Reflections | Projections

Christine Bakan
Vice President of Software and Bioinformatics @ Roche
Delivering Genomic Insights with Advanced Analytics
Fri Sept 20 4:00PM SC2405

Alfred Spector
CTO of Two Sigma
Data Science - Immense Good Yet Baffling Challenges
Fri Sept 20 6:00PM SC1404

Donald Kossmann
Director of Microsoft Research Redmond
The Global AI Supercomputer
Fri Sept 20 5:00PM SC2405

CS 466
Introduction to Bioinformatics
Lecture 7

Mohammed El-Kebir

September 18, 2019

Course Announcements

Instructor:

- Mohammed El-Kebir (melkebir)
- Office hours: Wednesdays, 3:15-4:15pm

TA:

- Ashwin Ramesh (aramesh7)
- Office hours: Fridays, 11:00-11:59am in SC 3405

Homework 1 due 9/18 by 11:59pm

Outline

- Multiple sequence alignment
- Carillo-Lipman algorithm
- Progressive alignment

Reading:

- Jones and Pevzner. Chapter 6.10
- Material based on Chapter 14.6 in book “Algorithms on Strings, Trees and Sequences” by Dan Gusfield
- Lecture notes

Multiple Sequence Alignment Problem w/ SP-Score

A **multiple sequence alignment** $\mathcal{M}$ between k strings $\mathbf{v}_1, \ldots, \mathbf{v}_k$ is a $k \times q$ matrix, where $q = \{\max\{|\mathbf{v}_i| : i \in [k]\}, \ldots, \sum_{i=1}^{k} |\mathbf{v}_i|\}$ such that the i-th row contains the characters of $\mathbf{v}_i$ in order with spaces '-' interspersed and no column contains k spaces

MSA-SP problem: Given strings strings $\mathbf{v}_1, \ldots, \mathbf{v}_k$ find multiple sequence alignment $\mathcal{M}^*$ with **minimum** value of SP-score$(\mathcal{M}^*) = \sum_{i=1}^{k} \sum_{j=i+1}^{k} S(\mathbf{v}_i, \mathbf{v}_j)$ where $S(\mathbf{v}_i, \mathbf{v}_j)$ is the score of the induced pairwise alignment of $(\mathbf{v}_i, \mathbf{v}_j)$ in $\mathcal{M}^*$

Sum-of-Pairs (SP) Score

$\mathbf{v}_1$	A	T	–	G	C	G	–
$\mathbf{v}_2$	A	–	C	G	T	–	C
$\mathbf{v}_3$	A	T	C	A	C	–	A

Multiple sequence alignment $\mathcal{M}$

$S(\mathbf{v}_i, \mathbf{v}_j)$ is score of induced pairwise alignment of sequences $(\mathbf{v}_i, \mathbf{v}_j)$

$\mathbf{v}_1$	A	T	–	G	C	G	–
$\mathbf{v}_2$	A	–	C	G	T	–	C

$\mathbf{v}_1$	A	T	–	G	C	G	–
$\mathbf{v}_3$	A	T	C	A	C	–	A

$\mathbf{v}_2$	A	–	C	G	T	–	C
$\mathbf{v}_3$	A	T	C	A	C	–	A

$$\text{SP-score}(\mathcal{M}) = \sum_{i=1}^{k} \sum_{j=i+1}^{k} S(\mathbf{v}_i, \mathbf{v}_j)$$

Sum-of-Pairs (SP) Score – Example

$\mathbf{v}_1$	A	T	G	–	C
$\mathbf{v}_2$	A	–	G	–	C
$\mathbf{v}_3$	A	T	C	C	C

Match score: 3
Mismatch score: 1
Gap score: -1

Question: Calculate SP-score$(\mathcal{M}) = \sum_{i=1}^{k} \sum_{j=i+1}^{k} S(\mathbf{v}_i, \mathbf{v}_j)$

Inverse Problem: From Pairwise to Multiple Alignment

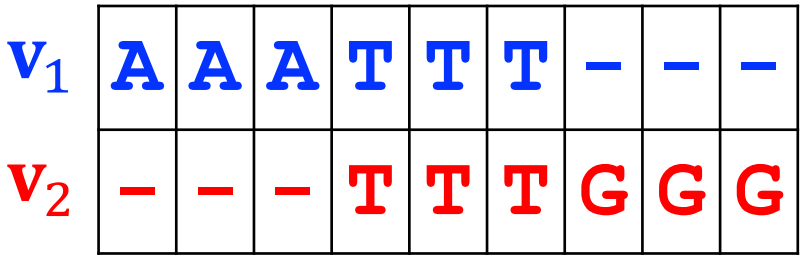
v_1	A	C	G	C	T	G	G	-	C
v_2	A	C	G	C	-	-	G	A	G

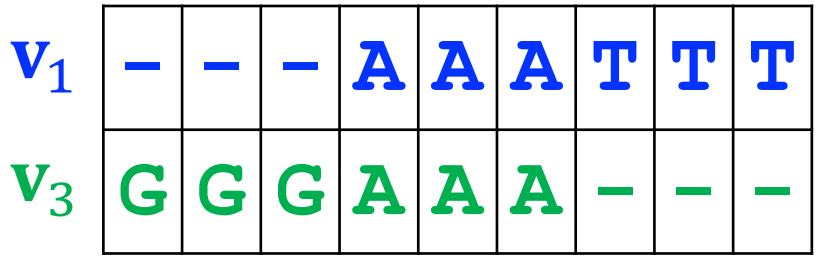
v_1	A	C	-	G	C	T	G	G	-	C
v_3	G	C	C	G	C	A	-	G	A	G

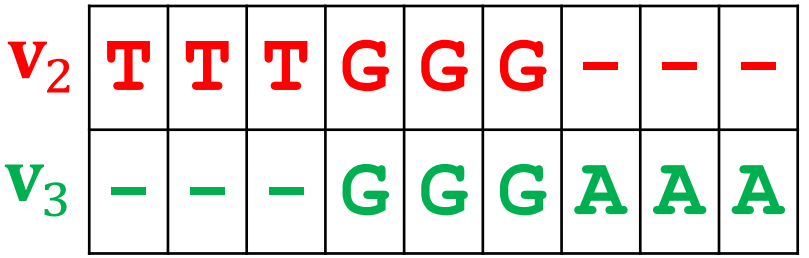
v_2	A	C	-	G	C	-	G	A	G
v_3	G	C	C	G	C	A	G	A	G

Question: Can we construct a multiple alignment that induces the above three pairwise alignments?

