Review

CS 4364/5364
Spring 2021
Exact String Matching

• Given string $P$, called the pattern, and a longer string $T$, called the text, the exact matching problem is to find all occurrences, if any, of $P$ in $T$.

• Example:
  • $P = "aba", T = "bbabaxababay"
  • $P$ occurs in $T$ at positions: 3, 7, & 9
  • Note, that 2 occurrences overlap
Exact String Matching

Naïve algorithm
• linearly compare the pattern to each starting position in the text $O(nm)$

Z-box preprocessing
• in linear time identifies the longest string at each position that matches a prefix of that string

Boyer-Moore
• Match from right to left in the pattern, and move by more than one character
Ukkonen's algorithm builds a suffix tree in $O(m)$-time using 3 rules:

• **Rule 1** In the current tree $S[i...j]$ ends at a leaf, append character $S[j+1]$ to the label.

• **Rule 2** $S[i...j]$ ends at an internal node or in the middle of a label, and no extension starts with $S[j+1]$, add new leaf.

• **Rule 3** Some path from $S[i...j]$ starts with $S[j+1]$, do nothing.

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**Suffix Trees**

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• **Rule 3** Some path from $S[i...j]$ starts with $S[j+1]$, do nothing.
Using Ukkonen's Algorithm
- build the tree for $S_1$
- match $S_2$ in the tree until a mismatch is found at $S_2[j]$
- restart the Ukkonen algorithm from $j$ (all suffixes of $S[1...j-1]$ are already in the tree)
- repeat for $S_3, S_4, \ldots, S_k$
A suffix array contains the starting position of the suffixes of a string when listed in lexicographic order.

One more concept:

\textit{lcp}(i,j) \text{ for positions } i \text{ and } j \text{ is the length of the longest common prefix of the suffixes at position } i \text{ and } j \text{ in the suffix array}
Global Alignment Problem

- An **alignment** of two sequences is formed by inserting gap characters, '–', in arbitrary locations along the sequences so that they end up with the same length and there are no two spaces at the same position of the two augmented strings.

  baseball---
  ----ballcap
Global Alignment Problem

• An **alignment** of two sequences is formed by inserting gap characters, '−', in arbitrary locations along the sequences so that they end up with the same length and there are no two spaces at the same position of the two augmented strings.

  baseball---  baseball
  ----ballcap  ballca-p
Global Alignment Problem

• An alignment of two sequences is formed by inserting gap characters, '−', in arbitrary locations along the sequences so that they end up with the same length and there are no two spaces at the same position of the two augmented strings.

  baseball   baseball---   baseball
  -ballcap   ----ballcap   ballca-p
Global Alignment Problem

• An **alignment** of two sequences is formed by inserting gap characters, '-' , in arbitrary locations along the sequences so that they end up with the same length and there are no two spaces at the same position of the two augmented strings.

```
  baseball    baseball---    baseball
  ballcap    -----ballcap    ballca-p
```

*How do we know which one of these is best?*
Needleman-Wunsch

- Define an $nxm$ array $V$, the cell $V(i,j)$ will hold the score of the best subalignments of $S[1...i]$ and $T[1...j]$
Needleman-Wunsch

- Define an \( n \times m \) array \( V \), the cell \( V(i,j) \) will hold the score of the best sub alignments of \( S[1...i] \) and \( T[1...j] \)

- The recurrence relation (the base of any DP)

\[
V(i, j) = \max \begin{cases} 
V(i-1, j-1) + \delta(S[i], T[i]) & \text{match/mismatch} \\
V(i-1, j) + \delta(S[i], -) & \text{delete} \\
V(i, j-1) + \delta(-, T[j]) & \text{insert}
\end{cases}
\]
Needleman-Wunsch

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  \end{cases}
  \]

- The initialization is:
  \[
  V(0,0) = 0 \\
  V(0, j) = V(0, j-1) + \delta(-, T[j]) \\
  V(i, 0) = V(i-1, 0) + \delta(S[i], -)
  \]
Needleman-Wunsch

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$V(0,j) = V(0,j-1) + \delta(-, T[j])$

$V(i,0) = V(i-1,0) + \delta(S[i], -)$

Optimal alignment score is in $V(n,m)$
Local Alignment

• Given two strings $S$ and $T$, find the two substrings, $A$ of $S$ and $B$ of $T$, with the highest alignment score.

• Brute-force: Align all substrings of $S$ with all substrings of $T$. There are $\binom{n}{2}$ substrings of $S$, and $\binom{m}{2}$ substrings of $T$. The total running time would be $O(n^3m^3)!$

• Smith and Waterman [1981] developed an algorithm, similar to Needleman-Wunch, that is able to find the optimal local alignment in $O(mn)$-time.
Smith-Waterman

• The recurrence relation

\[
V(i, j) = \max \begin{cases} 
0 & \text{align empty strings} \\
V(i - 1, j - 1) + \delta(S[i], T[i]) & \text{match/mismatch} \\
V(i - 1, j) + \delta(S[i], -) & \text{delete} \\
V(i, j - 1) + \delta(-, T[j]) & \text{insert}
\end{cases}
\]

• The initialization is:

\[V(0, j) = V(i, 0) = 0\]
## Semi-global Alignment

<table>
<thead>
<tr>
<th>Ignored spaces</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>The beginning of $S$</td>
<td>Initialize column 0 to 0s</td>
</tr>
<tr>
<td>The end of $S$</td>
<td>Search for the maximum value in the last column</td>
</tr>
<tr>
<td>The beginning of $T$</td>
<td>Initialize row 0 to 0s</td>
</tr>
<tr>
<td>The end of $T$</td>
<td>Search for the maximum value in the last row</td>
</tr>
</tbody>
</table>
Affine Gap Costs

• The one everyone uses!

• Attributed to Gotoh [1982]

• Define the function $f_{a,b}(k) = a + b \cdot k$ where $a$ and $b$ are tunable parameters (if $a=0$, this is the same as before)

• Can still be solved in $O(mn)$-time and $O(mn)$-space, but we need a bit more sophistication
Affine Gap Costs

\[ f_{\alpha,\beta,\gamma,\delta}(A) = \alpha \cdot mt_A - \beta \cdot ms_A - \gamma \cdot id_A - \delta \cdot gp_A \]

- \( mt_A \) -- number of columns where both characters match
- \( ms_A \) -- number of columns where there characters are different (mismatches)
- \( id_A \) -- number of gap characters (indels)
- \( gp_A \) -- number of gaps
Gotoh's Algorithm

Recursion

\[ F(i, j) = \max \begin{cases} F(i-1,j) - \gamma \\ G(i-1,j) - \gamma - \delta \end{cases} \]

\[ E(i, j) = \max \begin{cases} E(i,j-1) - \gamma \\ G(i,j-1) - \gamma - \delta \end{cases} \]

\[ G(i, j) = \begin{cases} G(i-1,j-1) + \alpha & \text{if } S[i] = T[i] \\ G(i-1,j-1) - \beta & \text{if } S[i] = T[i] \end{cases} \]

