CS 466
Introduction to Bioinformatics
Lecture 6

Mohammed El-Kebir

September 10, 2021

Course Announcements

Instructor:

- Mohammed El-Kebir (melkebir)
- Office hours: Wednesdays, 3:30-4:30pm

TA:

- Leah Weber (leahlw2), office hours: Mondays, 4-5pm via Zoom or in person 3rd floor Siebel by elevator
- Yuanyuan Qi (yq7), office hours: Fridays, 9-10am via Zoom or in person 3rd floor Siebel by elevator

Homework 1 due 9/16 by 11:59pm

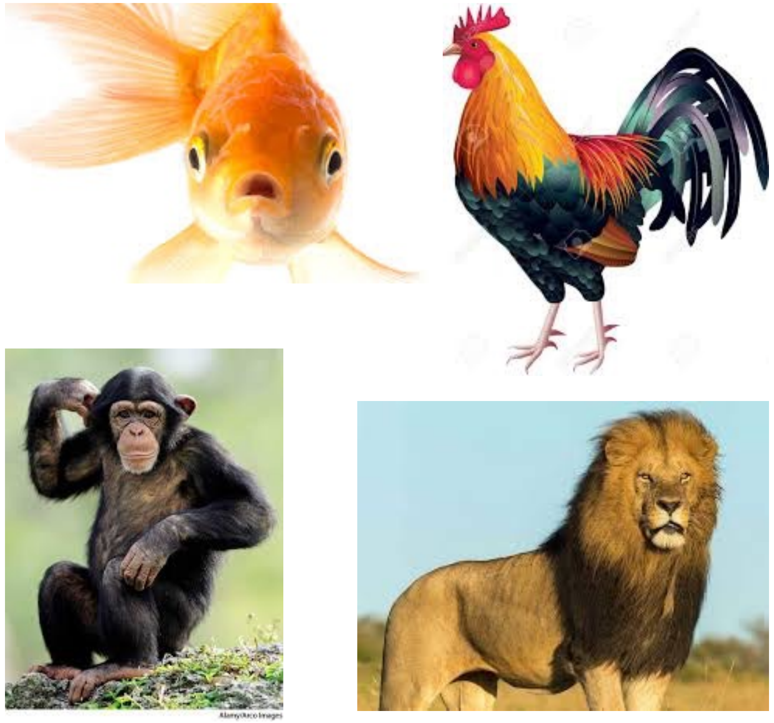
Outline

- Multiple sequence alignment
- Exact algorithm
- Sum-of-pairs (SP) score

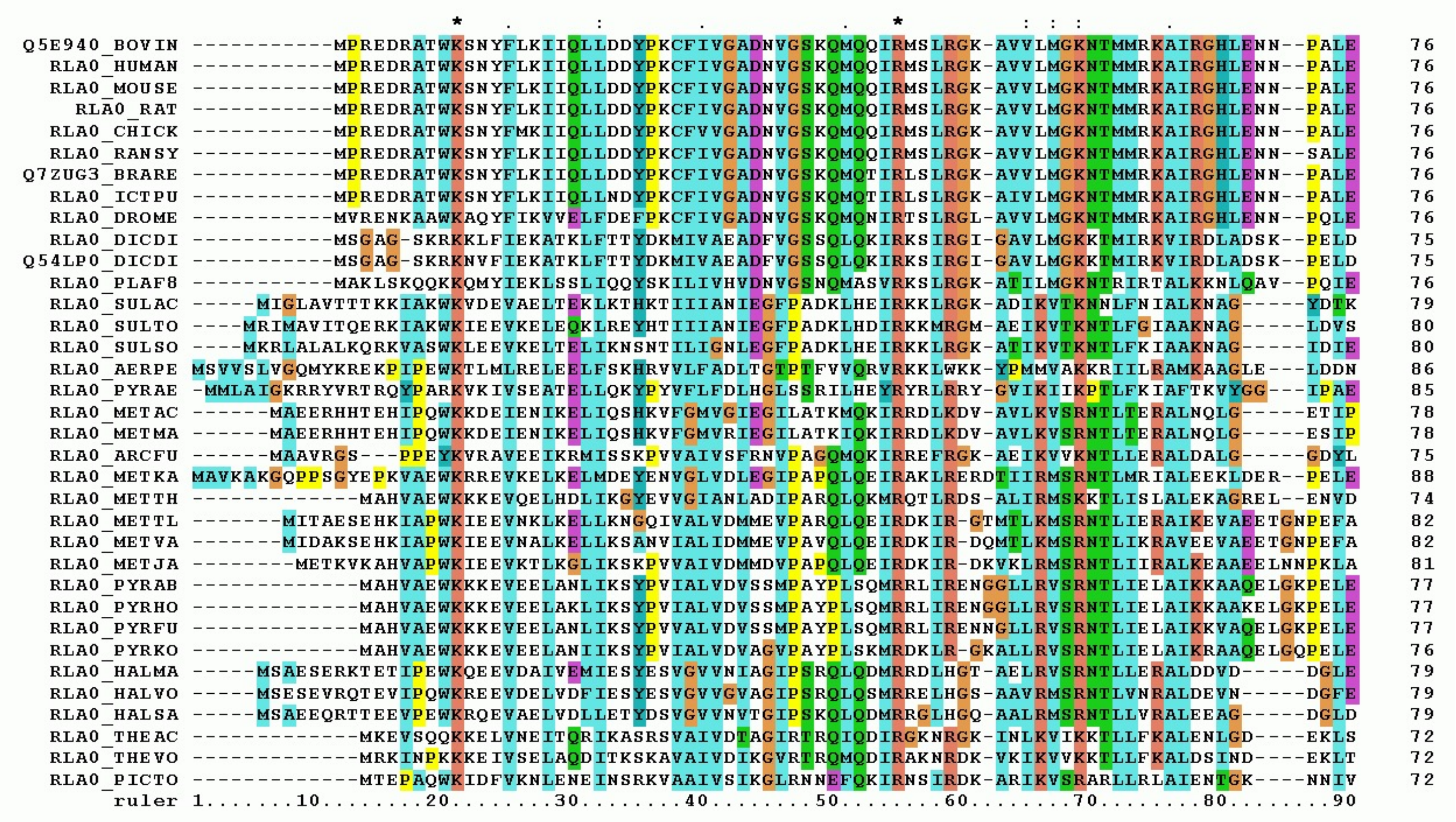
Reading:

- Jones and Pevzner. Chapter 6.10

Motivation



Simultaneous alignment of multiple (> 2) sequences enables inference of subtle similarities that are conserved in more than two species