Inverse Problem: From Pairwise to Multiple Alignment



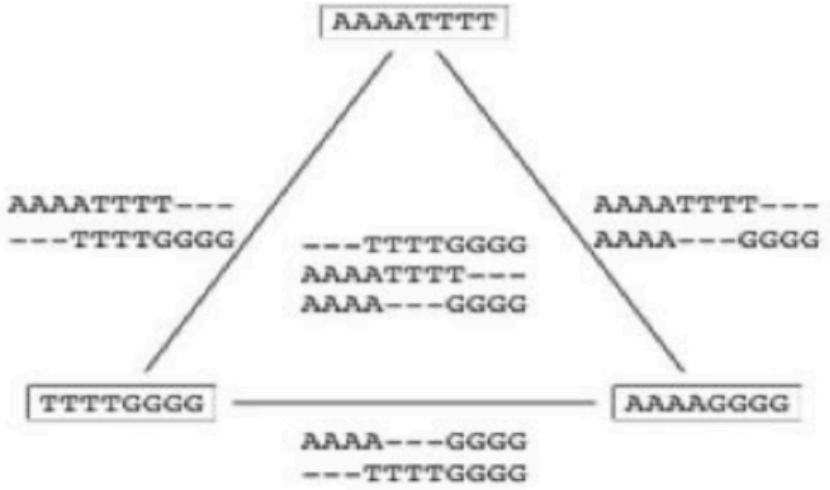




Question: Can we construct a multiple alignment that induces the above three pairwise alignments?

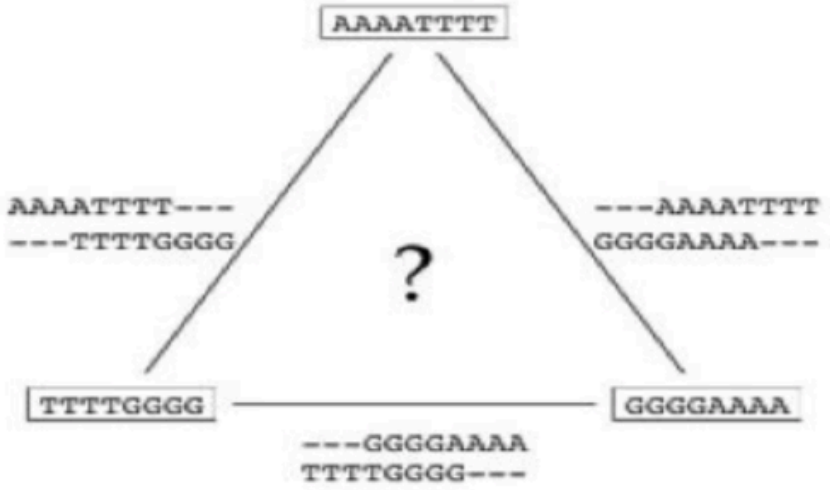
Compatibility

Compatible: Pairwise alignments can be combined into multiple alignment



(a) Compatible pairwise alignments

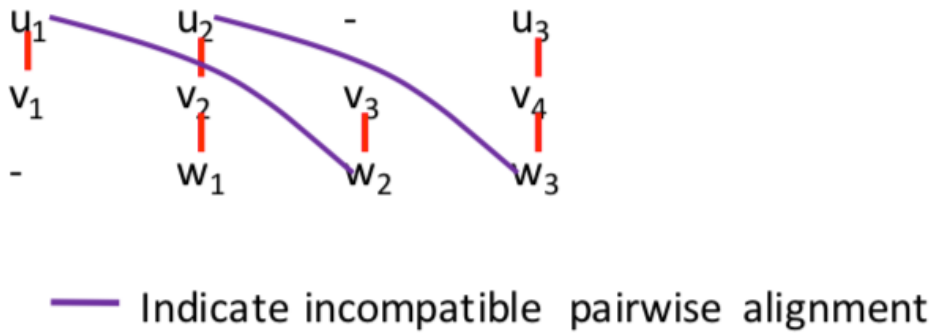
Incompatible: Pairwise alignments *cannot* be combined into multiple alignment