Initialization

\[ G(0,j) = E(0,j) = -1 \times (\gamma + \delta j) \]

\[ G(i,0) = F(i,0) = -1 \times (\gamma + \delta j) \]

\[ E(i,0) = -\infty \]

\[ F(0,j) = -\infty \]
An example

\[ s_1 = \text{AACCCG} \]
\[ s_1 = \text{AAGGCC} \]

<table>
<thead>
<tr>
<th>( A_1 )</th>
<th>( A_2 )</th>
<th>( A_3 )</th>
<th>( A_4 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>mt</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>ms</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>id</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>gp</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
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Question: what values of \( \alpha, \beta, \gamma, \) and \( \delta \) should we choose to get the “best” alignment?
Question: what values of $\alpha, \beta, \gamma$, and $\delta$ should we choose to get the “best” alignment?
Parametric Alignment

• when two parameters are free, there are only $O(n^2)$ different regions

• the boundaries are always lines

• the boundaries can be found in $O(n^4)$-time
Parametric Alignment

- when two parameters are free, there are only \( O(n^2) \) different regions
- the boundaries are always lines
- the boundaries can be found in \( O(n^4) \)-time
A Digression on Accuracy

How would we know how accurate an alignment was if we knew the right answer?

The sum-of-pairs accuracy measures the fraction of substitutions from the ground truth alignment that are recovered in a computed alignment.
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The (Sequence) Database Search Problem

Given a database $D$ of sequences (DNA, Protein, Books, Web Pages) and a query string $Q$ find the string(s) $S$ in $D$ which is/are closest matches to $Q$ under a defined scoring function.
The (Sequence) Database Search Problem

Given a database $D$ of sequences (DNA, Protein, Books, Web Pages) and a query string $Q$ find the string(s) $S$ in $D$ which is/are closest matches to $Q$ under a defined scoring function.

Scoring functions are typically either

- **Semi-global alignment** -- The best possible alignment score between a substring $A$ of $S$ and $Q$, or
- **Local alignment** -- The best possible alignment score between a substring $A$ of $S$ and a substring $B$ of $Q$. 
**FastA/FastP**

**Step 1:** Identify "hotspots" -- find $k$-mers that are shared between the query and the database using a lookup table (this table is $4^k$ for DNA and RNA, $20^k$ for Proteins)

**Step 2:** locating diagonal runs -- pairs (or larger groups) of hot spots such that the distance between the hot-spots is the same in both the query and the database sequence

**Step 3:** re-score the best diagonal runs -- rather than fixed inter-spot scores based on length, rescore the alignments using actual character matches

**Step 4 (FastA):** join diagonal runs -- using a fixed score based on the locations of the regions, join them with a fixed gap-style cost

**Step 5 (FastA):** (banded) Smith-Waterman -- using a fixed score based on the locations of the regions, join them with a fixed gap-style cost
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**Query**

```
CAACTTGCC
```

**Database**

```
ACGGTTACGTAGGTCCG
GCGTAGGCAGAAGTTGCCCGT
ACGAGTAGCCGTCAGTC
TAGTCGTATGAAGTCGTAGTC
```
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Basic Local Alignment Search Tool (BLAST)

**Step 1:** Query-preprocessing:
1. split the query into $k$-mers
2. create a set of neighbors of each $k$-mer, other $k$-mers such that the replacement scores are not too high (this can be done with a $\Sigma^k$ lookup table)

**Step 2:** Database scanning -- label any instance of a neighbor of $Q$ in any sequence $S$ of $D$ as a "hit", collect all of these hits

**Step 3:** Hit extension -- for any sequence $S$ in $D$, with two hits (for protein, one for DNA) extend in either direction without gaps until the score drops too low

**Step 4:** Gapped extension -- run modified Smith-Waterman in each direction from the mid-point of the hits until the alignment score goes too low.
Other Database Search Tools

MegaBLAST
  • only for DNA but searches multiple sequences at once

BLAT (BLAST-Like Alignment Tool)
  • only for DNA, indexes the database not the query

PatternHunter
  • uses spaced-seeds rather than substrings to search the database

PSI-BLAST (Position-Specific Iterated BLAST)
  • updates the replacement matrix using an MSA until unchanged

QUASAR (Q-gram Alignment base on Suffix ARrays)
  • uses the pigeon hole principle to find sequences in the database that are potential matches

LSH-ALL-PAIRS
  • uses k-mer orderings to find probable matching sequences using a minimizer scheme
Multiple Sequence Alignment Problem

Given
  • A set of sequences $s_1, s_2, \ldots, s_k$ (of length $n$)
  • An objective function

Find:
  • an $\ell$ by $k$ matrix ($\ell \geq n$)
  • where row $i$ contains the characters from sequence $s_i$ in order with inserted gap characters
  • that is optimal under the objective function.

Input

AGTPNGNP
AGPGNP
AGTTPNGNP
CGTPNP
ACGTUNGNP
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Find:
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Input

AGTPPNGNP
AGPGNP
AGTTPPNGNP
CGTPNP
ACGTUNGNP

Output

A−GT−PNGNP
A−G--P−GNP
A−GTTPNPGNP
−CGT−PN--P
ACGT−UNGNP
Multiple Sequence Alignment

What is the objective function:

- most popular -- **Sum-of-Pairs Objective**:
  - given some scoring function for a pairwise alignment $PairScore(s_1', s_2')$
  - the score of the multiple alignment is:

\[
SPScore(\{s'_1, s'_2, \ldots, s'_k\}) := \sum_{1 \leq i < j \leq k} PairScore(s'_i, s'_j)
\]
Finding an optimal MSA

Can we find an optimal multiple sequence alignment?
Finding an optimal MSA

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  • yes! we can use the same dynamic programming methods we had for pairwise alignment
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• assume there are only 3 sequences, then the recursion is the following:
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- assume there are only 3 sequences, then the recursion is the following:

\[
\begin{align*}
V[i, j, k] &= \max \left\{ \\
V[i-1, j-1, k-1] &+ \delta(s_1[i], s_2[j]) + \delta(s_2[j], s_3[k]) + \delta(s_1[i], s_3[k]) \\
V[i-1, j-1, k] &+ \delta(s_1[i], s_2[j]) + \delta(s_2[j], s_3[k]) + \delta(s_1[i], s_3[k]) \\
V[i-1, j, k-1] &+ \delta(s_1[i], s_2[j]) + \delta(s_2[j], s_3[k]) + \delta(s_1[i], s_3[k]) \\
V[i, j-1, k-1] &+ \delta(s_1[i], s_2[j]) + \delta(s_2[j], s_3[k]) + \delta(s_1[i], s_3[k]) \\
V[i-1, j, k] &+ 2\delta(s_1[i], s_2[j]) \\
V[i, j-1, k] &+ 2\delta(s_2[j], s_3[k]) \\
V[i, j, k-1] &+ 2\delta(s_3[k], s_3[k]) \\
\right\}
\]
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• assume there are only 3 sequences, then the recursion is the following:

\[
V[i, j, k] = \max \begin{cases} 
V[i - 1, j - 1, k - 1] + \delta(s_1[i], s_2[j]) + \delta(s_2[j], s_3[k]) + \delta(s_1[i], s_3[k]) \\
V[i - 1, j - 1, k] + \delta(s_1[i], s_2[j]) + \delta(s_2[j],'-' + \delta(s_1[i],')-') \\
V[i - 1, j, k - 1] + \delta(s_1[i],')-') + \delta(s_2[j], s_3[k]) + \delta(s_1[i], s_3[k]) \\
V[i, j - 1, k - 1] + \delta('-', s_2[j]) + \delta(s_2[j], s_3[k]) + \delta('-', s_3[k]) \\
V[i - 1, j, k] + 2\delta(s_1[i],')-') \\
V[i, j - 1, k] + 2\delta(s_2[j],')-') \\
V[i, j, k - 1] + 2\delta(s_3[k],')-') 
\end{cases}
\]

What happens with 4 sequences? How many clauses are in the max? How big is V?
Finding an optimal MSA

Can we find an optimal multiple sequence alignment?
• Yes! We can use the same dynamic programming methods we had for pairwise alignment.
• Assume there are only 3 sequences, then the recursion is the following:

\[
V[i, j, k] = \max \begin{cases} 
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V[i - 1, j - 1, k] + \delta(s_1[i], s_2[j]) + \delta(s_2[j], s_3[k], '-') + \delta(s_1[i], '-') \\
V[i - 1, j, k - 1] + \delta(s_1[i], '-') + \delta(s_2[j], s_3[k]) + \delta(s_1[i], s_3[k]) \\
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V[i, j - 1, k] + 2\delta(s_2[j], '-') \\
V[i, j, k - 1] + 2\delta(s_3[k], '-') \\
\end{cases}
\]

What happens with 4 sequences? How many clauses are in the max? How big is \(V\)?
The Center Star Method

\[ S_c = \arg \min_{1 \leq i \leq k} \left\{ \sum_{1 \leq j \leq k} D(S_i, S_j) \right\} \]

The final step is to build an alignment so that all of the alignments between \( S_c \) and \( S_i \) are satisfied.
Progressive Alignment

Similar to center star in that we use pairwise alignments to help build multiple alignments.

Introduced by Feng and Doolittle in 1987.

Basic idea:
- compute pairwise alignment scores for each pair of sequences
- generate a guide tree which ensures similar sequences are near to each other
- align sequences (or groups) one-by-one from the leaves of the tree
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"Progressive alignment from consensus sequences"

ClustalW

Algorithm
Algorithm

• Calculate the \( \binom{n}{2} \) pairwise alignments.
ClustalW

Algorithm

- Calculate the $\binom{n}{2}$ pairwise alignments.
- Compute the pairwise distance between sequences as $1 - \frac{x}{y}$ where $x$ is the number of gap characters, and $y$ is the number of matches.
Algorithm

- Calculate the \( \binom{n}{2} \) pairwise alignments.
- Compute the pairwise distance between sequences as \( 1 - \frac{x}{y} \) where \( x \) is the number of gap characters, and \( y \) is the number of matches.
- Use the neighbor-joining method to create the guide tree (we will talk about the details of this later).
ClustalW

Algorithm
- Calculate the \( \binom{n}{2} \) pairwise alignments.
- Compute the pairwise distance between sequences as \( 1 - \frac{x}{y} \) where \( x \) is the number of gap characters, and \( y \) is the number of matches.
- Use the neighbor-joining method to create the guide tree (we will talk about the details of this later).
- From the leaves compute the alignment at each internal node.
ClustalW

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- Use the neighbor-joining method to create the guide tree (we will talk about the details of this later).
- From the leaves compute the alignment at each internal node
  - each alignment will be between either: (i) two sequences, (ii) two partial alignment, or (iii) a sequence and a partial alignment.
MUSCLE
(MUltiple Sequence Comparison by Log-Expectation)

Algorithm:
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1. **draft progressive alignment** -- similar to ClustalW but with
   - LE score for aligning profiles,
   - a more efficient tree building algorithm, and
   - a more efficient pairwise comparison (using \( k \)-mer counting).
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   - redefine the pairwise distances using the Kimura distance $-\ln\left(1 - D - \frac{D^2}{5}\right)$
   - $D$ is the fraction of matches.
   - re-align.
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3. **refinement** -- deleting an edge in the guide tree creates two sub-groups of sequences with
   induced sub-alignments.
   - Extract those two sub-alignments and realign them.
   - Only keep the new alignment if the SP score is increased.
   - Stop when SP has not improved: in a predefined number of iterations or when all edges are visited.
Some terminology

Unrooted

A
E
D
B
C

Rooted

B
C

A
E
D
Tree Building Algorithms

Two major classes:

• **Distance-based methods**
  • for each pair of items, get some evolutionary distance (edit distance, melting temp for DNA hybridization, strength of antibody cross reactions)
  • find a tree that "agrees" with the distances either ultrametric or additive
  • most cases in real life don't match this so you have to find a good approx.

• **Maximum-Parsimony methods**
  • character-based data only (not necessarily DNA/RNA/Protein data)
  • infer sequences at the internal nodes and maximize parsimony (minimize the mutations) along branches
Let $D$ be a symmetric $n \times n$ matrix of real numbers. An ultrametric tree for $D$ is a rooted tree $T$ such that:

- $T$ contains $n$ leaves labeled by a unique row of $D$.
- Each internal node of $T$ is leveled by one entry from $D$ and has at least 2 children.
- Along any path from the root to a leaf, the numbers labeling the internal nodes are strictly decreasing.
- For any two leaves $i,j$ of $T$, $D(i,j)$ is the level of the least common ancestor of $i$ and $j$ in $T$.

Therefore, $T$ (if it exists) is a compact representation of $D$. 
Additive-distance trees

Ultrametric is the "holy grail", but when its not able to be obtained, we can use a less stringent model.

Definition

- Let $D$ be a symmetric $n$ by $n$ matrix where the numbers on the diagonal are all 0, and the off-diagonal numbers are all strictly positive.
- Let $T$ be an edge-weighted tree with at least $n$ nodes, where $n$ distinct nodes are labeled with rows of $D$.
- Tree $T$ is called an additive tree if for every pair of labeled nodes $(i, j)$, the path from node $i$ to node $j$ has total weight (or distance) exactly $D(i,j)$.

