BIOINFORMATICS

How do we compare biological sequences?

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Outline

1. Introduction to Sequence Alignment
2. Hamming distance for similarity between sequences
3. Alignment Game and the Longest Common Subsequence;
4. The Manhattan Tourist Problem;
5. The Change Problem;
6. Dynamic programming and backtracking pointers;
7. From Manhattan to Alignment Graph;
8. From Global to Local Alignment;
9. Penalizing Insertions and Deletions in Sequence Alignment;
10. Space-Efficient Sequence Alignment;
11. Multiple Sequence Alignment.

Chapter 5 in ***Bioinformatics Algorithms: An active Learning Approach (Vol.1).***

Part 4

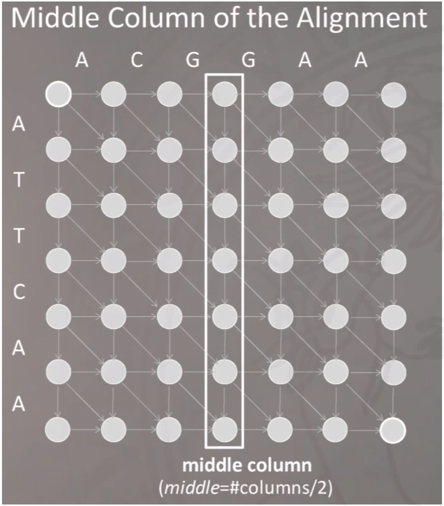
Space-Efficient Sequence Alignment

Space-Efficient Sequence Alignment

- Alignment runtime: proportional to the edge number (quadratic);
- Alignment memory: proportional to the edge number (quadratic);
- Increasing the length of sequences then **memory** can be bottleneck;
- In this course we will not introduce techniques to speed-up the execution time and reduce the memory utilization based on **Suffix Tree, FM-index, Burrows Wheeler transform.**

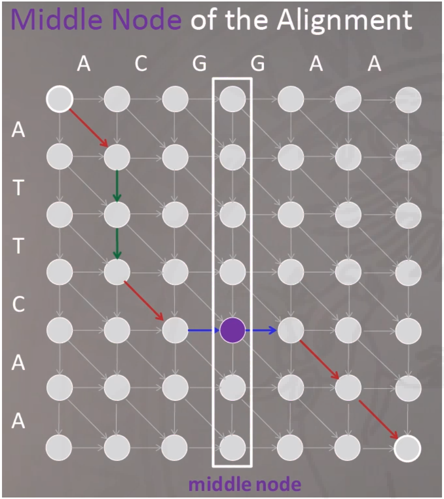
Space-Efficient Sequence Alignment

How to reduce the memory consumption



Space-Efficient Sequence Alignment

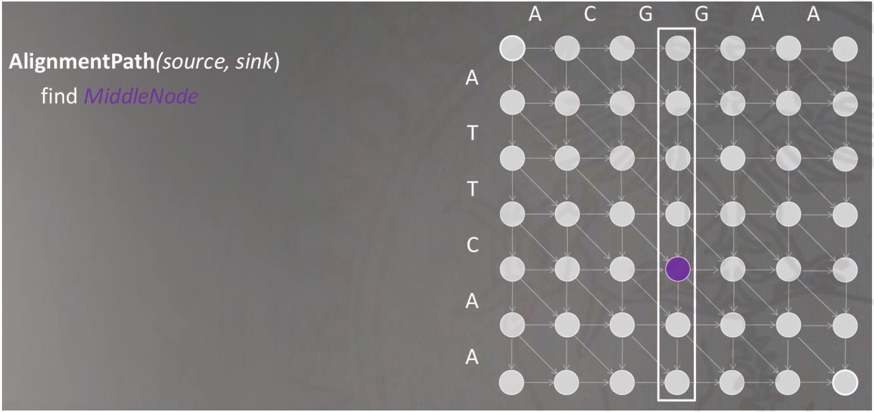
How to reduce the memory consumption



- The **middle node** is a node where an optimal alignment path crosses the middle column