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                                  *   .      :       .          .   *         : : :      .
Q5E940_BOVIN -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE     76
  RLA0_HUMAN -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE     76
  RLA0_MOUSE -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE     76
    RLA0_RAT -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE     76
  RLA0_CHICK -----------MPREDRATWKSNYFMKIIQLLDDYPKCFVVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE     76
  RLA0_RANSY -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--SALE     76
Q7ZUG3_BRARE -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQTIRLSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE     76
  RLA0_ICTPU -----------MPREDRATWKSNYFLKIIQLLNDYPKCFIVGADNVGSKQMQTIRLSLRGK-AIVLMGKNTMMRKAIRGHLENN--PALE     76
  RLA0_DROME -----------MVRENKAAWKAQYFIKVVELFDEFPKCFIVGADNVGSKQMQNIRTSLRGL-AVVLMGKNTMMRKAIRGHLENN--PQLE     76
  RLA0_DICDI -----------MSGAG-SKRKKLFIEKATKLFTTYDKMIVAEADFVGSSQLQKIRKSIRGI-GAVLMGKKTMIRKVIRDLADSK--PELD     75
Q54LP0_DICDI -----------MSGAG-SKRKNVFIEKATKLFTTYDKMIVAEADFVGSSQLQKIRKSIRGI-GAVLMGKKTMIRKVIRDLADSK--PELD     75
  RLA0_PLAF8 -----------MAKLSKQQKKQMYIEKLSSLIQQYSKILIVHVDNVGSNQMASVRKSLRGK-ATILMGKNTRIRTALKKNLQAV--PQIE     76
  RLA0_SULAC -----MIGLAVTTTKKIAKWKVDEVAELTEKLKTHKTIIIANIEGFPADKLHEIRKKLRGK-ADIKVTKNNLFNIALKNAG-----YDTK     79
  RLA0_SULTO ----MRIMAVITQERKIAKWKIEEVKELEQKLREYHTIIIANIEGFPADKLHDIRKKMRGM-AEIKVTKNTLFGIAAKNAG-----LDVS     80
  RLA0_SULSO ----MKRLALALKQRKVASWKLEEVKELTELIKNSNTILIGNLEGFPADKLHEIRKKLRGK-ATIKVTKNTLFKIAAKNAG-----IDIE     80
  RLA0_AERPE MSVVSLVGQMYKREKPIPEWKTLMLRELEELFSKHRVVLFADLTGTPTFVVQRVRKKLWKK-YPMMVAKKRIILRAMKAAGLE---LDDN     86
  RLA0_PYRAE -MMLAIGKRRYVRTRQYPARKVKIVSEATELLQKYPYVFLFDLHGLSSRILHEYRYRLRRY-GVIKIIKPTLFKIAFTKVYGG---IPAE     85
  RLA0_METAC ------MAEERHHTEHIPQWKKDEIENIKELIQSHKVFGMVGIEGILATKMQKIRRDLKDV-AVLKVSRNTLTERALNQLG-----ETIP     78
  RLA0_METMA ------MAEERHHTEHIPQWKKDEIENIKELIQSHKVFGMVRIEGILATKIQKIRRDLKDV-AVLKVSRNTLTERALNQLG-----ESIP     78
  RLA0_ARCFU ------MAAVRGS---PPEYKVRAVEEIKRMISSKPVVAIVSFRNVPAGQMQKIRREFRGK-AEIKVVKNTLLERALDALG-----GDYL     75
  RLA0_METKA MAVKAKGQPPSGYEPKVAEWKRREVKELKELMDEYENVGLVDLEGIPAPQLQEIRAKLRERDTIIRMSRNTLMRIALEEKLDER--PELE     88
  RLA0_METTH -------------MAHVAEWKKKEVQELHDLIKGYEVVGIANLADIPARQLQKMRQTLRDS-ALIRMSKKTLISLALEKAGREL--ENVD     74
  RLA0_METTL -------MITAESEHKIAPWKIEEVNKLKELLKNGQIVALVDMMEVPARQLQEIRDKIR-GTMTLKMSRNTLIERAIKEVAEETGNPEFA     82
  RLA0_METVA -------MIDAKSEHKIAPWKIEEVNALKELLKSANVIALIDMMEVPAVQLQEIRDKIR-DQMTLKMSRNTLIKRAVEEVAEETGNPEFA     82
  RLA0_METJA --------METKVKAHVAPWKIEEVKTLKGLIKSKPVVAIVDMMDVPAPQLQEIRDKIR-DKVKLRMSRNTLIIRALKEAAEELNNPKLA     81
  RLA0_PYRAB -------------MAHVAEWKKKEVEELANLIKSYPVIALVDVSSMPAYPLSQMRRLIRENGGLLRVSRNTLIELAIKKAAQELGKPELE     77
  RLA0_PYRHO -------------MAHVAEWKKKEVEELAKLIKSYPVIALVDVSSMPAYPLSQMRRLIRENGGLLRVSRNTLIELAIKKAAKELGKPELE     77
  RLA0_PYRFU -------------MAHVAEWKKKEVEELANLIKSYPVVALVDVSSMPAYPLSQMRRLIRENNGLLRVSRNTLIELAIKKVAQELGKPELE     77
  RLA0_PYRKO -------------MAHVAEWKKKEVEELANIIKSYPVIALVDVAGVPAYPLSKMRDKLR-GKALLRVSRNTLIELAIKRAAQELGQPELE     76
  RLA0_HALMA -----MSAESERKTETIPEWKQEEVDAIVEMIESYESVGVVNIAGIPSRQLQDMRRDLHGT-AELRVSRNTLLERALDDVD-----DGLE     79
  RLA0_HALVO -----MSESEVRQTEVIPQWKREEVDELVDFIESYESVGVVGVAGIPSRQLQSMRRELHGS-AAVRMSRNTLVNRALDEVN-----DGFE     79
  RLA0_HALSA -----MSAEEQRTTEEVPEWKRQEVAELVDLLETYDSVGVVNVTGIPSKQLQDMRRGLHGQ-AALRMSRNTLLVRALEEAG-----DGLD     79
  RLA0_THEAC -------------MKEVSQQKKELVNEITQRIKASRSVAIVDTAGIRTRQIQDIRGKNRGK-INLKVIKKTLLFKALENLGD----EKLS     72
  RLA0_THEVO -------------MRKINPKKKEIVSELAQDITKSKAVAIVDIKGVRTRQMQDIRAKNRDK-VKIKVVKKTLLFKALDSIND----EKLT     72
  RLA0_PICTO -------------MTEPAQWKIDFVKNLENEINSRKVAAIVSIKGLRNNEFQKIRNSIRDK-ARIKVSRARLLRLAIENTGK----NNIV     72
       ruler 1.......10........20........30........40........50........60........70........80........90
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“Pairwise alignment whispers ... multiple alignment shouts out loud”.

Hubbard, Lesk, Tramontano, Nature Structural Biology 1996.

Multiple Sequence Alignment (MSA)

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

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

Question: How to score a multiple sequence alignment?

Scoring a Multiple Sequence Alignment

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

Question: How to score a multiple sequence alignment?

Pairwise scoring function:

$$\delta : (\Sigma \cup \{-\}) \times (\Sigma \cup \{-\}) \to \mathbb{R}$$

Scoring a Multiple Sequence Alignment

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

Question: How to score a multiple sequence alignment?

