• Since \( i \) also splits \( v \), this means that some species not in \( O_j \) exists in \( O_i \), that is, \( O_i \nsubseteq O_j \)

• Thus, \( i \) and \( j \) are not pairwise compatible. which is a contradiction.

• Hence, at most one node can be split in every phase and the final tree constructed is a perfect phylogeny.

\[ \square \]

7.3.2.3 Simple Solution for Checking Whether \( M \) Admits a Perfect Phylogeny

Based on the previous lemma, the algorithm is as followed:

• Step 1: Apply “Majority Rule” to \( M \).

• Step 2: For every characters \( i \) and \( j \),
  - Check whether \( i \) and \( j \) are pairwise compatible
  - If no, return “can’t admit a perfect phylogeny!”

• Step 3: Return “Admit a perfect phylogeny!”

Application of “Majority Rule” takes \( O(mn) \) time. The construction of a set \( O_i \) takes \( O(n) \) time and the checking for containment or disjoint can be done in \( O(n) \) time. There are \( \frac{m(m-1)}{2} \) pairs of \((i, j)\) character to check. Hence, the total time complexity is \( O(m^2n) \).

7.3.2.4 Faster Solution for Checking Whether \( M \) Admits a Perfect Phylogeny

The bottleneck in the previous algorithm is the way that checking is done for containment and disjoint. Here, we describe an \( O(mn) \) time algorithm.

• Step 1: Apply “Majority Rule” to \( M \) and relabel the characters so that \( |O_i| \geq |O_j| \) if \( i < j \).
  See Figure 7.9 for example. The sequence is already in such sorted order, thus we can proceed to Step 2 without any changes.

• In Step 2: Create matrix \( L_{ij} \) from \( M_{ij} \).
  for every species \( i \) and character \( j \), do
    If \( M_{ij} = 1 \), let \( L_{ij} \) be the biggest \( k < j \) such that \( M_{ik} = 1 \). If such \( k \) does not exist, \( L_{ij} = -1 \)
    If \( M_{ij} = 0 \), let \( L_{ij} = 0 \).
  end for
Figure 7.9: Step 1

<table>
<thead>
<tr>
<th>M</th>
<th>X1</th>
<th>X2</th>
<th>X3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species 1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Species 2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Species 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Species 4</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Species 5</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L</th>
<th>X1</th>
<th>X2</th>
<th>X3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species 1</td>
<td>-1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Species 2</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Species 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Species 4</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Species 5</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 7.10: Step 2

Figure 7.10 show the matrix $L$ derived from $M$. For example $M_{11}$ has value 1, but there does not exist a smaller value of $k$ such that $M_{1k} = 1$, thus $L_{11} = -1$. As another example, $L_{13}$ has value 1 because $M_{11} = M_{13} = 1$. (Take note that the value 1 for $L_{13}$ comes from the column index of $M_{11}$ which is 1.) According to the algorithm, $L_{ij} = 0$ when $M_{ij} = 0$.

Next, we introduce **Technical Lemma** which uses the matrix $L$ to check for admission of perfect phylogeny.

**Lemma 7.3** For some character $j$, if there exist two nonzero entries $L_{ij}$ and $L_{kj}$ such that $L_{ij} \neq L_{kj}$, then $M$ does not admit a perfect phylogeny.

**Proof:**

- Suppose $L_{ij} = x$ and $L_{kj} = x'$. without loss of generality, $x > x'$.
- By definition, $M_{ij} = M_{kj} = 1, M_{ix} = 1, M_{kx} = 0$
- Thus, $O_j$ contains species i and species k and $O_x$ contains species i, but not species k. It means that (1) $O_j \cap O_x \neq \phi$, (2) $O_j$ is not subset of $O_x$
- Note that $j > x$. Thus, $|O_x| \geq |O_j|$
• As \( k \not\in O_x \), \( O_x \) should contain some species which does not appear in \( O_j \).
  So, (3) \( O_j \) is not subset of \( O_x \).

By Lemma 7.2, \( M \) does not admit a perfect phylogeny.