Space-Efficient Sequence Alignment

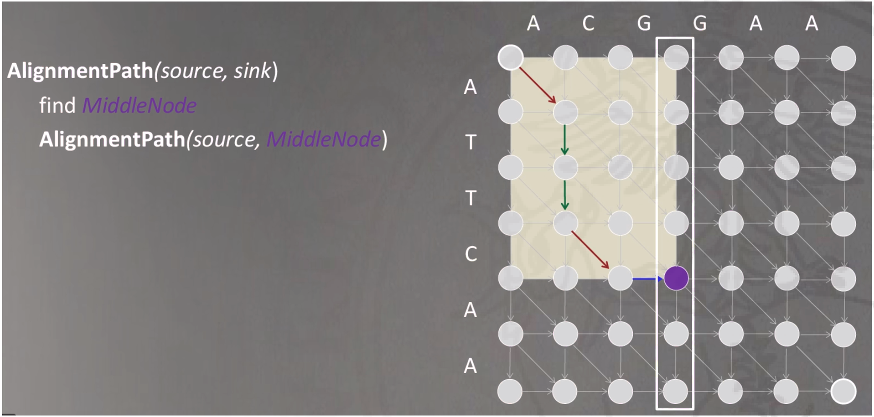
Divide and Conquer approach to sequence alignment



```
**AlignmentPath**(*source, sink*)
    find *MiddleNode*
```

Space-Efficient Sequence Alignment

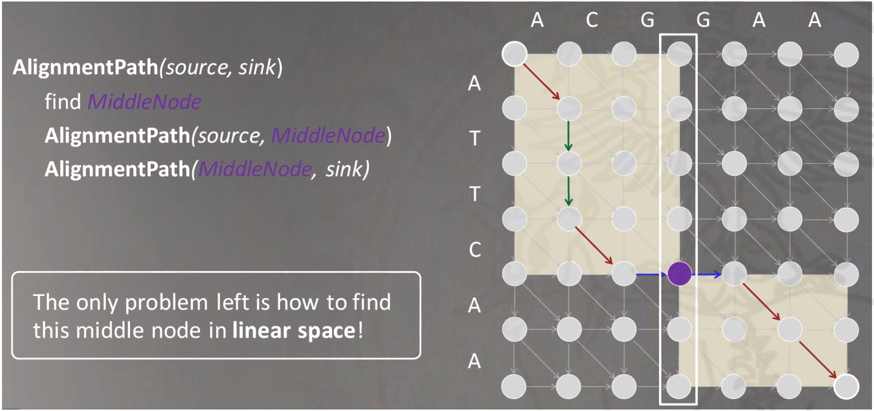
Divide and Conquer approach to sequence alignment



```
AlignmentPath(source, sink)
    find MiddleNode
    AlignmentPath(source, MiddleNode)
```

Space-Efficient Sequence Alignment

Divide and Conquer approach to sequence alignment

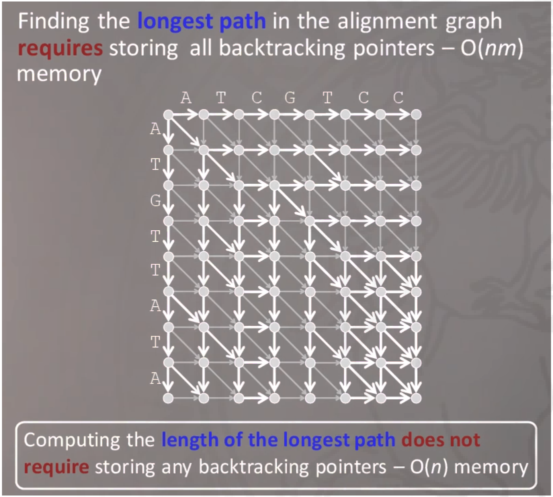


```
AlignmentPath(source, sink)
    find MiddleNode
    AlignmentPath(source, MiddleNode)
    AlignmentPath(MiddleNode, sink)
```

The only problem left is how to find this middle node in **linear space**!

Space-Efficient Sequence Alignment

Computing alignment score in Linear Space

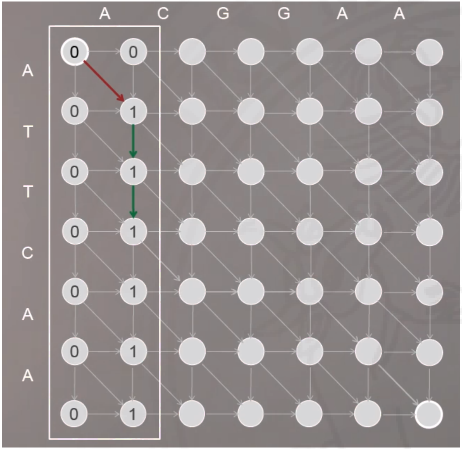


Finding the **longest path** in the alignment graph **requires** storing all backtracking pointers – O(*nm*) memory