Pairwise scoring function:

$$\delta : (\Sigma \cup \{-\}) \times (\Sigma \cup \{-\}) \to \mathbb{R}$$

k-wise scoring function:

$$\delta : (\Sigma \cup \{-\})^k \to \mathbb{R}$$

Outline

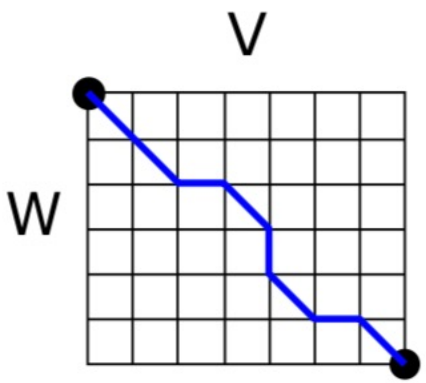
- Multiple sequence alignment
- Exact algorithm
- Sum-of-pairs (SP) score

Reading:

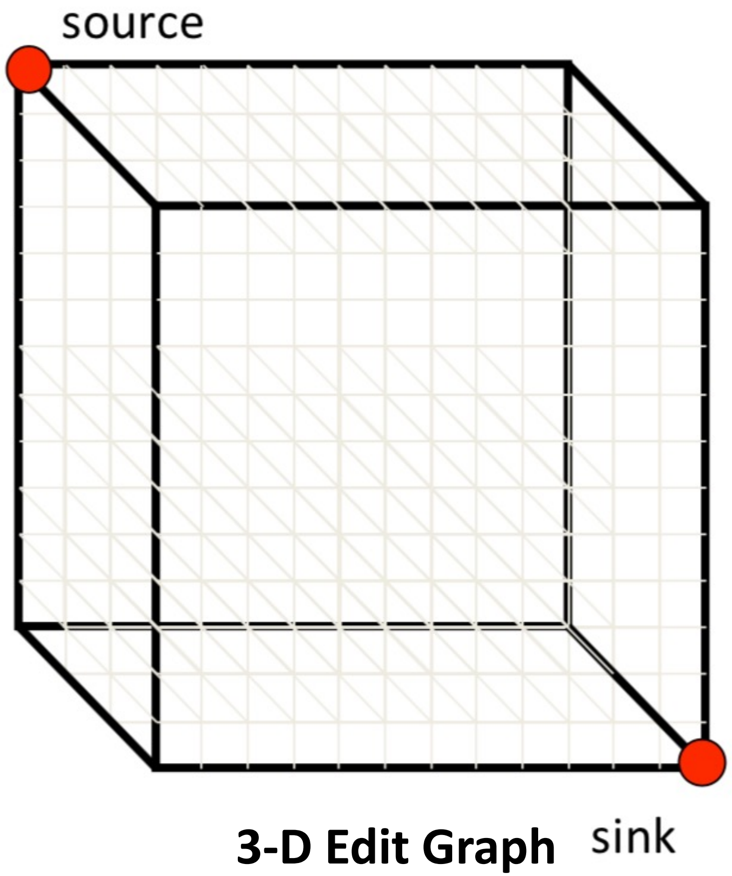
- Jones and Pevzner. Chapter 6.10

Aligning Three Sequences

- Same strategy as pairwise edit distance
- Use 3-D cube, with each axis representing an input sequence
- Alignment is a path from source to sink