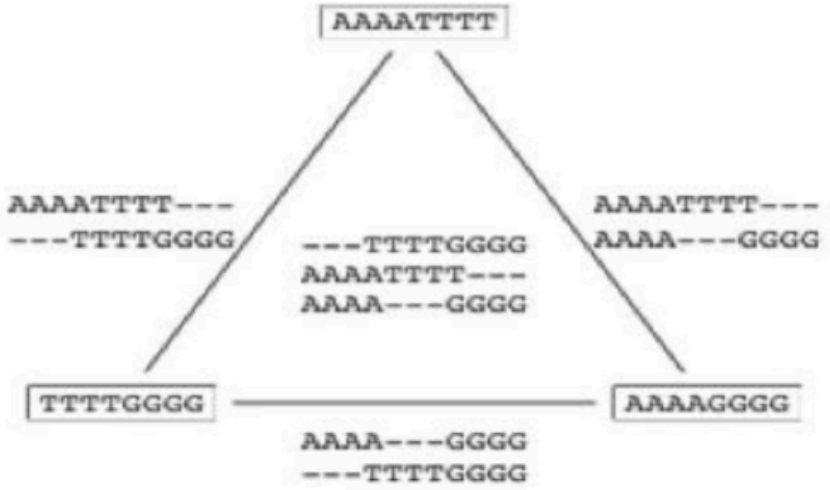
(b) Incompatible pairwise alignments

Compatibility

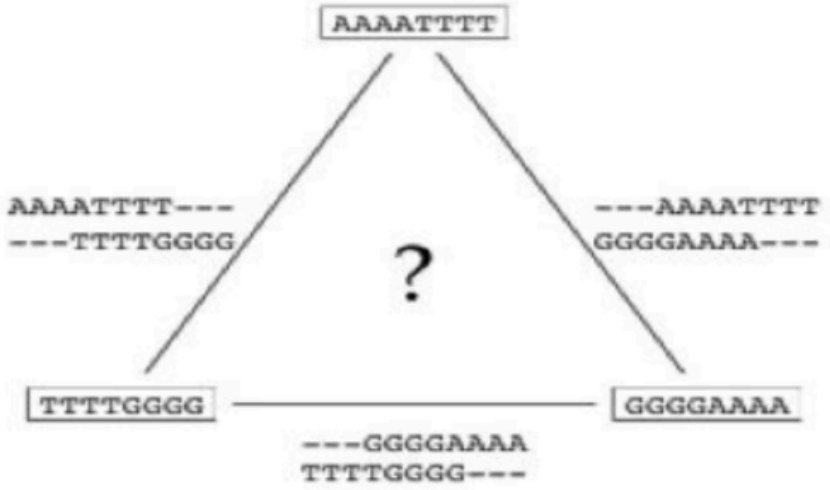
Compatible: Pairwise alignments can be combined into multiple alignment



Incompatible: Pairwise alignments *cannot* be combined into multiple alignment



(a) Compatible pairwise alignments



(b) Incompatible pairwise alignments

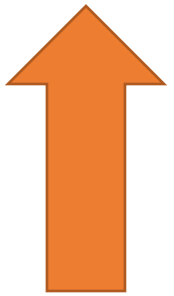
From Compatible Pairwise to Multiple Alignment

Optimal multiple alignment

Easy

Pairwise alignments between *all* pairs of sequences, but they are *not* necessarily optimal

(Sub)optimal multiple alignment



Challenging

Good (or optimal) *compatible* pairwise alignments between all sequences

Outline

- Multiple sequence alignment
- Carillo-Lipman algorithm
- Progressive alignment

Reading:

- Jones and Pevzner. Chapter 6.10
- Material based on Chapter 14.6 in book “Algorithms on Strings, Trees and Sequences” by Dan Gusfield
- Lecture notes

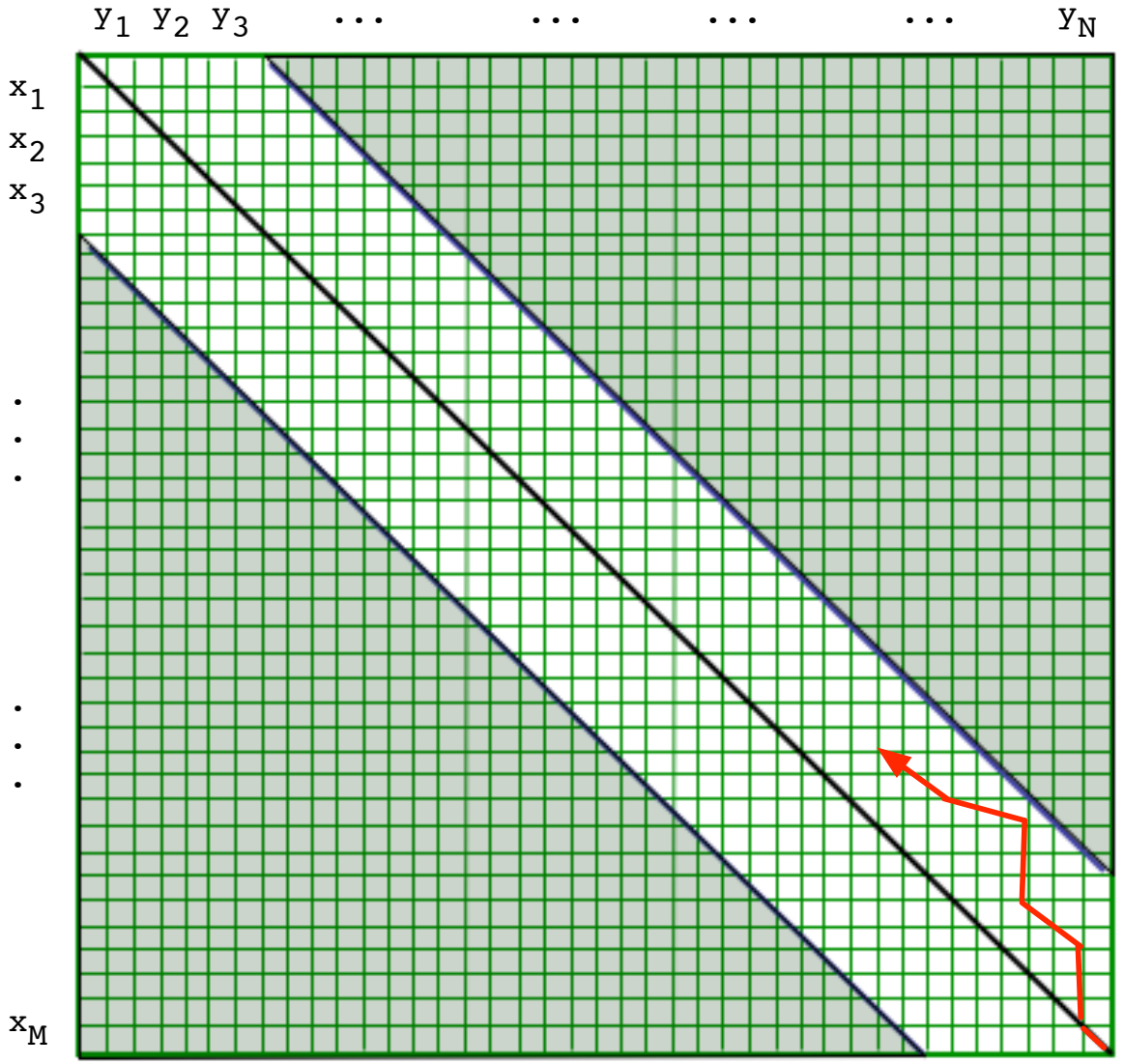
Recall: Banded Alignment

Alignment is a path from source $(0, 0)$ to target (m, n) in edit graph

Constraint path to band of width k around diagonal

Running time: $O(nk)$

Question: Alternative ways of constraining search space?