• **In Step 3**: Use Lemma 7.3 with matrix \( L \) to check for admission of perfect phylogeny.
  
  for every character \( j \), check if there exist \( i \) and \( k \) such that \( L_{ij} \neq L_{kj} \)
  and both \( L_{ij} \neq 0 \) and \( L_{kj} \neq 0 \)
  
  If yes, return “does not admit a perfect phylogeny”.

end for

Return “admits a perfect phylogeny”.

Examining the matrix \( L \) in Figure 7.10, all nonzero entries \( X_1 \) and \( X_2 \) are -1. For \( X_3 \), there is only one nonzero entry of value 1. Thus for every character \( j \) (column \( j \)), we can’t find two nonzero entries which are different. So, for all \( i, j \), \( O_i \) and \( O_j \) are disjoint or one of them contains the other. So this means that the original matrix \( M \) admits a perfect phylogeny.

**Time complexity:**

1. Step 1 takes \( O(mn) \) time using radix sort as it takes linear time.

2. Step 2 can be computed in \( O(mn) \) time as we need to process each entry in a \( m \times n \) matrix row wise which takes \( O(1) \) each.

3. Step 3 can similarly be computed in \( O(mn) \) time by processing each entry in the \( m \times n \) matrix \( L \) column wise which takes \( O(1) \) each.

  Thus, whether \( M \) admits a perfect phylogeny or not can be decided in \( O(mn) \) time.

### 7.3.3 Reconstruct Perfect Phylogeny from \( M \)

Given that we now know how to detect whether \( M \) admits a perfect phylogeny tree, we can construct the perfect phylogeny using the below algorithm if one is admitted.

**Algorithm**

• Let \( T \) be a tree containing a single root node \( r \). \( N(r) = \{1, ..., n\} \)

• For every character \( j \) where \( j = 1 \) to \( m \)
  
  – Find a node \( v \in T \) such that
* $N(v)$ can be partitioned into two non-empty sets $N_0$ and $N_1$ where
$N_s = \{ x \in N(v) | \text{character } j \text{ of species } x \text{ is of state } s \}$ for $s=0,1$
/* Note: we can only split one node $v$ */

- Create two children $v_0$ and $v_1$ for $v$
- Set $N(v_0) = N_0$, $N(v_1) = N_1$
- Set $N(v) = \phi$

- For every node $v$ such that $N(v)$ is nonempty,
  - If $|N(v)| > 1$, let the species in $N(v)$ be the children of $v$
  - If $|N(v)| = 1$, node $v$ represents the species in $N(v)$

As an example, consider the 5 species with 3 characters $X_1$, $X_2$ and $X_3$, whose matrix $M$ is shown in Figure 7.9. According to the previous rule, it admits a perfect phylogeny tree.

- In the initial case, we list down all species in a node.
- Using Character 1, $X_1$ as a base, we split the species into 2 partitions, the left side node holds all species whose character has state 1 while the right side node holds all species whose character has state 0. (See Figure 7.11.)

- The step is followed by Character 2 splitting. There is no change to the partition $\{1,5\}$ as they have the same value for $X_2$. The partition $\{2, 3, 4\}$ can be splitted into $\{2, 4\}$ having state 1 and $\{3\}$ having state 0. (See Figure 7.12.)

- In the next stage character 3, $X_3$, is split, dividing $\{1,5\}$ into $\{1\}$ having state 1 and $\{5\}$ having state 0. $\{2, 4\}$ is however not affected. (See Figure 7.13.)
Figure 7.12: character 2

Figure 7.13: character 3

Figure 7.14: final
• To complete the phylogeny tree, each species has to be a leaf and not a node itself, so the node \{2, 4\} is again split and for a new leaf for the species. (See Figure 7.14.)

Notice that for every character \(j\), it takes \(O(n)\) time to identify a node and to split the node. Thus, the total time taken is \(O(nm)\).

### 7.3.4 Large Compatibility Problem

The difficulty in solving the large compatibility problem is to find the maximum set of species which admits a perfect phylogeny, which is NP-hard.