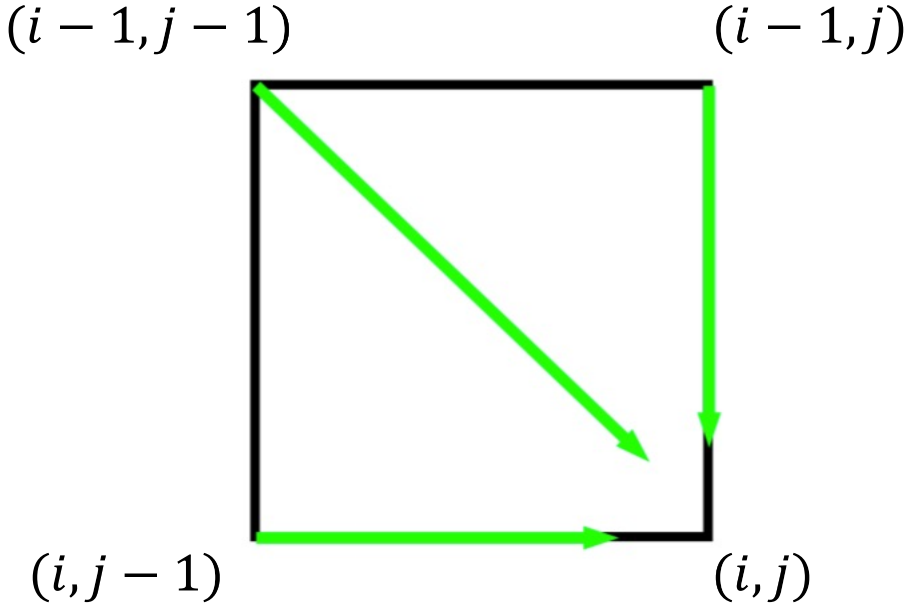


2-D Edit Graph

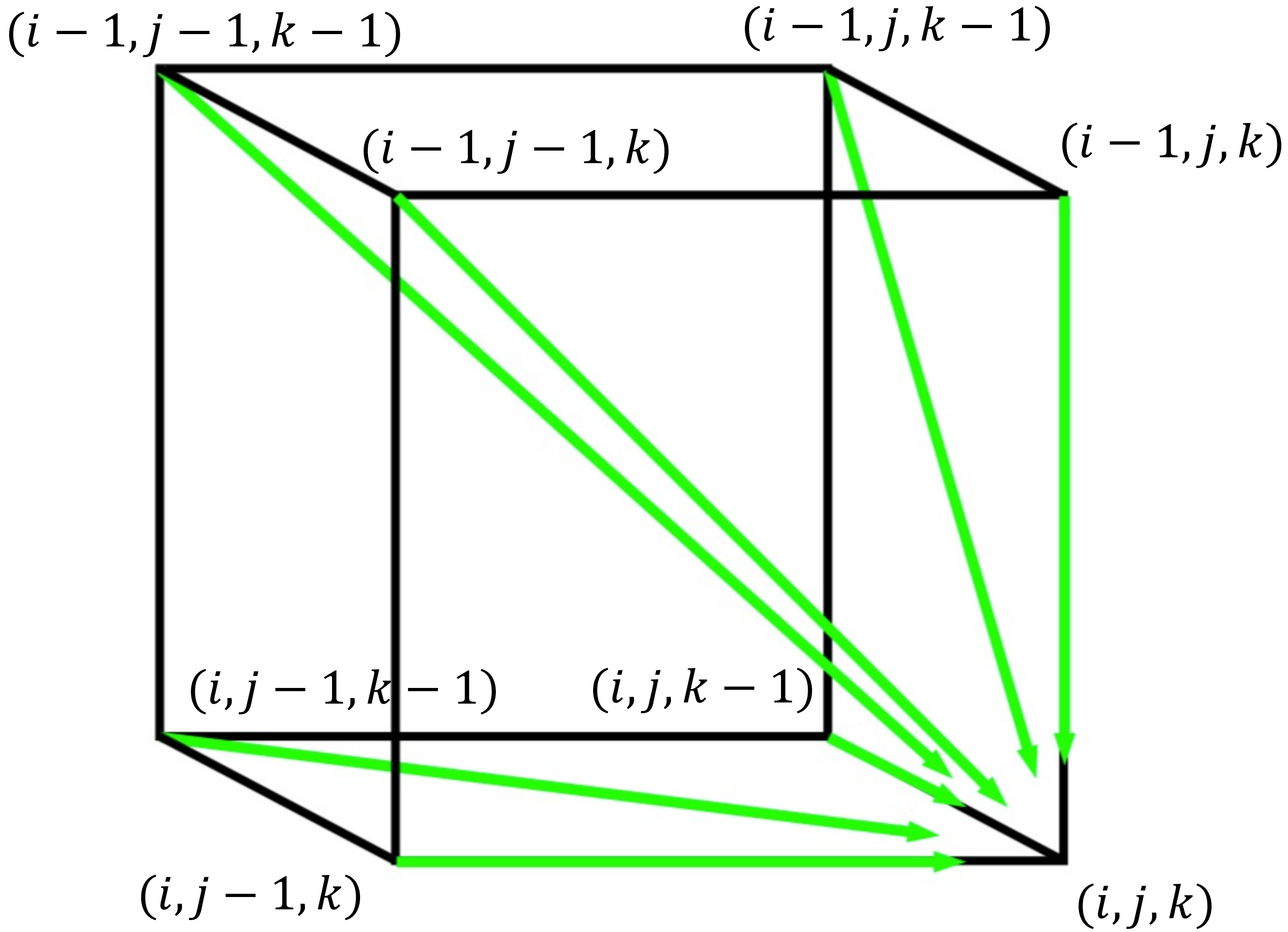


3-D Edit Graph

2-D vs 3-D Vertex Neighborhood

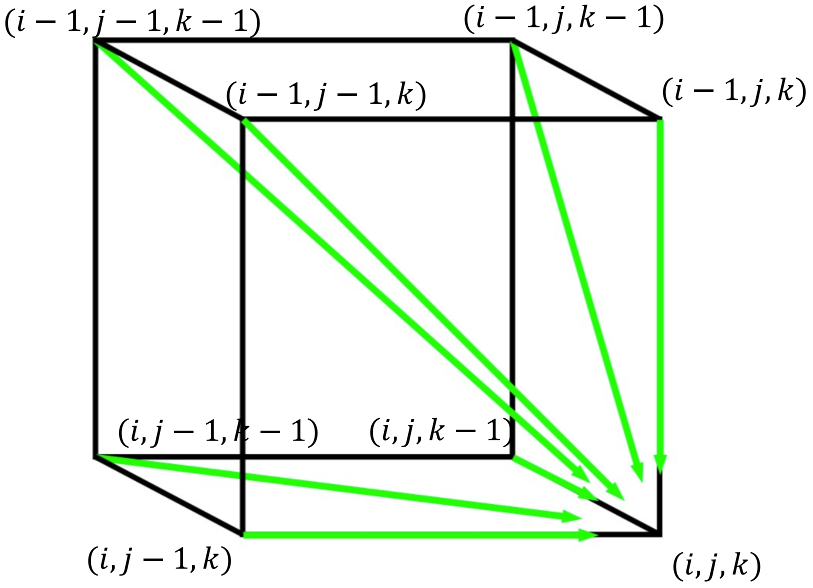


2-D Neighborhood
(3 edges)



3-D Neighborhood
(7 edges)

3-D Sequence Alignment

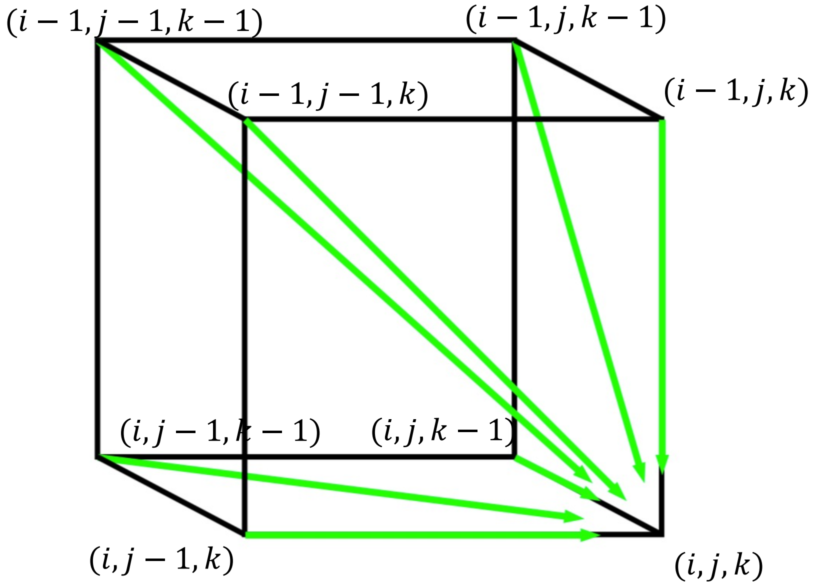


$\delta(x, y, z)$ is an entry in 3-D scoring matrix

3-D Sequence Alignment

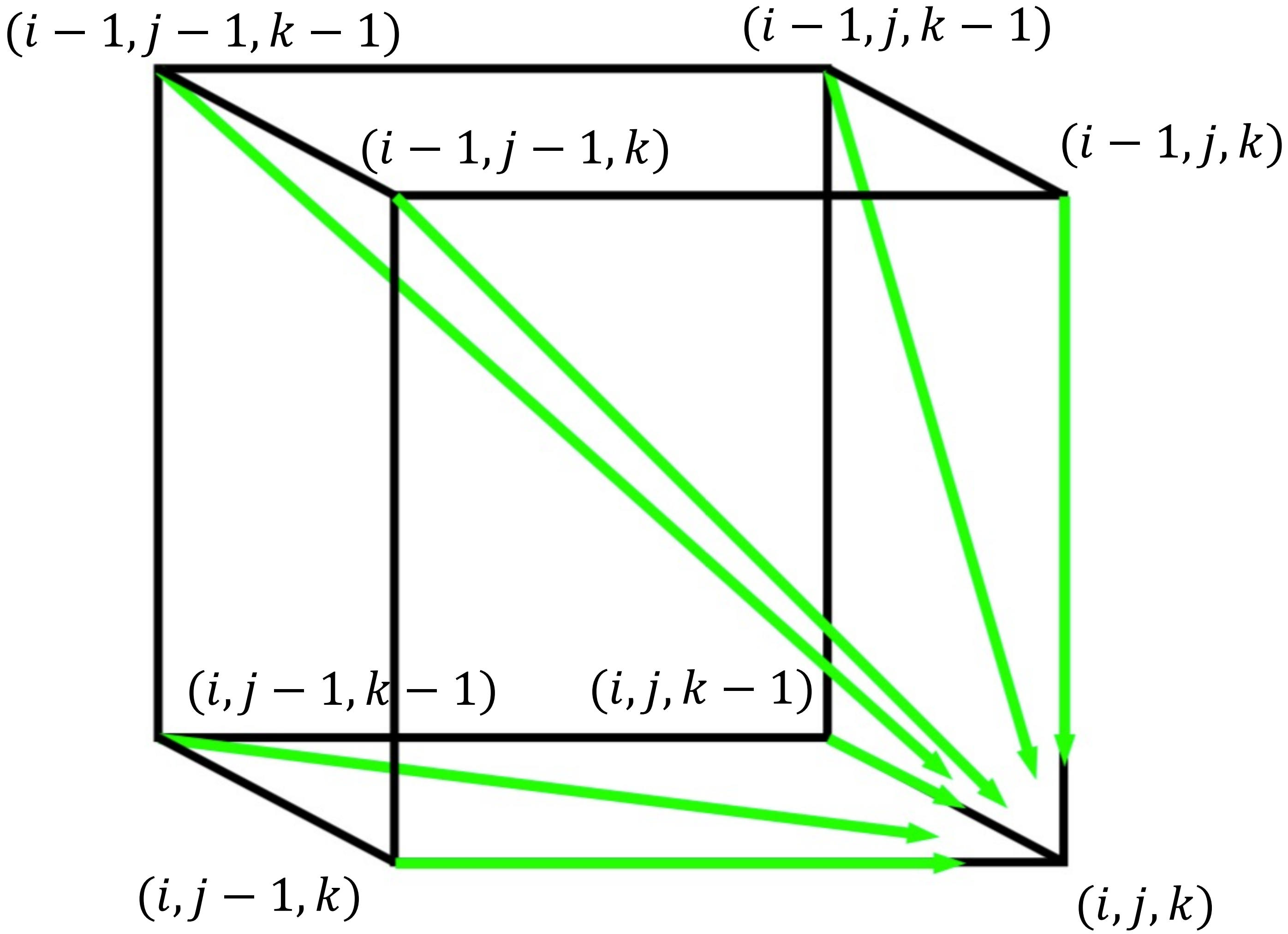
$\delta(x, y, z)$ is an entry in 3-D scoring matrix