Problem

- Given a matrix $D$ with 0s on the diagonals, and positive numbers in all other locations, find the additive tree $T$ or determine that one does not exist.
Parsimony

Parsimony's main principle: "if there exists more than one possible answer to the question, the simpler answer is more likely to be correct" (when you hear hooves think horses not zebra).
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Therefore, we can change the sequence data into a binary labeling
  • 0 if the character is unchanged in this sequence
  • 1 if it has already been modified
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Therefore, we can change the sequence data into a binary labeling
- 0 if the character is unchanged in this sequence
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**Definition** Given an $n$ by $m$ binary character matrix $M$, a phylogenetic tree for $M$ is a rooted tree $T$ with exactly $n$ leaves that obeys the following:
- each of the $n$ objects labels exactly 1 leaf of $T$
- each of the $m$ characters labels exactly 1 edge of $T$
- for any object $p$, the characters that label the edges along the unique path from the root to the leaf specify all of the characters of $p$ whose state is 1.
The Maximum Parsimony Problem (sometimes called the Large Parsimony Problem) is stated as follows:

- Given a matrix $M$ for a set $S$ of $n$ taxa
- find the tree $T$ which is leaf labeled by $S$ and minimizes the edges that are labeled by character position changes.

This problem is NP-Hard

Branch and Bound
- start with a 3-leaf tree, add each leaf at each edge by breaking it and adding a new internal node
- computation tree grows exponentially

2-approximation
- find the minimum spanning tree in the leaf graph, convert into a phylogeny by adding edges
- $O(n^2m)$ time
Neighbor Joining

**Algorithm** Given a distance matrix \( M \) with rows labeled \((1,2,3,...,n)\)

- let \( Z = \{\{1\},\{2\},\{3\},...\{n\}\} \) (* the set of initial clusters *)
- for all \( \{i\},\{j\} \in Z \) set \( D(\{i\},\{j\})=M_{i,j} \)
- while \( |Z|>1 \)
  - define \( u_A = 1/(n-2) \times \sum_{F \in Z} D(A,F) \) for all \( A \in Z \)
  - \((A,B) = \arg\min_{(A,B) \in Z} D(A,B) - u_A - u_B\)

- form \( C \) by creating a new cluster root and connecting it to the two cluster roots with edge weights \( \frac{1}{2} (D(A,B) + (u_A - u_B)) \) and \( \frac{1}{2} (D(A,B) + (u_B - u_A)) \) respectively.
- \( Z = Z \cup \{C\} - \{A,B\} \)
- define \( D(F,C) = D(C,F) = \frac{1}{2} ( D(A,F) + D(B,F) - D(A,B) ) \)
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2. for all \( \{i\},\{j\} \in Z \) set \( D(\{i\},\{j\})=M_{i,j} \)
3. while |\( Z \)|>1
   3.1 define \( u_A = 1/(n-2) \times \sum_{F \in Z} D(A,F) \) for all \( A \in Z \)
   3.2 \((A, B) = \arg \min_{(A,B) \in Z} D(A, B) - u_A - u_B\)
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$\mathcal{O}(n^3)$ total time
Burrows-Wheeler Transform

Remember our old friend the suffix array?

\[ T = \text{mississippi} \$

<table>
<thead>
<tr>
<th>( \text{SA}_T )</th>
<th>( \text{BWT}_T )</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>$\text{mississippi}$</td>
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<tr>
<td>11</td>
<td>i$\text{mississippi}$</td>
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\[
BWT_T = \begin{cases} 
T[SA_T[i] - 1] & \text{if } SA_T[i] > 1 \\
\$ & \text{if } SA_T[i] = 1 
\end{cases}
\]
A **BWT Index** for a sequence $T$ is a data structure with:

- the $BWT_T$ encoded as a wavelet tree; and
- the integer array $C[0...\sigma]$, where $C[c]$ stores the number of occurrences of the characters less than $c$ in $T$

With the BWT Index, you can:

- construct the Suffix Array
- recover $T$ in $O(\log n)$ per character
Counting Occurrences

Input
• pattern, \( P = p_1, p_2, p_3, \ldots, p_m \)
• count array, \( C \)
• \( BWT T_\$ \), \( L \)

Output
• number of occurrences of \( P \) in \( T \)
Counting Occurrences

\[ i = m \]

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\[
i = m
\]
\[
(sp, ep) = (1, n)
\]
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• count array, $C$
• $BWT_{T\$}, L$

Output
• number of occurrences of $P$ in $T$

$i = m$
$(sp, ep) = (1, n)$
while $sp \leq ep$ and $i \geq 1$ do
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• \( BWT_{T^\$} \), \( L \)

Output
• number of occurrences of \( P \) in \( T \)

\[
i = m
(\text{sp, ep}) = (1, n)
\text{while sp} \leq \text{ep and } i \geq 1 \text{ do}
\quad c = p_j
\quad \text{sp} = C[c] + \text{rank}_c(L, \text{sp}-1) + 1
\]
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\quad sp = C[c] + rank_c(L, sp-1)+1 \\
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i = i - 1
\]
\[
\textbf{if } ep < sp \textbf{ then}
\]
\[
\text{return } 0
\]
Counting Occurrences

Input
- pattern, \( P = p_1, p_2, p_3, \ldots, p_m \)
- count array, \( C \)
- \( BWT_T, L \)

Output
- number of occurrences of \( P \) in \( T \)

\[
i = m \\
(sp, ep) = (1, n) \\
\textbf{while} \ sp \leq ep \ \textbf{and} \ i \geq 1 \ \textbf{do} \\
\quad c = p_j \\
\quad sp = C[c] + rank_c(L, sp-1)+1 \\
\quad ep = C[c] + rank_c(L, ep) \\
\quad i = i - 1 \\
\textbf{if} \ ep < sp \ \textbf{then} \\
\quad \text{return} \ 0 \\
\textbf{else} \\
\]
Counting Occurrences

Input
- pattern, $P = p_1, p_2, p_3, \ldots, p_m$
- count array, $C$
- $BWT_{T^\$}, L$

Output
- number of occurrences of $P$ in $T$

\[
i = m
\]
\[
(sp, ep) = (1, n)
\]
\[
\textbf{while } sp \leq ep \textbf{ and } i \geq 1 \textbf{ do}
\]
\[
c = p_j
\]
\[
sp = C[c] + \text{rank}_c(L, sp-1) + 1
\]
\[
ep = C[c] + \text{rank}_c(L, ep)
\]
\[
i = i - 1
\]
\[
\textbf{if } ep < sp \textbf{ then}
\]
\[
\text{return } 0
\]
\[
\textbf{else}
\]
\[
\text{return } ep - sp + 1
\]
Bidirectional BWT

Given a string $T$ a **bidirectional BWT index** is a data structure with the following operations:
Bidirectional BWT

Given a string $T$ a **bidirectional BWT index** is a data structure with the following operations:

- `$isLeftMaximial(i,j)$` -- 1 if $BWT_{T}[i...j]$ contains more than one value, 0 otherwise
- `$isRightMaximial(i,j)$` -- 1 if $BWT_{T}[i...j]$ contains more than one value, 0 otherwise
Bidirectional BWT