Computing the **length of the longest path does not require** storing any backtracking pointers – O(*n*) memory

Space-Efficient Sequence Alignment

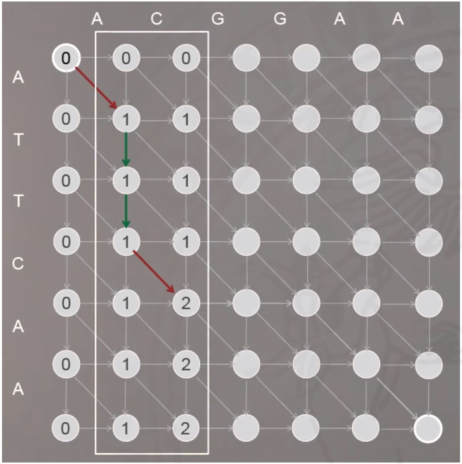
Computing alignment score in Linear Space



- For simplicity we consider the following score function: **||matches||**

Space-Efficient Sequence Alignment

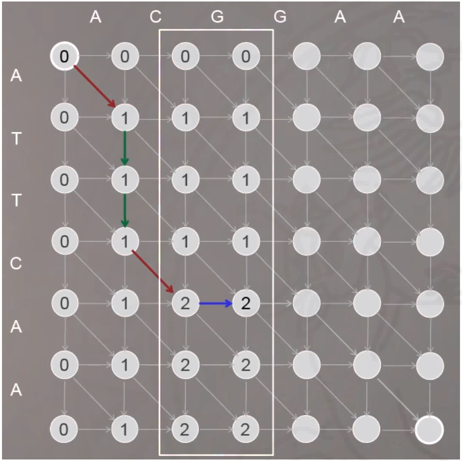
Computing alignment score in Linear Space



- the 1^{st} column is not needed anymore;
- it can be discarded to reuse the memory;

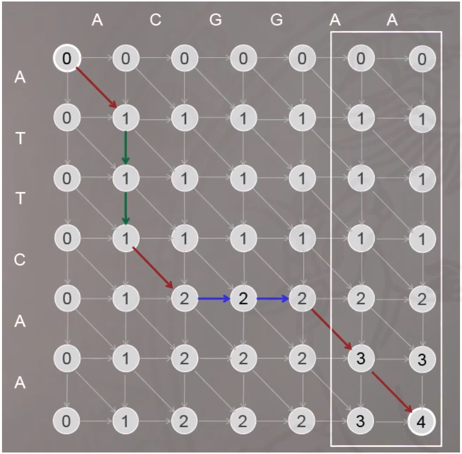
Space-Efficient Sequence Alignment

Computing alignment score in Linear Space



Space-Efficient Sequence Alignment

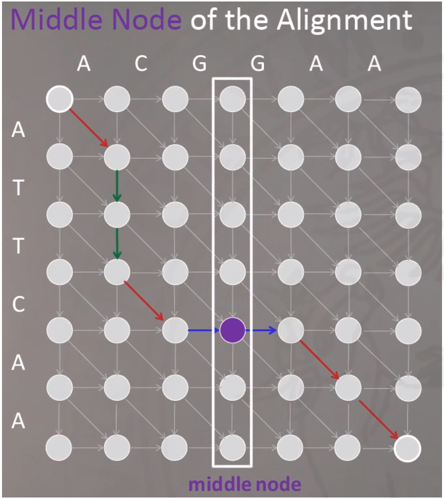
Computing alignment score in Linear Space



		A	C	G	G	A	A
	0	0	0	0	0	0	0
A	0	1	1	1	1	1	1
T	0	1	1	1	1	1	1
T	0	1	1	1	1	1	1
C	0	1	2	2	2	2	2
A	0	1	2	2	2	3	3
A	0	1	2	2	2	3	4