Given three sequences each of length n, running time: $O(n^3)$



$$s[i,j,k] = \max \left\{ \begin{array}{ll} \left. s[i-1,j-1,k-1] + \delta(v_i, w_j, u_k), \right\} & \textbf{no gaps} \\ \left. \begin{array}{l} s[i-1,j-1,k] + \delta(v_i, w_j, -), \\ s[i-1,j,k-1] + \delta(v_i, -, u_k), \\ s[i,j-1,k-1] + \delta(-, w_j, u_k), \end{array} \right\} & \textbf{one gap} \\ \left. \begin{array}{l} s[i-1,j,k] + \delta(v_i, -, -), \\ s[i,j-1,k] + \delta(-, w_j, -), \\ s[i,j,k-1] + \delta(-, -, u_k), \end{array} \right\} & \textbf{two gaps} \end{array} \right.$$

3-D vs k-D Vertex Neighborhood



3-D Neighborhood
(7 edges)

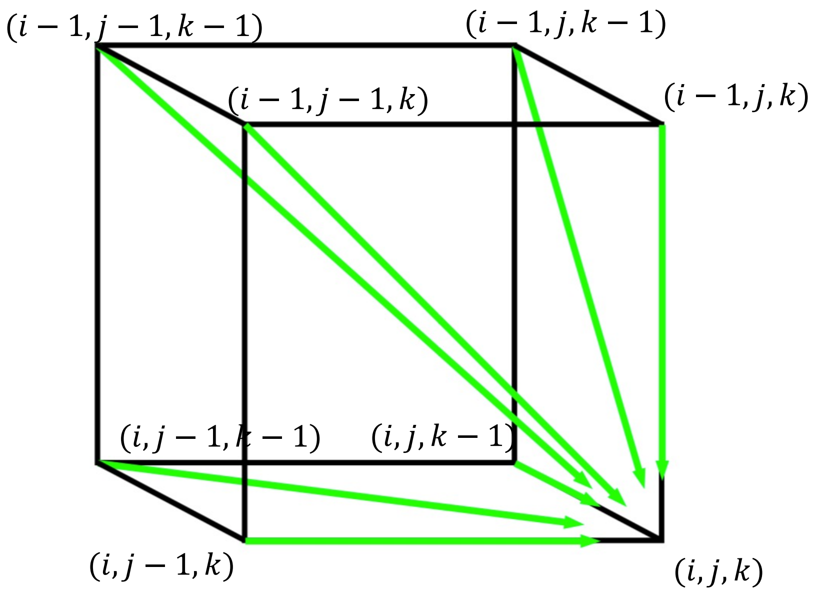
$$(i_1 - 1, i_2 - 1, \dots, i_{k-1} - 1, i_k - 1)$$
$$(i_1 - 1, i_2 - 1, \dots, i_{k-1} - 1, i_k)$$
$$\dots$$
$$(i_1, i_2 - 1, \dots, i_{k-1} - 1, i_k - 1)$$
$$\dots$$
$$(i_1 - 1, i_2, \dots, i_{k-1}, i_k)$$
$$\dots$$
$$(i_1, i_2, \dots, i_{k-1}, i_k - 1)$$

k-D Neighborhood
($2^k - 1$ edges)

k-D Sequence Alignment

$\delta(x_1, \ldots, x_k)$ is an entry in k-D scoring matrix

Given k sequences each of length n,
running time: $O(2^k n^k)$



$$s[i_1, i_2, \ldots, i_{k-1}, i_k] = \max \left\{ \begin{array}{ll}
\left. s[i_1-1, i_2-1, \ldots, i_{k-1}-1, i_k-1] + \delta(\mathbf{v_1}[i_1], \mathbf{v_2}[i_2], \ldots, \mathbf{v_{k-1}}[i_{k-1}], \mathbf{v_k}[i_k]) \right\} & \textbf{no gaps} \\
\left. \begin{array}{l} s[i_1-1, i_2-1, \ldots, i_{k-1}-1, i_k] + \delta(\mathbf{v_1}[i_1], \mathbf{v_2}[i_2], \ldots, \mathbf{v_{k-1}}[i_{k-1}], -) \\ \qquad \vdots \\ s[i_1, i_2-1, \ldots, i_{k-1}-1, i_k-1] + \delta(-, \mathbf{v_2}[i_2], \ldots, \mathbf{v_{k-1}}[i_{k-1}], \mathbf{v_k}[i_k]) \end{array} \right\} & \textbf{one gap} \\
\qquad \vdots & \\
\left. \begin{array}{l} s[i_1-1, i_2, \ldots, i_{k-1}, i_k] + \delta(\mathbf{v_1}[i_1], -, \ldots, -, -) \\ \qquad \vdots \\ s[i_1, i_2, \ldots, i_{k-1}, i_k-1] + \delta(-, -, \ldots, -, \mathbf{v_k}[i_k]) \end{array} \right\} & k-1 \textbf{ gaps}
\end{array} \right.$$

Multiple Sequence Alignment – Running Time

Given 2 sequences each of length n,
running time: $O(n^2)$

Given 3 sequences each of length n,
running time: $O(n^3)$

Given k sequences each of length n,
running time: $O(2^k n^k)$

Multiple Sequence Alignment – Running Time

Given 2 sequences each of length n, running time: $O(n^2)$

Given 3 sequences each of length n, running time: $O(n^3)$

Given k sequences each of length n, running time: $O(2^k n^k)$

Question: Can we align k sequences each of length n in time $O(\text{poly}(n))$?

Multiple Sequence Alignment – Running Time

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Question: Can we align k sequences each of length n in time $O(\text{poly}(n))$?