Given a string $T$ a bidirectional BWT index is a data structure with the following operations:

- $isLeftMaximal(i,j)$ -- 1 if $BWT_{T^\dagger}[i...j]$ contains more than one value, 0 otherwise
- $isRightMaximal(i,j)$ -- 1 if $BWT_{T^\dagger}[i...j]$ contains more than one value, 0 otherwise
- $enumerateLeft(i,j)$ -- return the distinct values $BWT_{T^\dagger}[i...j]$ in lexicographic order
- $enumerateRight(i,j)$ -- return the distinct values $BWT_{T^\dagger}[i...j]$ in lexicographic order
Bidirectional BWT

Given a string $T$ a **bidirectional BWT index** is a data structure with the following operations:

- $\text{isLeftMaximal}(i,j)$ -- 1 if $BWT_{T^\$}[i...j]$ contains more than one value, 0 otherwise
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- $\text{enumerateLeft}(i,j)$ -- return the distinct values $BWT_{T^\$}[i...j]$ in lexicographic order
- $\text{enumerateRight}(i,j)$ -- return the distinct values $BWT_{T^\$}[i...j]$ in lexicographic order
- $\text{extendLeft}(c,I(W,T),I(W,T))$ -- returns the pair $(I(cW,T),I(Wc,T))$
- $\text{extendRight}(c,I(W,T),I(W,T))$ -- returns the pair $(I(Wc,T),I(cW,T))$
**Suffix Tree Traversal**

*Given* bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

*Output* pairs $(v, |\ell(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$
Suffix Tree Traversal

Given bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

Output pairs $(v, |\ell(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$.

$S = \text{empty stack}$
Suffix Tree Traversal

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Output pairs $(v, |\ell(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

```plaintext
S = empty stack
S.push(([1...n+1], [1...n+1], 0))
```
Suffix Tree Traversal

**Given** bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

**Output** pairs $(v, |\ell(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

```python
S = empty stack
S.push(([1...n+1], [1...n+1], 0))
while S is not empty do
```

[Continue with the algorithm details]
**Suffix Tree Traversal**

**Given** bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

**Output** pairs $(v, |ℓ(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

---

$S = \text{empty stack}$

$S.push(([1...n+1], [1...n+1], 0))$

**while** $S$ is not empty **do**

$([i,j],[i',j'],d) = S.pop()$
Suffix Tree Traversal

Given bidirectional BWT idx of string T (interval [1...n+1] represents the root)

Output pairs (ν, ℓ(ν)) for all nodes ν in the suffix tree of T where ν is the interval of ν in the suffix array of T$

S = empty stack
S.push(([1...n+1], [1...n+1], 0))
while S is not empty do
  ([i,j],[i',j'],d) = S.pop()
  output ([i,j],d)
Suffix Tree Traversal

Given bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

Output pairs $(v, \ell(v))$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

$S = \text{empty stack}$

$S.push(([1...n+1], [1...n+1], 0))$

while $S$ is not empty do

$([i,j],[i',j'],d) = S.pop()$

output $([i,j],d)$

$\Sigma' = idx.\text{enumerateLeft}(i,j)$
Suffix Tree Traversal

**Given** bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

**Output** pairs $(v, |\ell(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

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S = empty stack
S.push(([1...n+1], [1...n+1], 0))
while S is not empty do
    ([i,j],[i',j'],d) = S.pop()
    output ([i,j],d)
    $\Sigma' = idx.enumerateLeft(i,j)$
    $l = \emptyset$
```
Suffix Tree Traversal

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Output pairs $(v, |\ell(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

S = empty stack
S.push(((1...n+1), (1...n+1), 0))

while S is not empty do
  $(i,j, [i',j'], d) = S.pop()$
  output $(i,j,d)$
  $\Sigma' = idx.enumerateLeft(i,j)$
  $l = \emptyset$
  for $c \in \Sigma'$ do
Suffix Tree Traversal

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output $(i,j,d)$

$\Sigma' = \text{idx.\text{enumerateLeft}}(i,j)$
$l = \emptyset$

for $c \in \Sigma'$ do

$l = l \cup \{\text{idx.\text{exgendLeft}}(c,i,j,i',j')\}$
Suffix Tree Traversal

**Given** bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

**Output** pairs $(v, |ℓ(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

```
S = empty stack
S.push(((1...n+1), 1...n+1, 0))

while S is not empty do
    ([i,j],[i',j'],d) = S.pop()
    output ([i,j],d)
    Σ' = idx.enumerateLeft(i,j)
    I = ∅
    for c ∈ Σ' do
        I = I ∪ {idx.exgendLeft(c,[i,j],[i',j'])}
    for ([i,j],[i',j']) ∈ I do
```


**Suffix Tree Traversal**

**Given** bidirectional BWT $idx$ of string $T$ (interval $[1...n+1]$ represents the root)

**Output** pairs $(v, |\ell(v)|)$ for all nodes $v$ in the suffix tree of $T$ where $v$ is the interval of $v$ in the suffix array of $T$

$$S = \text{empty stack}$$

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output $([i,j],d)$

$
\Sigma' = idx.\text{enumerateLeft}(i,j)$

$I = \emptyset$

**for** $c \in \Sigma'$ **do**

$I = I \cup \{idx.\text{extendLeft}(c,[i,j],[i',j'])\}$

**for** $([i,j],[i',j']) \in I$ **do**

if $idx.\text{isRightMaximal}(i',j')$ **then**


Suffix Tree Traversal

**Given** bidirectional BWT \( \text{idx} \) of string \( T \) (interval \([1...n+1]\) represents the root)

**Output** pairs \((v, |ℓ(v)|)\) for all nodes \( v \) in the suffix tree of \( T \) where \( v \) is the interval of \( v \) in the suffix array of \( T\$