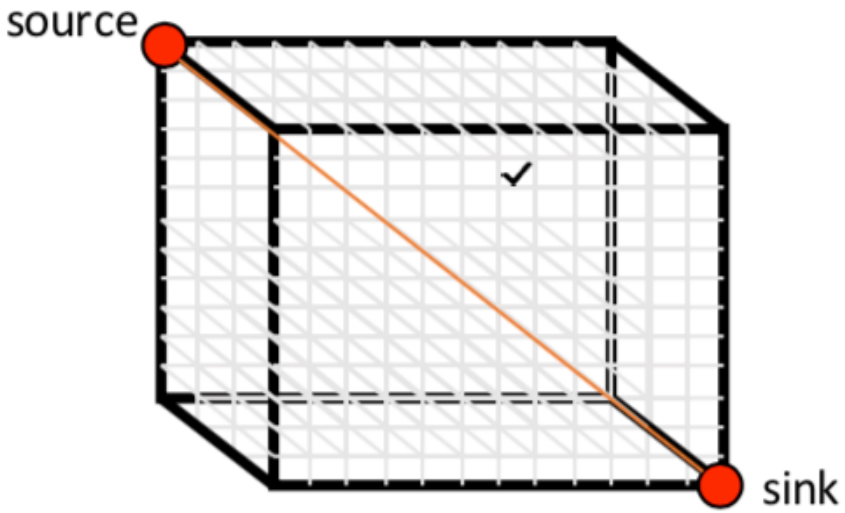
Constrain traceback to band of DP matrix (penalize big gaps)

Figure source: http://jinome.stanford.edu/stat366/pdfs/stat366_win0607_lecture04.pdf

Forward Dynamic Programming

Banded alignment: constraint path to polyhedron around diagonal

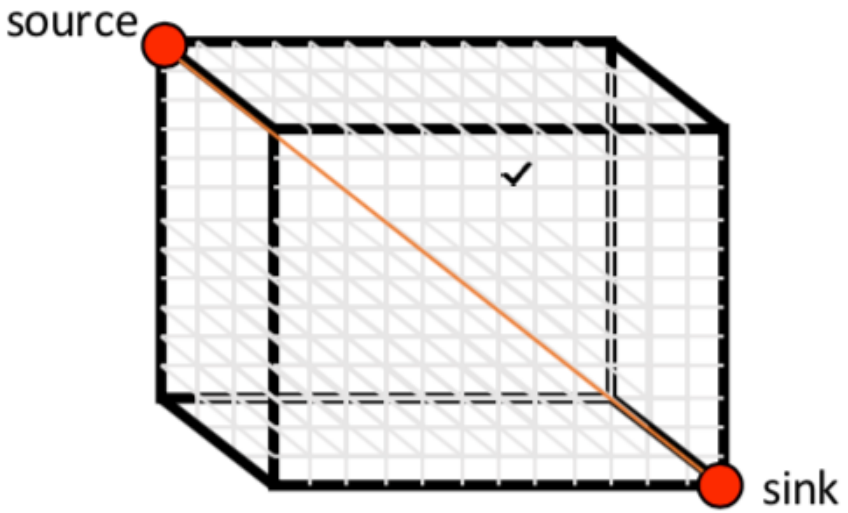
Alternatively: Stop computing when remaining alignment will be suboptimal

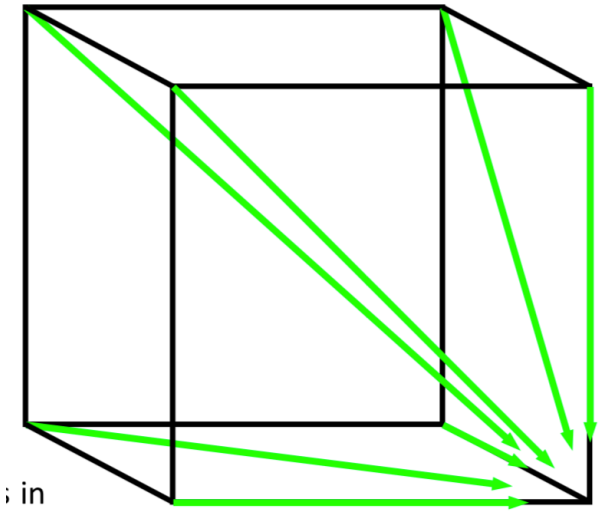


Forward Dynamic Programming

Banded alignment: constraint path to polyhedron around diagonal

Alternatively: Stop computing when remaining alignment will be suboptimal





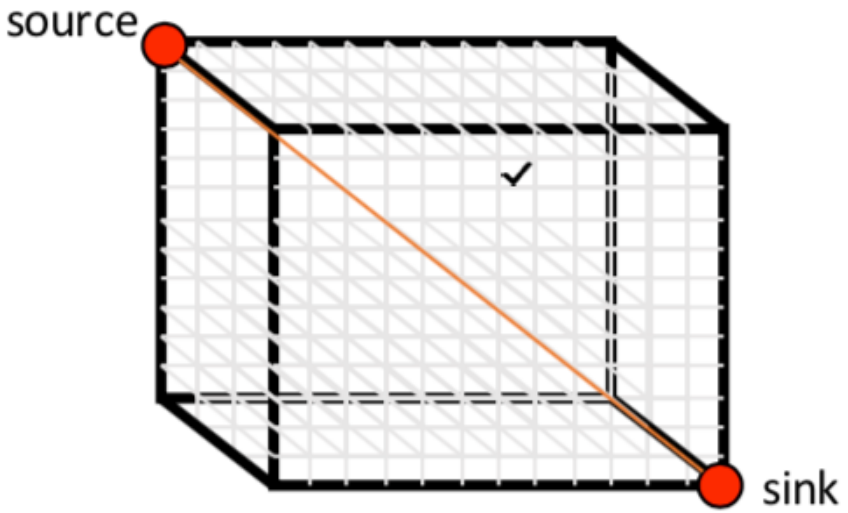
Forward dynamic programming – think of Dijkstra's algorithm:

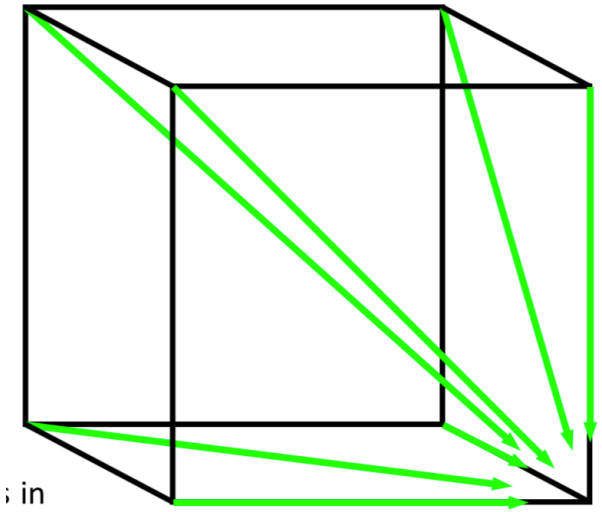
- Queue of unvisited vertices
- Maintain $p[i,j,k]$ shortest distance yet found from $(0,0,0)$ to (i,j,k).
- For each directed edge (i,j,k) to (i',j',k') with cost w, set $p[i',j',k'] = \min\{p[i',j',k'], p[i,j,k] + w\}$

Forward Dynamic Programming

Banded alignment: constraint path to polyhedron around diagonal

Alternatively: Stop computing when remaining alignment will be suboptimal





Forward dynamic programming – think of Dijkstra's algorithm:

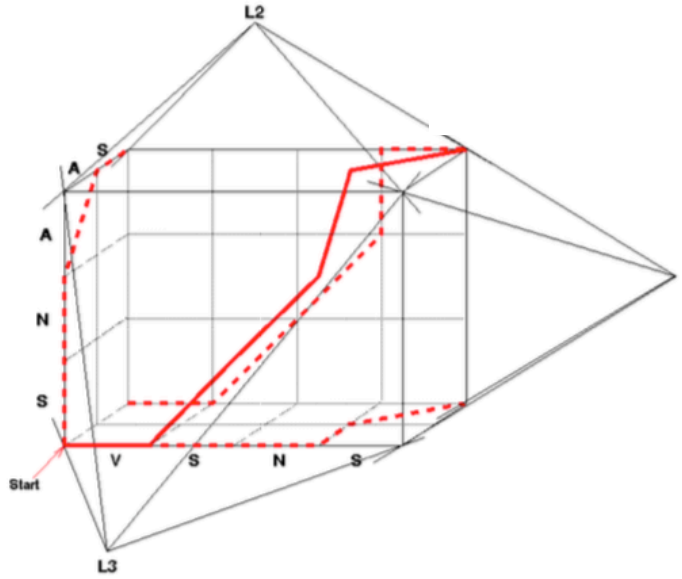
- Queue of unvisited vertices
- Maintain $p[i,j,k]$ shortest distance yet found from $(0,0,0)$ to (i,j,k).
- For each directed edge (i,j,k) to (i',j',k') with cost w, set $p[i',j',k'] = \min\{p[i',j',k'], p[i,j,k] + w\}$

Question: Can we remove vertices from consideration based on alignment score of prefix?

Alignment Projection and SP-score

Sequences $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$ each of length n

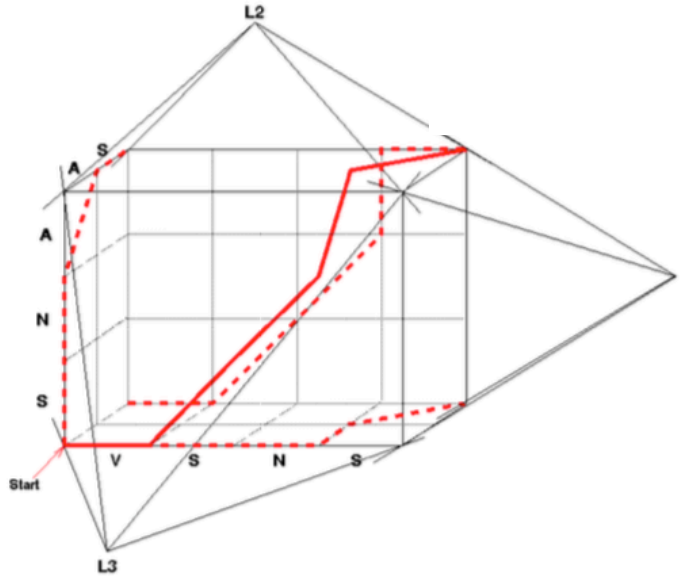
- $D(i,j,k)$ is min SP-cost of aligning $\mathbf{v}_1[1..i], \mathbf{v}_2[1..j], \mathbf{v}_3[1..k]$
- $d_{p,q}(i,j)$ is cost of induced alignment of $\mathbf{v}_p[1..i], \mathbf{v}_q[1..j]$
- $D_{p,q}(i,j)$ is min cost of aligning $\mathbf{v}_p[1..i], \mathbf{v}_q[1..j]$



Alignment Projection and SP-score

Sequences $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$ each of length n

- $D(i,j,k)$ is min SP-cost of aligning $\mathbf{v}_1[1..i], \mathbf{v}_2[1..j], \mathbf{v}_3[1..k]$
- $d_{p,q}(i,j)$ is cost of induced alignment of $\mathbf{v}_p[1..i], \mathbf{v}_q[1..j]$
- $D_{p,q}(i,j)$ is min cost of aligning $\mathbf{v}_p[1..i], \mathbf{v}_q[1..j]$