Let's look at a wieldier scoring function

Outline

- Multiple sequence alignment
- Exact algorithm
- Sum-of-pairs (SP) score

Reading:

- Jones and Pevzner. Chapter 6.10

Multiple Alignment Induces Pairwise Alignments

v_1	A	T	-	G	C	G	-
v_2	A	-	C	G	T	-	C
v_3	A	T	C	A	C	-	A

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

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

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

Resulting columns with -/- are removed

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

Multiple sequence alignment $\mathcal{M}$

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

Question: Calculate

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

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

Multiple sequence alignment $\mathcal{M}$

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

Question: Calculate SP-score$(\mathcal{M})$ =

$$\sum_{i=1}^{k}\sum_{j=i+1}^{k} S(\mathbf{v}_i, \mathbf{v}_j)$$

We can sum over scores for the columns, ignoring -/-

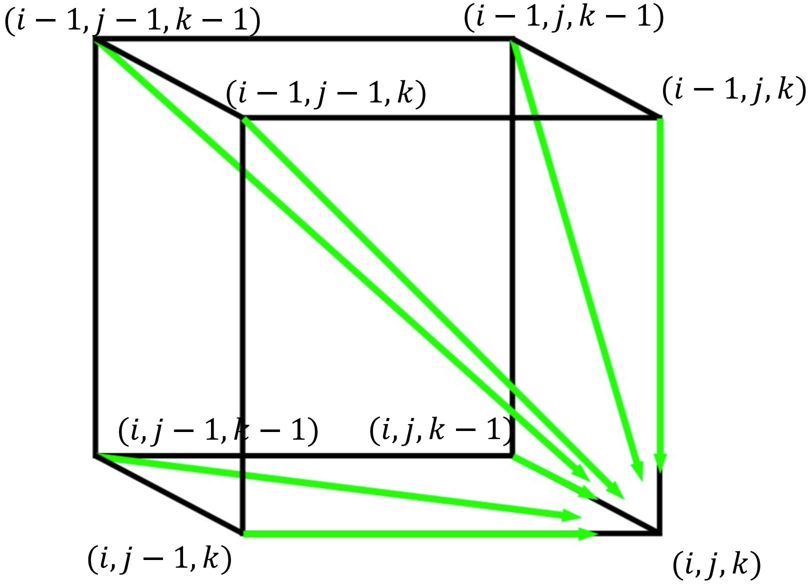
Multiple Sequence Alignment Problem w/ SP-Score

A **multiple sequence alignment** $\mathcal{M}$ between k strings $\mathbf{v}_1, \dots, \mathbf{v}_k$ is a $k \times q$ matrix, where $q = \{\max\{\,|\mathbf{v}_i| : i \in [k]\}, \dots, \sum_{i=1}^{k} |\mathbf{v}_i|\}$ 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 $\mathbf{v}_1, \dots, \mathbf{v}_k$ 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 $\mathcal{M}^*$

3-D MSA-SP

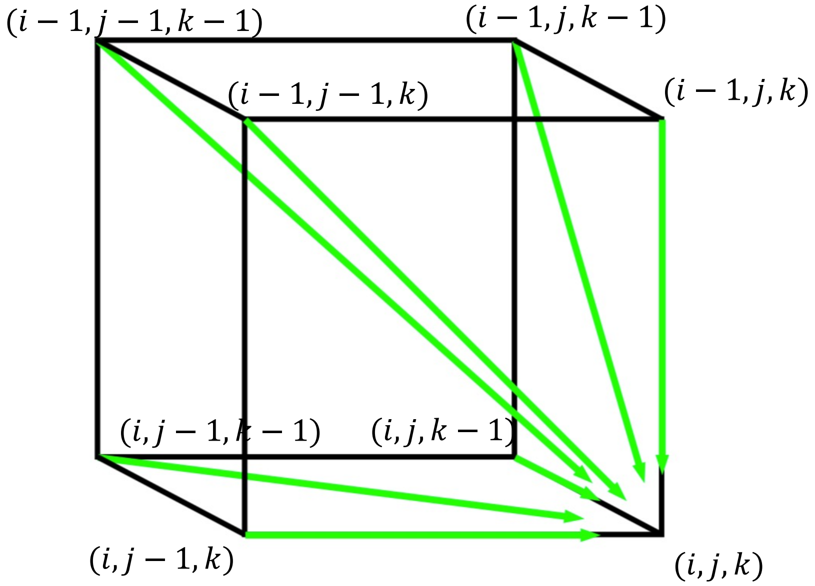
$\delta(x, y, z)$ is an entry in 3-D scoring matrix



3-D MSA-SP

$\delta(x, y, z)$ is an entry in 3-D scoring matrix

Given three sequences each of length n, running time: $O(n^3)$

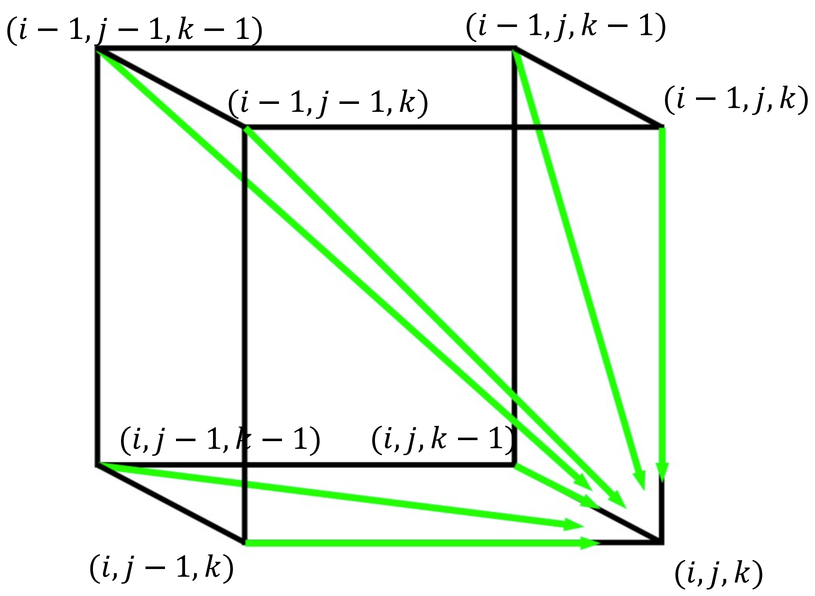


$$d[i_1, i_2, i_3] = \min \begin{cases} \left. d[i_1-1, i_2-1, i_3-1] + \delta(\mathbf{v_1}[i_1], \mathbf{v_2}[i_2]) + \delta(\mathbf{v_1}[i_1], \mathbf{v_3}[i_3]) + \delta(\mathbf{v_2}[i_2], \mathbf{v_3}[i_3]) \right\} \textbf{no gaps} \\ \left. \begin{array}{l} d[i_1-1, i_2-1, i_3] + \delta(\mathbf{v_1}[i_1], \mathbf{v_2}[i_2]) + 2\sigma \\ d[i_1-1, i_2, i_3-1] + \delta(\mathbf{v_1}[i_1], \mathbf{v_3}[i_3]) + 2\sigma \\ d[i_1, i_2-1, i_3-1] + \delta(\mathbf{v_2}[i_2], \mathbf{v_3}[i_3]) + 2\sigma \end{array} \right\} \textbf{one gap} \\ \left. \begin{array}{l} d[i_1-1, i_2, i_3] + 2\sigma \\ d[i_1, i_2-1, i_3] + 2\sigma \\ d[i_1, i_2, i_3-1] + 2\sigma \end{array} \right\} \textbf{two gaps} \end{cases}$$