Space-Efficient Sequence Alignment

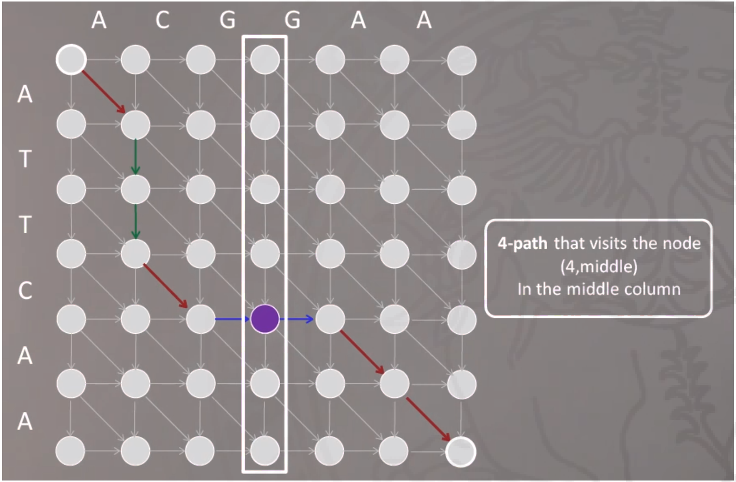
Computing alignment score in Linear Space



- We call **i-path**: the longest path among all paths that visit the node *i* in the middle column.

Space-Efficient Sequence Alignment

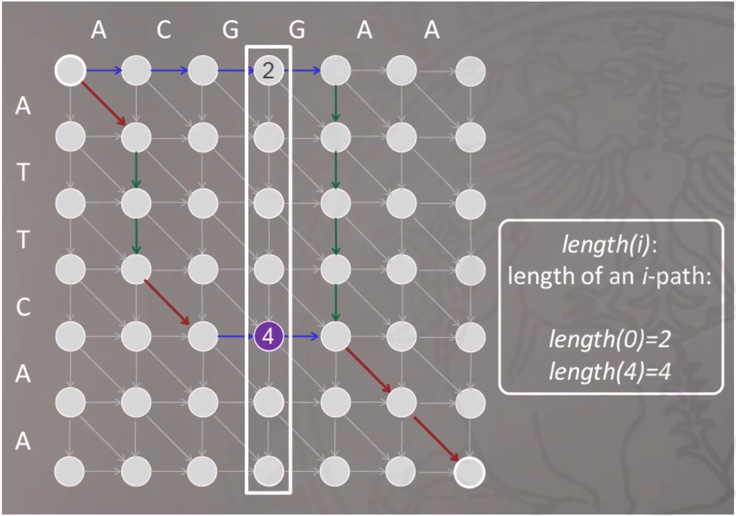
Computing alignment score in Linear Space



4-path that visits the node (4,middle) In the middle column

Space-Efficient Sequence Alignment

Computing alignment score in Linear Space

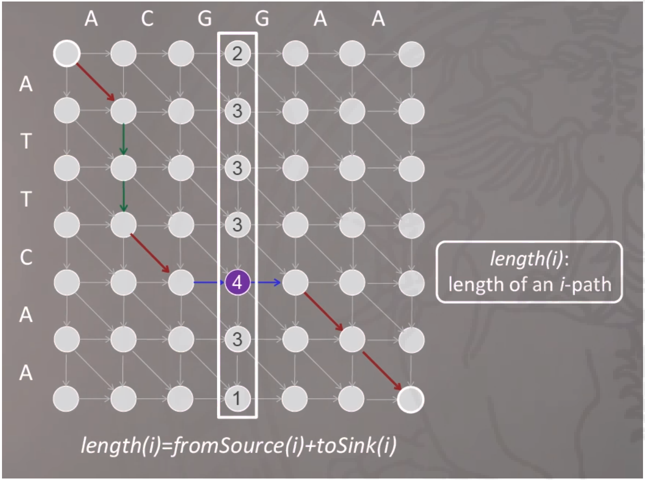


length(i):
length of an *i*-path:

length(0)=2
length(4)=4

Space-Efficient Sequence Alignment

How to efficiently compute the length of i-path

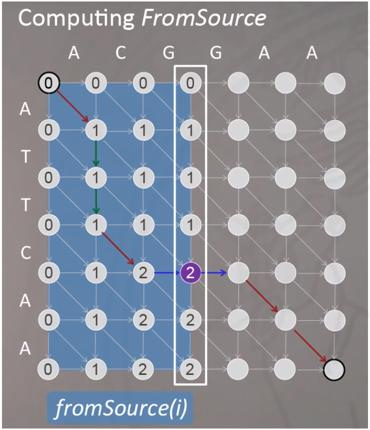


length(i):
length of an *i*-path

length(i)=fromSource(i)+toSink(i)