One way to solve the large compatibility problem is by transforming it to the CLIQUE Problem, which is defined as follows: "Given a graph \(G\), the CLIQUE problem tries to find the maximum size subgraph \(H\) such that \(H\) is a complete graph." For example, in Figure 7.15 below, the maximum size complete subgroup of \(G\) is in fact \(H\). (A CLIQUE is a complete graph where every two distinct vertices are adjacent.)

The transformation of a large compatibility problem to a CLIQUE problem is as followed:

• Given an instance of \(M\), define a graph \(G\) where
  
  - Each vertex \(i\) in \(G\) corresponds to a character in \(M\)
  - \((i, j)\) is an edge in \(G\) if \(i\) and \(j\) are pairwise compatible.

Thus, \(G\) contains a clique of size \(c\) if and only if \(M\) contains a subset of compatible characters whose size is \(c\). It is possible to construct \(G\) in polynomial time.

#### 7.3.4.1 Algorithm for solving large compatibility problem

**Input:** An instance \(M\);
1. Applying the “majority rule” to $M$;
2. Obtain $G$ based on $M$;
3. Find the maximum clique in $G$;
4. Recover the maximum subset of compatible characters;
5. Based on the tree construction algorithm described in Section 7.3.3, recover the phylogeny

The bottleneck is at Step 2 and it takes exponential time since CLIQUE problem is known to be NP-Complete.

7.3.5 Compatibility for characters with $k$ possible states

Now we generalize the problem when the characters are not binary as following:

**Definition 7.4** A character $c$ with $k$ possible states is compatible to a leaf-labeled tree $T$, if and only if there exist an assignment of states to the internal nodes of $T$ such that the total number of state changes is at most $k - 1$.

Let’s revisit the two computational problems for compatibility for characters with multiple states.

- Compatibility Problem
  - When the number of states is constant, polynomial time algorithm is still feasible;
  - When the number of states is variable, NP-Complete.

- Large Compatibility Problem: NP-Complete

7.4 Maximum Likelihood Based Model

In this section we study a maximum likelihood based model of phylogenetic trees reconstructions.

7.4.1 What is a Likelihood Based Model

Give a set of data $D$, maximum likelihood tries to find a model $M$ such that $Pr(D|M)$ is maximized. A model consists of two components. They are

- A rooted tree which models the evolution relationship;
- Every edge is associated with a stochastic model of evolution.

And we have two assumption for the stochastic model of evolution. They are
• The characters evolve identically and independently;
• The trees has the Markov property. That is, the evolution occurs at one subtree is independent to the other parts of the trees.

And examples of models include Cavender-Felsenstein model (also called Cavender-Farris model) [CF87], and Jukes-Cantor model [JC69]. In this lecture, we study the former one in detail.

7.4.2 Cavender-Felsenstein Model

We now introduce the Cavender-Felsenstein Model [CF87] in details. The Cavender-Felsenstein Model is the simplest possible Markov model of evolution.

7.4.2.1 Definition of the Model

The model assumes that each character has two states. Cavender-Felsenstein Model consists of the following.

• The topology of a rooted evolution tree $T$;
• A stochastic model of evolution for every edge $e$, that is, for every character $i$, a mutation probability $p_i(e)$ for each edge $e$ in $T$.

For the stochastic model of evolution, we have following assumption.

• $\forall i, \forall e = (u, v) \in T$, we have $0 < p_i(e) < 0.5$, and

<table>
<thead>
<tr>
<th>$u = 0$</th>
<th>$u = 1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v = 0$</td>
<td>$Pr(u = 0</td>
</tr>
<tr>
<td>$v = 1$</td>
<td>$Pr(u = 0</td>
</tr>
</tbody>
</table>

• $Pr(u|v) = Pr(v|u)$;
• For the root $r$, $Pr(r = 0) = Pr(r = 1) = 0.5$.

Thus given a data set $D_i$ for character $i$ of all species, we may use $(T, p_i)$ to represent a model, where $T$ is the topology of the evolution tree, and $p_i : E(T) \rightarrow (0,0.5)$ is the mutation probability for each edge in $T$, where $E(T)$ is the edge set of $T$.

We denote $Pr(D_i|T, p_i)$ the probability that the data is $D_i$ given that the model is $(T, p_i)$. Now we present an example for calculating $Pr(D_i|T, p_i)$.