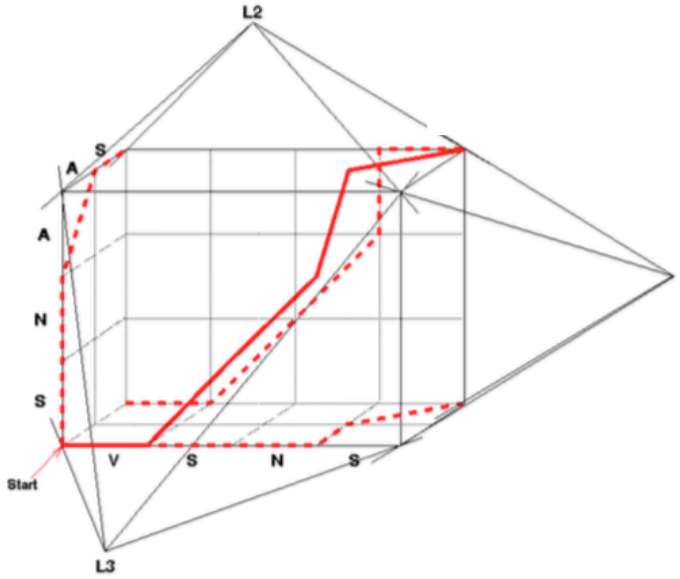


$$d_{p,q}(i,j) \geq D_{p,q}(i,j)$$

Alignment Projection and SP-score

Sequences $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$ each of length n

- $D(i,j,k)$ is min SP-cost of aligning $\mathbf{v}_1[1..i], \mathbf{v}_2[1..j], \mathbf{v}_3[1..k]$
- $d_{p,q}(i,j)$ is cost of induced alignment of $\mathbf{v}_p[1..i], \mathbf{v}_q[1..j]$
- $D_{p,q}(i,j)$ is min cost of aligning $\mathbf{v}_p[1..i], \mathbf{v}_q[1..j]$

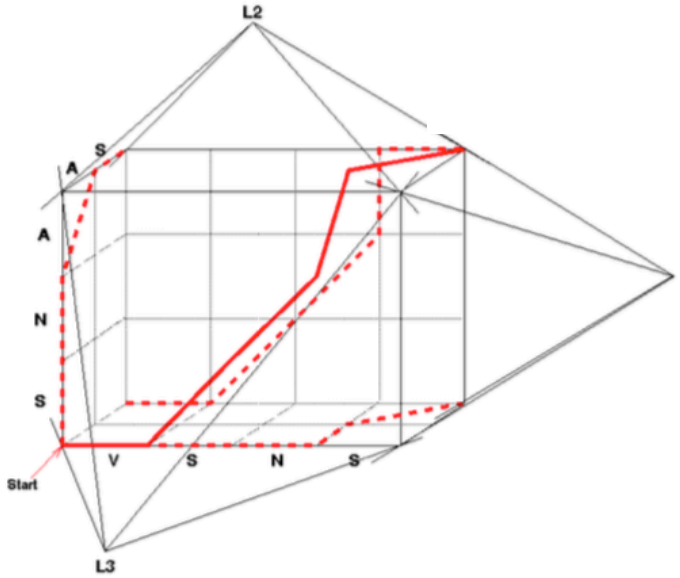


$$d_{p,q}(i,j) \geq D_{p,q}(i,j)$$

$$\begin{aligned} D(i,j,k) &= d_{1,2}(i,j) + d_{1,3}(i,k) + d_{2,3}(j,k) \\ &\geq D_{1,2}(i,j) + D_{1,3}(i,k) + D_{2,3}(j,k) \end{aligned}$$

Carillo-Lipman Method

- $D^+(i,j,k)$ is min SP-cost of alignment of **suffix** $\mathbf{v}_1[i..n], \mathbf{v}_2[j..n], \mathbf{v}_3[k..n]$
- $d^+_{p,q}(i,j)$ is cost of induced alignment of **suffix** $\mathbf{v}_p[i..n], \mathbf{v}_q[j..n]$
- $D^+_{p,q}(i,j)$ is min cost of alignment of **suffix** $\mathbf{v}_p[i..n], \mathbf{v}_q[j..n]$



$$d^+_{p,q}(i,j) \geq D^+_{p,q}(i,j)$$

$$\begin{aligned} D^+(i,j,k) &= d^+_{1,2}(i,j) + d^+_{1,3}(i,k) + d^+_{2,3}(j,k) \\ &\geq D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k) \end{aligned}$$

Carillo-Lipman Method

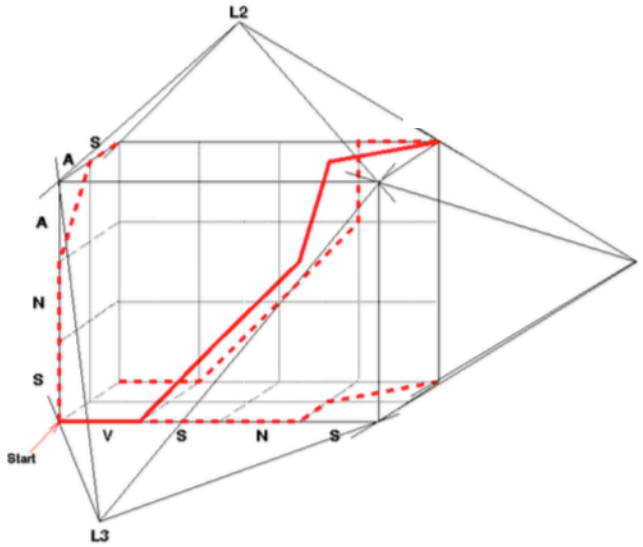
$$D^+(i,j,k) = d^+_{1,2}(i,j) + d^+_{1,3}(i,k) + d^+_{2,3}(j,k) \geq D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$

$$D(i,j,k) + D^+(i,j,k) \geq D(i,j,k) + D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$

Carillo-Lipman Method

$$D^+(i,j,k) = d^+_{1,2}(i,j) + d^+_{1,3}(i,k) + d^+_{2,3}(j,k) \geq D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$

$$D(i,j,k) + D^+(i,j,k) \geq D(i,j,k) + D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$