```plaintext
S = empty stack
S.push(([1...n+1], [1...n+1], 0))
while S is not empty do
    ([i,j],[i',j'],d) = S.pop()
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    for c ∈ Σ' do
        I = I ∪ {idx.exgendLeft(c,[i,j],[i',j'])}
    for ([i,j],[i',j']) ∈ I do
        if idx.isRightMaximal(i',j') then
            S.push(([i,j],[i',j'],d+1))
```
Computational Problem

Given
• a reference genome \( G \), and
• a set of reads \( R = (r_1, r_2, r_3, \ldots, r_k) \in (\Sigma^n)^k \) where each read \( r \) is a subsequence of \( G \) with a small number changes

Output
• the semi-global alignment of \( r_i \) and \( G \) for all \( r_i \in R \) with \(<k \) changes
Given

• a reference genome $G$, and
• a set of reads $R = (r_1, r_2, r_3, ..., r_k) \in (\Sigma^n)^k$ where each read $r$ is a subsequence of $G$ with a small number changes

Output

• the semi-global alignment of $r_i$ and $G$ for all $r_i \in R$ with $<k$ changes

call these $k$-error mappings
Aligning reads

AGGCCTAAAGGGCCTT

Only need to go to a depth of $2m$ since the best alignment can't be worse than deleting one string and inserting the other.
Aligning reads

AGGCCTAAAGGCCTT

Only need to go to a depth of $2m$ since the best alignment can't be worse than deleting one string and inserting the other.

We don't have the suffix tree!
Dynamic Programming using a BWT

**define** \( \text{Branch}(d, [i...j]) \):

\[
\text{for } c \in \text{idx.enumerateRight}(i, j) \text{ do}
\]

**process** \((c, d)\)

- **if** \( d = 2^m \text{ and score} > \text{threshold} \) **do**
  - **output** alignment
- **if** \( d < 2^m \) **do**
  - \( \text{Branch}(d+1, \text{idx.extendRight}(c, [i, j])) \)

*compute the dynamic programming table row using character c in row d*
Dynamic Programming using a BWT

\[
\text{define } \text{Branch}(d, [i...j]): \\
\text{for } \ c \in \text{idx.enumerateRight}(i, j) \ \text{do} \\
\quad \text{process } (c, d) \\
\quad \text{if } \ d = 2m \text{ and } \text{score} > \text{threshold} \ \text{do} \\
\quad \quad \text{output alignment} \\
\quad \text{if } \ d < 2m \ \text{do} \\
\quad \quad \text{Branch}(d+1, \text{idx.extendRight}(c, [i, j])) \\
\]

compute the dynamic programming table row using character \( c \) in row \( d \)

\( O(m\sigma) \)-time
Dynamic Programming using a BWT