Space-Efficient Sequence Alignment

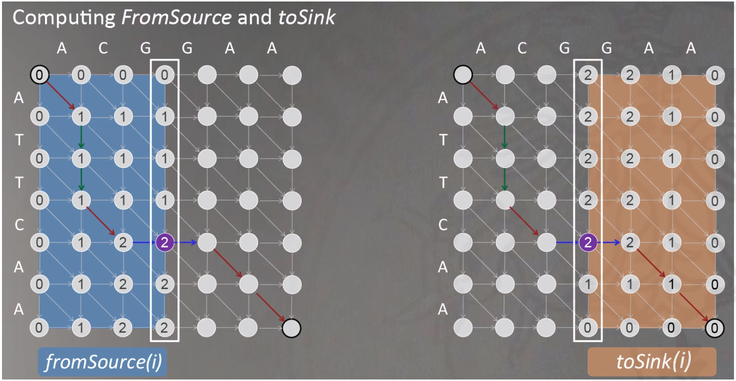
How to efficiently compute the length of i-path



- we can exploit the algorithm for **alignment score** previously defined.

Space-Efficient Sequence Alignment

How to efficiently compute the length of i-path



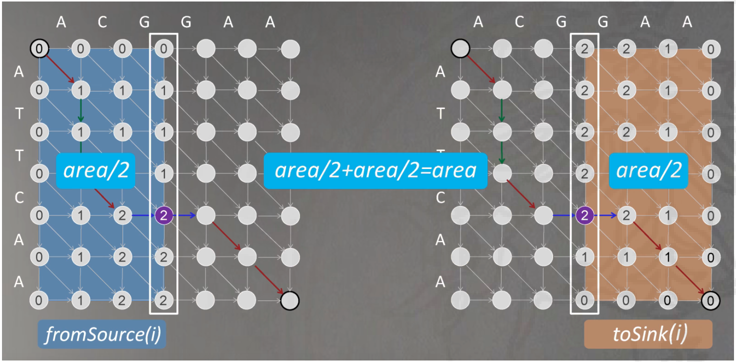
		A	C	G	G	A	A
	0	0	0	0			
A	0	1	1	1			
T	0	1	1	1			
T	0	1	1	1			
C	0	1	2	2			
A	0	1	2	2			
A	0	1	2	2			

		A	C	G	G	A	A
				2	2	1	0
A				2	2	1	0
T				2	2	1	0
T				2	2	1	0
C				2	2	1	0
A				1	1	1	0
A				0	0	0	0

- we can exploit the algorithm for **alignment score** previously defined (from source to middle node and from sink to middle node).

Space-Efficient Sequence Alignment

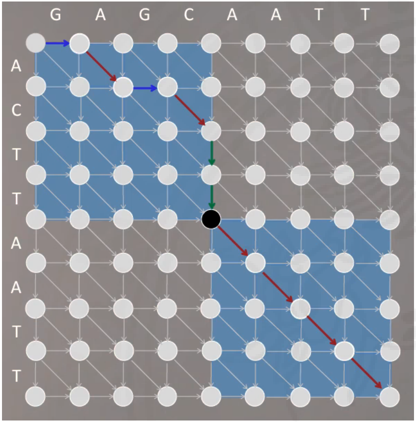
How to efficiently compute the length of i-path



- we can exploit the algorithm for **alignment score** previously defined (from source to middle node and from sink to middle node).

Space-Efficient Sequence Alignment

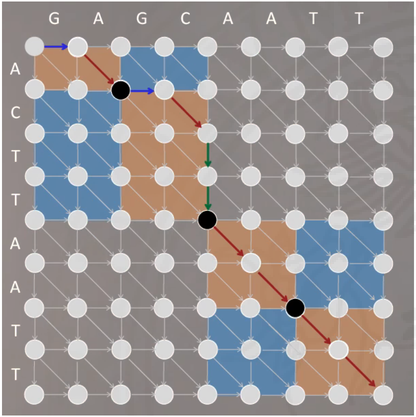
How to efficiently compute alignment using middle node approach



- when the middle node is found we can split the alignment problem into **two sub-alignment problems**;
- the two sub-alignments can be performed **in parallel**.

Space-Efficient Sequence Alignment

How to efficiently compute alignment using middle node approach



- when the middle node is found we can split the alignment problem into **two further sub-alignment problems**;
- the four sub-alignments can be performed **in parallel**.