Consider three species $a$, $b$, and $c$. Assume the tree topology $T$ of the model is as shown in Figure 7.16.
For a particular character \( i \), assume the mutation probability for every edge \( e \) is \( p_i(e) \);

\[
\begin{align*}
\sum_{k=0,1, j=0,1} Pr(r_i = k)Pr(a_i = 1|r_i = k)Pr(u_i = j|r_i = k)Pr(b_i = 1|u_i = j)Pr(c_i = 0|u_i = j).
\end{align*}
\]

Now we may obtain the probability that the data is \( D = D_1 \cup ... \cup D_n \), give that the model is \( (T, p_1, ..., p_n) \) as follows.

**Theorem 7.5** Given the data \( D = \cup_{1 \leq i \leq n} D_i \) and the model \( (T, \{p_i|1 \leq i \leq n\}) \), where \( T \) is the topology of the evolution and \( p_i \) is the mutation probability for character \( i \), we obtain that

\[
Pr(D|T, p_1, .., p_n) = \prod_{i=1}^{n} Pr(D_i|T, p_i). \tag{7.1}
\]

**7.4.2.2 Computational Problems**

There are two computational problems for Cavender-Felsenstein model.

- Likelihood of a model
  
  Give the model \( M \), for any data \( D \), try to compute \( Pr(D|M) \);
• Find model with maximum likelihood
  Give data $D$, try to find a model $M$ which maximizes $Pr(D|M)$.

We now discuss the algorithms of computing these two problems as following.

7.4.2.3 Likelihood of a model

We describe the computation problem of the likelihood of a model as

• Input
  Data $D$: $m$ species where each species is characterized by $n$ character;
  Model $M$: $M = (T, p_1, ..., p_n)$;

• Aim
  Compute $Pr(D|M)$.

It is obvious that we can compute $Pr(D|M)$ using (7.1), but it will take exponential time. However, we can define the likelihood recursively and compute the value using dynamic programming as following.

• Definition: For a particular character $i$, let $L_i(v, s)$ be the likelihood of the subtree rooted at $v$, given that character $i$ has state $s$.

• Basis: for all leaf $v$, and state $s$,

\[ L_i(v, s) = \begin{cases} 1 & \text{if } v_i = s \\ 0 & \text{otherwise.} \end{cases} \tag{7.2} \]

• Recurrence: Traverse the tree in postorder, for every internal node $v$ with children, says, $u$ and $w$,

\[ L_i(v, s) = \left[ \sum_{y=0,1} L_i(u, y) Pr(u_i = y | v_i = s) \right] \left[ \sum_{x=0,1} L_i(w, x) Pr(w_i = x | v_i = s) \right] \tag{7.3} \]

• For the Root: Finally, for the root, we have

\[ L = \prod_{i=1}^{m} \left[ \sum_{s=0,1} \left( \frac{1}{2} L_i(root, s) \right) \right] \tag{7.4} \]

Now we analyze the time complexity of the dynamic programming algorithm.

• For every node $v$ and every state $s$, $L_i(v, s)$ can be computed in $O(1)$ time according to (7.3);
• Since there are $n$ nodes and $m$ characters, all $L_i(v,s)$ can be computed in $O(mn)$ time;
• For $L$, it can be computed in $O(m)$ time;
• In total, Likelihood of a tree can be computed in $O(mn)$ time.

7.4.2.4 Find model with maximum likelihood

We describe the computation problem of the likelihood of a model as follows

• Input
  Data $D$: $m$ species where each species is characterized by $n$ character;

• Aim
  Find a model $M = (T, p_1, \ldots, p_n)$ which maximizes $Pr(D|M)$

This is a difficult problem, although we still don’t know whether it is NP-hard or not. A practical solution is to use heuristic method to get close to optima (like [PAUP]).

7.4.3 Final remark for Maximum Likelihood

For the Cavender-Felsenstein model, maximum likelihood is statically consistent, i.e. given long enough sequence, for the Cavender-Felsenstein model, maximum likelihood is able to recover the true tree with arbitrarily high probability.

References