k-D MSA-SP

Computing SP-score in each case: $O(k^2)$ time

Given k sequences each of length n,
running time: $O(k^2 2^k n^k)$

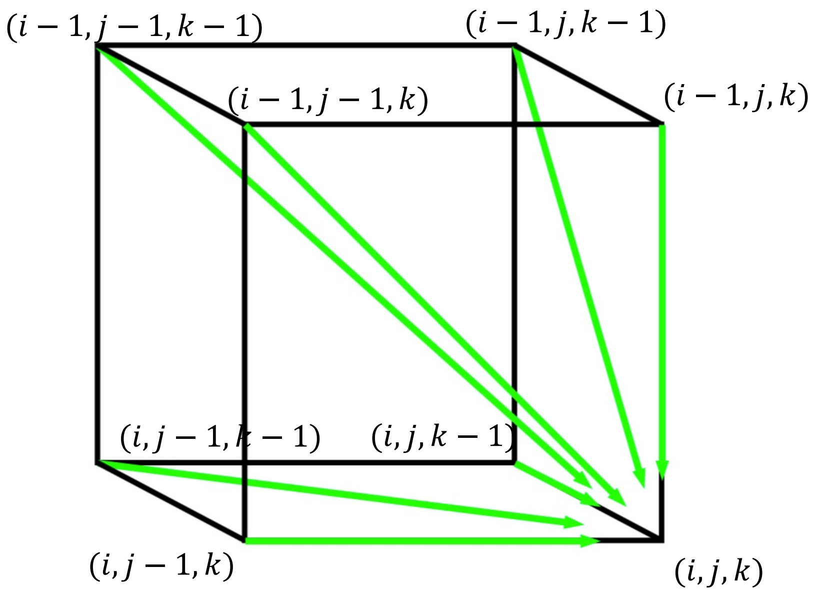


$$d[i_1,i_2,\ldots,i_{k-1},i_k]=\min\left\{\begin{array}{ll}
\left.s[i_1-1,i_2-1,\ldots,i_{k-1}-1,i_k-1]+\sum_{p=1}^{k}\sum_{q=p+1}^{k}\delta(\mathbf{v_p}[i_p],\mathbf{v_q}[i_q])\right\} & \textbf{no gaps}\\
\left.\begin{array}{l}
s[i_1-1,i_2-1,\ldots,i_{k-1}-1,i_k]+(k-1)\sigma+\sum_{p=1}^{k-1}\sum_{q=p+1}^{k-1}\delta(\mathbf{v_p}[i_p],\mathbf{v_q}[i_q])\\
\qquad\vdots\\
s[i_1,i_2-1,\ldots,i_{k-1}-1,i_k-1]+(k-1)\sigma+\sum_{p=2}^{k}\sum_{q=p+1}^{k}\delta(\mathbf{v_p}[i_p],\mathbf{v_q}[i_q])
\end{array}\right\} & \textbf{one gap}\\
\qquad\vdots & \\
\left.\begin{array}{l}
s[i_1-1,i_2,\ldots,i_{k-1},i_k]+(k-1)\sigma\\
\qquad\vdots\\
s[i_1,i_2,\ldots,i_{k-1},i_k-1]+(k-1)\sigma
\end{array}\right\} & k-1\ \textbf{gaps}
\end{array}\right.$$

k-D MSA-SP

Computing SP-score in each case: $O(k^2)$ time

Given k sequences each of length n,
running time: $O(k^2 2^k n^k)$



$$d[i_1,i_2,\ldots,i_{k-1},i_k]=\min\begin{cases} s[i_1-1,i_2-1,\ldots,i_{k-1}-1,i_k-1]+\sum_{p=1}^{k}\sum_{q=p+1}^{k}\delta(\mathbf{v_p}[i_p],\mathbf{v_q}[i_q]) & \text{no gaps} \\ s[i_1-1,i_2-1,\ldots,i_{k-1}-1,i_k]+(k-1)\sigma+\sum_{p=1}^{k-1}\sum_{q=p+1}^{k-1}\delta(\mathbf{v_p}[i_p],\mathbf{v_q}[i_q]) & \\ \qquad\vdots & \text{one gap} \\ s[i_1,i_2-1,\ldots,i_{k-1}-1,i_k-1]+(k-1)\sigma+\sum_{p=2}^{k}\sum_{q=p+1}^{k}\delta(\mathbf{v_p}[i_p],\mathbf{v_q}[i_q]) & \\ \qquad\vdots & \\ s[i_1-1,i_2,\ldots,i_{k-1},i_k]+(k-1)\sigma & \\ \qquad\vdots & k-1\ \text{gaps} \\ s[i_1,i_2,\ldots,i_{k-1},i_k-1]+(k-1)\sigma & \end{cases}$$

Question: How many cases have 2 gaps?

Multiple Sequence Alignment Problem w/ SP-Score

MSA-SP problem: Given 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 $\mathcal{M}^*$

Question: Can we align k sequences each of length n in time $O(\mathrm{poly}(n))$?

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Question: Can we align k sequences each of length n in time $O(\mathrm{poly}(n))$?

No, MSA-SP is NP-hard.

[WANG, L., & JIANG, T. (1994). On the Complexity of Multiple Sequence Alignment. *Journal of Computational Biology*, *1*(4), 337–348. http://doi.org/10.1089/cmb.1994.1.337]

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

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

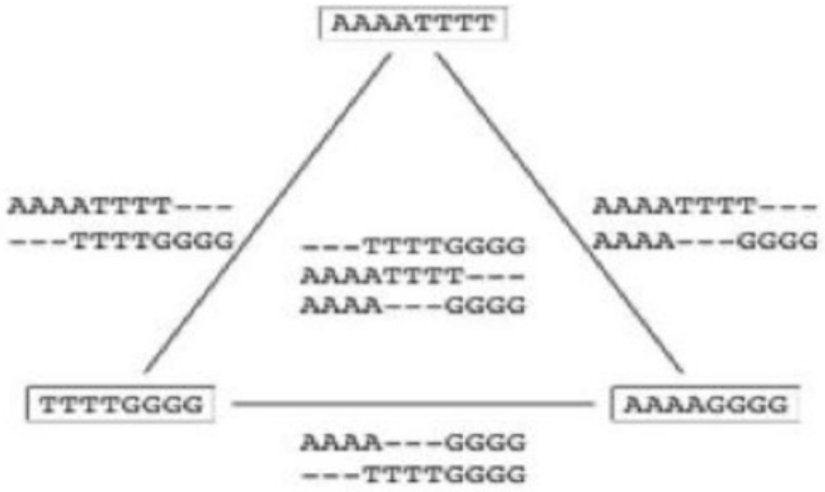
Question: Can we construct a multiple alignment that induces the above three pairwise alignments?

Not always!