```python
define Branch(d,[i...j]):
    for c ∈ idx.enumerateRight(i,j) do
        process (c,d)
        if d = 2m and score > threshold do
            output alignment
        if d < 2m do
            Branch(d+1,idx.extendRight(c, [i,j]))
```

compute the dynamic programming table row using character c in row d

$O(m\sigma)$-time
$O(m^2+m\sigma)$-space
Backtracking

Start by matching the exact sequence

If the algorithm reaches a point with no matches swap out characters already matched and restart search from that there

When ties occur, start with the character with the lowest quality score, keep the rest in a stack

Keep track of how many changes are made
Backtracking

Start by matching the exact sequence.

If the algorithm reaches a point with no matches swap out characters already matched and restart search from that there.

When ties occur, start with the character with the lowest quality score, keep the rest in a stack.

Keep track of how many changes are made.

"Bowtie conducts a quality-aware, greedy, randomized, depth-first search through the space of possible alignments."
Bowtie2

1. Extract seeds

   Soots
   +, 0: CCAGTACCGTCACAAGC
   +, 10: TCGGCTCTATTTTAAC
   +, 20: TTACCCCGGCGCTGTA
   -, 0: TACGGGCTGGTAAAA
   -, 10: GGTAAAATAGGCTGA
   -, 20: GGCTGAGGCTACTTG

   Seeds
   +, 0: CCAGTACCGTCACAAGC
   +, 10: TCGGCTCTATTTTAAC
   +, 20: TTACCCCGGCGCTGTA
   -, 0: TACGGGCTGGTAAAA
   -, 10: GGTAAAATAGGCTGA
   -, 20: GGCTGAGGCTACTTG

2. Align with FM Index

   Ungapped alignment with FM Index

3. Prioritize resolve

   Seed alignments (as Burrows-Wheeler ranges)
   
   Extension candidates

   BW row: 684: chr12: 1955
   BW row: 624: chr2: 462
   BW row: 211: chr4: 762
   BW row: 213: chr12: 1935
   BW row: 652: chr12: 1945

4. Extend

   SIMD dynamic programming align

   SAM alignments
   r1 0 chr12 1936 +
   AS:i:0 XS:i:-2 XM:i:0
   YM:i:0 MD:Z:36 YI:Z:0
   ...

   Walk-left with FM Index
Sequencing Applications

RNA sequencing

adapted from figure 1.2 in Mäkinen, et al. 2015
Sequencing Applications

RNA sequencing

adapted from figure 1.2 in Mäkinen, et al. 2015
Seed Searching

Maximal Mappable Prefix (MMP) for read $R$, read start location $i$, and genome $G$:

• the longest substring $R[i \ldots (i + MML - 1)]$

• such that there exists some set $J = \{j_1, j_2, \ldots, j_n\}$ where for all $j_k \in J$
  
  $R[i \ldots (i+MML-1)] = G[j \ldots (j_k+MML-1)]$

• where $MML$ is the Maximal Mapping Length

The basic algorithm is

• map from the start of the read as far as possible

• restart searching from the next position to the right
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![Diagram of RNA-seq read and Genome with MMP 1 highlighted]
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The "splice junctions" are inferred from the alignment.
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- where $MML$ is the Maximal Mapping Length

The basic algorithm is

- map from the start of the read as far as possible
- restart searching from the next position to the right

The key is that the re-mapping only happens from the end of MMP1 rather than finding all maximal matchings then stitching.

The "splice junctions" are inferred from the alignment.
Take Aways for STAR

Non-contiguous alignment for RNA-Seq is not a totally solved problem

STAR is specifically designed to take introns into account during alignment

Algorithm is extendable to longer read lengths since it can ignore poor quality regions and chimeric reads

Large memory consumption, but fast due to the use of uncompressed SAs
TopHat

Using strict alignment criteria, TopHat uses Bowtie to align reads to the whole genome

Construct the set of mapped sequences
  • the "islands" of sequence that map to the genome
  • using the assemble functionality of MAQ

Splice junctions usually happen with predictable bases
  • consider all possible pairs as potential splice locations
  • create a set of new sequences
  • store the $k$-mer surrounding such locations as a seed for mapping

For each unmapped read
  • extract all unique $k$-mers from the "high quality" region
  • here $k \sim 10$
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Splice junctions usually happen with predictable bases:
- consider all possible pairs as potential splice locations
- create a set of new sequences
- store the $k$-mer surrounding such locations as a seed for mapping

For each unmapped read:
- extract all unique $k$-mers from the "high quality" region
- here $k \approx 10$
Take Aways from TopHat

Uses existing software to do some of the heavy lifting

Strict parameters on the splice junctions make the algorithm fast

Limited in the splice junction sequence
De Bruijn Graphs

Definition a $k$-order de Bruijn Graph (DBG) $D = (V,E)$ has:

- $V = \Sigma^k$ -- there is a vertex for each possible $k$-mer
- $E = \{ax \to xb \mid a,b \in \Sigma, x \in \Sigma^{(k-1)}\}$ -- for each $(k+1)$-mer $axb$, there is an edge from the $k$-mer $ax$ to the $k$-mer $xb$
Sequence de Bruijin Graphs

What is most commonly used in practice for genome assembly is a subset of the DBG based on a given sequence

This is sometimes in literature referred to as simply a de Bruijin Graph
Assembly alternatives

Alternative 1: Overlap-Layout-Consensus (OLC) assembly
Alternative 2: De Bruijn graph (DBG) assembly
SOAPdenovo

A

Fragment and paired-end sequencing of libraries with variant insert sizes.

2~10 Kb

150~500 bp

B

Represent read sequence overlap using de Bruijn graph

Remove erroneous connections on the graph

C

(i) Clip tips
(ii) Remove low-coverage links
(iii) Resolve tiny repeats
(iv) Merge bubbles

D

Break at repeat boundaries and output contigs

Scaffold construction

E

F

Gap closure
Jaccard Similarity

Measures the similarity of two sets of items $A$ and $B$ as:

$$J(A, B) = \frac{|A \cap B|}{|A \cup B|} = \frac{|A \cap B|}{|A| + |B| - |A \cap B|}$$

$J(A, B)$ = \frac{|A \cap B|}{|A| + |B| - |A \cap B|}$
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Used also used in computer vision, sometimes called the "Intersection over Union" (IoU) metric.
Jaccard Similarity

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Used also used in computer vision, sometimes called the "Intersection over Union" (IoU) metric.

How would we use Jaccard for sequences?
Jaccard Similarity

In sequence analysis we construct a sets of $k$-mers for each of the strings being compared.
Min-Hash Sketch

Calculating the union and intersection of a set of anything (in particular $k$-mers) can be time consuming ($O(n)$ time)

Can we calculate it faster?
Min-Hash Sketch

Calculating the union and intersection of a set of anything (in particular $k$-mers) can be time consuming ($O(n)$ time)

Can we calculate it faster?

Consider the following scenario:
• given a hash function on $k$-mers $h: \Sigma^k \rightarrow \mathbb{Z}^+$
• and the sets of $k$-mers for two string $A$ and $B$,
• What is the probability that $\min_{c \in A} \{h(c)\} = \min_{c \in B} \{h(c)\}$?
Calculating the union and intersection of a set of anything (in particular $k$-mers) can be time consuming ($O(n)$ time)

Can we calculate it faster?

Consider the following scenario:

• given a hash function on $k$-mers $h: \Sigma^k \rightarrow \mathbb{Z}^+$
• and the sets of $k$-mers for two string $A$ and $B$,
• What is the probability that $\min_{c \in A} \{ h(c) \} = \min_{c \in B} \{ h(c) \}$?

Turns out that

$$Pr_h \left[ \min_{c \in A} \{ h(c) \} = \min_{c \in B} \{ h(c) \} \right] = J(A, B)$$
Min-Hash Sketch

Why is \( Pr_h \left[ \min_{c \in A} \{h(c)\} = \min_{c \in B} \{h(c)\} \right] = J(A, B) \)?
Min-Hash Sketch

Why is $Pr_h \left[ \min_{c \in A} \{h(c)\} = \min_{c \in B} \{h(c)\} \right] = J(A, B)$?

Think of $h$ as applying a randomized ordering on the $k$-mers.
Min-Hash Sketch

Why is $Pr_h \left[ \min_{c \in A} \{ h(c) \} = \min_{c \in B} \{ h(c) \} \right] = J(A, B)$?

Think of $h$ as applying a randomized ordering on the $k$-mers.

If the minimum $k$-mer from the union is in the intersection, it will be minimum for both $A$ and $B$. 
Min-Hash Sketch

Why is $Pr_h \left[ \min_{c \in A} \{ h(c) \} = \min_{c \in B} \{ h(c) \} \right] = J(A, B)$?

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How many minimum $k$-mers from the union can we choose?
Min-Hash Sketch

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Think of $h$ as applying a randomized ordering on the $k$-mers.

If the minimum $k$-mer from the union is in the intersection, it will be minimum for both $A$ and $B$.

How many minimum $k$-mers from the union can we choose?

What fraction of those are in the intersection?
Min Hash Sketch with 1 Hash

The idea is that you choose the minimum $n$ elements according to the hash $h$, and compute jaccard on these subsets.

This subset of $k$-mers is called a "sketch"

Sometimes called "MinHash bottom sketching"
Minimizer Schemes

For a window of $w$ consecutive $k$-mers from a sequence $S$, a minimizer scheme selects the minimum according to an ordering $o$ as a representative.

Minimizer schemes have two special properties:
- two sequences with a long exact match must select the same $k$-mers
- there are no large gap between selected $k$-mers

Use in $k$-mer counting, de Bruijn graph construction, data structure sparsification, etc.
Problems with Jaccard
Problem Formulation

Given:
- a read $A$,
- a maximum per-base error rate, $\epsilon_{\text{max}}$, and
- a reference genome, $B$.

Goal:
- identify target positions in $B$ where $A$ will map with $\leq \epsilon_{\text{max}} |A|$ errors
- identify target positions $B_i$ where:
  \[ J(A, B_i) \geq \mathcal{G}(\epsilon_{\text{max}}, k) - \delta \]

\[ \mathbb{E} (J (A, B_i)) \geq \mathcal{G}(\epsilon_{\text{max}}, k) \] but only in expectation, so $\delta = (90\% \text{ confidence interval})$ is subtracted to account for variance in the estimate
Stage 1

Find all ranges in $B$ that could be a match to $A$

- they have $\geq s\tau = m$ number of matching $k$-mers

This is actually performed somewhat in reverse

- first find all matching minimizers
- sort them by location
- in each range of $m$ matches
  - ask if they are they condensed enough

---

**Algorithm 1. Stage 1 of mapping read**

**Input:** read $A$, reference index
- map $\mathcal{H}$ (hash $k$-mer
  - $\rightarrow$ pos$[]$, s, $\tau$
**Output:** list $T$ of candidate
- regions in the reference

```
1 $m = \lceil s \cdot \tau \rceil$
2 $T = L = []$
3 for $e \in W_h(A)$ do
4     $L$.append($\mathcal{H}(e)$)
5 sort($L$)
6 for $i \leftarrow 0$ to $|L| - m$ do
7     $j \leftarrow i + (m - 1)$
8     if $(L[j] - L[i]) < |A|$ then
9         $T$.append($\langle L[j] - |A| + 1, L[i] \rangle$)
```
Stage 1

Find all ranges in $B$ that *could* be a match to $A$

- they have $\geq s\tau = m$ number of matching $k$-mers

This is actually performed somewhat in reverse

- first find all matching minimizers
- sort them by location
- in each range of $m$ matches
  - ask if they are they condensed enough

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map $H$ (hash $k$-mer $\rightarrow$ pos[]), $s$, $\tau$

**Output:** list $T$ of candidate regions in the reference

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3. for $e \in W_h(A)$ do
   4. $L.append(H(e))$
4. sort($L$)
5. for $i \leftarrow 0$ to $|L| - m$ do
   6. $j \leftarrow i + (m - 1)$
   7. if $(L[j] - L[i]) < |A|$ then
      8. $T.append(\langle L[j] - |A| + 1, L[i] \rangle)$

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3. for \(e \in W_k(A)\) do
   4. \(L.append(\mathcal{H}(e))\)
5. sort(\(L\))
6. for \(i \leftarrow 0\) to \(|L| - m\) do
   7. \(j \leftarrow i + (m - 1)\)
   8. if \((L[j] - L[i]) < |A|\) then
      9. \(T.append(\)
         10. \(\langle L[j] - |A| + 1, L[i]\rangle )\)
```
Stage 1