Exercises

Try to align globally the following sequences using the Divide and Conquer approach:

- ACCTG and TGATG;
- ACTCA and CACTC.

$$\textit{score matrix} = \begin{bmatrix} 1 & -2 & -2 & -2 & -1 \\ -2 & 1 & -2 & -2 & -1 \\ -2 & -2 & 1 & -2 & -1 \\ -2 & -2 & -2 & 1 & -1 \\ -1 & -1 & -1 & -1 & - \end{bmatrix}$$

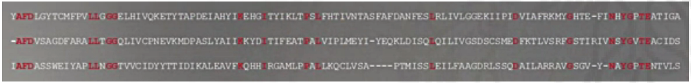
Part 4

Multiple Sequence Alignment

Multiple Sequence Alignment

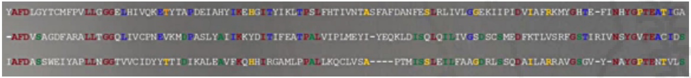
- Similarity between two sequences becomes more significant if it is present in many other sequences;
- Multiple alignments can better highlight similarities that pairwise alignments fail to reveal.

Multiple alignment output



```
YAFDLGYTCMFPVLLGGGELHIVQKETYTAPDEIAHYIKEHGITYIKLTPSLFHTIVNTASFAFDANFESLRLIVLGGEKIIPIDVIAFRKMYGHTE-FINHYGPTEATIGA
-AFDVSAGDFARALLTGGQLIVCPNEVKMDPASLYAIIKKYDITIFEATPALVIPLMEYI-YEQKLDISQLQILIVGSDSCSMEDFKTLVSRFGSTIRIVNSYGVTEACIDS
IAFDASSWEIYAPLLNGGTVVCIDYYTTIDIKALEAVFKQHHIRGAMLPPALLKQCLVSA----PTMISSLEILFAAGDRLSSQDAILARRAVGSGV-Y-NAYGPTENTVLS
```

Comparing pairwise alignment outputs

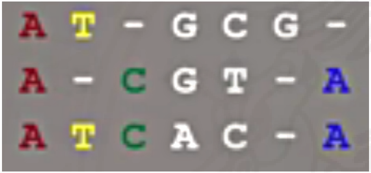


```
YAFDLGYTCMFPVLLGGGELHIVQKETYTAPDEIAHYIKEHGITYIKLTPSLFHTIVNTASFAFDANFESLRLIVLGGEKIIPIDVIAFRKMYGHTE-FINHYGPTEATIGA
-AFDVSAGDFARALLTGGQLIVCPNEVKMDPASLYAIIKKYDITIFEATPALVIPLMEYI-YEQKLDISQLQILIVGSDSCSMEDFKTLVSRFGSTIRIVNSYGVTEACIDS
IAFDASSWEIYAPLLNGGTVVCIDYYTTIDIKALEAVFKQHHIRGAMLPPALLKQCLVSA----PTMISSLEILFAAGDRLSSQDAILARRAVGSGV-Y-NAYGPTENTVLS
```

Multiple Sequence Alignment

Generalizing pairwise alignment to multiple one

- Alignment of 2 sequences is a 2-row matrix;
- Alignment of 3 sequence is a 3-row matrix;



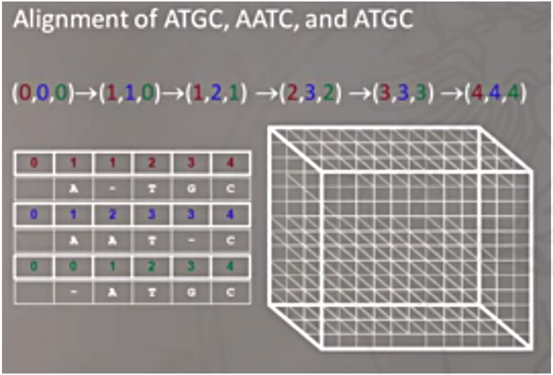
A	T	-	G	C	G	-
A	-	C	G	T	-	A
A	T	C	A	C	-	A

- Our scoring function should score alignments with conserved columns higher.

Multiple Sequence Alignment

Generalizing pairwise alignment to multiple one

- We search for a longest path in a 3D DAG;



Alignment of ATGC, AATC, and ATGC

(0,0,0)→(1,1,0)→(1,2,1) →(2,3,2) →(3,3,3) →(4,4,4)

0	1	1	2	3	4
	A	-	T	G	C
0	1	2	3	3	4
	A	A	T	-	C
0	0	1	2	3	4
	-	A	T	G	C