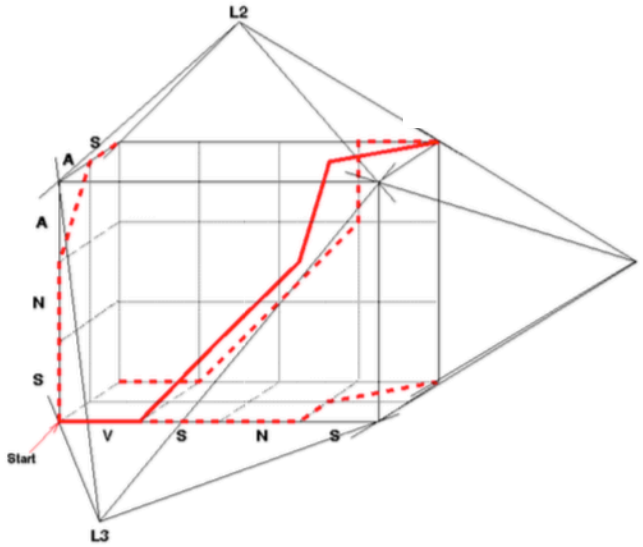


Question: What if we have an alignment with cost z?

Carillo-Lipman Method

$$D^+(i,j,k) = d^+_{1,2}(i,j) + d^+_{1,3}(i,k) + d^+_{2,3}(j,k) \geq D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$

$$D(i,j,k) + D^+(i,j,k) \geq D(i,j,k) + D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$



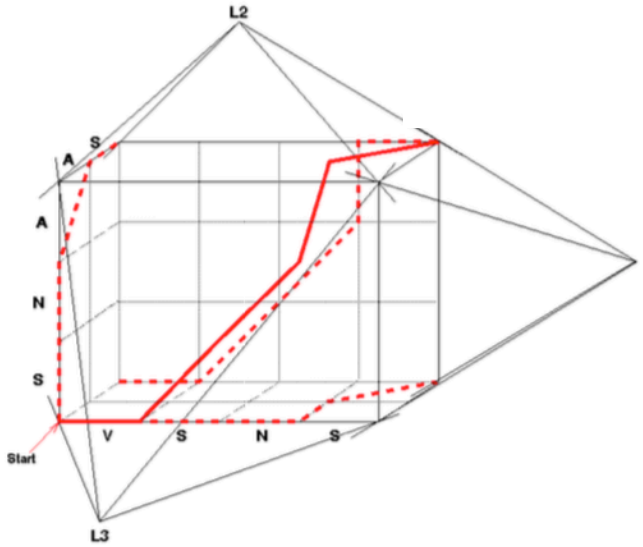
Question: What if we have an alignment with cost z?

If $z < D(i,j,k) + D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$
then (i,j,k) not on optimal path => **Prune**!

Carillo-Lipman Method

$$D^+(i,j,k) = d^+_{1,2}(i,j) + d^+_{1,3}(i,k) + d^+_{2,3}(j,k) \geq D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$

$$D(i,j,k) + D^+(i,j,k) \geq D(i,j,k) + D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$$



Question: What if we have an alignment with cost z?

Question: How to find this alignment?

If $z < D(i,j,k) + D^+_{1,2}(i,j) + D^+_{1,3}(i,k) + D^+_{2,3}(j,k)$
then (i,j,k) not on optimal path => **Prune**!

Outline

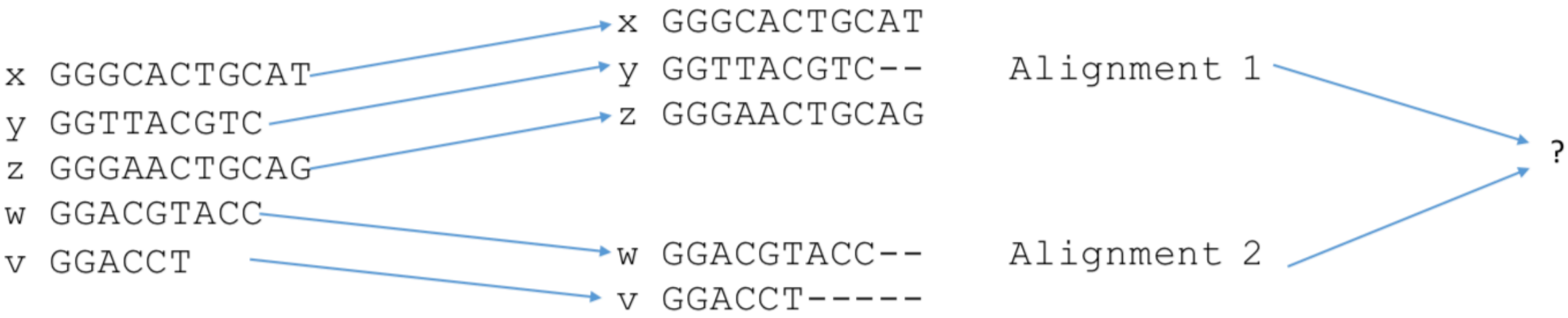
- Multiple sequence alignment
- Carillo-Lipman algorithm
- Progressive alignment

Reading:

- Jones and Pevzner. Chapter 6.10
- Material based on Chapter 14.6 in book “Algorithms on Strings, Trees and Sequences” by Dan Gusfield
- Lecture notes

Heuristic: Iterative/Progressive Alignment

Iteratively add strings (or alignments) to existing alignment(s).



Issues:

1. How to merge alignments?
2. What order to use in merging strings/alignments?

Heuristic Approach: Merge Pairwise Alignments

```
x GGGCACTGCAT
y GGTTACGTC--    Alignment 1
z GGGAACTGCAG

w GGACGTACC--    Alignment 2
v GGACCT-----
```

Question:
Can we align two alignments?