Find all ranges in $B$ that could be a match to $A$
- they have $\geq s\tau = m$ number of matching $k$-mers

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**Algorithm 1. Stage 1 of mapping read**

**Input:** read $A$, reference index
- map $\mathcal{H}$ (hash $k$-mer $\rightarrow$ pos[],), $s$, $\tau$

**Output:** list $T$ of candidate regions in the reference

```
1  m = \lceil s \cdot \tau \rceil
2  T = L = []
3  for e ∈ W_h(A) do
4      L.append(\mathcal{H}(e))
5  sort(L)
6  for i ← 0 to |L| − m do
7      j ← i + (m − 1)
8      if (L[j] − L[i]) < |A| then
9        T.append((L[j] − |A| + 1, L[i])
```

Algorithm 2: Stage 2 of mapping a read

Input: index \( M \), stage 1 output \( T \), \( s \), \( \tau \)
Output: \( \mathcal{P} \)

1. \( \mathcal{L}_0 = \{\} \);
2. \( \mathcal{L}_0.\text{insert}(W_h(A)) \);
3. for \( (x, y) \in T \) do
   4. \( i \leftarrow x \);
   5. \( j \leftarrow x + |A| \);
   6. \( \mathcal{L} \leftarrow \mathcal{L}_0 \);
   7. \( \mathcal{L}.\text{insert(} \text{getMinimizers}(i,j) \text{)} \);
   8. \( \mathcal{J} = \text{solveJaccard}(\mathcal{L}) \);
   9. if \( \mathcal{J} \geq \tau \) then
      10. \( \mathcal{P}.\text{append}(\langle i, \mathcal{J} \rangle) \);
   while \( i \leq y \) do
      11. \( \mathcal{L}.\text{delete(} \text{getMinimizers}(i,i+1) \text{)} \);
      12. \( \mathcal{L}.\text{insert(} \text{getMinimizers}(j,j+1) \text{)} \);
      13. \( \mathcal{J} = \text{solveJaccard}(\mathcal{L}) \);
      14. if \( \mathcal{J} \geq \tau \) then
         15. \( \mathcal{P}.\text{append}(\langle i, \mathcal{J} \rangle) \);
      16. \( i++ \);
      17. \( j++ \);
   18. Function getMinimizers(p,q):
      19. return \( \{ h : \langle h, \text{pos} \rangle \in W(B), p \leq \text{pos} \leq q \} \);
   20. Function solveJaccard(\( \mathcal{L} \)):
      21. return \( \frac{\sum_{0 \leq k \leq s-1} \mathcal{L}[k]}{s} \);

For every \( B_i \) in all potential places identified in stage 1
- estimate the jaccard using the winnowed sketch
- retain it as a match if its larger than \( \tau \)
CANU

Follows one of the same basic procedure we saw for short read assembly:
  • calculate the overlaps between reads
  • decide on a layout for the reads
  • construct contigs using the consensus sequences

Uses an adaptation of MHAP for overlaps which is an extension of MinHash
  • frequent $k$-mers like those in loops can sometimes interfere with overlap prediction
  • they use $tf-idf$ (term frequency–inverse document frequency) weights to bias the hashes used
So far we have only talked about sequences
• Many *interactions* in biology are not captured in sequences
• We use graph theory to make biological conclusions
Combined Networks

The meaning of the nodes and edges used in a network representation depends on the type of data used to build the network and this should be taken into account when analysing it.
Analyzing the topological features of a network is a useful way of identifying relevant participants and substructures that may be of biological significance.

Some methods
- centrality analysis
- topological clustering
- search for shortest paths
- motifs that are more often applied to networks with directionality
Annotation enrichment analysis
Annotation enrichment analysis

Annotation enrichment analysis uses gene/protein annotations to infer which annotations are over-represented in a list of genes/proteins taken from a network.

• Annotation tools perform statistical test tries to that answer:
  - When sampling $X$ proteins (test set) out of $N$ proteins (reference set; graph or annotation), what is the probability that $x$, or more, of these proteins belong to a functional category $C$ shared by $n$ of the $N$ proteins in the reference set.

• The result of this test provides us with a list of terms that describe the list/network, or rather a part of it, as a whole.
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- This is a widely used technique that helps characterize the network as a whole or sub-sets of it, such as inter-connected communities found through topological clustering analysis.
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More complex versions of this technique can factor in continuous variables such as expression fold change.
Pathway reconstruction problem

**Given**
- weighted, directed interactome, \( G \), with physical & regulatory interactions
- receptors, \( S \), in a signaling pathway of interest
- transcriptional regulators (TRs), \( T \), in the same pathway
- a parameter \( k \)

**Find**
- the \( k \) highest scoring loopless paths that begin at any receptor in \( S \) and end at any TR in \( T \)
- the score of the path is the product of the edge weights (all in \([0,1]\))
Modify the graph

- Add an extra source node $s$ and an extra sink node $t$
- Add edges $(s, x)$ for $x \in S$
- Add edges $(y, t)$ for $y \in T$
- Assign the following costs to each edge $(u, v)$

$$c_{uv} = \begin{cases} 
-\log(w_{uv}) & \text{if } u, v \in V \setminus \{s, t\} \\
0 & \text{if } u = s \text{ or } v = t
\end{cases}$$

- Let the cost of a path be the sum of the edges on the path.
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\end{cases}
\]

- Let the cost of a path be the sum of the edges on the path.

The least costly \( s \rightarrow t \) path will be the highest weight \( s \rightarrow t \) path.
PathLinker

Algorithm

• Find the set of $k$ highest scoring paths $P_1, P_2, ..., P_k$ where each $P_i = (V_i, E_i)$
• Return $G_k = \left( \bigcup_{1 \leq i \leq k} V_i, \bigcup_{1 \leq i \leq k} E_i \right)$
NetBox

Basic Algorithm

A. create human interactome (both interaction and pathway information)
B. find mutated or copy number variant genes for condition in question
C. extract these genes and their neighbors from the interactome
D. run the Newman-Girvan algorithm to find modules
E. analyze statistical significance
MashMap Idea

First find the winnowed representation of a read

Run the MinHash Sketch on this representation

Reduces the space the hash considers and speeds up computation

They define the **winnowed-minhash** estimate:

\[
\mathcal{J}(A, B_i) = \frac{\left| S \left( W(A) \cup W(B_i) \right) \cap S(W(A)) \cap S(W(B_i)) \right|}{\left| S \left( W(A) \cup W(B_i) \right) \right|}
\]