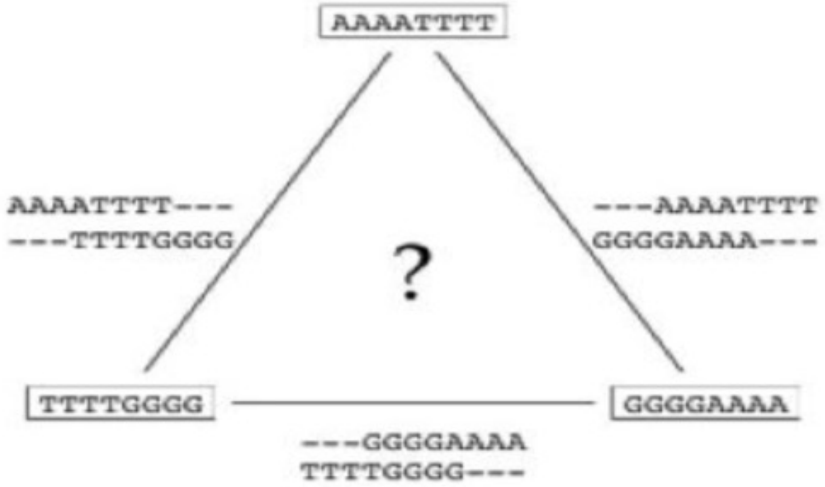
Compatibility

Compatible: Pairwise alignments can be combined into multiple alignment

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



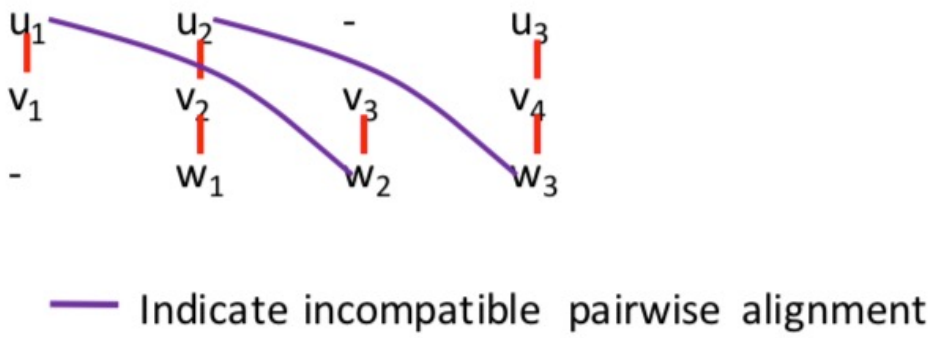
(a) Compatible pairwise alignments



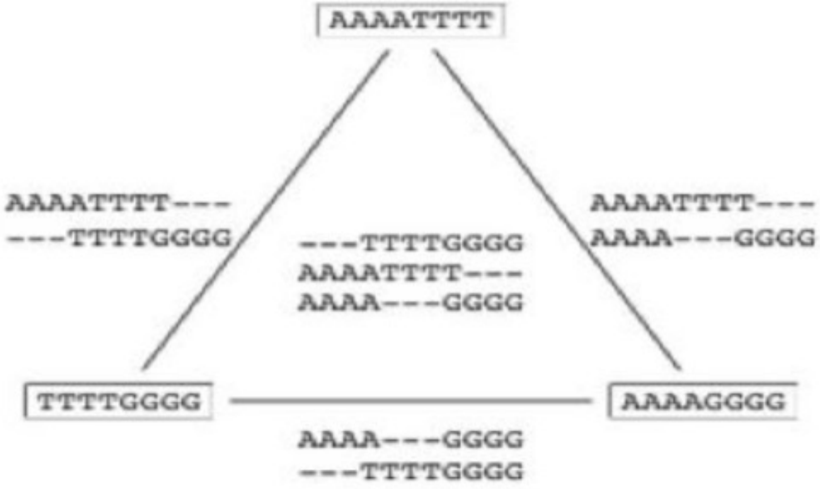
(b) Incompatible pairwise alignments

Compatibility

Compatible: Pairwise alignments can be combined into multiple alignment



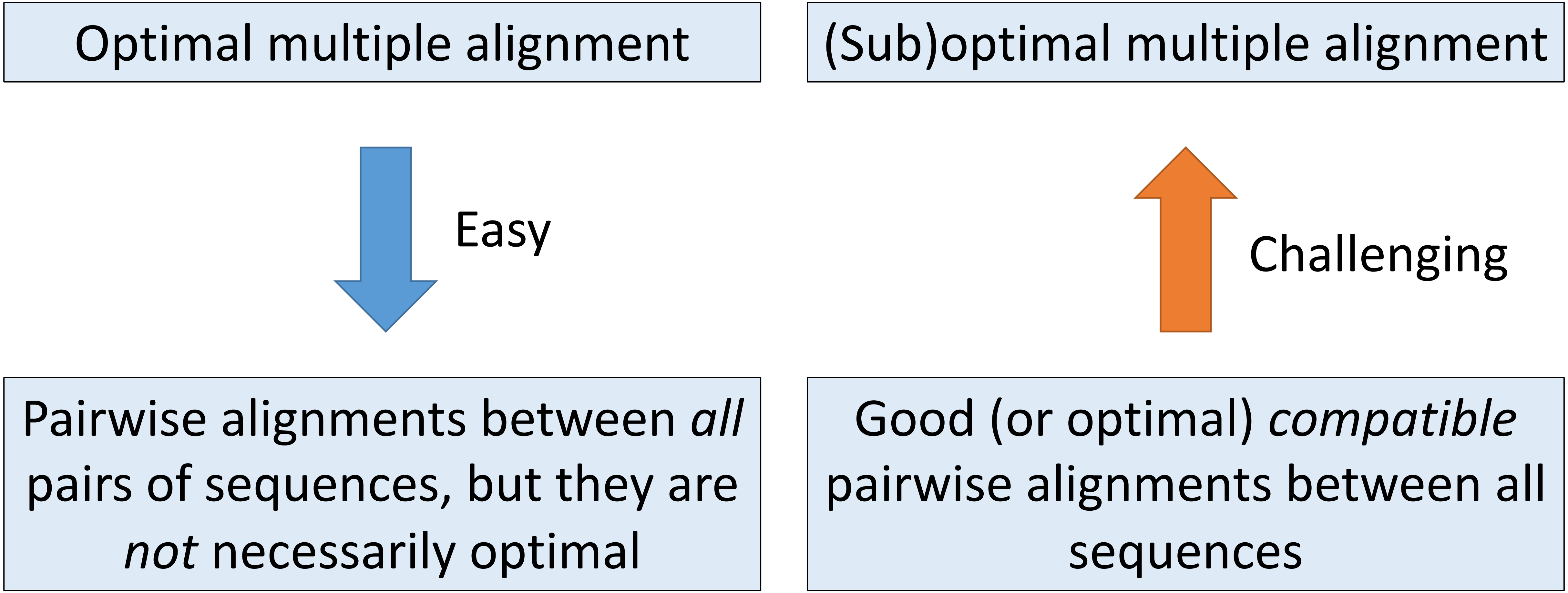
Incompatible: Pairwise alignments *cannot* be combined into multiple alignment



(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

Summary

- Multiple sequence alignment
- Exact algorithm
- Sum-of-pairs (SP) score

Reading:

- Jones and Pevzner. Chapter 6.10