Need a way to summarize an alignment and score merged alignments

Profile Representation of Multiple Alignment

```
  -  A  G  G  C  T  A  T  C  A  C  C  T  G
  T  A  G  -  C  T  A  C  C  A  -  -  -  G
  C  A  G  -  C  T  A  C  C  A  -  -  -  G
  C  A  G  -  C  T  A  T  C  A  C  -  G  G
  C  A  G  -  C  T  A  T  C  G  C  -  G  G

A     1           1        .8
C  .6        1        .4  1     .6 .2
G        1 .2                 .2        .4  1
T  .2              1     .6                .2
-  .2        .8                      .4 .8 .4
```

A **profile** $P = [p_{i,j}]$ is a $(|\Sigma| + 1) \times l$ matrix,
where $p_{i,j}$ is the frequency of i-th letter in j-th position of alignment

Profile Representation of Multiple Alignment

We know how to align sequence against sequence

```
 -  A  G  G  C  T  A  T  C  A  C  C  T  G
 T  A  G  -  C  T  A  C  C  A  -  -  -  G
 C  A  G  -  C  T  A  C  C  A  -  -  -  G
 C  A  G  -  C  T  A  T  C  A  C  -  G  G
 C  A  G  -  C  T  A  T  C  G  C  -  G  G
```

```
A      1              1        .8
C   .6          1        .4  1     .6 .2
G         1  .2                 .2        .4  1
T   .2                 1     .6              .2
-   .2        .8                       .4  .8 .4
```

Question: Can we align sequence against profile?

Question: Can we align profile against profile?

Aligning String to Profile

A **profile** $P = [p_{i,j}]$ is a $(|\Sigma| + 1) \times n$ matrix,
where $p_{i,j}$ is the frequency of i-th letter in j-th position of alignment

Given: Sequences $\mathbf{v} = v_1, \ldots, v_m$ and profile P with n columns

- $s[i, j]$ is optimal alignment of $v_1, \ldots, v_i$ and first j columns of P
- $\delta(x, y)$ is score for aligning characters x and y
- $\tau(x, j)$ is score for aligning character x and column j of P

Aligning String to Profile

$$\tau(x, j) = \sum_{y \in \Sigma \cup \{-\}} p_{y,j} \cdot \delta(x, y)$$

$$s[i, j] = \max \begin{cases} 0, & \text{if } i = 0 \text{ and } j = 0, \\ s[i-1, j] + \delta(v_i, -), & \text{if } i > 0, \\ s[i, j-1] + \tau(-, j), & \text{if } j > 0, \\ s[i-1, j-1] + \tau(v_i, j), & \text{if } i > 0 \text{ and } j > 0. \end{cases}$$

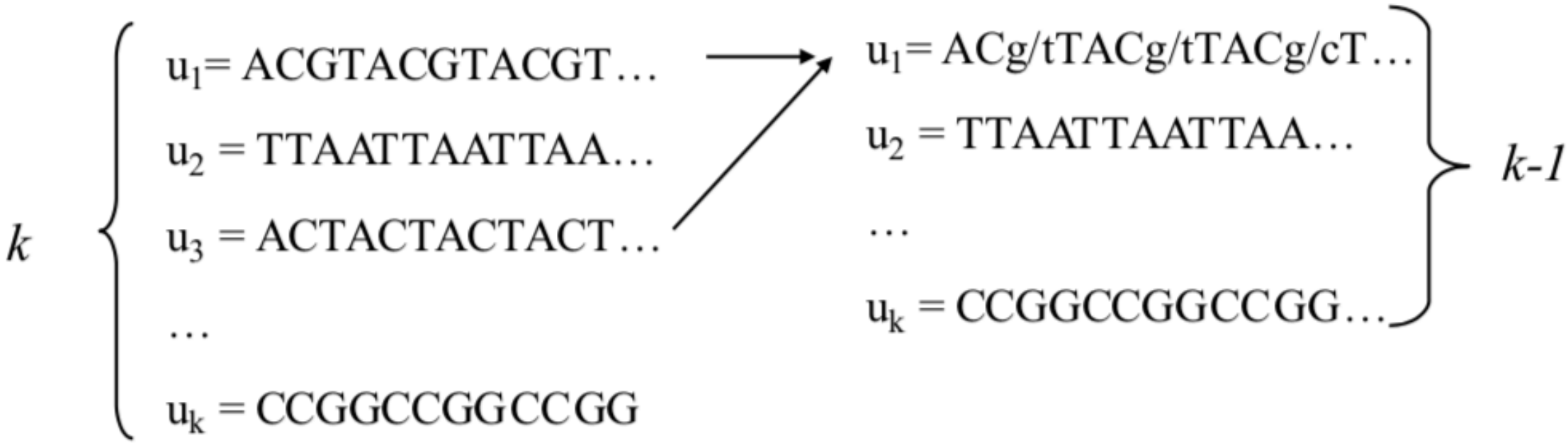
Insert space in profile

Insert space in string

- $s[i, j]$ is optimal alignment of $v_1, \ldots, v_i$ and first j columns of P
- $\delta(x, y)$ is score for aligning characters x and y
- $\tau(x, j)$ is score for aligning character x and column j of P

Progressive Multiple Alignment: Greedy Algorithm

Choose most similar pair among ***k*** input strings, combine into a profile. This reduces the original problem to alignment of ***k-1*** sequences to a profile. Repeat.



Example

Score of +1 for matches, -1 otherwise.

```
s2  GTCTGA
s4  GTCAGC (score = 2)

s1  GAT-TCA
s2  G-TCTGA (score = 1)

s1  GAT-TCA
s3  GATAT-T (score  = 1)

s1  GATTCA--
s4  G-T-CAGC(score = 0)

s2  G-TCTGA
s3  GATAT-T (score = -1)

s3  GAT-ATT
s4  G-TCAGC (score = -1)
```

Example

Score of +1 for matches, -1 otherwise.

```
s2  GTCTGA
s4  GTCAGC (score = 2)

s1  GAT-TCA
s2  G-TCTGA (score = 1)

s1  GAT-TCA
s3  GATAT-T (score  = 1)

s1  GATTCA--
s4  G-T-CAGC(score = 0)

s2  G-TCTGA
s3  GATAT-T (score = -1)

s3  GAT-ATT
s4  G-TCAGC (score = -1)
```

Question: Any theoretical guarantees on optimality?

No guarantees!

Outline

- Multiple sequence alignment
- Carillo-Lipman algorithm
- Progressive alignment

Reading:

- Jones and Pevzner. Chapter 6.10
- Material based on Chapter 14.6 in book “Algorithms on Strings, Trees and Sequences” by Dan Gusfield
- Lecture notes